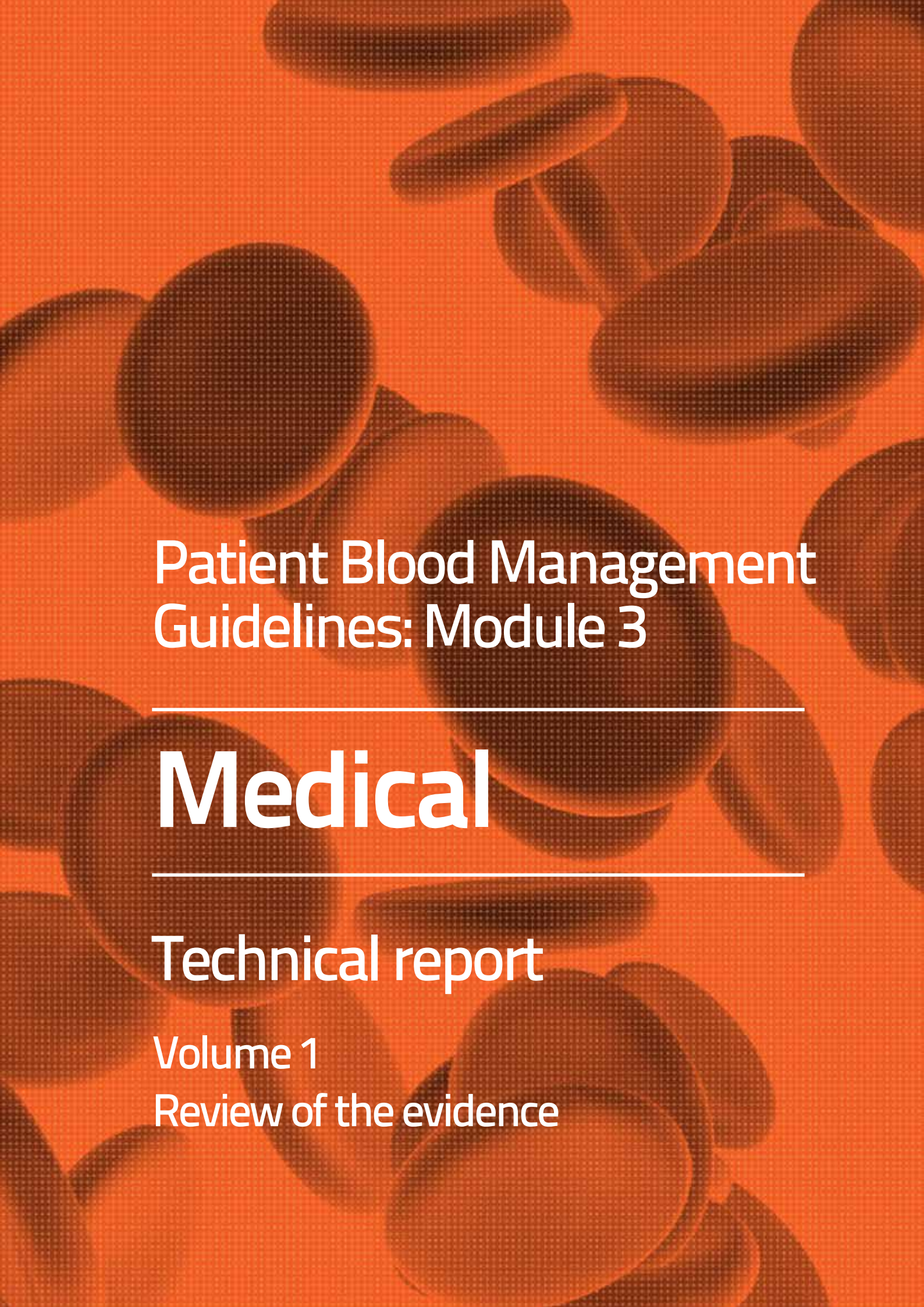

Patient Blood Management Guidelines: Module 3

Medical

Technical report

Volume 1
Review of the evidence

Note

This volume presents the main body of evidence found by a systematic literature review on medical patient blood management. Volume 2 presents the related appendixes (Appendix A to Appendix F). These two volumes cover all research questions developed for this topic.

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Abbreviations and acronyms

ACS	acute coronary syndrome
AHCDO	Australian Haemophilia Centre Directors' Organisation
AHMAC	Australian Health Ministers' Advisory Council
AHMC	Australian Health Ministers' Conference
AIDS	acquired immunodeficiency syndrome
ANZSBT	Australian & New Zealand Society of Blood Transfusion
APTT	activated partial thromboplastin time
ARCBS	Australian Red Cross Blood Service
ASBT	Australasian Society of Blood Transfusion
ASCO	American Society of Clinical Oncology
ASH	American Society of Haematology
CARI	Caring for Australasians with Renal Impairment
CHF	chronic heart failure
CKD	chronic kidney disease
CRG	Clinical/Consumer Reference Group
CTEPC	Clinical, Technical and Ethical Principal Committee
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
ES	evidence statement
ESA	erythropoiesis-stimulating agent
EWG	Expert Working Group
FACT	Functional Assessment of Cancer Therapy
FFP	fresh frozen plasma
FID	functional iron deficiency
GOG	Gynecologic Oncology Group
Hb	Hb
HIF	hypoxia-inducibile factor
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
IBD	inflammatory bowel disease
IV	intravenous
INR	international normalised ratio
JBC	Jurisdictional Blood Committee
KCCQ	Kansas City Cardiomyopathy Questionnaire
MDS	myelodysplastic syndrome
MI	myocardial infarction

MLHFQ	Minnesota Living with Heart Failure Questionnaire
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NYHA	New York Heart Association
NZBS	New Zealand Blood Service
PBS	Pharmaceutical Benefits Scheme
PICO	population, intervention, comparator and outcome
PP	practice point
PPO	population, predictor and outcome
PRO	population, risk factor and outcome
PT	prothrombin time
QLQ-C30	Quality of Life Questionnaire-C30
R	recommendation
RBC	red blood cell
RCT	randomised controlled trial
rFVIIa	recombinant activated factor VIIa
SD	standard deviation
SF-36	Short Form-36
SHOT	Serious Hazards of Transfusion
TACO	transfusion-associated circulatory overload
TGA	Therapeutic Goods Administration
TRICC	Transfusion Requirements in Critical Care Trial
WHO	World Health Organization

1 Introduction

This document presents the methods and results relating to the findings from a systematic literature review on medical patient blood management. It is the first volume of a technical report produced as part of the development process for the *Patient blood management guidelines: Module 3 – Medical* – the third in a series of six modules that focus on evidence-based patient blood management and will replace the 2001 National Health and Medical Research Council/Australasian Society of Blood Transfusion (NHMRC/ASBT) *Clinical practice guidelines on the use of blood components*[1] The six modules of the guidelines are being developed in three phases, as shown in Table 1.1.

Table 1.1 Phases of development of guideline modules

Phase	Modules
I	Critical bleeding/massive transfusion Perioperative
II	Medical Critical care
III	Obstetrics Paediatric/neonatal

This volume covers all the research questions. Volume 2 of the technical report presents the related appendixes.

The document Patient blood management guidelines: Module 3–Medical gives information on:

- governance arrangements for the guidelines
- committee memberships and affiliations
- the background research team.

2 Methods

2.1 Research question development

An Expert Working Group (EWG) met for the first time in July 2008. At this meeting members were provided with a comprehensive analysis of existing guidelines relevant to the clinical areas of focus. An independent systematic review expert provided a detailed presentation on framing clinical questions for systematic review. EWG members self-nominated to participate in relevant areas of clinical focus for each module. This action formed the basis for the establishment of a Consumer/Clinical Reference Group (CRG) for each module.

Following the July 2008 meeting, members of each CRG generated questions to be considered for inclusion in their respective guidelines. Before the next meeting, CRG members discussed first-draft questions, and acknowledged that question content would influence consideration of expanding CRG memberships to ensure relevant clinical and consumer representation. CRG members agreed that it would be appropriate to circulate draft questions to relevant clinical colleges and societies for input and feedback at an early stage and before inclusion in a statement of requirement for a systematic reviewer.

The EWG met in September 2008 to further develop and prioritise the proposed questions. During the development of research questions, it became apparent that several questions would be relevant for systematic review for all modules (Phases I to III). These became known as generic questions; six of these were ultimately developed.

Another two workshop meetings were held in November 2008. All EWG members attended these meetings, where questions were further prioritised, combined and refined. In January 2009, a meeting of the CRG Chairs finalised questions that were subsequently provided to systematic reviewers.

This process resulted in generic and specific foreground questions for systematic review and questions for background research. The background questions were to be addressed through general research undertaken by registrars supervised by CRG members. Background questions were designed to provide general information for the guidelines and to assist in providing generalised clinical practice tips. Background questions were intended to capture information that was considered to fall outside the scope of the foreground questions addressed by the systematic literature review. Foreground and background questions were further refined through consultation among the systematic reviewer/technical writer, CRG, National Blood Authority (NBA) and independent systematic review expert.

Research questions were developed for all but the critical care module. The requirement for this module was not identified until after the initial systematic review for Phase I had commenced.

Questions 1–5 are generic questions, relevant to all six modules of these guidelines; Question 6 is specific to medical transfusion (i.e. to this module):

- *Question 1* – In medical patients, is anaemia an independent risk factor for adverse outcomes? (Aetiological question)
- *Question 2* – In medical patients, what is the effect of RBC transfusion on patient outcomes? (Interventional question)
- *Question 3* – In medical patients, what is the effect of non-transfusion interventions to increase Hb concentration on morbidity, mortality and need for RBC blood transfusion? (Interventional question)
- *Question 4* – In medical patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? (Interventional question)
- *Question 5* – In medical patients, what INR (PT/APTT) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelets concentrates should patients be transfused to avoid risks of significant adverse events? (Interventional and prognostic question)
- *Question 6* – In specific regularly and chronically transfused patients, at what Hb threshold should patients be transfused to avoid adverse outcomes? (Interventional question).

A further question – What is the effect of rFVIIa (prophylaxis or treatment) on morbidity, mortality and transfusion rate? – was not covered in this review.

Intervention questions were intended to determine the effects of various strategies that can be used in patient blood management on patient outcomes. The aetiology question was designed to determine whether the risk factor anaemia causes adverse outcomes. The prognostic question was concerned with clinical information that predicts outcomes.

2.1.1 Background research question

The background research questions developed for medical patient blood management were:

- In patients with malignancies (solid tumours) undergoing radiotherapy, do interventions (transfusion or ESAs) aimed at raising the Hb concentration during radiotherapy affect patient outcomes (e.g. response rate, tumour recurrence or tumour-free survival)?
- *Background question 2* – When should a patient be retested after a transfusion to assess the response, guide if further transfusions are required and avoid over-transfusion?

Details of research question criteria are presented in **Appendix 1** of this volume.

2.1.2 Aboriginal and Torres Strait Islander Populations

Prevalence of anaemia in Aboriginal and Torres Strait Islander populations is known to be higher than in the general Australian population.[2] The electronic search terms did not specifically search for or limit retrieval of articles to studies that addressed socioeconomic, Aboriginal or Torres Strait Islander subgroups. However, in accordance with NHMRC guideline development requirements, the reviewers were required to isolate any papers addressing these populations for specific consideration by the CRG. No papers were identified that addressed these populations specifically.

2.2 Literature searches

NHMRC standards and procedures require that clinical practice guidelines be based on systematic identification and synthesis of the best available scientific evidence.[3] Three main strategies were used to identify potentially relevant literature: electronic database searching, manual searching, and literature recommended by expert members of the CRG.

2.2.1 Electronic databases

The systematic review/technical writing group carried out searches using the following primary databases:

- EMBASE and Medline via the EMBASE.com interface
- Cochrane Library Database: a database of systematic reviews, other reviews, clinical trials, methods studies, technology assessments, economic evaluations and Cochrane Groups
- PreMedline: Medline in process, accessed via the PubMed interface.

Additional secondary databases searched, where indicated, included:

- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- AMI (Australasian Medical Index).

Dates of searching the primary and secondary databases are presented in **Appendix A** (Volume 2).

Search strategies for primary and secondary databases were developed in consultation with a specialist search strategist. All strategies were based on the population, intervention, comparator, outcome (PICO), population, predictor, outcome (PPO) or population, risk, outcome (PRO) criteria developed for the research questions (**Appendix 1** in this volume). Full details of all search strategies for these primary and secondary databases are presented in **Appendix A** (Volume 2).

The search also included websites of health technology assessment (HTA) agencies, including the UK National Institute for Health and Clinical Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH), and relevant guidelines websites.

2.2.2 Manual searching of reference lists

Members of the systematic review/technical writing group manually searched reference lists included in relevant articles identified by the systematic literature search. This strategy identified some additional articles that were not found in electronic database searches. Additional articles found by manual searching are indicated in the literature search results presented in **Appendix C** (Volume 2).

2.2.3 Expert sources

Articles recommended by CRG members were considered for inclusion wherever inclusion and exclusion criteria were met.

2.2.4 Background question research

Research for background questions was undertaken by registrars under the supervision of CRG members. These questions were not researched by applying systematic review processes. Registrars were advised to use sources ranging from medical textbooks, grey literature, published scientific and review articles (identified through PubMed, EMBASE or Cochrane databases), series yearbooks and other relevant medical literature. Because the intention was to identify relevant information that could inform best practice, background research was not limited to evidence or general information only applicable to Australia and New Zealand.

2.2.5 Issues relevant to Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities

The focus of the systematic review was on physiological parameters surrounding the decision to transfuse. As such, there were no distinct physiological issues relevant to Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities.

The greater prevalence of certain conditions (e.g. anaemia, chronic kidney disease) in some Indigenous Australian communities has a socioeconomic, not physiological, basis. No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature searches for any research question

2.2.6 Cost effectiveness

While no published cost-effectiveness analyses on the use of a multidisciplinary, multimodal perioperative patient blood management program was identified in the literature searches, a number of studies published information about costs or savings.

When no cost-effectiveness studies relevant to a research question were identified, this is noted for that question in the technical report. Cost or savings analyses, when found, are discussed for each question in the technical report

2.3 Inclusion and exclusion criteria

Inclusion criteria were determined from the PICO, PPO or PRO criteria that formed the basis of the systematically reviewed research questions (**Appendix 1** in this volume). Studies that did not meet one or more of these criteria were excluded.

Additional reasons for excluding studies were:

- non-human studies
- non-English language studies
- non-systematic reviews, editorials, opinion pieces and letters
- research or systematic review protocols not defined.

Titles and abstracts of every record retrieved by searching the primary and secondary databases were reviewed, and full articles were retrieved for further assessment where considered to meet the inclusion criteria. Articles that could not be included or excluded on

the basis of information in the title or abstract were retrieved as full text before a final decision was made on inclusion or exclusion.

Articles reporting on the basis of the following study designs were considered for inclusion when PICO, PPO or PRO criteria were met:

- systematic reviews of randomised controlled trials (RCTs) and/or cohort studies
- RCTs or pseudo randomised controlled trials
- cohort studies
- case–control studies
- case series, pre–post or post studies
- socioeconomic studies, economic evaluations, cost-effectiveness analysis and so forth.

Studies that initially met inclusion criteria but were later excluded are documented, with reasons for their exclusion, in **Appendix B** (Volume 2). Examples of reasons for exclusion in this circumstance include different systematic reviews reporting the same primary studies, and inadequate data reporting.

2.4 Classification and assessment of evidence

Studies identified for inclusion from the literature search were classified according to the NHMRC levels of evidence hierarchy (Table 2.1). To ensure that modules were based on the best available evidence, studies of higher levels of evidence (Levels I or II) were included in preference to those presenting lower levels of evidence (Levels III or IV). This was to minimise the potential for bias in the evidence base for each systematically reviewed question. However, lower level studies were reviewed where evidence was not available in higher level studies for any of the primary outcomes.

Studies identified from the systematic literature review were assessed according to NHMRC dimensions of evidence (Table 2.2).[4]).[4] There are three main domains: strength of the evidence, size of the effect, and relevance of the evidence. The first domain was derived directly from the literature identified for a particular intervention, aetiology or prognostic study. The other two domains were determined in consultation with the CRG as part of the study assessment process during the review of the evidence considered for module development. An aspect of the strength of the evidence domain is the level of evidence of the study, which was determined as described above using the NHMRC levels of evidence hierarchy outlined in Table 2.1.

Table 2.1 NHMRC evidence hierarchy: designations of levels of evidence according to type of research question

Level	Intervention[a]	Prognosis	Aetiology[b]
I[c]	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies
II	A randomised controlled trial	A prospective cohort study[d]	A prospective cohort study
III-1	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)	All or none[e]	All or none[e]
III-2	A comparative study with concurrent controls: • non-randomised, experimental trial[f] • cohort study • case–control study • interrupted time series with a control group	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study
III-3	A comparative study without concurrent controls: • historical control study • two or more single arm study[g] • interrupted time series without a parallel control group	A retrospective cohort study	A case–control study
IV	Case series with either post-test or pre-test/post-test outcomes	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series

Source: NHMRC (2009)[4]

[a] Definitions of these study designs are provided on pages 7–8, *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000)[5]

[b] If it is possible and ethical to determine a causal relationship using experimental evidence, then the 'intervention' hierarchy of evidence should be used. If it is only possible or ethical to determine a causal relationship using observational evidence (e.g. groups cannot be allocated to a potential harmful exposure, such as nuclear radiation), then the 'aetiology' hierarchy of evidence should be utilised.

[c] A systematic review will only be assigned a level of evidence as high as the studies it contains, except where those studies contain Level II evidence. Systematic reviews of Level II evidence provide more data than the individual studies, and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome or result, as different studies (and study designs) might contribute to each different outcome.

[d] At study inception, the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

[e] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of smallpox after large-scale vaccination.

[f] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs. B and B vs. C to determine A vs. C).

[g] Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs. B and B vs. C to determine A vs. C, without statistical adjustment for B).

Table 2.2 NHMRC dimensions of evidence

Dimension	Definition
Strength of evidence	
Level	Each included study is assessed according to its place in the research hierarchy. This illustrates the potential of each included study to adequately answer a particular research question and indicates the

Dimension	Definition
	degree to which design has minimised the impact of bias on the results
Quality	Included studies are critically appraised for methodological quality. Each study is assessed according to the potential that bias, confounding and/or chance has influenced the results
Statistical precision	Primary outcomes of included studies are assessed to establish whether the effect is real, rather than due to chance. Using a level of significance such as a *p*-value and/or confidence interval, the precision of the estimate of the effect is evaluated. This considers the degree of certainty regarding the existence of a true effect
Size of effect	The clinical importance of the findings of each study is assessed. This concept refers to the measure of effect or point estimate reported in the results of each study (e.g. mean difference, relative risk). For meta-analysis pooled measures of effect are assessed. Size of effect refers to the distance of the point estimate from its null value and also the values included in the corresponding 95% confidence interval. Size of effect indicates the clinical impact a particular factor or intervention will have on a patient and is considered in the context of patient relevant clinical differences
Relevance of evidence	The translation of research evidence to clinical practice is addressed by this dimension. It is regarded as potentially the most subjective of the evidence assessments. There are two questions concerning the appropriateness of outcomes and relevance of study questions: Are the outcomes measured in the study relevant to patients? How closely do the elements of the study research question match with those of the clinical question being considered?

Source: NHMRC (2009)[4]

2.4.1 Quality appraisal

The methodological quality of the included studies was assessed using the criteria presented in **Appendix 3** of this volume.[5] Quality assessment criteria varied according to whether included studies were systematic reviews, RCTs, cohort studies or case–control studies. No weighting of quality criteria was applied, but studies that met all criteria, or all but one, were considered good quality with a low risk of bias. Quality assessments of included studies for all systematically reviewed research questions are presented in **Appendix E** (Volume 2).

2.4.2 Data extraction

Data and information were extracted into evidence summary tables according to the inclusion criteria (PICO, PRO or PPO). Evidence summary tables were based on NHMRC requirements for externally developed guidelines.[6] Extracted data and information included general study details (citation, study design, evidence level, country and setting), characteristics of study participants, details of interventions and comparators, details of internal (e.g. allocation and blinding) and external (applicability and generalisability) study validity; and results for outcomes specified in the inclusion criteria. Where relevant studies were identified, extracted data and information were used to construct study characteristics and results tables of included evidence for each systematically reviewed research question. Evidence summary tables for all included studies are presented in **Appendix F** (Volume 2).

2.5 Assessment of the body of evidence and formulation of recommendations

The body of evidence for each module recommendation was graded in accordance with the NHMRC framework for developing evidence-based recommendations.[4] Assessment of the

body of evidence considers the dimensions of evidence of studies relevant to that recommendation (Table 2.2). The NHMRC developed an evidence statement form to be used with each clinical research question considered in guidelines development (**Appendix 3** of this volume). Before the evidence statement form was completed, included studies were critically appraised and relevant data were summarised, as described. This information was required to formulate each recommendation and determine the overall grade of the body of evidence supporting each recommendation.

The key findings from included studies were summarised as evidence statements for each systematically reviewed research question. Where required, separate evidence statements were developed for different patient populations and outcomes. CRG input helped ensure that the size of effects and relevance of evidence were considered when developing evidence statements. Where no evidence or insufficient relevant evidence was identified, this was explained in the evidence statement and an evidence statement form was not included.

Completed evidence statement forms for each research question are presented in **Appendix D** (Volume 2).

2.5.1 Use of the NHMRC evidence statement form

The NHMRC evidence statement form was applied in five steps.

Step 1 Rating each of the five components

To inform grading of recommendations, the body of evidence underpinning each evidence statement was assessed. Five key components were rated (Table 2.3). The first two components—evidence base and consistency—were derived directly from the literature identified for each research question. During review of identified evidence, CRG guidance was also required to assess the clinical impact, generalisability and applicability of included studies.

For each evidence statement, the five components presented in Table 2.3 were rated according to the matrix shown in Table 2.4. This grading system was designed to accommodate variation in the body of evidence. For example, a large number of studies with minimal bias may be included, but have limited applicability to the Australian healthcare context. Alternatively, a body of evidence may consist of a small number of trials with a moderate risk of bias, but have a very significant clinical impact and high applicability to the Australian healthcare context. Body of evidence rating results were entered into the NHMRC evidence statement form, together with any additional explanatory information relevant to each component. The results section for each research question includes the body of evidence matrix rating assessment for each evidence statement.

Table 2.3 Components of the evidence statement

Component	Definition
Evidence base	
Quantity	Reflects the number of studies included as the evidence base. Also takes into account the number of patients in relation to frequency of the outcomes measured (i.e. study statistical power). Meta-analysis can be used to combine results of studies to increase the power and statistical precision of effect estimates
Level	Reflects the best study type for the specific type of research question (intervention, prognosis). Level I evidence would be the best evidence to answer each question
Quality	Reflects how well studies were designed and conducted in order to eliminate bias
Consistency	Assesses whether findings are consistent across included studies, including a range of study populations and study designs. Meta-analysis of randomised studies should present statistical analysis of heterogeneity that demonstrates little statistical difference between studies. Presentation of an I^2 statistic illustrates the extent of heterogeneity between studies. Clinical heterogeneity between studies should also be explored
Clinical impact	Measures the potential benefit from application of the guidelines to a population. Several factors need to be considered when estimating clinical impact, including relevance of the evidence to the clinical question; statistical precision and size of the effect; relevance of the effect to patients compared with other management options or none. Other relevant factors are the duration of therapy required to achieve the effect, and the balance of risks and benefits (taking into account the size of the patient population)
Generalisability	Addresses how well the subjects and settings of included studies match those of the recommendation. Population issues that could affect recommendations include sex, age, ethnicity, and baseline risk or level of care (e.g. community or hospital setting). This is an important consideration when evidence comes from randomised controlled trials, where setting and entry requirements are generally narrow and therefore may not be representative of all patients to whom the recommendation may be applied in practice. In this circumstance broader-based population studies may be useful for confirming evidence from randomised controlled trials
Applicability	Addresses whether the evidence base is relevant to the Australian healthcare setting in general or to more local settings for specific recommendations (e.g. rural areas or cities). Factors that will affect the applicability of study findings include organisational factors (e.g. availability of trained staff, specialised equipment and resources) and cultural factors (e.g. attitudes to health issues, including those that may affect compliance with guidelines recommendations)

Source: NHMRC (2009)[4]

Table 2.4 Body of evidence matrix

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review/multiple Level III studies with low risk of bias	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias	Level IV studies, or Level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guidelines	Population/s studied in the body of evidence are similar to the target population for the guidelines	Population/s studied in the body of evidence are different to the target population but it is clinically sensible to apply this evidence to the target population for the guidelines	Population/s studied in the body of evidence are different to the target population, and hard to judge whether it is sensible to generalise to the target population for the guidelines
Applicability	Directly applicable to the Australian healthcare context	Applicable to Australian healthcare context with a few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Source: NHMRC (2009)[4]

A rating of N/A was attributed for consistency when only one study was included.

Step 2 Preparation of an evidence statement matrix

An evidence statement matrix was completed to summarise the synthesis of the evidence relating to the evidence statement(s) for each research question. This summary presented ratings for the five components of the body of evidence matrix assessed for each evidence statement. Other relevant issues and dissenting opinions could be recorded if required.

In practice, Steps 1 and 2 to complete the NHMRC evidence statement forms were conducted concurrently for each evidence statement.

Step 3 Formulation of a recommendation based on the body of evidence

Step 3 involved formulating the wording of the recommendation. This wording was intended to reflect the strength of the body evidence; that is, where the evidence base was regarded as poor or unreliable, words such as 'must' or 'should' were not used. The wording of recommendations was developed in conjunction with the CRG during meetings to review the evidence base for research questions.

Step 4 Determination of the grade for the recommendation

The overall grade for each recommendation was determined from a summary of the rating for each component of the body of evidence. Definitions of the NHMRC grades of recommendations are presented in Table 2.5. In accordance with the NHMRC framework, recommendations were not graded A or B unless the evidence base and consistency of evidence were both rated A or B unless only one study was included and consistency was rated 'N/A'. In this situation the quality, size and strength of the evidence base was relied upon to grade the recommendation. The grading of recommendations was determined in conjunction with the CRG.

Developed recommendations were entered into the NHMRC evidence statement forms to accompany the corresponding evidence statement matrix, along with the overall grade determined in this step (**Appendix D**, Volume 2).

Table 2.5 Definitions of NHMRC grades for recommendations

Grade	Definition
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendations must be applied with caution

Source: NHMRC (2009)[4]

Step 5 Implementation of guidelines recommendations

The NHMRC framework directs that guidelines implementation should be considered at the same time that recommendations are formulated. The NHMRC evidence statement form contains questions related to the implementation of each module (**Appendix 3** in this volume). These are:

- Will this recommendation result in changes in usual care?
- Are there any resource implications associated with implementing this recommendation?
- Will the implementation of this recommendation require changes in the way care is currently organised?
- Is the guidelines development group aware of any barriers to the implementation of this recommendation?

This section of the NHMRC evidence statement form was completed in consultation with the CRG when each recommendation was formulated and graded. Implementation issues are recorded in the NHMRC evidence statement forms presented in **Appendix D** (Volume 2).

2.5.2 Practice points

Practice points were developed by the CRG through a facilitated group discussion (**Appendix 4** in this volume) in the following circumstances:

- where the underpinning evidence would have led to a grade D evidence-based recommendation
- where the CRG developed evidence-based recommendations graded C and above, but considered that additional information was required to guide clinical practice. Wherever possible, this guidance was sourced from other evidence-based guidelines assessed to be of high quality
- where insufficient evidence was identified to support the development of an evidence-based recommendation.

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3 Findings of systematic review

This chapter provides the findings of the systematic review, based on the six research questions given in Chapter 2.

3.1 Question 1

Question 1 (Aetiology)

In medical patients, is anaemia an independent risk factor for adverse outcomes?

3.1.1 Acute coronary syndrome

Evidence statements – acute coronary syndrome		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES1.1	In patients with ACS, anaemia is independently associated with all-cause mortality. (See evidence matrix EM1.A in Volume 2 of the technical report)	√√√	√√	√√	√√√	√√√
ES1.2	In patients with ACS, the effect of anaemia on cardiovascular mortality is uncertain. (See evidence matrix EM1.A in Volume 2 of the technical report)	√√√	√√	√√	√√√	√√√
ES1.3	In patients with NSTE-ACS, anaemia is independently associated with MI and recurrent ischaemia. (See evidence matrix EM1.B in Volume 2 of the technical report)	√√	NA	√√	√√√	√√
ACS, acute coronary syndrome; ES, evidence statement; MI, myocardial infarction; NSTE, non-ST segment elevation √√√=A; √√=B; √=C; X=D; NA, not applicable						

3.1.2 Heart failure

Evidence statements – heart failure		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.4	In patients with heart failure, anaemia is independently associated with mortality. (See evidence matrix EM1.C in Volume 2 of the technical report)	√√√	√√	√√	√√√	√√√
ES1.5	In patients with heart failure, anaemia may be independently associated with reduced functional or performance status and quality of life. (See evidence matrix EM1.D in Volume 2 of the technical report)	√√	NA	X	√√	√√
ES, evidence statement √√√=A; √√=B; √=C; X=D; NA, not applicable						

3.1.3 Community-dwelling elderly

Evidence statements – community-dwelling elderly		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.6	In a community-dwelling elderly population, anaemia is independently associated with mortality. (See evidence matrix EM1.E in Volume 2 of the technical report)	√√√	√√	√√	√√√	√√
ES1.7	In a community-dwelling elderly population, anaemia may be independently associated with reduced functional or performance status and quality of life. (See evidence matrix EM1.F in Volume 2 of the technical report)	√√	√√	X	√√	√√
ES, evidence statement √√√=A; √√=B; √=C; X=D; NA, not applicable						

3.1.4 Cancer

Evidence statements – cancer		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.8	In patients with cancer, anaemia is independently associated with mortality. (See evidence matrix EM1.G in Volume 2 of the technical report)	√√	√	√	√√	√√√
ES1.9	In patients with cancer, the effect of anaemia on functional or performance status and quality of life is uncertain. (See evidence matrix EM1.H in Volume 2 of the technical report)	√	√	X	√√	√√
ES, evidence statement √√√=A; √√=B; √=C; X=D; NA, not applicable						

3.1.5 Renal

Evidence statements – chronic kidney disease		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.10	In patients with CKD (including dialysis patients), anaemia is independently associated with all-cause or cardiovascular mortality. (See evidence matrix EM1.I in Volume 2 of the technical report)	√√	√√	√√	√√√	√√√
ES1.11	In adults with CKD, anaemia is independently associated with stroke. (See evidence matrix EM1.J in Volume 2 of the technical report)	√	NA	√√	√√	√√
ES1.12	In patients with CKD (including dialysis patients), Hb concentration is associated with reduced quality of life. (See evidence matrix EM1.K in Volume 2 of the technical report)	√	√√	√	√√√	√√
CKD, chronic kidney disease; ES, evidence statement; Hb, haemoglobin √√√=A; √√=B; √=C; X=D; NA, not applicable						

3.1.6 Summary of evidence

Five different populations were chosen for this question: (i) patients with acute coronary syndrome (ACS), (ii) patients with heart failure, (iii) a community-dwelling elderly population, (iv) patients with cancer and (v) patients with renal disease. Patients with ACS and the elderly, community-dwelling population were chosen by the CRG as being populations of particular interest. Patients with heart failure, cancer and renal disease were chosen after systematic reviews of evidence assessing the association between anaemia and adverse outcomes (including mortality) in these populations were identified during the literature search for Level I evidence.

As this is an aetiology question, the levels of evidence are as follows: Level I – a systematic review of two or more Level II studies; Level II – a prospective cohort study; Level III – (I) all or none, (II) a retrospective cohort study and (III) a case-control study; and Level IV – a cross-sectional study or case series. For this analysis, data from randomised controlled trials which have been analysed as cohort studies have been included as Level II studies, as have registries in which the data was collected prospectively. In some cases it was difficult to determine whether a cohort study was prospective or retrospective. Where data has been collected prospectively (ie, not collected from a review of medical records) the studies have been classified as prospective cohort studies. In addition, cross-sectional studies have been classified as Level II for functional/performance status outcomes only, where the outcome data has been collected prospectively.

As the question specifies it is assessing anaemia as an "independent" risk factor for adverse outcomes, only studies which have adjusted for potential confounding variables using multivariate analysis, have been included in this analysis; studies in which only univariate analyses have been undertaken have been excluded. It should be noted that the studies included for this question identified potential confounding variables in various ways. In some cases, variables have been identified which have been shown to be associated with anaemia or the specified outcome in previous studies, while in other cases a wide range of variables have been examined using univariate analysis and those shown to be associated with anaemia or the outcome have been included in the analysis. In some studies, all potential confounding variables have been included in the multivariate analysis, while in other studies different methods have been used (eg, backwards or forwards stepwise regression) to include only those variables which are shown to be independent predictors in the analysis.

While the results of these adjusted analyses indicate whether or not anaemia is an independent risk factor for adverse outcomes, they do not prove that anaemia *causes* these adverse outcomes. In addition, for most analyses, only data on the relative effects of anaemia is available; there is very little evidence on the absolute effect of anaemia on adverse outcome risk. However, where this data is available, it will be noted.

ACUTE CORONARY SYNDROME

The term acute coronary syndrome refers to a range of acute myocardial ischaemic states. It encompasses unstable angina, non-ST segment elevation myocardial infarction (NSTE-ACS; ST segment elevation generally absent), and ST segment elevation infarction (STEMI; persistent ST segment elevation usually present).[7]

Of the adverse outcomes specified for this question, two are covered for this population: mortality and cardiovascular/composite outcomes.

Methods

There were 12 studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews examining the aetiology of anaemia in patients with acute coronary syndrome.

Level II evidence

The literature search identified 12 Level II studies examining aetiology of anaemia in patients with acute coronary syndrome.

Level III evidence

Due to the substantial amount of Level II evidence identified, the literature was not searched for Level III evidence.

Level IV evidence

Due to the substantial amount of Level II evidence identified, the literature was not searched for Level IV evidence.

Results

Twelve Level II studies were included for this question; ten studies provided evidence for mortality and four studies provided evidence for composite and/or cardiovascular outcomes. The characteristics of the included studies are summarised in Table 3.1. Ten of the included studies specifically examined anaemia or Hb level as a potential predictor of adverse outcomes,[8-17] while the remaining two studies aimed to identify a number of potential predictors.[18,19]

Due to the large amount of evidence available for the mortality outcome and the requirement that analyses were adjusted for multiple potential confounders, studies were limited to those including >500 subjects. This resulted in the exclusion of one study including 151 patients.[20] Studies with smaller patient numbers were potentially available for inclusion for the cardiovascular/composite outcomes.

Table 3.1 Question 1 (ACS): Characteristics and quality of Level II evidence

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Anker et al (2009)[8]	Cohort analysis of a double-blind RCT (OPTIMAAL) *Fair*	AMI complicated by heart failure N = 5010	Mortality
Archbold et al (2006)[9]	Prospective cohort study *Fair*	Diagnosis of ACS N = 2310	Mortality
Aronson et al	Prospective cohort	Adults presenting to the coronary care unit with a	Mortality

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
(2007)[10]	study *Fair*	diagnosis of MI who were alive at discharge from hospital N = 1390	
Bassand et al (2010)[11]	Cohort analysis of two RCTs (OASIS 5 and 6) *Fair*	Adults presenting to hospital with symptoms of NSTE-ACS or STEMI N = 32,170	Mortality Mortality/MI
Burr et al (1992)[19]	Cohort analysis of a RCT (DART) *Poor*	Men without diabetes recovering from MI N = 1755	Mortality
Cavusoglu et al (2006)[12]	Prospective cohort study *Fair*	Men with ACS (ST-elevation AMI, non-ST segment elevation AMI and unstable angina pectoris) N = 191	Mortality/MI
Giraldez et al (2009)[13]	Two cohort analyses of two RCTs (InTIME II-TIMI17 and ExTRACT-TIMI) *Good*	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI N = 14,373 and 18,400	Mortality
Hasin et al (2009)[14]	Prospective cohort study *Fair*	Patients with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge N = 1065	Mortality/heart failure
Keough-Ryan et al (2005)[15]	Cohort analysis of a prospective population-based registry *Poor*	Adults admitted to hospital with a discharge diagnosis of acute coronary syndrome who survived to discharge N = 5549	Mortality
Mahaffey et al (2008)[18]	Cohort analysis of a RCT (SYNERGY) *Good*	High risk patients with ACS N = 9978	Mortality
Sabatine et al (2005)[16]	Cohort analysis of 16 RCTs[a] *Fair*	Adults presenting to hospital with symptoms of NSTE-ACS or STEMI N = 39,922	Mortality Cardiovascular mortality/MI/recurrent ischaemia Heart failure Myocardial infarction Recurrent Ischaemia
Valeur et al (2009)[17]	Cohort analysis of a RCT (TRACE) *Fair*	Patients with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI. N=1731	Mortality

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CHF, congestive heart failure; ECG, electrocardiograph; Hb, haemoglobin; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; RCT, randomised controlled trial; RI, recurrent ischaemia; STEMI, ST-segment elevation myocardial infarction.

[a] TIMI IIIB, 4, 9A, 9B, 10A, 10B, 11A, 11B, 12, 14, 16 (OPUS), 17 (InTIME II), 18 (TACTICS), 20 (INTEGRI), 23 (ENTIRE) and 24 (FASTER). InTIME II was included in the study by Giraldez et al (2009).[13]

Anaemia as an independent risk factor for mortality

Two studies assessed the association between **anaemia as defined by the World Health Organisation (WHO)[a] and mortality**, as shown in Table 3.2.[8,17] The study by Anker et al (2009)[8] showed that anaemia was an independent risk factor for all-cause mortality and death due to progressive heart failure in patients diagnosed with acute myocardial infarction (AMI)($P<0.001$ and $P=0.006$, respectively), but was not an independent risk factor for sudden cardiac death.

In the study by Valeur et al (2006)[17], anaemia was an independent risk factor for mortality in acute coronary syndrome (ACS) patients with heart failure ($P=0.048$), but not in patients without heart failure ($P=0.07$).

[a] Hb <12 g/dL for females and <13 g/dL for males.

Table 3.2 Question 1 (ACS): Results for Level II evidence – mortality (WHO or similar anaemia criteria)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ACUTE CORONARY SYNDROME									
ALL-CAUSE MORTALITY									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Anker 2009 Level II Fair	1 cohort analysis of a double-blind RCT (OPTIMAAL) N=5010	Adult patients with a diagnosis of AMI	Hospital Denmark, Finland, Germany, Ireland, Norway, Sweden, UK	Anaemia (WHO) vs no anaemia	Mortality (median 3 years)	NR	NR	HR 1.35 (1.16, 1.56) Adjusted for variables known to be of prognostic value in heart failure: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.	*Anaemia is an independent risk factor for mortality* P<0.0001
Valeur 2006 Level II Good	1 cohort analysis of a double-blind RCT (TRACE) N=1731	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI	Hospital Denmark	Anaemia (WHO) vs no anaemia	Mortality (up to12 years)	NR	NR	HR 1.06 (0.93, 1.21) Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.	*Anaemia is <u>not</u> an independent predictor of mortality* P=0.38
	1 cohort analysis of a double-blind RCT (TRACE) N=1195	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI <u>/with heart failure</u>	Hospital Denmark	Anaemia (WHO) vs no anaemia	Mortality (up to12 years)	NR	NR	HR 1.16 (1.01, 1.34) Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.	Anaemia is an independent predictor of mortality P=0.048
	1 cohort analysis of a double-blind RCT (TRACE) N=536	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI <u>/without heart failure</u>	Hospital Denmark	Anaemia (WHO) vs no anaemia	Mortality (up to 12 years)	NR	NR	HR 0.76 (0.57, 1.02) Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.	Anaemia is <u>not</u> an independent risk factor for mortality P=0.07

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
CARDIOVASCULAR MORTALITY									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Anker 2009 Level II Fair	1 cohort analysis of a double-blind RCT (OPTIMAAL) N=5010	Adult patients with a diagnosis of AMI	Hospital Denmark, Finland, Germany, Ireland, Norway, Sweden, UK	Anaemia (WHO) vs no anaemia	Sudden cardiac death (median 3 years)	NR	NR	HR 1.14 (0.89, 1.48)	*Anaemia is not an independent risk factor for sudden cardiac death* P=0.303
						Adjusted for variables known to be associated with heart failure: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			
					Death due to progressive heart failure (median 3 years)	NR	NR	HR 1.55 (1.13, 2.13)	*Anaemia is an independent risk factor for death due to progressive heart failure* P=0.006
						Adjusted for variables known to be associated with heart failure: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; dL, decilitre; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; RI, recurrent ischemia; SBP, systolic blood pressure; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; UK, United Kingdom; US, United States of America; WHO, World Health Organisation.
Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.
[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Six studies assessed the association between **various Hb levels and mortality**, as shown in Table 3.3.[9,10,13,15-17] Giraldez et al (2009)[13] examined the association between different baseline Hb levels and 30-day mortality in patients with ST-segment elevation myocardial infarction in cohorts based on two large randomised controlled trials. Five different Hb categories (<11 g/dL, 11-12 g/dL, 12-13 g/dL, 13-14 g/dL and 14-15 g/dL) were compared with a single Hb category (15-16 g/dL) in both trial cohorts. The majority of analyses showed lower Hb levels were a significant independent risk factor for 30-day mortality compared with the reference category; exceptions to this were the 14-15 g/dL category for the InTIME II-TIMI 17 trial cohort and the 13-14 g/dL and 14-15 g/dL categories for the ExTRACT-TIMI 25 trial cohort.

The study by Aronson et al (2007)[10] assessed the association between different baseline, nadir and discharge Hb levels, changes in Hb levels from baseline to discharge, and longer-term mortality (mean follow-up 2 years) in patients presenting to a coronary care unit with a diagnosis of myocardial infarction who survived to discharge. None of the analyses comparing baseline Hb showed a significant association with mortality. The authors note that because patients who died during hospitalisation were excluded from the analysis, the power to detect an association between baseline Hb level and mortality was probably reduced. Two out of three comparisons between nadir Hb (≤11.3 g/dL versus ≥14.0 g/dL and 11.4-12.8 g/dL versus ≥14.8 g/dL) and mortality showed a significant association; the final comparison of nadir Hb 12.9-13.9 g/dL with ≥14.0 g/dL was not significant. Similarly, comparisons of discharge Hb ≤11.9 g/dL and 12.0-13.3 g/dL with ≥14.6 g/dL were shown to be significantly associated with mortality while a comparison between a discharge Hb of 13.3-14.5 g/dL with ≥14.6 g/dL was not. Finally, a decrease in Hb from baseline to discharge of ≥2.3 g/dL, compared with a decrease of ≤0.5 g/dL, showed a significant association with mortality, while smaller decreases of 1.4-2.2 g/dL and 0.6-1.3 g/dL did not.

The study by Keough-Ryan et al (2005)[15] assessed the impact of chronic renal insufficiency, cardiac interventions and anaemia on mortality in patients with a discharge diagnosis of acute coronary syndrome. Hb levels were classified as mild anaemia (10.5-12.0 g/dL), moderate anaemia (9.0-10.5 g/dL) and severe anaemia (<9.0 g/dL). Multivariate analysis showed that only severe anaemia was independently associated with long-term mortality (mean follow-up 5.6 years).

The study by Valeur et al (2006)[17] assessed the association between different levels of anaemia (mild, moderate and severe) or the lowest decile of anaemia and long-term mortality, with follow-up being approximately 10-12 years. The analysis was conducted in patients with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI who had taken part in an RCT. When all patients were considered in the analysis, only severe anaemia (Hb <10 g/dL in women and <11 g/dL in men) and the lowest decile of anaemia (<11 g/dL in women and <12 g/dL in men) were shown to be independent risk factors compared with no anaemia. When the analysis was restricted to patients with heart failure, similar results were seen. Finally, when the analysis was restricted to patients without heart failure, there was no significant association between any level of anaemia and long-term mortality. Despite the long-term follow-up, the authors note that the prognostic significance of anaemia was confined to the first year following myocardial infarction; they state this is an important new finding.

Archbold et al (2006)[9] assessed the association between four different levels of Hb and in-hospital cardiac death, and in three analyses, Hb levels of 12.5-13.6 g/dL, 13.7-14.7 g/dL and >14.7 g/dL were compared with <12.5 g/dL, and showed no significant difference. There are

three points to note regarding these results: (i) in this study, progressively higher Hb levels are compared to a single low Hb level – this differs from the majority of other included studies in which progressively lower Hb levels are compared to a "normal" or higher Hb level; (ii) the mortality outcome was limited to in-hospital cardiac mortality; and (iii) the authors note that a large proportion of included subjects had biomarker-negative unstable angina, which resulted in a low in-hospital mortality (3%), highlighting that this study may be insufficiently powered to show an association between Hb level and mortality.

Sabatine et al (2005)[16] examined the association between different Hb levels and 30-day cardiovascular mortality in a cohort of patients from 16 RCTs; patients with STEMI and non-ST-segment elevation acute coronary syndromes (NSTE-ACS) were analysed separately. It should be noted that there is likely to be some data duplication between this study and the Giraldez et al (2009)[13] study as data from the InTIME II study are included in both. In STEMI patients, five Hb categories (<10 g/dL; 10-11 g/dL, 11-12 g/dL, 12-13 g/dL and 13-14 g/dL) were compared with a Hb level of 14-15 g/dL. All Hb categories except 13-14 g/dL showed a significantly increased 30-day cardiovascular mortality risk compared with 14-15 g/dL Hb. When Hb levels of <14 g/dL and 14-15 g/dL were compared, there was a significant independent association with 30-day cardiovascular mortality. In NSTE-ACS patients, only Hb levels of <11 g/dL and 15-16 g/dL were compared for this outcome. This analysis suggested Hb <11 g/dL was not an independent risk factor for 30-day cardiovascular mortality in this patient group.

Table 3.3 Question 1 (ACS): Results for Level II evidence – mortality (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ACUTE CORONARY SYNDROME									
ALL-CAUSE MORTALITY									
SHORT-TERM FOLLOW-UP (UP TO 1 YEAR)									
Giraldez 2009 Level II Good	1 cohort analysis of a RCT (InTime II-TIMI17) N=3667	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb <11 g/dL vs Hb 15-16 g/dL	Mortality (30 days)	NR	NR	OR 2.51 (1.68, 3.74) Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	*A Hb level <11 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15-16 g/dL* P<0.001
	1 cohort analysis of a RCT (InTime II-TIMI17) N=3899	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb 11-12 g/dL vs Hb 15-16 g/dL	Mortality (30 days)	NR	NR	OR 2.25 (1.62, 3.15) Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	*A Hb level 11-12 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15-16 g/dL* P<0.001
	1 cohort analysis of a RCT (InTime II-TIMI17) N=4739	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb 12-13 g/dL vs Hb 15-16 g/dL	Mortality (30 days)	NR	NR	OR 1.83 (1.40, 2.39) Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	*A Hb level 12-13 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15-16 g/dL* P<0.001
	1 cohort analysis of a RCT (InTime II-TIMI17) N=6351	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb 13-14 g/dL vs Hb 15-16 g/dL	Mortality (30 days)	NR	NR	OR 1.39 (1.09, 1.76) Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	*A Hb level 13-14 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15-16 g/dL* P=0.008
	1 cohort analysis of a RCT (InTime II-TIMI17) N=7549	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb 14-15 g/dL vs Hb 15-16 g/dL	Mortality (30 days)	NR	NR	OR 1.11 (0.88, 1.40) Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	*A Hb level 14-15 g/dL is <u>not</u> an independent risk factor for 30-day mortality compared with a Hb level 15-16 g/dL* P=0.40

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Giraldez 2009 Level II Good	1 cohort analysis of a RCT (ExTRACT-TIMI 25) N=4449	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb <11 g/dL vs Hb 15-16 g/dL	Mortality (30 days)	NR	NR	OR 1.82 (1.30, 2.57) Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	*A Hb level <11 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15-16 g/dL* P<0.01
	1 cohort analysis of a RCT (ExTRACT-TIMI 25) N=4848	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb 11-12 g/dL vs Hb 15-16 g/dL	Mortality (30 days)	NR	NR	OR 1.39 (1.03, 1.88) Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	*A Hb level 11-12 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15-16 g/dL* P=0.03
	1 cohort analysis of a RCT (ExTRACT-TIMI 25) N=5966	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb 12-13 g/dL vs Hb 15-16 g/dL	Mortality (30 days)	NR	NR	OR 1.33 (1.04, 1.70) Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	*A Hb level 12-13 g/dL is an independent risk factor for 30-day mortality compared with a Hb level 15-16 g/dL* P=0.02
	1 cohort analysis of a RCT (ExTRACT-TIMI 25) N=7676	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb 13-14 g/dL vs Hb 15-16 g/dL	Mortality (30 days)	NR	NR	OR 1.22 (0.98, 1.53) Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	*A Hb level 13-14 g/dL is <u>not</u> an independent risk factor for 30-day mortality compared with a Hb level 15-16 g/dL* P=0.08
	1 cohort analysis of a RCT (ExTRACT-TIMI 25) N=8911	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb 14-15 g/dL vs Hb 15-16 g/dL	Mortality (30 days)	NR	NR	OR 1.05 (0.84, 1.31) Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.	*A Hb level 14-15 g/dL is <u>not</u> an independent risk factor for 30-day mortality compared with a Hb level 15-16 g/dL* P=0.69
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Aronson 2007	1 prospective cohort study	Adults presenting to	Coronary care unit	Baseline Hb ≤13.1	Mortality (median 24	76/361 (21.1)	24/328 (7.3)	HR 1.6 (0.9, 2.6)	*Baseline Hb ≤13.1*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Level II Fair	N=689	the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Israel	g/dL vs baseline Hb ≥15.5 g/dL	months)	Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.			*g/dL is not an independent risk factor for* post-discharge mortality *compared with Hb ≥15.5 g/dL* P=0.07
	1 prospective cohort study N=673	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Baseline Hb 13.2-14.3 g/dL vs baseline Hb ≥15.5 g/dL	Mortality (median 24 months)	31/345 (9.0)	24/328 (7.3)	HR 1.2 (0.8, 2.1)	*Baseline Hb 13.2-14.3 g/dL is not an independent risk factor for* post-discharge mortality *compared with Hb ≥15.5 g/dL* P=0.07
						Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.			
	1 prospective cohort study N=684	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Baseline Hb 14.4-15.4 g/dL vs baseline Hb ≥15.5 g/dL	Mortality (median 24 months)	26/356 (7.3)	24/328 (7.3)	HR 1.2 (0.7, 2.1)	*Baseline Hb 14.4-15.4 g/dL is not an independent risk factor for* post-discharge mortality *compared with Hb ≥15.5 g/dL* P=0.07
						Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.			
Aronson 2007 Level II Fair	1 prospective cohort study N=678	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Decrease in Hb during hospitalisation ≥2.3 g/dL vs decrease in Hb during hospitalisation ≤0.5 g/dL	Mortality (median 24 months)	58/341 (17.0)	27/337 (8.0)	HR 1.7 (1.1, 2.8)	*A decrease in Hb during hospitalisation of ≥2.3 g/dL is an independent risk factor for increased post-discharge mortality compared with a decrease of ≤0.5 g/dL* P=0.03
						Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.			
	1 prospective cohort study N=687	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Decrease in Hb during hospitalisation 1.4-2.2 g/dL vs decrease in Hb during hospitalisation ≤0.5 g/dL	Mortality (median 24 months)	39/350 (11.1)	27/337 (8.0)	HR 1.3 (0.8, 2.2)	*A decrease in Hb during hospitalisation of 1.4-2.2 g/dL is not an independent risk factor for post-discharge mortality compared with a decrease of ≤0.5 g/dL* P=0.25
						Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 prospective cohort study N=699	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Decrease in Hb during hospitalisation 0.6-1.3 g/dL vs decrease in Hb during hospitalisation ≤0.5 g/dL	Mortality (median 24 months)	33/362 (9.1)	27/337 (8.0)	HR 1.3 (0.7, 2.1) Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.	*A decrease in Hb during hospitalisation of 0.6-1.3 g/dL is not an independent risk factor for post-discharge mortality compared with a decrease of ≤0.5 g/dL* P=0.25
Aronson 2007 Level II Fair	1 prospective cohort study N=691	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Nadir Hb ≤11.3 g/dL vs nadir Hb ≥14.0 g/dL	Mortality (median 24 months)	88/350 (25.1)	12/341 (3.5)	HR 3.3 (1.7, 6.3) Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.	Nadir Hb ≤11.3 g/dL is an independent risk factor for increased post-discharge mortality compared with nadir Hb ≥14.0 g/dL P<0.001
	1 prospective cohort study N=698	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Nadir Hb 11.4-12.8 g/dL vs nadir Hb ≥14.0 g/dL	Mortality (median 24 months)	40/357 (11.2)	12/341 (3.5)	HR 2.1 (1.1, 4.1) Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.	Nadir Hb 11.4-12.8 g/dL is an independent risk factor for increased post-discharge mortality compared with nadir Hb ≥14.0 g/dL P=0.03
	1 prospective cohort study N=683	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Nadir Hb 12.9-13.9 g/dL vs nadir Hb ≥14.0 g/dL	Mortality (median 24 months)	17/342 (5.0)	12/341 (3.5)	HR 1.1 (0.5, 2.3) Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.	Nadir Hb 12.9-13.9 g/dL is not an independent risk factor for increased post-discharge mortality compared with nadir Hb ≥14.0 g/dL P=0.83

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						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Aronson 2007 Level II Fair	1 prospective cohort study N=685	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Discharge Hb ≤11.9 g/dL vs discharge Hb ≥14.6 g/dL	Mortality (median 24 months)	82/344 (23.8)	15/341 (4.4)	HR 2.6 (1.5, 4.7) Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.	Discharge Hb ≤11.9 g/dL is an independent risk factor for increased post-discharge mortality compared with discharge Hb ≥14.6 g/dL P=0.001
	1 prospective cohort study N=691	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Discharge Hb 12.0-13.3 g/dL vs discharge Hb ≥14.6 g/dL	Mortality (median 24 months)	39/350 (11.1)	15/341 (4.4)	HR 2.0 (1.1, 3.7) Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.	Discharge Hb 12.0-13.3 g/dL may be an independent risk factor for increased post-discharge mortality compared with discharge Hb ≥14.6 g/dL P=0.03
	1 prospective cohort study N=696	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Discharge Hb 13.3-14.5 g/dL vs discharge Hb ≥14.6 g/dL	Mortality (median 24 months)	21/355 (5.9)	15/341 (4.4)	HR 1.4 (0.7, 2.7) Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.	Discharge Hb 13.3-14.5 g/dL is not an independent risk factor for increased post-discharge mortality compared with discharge Hb ≥14.6 g/dL P=0.32
Keough-Ryan 2005 Level II Poor	1 cohort analysis of a prospective population-based registry N=NR[c]	Adults admitted to hospital with a discharge diagnosis of acute coronary syndrome who survived to discharge	Hospital Canada	Mild anaemia (Hb 10.5-12.0 g/dL) vs no anaemia (Hb >12.0 g/dL)	Mortality (mean 5.6 years)	NR	NR	HR 0.968 (0.924, 1.015) Adjusted for: age, sex, diabetes, hypertension, smoking, previous CABG, cardiac catheterization, CABG, thrombolysis, medications on discharge. Note: a large number of potential confounders not considered (including BMI, history of MI, peripheral vascular disease, cerebrovascular accident, TIA, CHF, family history of ischaemic heart disease) due to missing data.	*Mild anaemia is not an independent risk factor for mortality* P=NR
	1 cohort analysis of a prospective population-based registry N=NR[c]	Adults admitted to hospital with a discharge diagnosis of acute coronary syndrome who survived to discharge	Hospital Canada	Moderate anaemia (Hb 9.0-10.5 g/dL) vs no anaemia (Hb >12.0 g/dL)	Mortality (mean 5.6 years)	NR	NR	HR 1.050 (0.965, 1.114) Adjusted for: age, sex, diabetes, hypertension, smoking, previous CABG, cardiac catheterization, CABG, thrombolysis, medications on discharge. Note: a large number of potential confounders not considered (including BMI, history of MI, peripheral vascular disease, cerebrovascular accident, TIA, CHF, family history of ischaemic heart disease) due to missing data.	*Moderate anaemia is not an independent risk factor for mortality* P=NR

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 cohort analysis of a prospective population-based registry N=NR[c]	Adults admitted to hospital with a discharge diagnosis of acute coronary syndrome who survived to discharge	Hospital Canada	Severe anaemia (Hb <9.0 g/dL)vs no anaemia (Hb >12.0 g/dL)	Mortality (mean 5.6 years)	NR	NR	HR 1.376 (1.179, 1.606)	*Severe anaemia is an independent risk factor for mortality* P=NR
						Adjusted for: age, sex, diabetes, hypertension, smoking, previous CABG, cardiac catheterization, CABG, thrombolysis, medications on discharge. Note: a large number of potential confounders not considered (including BMI, history of MI, peripheral vascular disease, cerebrovascular accident, TIA, CHF, family history of ischaemic heart disease) due to missing data.			
Valeur 2006 Level II Good	1 cohort analysis of a double-blind RCT (TRACE) N=1558	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI	Hospital Denmark	Mild anaemia (11.0-<12.0 g/dL in women; 12.0-<13.0 g/dL in men) vs no anaemia	Mortality (up to 12 years)	NR	NR	HR 0.96 (0.82, 1.13)	Mild anaemia is <u>not</u> an independent predictor of mortality P=0.65
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
	1 cohort analysis of a double-blind RCT (TRACE) N=1408	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI	Hospital Denmark	Moderate anaemia (10.0-<11.0 g/dL in women; 11.0-<12.0 g/dL in men) vs no anaemia	Mortality (up to 12 years)	NR	NR	HR 1.08 (0.86, 1.36)	Moderate anaemia is <u>not</u> an independent predictor of mortality P=0.50
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
	1 cohort analysis of a double-blind RCT (TRACE) N=1353	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI	Hospital Denmark	Severe anaemia (<10.0 g/dL in women; <11.0 g/dL in men) vs no anaemia	Mortality (up to12 years)	NR	NR	HR 1.59 (1.20, 2.11)	Severe anaemia is an independent predictor of mortality P=0.001
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
	1 cohort analysis of a double-blind RCT (TRACE) N=NR	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI	Hospital Denmark	Lowest decile anaemia (<11.0 g/dL in women; <12.0 g/dL in men)vs no anaemia	Mortality (up to12 years)	NR	NR	HR 1.24 (1.04, 1.48)	Lowest decile anaemia is an independent predictor of mortality P=0.017
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
Valeur 2006 Level II Good	1 cohort analysis of a double-blind RCT (TRACE) N=1069	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI/<u>with heart failure</u>	Hospital Denmark	Mild anaemia (11.0-<12.0 g/dL in women; 12.0-<13.0 g/dL in men) vs no anaemia	Mortality (up to12 years)	NR	NR	HR 1.05 (0.88, 1.25)	Mild anaemia is <u>not</u> an independent predictor of mortality P=0.60
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
	1 cohort analysis of a double-blind RCT (TRACE) N=960	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI/<u>with heart failure</u>	Hospital Denmark	Moderate anaemia (10.0-<11.0 g/dL in women; 11.0-<12.0 g/dL in men) vs no anaemia	Mortality (up to12 years)	NR	NR	HR 1.20 (0.93, 1.56)	Moderate anaemia is <u>not</u> an independent predictor of mortality P=0.17
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
	1 cohort analysis of a double-	Adults with left	Hospital	Severe anaemia	Mortality (up to12	NR	NR	HR 1.65 (1.21, 2.25)	Severe anaemia is an

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						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	blind RCT (TRACE) N=928	ventricular systolic dysfunction 2-6 days following enzyme-verified AMI /with heart failure	Denmark	(<10.0 g/dL in women; <11.0 g/dL in men) vs no anaemia	years)	Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			independent predictor of anaemia P=0.002
	1 cohort analysis of a double-blind RCT (TRACE) N=NR	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI/with heart failure	Hospital Denmark	Lowest decile anaemia (<11.0 g/dL in women; <12.0 g/dL in men)vs no anaemia	Mortality (up to12 years)	NR	NR	HR 1.32 (1.08, 1.61)	Lowest decile anaemia is an independent predictor of mortality P=0.007
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
Valeur 2006 Level II Good	1 cohort analysis of a double-blind RCT (TRACE) N=489	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI/without heart failure	Hospital Denmark	Mild anaemia (11.0-<12.0 g/dL in women; 12.0-<13.0 g/dL in men) vs no anaemia	Mortality (up to12 years)	NR	NR	Incorrect[e]	Mild anaemia is not an independent risk factor for mortality P=0.5
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
	1 cohort analysis of a double-blind RCT (TRACE) N=448	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI/without heart failure	Hospital Denmark	Moderate anaemia (10.0-<11.0 g/dL in women; 11.0-<12.0 g/dL in men) vs no anaemia	Mortality (up to12 years)	NR	NR	HR 0.80 (0.49, 1.29)	Moderate anaemia is not an independent risk factor for mortality P=0.36
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
	1 cohort analysis of a double-blind RCT (TRACE) N=425	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI /without heart failure	Hospital Denmark	Severe anaemia (<10.0 g/dL in women; <11.0 g/dL in men) vs no anaemia	Mortality (up to12 years)	NR	NR	HR 1.18 (0.58, 2.41)	Severe anaemia is not an independent risk factor for mortality P=0.64
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
	1 cohort analysis of a double-blind RCT (TRACE) N=NR	Adults with left ventricular systolic dysfunction 2-6 days following enzyme-verified AMI/without heart failure	Hospital Denmark	Lowest decile anaemia (<11.0 g/dL in women; <12.0 g/dL in men)vs no anaemia	Mortality (up to12 years)	NR	NR	HR 0.99 (0.66, 1.49)	Lowest decile anaemia is not an independent risk factor for mortality P=0.96
						Adjusted for: age, gender, history of hypertension, diabetes, atrial fibrillation, smoking, BMI, Wall Motion Index, creatinine, heart failure (all patients model only), treatment with fibrinolysis and ACEIs.			
CARDIAC MORTALITY									
SHORT-TERM FOLLOW-UP (UP TO 1 YEAR)									
Archbold 2006	1 prospective cohort study	Adults with a	Coronary care unit	Hb 12.5-13.6 g/dL	Cardiac mortality (in	NR	NR	OR 1.56 (0.76, 3.22)	*Hb <12.5 g/dL is not*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Level II Fair	N=1140	diagnosis of ACS	UK	vs Hb <12.5 g/dL	hospital)	Adjusted for variable with P<0.1 in univariate analysis: age, sex, race, diabetes, hypertension, smoking, previous angina, previous ACS, renal function, background aspirin, ACEI, diuretic, statin therapy, heart rate, SBP, reperfusion therapy and ACS presentation.			*an independent risk factor for in-hospital cardiac death compared with Hb 12.5-13.6 g/dL* P=NR
	1 prospective cohort study N=1152	Adults with a diagnosis of ACS	Coronary care unit UK	Hb 13.7-14.7 g/dL vs Hb <12.5 g/dL	Cardiac mortality (in hospital)	NR	NR	OR 1.00 (0.42, 2.36)	*Hb <12.5 g/dL is <u>not</u> an independent risk factor for in-hospital cardiac death compared with Hb 13.7-14.7 g/dL* P=NR
						Adjusted for variable with P<0.1 in univariate analysis: age, sex, race, diabetes, hypertension, smoking, previous angina, previous ACS, renal function, background aspirin, ACEI, diuretic, statin therapy, heart rate, SBP, reperfusion therapy and ACS presentation.			
	1 prospective cohort study N=1134	Adults with a diagnosis of ACS	Coronary care unit UK	Hb >14.7 g/dL vs Hb <12.5 g/dL	Cardiac mortality (in hospital)	NR	NR	OR 1.73 (0.76, 3.97)	*Hb <12.5 g/dL is <u>not</u> an independent risk factor for in-hospital cardiac death compared with Hb >14.7 g/dL* P=NR
						Adjusted for variable with P<0.1 in univariate analysis: age, sex, race, diabetes, hypertension, smoking, previous angina, previous ACS, renal function, background aspirin, ACEI, diuretic, statin therapy, heart rate, SBP, reperfusion therapy and ACS presentation.			
Sabatine 2005 Level II Fair	1 cohort analysis of 16 RCTs[d] N=12,003	Adults with STEMI	Hospital Various	Hb 13-14 g/dL vs Hb 14-15 g/dL	Cardiovascular mortality (30 days)	NR	NR	OR 1.17 (0.93, 1.47)	*A Hb level of 13-14 g/dL is <u>not</u> an independent risk factor for 30-day cardiovascular mortality compared with a Hb level of 14-15 g/dL* P=0.175
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
	1 cohort analysis of 16 RCTs[d] N=9428	Adults with STEMI	Hospital Various	Hb 12-13 g/dL vs Hb 14-15 g/dL	Cardiovascular mortality (30 days)	NR	NR	OR 1.40 (1.09, 1.80)	A Hb level of 12-13 g/dL is an independent risk factor for 30-day cardiovascular mortality compared with a Hb level of 14-15 g/dL P=0.009
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 cohort analysis of 16 RCTs[d] N=7888	Adults with STEMI	Hospital Various	Hb 11-12 g/dL vs Hb 14-15 g/dL	Cardiovascular mortality (30 days)	NR	NR	OR 1.63 (1.19, 2.24)	A Hb level of 11-12 g/dL is an independent risk factor for 30-day cardiovascular mortality compared with a Hb level of 14-15 g/dL P=0.003
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
	1 cohort analysis of 16 RCTs[d] N=7214	Adults with STEMI	Hospital Various	Hb 10-11 g/dL vs Hb 14-15 g/dL	Cardiovascular mortality (30 days)	NR	NR	OR 1.98 (1.24, 3.15)	A Hb level of 10-11 g/dL is an independent risk factor for 30-day cardiovascular mortality compared with a Hb level of 14-15 g/dL P=0.004
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
	1 cohort analysis of 16 RCTs[d] N=7117	Adults with STEMI	Hospital Various	Hb <10 g/dL vs Hb 14-15 g/dL	Cardiovascular mortality (30 days)	NR	NR	OR 2.50 (1.42, 4.39)	A Hb level of <10 g/dL is an independent risk factor for 30-day cardiovascular mortality compared with a Hb level of 14-15 g/dL P=0.001
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
	1 cohort analysis of 16 RCTs[d] N=15,946	Adults with STEMI	Hospital Various	Hb <14 g/dL vs Hb 14-15 g/dL	Cardiovascular mortality (30 days)	NR	NR	OR 1.35 (1.11, 1.64)	A Hb level <14 g/dL is an independent risk factor for 30-day cardiovascular mortality compared with a Hb level of 14-15 g/dL P=0.003
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
Sabatine 2005	1 cohort analysis of 16 RCTs[d]	Adults with NSTE-	Hospital	Hb <11 g/dL vs Hb	Cardiovascular	NR	NR	OR 1.35 (0.74, 2.45)	A Hb level of <11 g/dL

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Level II Fair	N=2915	ACS	Various	15-16 g/dL	mortality (30 days)	Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			is not an independent risk factor for 30-day CV mortality compared with a Hb level of 15-16 g/dL P=NR

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; dL, decilitre; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; RI, recurrent ischemia; SBP, systolic blood pressure; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; UK, United Kingdom; US, United States of America; WHO, World Health Organisation.
Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Total included population N=5549.

[d] TIMI IIIB, 4, 9A, 9B, 10A, 10B, 11A, 11B, 12, 14, 16 (OPUS), 17 (InTIME II), 18 (TACTICS), 20 (INTEGRI), 23 (ENTIRE) and 24 (FASTER). Analysis of data from this trial was also carried out by Giraldez 2009.

[e] Shown in Table 4 of publication as 0.70 (0.99, 1.00). P value = 0.5.

Seven studies assessed the association between **Hb as a continuous variable and mortality**, as shown in Table 3.4.[8,10,11,13,16,18,19] Bassand et al (2010)[11] examined the association between increased Hb and mortality in >28,000 patients with NSTE-ACS or STEMI. The results of their analysis showed that a 1 g/dL increase in Hb resulted in a 6% reduced risk of 30-day mortality.

Giraldez et al (2009)[13] showed that a decrease in Hb significantly increased the risk of mortality in two large trial cohorts including patients with STEMI. In the analyses of the InTIME-TIMI17 (>14,000 patients) and ExTRACT-TIMI 25 (>18,000 patients) trials, a 1 g/dL decrease in Hb was associated with a significantly increased risk of 30-day mortality (P<0.001 for both).

The study by Mahaffey et al (2008)[18] examined the association between increased Hb and mortality in >9000 patients who took part in the SYNERGY trial. A 1 g/dL increase in Hb (truncated at 15 g/dL) was not associated with 30-day or 1-year mortality when all patients were included in the analysis. However, when the analysis was limited to patients surviving through 30 days, 1 g/dL increase in Hb (truncated at 15 g/dL) resulted in a 19.5% reduction in risk of 1-year mortality.

The study by Burr et al (1992)[19] assessed the association between change in Hb and 18-month mortality in 1755 non-diabetic men recovering from myocardial infarction. The results of the analysis showed that a 1 standard deviation (SD) change in Hb resulted in a significant decrease in mortality (P<0.001).

The study by Aronson et al (2007)[10] assessed baseline, nadir and discharge Hb levels as continuous variables to determine their association with mortality. A 1 g/dL decrease in nadir Hb and discharge Hb results in a 36% and 27% increased risk of mortality, respectively. A 1 g/dL decrease in baseline Hb was not significantly associated with an increased risk of mortality (P=0.06); however, as discussed previously, the exclusion of subjects who died during hospitalisation may have reduced the power of this analysis. A 1 SD reduction in Hb during hospitalisation was also significantly associated with an increased risk of mortality (21%).

Anker at al (2009)[8] showed that an increase in Hb of 1 SD resulted in a significantly decreased risk of all-cause mortality (12% reduction) and death due to progressive heart failure (20% reduction). There was no significantly decreased risk of sudden cardiac death associated with a 1 SD increase in Hb. Further analysis in patients still alive after 12 months showed that a 12-month change in Hb of 1 SD was associated with a 27% decreased risk of all-cause mortality. When broken down into 12-month increases and decreases in Hb, a 12-month 1 SD increase in Hb was associated with a 33% reduction in the risk of all-cause mortality, while a 12-month 1 SD decrease Hb was associated with a 27% increase in the risk of all-cause mortality.

Sabatine et al (2005)[16] assessed the association between a 1 g/dL decrease in Hb below 14 g/dL in patients with STEMI. The results of the analysis showed that a decrease in Hb was significantly associated with an increase in 30-day cardiovascular mortality (P<0.001).

Table 3.4 Question 1 (ACS): Results for Level II evidence – mortality (Hb as a continuous variable)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ACUTE CORONARY SYNDROME									
ALL-CAUSE MORTALITY									
SHORT-TERM FOLLOW-UP (UP TO 1 YEAR)									
Bassand 2010 Level II Fair	1 cohort analysis of two RCTs (OASIS 5 and 6) N=28,907	Adults presenting to hospital with symptoms of NSTE-ACS or STEMI	Hospital Various[c]	Hb increase (g/dL)	Mortality (30 days)	NA	NA	OR 0.94 (0.90, 0.98)	*A 1 g/dL increase in Hb results in a 6% decreased risk of mortality* P=NR
						Adjusted for: Baseline demographics, prior medical history, cardiovascular risk factors, randomised treatment allocation, co-interventions.			
Giraldez 2009 Level II Good	1 cohort analysis of a RCT (InTime II-TIMI17) N=14,373	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb decrease in patients with baseline Hb <15 g/dL (1 g/dL)	Mortality (30 days)	NA	NA	OR 1.22 (1.15, 1.29)	*A 1 g/dL decrease in Hb in patients with baseline Hb <15 g/dL results in a 22% increased risk of 30-day mortality by* P<0.001
						Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.			
	1 cohort analysis of a RCT (ExTRACT-TIMI 25) N=18,400	Adults presenting within 6 hrs of onset of symptoms of MI and ECG changes compatible with STEMI	Hospital US	Hb decrease in patients with baseline Hb <15 g/dL (1 g/dL)	Mortality (30 days)	NA	NA	OR 1.10 (1.04, 1.16)	*A 1 g/dL decrease in Hb in patients with baseline Hb <15 g/dL results in a 10% increased risk of 30-day mortality* P<0.001
						Adjusted for: age, Killip class, heart rate, anterior myocardial infarction, left bundle branch block, SBP, time to thrombolysis, weight, prior angina, diabetes, hypertension, sex, race, smoking, prior MI and PCI during hospitalisation.			
Mahaffey 2008 Level II Good	1 cohort analysis of a RCT (SYNERGY) N=9978	High risk patients with ACS	Hospital Australia, Belgium, Canada, New Zealand, US	Hb increase truncated at 15 g/dL (1 g/dL)	Mortality (30 days)	NA	NA	NR	*A 1 g/dL increase in Hb (up to 15 g/dL) is not associated with an increased risk in 30-day mortality* P=NR
						Potential variables measured included: age, sex, weight, height, race, time from symptoms to randomisation, region of the world, smoking status, creatinine clearance, Killip class, systolic and diastolic blood pressures, ST-segment elevation and depression, T-wave inversion, diabetes, hypertension, concomitant medications, prior coronary artery disease, recent angina, prior congestive heart failure, prior PCI, prior CABG, criteria for enrolment, heart rate, rales, Hb, haematocrit and platelet count.			
Mahaffey 2008 Level II Good	1 cohort analysis of a RCT (SYNERGY) N=9978	High risk patients with ACS	Hospital Australia, Belgium, Canada, New Zealand, US	Hb increase truncated at 15 g/dL (1 g/dL)	Mortality (1 year)	NA	NA	NR	*A 1 g/dL increase in Hb (up to 15 g/dL) is not associated with an increased risk in 1-year mortality* P=NR
						Potential variables measured included: age, sex, weight, height, race, time from symptoms to randomisation, region of the world, smoking status, creatinine clearance, Killip class, systolic and diastolic blood pressures, ST-segment elevation and depression, T-wave inversion, diabetes, hypertension, concomitant medications, prior coronary artery disease, recent angina, prior congestive heart failure, prior PCI, prior CABG, criteria for enrolment, heart rate, rales, Hb, haematocrit and platelet count.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 cohort analysis of a RCT (SYNERGY) N=9664	High risk patients with ACS who survived at least 30 days	Hospital Australia, Belgium, Canada, New Zealand, US	Hb increase truncated at 15 g/dL (1 g/dL)	Mortality (1 year)	NA	NA	HR 0.805 (0.748, 0.868)	*A 1 g/dL increase in Hb (up to 15 g/dL) is related to a 19% decreased risk of 1-year mortality* P=NR
						Potential variables measured included: age, sex, weight, height, race, time from symptoms to randomisation, region of the world, smoking status, creatinine clearance, Killip class, systolic and diastolic blood pressures, ST-segment elevation and depression, T-wave inversion, diabetes, hypertension, concomitant medications, prior coronary artery disease, recent angina, prior congestive heart failure, prior PCI, prior CABG, criteria for enrolment, heart rate, rales, Hb, haematocrit and platelet count.			
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Burr 1992 Level II Poor	1 cohort analysis of a RCT (DART) N=1755	Men without diabetes recovering from MI	Community UK	Hb change (1 SD)	Mortality (18 months)	NA	NA	SOR 0.72	*A 1 SD change in Hb is an independent risk factor for decreased mortality* P<0.001
						Adjusted for: age, smoking, energy, diet group.			
Aronson 2007 Level II Fair	1 prospective cohort study N=1390	Adults presenting to the coronary care unit with a diagnosis of MI who were alive at discharge from hospital	Coronary care unit Israel	Decrease in baseline Hb of 1 g/dL	Mortality (median 24 months)	NA	NA	HR 1.10 (0.99, 1.21)	A 1 g/dL decrease in Hb at baseline may be an independent risk factor for increased post-discharge mortality P=0.06
						Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.			
				Decrease in Hb during hospitalisation of 1 SD	Mortality (median 24 months)	NA	NA	HR 1.21 (1.0, 1.45)	A 1 SD decrease in Hb during hospitalisation may be an independent risk factor for increased post-discharge mortality P=0.03
						Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.			
				Decrease in nadir Hb of 1 g/dL	Mortality (median 24 months)	NA	NA	HR 1.36 (1.19, 1.55)	A 1 g/dL decrease in nadir Hb is an independent risk factor for increased post-discharge mortality P<0.001
						Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.			
				Decrease in discharge Hb of 1 g/dL	Mortality (median 24 months)	NA	NA	HR 1.27 (1.16, 1.40)	A 1 g/dL decrease in discharge Hb is an independent risk factor for increased post-discharge mortality P<0.001
						Adjusted for variables thought to have clinical importance or with P<0.1 in the univariate model : age, gender, eGFR, previous infarction, hypertension, diabetes, smoking, ST-elevation, Killip class, heart rate, blood pressure on admission, coronary revascularisation, LVEF, length of hospital stay.			
Anker 2009	1 cohort analysis	Adult patients with a	Hospital	Increase in Hb of 1	Mortality (median 3	NA	NA	HR 0.88 (0.83, 0.93)	*A one SD increase in Hb results*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Level II Fair	of a double-blind RCT (OPTIMAAL) N=5010	diagnosis of AMI	Denmark, Finland, Germany, Ireland, Norway, Sweden, UK	SD	years)	Adjusted for variables known to be of prognostic value in heart failure: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			*in a 12% reduced risk of mortality* P<0.001
	1 cohort analysis of a double-blind RCT (OPTIMAAL) N=3921	Adult patients with a diagnosis of AMI <u>alive at 12 months</u>	Hospital Denmark, Finland, Germany, Ireland, Norway, Sweden, UK	12-month change in Hb of 1 SD	Mortality (median 3 years)	NA	NA	HR 0.73 (0.63, 0.85)	*A 12-month change of Hb of 1 SD results in a 27% reduced risk of mortality* *P<0.001*
						Adjusted for variables known to be of prognostic value in heart failure: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			
				12-month <u>increase</u> in Hb of 1 SD	Mortality (median 3 years)	NA	NA	HR 0.67 (0.51, 0.81)	*A 12-month increase of Hb of 1 SD results in a 33% reduced risk of mortality* *P<0.01*
						Adjusted for variables known to be of prognostic value in heart failure: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			
				12-month <u>decrease</u> in Hb of 1 SD	Mortality (median 3 years)	NA	NA	HR 1.27 (1.00, 1.60)	*A 12-month decrease of Hb of 1 SD <u>may</u> result in a 27% increased risk of mortality* *P=0.05*
						Adjusted for variables known to be of prognostic value in heart failure: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			
CARDIOVASCULAR MORTALITY									
SHORT-TERM FOLLOW-UP (UP TO 1 YEAR)									
Sabatine 2005 Level II Fair	1 cohort analysis of 16 RCTs (TIMI IIIB, 4, 9A, 9B, 10A, 10B, 11A, 11B, 12, 14, 16 (OPUS), 17 (InTIME II)[d], 18 (TACTICS), 20 (INTEGRI), 23 (ENTIRE) and 24 (FASTER). N=NR	Adults with STEMI	Hospital Various	Hb decrease below 14 g/dL in subjects with baseline Hb 14-15 g/dL (1 g/dL)	Cardiovascular mortality (30 days)	NA	NA	OR 1.21 (1.12, 1.30)	*A 1 g/dL decrease in Hb below 14 g/dL is related to a 21% increased risk of 30-day cardiovascular mortality* P<0.001
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Anker 2009	1 cohort analysis	Adult patients with a	Hospital	Increase in Hb of 1	Sudden cardiac	NA	NA	HR 0.86 (0.80, 1.03)	*A one SD increase in Hb*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Level II Fair	of a double-blind RCT (OPTIMAAL) N=5010	diagnosis of AMI	Denmark, Finland, Germany, Ireland, Norway, Sweden, UK	SD	death (median 3 years)	Adjusted for variables known to be of prognostic value in heart failure: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			*does <u>not</u> result in a significantly reduced risk of sudden cardiac death* P=0.141
					Death due to progressive heart failure (median 3 years)	NA	NA	HR 0.80 (0.69, 0.94)	*A one SD increase in Hb results in a 20% reduced risk of death due to progressive heart failure* P=0.006
						Adjusted for variables known to be of prognostic value in heart failure: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; dL, decilitre; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; RI, recurrent ischemia; SBP, systolic blood pressure; SD, standard deviation; SOR, standardised odds ratio; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; UK, United Kingdom; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Two studies assessed the association between **anaemia as defined by the World Health Organisation (WHO) and mortality in a composite outcome including cardiovascular outcomes**, as shown in Table 3.5[12,14] Cavusoglu et al (2006)[12] examined the association between anaemia and the composite outcome mortality/myocardial infarction (MI) in 191 men with acute coronary syndrome, and showed that anaemia was an independent risk factor for mortality/MI (P=0.04). One potential issue identified during the evaluation of this study is the lack of adjustment for race in the analyses, given that the largest proportion of the population were Black or Hispanic. A number of other studies have suggested differences in the association between anaemia and mortality by race.

The study by Hasin et al (2009)[14] assessed the association between anaemia and mortality/heart failure in patients with acute MI who survived hospitalisation. When all patients were included in the analysis, those with new-onset anaemia or persistent anaemia had a significantly greater risk of mortality/heart failure (mean follow-up 27 months), while those with resolved anaemia had no greater risk. Similar results were seen when the analysis was restricted to those without malignancy. In patients with no anaemia at baseline, both new-onset anaemia and persistent anaemia were independent risk factors for mortality.

Table 3.5 Question 1 (ACS): Results for Level II evidence – mortality in a composite outcome including cardiovascular outcomes (WHO or similar anaemia criteria)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ALL-CAUSE MORTALITY									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Cavusoglu 2006 Level II Fair	1 prospective cohort study N=191	Men with ACS (ST-elevation AMI, non-ST segment elevation AMI and unstable angina pectoris)	Hospital US	Anaemia (WHO) vs no anaemia	Mortality/MI (2 years)	NR	NR	HR 1.86 (1.02, 3.40) Adjusted for variables with p<0.05: age, number of diseased coronary arteries, left ventricular function, Hb, serum creatinine.	*Anaemia is an independent risk factor for death/MI* P=0.0429
Hasin 2009 Level II Fair	1 prospective cohort study N=802	Patients with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge	Hospital Israel	Resolved anaemia (WHO) vs no anaemia	Mortality/heart failure (mean 27 months)	19/162 (11.7)	70/640 (10.9)	HR 0.8 (0.5, 1.3) Adjusted for: age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Killip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.	*Resolved anaemia is not an independent risk factor for mortality or heart failure* P=0.40
	1 prospective cohort study N=695	Patients with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge	Hospital Israel	New-onset anaemia (WHO) vs no anaemia	Mortality/heart failure (mean 27 months)	15/55 (27.3)	70/640 (10.9)	HR 1.9 (1.1, 3.3) Adjusted for: age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Killip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.	*New-onset anaemia is an independent risk factor for mortality or heart failure* P=0.03
	1 prospective cohort study N=848	Patients with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge	Hospital Israel	Persistent anaemia (WHO) vs no anaemia	Mortality/heart failure (mean 27 months)	70/208 (33.7)	70/640 (10.9)	HR 1.8 (1.2, 2.5) Adjusted for: age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Killip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.	*Persistent anaemia is an independent risk factor for mortality or heart failure* P=0.003

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Hasin 2009 Level II Fair	1 prospective cohort study N=753	Patients <u>without malignancy</u> with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge	Hospital Israel	<u>Resolved</u> anaemia (WHO) vs no anaemia	Mortality/heart failure (mean 27 months)	17/150 (11.3)	61/603 (10.1)	HR 0.8 (0.5, 1.4) Adjusted for: age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Killip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.	*Resolved anaemia is <u>not</u> an independent risk factor for mortality or heart failure* *P=0.47*
	1 prospective cohort study N=653	Patients <u>without malignancy</u> with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge	Hospital Israel	<u>New-onset</u> anaemia (WHO) vs no anaemia	Mortality/heart failure (mean 27 months)	13/50 (26.0)	61/603 (10.1)	HR 1.9 (1.1, 3.6) Adjusted for: age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Killip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.	*New-onset anaemia is an independent risk factor for mortality or heart failure* *P<0.001*
	1 prospective cohort study N=781	Patients <u>without malignancy</u> with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge	Hospital Israel	<u>Persistent</u> anaemia (WHO) vs no anaemia	Mortality/heart failure (mean 27 months)	61/178 (34.3)	61/603 (10.1)	HR 1.7 (1.2, 2.6) Adjusted for: age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Killip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.	*Persistent anaemia is an independent risk factor for mortality or heart failure* *P=0.008*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Hasin 2009 Level II Fair	1 prospective cohort study N=743	Patients with no anaemia at baseline with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge	Hospital Israel	Resolved anaemia (WHO) vs no anaemia	Mortality/heart failure (mean 27 months)	11/127 (8.7)	67/616 (10.9)	HR 0.7 (0.4, 1.4) Adjusted for: age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Killip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.	*Resolved anaemia is not an independent risk factor for mortality or heart failure* *P=0.31*
	1 prospective cohort study N=659	Patients with no anaemia at baseline with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge	Hospital Israel	New-onset anaemia (WHO) vs no anaemia	Mortality/heart failure (mean 27 months)	11/43 (25.6)	67/616 (10.9)	HR 1.7 (1.0, 3.3) Adjusted for: age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Killip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.	*New-onset anaemia may be an independent risk factor for mortality or heart failure* *P=0.05*
	1 prospective cohort study N=720	Patients with no anaemia at baseline with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge	Hospital Israel	Persistent anaemia (WHO) vs no anaemia	Mortality/heart failure (mean 27 months)	30/104 (28.8)	67/616 (10.9)	HR 1.8 (1.1, 2.8) Adjusted for: age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Killip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.	*Persistent anaemia is an independent risk factor for mortality or heart failure* *P=0.01*

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AIIRA, angiotensin II receptor antagonists; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; RCT, randomised controlled trial; RI, recurrent ischemia; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Two studies assessed the association between **various Hb levels and mortality in a composite outcome including cardiovascular outcomes**, as shown in Table 3.6.[12,16] Cavusoglu et al (2006)[12] assessed the association between low Hb (defined as Hb <10.5 g/dL) and mortality/MI in 191 men with ACS. The results of the analysis showed no significant association between a low Hb and mortality/MI (P=0.07).

The study by Sabatine et al (2005)[16] examined the association between different Hb levels and cardiovascular mortality/MI/recurrent ischaemia in patients with NSTE-ACS. A significant association between Hb and 30-day cardiovascular mortality/MI/recurrent ischaemia was seen for Hb levels of 9-10 g/dL, 8-9 g/dL and <8 g/dL compared with 15-16 g/dL; the results were not significant for other categories up to 14-15 g/dL. The result was also significant when the categories were collapsed into a Hb <11 g/dL versus 15-16 g/dL (P<0.001).

Table 3.6 Question 1 (ACS): Results for Level II evidence – mortality in a composite outcome including cardiovascular outcomes (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ALL-CAUSE MORTALITY									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Cavusoglu 2006 Level II Fair	1 prospective cohort study N=NR	Men with ACS (ST-elevation AMI, non-ST segment elevation AMI and unstable angina pectoris)	Hospital US	Hb <10.5 g/dL vs Hb >12.5 g/dL	Mortality/MI (2 years)	NR	NR	HR 2.37 (0.94, 5.99) Adjusted for variables with p<0.05: age, number of diseased coronary arteries, left ventricular function, Hb, serum creatinine.	*Hb <10.5 g/dL is not an independent risk factor for death/MI compared with Hb >12.5 g/dL* P=0.0681
CARDIOVASCULAR MORTALITY									
SHORT-TERM FOLLOW-UP (UP TO 1 YEAR)									
Sabatine 2005 Level II Fair	1 cohort analysis of 16 RCTs[c] N=5520	Adults with NSTE-ACS	Hospital Various	Hb 14-15 g/dL vs Hb 15-16 g/dL	Cardiovascular mortality/MI/recurrent ischaemia (30 days)	NR	NR	OR 1.11 (0.93, 1.33) Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)	A Hb level of 14-15 g/dL is not an independent risk factor for 30-day CV mortality, MI or RI compared with a Hb level of 15-16 g/dL P=0.251
	1 cohort analysis of 16 RCTs[c] N=5650	Adults with NSTE-ACS	Hospital Various	Hb 13-14 g/dL vs Hb 15-16 g/dL	Cardiovascular mortality/MI/recurrent ischaemia (30 days)	NR	NR	OR 1.04 (0.86, 1.24) Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)	A Hb level of 13-14 g/dL is not an independent risk factor for 30-day CV mortality, MI or RI compared with a Hb level of 15-16 g/dL P=0.709
	1 cohort analysis of 16 RCTs[c] N=4461	Adults with NSTE-ACS	Hospital Various	Hb 12-13 g/dL vs Hb 15-16 g/dL	Cardiovascular mortality/MI/recurrent ischaemia (30 days)	NR	NR	OR 1.07 (0.88, 1.30) Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)	A Hb level of 12-13 g/dL is not an independent risk factor for 30-day CV mortality, MI or RI compared with a Hb level of 15-16 g/dL P=0.514

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 cohort analysis of 16 RCTs[c] N=3106	Adults with NSTE-ACS	Hospital Various	Hb 11-12 g/dL vs Hb 15-16 g/dL	Cardiovascular mortality/MI/recurrent ischaemia (30 days)	NR	NR	OR 1.04 (0.81, 1.34)	A Hb level of 11-12 g/dL is <u>not</u> an independent risk factor for 30-day CV mortality, MI or RI compared with a Hb level of 15-16 g/dL P=0.755
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
	1 cohort analysis of 16 RCTs[c] N=2473	Adults with NSTE-ACS	Hospital Various	Hb 10-11 g/dL vs Hb 15-16 g/dL	Cardiovascular mortality/MI/recurrent ischaemia (30 days)	NR	NR	OR 1.29 (0.92, 1.82)	A Hb level of 10-11 g/dL is <u>not</u> an independent risk factor for 30-day CV mortality, MI or RI compared with a Hb level of 15-16 g/dL P=0.145
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
	1 cohort analysis of 16 RCTs[c] N=2472	Adults with NSTE-ACS	Hospital Various	Hb 9-10 g/dL vs Hb 15-16 g/dL	Cardiovascular mortality/MI/recurrent ischaemia (30 days)	NR	NR	OR 2.69 (2.01, 3.60)	A Hb level of 9-10 g/dL is an independent risk factor for 30-day CV mortality, MI or RI compared with a Hb level of 15-16 g/dL P<0.001
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
	1 cohort analysis of 16 RCTs[c] N=2436	Adults with NSTE-ACS	Hospital Various	Hb 8-9 g/dL vs Hb 15-16 g/dL	Cardiovascular mortality/MI/recurrent ischaemia (30 days)	NR	NR	OR 2.45 (1.80, 3.33)	A Hb level of 8-9 g/dL is an independent risk factor for 30-day CV mortality, MI or RI compared with a Hb level of 15-16 g/dL P<0.001
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
	1 cohort analysis	Adults with NSTE-	Hospital	Hb <8 g/dL vs Hb 15-	Cardiovascular	NR	NR	OR 3.49 (2.35, 5.20)	A Hb level of <8 g/dL is

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	of 16 RCTs[c] N=2267	ACS	Various	16 g/dL	mortality/MI/recurrent ischaemia (30 days)	Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			an independent risk factor for 30-day CV mortality, MI or RI compared with a Hb level of 15-16 g/dL P<0.001
	1 cohort analysis of 16 RCTs[c] N=2915	Adults with NSTE-ACS	Hospital Various	Hb <11 g/dL vs Hb 15-16 g/dL	Cardiovascular mortality/MI/recurrent ischaemia (30 days)	NR	NR	OR 2.26 (1.83, 2.79)	A Hb level of <11 g/dL is an independent risk factor for 30-day CV mortality, MI or RI compared with a Hb level of 15-16 g/dL P<0.001
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AIIRA, angiotensin II receptor antagonists; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; RCT, randomised controlled trial; RI, recurrent ischemia; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] TIMI IIIB, 4, 9A, 9B, 10A, 10B, 11A, 11B, 12, 14, 16 (OPUS), 17 (InTIME II)[c], 18 (TACTICS), 20 (INTEGRI), 23 (ENTIRE) and 24 (FASTER). Analysis of data from this InTIME II trial was also carried out by Giraldez 2009.

Four studies assessed the association between **Hb as a continuous variable and mortality in a composite outcome including cardiovascular outcomes**, as shown in Table 3.7.[11,12,14,16] The study by Bassand et al (2010)[11] assessed the association between increased Hb and mortality/MI in >28,000 patients with symptoms of STEMI OR NSTE-ACS. A 1 g/dL increase in Hb was associated with a significantly decreased risk of 30-day mortality/MI (OR 0.96; 95% CI 0.93, 0.99).

Cavusoglu et al (2006)[12] assessed the association between Hb and 2-year mortality/MI in men with ACS. A 1 g/dL increase in Hb was associated with a 26% decreased risk of mortality/MI.

The study by Hasin et al (2009)[14] examined the relationship between a change in Hb from baseline to follow-up and mortality/heart failure. A 1 SD decrease in Hb was associated with a 48% increased risk of mortality/heart failure.

Sabatine et al (2005)[16] assessed the association between Hb and the composite outcome 30-day cardiovascular mortality/MI/recurrent ischaemia in patients with NSTE-ACS. A 1 g/dL decrease below 11 g/dL in patients with a baseline Hb of 15-16 g/dL was associated with a 45% increased risk of the composite outcome.

Table 3.7 Question 1 (ACS): Results for Level II evidence – mortality in a composite outcome including cardiovascular outcomes (Hb as a continuous variable)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ALL-CAUSE MORTALITY									
SHORT-TERM FOLLOW-UP (UP TO 1 YEAR)									
Bassand 2010 Level II Fair	1 cohort analysis of two RCTs (OASIS 5 and 6) N=28,907	Adults presenting to hospital with symptoms of NSTE-ACS or STEMI	Hospital Various[c]	Hb increase (g/dL)	Mortality/MI (30 days)	NA	NA	OR 0.96 (0.93, 0.99) Adjusted for: Baseline demographics, prior medical history, cardiovascular risk factors, randomised treatment allocation, co-interventions.	*A 1 g/dL increase in Hb results in a 4% decreased risk of mortality/MI* P=NR
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Cavusoglu 2006 Level II Fair	1 prospective cohort study N=191	Men with ACS (ST-elevation AMI, non-ST segment elevation AMI and unstable angina pectoris)	Hospital US	Hb increase (1 g/dL)	Mortality/MI (2 years)	NA	NA	HR 0.74 (0.55, 0.99) Adjusted for variables with p<0.05: age, number of diseased coronary arteries, left ventricular function, Hb, serum creatinine.	*A 1 g/dL increase in Hb results in a 26% decreased risk of death/MI* P=0.0411
Hasin 2009 Level II Fair	1 prospective cohort study N=1065	Patients with a diagnosis of AMI who survived the index hospitalisation and who received Hb measurement ≥28 days after hospital discharge	Hospital Israel	Hb decrease from discharge to follow-up (1 SD)	Mortality/heart failure (mean 27 months)	NA	NA	HR 1.48 (1.25, 1.75) Adjusted for: age, gender, history of hypertension and diabetes, smoking habit, previous infarction, presence of anterior infarction, ST elevation infarction, revascularisation during hospital course, eGFR, Kilip class at admission, LVEF, medical therapy prescribed at discharge including antiplatelet agents, β blockers, ACEIs, AIIRAs and statins.	*A 1 SD decrease in Hb between discharge and follow-up results in a 48% increased risk of mortality or heart failure* P<0.001

CARDIOVASCULAR MORTALITY									
SHORT-TERM FOLLOW-UP (UP TO 1 YEAR)									
Sabatine 2005 Level II Fair	1 cohort analysis of 16 RCTs[d] N=NR	Adults with NSTE-ACS	Hospital Various	Hb decrease below 11 g/dL in subjects with baseline Hb 15-16 g/dL (1 g/dL)	Cardiovascular mortality/MI/recurrent ischaemia (30 days)	NA	NA	OR 1.45 (1.33, 1.58)	*A 1 g/dL decrease in Hb below 11 g/dL is related to a 45% increased risk of 30-day CV mortality, MI or RI* P<0.001
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AIIRA, angiotensin II receptor antagonists; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; RCT, randomised controlled trial; RI, recurrent ischemia; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hong Kong, Hungary, India, Italy, Latvia, Lithuania, Mexico, the Netherlands, Poland, Portugal, Russia, Singapore, Slovakia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Ukraine, UK, US.

[d] TIMI IIIB, 4, 9A, 9B, 10A, 10B, 11A, 11B, 12, 14, 16 (OPUS), 17 (InTIME II)[e], 18 (TACTICS), 20 (INTEGRI), 23 (ENTIRE) and 24 (FASTER). Analysis of data from this trial was also carried out by Giraldez 2009.

Anaemia as an independent risk factor for cardiovascular outcomes

One study assessed the association between **various Hb levels and cardiovascular outcomes**, as shown in Table 3.8.[16] The study by Sabatine et al (2005)[16] examined the association between different Hb levels and a selection of cardiovascular outcomes. A Hb level of <14 g/dL was shown to be an independent predictor of 30-day heart failure in patients with STEMI, when compared with a Hb level of 14-15 g/dL. In patients with NSTE-ACS, a Hb level <11 g/dL was a significant predictor of MI and recurrent ischaemia compared with a Hb level of 15-16 g/dL in patients with NTSE-ACS.

Anaemia as an independent risk factor for functional/performance status

No studies were identified which presented data on functional/performance status using validated instruments.

Summary

The majority of results presented for acute coronary syndromes suggest that anaemia/low Hb is an independent risk factor for both mortality and cardiovascular outcomes. Where no significant association between anaemia/low Hb was found, this was often when the Hb levels were not sufficiently low (eg, Hb levels corresponding to mild or negligible anaemia), where the outcome was limited to cardiovascular mortality, or where the population examined was small (eg, the Cavusoglu (2006)[12] study which included only 191 patients). Of particular interest are the analyses carried out by Valeur et al (2006)[17] in which the effect of anaemia or low Hb as an independent risk factor for mortality appears to occur only in the subgroup of patients with heart failure, and not those with acute coronary syndrome without heart failure.

Table 3.8 Question 1 (ACS): Results for Level II evidence – cardiovascular outcomes (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
SHORT-TERM FOLLOW-UP (UP TO 1 YEAR)									
Sabatine 2005 Level II Fair	1 cohort analysis of 16 RCTs[c] N=15,946	Adults with STEMI	Hospital Various	Hb <14 g/dL vs Hb 14-15 g/dL	Heart failure (30 days)	NR	NR	OR 1.20 (1.05, 1.38)	*A Hb level <14 g/dL is an independent risk factor for 30-day heart failure compared with a Hb level of 14-15 g/dL* *P=0.009*
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
	1 cohort analysis of 16 RCTs[c] N=2915	Adults with NSTE-ACS	Hospital Various	Hb <11 g/dL vs Hb 15-16 g/dL	Myocardial infarction (30 days)	NR	NR	OR 1.63 (1.07, 2.48)	A Hb level of <11 g/dL is an independent risk factor for 30-day myocardial infarction compared with a Hb level of 15-16 g/dL P=NR
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			
	1 cohort analysis of 16 RCTs[c] N=2915	Adults with NSTE-ACS	Hospital Various	Hb <11 g/dL vs Hb 15-16 g/dL	Recurrent ischaemia (30 days)	NR	NR	OR 2.60 (2.08, 3.26)	A Hb level of <11 g/dL is an independent risk factor for 30-day recurrent compared with a Hb level of 15-16 g/dL P=NR
						Candidate variables for which there was data in 80% of subjects and that either demonstrated association with baseline Hb levels (at a significance threshold of P0.25) or were of known clinical importance were included in the final model: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, index revascularisation (NSTE-ACS) + anterior location of index MI (STEMI only addition)			

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AIIRA, angiotensin II receptor antagonists; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; OR, odds ratio; RCT, randomised controlled trial; RI, recurrent ischemia; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] TIMI IIIB, 4, 9A, 9B, 10A, 10B, 11A, 11B, 12, 14, 16 (OPUS), 17 (InTIME II)[c], 18 (TACTICS), 20 (INTEGRI), 23 (ENTIRE) and 24 (FASTER). Analysis of data from this InTIME II trial was also carried out by Giraldez 2009.

HEART FAILURE

Heart failure occurs when abnormal cardiac function causes failure of the heart to pump blood at a rate sufficient for metabolic requirements under normal filling pressure. It is characterised clinically by breathlessness, effort intolerance, fluid retention, and poor survival. Heart failure can be caused by systolic or diastolic dysfunction, and is associated with neurohormonal changes.[a]

Of the adverse outcomes specified for this question, two are covered for this population: mortality and functional status (disability).

Methods

There were 18 studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified three systematic reviews examining the aetiology of anaemia in patients with heart failure.

Level II evidence

The literature search identified 15 Level II studies examining aetiology of anaemia in patients with heart failure.

Level III evidence

Due to the substantial amount of Level II evidence identified, the literature was not searched for Level III evidence.

Level IV evidence

Due to the substantial amount of Level II evidence identified, the literature was not searched for Level IV evidence.

Results

Level I evidence

Three Level I studies were included for this question: all three studies provided evidence for mortality and specifically examined anaemia in heart failure patients, as summarised in Table 3.9. [21-23] Two of the three studies included data from study types other than prospective cohort studies.[21,23] Only the study by He et al (2009)[22] was limited to Level II studies; however, in this study the pooled analysis was not adjusted for potential confounding variables.

As such, none of these Level I studies will be used as the basis for the review of this question; however, their results will be briefly described and they will be used to help identify Level II studies.

[a] http://clinicalevidence.bmj.com/ceweb/conditions/cvd/0204/0204_background.jsp

Table 3.9 Question 1 (heart failure): Characteristics and quality of Level I evidence

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Groenveld et al (2008)[21]	Systematic review and meta-analysis of literature. Includes data from 34 studies including 8 prospective cohort studies, 9 secondary analyses of RCTs, and 17 retrospective cohort studies. *Good*	Diagnosed with chronic heart failure (diastolic or systolic) and ≥18 years (definitions of heart failure varied between studies. N=up to 152,770	Mortality
He et al (2009)[22]	Systematic review and meta-analysis of literature. Includes data from 21 prospective observational studies. *Good*	Heart failure (LVEF ranged from <23% to ≥50% across the included studies, although most were <40). N=12,475	Mortality
Lindenfield et al (2005)[23]	Systematic review of literature. Includes data from 29 studies (3 Medicare populations), 6 hospital cohorts, 10 outpatient cohorts and 7 clinical research studies) *Fair*	Diagnosis of heart failure. N=NR	Mortality

LVEF, left ventricular ejection fraction; NR, not reported; RCT, randomised controlled trial.

All three identified reviews found that anaemia was associated with adverse outcomes. Groenveld et al (2008)[21] examined the association between anaemia and mortality using data from 34 studies assessing heart failure patients. They concluded that "[anaemia] is associated with an increased risk of mortality in both systolic and diastolic heart failure". The study by He et al (2009)[22] used data from 97,699 patients included in 20 studies to assess the relationship between anaemia and the prognosis of chronic heart failure. The authors concluded that "[anaemia] is associated with an increased risk of mortality…" Finally, Lindefield et al (2005)[23] reviewed data from 29 studies and found that anaemia was "consistently associated with poorer survival in all patient populations [in patients with heart failure] , but there are substantial differences in the patient populations and definition of [anaemia]".

Level II evidence

Fifteen Level II studies were included for this question; 14 studies provided evidence for mortality and one study provided evidence for functional status/quality of life.[8,24-37] The characteristics of the included studies are summarised in Table 3.10. Twelve of the included studies specifically examined anaemia or Hb level as a potential predictor of adverse outcomes[8,24-28,31-35,37]while the remaining three studies aimed to identify a number of potential predictors.[29,30,36]

Due to the large amount of evidence available for the mortality outcome, and the requirement that analyses were adjusted for multiple potential confounders, studies were limited to those including >500 subjects. This resulted in the exclusion of 12 studies including 26 to 442 patients.[38-49] Studies with smaller patient numbers were potentially available for inclusion for the functional status/quality of life outcomes, although none were identified.

Table 3.10 Question 1 (heart failure): Characteristics and quality of Level II evidence

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Adams et al (2009)[24]	Cohort analysis of a prospective registry (STAMINA-HFP) *Good*	Rando mLy selected outpatients with heart failure recruited from selected heart failure specialty practices and community-based cardiology practices with an interest in heart failure. N=826	Functional/performance status
Anand et al (2005)[25]	Cohort analysis of a double-blind RCT (Val HeFT) *Fair*	Chronic heart failure (≥18 years, heart failure for at least 3 months prior to screening, NYHA Class II-IV, clinically stable, fixed dose regimen of ACEI, diuretic, digoxin or β-blocker for at least 2 weeks, documented LVEF <40% and LV dilatation with an echocardiographically measured short axis internal dimension at end diastole greater than 2.9 cm per square metre of body surface area). N=5002	Mortality
Anker et al (2009)[8]	Cohort analysis of a double-blind RCT (OPTIMAAL) *Fair*	Diagnosis of acute myocardial infarction and signs or symptoms of heart failure during the acute phase suggested by one or more of the following: treatment with diuretic or intravenous vasodilator therapy for heart failure; pulmonary rales; third heart sound; persistent sinus tachycardia (≥100 bpm); radiographic evidence of pulmonary congestion. Also, AMI and a LVEF <35% or a left-ventricular end-diastolic dimension or greater than 65 mm (optional) and/or a new Q-wave anterior wall AMI, or any reinfarction with previous pathological Q-waves in the anterior wall. N = 5010	Mortality
Baggish et al (2007)[26]	Prospective hospital registry *Fair*	Community-based patients diagnosed with acute heart failure. N=690	Mortality

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Ceresa et al (2005)[27]	Prospective cohort study *Poor*	Patients with CHF caused by ischaemia, idiopathic dilated cardiomyopathy or other disease (eg, hypertension, valvular disease) entering a heart transplant programme. N=980	Mortality
Felker et al (2003)[28]	Cohort analysis of a double-blind RCT (OPTIME-CHF) *Good*	Patients with systolic dysfunction and exacerbations of heart failure: ≥18 years and demonstrated LVEF <40%. N=906	Mortality
Garty et al (2007)[29]	Prospective observational survey *Good*	Hospitalised heart failure patients with stages B-D[a] according to ACC/AHA definitions. N=4102	Mortality
Hamaguchi et al (2009)[31]	Prospective cohort study *Fair*	Patients hospitalised due to worsening heart failure as the primary cause of admission. N=1960	Mortality
Ingle et al (2007)[30]	Prospective cohort study *Fair*	Older patients with chronic heart failure. Patients referred to local community clinic with signs of breathlessness. Heart failure was defined as current symptoms of heart failure, or a history of symptoms controlled by medication, due to cardiac dysfunction and in the absence of any more likely cause. N=1592	Mortality
Kalra et al (2003)[32]	Prospective cohort study *Fair*	Patients with newly diagnosed heart failure. N=552	Mortality
Komajda et al (2006)[33]	Cohort analysis of a RCT (COMET) *Good*	Chronic heart failure: NYHA class II-IV, optimal background therapy with diuretics and ACEIs, LVEF <35% and a previous admission for a cardiovascular reason. N=2996	Mortality
Maggioni et al (2005)[34]	Cohort analysis of a RCT (Val-HeFT)[b] and prospective registry (IN-CHF) *Good*	Patients with heart failure: ≥18 years; history and clinical findings of heart failure for at least 3 months before screening; NYHA class II-IV; clinically stable; on a stable dose drug regimen that might include ACEI, diuretic, digoxin or β-blockers for at least 2 weeks; documented LVEF <40% and echocardiographically measured left ventricular internal diameter in diastole/body surface area>2.9 cm/m2 (ValHeFT) and diagnosis of heart failure according to the criteria described by the European Society of Cardiology (IN-CHF) N=5010 and 2411	Mortality

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Maraldi et al (2006)[35]	Prospective cohort study *Good/fair*[c]	Non-disabled, hospitalised with heart failure and aged ≥65 years: heart diagnosis carried out by means of the Clinical History Form, resulting in a summary score with a score of >4 corresponding to a diagnosis of heart failure. N=567	Mortality Functional status
Poole-Wilson et al (2003)[36]	Cohort analysis of a RCT (ATLAS) *Good*	Adults with mild, moderate or severe chronic heart failure (NYHA class II-IV). N=3164	Mortality
Young et al (2008)[37]	Prospective registry *Fair*	Patients hospitalised for an episode of a new or worsening heart failure as the primary cause of admission, or if significant HF symptoms developed for another primary diagnosis and HF was given as the primary discharge diagnosis. N=48,612	Mortality

ACC, Amercian College of Carfiology; ACS, acute coronary syndrome; AHA, American Heart Assocaition; AMI, acute myocardial infarction; bpm, beats per minute; CHF, congestive heart failure; CVD, Hb, haemoglobin; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NYHA, New York heart association; RI, recurrent ischaemia; STEMI, ST-segment elevation myocardial infarction.

[a] A: patients at high risk of developing heart failure, but without structural heart disease of heart failure symptoms; B: patients with structural heart disease but without heart failure symptoms; C: patients with structural heart disease with prior or current symptoms of heart failure; D: refractor heart failure patients who require specialised interventions.

[b] Dataset also analysed by Anand et al (2005).[25]

[c] Quality rated as good for the mortality outcome and fair for the disability outcome.

Anaemia as an independent risk factor for mortality

Eight studies assessed the association between **anaemia as defined by the World Health Organisation (WHO)** and mortality, as shown in Table 3.11.[8,25-27,29,33-35] The study by Garty et al (2007)[29] assessed the association between anaemia and in-hospital and 1-year mortality in 4102 patients with heart failure stages B-D based on ACC/AHA Guidelines. The results of the analysis showed that anaemia was an independent risk factor for 1-year mortality but not in-hospital mortality.

The study by Baggish et al (2007)[26] assessed the association between anaemia and 60-day mortality in 690 patients diagnosed with acute heart failure. The results of the analysis showed that anaemia was an independent risk factor for 60-day mortality (P=0.032).

The study by Maggioni et al (2006)[34] examined the association between anaemia and mortality in cohorts taken from one RCT (Val-HeFT; N=5010) and one prospective registry (IN-CHF; N=2411). It should be noted that data from the Val-HeFT was also analysed by Anand et al (2005), as described above. The results of the analyses showed that anaemia was an independent risk factor for 2-year mortality in the Val-HeFT cohort and 1-year mortality in the IN-CHF cohort.

Maraldi et al (2006)[35] assessed the association between anaemia and 12-month mortality in a prospective cohort including 567 patients. When the cohort as a whole was examined, there was no significant association between anaemia and mortality. When the cohort was

divided into gender-based subgroups, the results showed that anaemia was an independent risk factor for mortality in women (N=266), but not in men (N=301).

The study by Anand et al (2005)[25] included 5002 patients with chronic heart failure, and showed that anaemia is an independent risk factor for 2-year mortality (P=0.02).

Anker et al (2009)[8] assessed the association between anaemia and three types of mortality: all-cause mortality, sudden cardiac mortality and progressive heart failure mortality. In 5010 subjects with a diagnosis of acute myocardial infarction with signs or symptoms of heart failure during the acute phase, anaemia was shown to be independently associated with all-cause and heart failure mortality (P<0.0001 and 0.006, respectively) and not associated with sudden cardiac death during a median 3 years of follow-up.

Komajda et al (2006)[33] performed a cohort analysis of the association between anaemia and mortality in 2996 patients with chronic heart failure who took part in the COMET RCT. Over a median of 58 months of follow-up, anaemia was shown to be an independent risk factor for mortality (P<0.001).

Ceresa et al (2005)[27] examined the association between anaemia and cardiac mortality which included urgent heart transplantation, as it was considered that without the transplant the patient would have died. In 980 patients with chronic heart failure entering a heart transplant programme, anaemia was not shown to be an independent predictor of cardiac mortality.

Only the studies by Baggish et al (2007)[26] and Maraldi et al (2006)[35] studies provided data on the baseline risk of mortality associated with heart failure. Baggish et al (2007) showed that the unadjusted risk of mortality in patients without heart failure was 8.8%, while in patients with heart failure it was 16.4%. In the study by Maraldi (2006), the risk of mortality in patients without anaemia was 11.5%, and increased to 18.2% in patients with anaemia. However, the results were somewhat different when analysed by gender. The risk of mortality in females without anaemia was 9.1%, and this increased to 20.5% in females with anaemia. In men, the effect of anaemia seemed to be much less pronounced, with the risk increasing from 13.8% in men with anaemia compared with 16.3% in men with anaemia.

Table 3.11 Question 1 (heart failure): Results for Level II evidence – mortality (WHO or similar anaemia criteria)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ALL-CAUSE MORTALITY									
SHORT-TERM FOLLOW-UP (UP TO 1 YEAR)									
Garty 2007 Level II *Good*	1 prospective observational survey N=4102	Adult patients with heart failure stages B-D[e]	Hospital/Israel	Anaemia (Hb ≤12 g/dL) vs no anaemia	Mortality (in-hospital)	NR	NR	NR	Anaemia is not an independent risk factor for in-hospital mortality P≥0.05
						Adjusted for: gender, age, hypertension, diabetes mellitus, dyslipidaemia, obesity, current smoking, coronary artery disease, acute coronary syndrome, valvular heart disease, cardiomyopathy (non-ischaemic), atrial fibrillation, renal failure (creatinine ≥1.5 mg/dL), chronic obstructive pulmonary disorder, stroke/transient ischaemic attack, various treatments.			
					Mortality (12 months)	NR	NR	OR 1.50 (1.29, 1.75)	Anaemia is an independent risk factor for in-hospital mortality P<0.05
						Adjusted for: gender, age, hypertension, diabetes mellitus, dyslipidaemia, obesity, current smoking, coronary artery disease, acute coronary syndrome, valvular heart disease, cardiomyopathy (non-ischaemic), atrial fibrillation, renal failure (creatinine ≥1.5 mg/dL), chronic obstructive pulmonary disorder, stroke/transient ischaemic attack, various treatments.			
Baggish 2007 Level II *Fair*	1 cohort analysis of data from a registry comprising subjects from 3 clinical trials and a prospective registry (ICON) N=690	Adult patients diagnosed with acute heart failure	Hospital/US, the Netherlands, Spain, New Zealand	Anaemia (WHO) vs no anaemia	Mortality (60 days)	50/305 (16.4)	34/385 (8.8)	OR 1.72 (1.05, 2.80)	*Anaemia is an independent risk factor for 60-day mortality* P=0.032
						Adjusted for: age, hypertension, coronary artery disease, loop diuretic use, paroxysmal nocturnal dyspnoea, fever, ECG left bundle branch block, creatinine, creatinine clearance, troponin, NT-pro-BNP; NYHA class, signs of haemodilution.			
Maggioni 2005 Level II *Good*	1 prospective registry (IN-CHF) N=2411	Adults patients with heart failure	Not stated/Italy (IN-CHF)	Anaemia (WHO) vs no anaemia	Mortality (12 months)	NR	NR	HR 1.54 (1.20, 1.97)	*Anaemia is an independent risk factor for mortality* P<0.05
						Adjusted for: age, sex, SBP, heart rate, NYHA class, presence of coronary heart disease aetiology, ejection fraction, third heart sound, BMI, creatinine, use of ACEIs and β-blockers.			
Maraldi 2006 Level II *Good*	1 prospective cohort study N=567	Adults aged ≥65 years hospitalised with heart failure	Hospital/Italy	Anaemia (WHO) vs no anaemia	Mortality (12 months)	46/253 (18.2)	36/314 (11.5)	OR 1.15 (0.69, 1.91)	Anaemia is not an independent predictor of mortality compared with no anaemia P≥0.05
						Adjusted for: age, gender, cognitive status, Short Physical Performance Battery score, SBP, DBP, heart rate, BMI, serum albumin, cholesterol, serum sodium, creatinine clearance, NYHA class, Cumulative Illness Rating Scale score, use of ACEIs.			
	1 prospective	Females aged ≥65	Hospital/Italy	Anaemia (WHO) vs	Mortality (12	23/112 (20.5)	14/154 (9.1)	OR 2.33 (1.02, 5.30)	*Anaemia is an*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis cohort study N=266 (subgroup)	Patient population years hospitalised with heart failure	Setting Location	Risk factor no anaemia	Outcome months)	Results Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
						Adjusted for: age, gender, cognitive status, Short Physical Performance Battery score, SBP, DBP, heart rate, BMI, serum albumin, cholesterol, serum sodium, creatinine clearance, NYHA class, Cumulative Illness Rating Scale score, use of ACEIs.			*independent predictor of mortality compared with no anaemia in females* P<0.05
	1 prospective cohort study N=301 (subgroup)	Males aged ≥65 years hospitalised with heart failure	Hospital/Italy	Anaemia (WHO) vs no anaemia	Mortality (12 months)	23/141 (16.3)	22/160 (13.8)	OR 0.65 (0.32, 1.35)	Anaemia is not an independent predictor of mortality compared with no anaemia in males P≥0.05
						Adjusted for: age, gender, cognitive status, Short Physical Performance Battery score, SBP, DBP, heart rate, BMI, serum albumin, cholesterol, serum sodium, creatinine clearance, NYHA class, Cumulative Illness Rating Scale score, use of ACEIs.			
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Anand 2005 Level II *Fair*	1 cohort analysis of a double-blind RCT (Val-HeFT) N=5002	Adult patients with chronic heart failure	Not stated Various countries[c]	Anaemia (WHO)[d] vs no anaemia	Mortality (24 months)	NR	NR	HR 1.21	*Anaemia is an independent risk factor for 2-year mortality* P=0.02
						Adjusted for variables shown to be independently associated with anaemia at baseline: BNP category, NYHA category, uric acid, absolute neutrophil count, LVIDd/BSA, PRA, baseline use of β-blockers, origin (ischaemic vs non-ischaemic), age, creatinine, NE, category, absolute, lymphocyte count, LVEF, aldosterone, treatment (valsartan vs placebo).			
Maggioni 2005 Level II *Good*	1 cohort analysis of a double-blind RCT (Val-HeFT)[g] N=5010	Adults patients with heart failure	Not stated/Various[c] (Val-HeFT)	Anaemia (WHO) vs no anaemia	Mortality (2 years)	NR	NR	HR 1.26 (1.04, 1.52)[g]	*Anaemia is an independent risk factor for mortality* P<0.05
						Adjusted for: age, sex, SBP, heart rate, NYHA class, presence of coronary heart disease aetiology, ejection fraction, third heart sound, BMI, creatinine, use of ACEIs and β-blockers.			
Anker 2009 Level II *Fair*	1 cohort analysis of a double-blind RCT (OPTIMAAL) N=5010	Adult patients with a diagnosis of AMI and signs or symptoms of heart failure during the acute phase	Not stated Denmark, Finland, Germany, Ireland, Norway, Sweden, UK	Anaemia (WHO) vs no anaemia	Mortality (median 3 years)	NR	NR	HR 1.35 (1.16, 1.56)	*Anaemia is an independent risk factor for mortality* P<0.0001
						Adjusted for: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			
Komajda 2006 Level II *Good*	1 cohort analysis of a double-blind RCT (COMET) N=2996	Adults with chronic heart failure	Not stated/Various[f]	Anaemia (WHO) vs no anaemia	Mortality (median 58 months)	NR	NR	RR 1.47 (1.27, 1.71)	*Anaemia is an independent risk factor for all-cause mortality* P<0.001
						Adjusted for: randomised treatment, age, SBP, NYHA class, creatinine, sodium, BMI, diabetes, duration of HF, ischaemic aetiology, LVEF, lipid-lowering agent, gender, anticoagulants, aspirin.			

CARDIOVASCULAR MORTALITY									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Anker 2009 Level II *Fair*	1 cohort analysis of a double-blind RCT (OPTIMAAL) N=5010	Adult patients with a diagnosis of AMI and signs or symptoms of heart failure during the acute phase	Not stated Denmark, Finland, Germany, Ireland, Norway, Sweden, UK	Anaemia (WHO) vs no anaemia	Sudden cardiac mortality (median 3 years)	NR	NR	HR 1.14 (0.89, 1.48) Adjusted for: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.	Anaemia is not an independent risk factor for sudden cardiac death P=0.303
					Progressive heart failure mortality (median 3 years)	NR	NR	HR 1.55 (1.13, 2.13) Adjusted for: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.	*Anaemia is an independent risk factor for death due to progressive heart failure* P=0.006
Ceresa 2005 Level II *Poor*	1 prospective cohort study N=980	Adults patients with chronic heart failure entering a heart transplant programme	Hospital/Italy	Anaemia (Hb ≤12 g/dL) vs no anaemia	Cardiac mortality or urgent heart transplant (3 years)	NR	NR	NR Adjusted for: RAP, sodium, LVEF, mitral regurgitation, NYHA class and possibly others.	Anaemia is not an independent risk factor for cardiac mortality/urgent heart transplant

6-MWT, six minute walk test; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, Brain-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; DBP, diastolic blood pressure; dL, decilitre; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HF, heart failure; HR, hazard ratio; IHD, in hospital death; LVEF, left ventricular ejection fraction; LVIDd/BSA, left ventricular internal diastolic diameter/body surface area; LVSD, left ventricular systolic dysfunction; NE, norepinephrine; NR, not reported; NT-pro-BNP, N-terminal-pro-Brain-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PRA, plasma renin activity; RAP, right atrial pressure; RCT, randomised controlled trial; RR, risk ratio; SBP, systolic blood pressure; SD, standard deviation; SOB, signs of breathlessness; UK, United Kingdom; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Norway, Spain, Sweden, UK, US.

[d] Hb <13 g/dL in men and <12 g/dL in women.

[e] According to ACC/AHA definitions. A: patients at high risk of developing heart failure, but without structural heart disease of heart failure symptoms; B: patients with structural heart disease but without heart failure symptoms; C: patients with structural heart disease with prior or current symptoms of heart failure; D: refractor heart failure patients who require specialised interventions.

[f] Australia, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Norway, Portugal, Sweden, Switzerland, UK.

[g] An analysis of the Val-HeFT study data was also conducted in the Anand 2005 study, and resulted in similar HRs (1.26 vs 1.21).

Three studies assessed the association between **various Hb levels and mortality**, as shown in Table 3.12.[25,31,33] Anand et al (2005)[25] assessed the association between different 12-month changes in Hb level and 12-month mortality. A substantial reduction in Hb level from baseline over 12 months (mean -1.64 g/dL; range -6.3 to -0.9 g/dL) was an independent predictor of 12-month mortality compared with no change (mean 0.14 g/dL; range -0.1 to 0.4 g/dL). However, a small reduction in Hb level from baseline over 12 months (mean -0.48 g/dL; range -0.8 to -0.2 g/dL) was not associated with 12-month mortality compared with no change.

The study by Hamaguchi et al (2009)[31] assessed the association between various Hb levels and mortality in patients hospitalised due to worsening heart failure during a mean 2.4 year follow-up. The results of the analysis showed that lower Hb levels at discharge (<10.2 g/dL and 10.1-11.9 g/dL) were significantly associated with all-cause and cardiac mortality when compared with a Hb level of ≥13.7 g/dL. There was no association between Hb levels of 12.0-13.6 g/dL compared with ≥13.7 g/dL and all-cause or cardiac mortality.

Komajda et al (2006)[33] examined various levels and changes in Hb and their association with mortality over a median follow-up period of 58 months. Hb levels were divided into six groups and the three lowest groups (1, 2 and 3) and the two highest groups (5 and 6) were compared with Group 4. For the purposes of the results presented here, Group 1 (<11.5 g/dL male or <10.5 g/dL female) has been designated as severe/moderate anaemia, Group 2 (11.5-13.0 g/dL male or 10.5-12.0 g/dL female) has been designated as mild anaemia and Group 3 (13.0-14.0 g/dL male or 12.0-13.0 g/dL female) has been designated no anaemia. The reference group, Group 4, encompasses Hb from 14.0-15.0 g/dL for males or 13.0-14.0 g/dL for females. The results of the analysis show that severe/moderate anaemia and mild anaemia are independent risk factors for mortality compared with the Hb level in Group 4.

Komajda et al (2006)[33] also assessed the association between *change* in Hb and mortality. A reduction in Hb during the study of ≥3 g/dL and 2-3 g/dL were significantly associated with increased mortality compared with an increase in Hb of >0-1 g/dL. There was no significant association between reductions of 1-2 g/dL or 0-1 g/dL and increases of >0-1 g/dL.

Table 3.12 Question 1 (heart failure): Results for Level II evidence – mortality (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ALL-CAUSE MORTALITY									
SHORT-TERM FOLLOW-UP (UP TO 1 YEAR)									
Anand 2005 Level II *Fair*	1 cohort analysis of a double-blind RCT (Val-HeFT) N=1499	Adult patients with chronic heart failure	Not stated Various countries[c]	12-month change in Hb (- 1.64 g/dL change (range -6.3 to -0.9) vs 0.14 g/dL change (range -0.1 to 0.4)	Mortality (12 months)	NR	NR	HR 1.6 (1.16, 2.2) Adjusted for variables shown to be independently associated with anaemia at baseline: BNP category, NYHA category, uric acid, absolute neutrophil count, LVIDd/BSA, PRA, baseline use of β-blockers, origin (ischaemic vs non-ischaemic), age, creatinine, NE, category, absolute, lymphocyte count, LVEF, aldosterone, treatment (valsartan vs placebo).	*A substantial reduction in Hb from baseline over 12 months is significantly associated with an increased risk of subsequent mortality* P=0.004
	1 cohort analysis of a double-blind RCT (Val-HeFT) N=1532	Adult patients with chronic heart failure	Not stated Various countries[c]	12-month change in Hb (-0.48 g/dL change (range -0.8 to -0.2)vs 0.14 g/dL change (range -0.1 to 0.4)	Mortality (12 months)	NR	NR	HR 1.10 (0.79, 1.55) Adjusted for variables shown to be independently associated with anaemia at baseline: BNP category, NYHA category, uric acid, absolute neutrophil count, LVIDd/BSA, PRA, baseline use of β-blockers, origin (ischaemic vs non-ischaemic), age, creatinine, NE, category, absolute, lymphocyte count, LVEF, aldosterone, treatment (valsartan vs placebo).	A small reduction in Hb from baseline is not independently associated with an increased risk of mortality P=0.57
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Hamaguchi 2009 Level II *Fair*	1 prospective cohort study N=777	Adult patients hospitalised due to worsening heart failure	Hospital/Japan	Discharge Hb <10.1 g/dL vs Hb ≥13.7 g/dL	Mortality (mean 2.4 years)	NR	NR	HR 1.963 (1.300, 2.963) Adjusted for: demographic (age, sex, BMI), causes of heart failure (ischaemic, hypertensive, valvular heart disease, dilated cardiomyopathy), medical history (hyperuricaemia, stroke, smoking, chronic arterial fibrillation or flutter), serum creatinine, NYHA functional class at discharge, BNP at discharge, LVEF at discharge and medication use (ACEI, ARB, β-blocker, digitalis, Ca channel blocker, nitrates, antiarrhythmic, warfarin).	*Moderate-severe anaemia (Hb <10.1 g/dL) is an independent risk factor for mortality compared with no anaemia (Hb ≥13.7 g/dL)* P<0.05
	1 prospective cohort study N=823	Adult patients hospitalised due to worsening heart failure	Hospital/Japan	Discharge Hb 10.1–11.9 g/dL vs Hb ≥13.7 g/dL	Mortality (mean 2.4 years)	NR	NR	HR 1.606 (1.067, 2.417) Adjusted for: demographic (age, sex, BMI), causes of heart failure (ischaemic, hypertensive, valvular heart disease, dilated cardiomyopathy), medical history (hyperuricaemia, stroke, smoking, chronic arterial fibrillation or flutter), serum creatinine, NYHA functional class at discharge, BNP at discharge, LVEF at discharge and medication use (ACEI, ARB, β-blocker, digitalis, Ca channel blocker, nitrates, antiarrhythmic, warfarin).	*Mild-moderate anaemia (Hb 10.1-11.9 g/dL) is an independent risk factor for all-cause mortality compared with no anaemia (Hb ≥13.7 g/dL)* P<0.05
	1 prospective	Adult	Hospital/Japan	Discharge Hb 12.0-	Mortality (mean	NR	NR	HR 1.315 (0.858, 2.016)	Very mild anaemia (Hb

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	cohort study N=826	patients hospitalised due to worsening heart failure		13.6 g/dL vs Hb ≥13.7 g/dL	2.4 years)	Adjusted for: demographic (age, sex, BMI), causes of heart failure (ischaemic, hypertensive, valvular heart disease, dilated cardiomyopathy), medical history (hyperuricaemia, stroke, smoking, chronic arterial fibrillation or flutter), serum creatinine, NYHA functional class at discharge, BNP at discharge, LVEF at discharge and medication use (ACEI, ARB, β-blocker, digitalis, Ca channel blocker, nitrates, antiarrhythmic, warfarin).			12.0-13.6 g/dL) is not an independent risk factor for mortality compared with no anaemia (Hb ≥13.7 g/dL) P≥0.05
Komajda 2006 Level II *Good*	1 cohort analysis of a double-blind RCT (COMET) N=929	Adults with chronic heart failure	Not stated/Various[f]	Severe/moderate anaemia (Hb <11.5 g/dL male or <10.5 g/dL female) vs normal Hb (Hb 14.0-15.0 g/dL male or 13.0-14.0 g/dL female)	Mortality (median 58 months)	NR	NR	RR 1.558 (1.145, 2.121)	*Severe/moderate anaemia is an independent risk factor for mortality compared with normal Hb* P=0.0048
						Adjusted for: randomised treatment, age, SBP, NYHA class, creatinine, sodium, BMI, diabetes, duration of HF, ischaemic aetiology, LVEF, lipid-lowering agent, gender, anticoagulants, aspirin.			
	1 cohort analysis of a double-blind RCT (COMET) N=1206	Adults with chronic heart failure	Not stated/Various[f]	Mild anaemia (Hb 11.5-13.0 g/dL male or 10.5-12.0 g/dL female)vs normal Hb (Hb 14.0-15.0 g/dL male or 13.0-14.0 g/dL female)	Mortality (median 58 months)	NR	NR	RR 1.405 (1.16, 1.703)	*Moderate anaemia is an independent risk factor for mortality compared with normal* Hb P<0.001
						Adjusted for: randomised treatment, age, SBP, NYHA class, creatinine, sodium, BMI, diabetes, duration of HF, ischaemic aetiology, LVEF, lipid-lowering agent, gender, anticoagulants, aspirin.			
	1 cohort analysis of a double-blind RCT (COMET) N=1463	Adults with chronic heart failure	Not stated/Various[f]	No anaemia (Hb 13.0-14.0 g/dL male or 12.0-13.0 g/dL female)vs normal Hb (Hb 14.0-15.0 g/dL male or 13.0-14.0 g/dL female)	Mortality (median 58 months)	NR	NR	RR 0.942 (0.783, 1.134)	No anaemia is not an independent risk factor for mortality compared with normal Hb P=0.529
						Adjusted for: randomised treatment, age, SBP, NYHA class, creatinine, sodium, BMI, diabetes, duration of HF, ischaemic aetiology, LVEF, lipid-lowering agent, gender, anticoagulants, aspirin.			
Komajda 2006 Level II *Good*	1 cohort analysis of a double-blind RCT (COMET) N=NR	Adults with chronic heart failure	Not stated/Various[f]	Δ Hb ≤–3 g/dL vs Δ Hb >0-1 g/dL	Mortality (median 58 months)	NR	NR	RR 3.37 (2.464, 4.611)	*A large reduction in Hb over time is an independent risk factor for mortality compared with no reduction in Hb* P<0.001
						Adjusted for: randomised treatment, age, SBP, NYHA class, creatinine, sodium, BMI, diabetes, duration of HF, ischaemic aetiology, LVEF, lipid-lowering agent, gender, anticoagulants, aspirin.			
	1 cohort analysis of a double-blind RCT (COMET) N=NR	Adults with chronic heart failure	Not stated/Various[f]	Δ Hb >–3 to–2 g/dL vs Δ Hb >0-1 g/dL	Mortality (median 58 months)	NR	NR	RR 1.466 (1.092, 1.969)	*A moderate reduction in Hb over time is an independent risk factor for mortality compared with no reduction in Hb* P=0.0109
						Adjusted for: randomised treatment, age, SBP, NYHA class, creatinine, sodium, BMI, diabetes, duration of HF, ischaemic aetiology, LVEF, lipid-lowering agent, gender, anticoagulants, aspirin.			
	1 cohort analysis	Adults with chronic	Not stated/Various[f]	Δ Hb >–2 to–1 g/dL	Mortality (median	NR	NR	RR 1.178 (0.944, 1.471)	A small reduction in Hb

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	of a double-blind RCT (COMET) N=NR	heart failure		vs Δ Hb >0-1 g/dL	58 months)	Adjusted for: randomised treatment, age, SBP, NYHA class, creatinine, sodium, BMI, diabetes, duration of HF, ischaemic aetiology, LVEF, lipid-lowering agent, gender, anticoagulants, aspirin.			over time is <u>not</u> an independent risk factor for mortality compared with no reduction in Hb P=0.1474
	1 cohort analysis of a double-blind RCT (COMET) N=NR	Adults with <u>chronic</u> heart failure	Not stated/Various[f]	Δ Hb >–1 to 0 g/dL vs Δ Hb >0-1 g/dL	Mortality (median 58 months)	NR	NR	RR 1.005 (0.831, 1.215)	A very small reduction in Hb over time is <u>not</u> an independent risk factor for all-cause anaemia compared with no reduction in Hb P=0.9595
						Adjusted for: randomised treatment, age, SBP, NYHA class, creatinine, sodium, BMI, diabetes, duration of HF, ischaemic aetiology, LVEF, lipid-lowering agent, gender, anticoagulants, aspirin.			

CARDIOVASCULAR MORTALITY									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Hamaguchi 2009 Level II *Fair*	1 prospective cohort study N=777	Adult patients hospitalised due to worsening heart failure	Hospital/Japan	Discharge Hb <10.1 g/dL vs Hb ≥13.7 g/dL	Cardiac mortality (mean 2.4 years)	NR	NR	HR 2.155 (1.308, 3.548) Adjusted for: demographic (age, sex, BMI), causes of heart failure (ischaemic, hypertensive, valvular heart disease, dilated cardiomyopathy), medical history (hyperuricaemia, stroke, smoking, chronic arterial fibrillation or flutter), serum creatinine, NYHA functional class at discharge, BNP at discharge, LVEF at discharge and medication use (ACEI, ARB, β-blocker, digitalis, Ca channel blocker, nitrates, antiarrhythmic, warfarin).	*Moderate-severe anaemia (Hb <10.1 g/dL) is an independent risk factor for cardiac death compared with no anaemia (Hb ≥13.7 g/dL)* P<0.05
	1 prospective cohort study N=823	Adult patients hospitalised due to worsening heart failure	Hospital/Japan	Discharge Hb 10.1–11.9 g/dL vs Hb ≥13.7 g/dL	Cardiac mortality (mean 2.4 years)	NR	NR	HR 1.706 (1.039, 2.800) Adjusted for: demographic (age, sex, BMI), causes of heart failure (ischaemic, hypertensive, valvular heart disease, dilated cardiomyopathy), medical history (hyperuricaemia, stroke, smoking, chronic arterial fibrillation or flutter), serum creatinine, NYHA functional class at discharge, BNP at discharge, LVEF at discharge and medication use (ACEI, ARB, β-blocker, digitalis, Ca channel blocker, nitrates, antiarrhythmic, warfarin).	*Mild-moderate anaemia (Hb 10.1-11.9 g/dL) is an independent risk factor for cardiac death compared with no anaemia (Hb ≥13.7 g/dL)* P<0.05
	1 prospective cohort study N=826	Adult patients hospitalised due to worsening heart failure	Hospital/Japan	Discharge Hb 12.0-13.6 g/dL vs Hb ≥13.7 g/dL	Cardiac mortality (mean 2.4 years)	NR	NR	HR 1.39 (0.832, 2.324) Adjusted for: demographic (age, sex, BMI), causes of heart failure (ischaemic, hypertensive, valvular heart disease, dilated cardiomyopathy), medical history (hyperuricaemia, stroke, smoking, chronic arterial fibrillation or flutter), serum creatinine, NYHA functional class at discharge, BNP at discharge, LVEF at discharge and medication use (ACEI, ARB, β-blocker, digitalis, Ca channel blocker, nitrates, antiarrhythmic, warfarin).	Very mild anaemia (Hb 12.0-13.6 g/dL) is not an independent risk factor for cardiac death compared with no anaemia (Hb ≥13.7 g/dL) P≥0.05

6-MWT, six minute walk test; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, Brain-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; DBP, diastolic blood pressure; dL, decilitre; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HF, heart failure; HR, hazard ratio; IHD, in hospital death; LVEF, left ventricular ejection fraction; LVIDd/BSA, left ventricular internal diastolic diameter/body surface area; LVSD, left ventricular systolic dysfunction; NE, norepinephrine; NR, not reported; NT-pro-BNP, N-terminal-pro-Brain-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PRA, plasma renin activity; RAP, right atrial pressure; RCT, randomised controlled trial; RR, risk ratio; SBP, systolic blood pressure; SD, standard deviation; SOB, signs of breathlessness; UK, United Kingdom; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Norway, Spain, Sweden, UK, US.

Eight studies assessed the association between **Hb as a continuous variable and mortality**, as shown in Table 3.13.[8,25,28,30,32,34,36,37] Felker et al (2003)[28] assessed the association between Hb level and 60-day mortality in 906 patients with systolic dysfunction and exacerbation of heart failure who took part in the OPTIME-CHF RCT. The results of this study showed that a 1 g/dL increase in Hb was not associated with 60-day mortality.

Anand et al (2005)[25] assessed the association between Hb as a continuous variable and 12-month mortality in two populations: (i) those with anaemia at baseline (N=668) and (ii) those without anaemia at baseline (N=2424). The results of the analysis showed that a 1 g/dL increase in Hb was associated with a substantial reduction in 12-month mortality risk in both patient populations (22% and 21% reduction, respectively).

Maggioni et al (2005)[34] examined the association between Hb and mortality in cohorts from one RCT (Val-HeFT) and one prospective registry (IN-CHF). As noted previously, data from the Val-HeFT trial was also used for the analysis by Anand et al (2005). Using data from the Val-HeFT trial, Maggioni et al (2005) showed that a 1 g/dL increase in Hb resulted in a significantly decreased risk of mortality at 2 years and 1 year (7.8% and 11% reductions in the risk of mortality, respectively). Similarly, analysis of data from the IN-CHF study also showed a reduction in mortality associated with an increase of 1 g/dL in Hb (9.7% reduction).

The study by Anker et al (2009)[8] examined the association between Hb levels or change in Hb levels and mortality. A 1 SD increase in Hb was significantly associated with a 12% reduction in the risk of all-cause mortality and a 20% reduction in the risk of progressive heart failure mortality during a mean of 3 years of follow-up. There was no association between a 1 SD increase in Hb and sudden cardiac mortality. A 12-month change (increase or decrease) in Hb was significantly associated with mortality; a 12-month change was associated with a 27% reduction in mortality risk (P<0.01) while a 12-month increase was associated with a 33% reduction in mortality risk (P<0.01). A 12-month decrease in Hb level may be associated with a 27% increase in the risk of mortality (P=0.05).

The study by Ingle et al (2007)[30] aimed to examine the relationship between Hb and mortality in 1592 elderly patients with chronic heart failure. During a mean of 36.6 months of follow-up, a 1 g/dL increase in Hb was significantly associated with a 17.1% reduction in mortality.

Kalra et al (2003)[32] used a prospective cohort study design to assess the association between Hb and survival in 531 adults with newly diagnosed heart failure. The results of the analysis showed there was no significant association between a 1 g/dL increase in Hb and survival.

The study by Poole-Wilson et al (2003)[36] examined the association between Hb and a number of different types of mortality: (all-cause mortality, cardiovascular mortality, chronic heart failure mortality, sudden death and out-of-hospital death) in 3164 patients with mild-severe heart failure taking part in the ATLAS RCT. Over a mean follow-up period of 46 months, a 1 g/dL increase in Hb was significantly associated with a reduction in chronic heart failure mortality only.

Young et al (2008)[37] assessed the association between a decrease in Hb and mortality in >48,000 patients hospitalised for new or worsening heart failure. The results of the study showed that a 1 g/dL decrease in Hb was associated with an increased risk of in-hospital mortality, but not 60-90-day mortality.

Table 3.13 Question 1 (heart failure): Results for Level II evidence – mortality (Hb as a continuous variable)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ALL-CAUSE MORTALITY									
SHORT-TERM FOLLOW-UP (UP TO 12 MONTHS)									
Felker 2003 Level II Good	1 cohort analysis of a double-blind RCT (OPTIME-CHF) N=906	Adult patients with systolic dysfunction and exacerbation of heart failure	Hospital/US	1 g/dL increase in Hb	Mortality (60 days)	NA	NA	NR	*A 1 g/dL increase in Hb is not independently associated with a change in the risk of 60-day mortality* *P≥0.05*
						Adjusted for: 41 candidate variables that reflected demographics, cardiac history, co-morbid conditions, bedside assessment, and laboratory studies; to adjust for varying degrees of volume overload, variables assessed included presence of increased jugular venous pressure, peripheral oedema or a third heart sound.			
Anand 2005 Level II *Fair*	1 cohort analysis of a double-blind RCT (Val-HeFT) N=668	Adult patients with chronic heart failure with anaemia at baseline who survived 12 months	Not stated Various countries[c]	Increase in Hb of 1 g/dL	Mortality (12 months)	NA	NA	HR 0.78 (0.65, 0.93)	*A 1 g/dL increase in Hb in patients with anaemia at baseline who survived 12 months is independently associated with a 22% reduction in the risk of 12-month mortality* P=NR
						Adjusted for variables shown to be independently associated with anaemia at baseline: BNP category, NYHA category, uric acid, absolute neutrophil count, LVIDd/BSA, PRA, baseline use of β-blockers, origin (ischaemic vs non-ischaemic), age, creatinine, NE, category, absolute, lymphocyte count, LVEF, aldosterone, treatment (valsartan vs placebo).			
	1 cohort analysis of a double-blind RCT (Val-HeFT) N=2424	Adult patients with chronic heart failure without anaemia at baseline who survived 12 months	Not stated Various countries[c]	Increase in Hb of 1 g/dL	Mortality (12 months)	NA	NA	HR 0.79 (0.71, 0.89)	*A 1 g/dL increase in Hb in patients without anaemia at baseline who survived 12 months is independently associated with a 21% reduction in the risk of 12-month mortality* P=NR
						Adjusted for variables shown to be independently associated with anaemia at baseline: BNP category, NYHA category, uric acid, absolute neutrophil count, LVIDd/BSA, PRA, baseline use of β-blockers, origin (ischaemic vs non-ischaemic), age, creatinine, NE, category, absolute, lymphocyte count, LVEF, aldosterone, treatment (valsartan vs placebo).			
Maggioni 2005 Level II *Good*	1 cohort analysis of a double-blind RCT (Val-HeFT)[d] N=5010	Adults patients with heart failure	Not stated/Various[c] (Val-HeFT)	1 g/dL increase in Hb	Mortality (12 months)	NA	NA	HR 0.89 (0.83, 0.95)	*A 1 g/dL increase in Hb is independently associated with an 11% decrease in the risk of mortality* P<0.05
						Adjusted for: age, sex, SBP, heart rate, NYHA class, presence of coronary heart disease aetiology, ejection fraction, third heart sound, BMI, creatinine, use of ACEIs and β-blockers.			
	1 prospective registry (IN-CHF) N=2411	Adults patients with heart failure	Not stated/Italy (IN-CHF)	1 g/dL increase in Hb	Mortality (12 months)	NA	NA	HR 0.903 (0.839, 0.973)	*A 1 g/dL increase in Hb is independently associated with an 9.7% decrease in the risk of mortality* P<0.05
						Adjusted for: age, sex, SBP, heart rate, NYHA class, presence of coronary heart disease aetiology, ejection fraction, third heart sound, BMI, creatinine, use of ACEIs and β-blockers.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity[b]*
LONGER-TERM FOLLOW-UP (>12 MONTHS)									
Maggioni 2005 Level II Good	1 Cohort analysis of a double-blind RCT (Val-HeFT) N=5010	Adults patients with heart failure	Not stated/Various[c] (Val-HeFT)	1 g/dL increase in Hb	Mortality (2 years)	NA	NA	HR 0.922 (0.881, 0.966)	*A 1 g/dL increase in Hb is independently associated with a 7.8% decrease in the risk of mortality* *P<0.05*
						Adjusted for: age, sex, SBP, heart rate, NYHA class, presence of coronary heart disease aetiology, ejection fraction, third heart sound, BMI, creatinine, use of ACEIs and β-blockers.			
Anker 2009 Level II Fair	1 cohort analysis of a double-blind RCT (OPTIMAAL) N=5010	Adult patients with a diagnosis of AMI and signs or symptoms of heart failure during the acute phase	Not stated Denmark, Finland, Germany, Ireland, Norway, Sweden, UK	Increase in Hb of 1 SD	Mortality (median 3 years)	NA	NA	HR 0.88 (0.83, 0.93)	*A 1 SD increase in Hb is independently associated with a 12% reduction in the risk of mortality* *P<0.001*
						Adjusted for: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			
	1 cohort analysis of a double-blind RCT (OPTIMAAL) N=3921	Adult patients with a diagnosis of AMI and signs or symptoms of heart failure during the acute phase <u>who survived 12 month</u>	Not stated Denmark, Finland, Germany, Ireland, Norway, Sweden, UK	12-month <u>change</u> in Hb of 1 SD	Mortality (median 3 years)	NA	NA	HR 0.73 (0.63, 0.85)	*A 12-month change of Hb of 1 SD is independently associated with a 27% reduction in the risk of mortality* *P<0.001*
						Adjusted for: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			
				12-month <u>increase</u> in Hb of 1 SD	Mortality (median 3 years)	NA	NA	HR 0.67 (0.51, 0.81)	*A 12-month increase of Hb of 1 SD is independently associated with a 33% reduction in mortality* P<0.01
						Adjusted for: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			
				12-month <u>decrease</u> in Hb of 1 SD	Mortality (median 3 years)	NA	NA	HR 1.27 (1.00, 1.60)	*A 12-month decrease in Hb of 1 SD <u>may</u> be independently associated with a 27% increase in the risk of mortality* P=0.05
						Adjusted for: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.			
Ingle 2007 Level II Fair	1 prospective cohort study N=1592	'Older' patients with chronic heart failure (all aged >65 years)	Community/UK	1 g/dL increase in Hb	Mortality (mean 36.6 months)	NA	NA	HR 0.829 (0.808, 0.850)	A 1 g/dL increase in Hb is independently associated with a 17.1% reduction in the risk of mortality P<0.05
						Adjusted for: gender, age, BMI, NYHA class, LVSD, 6-MWT, sodium, potassium, urea, creatinine, LVEF, SBP, heart rate, QRS duration, log NT-pro-BNP, AF, angina, diabetes, ACEIs, β-blockers, loop diuretics, ankle swelling, SOB, fatigue.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Kalra 2003 Level II *Fair*	1 prospective cohort study N=531	Adults with newly diagnosed heart failure	Community/UK	1 g/dL increase in Hb	Survival (median 3 years)	NA	NA	HR 0.98 (0.92, 1.04)	*A 1 g/dL increase in Hb is not independently associated with a change in survival.* P=0.54
						Adjusted for: age, DBP, creatinine, NYHA class, left-ventricular systolic function.			
Poole-Wilson 2003 Level II *Good*	1 cohort analysis of a RCT (ATLAS) N=3164	Adults with mild-severe chronic heart failure	Hospital and community/various[e]	1 g/dL increase in Hb	Mortality (mean 46 months)	NA	NA	HR 0.983	*A 1 g/dL increase in Hb is not independently associated with a decrease in risk of mortality* P ≥0.05
						Adjusted for: lisinopril dose, age, sex, IHD, LVEF, NYHA class, SBP, DBP, heart rate, drugs at randomisation including antidiabetic, aspirin, β-blockers, long-acting nitrates, short-acting nitrates, previous ACEI, antiarrythmics, calcium channel blockers, anticoagulants/warfarin.			
					Sudden death (mean 46 months)	NA	NA	HR 1.036	*A 1 g/dL increase in Hb is not independently associated with a decrease in risk of sudden death* P ≥0.05
						Adjusted for: lisinopril dose, age, sex, IHD, LVEF, NYHA class, SBP, DBP, heart rate, drugs at randomisation including antidiabetic, aspirin, β-blockers, long-acting nitrates, short-acting nitrates, previous ACEI, antiarrythmics, calcium channel blockers, anticoagulants/warfarin.			
					Out-of-hospital death (mean 46 months)	NA	NA	HR 0.983	*A 1 g/dL increase in Hb is not independently associated with a decrease in risk of out-of-hospital death* P ≥0.05
						Adjusted for: lisinopril dose, age, sex, IHD, LVEF, NYHA class, SBP, DBP, heart rate, drugs at randomisation including antidiabetic, aspirin, β-blockers, long-acting nitrates, short-acting nitrates, previous ACEI, antiarrythmics, calcium channel blockers, anticoagulants/warfarin.			
Young 2008 Level II *Fair*	1 Prospective registry cohort study (OPTIMIZE-HF) N=48,612	Adults hospitalised for new or worsening heart failure, or if heart failure was the discharge diagnosis	Hospital/US	1 g/dL decrease in Hb (up to 13 g/dL)	Mortality (in hospital)	NA	NA	OR 1.077 (1.031, 1.126)	*A 1 g/dL decrease in Hb is independently associated with a 7.7% increase in the risk of in-hospital mortality* P=0.001
						Adjusted for: age, race, heart rate, SBP, DBP, sodium, creatinine, heart failure as primary reason for admission, prior CVA/TIA, hyperlipidaemia, liver disease, recent smoker, COPD, peripheral vascular disease, no prior heart failure, LVSD, ACEI, β-blocker.			
	1 Prospective registry cohort study N=5791	Adults hospitalised for new or worsening heart failure, or if heart failure was the discharge diagnosis	Hospital/US	1 g/dL decrease in Hb (up to 13 g/dL)	Mortality (60-90 days)	NA	NA	OR 1.021 (0.945, 1.104)	A 1 g/dL decrease in Hb is not independently associated with a change in the risk of 60-90 day mortality P=0.5939
						Adjusted for: SBP, creatinine, age, reactive airway disease, weight, lower extremity oedema, statin at discharge, sodium, depression, β-blocker, discharge SBP, liver disease.			

ALL-CAUSE MORTALITY									
LONGER-TERM FOLLOW-UP (>12 MONTHS)									
Anker 2009 Level II *Fair*	1 cohort analysis of a double-blind RCT (OPTIMAAL) N=5010	Adult patients with a diagnosis of AMI and signs or symptoms of heart failure during the acute phase	Not stated Denmark, Finland, Germany, Ireland, Norway, Sweden, UK	Increase in Hb of 1 SD	Sudden cardiac mortality (median 3 years)	NA	NA	HR 0.86 (0.80, 1.03) Adjusted for: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.	A 1 SD increase in Hb is not independently associated with a reduction in the risk of sudden cardiac mortality P=0.141
					Progressive heart failure mortality (median 3 years)	NA	NA	HR 0.80 (0.69, 0.94) Adjusted for: age, sex, randomised treatment group, baseline BMI, eGFR, baseline creatinine, baseline uric acid, Killip class, heart rate, systolic blood pressure, total cholesterol, current smoking, history of diabetes, in-hospital beta-blocker, statin, digitalis nitrate, aspirin, warfarin and diuretic use.	*A 1 SD increase in Hb is independently associated with a 20% reduction in the risk of progressive heart failure mortality* P=0.006
Poole-Wilson 2003 Level II *Good*	1 cohort analysis of a RCT (ATLAS) N=3164	Adults with mild-severe chronic heart failure	Hospital and community/various[e]	1 g/dL increase in Hb	Cardiovascular mortality (mean 46 months)	NA	NA	HR 0.999 Adjusted for: lisinopril dose, age, sex, IHD, LVEF, NYHA class, SBP, DBP, heart rate, drugs at randomisation including antidiabetic, aspirin, β-blockers, long-acting nitrates, short-acting nitrates, previous ACEI, antiarrythmics, calcium channel blockers, anticoagulants/warfarin.	*A 1 g/dL increase in Hb is not independently associated with a decrease in risk of cardiovascular mortality* P ≥0.05
					CHF mortality (mean 46 months)	NA	NA	HR 0.927 Adjusted for: lisinopril dose, age, sex, IHD, LVEF, NYHA class, SBP, DBP, heart rate, drugs at randomisation including antidiabetic, aspirin, β-blockers, long-acting nitrates, short-acting nitrates, previous ACEI, antiarrythmics, calcium channel blockers, anticoagulants/warfarin.	*A 1 g/dL increase in Hb is independently associated with a 7.3% decrease in risk of CHF mortality* P <0.05

6-MWT, six minute walk test; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, Brain-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischemic attack; DBP, diastolic blood pressure; dL, decilitre; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HF, heart failure; HR, hazard ratio; IHD, in hospital death; LVEF, left ventricular ejection fraction; LVIDd/BSA, left ventricular internal diastolic diameter/body surface area; LVSD, left ventricular systolic dysfunction; NE, norepinephrine; NR, not reported; NT-pro-BNP, N-terminal-pro-Brain-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PRA, plasma renin activity; RAP, right atrial pressure; RCT, randomised controlled trial; RR, risk ratio; SBP, systolic blood pressure; SD, standard deviation; SOB, signs of breathlessness; UK, United Kingdom; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Norway, Spain, Sweden, UK, US.

d An analysis of the Val-HeFT study data was also conducted in the Anand 2005 study, and resulted in similar HRs (1.26 vs 1.21).

[e] Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Hungary, Ireland, the Netherlands, Norway, Portugal, Slovak Republic, Spain, Switzerland, United Kingdom, United States.

Anaemia as an independent risk factor for stroke/MI

No studies were identified which presented data on stroke/MI.

Anaemia as an independent risk factor for functional/performance status

One study assessed the association between **various Hb levels and functional/performance status**, as shown in Table 3.14. Adams et al (2009)[24] assessed the association between baseline Hb and baseline quality of life, and 12-month change in Hb and 12-month change in quality of life, using two validated, disease-specific quality of life instruments: the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Based on a categorical analysis of Hb levels (with categories predominantly from 11 to 14 g/dL), baseline Hb level was shown to be significantly associated with improvements in three domains of the KCCQ (functional, P=0.0010; symptoms, P<0.001; and clinical, P=0.006) and one domain of the MLHFQ (physical, P=0.029).

Table 3.14 Question 1 (heart failure): Results for Level II evidence – functional/performance status (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity[b]*
HEART FAILURE									
CATEGORICAL ANALYSES									
Other anaemia criteria/Hb levels/change									
Adams 2009 Level II *Good*	1 cohort analysis of a prospective registry (STAMINA-HFP) N=826	Adult patients with heart failure with baseline Hb and QoL	Outpatient US	Categories of Hb predominantly from 11 to 14 g/dL	KCCQ-Functional	NR	NR	MD 1.1 (0.4, 1.8) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*Higher baseline Hb concentration is significantly associated with higher (improved) KCCQ-functional scores* P=0.001
		Adult patients with heart failure with baseline Hb and QoL	Outpatient US	Categories of Hb predominantly from 11 to 14 g/dL	KCCQ-Symptoms	NR	NR	MD 1.5 (0.7, 2.3) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*Higher baseline Hb concentration is significantly associated with higher (improved) KCCQ-symptoms scores* P<0.001
		Adult patients with heart failure with baseline Hb and QoL	Outpatient US	Categories of Hb predominantly from 11 to 14 g/dL	KCCQ-Clinical	NR	NR	MD 0.9 (0.3, 1.6) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*Higher baseline Hb concentration is significantly associated with higher (improved) KCCQ-clinical scores* P=0.006
	1 cohort analysis of a prospective registry (STAMINA-HFP) N=up to 826	Adult patients with heart failure with baseline Hb and QoL	Outpatient US	Categories of Hb predominantly from 11 to 14 g/dL	MLHFQ-Physical	NR	NR	MD -0.4 (-0.8, -0.04) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*Higher baseline Hb concentration is significantly associated with lower (improved) MLHFQ-physical scores* P=0.029
		Adult patients with heart failure with baseline Hb and QoL	Outpatient US	Categories of Hb predominantly from 11 to 14 g/dL	MLHFQ-Emotional	NR	NR	MD -0.2 (-0.4, 0.06) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*Higher baseline Hb concentration is not significantly associated with MLHFQ-emotional scores* P=0.14
		Adult patients with	Outpatient	Categories of Hb	MLHFQ-Summary	NR	NR	MD -0.7 (-1.5, 0.1)	*Higher baseline Hb*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
		heart failure <u>with baseline Hb and QoL</u>	US	predominantly from 11 to 14 g/dL		Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.			*concentration is <u>not</u> significantly associated with MLHFQ-summary scores* P=0.092

CI, confidence interval; Hb, haemoglobin; KCCQ, Kansas City Cardiomyopathy Questionnaire; MD, mean difference; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NR, not reported; QoL, quality of life; US, United States of America

Notes: Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

One study assessed the association between **change in Hb as a continuous variable and functional/performance status**, as shown in Table 3.15. Adams et al (2005)[24] assessed the association between change in Hb as a continuous variable and change in quality of life, as measured by the KCCQ and MLHFQ. Based on a continuous analysis of Hb, a change in Hb was shown to be significantly associated with improvements in three domains of the KCCQ (functional, P<0.0010; symptoms, P<0.001; and clinical, P<0.006) and two domains of the MLHFQ (physical, P=0.004; and summary, P=0.002).

Summary

The majority of results presented for heart failure suggest that anaemia/low Hb is an independent risk factor for mortality. Where no significant association between anaemia/low Hb was found, this was often when the Hb levels were not sufficiently low (eg, Hb levels corresponding to mild or negligible anaemia) or where the outcome was limited to cardiovascular mortality or sudden death. There were also a number of results showing no significant association between anaemia/low Hb and mortality relating to the follow-up period (60-90 days, in-hospital or specifically out-of-hospital) and one showing a difference by gender (no association in men). The results of the study which examined functional/performance status suggest that low Hb level is an independent risk factor for reduced quality of life.

Table 3.15 Question 1 (heart failure): Results for Level II evidence – functional/performance status (Hb as a continuous variable)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
HEART FAILURE									
CONTINUOUS ANALYSES									
Adams 2009 Level II *Good*	1 cohort analysis of a prospective registry (STAMINA-HFP) N=536	Adult patients with heart failure with baseline and all follow-up Hb and QoL	Outpatient US	1 g/dL change in Hb through 12 months	KCCQ-Functional	NA	NA	MD 1.3 (0.7, 1.8) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*A 1 g/dL change in Hb over 12 months is significantly associated with improved QoL* P<0.001
		Adult patients with heart failure with baseline and all follow-up Hb and QoL	Outpatient US	1 g/dL change in Hb through 12 months	KCCQ-Symptoms	NA	NA	MD 1.5 (0.8, 2.1) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*A 1 g/dL change in Hb over 12 months is significantly associated with improved QoL* P<0.001
		Adult patients with heart failure with baseline and all follow-up Hb and QoL	Outpatient US	1 g/dL change in Hb through 12 months	KCCQ-Clinical	NA	NA	MD 1.2 (0.7, 1.7) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*A 1 g/dL change in Hb over 12 months is significantly associated with improved QoL* P<0.001
	1 cohort analysis of a prospective registry (STAMINA-HFP) N=up to 536	Adult patients with heart failure with baseline and all follow-up Hb and QoL	Outpatient US	1 g/dL change in Hb through 12 months	MLHFQ-Physical	NA	NA	MD -0.5 (-0.8, -0.1) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*A 1 g/dL change in Hb over 12 months is significantly associated with improved QoL* P=0.004
		Adult patients with heart failure with baseline and all follow-up Hb and QoL	Outpatient US	1 g/dL change in Hb through 12 months	MLHFQ-Emotional	NA	NA	MD -0.1 (-0.3, 0.1) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*A 1 g/dL change in Hb over 12 months is not significantly associated with a change in QoL* P=0.389
		Adult patients with heart failure with baseline and all follow-up Hb and QoL	Outpatient US	1 g/dL change in Hb through 12 months	MLHFQ-Summary	NA	NA	MD -1.1 (-1.7, -0.4) Adjusted for gender, race, age, eGFR, history of diabetes, duration of heart failure, LVEF, hypertension, ischaemic heart disease, SBP, DBP, current smoking, ACEI, ARB, ACEI or ARB, β-blocker, digoxin, any diuretic, loop diuretic and NYHA class.	*A 1 g/dL change in Hb over 12 months is significantly associated with improved QoL* P=0.002

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; DBP, diastolic blood pressure; dL, decilitre; ECG, electrocardiograph; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MD, mean difference; MLHFQ, Minnesota Living with heart Failure Questionnaire; NR, not reported; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; SOB, signs of breathlessness; US, United States of America.
Notes: Statistically significant results shown in shading.
[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Level I studies only. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

THE COMMUNITY-DWELLING ELDERLY

For this question, an elderly population was defined as those aged ≥65 years who were community-dwelling and without significant morbidity.

Of the adverse outcomes specified for this question, two are covered for this population: mortality and functional status (disability).

Methods

There were 12 studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews examining the aetiology of anaemia in an elderly, community-dwelling population.

Level II evidence

The literature search identified 12 Level II studies examining aetiology of anaemia in an elderly, community-dwelling population.

Level III evidence

Due to the substantial amount of Level II evidence identified, the literature was not searched for Level III evidence.

Level IV evidence

Due to the substantial amount of Level II evidence identified, the literature was not searched for Level IV evidence.

Results

Twelve Level II studies were included for this question; ten studies provided evidence for mortality and two studies provided evidence for functional/performance status.[50-61] The characteristics of the included studies are summarised in Table 3.16. All of the included studies specifically examined anaemia or Hb level as a potential predictor of adverse outcomes.

Due to the large amount of evidence available for the mortality outcome, and the requirement that analyses were adjusted for multiple potential confounders, studies were limited to those including >500 subjects. This resulted in the exclusion of one study including 205 patients.[62] Studies with smaller patient numbers were potentially available for inclusion for the functional status/quality of life. Two studies were included.

Table 3.16 Question 1 (elderly): Characteristics and quality of Level II evidence

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Chaves et al (2004)[50]	Prospective cohort study *Fair*	Women aged ≥65 years, Medicare-eligible, a MMSE ≥18 and self-reported difficulty performing activities in two or more physical function domains. N=686	Mortality
Denny et al (2006)[51]	Prospective cohort study *Fair*	Community-dwelling adults aged ≥65 years at enrolment; at the time of baseline Hb measurement (at visit 6) participants were aged ≥71 years. N=1744	Mortality
Dong et al (2008)[52]	Prospective cohort study *Fair*	Rando mLy selected residents aged ≥65 years residing in three adjacent neighbourhoods in Chicago. N=1806	Mortality
Endres et al (2009)[53]	Prospective cohort study *Good*	Community-dwelling, primary-care patients aged ≥65 years, able to co-operate and provide written informed consent and a life expectancy >6 months as judged by the treating family physician. N=6880	Mortality
Izaks et al (1999)[54]	Prospective cohort study *Fair*	Inhabitants of Leiden, the Netherlands, aged 85 years and older at the start of the study. N=755	Mortality
Lucca et al (2009)[55]	Cross-sectional cohort study *Good*	Residents of Biella, Italy, aged 65-84 without neurological or psychiatric disease, severe sensory deficits, renal insufficiency, severe organ insufficiency, terminal illness, hospitalisation, institutionalisation and illiteracy. N=717	Functional/performance status
Patel et al (2007)[56]	Prospective cohort study *Fair*	Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability. N=2601	Mortality
Patel et al (2009)[57]	Prospective cohort study *Good*	Civilian, non-institutionalised population aged ≥65 years who identified their race as non-Hispanic white, non-Hispanic black or Mexican American. N=4089	Mortality
Pennix et al (2006)[58]	Prospective cohort study *Fair*	Community-dwelling adults aged ≥65 years in East Boston, Massachusetts; New haven, Connecticut; and Iowa and Washington counties in rural Iowa. N=3607	Mortality
Riva et al (2009)[59]	Prospective cohort study *Good*	Residents of Biella, Italy aged 65-84 years. N=7536 (all); 4501 (participants)	Mortality
Thein et al (2009)[60]	Cross-sectional cohort study *Fair*	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months. N=328	Functional/performance status

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Zakai et al (2005)[61]	Prospective cohort study *Fair*	Community-dwelling (non-institutionalised) men and women aged ≥65 years, identified via Medicare eligibility lists. N=5797	Mortality

MMSE, Mini-Mental State Examination

Anaemia as an independent risk factor for mortality

Due to the large amount of subgroup analysis that was carried out for this outcome, separate tables will be presented as follows: (i) the overall results; (ii) results by gender; (iii) results by race; (iv) results by anaemia subtype; and (v) results for other subgroups.

Four studies assessed the association between **anaemia as defined by the World Health Organisation (WHO)** and mortality in the **overall population**, as shown in Table 3.17.[51,54,58,61] Penninx et al (2006)[58] examined the relationship between anaemia and mortality in 3607 community-dwelling adults aged ≥65 years, and found that during a mean follow-up of 4.1 years, anaemia was an independent predictor of increased mortality whether or not subjects had baseline disease. The results remained consistent when the analysis was restricted to 0-2 years follow-up or from 2+ years follow-up.

The study by Izaks et al (1999)[54] assessed the association between anaemia and mortality in 755 community dwelling adults aged ≥85 years. After adjusting for various potential confounders including age, age and sex, age and sex and disease, age and sex and functional status, and age and sex excluding subjects with clinical disease, anaemia was shown to be an independent predictor of increased mortality during a 0-5 year follow-up period, with the mortality rate ranging from 1.74 to 2.21. When these analyses were repeated for the 5-10 year follow-up period, there was no significant association between anaemia and mortality.

Denny et al (2006)[51] examined the association between anaemia and mortality in 1701 community-dwelling adults aged ≥65 years. After 8 years follow-up, the results showed that anaemia is an independent risk factor for increased mortality.

Zakai et al (2005)[61] examined 5797 community-dwelling (non-institutionalised) adults aged ≥65 years in order to assess the association between anaemia and three types of mortality: all-cause mortality, cardiovascular mortality and non-cardiovascular mortality. Anaemia was shown to be an independent predictor of all-cause mortality and non-cardiovascular mortality but not cardiovascular mortality.

Table 3.17 Question 1 (elderly): Results for Level II evidence – mortality (WHO or similar anaemia criteria)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Penninx 2006 Level II *Fair*	1 prospective cohort study N=3607	Community-dwelling adults aged ≥65 years	Community US	Anaemia (WHO) vs no anaemia	Mortality (0-2 years)	NR	NR	RR 1.63 (1.23, 2.17)	*Anaemia is an independent risk factor for mortality during 0-2 years follow-up* P=0.001
						Adjusted for variables shown to be (borderline) associated with anaemia: age, sex, race, education, smoking status, BMI, coronary heart disease, chronic heart failure, diabetes, cancer, infectious disease, kidney disease and hospitalisation in past year.			
					Mortality (2+ years)	NR	NR	RR 1.51 (1.19, 1.92)	*Anaemia is an independent risk factor for mortality during 2+ years follow-up* P=0.001
						Adjusted for variables shown to be (borderline) associated with anaemia: age, sex, race, education, smoking status, BMI, coronary heart disease, chronic heart failure, diabetes, cancer, infectious disease, kidney disease and hospitalisation in past year.			
					Mortality (mean 4.1 years)	NR	NR	RR 1.63 (1.37, 1.95)	*Anaemia is an independent risk factor for mortality* P<0.001
						Adjusted for variables shown to be (borderline) associated with anaemia: age, sex, race, education, smoking status, BMI, coronary heart disease, chronic heart failure, diabetes, cancer, infectious disease, kidney disease and hospitalisation in past year.			
	1 prospective cohort study N=1538	Community-dwelling adults aged ≥65 years <u>without baseline disease</u>	Community US	Anaemia (WHO) vs no anaemia	Mortality (mean 4.1 years)	NR	NR	RR 2.12 (1.48, 3.04)	*Anaemia is an independent risk factor for mortality in subjects <u>without baseline disease</u>* P<0.001
						Adjusted for variables shown to be (borderline) associated with anaemia: age, sex, race, education, smoking status, BMI, coronary heart disease, chronic heart failure, diabetes, cancer, infectious disease, kidney disease and hospitalisation in past year.			
	1 prospective cohort study N=2069	Community-dwelling adults aged ≥65 years <u>with baseline disease</u>	Community US	Anaemia (WHO) vs no anaemia	Mortality (mean 4.1 years)	NR	NR	RR 1.43 (1.16, 1.76)	*Anaemia is an independent risk factor for mortality in subjects <u>with baseline disease</u>* P=0.001
						Adjusted for variables shown to be (borderline) associated with anaemia: age, sex, race, education, smoking status, BMI, coronary heart disease, chronic heart failure, diabetes, cancer, infectious disease, kidney disease and hospitalisation in past year.			
Izaks 1999 Level II *Fair*	1 prospective cohort study N=755	Inhabitants of Leiden, the Netherlands, aged <u>85 years and older</u> at the start of the study	Community The Netherlands	Anaemia (WHO) vs no anaemia	Mortality (0-5 years)	NR	NR	MR 1.84 (1.50, 2.25)	*Anaemia is an independent risk factor for 0-5 year mortality* P=NR
						Adjusted for: age and sex			
						NR	NR	MR 1.84 (1.49, 2.27)	*Anaemia is an independent risk factor for 0-5 year mortality* P=NR
						Adjusted for: age and sex and disease.			
						NR	NR	MR 1.74 (1.41, 2.15)	*Anaemia is an*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
						Adjusted for: age, sex and functional status.			*independent risk factor for 0-5 year mortality* P=NR
						NR	NR	MR 2.21 (1.37, 3.57)	*Anaemia is an independent risk factor for 0-5 year mortality* P=NR
						Adjusted for: age and sex and excludes patients with clinical disease.			
					Mortality (5-10 years)	NR	NR	MR 0.99 (0.56, 1.76)	*Anaemia is <u>not</u> an independent risk factor for 5-10 year mortality* P=NR
						Adjusted for: age and sex			
						NR	NR	MR 0.91 (0.50, 1.64)	*Anaemia is <u>not</u> an independent risk factor for 5-10 year mortality* P=NR
						Adjusted for: age and sex and disease.			
						NR	NR	MR 1.07 (0.74, 2.33)	*Anaemia is <u>not</u> an independent risk factor for 5-10 year mortality* P=NR
						Adjusted for: age, sex and functional status.			
						NR	NR	MR 0.64 (0.15, 2.68)	*Anaemia is <u>not</u> an independent risk factor for 5-10 year mortality* P=NR
						Adjusted for: age and sex and excludes patients with clinical disease.			
Denny 2006 Level II *Fair*	1 prospective cohort study N=1701	Community-dwelling adults aged ≥65 years[c]	Community US	Anaemia (WHO) vs no anaemia	Mortality (8 years)	NR	NR	RR 1.4 (1.2, 1.6)	*Anaemia is an independent risk factor for mortality* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			
Zakai 2005 Level II *Fair*	1 prospective cohort study N=5797	Community-dwelling (non-institutionalised) men and women aged ≥65 years	Community/US	Anaemia (WHO) vs no anaemia	Mortality (mean 11.2 years)	NR	NR	HR 1.38 (1.19, 1.59)	*Anaemia (WHO) is an independent risk factor for all-cause mortality* *P=NR*
						Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.			
					<u>Cardiovascular</u> mortality (mean 11.2 years)	NR	NR	HR 1.20 (0.96, 1.51)	*Anaemia (WHO) is <u>not</u> an independent risk factor for cardiovascular mortality* *P=NR*
						Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.			
					<u>Non-</u>	NR	NR	HR 1.53 (1.28, 1.84)	*Anaemia (WHO) is an*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
					cardiovascular mortality (mean 11.2 years)	Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.			*independent risk factor for non-cardiovascular mortality* *P=NR*

BMI, body mass index; CI, confidence interval; dL, decilitre; FVC, forced vital capacity; g, grams; GFR, glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio; NR, not reported; RR, risk ratio; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] At the time of baseline Hb measurement all subjects were aged ≥71 years.

Three studies assessed the association between **anaemia as defined by the World Health Organisation (WHO) and mortality by gender**, as shown in Table 3.18.[51,53,54] Izaks et al (1999)[54] assessed the association between anaemia and mortality in men and women aged ≥85 years followed up for 0-5 years, and showed that anaemia is an independent risk factor for increased mortality in both men and women (P<0.001 for both).

The study by Endres et al (2009)[53] analysed the relationship between anaemia and mortality in 6876 adults aged ≥65 years with a life expectancy of greater than 6 months and in 6625 adults aged ≥65 years with a life expectancy of greater than 6 months without potential occult early-stage cancer at baseline. The results of these analyses showed that anaemia was an independent risk factor for increased mortality in these two populations in men (P<0.001 and 0.002), but not in women.

Denny et al (2006)[51] examined the association between anaemia and mortality in community-dwelling adults aged ≥65 years. Analysis by gender revealed that anaemia is a significant predictor of mortality in women (RR 1.4; 95% CI 1.2, 1.8) and may be a significant predictor in men (RR 1.3; 95% CI 1.0, 1.7).

Only one study provided information of the risk of mortality associated with and without anaemia. Endres et al (2009) showed that the risk of mortality approximately doubled in elderly community-dwelling subjects. However, the absolute increase in risk was greater in men (14.4% in men without anaemia and 35.8% in men with anaemia) compared with women (8.8% in women without anaemia and 15.0% in women with anaemia).

Table 3.18 Question 1 (elderly): Results for Level II evidence – mortality (WHO or similar anaemia criteria – gender subgroup analyses)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity[b]*
ANALYSES BY GENDER									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Izaks 1999 Level II *Fair*	1 prospective cohort study N=544	Inhabitants of Leiden, the Netherlands, women aged 85 years and older at the start of the study	Community The Netherlands	Anaemia (WHO) vs no anaemia	Mortality (0-5 years)	NR	NR	MR 1.60 (1.24, 2.06)	*Anaemia is an independent risk factor for 0-5 year mortality in women* P <0.001
						Adjusted for: age			
	1 prospective cohort study N=211	Inhabitants of Leiden, the Netherlands, men aged 85 years and older at the start of the study	Community The Netherlands	Anaemia (WHO) vs no anaemia	Mortality (0-5 years)	NR	NR	MR 2.29 (1.60, 3.26)	*Anaemia is an independent risk factor for 0-5 year mortality in men* P=<0.001
						Adjusted for: age			
Endres 2009 Level II *Good*	1 prospective cohort study N=3975	Community-dwelling women, primary-care patients aged ≥65 years with life expectancy >6 months	Primary-care Germany	Anaemia (WHO) vs no anaemia	Mortality (maximum 5.3 years)	36/240 (15.0)	326/3695 (8.8)	HR 1.13 (0.79, 1.61)	*Anaemia is not an independent risk factor for mortality in women* P= 0.51
						Adjusted for medically meaningful variables and those with p<0.2 after backward selection: Age, BMI, diabetes, TC/HDL, MI, stroke, PAD, smoking, HCY, hs-CRP, eGFR, high-school graduation.			
	1 prospective cohort study N=2901	Community-dwelling men, primary-care patients aged ≥65 years with life expectancy >6 months	Primary-care Germany	Anaemia (WHO) vs no anaemia	Mortality (maximum 5.3 years)	83/232 (35.8)	379/2637 (14.4)	HR 1.89 (1.47, 2.44)	*Anaemia is an independent risk factor for mortality in men* P= <0.001
						Adjusted for medically meaningful variables and those with p<0.2 after backward selection: Age, BMI, diabetes, TC/HDL, MI, stroke, PAD, smoking, HCY, hs-CRP, eGFR, high-school graduation.			
	1 prospective cohort study N=3865	Community-dwelling women, primary-care patients aged ≥65 years with life expectancy >6 months without potential occult early-stage cancer at baseline	Primary-care Germany	Anaemia (WHO) vs no anaemia	Mortality (maximum 5.3 years)	NR	NR	HR 1.20 (0.81, 1.79)	*Anaemia is not an independent risk factor for non-cancer mortality in women* P= 0.360
						Adjusted for medically meaningful variables and those with p<0.2 after backward selection: Age, BMI, diabetes, TC/HDL, MI, stroke, PAD, smoking, HCY, hs-CRP, eGFR, high-school graduation.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 prospective cohort study N=2760	Community-dwelling men, primary-care patients a ged ≥65 years with life expectancy >6 months without potential occult early-stage cancer at baseline	Primary-care Germany	Anaemia (WHO) vs no anaemia	Mortality (maximum 5.3 years)	NR	NR	HR 1.66 (1.21, 2.27)	*Anaemia is an independent risk factor for non-cancer mortality in men* P= 0.002
						Adjusted for medically meaningful variables and those with p<0.2 after backward selection: Age, BMI, diabetes, TC/HDL, MI, stroke, PAD, smoking, HCY, hs-CRP, eGFR, high-school graduation.			
Denny 2006 Level II *Fair*	1 prospective cohort study N=1134	Community-dwelling women aged ≥65 years[c]	Community US	Anaemia (WHO) vs no anaemia	Mortality (8 years)	NR	NR	RR 1.4 (1.2, 1.8)	*Anaemia is an independent risk factor for mortality in women* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			
	1 prospective cohort study N=567	Community-dwelling men aged ≥65 years[c]	Community US	Anaemia (WHO) vs no anaemia	Mortality (8 years)	NR	NR	RR 1.3 (1.0, 1.7)	*Anaemia may be an independent risk factor for mortality in men* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			

BMI, body mass index; CI, confidence interval; dL, decilitre; eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; g, grams; GFR, glomerular filtration rate; Hb, haemoglobin; HCY, homocysteine; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction; MMSE, mini-mental state examination; NR, not reported; PAD, peripheral artery disease; RR, risk ratio; TC/HDL, total cholesterol/high-density lipoprotein cholesterol ratio; TSH, thyroid stimulating hormone; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] At the time of baseline Hb measurement all subjects were aged ≥71 years.

Three studies assessed the association between **anaemia as defined by the World Health Organisation (WHO) and mortality by race**, as shown in Table 3.19.[51,52,56]

The study by Dong et al (2008)[52] assessed the association between anaemia and mortality in 1806 adults aged ≥65 years during a mean follow-up period of 3.9 years. The results of this analysis showed that anaemia is an independent risk factor for increased mortality in both African-American and Caucasian populations.

Patel et al (2007)[56] examined the relationship between anaemia, mortality and race in 2601 adults aged 71-82 without substantial disability. There was no significant association between anaemia and mortality during up to 6 years follow-up in African-Americans, regardless of whether the analysis included the full cohort (N=1018) or only those without major disease (N=395). However, in a Caucasian population anaemia was an independent risk factor for increased mortality in both the full cohort (N=1583) and the cohort without major disease (N=537). It should be noted that these analyses were adjusted for age and sex only.

Denny et al (2006)[51] examined the association between anaemia and mortality in community-dwelling adults aged ≥65 years. Analysis by race revealed that anaemia is a significant predictor of mortality in an African-American population (RR 1.4; 95% CI 1.2, 1.8) and may be a significant predictor in a Caucasian population (RR 1.3; 95% CI 1.0, 1.6).

Patel et al (2007) provide data on the risk of mortality in an elderly population with and without anaemia. In an elderly African-American population, the risk of mortality in subjects with and without anaemia was 27.2% versus 21.9%. In the same population, excluding those with major diseases, the risk of mortality with and without anaemia was 12.7% versus 15.4%. In a Caucasian population there appeared to be a much greater effect of anaemia on mortality risk. In all elderly patients, the risk of mortality in subjects without anaemia was 15.0%, while the risk in subjects with anaemia was 32.9%. In a Caucasian population without major disease, a similar increase in risk was associated with anaemia, with the risk in subjects with and without anaemia being 25.0% and 12.0%, respectively.

Table 3.19 Question 1 (elderly): Results for Level II evidence – mortality (WHO or similar anaemia criteria – race subgroup analyses)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ANALYSES BY RACE									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Dong 2008 Level II *Fair*	1 prospective cohort study N=897	Community dwelling African-American adults aged ≥65 years	Community US	Anaemia (WHO) vs no anaemia	Mortality (mean 3.9 years)	NR	NR	HR 1.90 (1.43, 2.53)	*Anaemia is an independent risk factor for increased mortality in an African-American population* P=NR
						Adjusted for: age, sex, education, race, global cognition, income, coronary artery disease, diabetes, hypertension, stroke, cancer, hip fracture, Katz ADL, Center for Epidemiological Study of Depression scale, smoking status, self-reported health status, BMI, GFR, serum cholesterol, mean cell volume.			
	1 prospective cohort study N=909	Community dwelling Caucasian adults aged ≥65 years	Community US	Anaemia (WHO) vs no anaemia	Mortality (mean 3.9 years)	NR	NR	HR 1.85 (1.32, 2.59)	*Anaemia is an independent risk factor for increased mortality in a Caucasian population* P=NR
						Adjusted for: age, sex, education, race, global cognition, income, coronary artery disease, diabetes, hypertension, stroke, cancer, hip fracture, Katz ADL, Center for Epidemiological Study of Depression scale, smoking status, self-reported health status, BMI, GFR, serum cholesterol, mean cell volume.			
Patel 2007 Level II *Fair*	1 prospective cohort study N=1018	African-American Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability	Community US	Anaemia (WHO) vs no anaemia	Mortality (up to 6 years)	63/232 (27.2)	172/786 (21.9)	HR 1.28 (0.95, 1.70)	*Anaemia is not an independent risk factor for mortality in African-Americans* P=NR
						Adjusted for age and sex only			
	1 prospective cohort study N=1583	Caucasian Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability	Community US	Anaemia (WHO) vs no anaemia	Mortality (up to 6 years)	55/167 (32.9)	212/1416 (15.0)	HR 2.19 (1.62, 2.95)	*Anaemia is an independent risk factor for mortality in Caucasians* P=NR
						Adjusted for age and sex only			
	1 prospective cohort study N=395	African-American Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability and without major diseases	Community US	Anaemia (WHO) vs no anaemia	Mortality (up to 6 years)	9/71 (12.7)	50/324 (15.4)	HR 0.87 (0.43, 1.77)	*Anaemia is not an independent risk factor for mortality in African-Americans without major diseases* P=NR
						Adjusted for age and sex only			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 prospective cohort study N=537	Caucasian Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability and without major diseases	Community US	Anaemia (WHO) vs no anaemia	Mortality (up to 6 years)	9/36 (25.0)	60/501 (12.0)	HR 2.07 (1.01, 4.22)	*Anaemia is an independent risk factor for mortality in Caucasians without major diseases* P=NR
						Adjusted for age and sex only			
Denny 2006 Level II *Fair*	1 prospective cohort study N=765	Community-dwelling Caucasian adults aged ≥65 years[c]	Community US	Anaemia (WHO) vs no anaemia	Mortality (8 years)	NR	NR	RR 1.3 (1.0, 1.6)	*Anaemia may be an independent risk factor for mortality in a Caucasian population* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			
	1 prospective cohort study N=936	Community-dwelling African-American adults aged ≥65 years[c]	Community US	Anaemia (WHO) vs no anaemia	Mortality (8 years)	NR	NR	RR 1.4 (1.2, 1.8)	*Anaemia is an independent risk factor for mortality in an African-American population* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			

ADL, activities of daily living; BMI, body mass index; CI, confidence interval; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; GFR, glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio; NR, not reported; RR, risk ratio; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] At the time of baseline Hb measurement all subjects were aged ≥71 years.

Two studies assessed the association between **anaemia as defined by the World Health Organisation (WHO) and mortality by anaemia subtype**, as shown in Table 3.20.[54,57] Izaks et al (1999)[54] examined the association between different types of anaemia and mortality during two time periods: 0-5 years and 5-10 years. During the 0-5 year follow-up period, microcytic anaemia and normocytic anaemia were significantly associated with increased mortality, while macrocytic anaemia was not. During the 5-10 year follow-up period, only normocytic anaemia had sufficient data to perform an analysis and this showed no association with mortality.

Patel et al (2009)[57] assessed the relationship between different anaemia types in 4089 community dwelling adults aged ≥65 years. Anaemia with nutrient deficiency and anaemia with chronic inflammation were both independent risk factors for increased mortality, while anaemia with reduced kidney function (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2), anaemia with low kidney function and chronic inflammation, and unexplained anaemia were not.

Table 3.20 Question 1 (elderly): Results for Level II evidence – mortality (WHO or similar anaemia criteria – anaemia type subgroup analyses)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ANALYSES BY ANAEMIA TYPE									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Izaks 1999 Level II *Fair*	1 prospective cohort study N=617	Inhabitants of Leiden, the Netherlands, aged 85 years and older at the start of the study	Community The Netherlands	Microcytic anaemia (WHO) vs no anaemia	Mortality (0-5 years)	NR	NR	MR 1.84 (1.01, 3.35)	*Microcytic anaemia is an independent risk factor for 0-5 year mortality* P=NR
						Adjusted for: age and sex			
	1 prospective cohort study N=732	Inhabitants of Leiden, the Netherlands, aged 85 years and older at the start of the study	Community The Netherlands	Normocytic anaemia (WHO) vs no anaemia	Mortality (0-5 years)	NR	NR	MR 1.86 (1.51, 2.31)	*Normocytic anaemia is an independent risk factor for 0-5 year mortality* P=NR
						Adjusted for: age and sex			
	1 prospective cohort study N=614	Inhabitants of Leiden, the Netherlands, aged 85 years and older at the start of the study	Community The Netherlands	Macrocytic anaemia (WHO) vs no anaemia	Mortality (0-5 years)	NR	NR	MR 1.52 (0.78, 2.96)	*Macrocytic anaemia is not an independent risk factor for 0-5 year mortality* P=NR
						Adjusted for: age and sex			
	1 prospective cohort study N=617	Inhabitants of Leiden, the Netherlands, aged 85 years and older at the start of the study	Community The Netherlands	Microcytic anaemia (WHO) vs no anaemia	Mortality (5-10 years)	NR	NR	-	-
						-			
	1 prospective cohort study N=732	Inhabitants of Leiden, the Netherlands, aged 85 years and older at the start of the study	Community The Netherlands	Normocytic anaemia (WHO) vs no anaemia	Mortality (5-10 years)	NR	NR	MR 0.90 (0.52, 1.79)	*Normocytic anaemia is not an independent risk factor for 5-10 year mortality* P=NR
						Adjusted for: age and sex			
	1 prospective cohort study N=617	Inhabitants of Leiden, the Netherlands, aged 85 years and older at the start of the study	Community The Netherlands	Macrocytic anaemia (WHO) vs no anaemia	Mortality (5-10 years)	NR	NR	-	-
						-			
Patel 2009 Level II *Good*	1 prospective cohort study N=1790	Civilian, non-institutionalised population aged ≥65	Community US	Anaemia (WHO) with nutrient deficiency vs no anaemia	Mortality (12 years)	NR	NR	HR 1.73 (1.15, 2.60)	*WHO-defined anaemia + nutrient deficiency is an independent risk factor for increased mortality* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 prospective cohort study N=1743	Civilian, non-institutionalised population aged ≥65 years	Community US	Anaemia (WHO) with eGFR <60 mL/min/1.73 m^2 vs no anaemia	Mortality (12 years)	NR	NR	HR 1.14 (0.68, 1.93)	*WHO-defined anaemia + eGFR <60 mL/min/1.73m^2 is not an independent risk factor for increased mortality* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective cohort study N=1734	Civilian, non-institutionalised population aged ≥65 years	Community US	Anaemia (WHO) with chronic inflammation vs no anaemia	Mortality (12 years)	NR	NR	HR 2.48 (1.22, 5.05)	*WHO-defined anaemia + chronic inflammation is an independent risk factor for increased mortality* *P=NR*
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective cohort study N=1731	Civilian, non-institutionalised population aged ≥65 years	Community US	Anaemia (WHO) with eGFR <60 mL/min/1.73m^2 and chronic inflammation vs no anaemia	Mortality (12 years)	NR	NR	HR 1.64 (0.86, 3.14)	*WHO-defined anaemia with eGFR <60 mL/min/1.73 m^2 and chronic inflammation is not an independent risk factor for increased mortality* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective cohort study N=1748	Civilian, non-institutionalised population aged ≥65 years	Community US	Anaemia (WHO) but unexplained vs no anaemia	Mortality (12 years)	NR	NR	HR 1.61 (0.97, 2.67)	*WHO-defined anaemia of an unexplained cause is not an independent risk factor for increased mortality* *P=NR*
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; m, metre; min, minute; mL, millilitre; MR, mortality risk; NR, not reported; RR, risk ratio; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

One study assessed the association between **anaemia as defined by the World Health Organisation (WHO) and mortality by other subgroups (in this case by race and gender combined)**, as shown in Table 3.21. Patel et al (2007)[56] showed that anaemia is an independent risk factor for increased mortality in Caucasian women and Caucasian men (HR 2.68; 95% CI 1.52, 4.69 and HR 1.62; 95% CI 1.08, 2.44, respectively), while anaemia was not associated with mortality in African-American women and men. These results are consistent with their separate analyses by race, as described previously.

The unadjusted risk of mortality in each population was reported in this study. In African-American women without anaemia, the risk of mortality was 17.9% while in Caucasian women it was 12.3%. However, anaemia had a greater effect on mortality in Caucasian women, increasing to 32.7%, compared with only 22.6% in African-American women. Similar results were seen in men, with risk increasing from 28.6% in African-American men without anaemia to 33.3% in African-American men with anaemia, and from 17.8% in Caucasian men without anaemia to 33.6% in Caucasian men with anaemia. The lack of effect of anaemia in the African-American population likely reflects the fact that the definition of anaemia is this population is different to the definition in the Caucasian population.

Table 3.21 Question 1 (elderly): Results for Level II evidence – mortality (WHO or similar anaemia criteria – other subgroup analyses)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ANALYSES BY SEX AND RACE									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Patel 2007 Level II *Fair*	1 prospective cohort study N=587	African-American female Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Anaemia (WHO) vs no anaemia	Mortality (up to 6 years)	28/124 (22.6)	83/463 (17.9)	HR 1.17 (0.72, 1.89) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Anaemia is not an independent risk factor for mortality in African-American women* P=NR
	1 prospective cohort study N=745	Caucasian female Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Anaemia (WHO) vs no anaemia	Mortality (up to 6 years)	17/52 (32.7)	85/693 (12.3)	HR 2.68 (1.52, 4.69) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Anaemia is an independent risk factor for mortality in Caucasian women* P=NR
	1 prospective cohort study N=416	African-American male Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Anaemia (WHO) vs no anaemia	Mortality (up to 6 years)	35/105 (33.3)	89/311 (28.6)	HR 0.88 (0.56, 1.38) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Anaemia is not an independent risk factor for mortality in African-American men* P=NR
	1 prospective cohort study N=826	Caucasian male Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability	Community US	Anaemia (WHO) vs no anaemia	Mortality (up to 6 years)	38/113 (33.6)	127/713 (17.8)	HR 1.62 (1.08, 2.44) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Anaemia is an independent risk factor for mortality in Caucasian men* P=NR

BMI, body mass index; CI, confidence interval; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; NR, not reported; RR, risk ratio; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Hb <12.4 g/dL and 13.4 g/dL in non-Hispanic white women and men, respectively; <11.3 g/dL and <12.3 g/dL in non-Hispanic black women and men, respectively; <12.2 g/dL and <13.2 g/dL in Mexican American women and men, respectively.

Three studies assessed the association between **various Hb levels and mortality**, as shown in Table 3.22.[58,59,61] Riva et al (2009)[59] examined the relationship between mild anaemia (defined as a Hb level of 10-11.9 g/dL for women and 10-12.9 g/dL for men) and mortality during various follow-up periods (0-2 years, 2-3.5 years and 0-3.5 years). In addition, each analysis was adjusted for two sets of potential confounders: (i) age, sex, education, smoking history, BMI, diabetes, hypertension, myocardial infarction, heart failure, respiratory failure, renal failure, neurological diseases, cancer and hospitalisation; and (ii) age, sex, education, smoking history, BMI, co-morbid disease severity and hospitalisation. The results of the all analyses showed that mild anaemia is an independent risk factor for increased mortality, with HRs ranging from 1.84 to 2.01.

Pennix et al (2006)[58] assessed the association between different levels of Hb and mortality during a mean of 4.1 years of follow-up; all Hb levels were assessed relative to a Hb level 1.1-2 g/dL above the WHO anaemia cut-off of 12 g/dL for women and 13 g/dL for men. Hb levels of >1 g/dL below the WHO cut-off, 0-0.9 g/dL below the WHO cut-off and 0.1 to 1.0 g/dL above the WHO cut-off were all independent risk factors for increased mortality, with the magnitude of risk reducing as the Hb levels approach the reference Hb level (RR 1.91, RR 1.66 and RR 1.32, respectively).

The study by Zakai et al (2005)[61] analysed the association between Hb levels by quintiles and three mortality outcomes: all-cause mortality, cardiovascular mortality and non-cardiovascular mortality. When subjects with Hb levels in quintile 1 (≤12.6 g/dL for females and ≤13.7 g/dL for males) were compared with subjects with subjects with Hb levels in quintile 4 (13.9 to 14.4 g/dL for females and 15.1 to 15.6 g/dL for males), low Hb was an independent risk factor for non-cardiovascular mortality but not all-cause mortality or cardiovascular mortality. There was no significant association between Hb level and all-cause mortality when quintile 2 (12.7 to 13.2 g/dL for females and 13.8 to 14.4 g/dL for males) and quintile 3 (13.3 to 13.8 g/dL for females and 14.5 to 15.0 g/dL for males) was compared with quintile 4.

Table 3.22 Question 1 (elderly): Results for Level II evidence – mortality (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Riva 2009 Level II *Good*	1 prospective cohort study N=4470	Residents of Biella, Italy aged 65-84 years	Community Italy	Mild anaemia (women: Hb 10.0-11.9 g/dL; men: Hb 10.0-12.9 g/dL) vs no anaemia	Mortality (0-2 years)	NR	NR	HR 1.84 (1.14, 2.87)	*Mild anaemia is an independent risk factor for mortality* P=NR
						Adjusted for: age, sex, education, smoking history, BMI, diabetes, hypertension, myocardial infarction, heart failure, respiratory failure, renal failure, neurological diseases, cancer and hospitalisation.			
						NR	NR	HR 2.01 (1.25, 3.09)	*Mild anaemia is an independent risk factor for mortality* P=NR
						Adjusted for: age, sex, education, smoking history, BMI, co-morbid disease severity and hospitalisation.			
					Mortality (2-3.5 years)	NR	NR	HR 1.88 (1.20, 2.85)	*Mild anaemia is an independent risk factor for mortality* P=NR
						Adjusted for: age, sex, education, smoking history, BMI, diabetes, hypertension, myocardial infarction, heart failure, respiratory failure, renal failure, neurological diseases, cancer and hospitalisation.			
						NR	NR	HR 1.96 (1.26, 2.95)	*Mild anaemia is an independent risk factor for mortality* P=NR
						Adjusted for: age, sex, education, smoking history, BMI, co-morbid disease severity and hospitalisation.			
					Mortality (0-3.5 years)	NR	NR	HR 1.86 (1.34, 2.53)	*Mild anaemia is an independent risk factor for mortality* P=NR
						Adjusted for: age, sex, education, smoking history, BMI, diabetes, hypertension, myocardial infarction, heart failure, respiratory failure, renal failure, neurological diseases, cancer and hospitalisation.			
						NR	NR	HR 1.98 (1.44, 2.67)	*Mild anaemia is an independent risk factor for mortality* P=NR
						Adjusted for: age, sex, education, smoking history, BMI, co-morbid disease severity and hospitalisation.			
Penninx 2006 Level II *Fair*	1 prospective cohort study N=NR	Community-dwelling adults aged ≥65 years	Community US	Hb ≥1 g/dL below the WHO cut-off vs Hb 1.1-2 g/dL above the WHO cut-off	Mortality (mean 4.1 years)	NR	NR	RR 1.91 (1.44, 2.53)	*Hb ≥1 g/dL below the WHO cut-off is an independent risk factor for mortality compared with Hb 1.1-2 g/dL above the WHO cut-off* P=NR
						Adjusted for variables shown to be (borderline) associated with anaemia: age, sex, race, education, smoking status, BMI, coronary heart disease, chronic heart failure, diabetes, cancer, infectious disease, kidney disease and hospitalisation in past year.			
				Hb 0-0.9 g/dL below	Mortality (mean 4.1	NR	NR	RR 1.66 (1.30, 2.12)	*Hb 0-0.9 g/dL below the*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
				the WHO cut-off vs Hb 1.1-2 g/dL above the WHO cut-off	years)	Adjusted for variables shown to be (borderline) associated with anaemia: age, sex, race, education, smoking status, BMI, coronary heart disease, chronic heart failure, diabetes, cancer, infectious disease, kidney disease and hospitalisation in past year.			*WHO cut-off is an independent risk factor for mortality compared with Hb 1.1-2 g/dL above the WHO cut-off* P=NR
				Hb 0.1-1.0 g/dL above the WHO cut-off vs Hb 1.1-2 g/dL above the WHO cut-off	Mortality (mean 4.1 years)	NR	NR	RR 1.32 (1.08, 1.60)	*Hb 0.1-1.0 g/dL above the WHO cut-off is an independent risk factor for mortality compared with Hb 1.1-2 g/dL above the WHO cut-off* P=NR
						Adjusted for variables shown to be (borderline) associated with anaemia: age, sex, race, education, smoking status, BMI, coronary heart disease, chronic heart failure, diabetes, cancer, infectious disease, kidney disease and hospitalisation in past year.			
Zakai 2005 Level II *Fair*	1 prospective cohort study N=2300	Community-dwelling (non-institutionalised) men and women aged ≥65 years	Community/US	Quintile 1 (female: Hb ≤12.6 g/dL; male: Hb ≤13.7 g/dL) vs Quintile 4 (female: Hb 13.9 to 14.4 g/dL; male: Hb 15.1 to 15.6 g/dL)	Mortality (mean 11.2 years)	NR	NR	HR 1.33 (1.15, 1.54)	*Anaemia (Quintile 1) is an independent risk factor for mortality compared with no anaemia (Quintile 4)* *P=NR*
						Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.			
	1 prospective cohort study N=2226	Community-dwelling (non-institutionalised) men and women aged ≥65 years	Community/US	Quintile 2 (female: Hb 12.7 to 13.2 g/dL; male: Hb 13.8 to 14.4 g/dL) vs Quintile 4 (female: Hb 13.9 to 14.4 g/dL; male: Hb 15.1 to 15.6 g/dL)	Mortality (mean 11.2 years)	NR	NR	HR 1.15 (0.99, 1.33)	*Anaemia (Quintile 2) is <u>not</u> an independent risk factor for mortality compared with no anaemia (Quintile 4)* *P=NR*
						Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.			
	1 prospective cohort study N=2226	Community-dwelling (non-institutionalised) men and women aged ≥65 years	Community/US	Quintile 3 (female: Hb 13.3 to 13.8 g/dL; male: Hb 14.5 to 15.0 g/dL) vs Quintile 4 (female: Hb 13.9 to 14.4 g/dL; male: Hb 15.1 to 15.6 g/dL)	Mortality (mean 11.2 years)	NR	NR	HR 1.03 (0.89, 1.20)	*Anaemia (Quintile 3) is <u>not</u> an independent risk factor for mortality compared with no anaemia (Quintile 4)* *P=NR*
						Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.			
	1 prospective	Community-dwelling	Community/US	Quintile 1 (female:	<u>Cardiovascular</u> mortality	NR	NR	HR 1.17 (0.94, 1.46)	*Anaemia (Quintile 1)*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	cohort study N=2300	(non-institutionalised) men and women aged ≥65 years		Hb ≤12.6 g/dL; male: Hb ≤13.7 g/dL) vs Quintile 4 (female: Hb 13.9 to 14.4 g/dL; male: Hb 15.1 to 15.6 g/dL)	(mean 11.2 years)	Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.			*is <u>not</u> an independent risk factor for cardiovascular mortality compared with no anaemia (Quintile 4)* *P=NR*
					<u>Non-cardiovascular</u> mortality (mean 11.2 years)	NR	NR	HR 1.48 (1.23, 1.79)	*Anaemia (Quintile 1) is an independent risk factor for non-cardiovascular mortality compared with no anaemia (Quintile 4)* *P=NR*
						Age, sex, race, baseline cardiovascular disease, congestive heart failure, diabetes mellitus, prebaseline cancer, ankle-arm index, self-reported health status, history of cigarette smoking and FVC.			

BMI, body mass index; CI, confidence interval; dL, decilitre; FVC, forced vital capacity; g, grams; GFR, glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio; NR, not reported; RR, risk ratio; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Two studies assessed the association between **various Hb levels and mortality by gender**, as shown in Table 3.23.[50,51] Chaves et al (2004)*[50]* examined the association between different Hb levels and mortality during a median of 5 years follow-up in women aged ≥with some physical disability. Eleven different Hb categories (8 g/dL, 8.5 g/dL, 9 g/dL, 9.5 g/dL, 10 g/dL, 11 g/dL, 12.5 g/dL, 13 g/dL, 13.5 g/dL, 14 g/dL and 14.5 g/dL) were compared with a reference category of 12 g/dL, which was considered to be low-normal. When compared with the reference category, all six Hb categories below 12 g/dL were shown to be independent predictors of increased mortality. All five categories above 12 g/dL were shown to be independent predictors of decreased mortality compared with the reference category of 12 g/dL. It is important to note here that while studies were only included in the analysis if they assessed >500 subjects, in this case the subject numbers in each of the Hb subgroup categories are likely to be quite small, as there were a total of 12 Hb categories and only a total of 686 subjects included in the study.

The study by Denny et al (2006)[51] assessed the association between different Hb categories and mortality in community-dwelling adults aged ≥65 years. Hb categories assessed for women included 0-10 g/dL, 10-11 g/dL and 11-12 g/dL compared with a reference category of 12-13 g/dL, and for men included 0-10 g/dL, 10-11 g/dL, 11-12 g/dL and 12-13 g/dL compared with a reference category of 13-14 g/dL. With regards to women, the two lowest Hb categories (<10 g/dL and 10-11 g/dL) were significantly associated with increased mortality, while the Hb category 11-12 g/dL may be associated with increased mortality. In men, none of the Hb categories were significantly associated with increased mortality. A total of 567 men were included in the analysis for this study and the numbers within each of the five included Hb categories would be significantly less than this. The RRs for each of these analyses ranged from 1.2 to 1.7, and the lower 95% CIs ranged from 0.5 to 0.9. Therefore, it is possible that this analysis was underpowered to detect an association between Hb level and mortality in men.

Table 3.23 Question 1 (elderly): Results for Level II evidence – mortality (other anaemia criteria, Hb levels or change in Hb levels – gender subgroup analyses)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity[b]*
ANALYSES BY GENDER									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Chaves 2004 Level II *Fair*	1 prospective cohort study N=NR[c]	Women aged ≥65 years, a MMSE ≥18 and self-reported difficulty performing activities in two or more physical function domains	Community US	Hb 8 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 2.3 (1.3, 4.0)	*A Hb of 8 g/dL is an independent risk factor for <u>increased</u> mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			
				Hb 8.5 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 2.0 (1.2, 3.4)	*A Hb of 8.5 g/dL is an independent risk factor for <u>increased</u> mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			
				Hb 9.0 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 1.8 (1.2, 2.8)	*A Hb of 9 g/dL is an independent risk factor for <u>increased</u> mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			
				Hb 9.5 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 1.7 (1.2, 2.4)	*A Hb of 9.5 g/dL is an independent risk factor for <u>increased</u> mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
				Hb 10 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 1.5 (1.1, 2.0)	*A Hb of 10 g/dL is an independent risk factor for increased mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			
				Hb 11 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 1.2 (1.1, 1.4)	*A Hb of 11 g/dL is an independent risk factor for increased mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			
				Hb 12.5 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 0.90 (0.84, 0.97)	*A Hb of 12.5 g/dL is an independent risk factor for decreased mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			
				Hb 13.0 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 0.82 (0.71, 0.94)	*A Hb of 13 g/dL is an independent risk factor for decreased mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
				Hb 13.5 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 0.76 (0.63, 0.92)	*A Hb of 13.5 g/dL is an independent risk factor for decreased mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			
				Hb 14.0 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 0.74 (0.59, 0.92)	*A Hb of 14 g/dL is an independent risk factor for decreased mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			
				Hb 14.5 g/dL vs Hb 12 g/dL (low-normal)	Mortality (median 5 years)	NR	NR	HR 0.75 (0.57, 0.98)	*A Hb of 14.5 g/dL is an independent risk factor for decreased mortality compared with a low-normal Hb* P=NR
						Adjusted for: age, race, education, smoking status, drinking habits, coronary artery disease, congestive heart failure, peripheral artery disease, chronic or restrictive pulmonary disease, hip fracture, diabetes mellitus, lower-extremity osteoarthritis, rheumatoid arthritis, cancer, comorbidity index, MMSE, short Geriatric Depression Scale score, Short Physical battery score, creatinine clearance, FEV1, ankle-arm index, TSH, total serum cholesterol, serum albumin, serum interleukin-6 and BMI.			
Denny 2006 Level II *Fair*	1 prospective cohort study N=NR[d]	Community-dwelling women aged ≥65 years[e]	Community US	Hb 0-10 g/dL vs Hb 12-13 g/dL	Mortality (8 years)	NR	NR	RR 1.9 (1.2, 3.0)	*Hb 0-10 g/dL is an independent risk factor for mortality in women* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			
				Hb 10-11 g/dL vs Hb 12-13 g/dL	Mortality (8 years)	NR	NR	RR 2.2 (1.5, 3.1)[f]	*Hb 10-11 g/dL is an independent risk factor for mortality in women compared with Hb 12-13 g/dL* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			
				Hb 11-12 g/dL vs Hb	Mortality (8 years)	NR	NR	RR 1.2 (1.0, 1.8)	*Hb 11-12 g/dL may be an*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
				12-13 g/dL		Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			*independent risk factor for mortality in women compared with Hb 12-13 g/dL* P=NR
	1 prospective cohort study N=NR[d]	Community-dwelling <u>men</u> aged ≥65 years[e]	Community US	Hb 0-10 g/dL vs Hb 13-14 g/dL	Mortality (8 years)	NR	NR	RR 1.3 (0.5, 3.3)	*Hb 0-10 g/dL is <u>not</u> an independent risk factor mortality in men for compared with Hb 13-14 g/dL* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			
				Hb 10-11 g/dL vs Hb 13-14 g/dL	Mortality (8 years)	NR	NR	RR 1.7 (0.9, 3.3)	*Hb 10-11 g/dL is <u>not</u> an independent risk factor for mortality in men compared with Hb 13-14 g/dL* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			
				Hb 11-12 g/dL vs Hb 13-14 g/dL	Mortality (8 years)	NR	NR	RR 1.3 (0.7, 2.4)	*Hb 11-12 g/dL is <u>not</u> an independent risk factor for mortality in men compared with Hb 13-14 g/dL* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			
				Hb 12-13 g/dL vs Hb 13-14 g/dL	Mortality (8 years)	NR	NR	RR 1.2 (0.9, 1.7)	*Hb 12-13 g/dL is <u>not</u> an independent risk factor for mortality in men compared with Hb 13-14 g/dL* P=NR
						Adjusted for: age, education, BMI, GFR, hospitalisation, institutionalisation and health condition.			

BMI, body mass index; CI, confidence interval; dL, decilitre; eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; g, grams; GFR, glomerular filtration rate; Hb, haemoglobin; HCY, homocysteine; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction; MMSE, mini-mental state examination; NR, not reported; PAD, peripheral artery disease; RR, risk ratio; TC/HDL, total cholesterol/high-density lipoprotein cholesterol ratio; TSH, thyroid stimulating hormone; US, United States of America; WHO, World Health Organisation.
Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.
[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Total study includes 686 women.
[d] Total study includes 1134 women and 567 men.
[e] At the time of baseline Hb measurement all subjects were aged ≥71 years.
[f] Different RRs shown in the table (2.2) and text (2.1) of this publication. The table RR has been used here.

Two studies assessed the association between **various Hb levels and mortality by race**, as shown in Table 3.24.[52,57] Dong et al (2008)[52] assessed the association between different Hb levels below the WHO anaemia cut-off (12 g/dL for women and 13 g/dL for men) and mortality during a mean follow-up of 3.9 years. In an African-American population, a Hb level >1 g/dL below the WHO cut-off was an independent predictor of increased mortality compared with a Hb level 1-1.2 g/dL above the WHO cut-off, while a Hb level 0-0.9 g/dL below the WHO cut-off was not an independent predictor if mortality. In a Caucasian population both Hb levels below the WHO cut-off were independent predictors for increased mortality.

The study by Patel et al (2009)[57] also examined the relationship between different Hb levels relative to the WHO cut-off and mortality, in this case during 12 years of follow-up. Four Hb categories relative to the WHO cut-off (>1.0 g/dL below, 0.51-1 g/dL below, 0.01-0.5 g/dL below and 0-0.99 g/dL below) were compared with a reference category of 1.0-1.9 g/dL above the WHO cut-off in three populations: Caucasians, African-Americans and Hispanics. In a Caucasian population, all four categories below the WHO cut-off were associated with a significant increased risk of mortality compared with the reference category. In the African-American and Hispanic populations, only a Hb level of >1 g/dL below the WHO cut-off was significantly associated with an increased risk of mortality compared with the reference Hb level. However, the subject numbers included in the analyses for these populations were small, ranging from 237 to 427 for the African-American population and 18 to 347 for the Hispanic population. Patel et al (2009) conclude that “the Hb threshold below which mortality rises significantly is a full g/dL lower in [African-Americans] than in [Caucasians] and [Hispanics]” and suggest that a revised definition of anaemia is needed that takes race into account.

Table 3.24 Question 1 (elderly): Results for Level II evidence – mortality (other anaemia criteria, Hb levels or change in Hb levels – race subgroup analyses)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity[b]*
ANALYSES BY RACE									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Dong 2008 Level II *Fair*	1 prospective cohort study N=NR	Community dwelling African-American adults aged ≥65 years	Community US	Hb >1 g/dL below the WHO cut-off vs Hb 1.1-2 g/dL above the WHO cut-off	Mortality (mean 3.9 years)	NR	NR	HR 1.95 (1.24, 3.06) Adjusted for: age, sex, education, race, global cognition, income, coronary artery disease, diabetes, hypertension, stroke, cancer, hip fracture, Katz ADL, Center for Epidemiological Study of Depression scale, smoking status, self-reported health status, BMI, GFR, serum cholesterol, mean cell volume.	*Hb >1 g/dL below the WHO cut-off is an independent risk factor for increased mortality compared with Hb 1.1-2 g/dL above the WHO cut-off in an African-American population* P=NR
		Community dwelling Caucasian adults aged ≥65 years	Community US	Hb >1 g/dL below the WHO cut-off vs Hb 1.1-2 g/dL above the WHO cut-off	Mortality (mean 3.9 years)	NR	NR	HR 2.17 (1.28, 3.65) Adjusted for: age, sex, education, race, global cognition, income, coronary artery disease, diabetes, hypertension, stroke, cancer, hip fracture, Katz ADL, Center for Epidemiological Study of Depression scale, smoking status, self-reported health status, BMI, GFR, serum cholesterol, mean cell volume.	*Hb >1 g/dL below the WHO cut-off is an independent risk factor for increased mortality compared with Hb 1.1-2 g/dL above the WHO cut-off in a Caucasian population* P=NR
		Community dwelling African-American adults aged ≥65 years	Community US	Hb 0-0.9 g/dL below the WHO cut-off vs Hb 1.1-2 g/dL above the WHO cut-off	Mortality (mean 3.9 years)	NR	NR	HR 1.35 (0.88, 2.05) Adjusted for: age, sex, education, race, global cognition, income, coronary artery disease, diabetes, hypertension, stroke, cancer, hip fracture, Katz ADL, Center for Epidemiological Study of Depression scale, smoking status, self-reported health status, BMI, GFR, serum cholesterol, mean cell volume.	*Hb 0-0.9 g/dL below the WHO cut-off is not an independent risk factor for increased mortality compared with Hb 1.1-2 g/dL above the WHO cut-off in an African-American population* P=NR
		Community dwelling Caucasian adults aged ≥65 years	Community US	Hb 0-0.9 g/dL below the WHO cut-off vs Hb 1.1-2 g/dL above the WHO cut-off	Mortality (mean 3.9 years)	NR	NR	HR 2.14 (1.39, 3.30) Adjusted for: age, sex, education, race, global cognition, income, coronary artery disease, diabetes, hypertension, stroke, cancer, hip fracture, Katz ADL, Center for Epidemiological Study of Depression scale, smoking status, self-reported health status, BMI, GFR, serum cholesterol, mean cell volume.	*Hb 0-0.9 g/dL below the WHO cut-off is an independent risk factor for increased mortality compared with Hb 1.1-2 g/dL above the WHO cut-off in a Caucasian population* P=NR

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Patel 2009 Level II *Good*	1 prospective cohort study N=1018	Civilian, non-institutionalised population aged ≥65 years who identified their race as Caucasian	Community US	Hb >1.0 g/dL below the WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	Mortality (12 years)	NR	NR	HR 2.11 (1.51, 2.94) Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.	*A Hb level >1 g/dL below the WHO cut-off is an independent risk factor for mortality in a Caucasian population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
	1 prospective cohort study N=994	Civilian, non-institutionalised population aged ≥65 years who identified their race as Caucasian	Community US	Hb 0.51-1 g/dL below the WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	Mortality (12 years)	NR	NR	HR 2.04 (1.47, 2.84) Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.	*A Hb level 0.51-1 g/dL below the WHO cut-off is an independent risk factor for mortality in a Caucasian population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
	1 prospective cohort study N=1040	Civilian, non-institutionalised population aged ≥65 years who identified their race as Caucasian	Community US	Hb 0.01-0.5 g/dL below the WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	Mortality (12 years)	NR	NR	HR 1.43 (1.07, 1.92) Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.	*A Hb level 0.01-0.5 g/dL below the WHO cut-off is an independent risk factor for mortality in a Caucasian population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
	1 prospective cohort study N=1481	Civilian, non-institutionalised population aged ≥65 years who identified their race as Caucasian	Community US	Hb 0-0.99 g/dL below the WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	Mortality (12 years)	NR	NR	HR 1.24 (1.03, 1.51) Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.	*A Hb level 0.00-0.99 g/dL below the WHO cut-off is an independent risk factor for mortality in a Caucasian population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
	1 prospective	Civilian, non-	Community	Hb >1 g/dL below the	Mortality (12	NR	NR	HR 2.07 (1.26, 3.39)	*A Hb level >1 g/dL below*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	cohort study N=274	institutionalised population aged ≥65 years who identified their race as African-American	US	WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	years)	Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			*the WHO cut-off is an independent risk factor for mortality in an African-American population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
	1 prospective cohort study N=237	Civilian, non-institutionalised population aged ≥65 years who identified their race as African-American	Community US	Hb 0.51-1 g/dL below the WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	Mortality (12 years)	NR	NR	HR 1.33 (0.82, 2.18)	*A Hb level 0.51-1 g/dL below the WHO cut-off is not an independent risk factor for mortality in an African-American population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective cohort study N=265	Civilian, non-institutionalised population aged ≥65 years who identified their race as African-American	Community US	Hb 0.01-0.5 g/dL below the WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	Mortality (12 years)	NR	NR	HR 0.73 (0.45, 1.19)	*A Hb level 0.01-0.5 g/dL below the WHO cut-off is not an independent risk factor for mortality in an African-American population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective cohort study N=427	Civilian, non-institutionalised population aged ≥65 years who identified their race as African-American	Community US	Hb 0-0.99 g/dL below the WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	Mortality (12 years)	NR	NR	HR 0.80 (0.57, 1.12)	*A Hb level 0.00-0.99 g/dL below the WHO cut-off is not an independent risk factor for mortality in an African-American population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective	Civilian, non-	Community	Hb >1 g/dL below the	Mortality (12	NR	NR	HR 4.56 (2.23, 9.31)	*A Hb level >1 g/dL below*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	cohort study N=28	institutionalised population aged ≥65 years who identified their race as Hispanic	US	WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	years)	Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			*the WHO cut-off is an independent risk factor for mortality in a Hispanic population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
	1 prospective cohort study N=18	Civilian, non-institutionalised population aged ≥65 years who identified their race as Hispanic	Community US	Hb 0.51-1 g/dL below the WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	Mortality (12 years)	NR	NR	HR 1.47 (0.59, 3.65)	*A Hb level 0.51-1 g/dL below the WHO cut-off is not an independent risk factor for mortality in a Hispanic population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective cohort study N=246	Civilian, non-institutionalised population aged ≥65 years who identified their race as Hispanic	Community US	Hb 0.01-0.5 g/dL below the WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	Mortality (12 years)	NR	NR	HR 1.38 (0.73, 2.62)	*A Hb level 0.01-0.5 g/dL below the WHO cut-off is not an independent risk factor for mortality in a Hispanic population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective cohort study N=347	Civilian, non-institutionalised population aged ≥65 years who identified their race as Hispanic	Community US	Hb 0-0.99 g/dL below the WHO cut-off vs 1.0-1.99 g/dL above the WHO cut-off	Mortality (12 years)	NR	NR	HR 1.54 (0.91, 2.60)	*A Hb level 0.00-0.99 g/dL below the WHO cut-off is not an independent risk factor for mortality in a Hispanic population compared with a Hb level 1.0-1.99 g/dL above the WHO cut-off* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			

ADL, activities of daily living; BMI, body mass index; CI, confidence interval; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; GFR, glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio; NR, not reported; RR, risk ratio; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] At the time of baseline Hb measurement all subjects were aged ≥71 years.

One study assessed the association between **various Hb levels and mortality by anaemia subtype**, as shown in Table 3.25. Riva et al (2009)[59] examined the relationship between the anaemia of chronic disease and mortality over 3.5 years of follow-up. The results of this study suggest that anaemia of chronic disease (with or without β-thalassemia minor) is an independent risk factor for increased mortality. It should be noted that while this study was rated as good quality overall, for this outcome the quality is likely to be lower, as it is unclear how many subjects were included in the analyses and it is possible that there were only 13 subjects included in the analysis excluding subjects with β-thalassemia.

Table 3.25 Question 1 (elderly): Results for Level II evidence – mortality (other anaemia criteria, Hb levels or change in Hb levels – anaemia type subgroup analyses)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ANALYSES BY ANAEMIA TYPE									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Riva 2009 Level II *Good*[c]	1 prospective cohort study N=NR[c]	Residents of Biella, Italy aged 65-84 years	Community Italy	Mild anaemia of chronic disease vs no anaemia	Mortality (0-3.5 years)	NR	NR	HR 5.44 (3.53, 8.06)	*Mild anaemia of chronic disease is an independent risk factor for mortality* P=NR
						Fully adjusted (no further details reported)			
				Mild anaemia of chronic disease (excluding β-thalassemia minor) vs no anaemia	Mortality (0-3.5 years)	NR	NR	HR 2.18 (1.56, 2.99)	*Mild anaemia of chronic disease (excluding β-thalassemia minor) is an independent risk factor for mortality* P=NR
						Fully adjusted (no further details reported)			

CI, confidence interval; Hb, haemoglobin; HR, hazard ratio; NR, not reported;

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] The subject number included in these analyses is unclear so study could be considered to be fair or poor quality for this subgroup analysis. According to the baseline characteristics table, 943 subjects had anaemia of chronic disease (including iron deficiency) and 930 had β-thalassemia minor. If this is the case, it would mean there are only 13 subjects included in the second analysis.

Two studies assessed the association between **various Hb levels and mortality by other subgroups**, as shown in Table 3.26.[56,57] Patel et al (2007)[56] analysed the relationship between different Hb levels and mortality during up to 6 years of follow-up by gender and race subgroups. The results of the analysis showed that low Hb (defined as <11 g/dL and 11 to 11.9 g/dL) was an independent risk factor for increased mortality compared with Hb 12 to 12.9 g/dL in Caucasian women but not African-American women. Similarly Hb levels of <11 g/dL and 11-11.9 g/dL were independent risk factor for increased mortality in Caucasian men, compared with a Hb level of 13 to 13.9 g/dL, while there was no significant association for these levels in African-American men. There was no significant association between a Hb level of 12 to 12.9 g/dL and mortality in either African-American men or Caucasian men.

As described previously, Patel et al (2009)[57] concluded that a revised definition of anaemia taking into account race should be developed. In light of this, Patel (et al 2009) repeated their analyses of anaemia by subtype using race-specific anaemia criteria. These criteria were as follows: Hb <12.4 g/dL and <13.4 g/dL in Caucasian women and men, respectively; <11.3 g/dL and 12.3 g/dL in African-American women and men, respectively; and <12.2 g/dL and 13.2 g/dL in Hispanic women and men, respectively. There was a significant association between ethnicity-specific /chronic inflammation anaemia and increased 12-year mortality, as well as ethnicity-specific /unexplained anaemia and increased 12-year mortality. There was no association between ethnicity-specific anaemia/other types of anaemia (nutrient deficiency, reduced kidney function and reduced kidney function + chronic inflammation) and 12-year mortality.

Table 3.26 Question 1 (elderly): Results for Level II evidence – mortality (other anaemia criteria, Hb levels or change in Hb levels – other subgroup analyses)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ANALYSES BY GENDER, RACE AND ANAEMIA TYPE									
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Patel 2007 Level II *Fair*	1 prospective cohort study N=234	African-American female Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Hb <11.0 g/dL vs Hb 12.0-12.9 g/dL	Mortality (up to 6 years)	4/29 (13.8)	29/205 (14.1)	HR 0.77 (0.26, 2.25) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Hb <11.0 g/dL is not an independent risk factor for mortality compared with Hb 12.0-12.9 g/dL in African-American women* P=NR
	1 prospective cohort study N=300	African-American female Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Hb 11.0-11.9 g/dL vs Hb 12.0-12.9 g/dL	Mortality (up to 6 years)	24/95 (25.3)	29/205 (14.1)	HR 1.66 (0.92, 3.00) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Hb 11.0-11.9 g/dL is not an independent risk factor for mortality compared with Hb 12.0-12.9 g/dL in African-American women* P=NR
	1 prospective cohort study N=185	Caucasian female Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Hb <11.0 g/dL vs Hb 12.0-12.9 g/dL	Mortality (up to 6 years)	9/16 (56.3)	17/169 (10.1)	HR 3.70 (1.55, 8.85) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Hb <11.0 g/dL is an independent risk factor for mortality compared with Hb 12.0-12.9 g/dL in Caucasian women* P=NR
	1 prospective cohort study N=206	Caucasian female Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Hb 11.0-11.9 g/dL vs Hb 12.0-12.9 g/dL	Mortality (up to 6 years)	8/37 (21.6)	17/169 (10.1)	HR 2.90 (1.22, 6.90) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Hb 11.0-11.9 g/dL is an independent risk factor for mortality compared with Hb 12.0-12.9 g/dL in Caucasian women* P=NR
	1 prospective cohort study N=162	African-American male Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Hb <11.0 g/dL vs Hb 13.0-13.9 g/dL	Mortality (up to 6 years)	11/20 (55.0)	48/142 (33.8)	HR 1.74 (0.85, 3.57) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Hb <11.0 g/dL is not an independent risk factor for mortality compared with Hb 13.0-13.9 g/dL in African-American men* P=NR

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 prospective cohort study N=206	African-American male Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Hb 11.0-11.9 g/dL vs Hb 13.0-13.9 g/dL	Mortality (up to 6 years)	7/24 (29.2)	48/142 (33.8)	HR 0.43 (0.17, 1.08) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Hb 11.0-11.9 g/dL is not an independent risk factor for mortality compared with Hb 13.0-13.9 g/dL in African-American men* P=NR
	1 prospective cohort study N=162	African-American male Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Hb 21.0-12.9 g/dL vs Hb 13.0-13.9 g/dL	Mortality (up to 6 years)	17/64 (26.6)	48/142 (33.8)	HR 0.67 (0.37, 1.21) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Hb 12.0-12.9 g/dL is not an independent risk factor for mortality compared with Hb 13.0-13.9 g/dL in African-American men* P=NR
	1 prospective cohort study N=162	Caucasian male Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Hb <11.0 g/dL vs Hb 13.0-13.9 g/dL	Mortality (up to 6 years)	4/8 (50.0)	35/174 (20.1)	HR 3.19 (1.04, 9.84) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Hb <11.0 g/dL is an independent risk factor for mortality compared with Hb 13.0-13.9 g/dL in Caucasian men* P=NR
	1 prospective cohort study N=197	Caucasian male Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Hb 11.0-11.9 g/dL vs Hb 13.0-13.9 g/dL	Mortality (up to 6 years)	12/23 (52.2)	35/174 (20.1)	HR 2.23 (1.04, 4.76) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Hb 11.0-11.9 g/dL is an independent risk factor for mortality compared with Hb 13.0-13.9 g/dL in Caucasian men* P=NR
	1 prospective cohort study N=197	Caucasian male Medicare beneficiaries living in designated areas of Pittsburgh and Memphis aged 71-82 without substantial disability;	Community US	Hb 21.0-12.9 g/dL vs Hb 13.0-13.9 g/dL	Mortality (up to 6 years)	22/83 (26.5)	35/174 (20.1)	HR 1.20 (0.69, 2.08) Adjusted for: age, sex, level of education, study site, BMI, smoking status, hospitalisation, albumin, creatinine, cystatin C, eGFR, cancer, cerebrovascular disease, congestive heart failure, coronary heart disease, diabetes, gastrointestinal bleed/ulcer, hypertension, peripheral arterial disease, pulmonary disease.	*Hb 12.0-12.9 g/dL is not an independent risk factor for mortality compared with Hb 13.0-13.9 g/dL in white men* P=NR
Patel 2009	1 prospective	Civilian, non-	Community	Anaemia (ethnicity-	Mortality (12	NR	NR	HR 1.53 (0.99, 2.04)	*Ethnicity-specific*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Level II *Good*	cohort study N=1764	institutionalised population aged ≥65 years	US	specific)[c] with nutrient deficiency vs no anaemia	years)	Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			*anaemia with nutrient deficiency is <u>not</u> associated with an increased risk of mortality* P=NR
	1 prospective cohort study N=1716	Civilian, non-institutionalised population aged ≥65 years	Community US	Anaemia (ethnicity-specific)[c] with eGFR <60 mL/min/1.73 m^2 vs no anaemia	Mortality (12 years)	NR	NR	HR 1.43 (0.94, 2.16)	*Ethnicity-specific anaemia with eGFR <60 mL/min/1.73 m^2 is <u>not</u> is not an independent risk factor for increased mortality* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective cohort study N=1696	Civilian, non-institutionalised population aged ≥65 years	Community US	Anaemia (ethnicity-specific)[c] with chronic inflammation vs no anaemia	Mortality (12 years)	NR	NR	HR 2.40 (1.28, 4.51)	*Ethnicity-specific anaemia with chronic inflammation is an independent risk factor for increased mortality* *P=NR*
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective cohort study N=1700	Civilian, non-institutionalised population aged ≥65 years	Community US	Anaemia (ethnicity-specific)[c] with eGFR <60 mL/min/1.73m^2 and chronic inflammation vs no anaemia	Mortality (12 years)	NR	NR	HR 1.66 (0.96, 2.88)	*Ethnicity-specific anaemia with eGFR <60 mL/min/1.73 m^2 and chronic inflammation is <u>not</u> an independent risk factor for increased mortality* P=NR
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			
	1 prospective cohort study N=1722	Civilian, non-institutionalised population aged ≥65 years	Community US	Anaemia (ethnicity-specific)[c] but unexplained vs no anaemia	Mortality (12 years)	NR	NR	HR 1.73 (1.08, 2.79)	*Ethnicity-specific anaemia of an unexplained cause is an independent risk factor for increased mortality* *P=NR*
						Adjusted for: age, sex, education, poverty to income ratio, BMI, smoking status, C reactive protein level, cancer, congestive heart failure, heart attack, pulmonary disease, eGFR, rheumatoid arthritis, stroke and mobility limitations.			

BMI, body mass index; CI, confidence interval; dL, decilitre; eGFR, estimated glomerular filtration rate; g, grams; Hb, haemoglobin; HR, hazard ratio; NR, not reported; RR, risk ratio; US, United States of America; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Hb <12.4 g/dL and 13.4 g/dL in Caucasian women and men, respectively; <11.3 g/dL and <12.3 g/dL in African-American women and men, respectively; <12.2 g/dL and <13.2 g/dL in Hispanic women and men, respectively.

Anaemia as an independent risk factor for stroke/MI

No studies were identified which presented data on stroke/MI.

Anaemia as an independent risk factor for functional/performance status

Two studies assessed the association between **anaemia or various Hb levels and functional/performance status** using validated quality of life instruments.[55,60] Lucca et al (2008)[55] used the Short-Form health survey (SF-12), the Functional Assessment of Cancer Therapy–Anaemia questionnaire (FACT) and the Instrumental Activities of Daily Living scale (IADL) to assess the relationship between mild anaemia and quality of life/functional ability. Mild anaemia was defined in two ways: (i) using WHO criteria (Hb 10-11.9 g/dL for women and 10-12.9 g/dL for men; see Table 3.27); and (ii) using modified criteria (Hb 10-12.1 g/dL for women and 10.13.1 g/dL for men; see Table 3.28). Mild anaemia, as measured by the WHO criteria, was found to be potentially associated with an SF-12 Physical score of <40, and significantly associated with disease-specific measures of quality of life including the FACT-An Anaemia and Fatigue scales. When mild anaemia was defined as being 0.2 g/dL higher than the WHO criteria, mild anaemia was significantly associated with the SF-12 Physical score (both mean scores and scores <40), and the FACT-An Anaemia and Fatigue scores.

The study by Thein et al (2009)[60] assessed the association between different Hb levels and quality of life and physical function using the Short Form-36 Health Survey (SF-36), FACIT-Anaemia (FACIT-An) and the IADL. As shown in Table 3.28, when a Hb level of <12 g/dL was compared with a Hb level of ≥15 g/dL, lower Hb was significantly associated with a reduced SF-36 Physical component score and the following SF-36 subscale scores: physical functioning, role physical, body pain, general health, vitality, social functioning and mental health. Using these Hb level comparisons, low Hb was also significantly associated with lower FACIT Anaemia and Fatigue scores. When a range of Hb categories were compared with various quality of life and functional scales, declining Hb levels were associated with reduced SF-36 physical and mental component scores, reduced SF-36 subscale scores (including physical functioning, role physical, body pain, general health, vitality, social functioning and role emotional), reduced FACIT Anaemia and Fatigue scores, and worsening functional ability (increasing IADL scores).

Summary

The majority of results presented for the elderly population suggest that anaemia/low Hb is an independent risk factor for mortality. Where no significant association between anaemia/low Hb was found, this was often when the Hb levels were not sufficiently low (eg, Hb levels corresponding to mild or negligible anaemia) or where the outcome was limited to cardiovascular mortality. There were also a number of results showing no significant association between anaemia/low Hb and mortality relating to gender (no association in men or women in different studies) or different subtypes of anaemia (ie, no association in macrocytic anaemia or anaemia associated with reduced kidney function).

There were mixed results for mortality according to race. There were fewer significant associations in an African-American population than a Caucasian population using the WHO definition of anaemia. When different Hb cut-offs were assessed, a lower cut-off showed a significant association in an African-American and Hispanic population than in a Caucasian population. Based on these results, the authors of this study suggest that a revised definition of anaemia is needed that takes race into account.

This difference by race was also seen in the assessment of mobility disability, where significant associations were seen only for the Caucasian population and not the African-American population; however, it should be noted that this analysis looked only at the WHO definition of anaemia and not other potential Hb cut-offs.

The two studies that assessed functional/performance status showed that low Hb was associated with worse disease-specific quality of life (i.e. anaemia and fatigue subscales of the FACT-An scale). One study also suggested worse QoL using a number of the SF-36 subscales and worse function based on the IADL; however, this study used a reference Hb value of >15 g/dL that is considered to be at the high end of normal.

Table 3.27 Question 1 (elderly): Results for Level II evidence – functional/performance status (WHO anaemia criteria)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor Mean ± SD or n/N (%)	No risk factor Mean ± SD or n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity[b]*
Lucca 2008 *Good*	1 cross-sectional cohort study N=717	Residents of Biella, Italy, aged 65-84 without neurological or psychiatric disease, severe sensory deficits, renal insufficiency, severe organ insufficiency, terminal illness, hospitalisation, institutionalisation and illiteracy	Community Italy	Mild anaemia (WHO)[c] vs no anaemia	SF-12 Physical (0-100 scale)	45.3 ± 10.0	47.3 ± 8.7	NR	Mild anaemia is <u>not</u> an independent risk factor for a lower mean SF-12-Physical score compared with no anaemia P=0.1650
						Adjusted for: oncologic status, age, sex, education, Geriatric Depression Scale, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					SF-12 Physical score <40	29.9%	19.5%	NR	Mild anaemia <u>may</u> be an independent risk factor for SF-12-Physical score <40 compared with no anaemia P=0.0665
						Adjusted for: oncologic status, age, sex, education, Geriatric Depression Scale hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					SF-12 Mental (0-100 scale)	52.5 ± 8.6	51.8 ± 9.1	NR	Mild anaemia is <u>not</u> an independent risk factor for a lower mean SF-12-Mental score compared with no anaemia P=0.0991
						Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					SF-12 Mental score <40	9.2%	11.3%	NR	Mild anaemia is <u>not</u> an independent risk factor for SF-12-Mental score <40 compared with no anaemia P=0.1323
						Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					FACT-An (0-188 scale)	136.7 ± 21.5	141.0 ± 18.3	NR	Mild anaemia is <u>not</u> an independent risk factor for a lower mean FACT-An score compared with no anaemia P=0.1770
						Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					FACT-General (0-108 scale)	73.8 ± 12.9	75.8 ± 12.2	NR	Mild anaemia is <u>not</u> an independent risk factor for a lower mean FACT-General score compared with no anaemia P=0.4003
						Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					FACT-An Anaemia	62.7 ± 10.2	65.1 ± 7.8	NR	*Mild anaemia is an*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor Mean ± SD or n/N (%)	No risk factor Mean ± SD or n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
					(0-80 scale)	Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			*independent risk factor for a lower mean FACT-An Anaemia score compared with no anaemia* P=0.0456
					FACT-An Fatigue (0-52 scale)	41.5 ± 7.7	43.4 ± 5.8	NR	Mild anaemia is an independent risk factor for a lower mean FACT-An Fatigue score compared with no anaemia P=0.0109
						Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					IADL (disability >5%))	20.1%	11.2%	NR	Mild anaemia is not an independent risk factor for disability >5% measured by the IADL P=0.1966
						Adjusted for: oncologic status, age, sex, education, Geriatric Depression Scale hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			

An, anaemia; CI, confidence interval; FACT, Functional Assessment of cancer Therapy; IADL, Instrumental Activities of Daily Living; NR, not reported; SF-12, Short-Form-12; WHO, World Health Organisation.
Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.
[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.
[c] Defined as a Hb of 10-11.9 g/dL for women and 10-12.9 g/dL for men

Table 3.28 Question 1 (elderly): Results for Level II evidence – functional/performance status (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor Mean ± SD or n/N (%)	No risk factor Mean ± SD or n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Lucca 2008 *Good*	1 cross-sectional cohort study N=717	Residents of Biella, Italy, aged 65-84 without neurological or psychiatric disease, severe sensory deficits, renal insufficiency, severe organ insufficiency, terminal illness, hospitalisation, institutionalisation and illiteracy	Community Italy	Mild anaemia (modified)[c] vs no anaemia	SF-12 Physical (0-100)	44.9 ± 10.1	47.6 ± 8.5	NR	Mild anaemia is an independent risk factor for a lower mean SF-12-Physical score compared with no anaemia P=0.0295
						Adjusted for: oncologic status, age, sex, education, Geriatric Depression Scale hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					SF-12 Physical score <40	31.7%	18.6%	NR	Mild anaemia is an independent risk factor for SF-12-Physical score <40 compared with no anaemia P=0.0128
						Adjusted for: oncologic status, age, sex, education, Geriatric Depression Scale hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					SF-12 Mental (0-100)	52.2 ± 9.7	51.9 ± 9.0	NR	Mild anaemia is <u>not</u> an independent risk factor for a lower mean SF-12-Mental score compared with no anaemia P=0.1847
						Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					SF-12 Mental score <40	10.0%	11.3%	NR	Mild anaemia is not an independent risk factor for SF-12-Mental score <40 compared with no anaemia P=0.1323
						Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					Fact-An (0-188)	136.3 ± 21.6	141.2 ± 21.6	NR	Mild anaemia is not an independent risk factor for a lower mean FACT-An score compared with no anaemia P=0.0830
						Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					Fact-General (0-108)	73.7 ± 13.0	75.9 ± 12.1	NR	Mild anaemia is not an independent risk factor for a lower mean FACT-General score compared with no anaemia P=0.2942
						Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					Fact-An anaemia	62.5 ± 10.3	65.3 ± 7.6	NR	Mild anaemia is an

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor Mean ± SD or n/N (%)	No risk factor Mean ± SD or n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
					(0-80)	Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			independent risk factor for a lower mean FACT-An anaemia score compared with no anaemia P=0.0099
					Fact-An fatigue (0-52)	41.4 ± 7.8	43.5 ± 5.6	NR	Mild anaemia is an independent risk factor for a lower mean FACT-An fatigue score compared with no anaemia P=0.0032
						Adjusted for: oncologic status, age, sex, education, hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
					IADL (disability >5%))	20.0%	10.9%	NR	Mild anaemia is <u>not</u> an independent risk factor for disability >5% measured by the IADL P=0.2042
						Adjusted for: oncologic status, age, sex, education, Geriatric Depression Scale hypertension, diabetes, heart failure, myocardial infarction, respiratory failure, neurologic disorders.			
Thein 2009 *Fair*	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	SF-36 Physical component score (0-100)	39.2 ± 1.1	45.6 ± 1.4	NR	Hb <12 g/dL is an independent risk factor for reduced SF-36 Physical Component Score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	SF-36 Physical component score (0-100)	39.2 ± 1.1; 42.3 ± 1.0; 43.7 ± 1.0; 44.3 ±1.1; 45.6 ± 1.4		NR	Declining Hb level is an independent risk factor for declining SF-36 Physical Component Score P trend=0.002
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	SF-36 Mental component score (0-100)	51.6 ± 1.2	56.1 ± 1.5	NR	Hb <12 g/dL is an independent risk factor for reduced SF-36 Mental Component Score compared with Hb ≥15 g/dL P<0.05
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor Mean ± SD or n/N (%)	No risk factor Mean ± SD or n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 Prospective cross-sectional survey N=328	transplant, or recipient of blood transfusion or erythropoietin within 3 months		Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	SF-36 Mental component score (0-100)	51.6 ± 1.2; 53.4 ± 1.1; 54.1 ± 1.1; 52.8 ±1.2; 56.1 ± 1.5		NR	Declining Hb level is not an independent risk factor for declining SF-36 Mental Component Score P trend=0.077
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	SF-36 Physical functioning subscale (0-100)	51.4 ± 3.3	66.6 ± 4.2	NR	Hb <12 g/dL is an independent risk factor for reduced SF-36 Physical Functioning Subscale score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	SF-36 Physical functioning subscale (0-100)	51.4 ± 3.3; 62.2 ± 3.0; 63.2 ± 2.9; 66.9 ±3.2; 66.6 ± 4.2		NR	Declining Hb level is an independent risk factor for declining SF-36 Physical Functioning Subscale score P trend=0.002
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	SF-36 Role physical subscale (0-100)	48.9 ± 5.0	77.2 ± 6.4	NR	Hb <12 g/dL level is an independent risk factor for reduced SF-36 Role Physical Subscale score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	SF-36 Role physical subscale (0-100)	48.9 ± 5.0; 52.2 ± 4.6; 64.2 ± 4.4; 61.7 ± 5.0; 77.2 ± 6.4		NR	Declining Hb level is an independent risk factor for declining SF-36 Role Physical Subscale score P trend=0.001
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	SF-36 Body pain subscale (0-100)	59.3 ± 2.9	73.4 ± 3.7	NR	Hb <12 g/dL is an independent risk factor for reduced SF-36 Body Pain Subscale score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor Mean ± SD or n/N (%)	No risk factor Mean ± SD or n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 Prospective cross-sectional survey N=328	transplant, or recipient of blood transfusion or erythropoietin within 3 months		Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	SF-36 Body pain subscale (0-100)	59.3 ± 2.9; 64.9 ± 2.7; 67.2 ± 2.5; 65.1 ± 2.8; 73.4 ± 3.7		NR	Declining Hb level is an independent risk factor for declining SF-36 Body Pain Subscale score P trend=0.011
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	SF-36 General health subscale (0-100)	58.3 ± 2.4	78.7 ± 3.1	NR	Hb <12 g/dL is an independent risk factor for reduced SF-36 General Health Subscale score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	SF-36 General health subscale (0-100)	58.3 ± 2.4; 66.6 ± 2.3; 67.0 ± 2.1; 70.1 ± 2.4; 78.7 ± 3.1		NR	Declining Hb level is an independent risk factor for declining SF-36 General Health Subscale score P trend<0.001
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	SF-36 Vitality subscale (0-100)	50.6 ± 2.8	66.7 ± 3.6	NR	Hb <12 g/dL is an independent risk factor for reduced SF-36 Vitality Subscale score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	SF-36 Vitality subscale (0-100)	50.6 ± 2.8; 57.1 ± 2.6; 55.2 ± 2.5; 57.1 ± 2.8; 66.7 ± 3.6		NR	Declining Hb level is an independent risk factor for declining SF-36 Vitality Subscale score P trend=0.005
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	SF-36 Social functioning subscale (0-100)	76.5 ± 2.9	90.5 ± 3.7	NR	Hb <12 g/dL is an independent risk factor for reduced SF-36 Social Functioning Subscale score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor Mean ± SD or n/N (%)	No risk factor Mean ± SD or n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	SF-36 Social functioning subscale (0-100)	76.5 ± 2.9; 82.2 ± 2.7; 84.5 ± 2.6; 84.9 ± 2.9; 90.5 ± 3.7		NR	Declining Hb level is an independent risk factor for declining SF-36 Social Functioning Subscale score P trend=0.005
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	SF-36 Role emotional subscale (0-100)	70.1 ± 4.4	80.2 ± 5.5	NR	Hb <12 g/dL is <u>not</u> an independent risk factor for reduced SF-36 Role Emotional Subscale score compared with Hb ≥15 g/dL P≥0.05
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	SF-36 Role emotional subscale (0-100)	70.1 ± 4.4; 70.6 ± 4.0; 85.3 ± 3.8; 81.2 ± 4.3; 80.2 ± 5.5		NR	Declining Hb level is an independent risk factor for declining SF-36 Role Emotional Subscale score P trend=0.022
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	SF-36 Mental health subscale (0-100)	74.1 ± 2.2	85.3 ± 2.8	NR	Hb <12 g/dL level is an independent risk factor for reduced SF-36 Mental Health Subscale score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	SF-36 Mental health subscale (0-100)	74.1 ± 2.2; 80.0 ± 2.1; 78.5 ± 2.0; 75.7 ± 2.2; 85.3 ± 2.8		NR	*Declining Hb level is <u>not</u> an independent risk factor for declining SF-36 Mental Health Subscale score* P trend=0.070
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	FACIT Anaemia score (0-100)	46.4 ± 1.1	51.3 ± 1.4	NR	Hb <12 g/dL is an independent risk factor for reduced FACIT-Anaemia score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor Mean ± SD or n/N (%)	No risk factor Mean ± SD or n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
	1 Prospective cross-sectional survey N=328	transplant, or recipient of blood transfusion or erythropoietin within 3 months		Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	FACIT Anaemia score (0-100)	46.4 ± 1.1; 47.8 ± 1.0; 48.0 ± 1.0; 48.5 ± 1.1; 51.3 ± 1.4		NR	Declining Hb level is an independent risk factor for declining FACIT-Anaemia score P trend=0.017
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	FACIT Fatigue score (0-100)	35.8 ± 1.2	41.1 ± 1.5	NR	Hb <12 g/dL is an independent risk factor for reduced FACIT-Fatigue score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	FACIT Fatigue score (0-100)	35.8 ± 1.2; 37.9 ± 1.1; 38.4 ± 1.1; 38.5 ± 1.2; 41.1 ± 1.5		NR	Declining Hb level is an independent risk factor for declining FACIT-Fatigue score P trend=0.015
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	FACIT Non-fatigue score (0-100)	22.5 ± 0.4	23.0 ± 0.5	NR	Hb <12 g/dL is not an independent risk factor for reduced FACIT-Non-fatigue score compared with Hb ≥15 g/dL P≥0.05
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	FACIT Non-fatigue score (0-100)	22.5 ± 0.4; 22.3 ± 0.4; 21.9 ± 0.4; 22.3 ± 0.4; 23.0 ± 0.5		NR	Declining Hb level is not an independent risk factor for declining FACIT-Fatigue score P trend=0.699
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=109	Outpatients aged ≥65 years, no previous diagnosis of cancer (excl BCC of skin), underlying blood disorder, end stage renal failure or transplant, or recipient of blood transfusion or erythropoietin within 3 months	Outpatient US	Hb <12 g/dL vs Hb ≥15 g/dL	IADL (0-100)	2.0 ± 0.3	0.6 ± 0.4	NR	Hb <12 g/dL level is an independent risk factor for increased IADL score compared with Hb ≥15 g/dL P<0.01
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			
	1 Prospective cross-sectional survey N=328			Hb categories (<12 g/dL; 12.0-12.9 g/dL; 13.0-13.9 g/dL; 14.0-14.9 g/dL; ≥15 g/dL)	IADL (0-100)	2.0 ± 0.3; 1.1 ± 0.3; 1.0 ± 0.2; 1.3 ± 0.3; 0.6 ± 0.4		NR	Declining Hb level is an independent risk factor for increasing IADL score P trend=0.012
						Adjusted for: age, sex, race, diabetes mellitus, rheumatoid arthritis, hypertension and chronic inflammatory conditions.			

An, anaemia; CI, confidence interval; FACT, Functional Assessment of Cancer Therapy; FACIT, Functional Assessment of Chronic Illness Therapy; IADL, Instrumental Activities of Daily Living; NR, not reported; SF-12, Short-Form-12; SF-36, Short-Form-36; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Defined as a Hb of 10-12.1 g/dL for women and 10-13.1 g/dL for men.

CANCER

Of the adverse outcomes specified for this question, two are covered for this population: mortality and functional status (disability).

Methods

There were 17 studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified four systematic reviews examining the aetiology of anaemia in patients with cancer.

Level II evidence

The literature search identified 13 Level II studies examining the aetiology of anaemia in patients with cancer.

Level III evidence

Due to the substantial amount of Level II evidence identified, the literature was not searched for Level III evidence.

Level IV evidence

Due to the substantial amount of Level II evidence identified, the literature was not searched for Level IV evidence.

Results

Level I evidence

Four Level I studies were included for this question: all four studies provided evidence for mortality and one study provided evidence for functional status/quality of life, as summarised in Table 3.29. [63-66] All four studies were considered to be of poor methodological quality and included studies were not limited to prospective cohort studies. The majority of studies included in the Knight et al (2004)[65] review that assessed quality of life assessed the effect of anaemia treatment on functional status/quality of life, rather than the independent effect of anaemia on functional status/quality of life. In the two studies that assessed the association of anaemia with quality of life, neither was a Level II study. As such, none of these will be used as the basis for the review of this question; however, their results will be briefly described and they will be used to help identify Level II studies.

Table 3.29 Question 1 (cancer): Characteristics and quality of Level I evidence

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Caro et al (2001)[63]	Systematic review and meta-analysis of literature. Includes data from 60 studies including 39 cohort studies, 19 RCTs, and 2 case-referent studies. *Poor*	Diagnosis of cancer (accepted the authors' definitions for each malignancy). N=NR	Mortality
Hauser et al (2006)[64]	Systematic review of literature. Includes data from 53 studies (study types not specified) *Poor*	Adults with one or more kind of solid tumour. N=8998	Survival
Knight et al (2004)[65]	Systematic review of literature. Includes data from 18 studies for survival/mortality and 16 studies for functional status/QoL (study types not specified) *Poor*	Cancer (type not limited) N=NR	Mortality
Varlotto et al (2005)[66]	Systematic review of literature. Includes data from 19 studies which used multivariate analysis (study types not specified) *Poor*	Diagnosis of cancer N=NR	Survival

LVEF, left ventricular ejection fraction; NR, not reported; QoL, quality of life; RCT, randomised controlled trial.

The four identified systematic reviews all concluded that anaemia was associated with adverse outcomes in patients with cancer. Caro et al (2001)[63] performed a systematic review and meta-analysis of data from a large number of studies including 39 cohort studies, 19 RCTs and 2 case-referent studies. Based on their analyses they concluded that anaemia is "associated with reduced survival times for patients with lung carcinoma, cervicouterine carcinoma, head and neck carcinoma, prostate carcinoma, lymphoma and multiple myeloma. Hauser et al (2006)[64] performed a systematic literature search and included 53 studies in their review. They concluded that anaemia was one of a number of "laboratory tests"

associated with shorter survival. Knight et al (2004)[65] the association between anaemia and survival and functional status/quality of life in patients with cancer. They found that "patients with [anaemia] had poorer survival and local control than did their [nonanaemic] counterparts in 15 of 18 studies" and that quality of life was "positively correlated with [Hb] levels in 15 of 16 studies". Finally, Varlotto et al (2005)[66] identified 19 studies which used multivariate analysis to assess the relationship between anaemia and adverse outcomes and found that "all studies have shown a correlation between low Hb levels…..with poorer prognosis".

One additional study by Liou et al (2007) while not officially included as it did not meet the inclusion criteria, will be briefly described as it provides data on the economic burden of anaemia.[67] Following a systematic review of evidence published between 1990 and 2006 which identified eight relevant studies, Liou et al found that the total direct cost attributable to anaemia in the US ranged from $US18,418 to $US69,478 per year (2006 values), while in other countries (including Belgium, Canada, France, Germany Italy, the Netherlands and Spain), the total cost per episode of anaemia ranged from $US124 to $US2704 (2006 values).

Level II evidence

Thirteen Level II studies were included for this question; 11 studies provided evidence for mortality/survival and two provided evidence for functional/performance status.[68-80] The characteristics of the included studies are summarised in Table 3.30. Three of the included studies specifically examined anaemia or Hb level as a potential predictor of adverse outcomes,[69,73,80] two studies examined other specific factors (bone metabolism and progression-free survival),[70,71] and the remaining eight studies aimed to identify a number of potential predictors.[68,72,74-79]

Due to the large amount of evidence available for the mortality outcome, and the requirement that analyses were adjusted for multiple potential confounders, studies were limited to those including >500 subjects. This resulted in the exclusion of 129 studies. Nine of these excluded studies had between 400 and 500 subjects.[81-89] Studies with smaller patient numbers were potentially available for inclusion for the functional status/quality of life outcomes.

Table 3.30 Question 1 (cancer): Characteristics and quality of Level II evidence

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Armstrong et al (2010)[68]	Cohort analysis of a RCT (TAX327) *Good*	Men with documented metastatic prostatic adenocarcinoma in the face of castrate levels of serum testosterone (<50 ng/ mL), and if they had evidence of progression as defined by clinically or radiographically measurable disease or by PSA criteria. N=640	Mortality/survival
Beer et al (2006)[69]	Cohort analysis of a RCT (SWOG Study S8894) *Good*	Men with histologically proven diagnosis of adenocarcinoma of the prostate with bone or distant soft tissue metastases. N=817	Mortality/survival

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Cook et al (2006)[70]	Cohort analysis of a RCT *Fair*	Men with histologically confirmed prostate cancer, bone metastases and disease progression despite medical or surgical castration. N=592	Mortality/survival
Halabi et al (2009)[71]	Cohort analysis of 9 RCTs *Poor*	Men with prostate cancer who had progressed during androgen deprivation therapy. N=1201	Mortality/survival
Kohne et al (2002)[72]	Cohort analysis of 19 RCTs and 3 phase II trials *Poor*	Patients treated with 5-FU for metastatic colorectal cancer. N=3825	Mortality/survival
Laurie et al (2007)[73]	Cohort analysis of 2 RCTs (BR.3 and BR.6) *Fair*	Patients with NSCLC. N=652	Mortality/survival
Mandrekar et al (2006)[74]	Cohort analysis of 9 RCTs[a] *Poor*	Patients with advanced-stage NSCLC (stage IIB with pleural effusion and stage IV). N=782	Mortality/survival
Négrier et al (2002)[75]	Cohort analysis of 5 RCTs *Fair*	Adults 18-80 with histologically confirmed and measurable metastatic renal cell carcinoma. N=782	Mortality/survival
Nieboer et al (2005)[76]	Cross-sectional analysis of a RCT *Poor*	Women aged <56 years with stages II and III breast cancer and ≥4 positive axillary lymph nodes, a normal chest x-ray, normal bone-scan, normal liver sonogram, a WHO performance status of 0 or 1, and no prior treatment other than surgery who were disease-free until at least 3 years after surgery. N=426	Functional/performance status
Østerlind et al (1986)[77]	Cohort analysis of 6 controlled trials *Poor*	Adults with small cell lung cancer. N=778	Mortality/survival
Paesmans et al (1995)[78]	Cohort analysis of 7 RCTs *Fair*	Adults with NSCLC treated by chemotherapy. N=1052	Mortality/survival
Paesmans et al (2000)[79]	Cohort analysis of 4 RCTs *Fair*	Adults with small-cell lung cancer. N=763	Mortality/survival
Wisløff et al (2005)[80]	Cross-sectional analysis of 2 prospective trials *Poor*	Newly diagnosed patients with multiple myeloma. N=745	Functional/performance status

5-FU, 5-fluorouracil; NSCLC, non-small-cell lung cancer; PSA, prostate specific antigen; RCT, randomised controlled trial.

[a] Trial IDs: 852251, 872451, 882452, 892451, 922453, 932451, 952452, 982452, N0026, S9509.

Anaemia as an independent risk factor for mortality

One study assessed the association between **anaemia as defined by the World Health Organisation (WHO) [a]** and mortality, as shown in Table 3.31. The study by Armstrong et al (2010)[68] examined the association between a number of risk factors, including anaemia, and post-progression survival in 640 men with documented metastatic prostate carcinoma who had progressed while on therapy. The results of this analysis showed that anaemia is an independent risk factor for post-progression survival (P=0.012). While the study does not specify the direct of the association, it has been assumed for this review that anaemia is associated with a decreased post-progression survival, as this has been the overwhelming trend across all studies examined in this review.

[a] Hb <12 g/dL for females and <13 g/dL for males.

Table 3.31 Question 1 (cancer): Results for Level II evidence – mortality (WHO or similar anaemia criteria)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity[b]*
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Armstrong 2010 Level II *Good*	1 cohort analysis of a RCT (TAX327) N=640	Men with metastatic prostatic adenocarcinoma, castrate levels of serum testosterone (<50 ng/ mL), and evidence of progression	Hospital Various[c]	Hb <13.0 g/dL vs no anaemia	Post-progression survival (>12 months follow-up)	NR	NR	HR 1.30 (1.05, 1.58) Variables include in the multivariable model: prechemotherapy variables including liver metastases, significant pain, >2 metastatic sites, KPS ≤70, time since diagnosis, alkaline phosphatase and post-chemotherapy variables including duration of first-line therapy, number of progression factors and progression on chemotherapy (treatment group not associated with survival after adjustment for other prognostic variables so not included in the model).	*Anaemia is an independent risk factor for reduced post-progression survival* P=0.012

CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance scale; NR, not reported; RCT, randomised controlled trial.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Finland, France, Germany, Hungary, Italy, Lebanon, the Netherlands, Poland, Russia, Slovak Republic, South Africa, Spain, Sweden, United Kingdom, United States.

Eight studies assessed the association between **various Hb levels and mortality**, as shown in Table 3.32.[70,72-75,77-79] In the study by Østerlind et al (1986)[77], data from six RCTs (N=up to 778) was examined to assess the association between a Hb level of <12 g/dL and survival in patients with small-cell lung cancer (SCLC). Two analyses (one which included interactions and one which ignored interactions) showed that low Hb was an independent risk factor for reduced survival (P<0.001 and P<0.05).

Cook et al (2006)[70] assessed the relationship between Hb level and survival in 592 men with prostate cancer, bone metastases and disease progression despite medical or surgical castration. When Hb level was dichotomised or divided into quartiles, "lower Hb was associated with shorter survival" (p<0.001 for both). The cut-offs for the dichotomised and quartiles of Hb level were not stated in the publication.

The study by Mandrekar et al (2006)[74] analysed the relationship between low Hb and survival in patients with NSCLC using two cohorts: (i) an initial cohort comprised of data from nine RCTs (N=782) and (ii) a validation cohort comprised of data from one RCT (N=426). In the initial cohort, low Hb (defined as Hb <13.2 g/dL for males and <11.5 g/dL for females) was an independent risk factor for decreased survival (HR 1.51; P<0.001); however, in the validation cohort this analysis failed to reach statistical significance (HR 1.21; P=0.07).

Negrier et al (2002)[75] examined the relationship between low Hb and survival in 782 patients with metastatic renal cell carcinoma. The analysis showed that low Hb, defined as <11.5 g/dL in females and <13.0 g/dL in males, was an independent risk factor for decreased survival (RR 1.4; P<0.001).

Paesmans et al (1995)[78] assessed the relationship between haemoglobinaemia (defined as a Hb level <12 g/dL and >18 g/dL) and survival in 1052 patients with NSCLC. While haemoglobinaemia was a predictor in the univariate analysis, it was excluded from the multivariate analysis during the stepwise procedure, suggesting that it is not an independent predictor of survival. A similar result was found by Paesmans et al (2000; fair quality)[79] in 756 patients with SCLC, although in this analysis haemoglobinaemia was also not significantly associated with survival at either the univariate or multivariate level.

The study by Kohne et al (2002)[72] examined the association between Hb and survival in 3825 patients treated with 5-FU for metastatic colorectal cancer, included in 22 clinical trials. The results of this analysis showed that a Hb level <11 g/dL was an independent risk factor for reduced survival.

Laurie et al (2007)[73] assessed the association between various measures of Hb and survival in up to 633 patients with non-small-cell lung cancer (NSCLC). When a nadir Hb <10 g/dL was compared with a nadir Hb ≥10 g/dL, there was no significant association with survival. Similarly, when Hb reductions of 10-30% and >30% were compared with reductions of <10%, there was no association with survival. Finally, a pre-prophylactic cranial irradiation (PCI) Hb level of <10 g/dL was also not associated with survival when compared with a PCI of ≥10 g/dL.

Table 3.32 Question 1 (cancer): Results for Level II evidence – mortality (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Østerlind 1986 Level II Poor	1 cohort analysis of six RCTs N=746	Adults with small cell lung cancer	Hospital/Denmark	Hb <12 g/dL vs Hb ≥12 g/dL	Survival (18 months follow-up)	NR	NR	NR Adjusted for variables with significant influence in at least one of the disease categories: performance status, LDH, sodium, urate, sex, age, alternating regimen.	<u>*Analysis 1 (includes interactions)*</u> *Hb <12 g/dL is an independent risk factor for reduced survival* P<0.001
	1 cohort analysis of six RCTs N=778	Adults with small cell lung cancer	Hospital/Denmark	Hb <12 g/dL vs Hb ≥12 g/dL	Survival (18 months follow-up)	NR	NR	NR Adjusted for variables with significant influence in at least one of the disease categories: performance status, LDH, resected patients, sodium, sex, age, alternating regimen, extensive disease.	<u>*Analysis 2 (ignores interactions)*</u> *Hb <12 g/dL is an independent risk factor for reduced survival* P<0.05
Cook 2006 Level II *Fair*	1 cohort analysis of a RCT N=592	Men with <u>prostate cancer</u>, bone metastases and disease progression despite medical or surgical castration	Hospital Various[c]	Hb dichotomised (no further details provided)	Overall survival (up to 2 years follow-up)	NR	NR	RR 0.84 (0.78, 0.91) Variables included in the multivariable model: age, PSA, LDH, analgesic, BAP.	*A lower Hb is an independent risk factor for reduced survival* P<0.001
				Hb in quartiles (no further details provided)	Overall survival (up to 2 years follow-up)	NR	NR	RR 0.84 (0.78, 0.90) Variables included in the multivariable model: age, PSA, LDH, analgesic, BAP.	*A low Hb is an independent risk factor for reduced survival* P<0.001
Mandrekar 2006 Level II *Poor*	1 cohort analysis of 9 RCTs N=782	Patients with advanced-stage <u>NSCLC</u>	Hospital US, Canada	Low Hb (Hb <13.2 g/dL for males and <11.5 g/dL for females) vs normal Hb	Overall survival (up to 2 years follow-up)	NR	NR	HR 1.51 (1.28, 1.78) Adjusted for: age, gender, ECOG PS, cancer stage, BMI, WBC.	*Low Hb is an independent risk factor for reduced survival* P<0.001
	1 validation cohort analysis of 1 RCT N=426	Patients with advanced-stage <u>NSCLC</u>	Hospital US, Canada	Low Hb (Hb <13.2 g/dL for males and <11.5 g/dL for females) vs normal Hb	Overall survival (up to 2 years follow-up)	NR	NR	HR 1.21 (0.98, 1.50) Adjusted for: age, gender, ECOG PS, cancer stage, BMI, WBC.	*Low Hb is not an independent risk factor for survival* P=0.07
Négrier 2002 Level II Fair	1 cohort analysis of five prospective trials N=782	Adults 18-80 with histologically confirmed and measurable metastatic renal cell carcinoma	Hospital France	Hb <11.5 g/dL (female) or <13.0 g/dL (male) vs no normal Hb	Overall survival (median 77 months follow-up)	158/352 (45)	230/424 (54)	RR 1.400 (1.167, 1.684) Adjusted for variables with P<0.1 in univariate analysis: inflammation, time from tumour to metastases, ECOG performance status, number of metastatic sites, neutrophils, alkaline phosphatase, liver metastasis, bone metastasis, mediastinum metastasis.	*Low Hb is an independent risk factor for decreased survival* P<0.001
Paesmans 1995	1 cohort analysis	Adults with non-small-	Hospital	Haemoglobinaemia	Survival (median	NR	NR	NR	*Haemoglobinaemia is <u>not</u>*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Level II Fair	of seven RCTs N=1052	cell lung cancer	Europe	(Hb <12 g/dL and >18 g/dL) vs no haemoglobinaemia	follow-up 270 weeks)	Variables included in the best-fit model from 23 initial variables: disease extent, KPS, WBC count, skin metastases, calcium, neutrophil, age, sex.			*an independent risk factor for survival* P=NR
Paesmans 2000 Level II Fair	1 cohort analysis of seven RCTs N=756	Adults with small-cell lung cancer	Hospital Europe	Haemoglobinaemia (Hb <12 g/dL and >18 g/dL) vs no haemoglobinaemia	Survival (a>5 years follow-up)	NR	NR	NR	*Haemoglobinaemia is <u>not</u> an independent risk factor for survival* P=NR
						Variables included in the best-fit model from 21 initial variables: KPS, sex, female gender, neutrophil rate.			
FOLLOW-UP UNKNOWN									
Kohne 2002 Level II *Poor*	1 cohort analysis of 19 RCTs and 3 phase II trials N=3825	Patients treated with 5-FU for <u>metastatic colorectal cancer</u>	Hospital Europe	Hb <11 g/dL vs Hb ≥11 g/dL	Overall survival (follow-up not stated)	NR	NR	NR	*Hb <11 g/dL is an independent risk factor for reduced survival* P=NR
						Adjusted for: other laboratory parameters.			
Laurie 2007 Level II *Fair*	1 cohort analysis of 2 RCTs N=633	Patients with <u>NSCLC</u>	Hospital Canada	Nadir Hb <10.0 g/dL vs nadir Hb ≥10.0 g/dL	Overall survival (follow-up not stated)	NR	NR	HR 1.09 (0.92, 1.31)	*Nadir Hb <10.0 g/dL is not an independent risk factor for survival* P=0.33
						Adjusted for: gender, ECOG PS, LDH.			
	1 cohort analysis of 2 RCTs N=NR	Patients with <u>NSCLC</u>	Hospital Canada	Hb % reduction 10-30% vs Hb % reduction <10 %	Overall survival (follow-up not stated)	NR	NR	HR 0.83 (0.60, 1.14)	*Hb % reduction 10-30% is not an independent risk factor for survival* P=0.25
						Adjusted for: gender, ECOG PS, LDH.			
	1 cohort analysis of 2 RCTs N=NR	Patients with <u>NSCLC</u>	Hospital Canada	Hb % reduction >30% vs Hb % reduction <10 %	Overall survival (follow-up not stated)	NR	NR	HR 0.94 (0.68, 1.31)	*Hb % reduction >30% is not an independent risk factor for survival* P=0.73
						Adjusted for: gender, ECOG PS, LDH.			
	1 cohort analysis of 2 RCTs N=523	Patients with <u>NSCLC</u>	Hospital Canada	Pre-PCI Hb <10.0 g/dL vs pre-PCI Hb ≥10.0 g/dL	Overall survival (follow-up not stated)	NR	NR	NR	*Pre-PCI Hb <10.0 g/dL is not an independent risk factor for survival* P=0.31
						Adjusted for: gender, ECOG PS, LDH.			

5-FU, 5-flurourocrit; ASA, acetylsalicylic acid; BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Hb, haemoglobin; *het*, heterogeneity; HR, hazard ratio; KPS, Karnofsky performance scale; LDH, lactate dehydrogenase; IV, intravenous; NA, not applicable; NSCLC, non-small cell lung cancer; NR, not reported; OR, odds ratio; PCI Hb, prophylactic cranial irradiation Hb level; PSA, prostate specific antigen; RBC, red blood cell; RCT, randomised controlled trial; RR, risk ratio; WBC, white blood cell

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] US, Argentina, Australia, Canada, France, Brazil, Germany, UK, New Zealand, Italy, Chile, Switzerland, Austria, Belgium, Peru, Sweden, Uruguay.

Three studies assessed the association between **Hb as a continuous variable and mortality**, as shown in Table 3.33.[69-71] In the study by Halabi et al (2009)[71] the association between change in Hb and survival was examined in 1201 men with prostate cancer who had progressed during androgen deprivation therapy. The study found that a 1 g/dL change (assumed to be a decrease) in Hb resulted in a 9% decrease in survival.

Beer et al (2006)[69] assessed the association between two continuous measures of Hb and survival in 817 patients with adenocarcinoma of the prostate with bone or distant soft tissue metastases. A 1 g/dL increase in baseline Hb (centred at 13.7 g/dL) was found to be associated with a 12% increase in survival (P<0.001), while a 3-month decrease in survival of 1 g/dL was shown to be associated with a 10% decrease in survival (P=0.0035).

In men with prostate cancer, bone metastases and progression despite medical or surgical castration, Cook et al (2006)[70] showed that a 1 g/dL decrease in Hb was independently associated with a 36% decrease in survival.

Table 3.33 Question 1 (cancer): Results for Level II evidence – mortality (Hb as a continuous variable)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
LONGER-TERM FOLLOW-UP (>1 YEAR)									
Halabi 2009 Level II *Poor*	1 cohort analysis of 9 RCTs N=1201	Men with prostate cancer who had progressed during androgen deprivation therapy	Hospital US	Hb (1 g/dL change)[e]	Overall survival (>12 months follow-up)	NA	NA	HR 0.91 (0.86, 0.97) Adjusted for known prognostic variables: progression at 3 months, age, performance status, presence of visceral disease, BMI, Gleason score, testosterone, race, prior radiotherapy, alkaline phosphatase, years since diagnosis, PSA, LDH.	*A change in Hb of 1 g/dL is independently associated with a 9% decrease in survival*[g] P=0.002
Beer 2006 Level II *Good*	1 cohort analysis of a RCT N=817	Men with adenocarcinoma of the prostate with bone or distant soft tissue metastases	Hospital US	Baseline Hb centred at 13.7 g/dL (1-unit increment)	Overall survival (>2 years follow-up)	NA	NA	HR 0.88 (0.83, 0.93) Adjusted for: race, PSA, bone pain, performance status, extensive disease, age, prior radiotherapy, radical prostatectomy, Gleason score, flutamide treatment, baseline Hb, 3-month change in Hb, African American baseline Hb.	*A 1 g/dL increase in Hb is independently associated with a 12% increase in survival* *P<0.001*
				3-month Hb change of 1 g/dL	Overall survival (>2 years follow-up)	NA	NA	HR 1.10 (1.03, 1.16)[c] Adjusted for: race, PSA, bone pain, performance status, extensive disease, age, prior radiotherapy, radical prostatectomy, Gleason score, flutamide treatment, baseline Hb, 3-month change in Hb, African American baseline Hb.	*A 1 g/dL decrease in Hb from baseline to 3 months is independently associated with a 10% decrease in survival* *P=0.0035*
Cook 2006 Level II *Fair*	1 cohort analysis of a RCT N=592	Men with prostate cancer, bone metastases and disease progression despite medical or surgical castration	Hospital Various[d]	Hb (1 g/dL decrease)	Overall survival (up to 2 years follow-up)	NA	NA	RR 0.84 (0.78, 0.90) Variables included in the multivariable model: age, PSA, LDH, analgesic, BAP.	*A 1 g/dL reduction in Hb is independently associated with a 36% decrease in survival* P<0.001

CI, confidence interval; Hb, haemoglobin; HR, hazard ratio; NA, not applicable; RCT, randomised controlled trial; RR, risk ratio.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] The table in the publication shows a confidence interval of 1.03, 0.16. This is assumed to be an error and 1.16 has been shown above.

[d] US, Argentina, Australia, Canada, France, Brazil, Germany, UK, New Zealand, Italy, Chile, Switzerland, Austria, Belgium, Peru, Sweden, Uruguay.

[e] An assumption had to be made regarding the interpretation of the results; it is assumed that the "change" in Hb is actually a decrease of 1 g/dL, and that the HR of 0.91 (0.86, 0.97) relates to a decrease in survival.

Anaemia as an independent risk factor for stroke/MI

No studies were identified which presented data on stroke/MI.

Anaemia as an independent risk factor for functional/performance status

One study assessed the association between **other anaemia definitions and functional/performance status**, as shown in Table 3.34.[76] In the study by Nieboer et al (2005),[76] data from a RCT (N=up to 426) was examined to assess the association between anaemia, defined as a Hb level of ≤12 g/dL, and fatigue in women with high-risk breast cancer. Fatigue was defined as a score of ≤46 on the SF-36 Vitality scale. Cross-sectional analyses were conducted at four time points: at baseline (prior to treatment), and post-treatment at 1, 2 and 3 years. The results of the study showed a strong association between anaemia (Hb ≤12 g/dL) and fatigue (OR 3.5; 1.7, 7.1) when the measurements were made prior to treatment. This finding was not repeated at the other post-treatment time-points, although the lack of significance at 3 years (OR 2.0; 0.7, 5.5) may possibly have reflected the smaller sample size (N=292).

Table 3.34 Question 1 (cancer): Results for Level II evidence – functional/performance status (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
Nieboer 2005 Level II *Poor*	1 cross-sectional analysis of a RCT N=426	Women aged <56 years with stages II and III breast cancer and ≥4 positive axillary lymph nodes, a normal chest x-ray, normal bone-scan, normal liver sonogram, a WHO performance status of 0 or 1, and no prior treatment other than surgery who were disease-free until at least 3 years after surgery	Hospital The Netherlands	Hb ≤12 g/dL vs >12 g/dL	Fatigue (SF-36 Vitality score ≤46) at randomisation (pre-treatment)	NR	NR	OR 3.5 (1.7, 7.1)	*Hb ≤12 g/dL is an independent risk factor for fatigue compared with Hb >12 g/dL at randomisation.* P=0.001
						Adjusted for: mental health score, muscle pain, joint pain, treatment group, menopausal status.			
	1 cross-sectional analysis of a RCT N=410				Fatigue (SF-36 Vitality score ≤46) at 1 year (post-treatment)	NR	NR	OR 1.1 (0.5, 2.2)	*Hb ≤12 g/dL is not an independent risk factor for fatigue compared with Hb >12 g/dL at 1 year.* P=0.789
						Adjusted for: mental health score, muscle pain, joint pain, treatment group, menopausal status.			
	1 cross-sectional analysis of a RCT N=394				Fatigue (SF-36 Vitality score ≤46) at 2 years (post-treatment)	NR	NR	OR 0.9 (0.7, 2.0)	*Hb ≤12 g/dL is not an independent risk factor for fatigue compared with Hb >12 g/dL at 2 years.* P=0.724
						Adjusted for: mental health score, muscle pain, joint pain, treatment group, menopausal status.			
	1 cross-sectional analysis of a RCT N=292				Fatigue (SF-36 Vitality score ≤46) at 3 years (post-treatment)	NR	NR	OR 2.0 (0.7, 5.5)	*Hb ≤12 g/dL is not an independent risk factor for fatigue compared with Hb >12 g/dL at 3 years.* P=0.176
						Adjusted for: mental health score, muscle pain, joint pain, treatment group, menopausal status.			

CI, confidence interval; Hb, haemoglobin; OR, odds ratio; NR, not reported; RCT, randomised controlled trial; SF-36, Short-Form-36; WHO, World Health Organisation.
Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.
[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

One study assessed the association between **Hb as a continuous variable and functional/performance status**, as shown in Table 3.35.[80] In the study by Wisløff et al (2005)[80], data from two prospective trials (N=745) was examined to assess the association between Hb level and quality of life in adults with multiple myeloma. The European Organisation for Research and Treatment of Cancer QLQ-C30 scale (EORTC-QLQ-C30) questionnaire was used to assess quality of life and various scales and subscales were reported. Wisløff et al found that Hb level was associated with fatigue and global quality of life both prior to treatment and at 12 months (following treatment). Other dimensions of quality of life that were not shown to be associated with Hb included physical functioning, role functioning and pain.

Table 3.35 Question 1 (cancer): Results for Level II evidence – functional/performance status (Hb as a continuous variable)

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity[b]*
Wisløff 2005 Level II *Poor*	1 cross-sectional analysis of data from 2 prospective trials (NMSG # 4/90 and NMSG # 5/94) N=745	Newly diagnosed patients with multiple myeloma.	Hospital Denmark, Norway and Sweden	Hb as a continuous variable	EORTC-QLQ-C30 Physical functioning at randomisation	NA	NA	NR	Hb level is <u>not</u> significantly associated with EORTC-QLQ-C30 Physical functioning score P=0.674
						Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii) and extent of skeletal disease.			
					EORTC-QLQ-C30 Physical functioning at 12-months (post-treatment)	NA	NA	NR	*Hb level is <u>not</u> significantly associated with EORTC-QLQ-C30 Physical functioning score* P=0.300
						Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii), extent of skeletal disease and treatment response category.			
					EORTC-QLQ-C30 Role functioning at randomisation	NA	NA	NR	Hb level is <u>not</u> significantly associated with EORTC-QLQ-C30 Role functioning score P=0.989
						Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii) and extent of skeletal disease.			
					EORTC-QLQ-C30 Role functioning at 12-months (post-treatment)	NA	NA	NR	*Hb level is <u>not</u> significantly associated with EORTC-QLQ-C30 Role functioning score* P=0.079
						Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii), extent of skeletal disease and treatment response category.			
					EORTC-QLQ-C30 Global QoL at randomisation	NA	NA	NR	Hb level is significantly associated with EORTC-QLQ-C30 Global QoL score P=0.041
						Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii) and extent of skeletal disease.			
					EORTC-QLQ-C30 Global QoL at 12-months (post-treatment)	NA	NA	NR	*Hb level <u>may</u> be associated with EORTC-QLQ-C30 Global QoL score* P=0.052
						Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii), extent of skeletal disease and treatment response category.			

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
					EORTC-QLQ-C30 Fatigue at randomisation	NA	NA	NR	Hb level is significantly associated with EORTC-QLQ-C30 Physical functioning score P=0.001
						Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii) and extent of skeletal disease.			
					EORTC-QLQ-C30 Fatigue at 12-months (post-treatment)	NA	NA	NR	*Hb level is significantly associated with EORTC-QLQ-C30 Fatigue score* P=0.010
						Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii), extent of skeletal disease and treatment response category.			
					EORTC-QLQ-C30 Pain at randomisation	NA	NA	NR	Hb level is <u>not</u> significantly associated with EORTC-QLQ-C30 Pain score P=0.417
						Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii) and extent of skeletal disease.			
					EORTC-QLQ-C30 Pain at 12-months (post-treatment)	NA	NA	NR	*Hb level is not a significantly associated with EORTC-QLQ-C30 Pain score* P=0.946
						Adjusted for: age, gender, serum creatinine, serum albumin, corrected serum calcium, serum β-2 microglobulin, disease stage according to Durie and Salmon (i-iii), extent of skeletal disease and treatment response category.			

An, anaemia; CI, confidence interval; EORTC QLQ-30, European Organization for Research and Treatment of Cancer QLQ-C30; Hb Hb; NR, not reported; SF-12, Short-Form-12; SF-36, Short-Form-36; WHO, World Health Organisation.

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Summary

The majority of results presented for the cancer population suggest that anaemia/low Hb is an independent risk factor for mortality. Where no significant association between anaemia/low Hb was found, as was shown in a study in patients with NSCLC, the number of patients included in the analysis was not known, but was likely to be small.[73] In addition, one study which showed no significant association assessed haemoglobinaemia, which included patients with Hb levels outside a restricted range; thus, it included patients with high Hb as well as anaemia.[79]

The results of the analysis of anaemia and functional/performance status suggest that anaemia is an independent risk factor for fatigue. There was also a possible association between Hb level and global quality of life, although no associations were shown for more specific domains, including physical functioning, role functioning and pain.

The studies included for this population were generally considered to be of poorer methodological quality, being older and less well reported.

RENAL DISEASE

Of the adverse outcomes specified for this question, three are covered for this population: mortality, stroke and functional status (quality of life).

Methods

There were 16 studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified one systematic review examining the aetiology of anaemia in patients with renal disease.

Level II evidence

The literature search identified 15 Level II studies examining the aetiology of anaemia in patients with renal disease.

Level III evidence

Due to the substantial amount of Level II evidence identified, the literature was not searched for Level III evidence.

Level IV evidence

Due to the substantial amount of Level II evidence identified, the literature was not searched for Level IV evidence.

Results

Level I evidence

One fair quality Level I study was included for this question, as summarised in Table 3.36.[90] This study assessed the association between Hb/haematocrit and all-cause mortality in RCTs and cohort studies, although the majority of cohort studies included in the Volkova et al

(2006) [90] review were retrospective studies. In addition, the included RCTs all assessed the effect of EPO on patient outcomes. As such, this study will not be used as the basis for the review of this question; however, its results will be briefly described and it will be used to help identify Level II studies.

Table 3.36 Question 1 (renal): Characteristics and quality of Level I evidence

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Volkova et al (2006)[90]	Systematic review of literature. Includes data from 18 studies including 5 RCTs and 13 cohort studies *Fair*	Dialysis patients N=NR	Mortality

NR, not reported; RCT, randomised controlled trial.

Volkova et al (2006) [90] note that "observational studies that analysed haematocrit and/or Hgb values categorically consistently showed increased mortality associated with Hgb levels less that their individual reference range. They conclude that "controversies still exist for the relationship between complete resolution of anemia and dialysis patient survival. These controversies have been exacerbated by the lack of adequately designed RCTs and the high level of heterogeneity across observational studies. In addition, although observational studies may show the association between natural Hgb levels and mortality, RCTs look at the achieved or study-directed Hb levels, which also contributes to varying results."

Level II evidence

Fifteen Level II studies were included for this question; eight studies provided evidence for mortality, one provided evidence for stroke and six studies provide evidence for functional/performance status. The characteristics of the included studies are summarised in Table 3.37. Nine of the included studies specifically examined anaemia or Hb level as a potential predictor of adverse outcomes,[91-99] four studies examined other specific factors (depression, calcium/phosphate/parathyroid levels, erectile dysfunction and body mass),[100-103] while the remaining two studies aimed to identify a number of potential predictors.[104,105]

Due to the large amount of evidence available for the mortality outcome, and the requirement that analyses were adjusted for multiple potential confounders, studies were limited to those including >500 subjects. This resulted in the exclusion of one study.[106] Studies with smaller patient numbers were potentially available for inclusion for the stroke/MI and function status/quality of life outcomes. One additional study which reported quality of life outcomes was excluded as it assessed <100 subjects.[107]

One potential confounding factor in the analyses of patients with renal disease is the use of exogenous erythropoietin, as it acts by increasing production of red blood cells and subsequently increasing Hb levels. Therefore, studies which reported erythropoietin use among their patients which did not subsequently account for this in the analysis (eg, by adjusting for erythropoietin use in the analysis, or by measuring Hb in a time-dependent manner rather than at a single timepoint) were excluded. Two publications from the Dialysis Outcomes and Practice Patterns Study (DOPPS) were excluded for this reason.[108,109]

Table 3.37 Question 1 (renal): Characteristics and quality of Level II evidence

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Abramson et al (2003)[91]	Prospective cohort study (ARIC) *Fair*	A community-based middle-aged population aged 45-64 years (N=15,792). For the present study, participants were excluded if they had a self-reported history of stroke at baseline or if they had missing data on renal function, anaemia or other covariates of interest N=13,716	Stroke
Astor et al (2006)[92]	Prospective cohort study (ARIC) *Fair*	A community-based middle-aged population aged 45-64 years (N=15,792). For the present study, participants were excluded if they had a self-reported history of stroke at baseline or if they had missing data on renal function, anaemia or other covariates of interest N=14,971	Mortality
Avram et al (2003)[93]	Prospective cohort study *Fair*	Patients on haemodialysis (HD) or peritoneal dialysis (PD). N=529 (HD) and 326 (PD)	Mortality
Finkelstein et al (2009)[94]	Cross-sectional analysis of prospectively collected data *Fair*	Patients with CKD, defined as a eGFR <60 mL/min/1.73m2 (MDRD) stages 3-5 not on dialysis and aged 18 or older. N=1186	Quality of life
Fort et al (2010)[95]	Prospective cohort study (ANSWER) *Fair*	Patients starting haemodialysis, who had received haemodialysis for ≤30 days, aged ≥18 years. N=2310	Mortality
Leeder et al (2006)[96]	Prospective cohort study *Good*	Residents of two postcode areas in the Blue Mountains born before January 1, 1943 Only subjects with CKD based on three estimation methods (N=1639, 1427 and 1258) or low serum creatinine (N=294) are included in this review.	Mortality
Merkus et al (1997)[105]	Cross-sectional analysis of prospectively collected data *Fair*	Adults started on chronic haemodialysis or peritoneal dialysis in 13 Dutch dialysis centres between October 1993 and April 1995. N=226	Quality of life
Mollaoglu et al (2004)[100]	Cross-sectional analysis of prospectively collected data *Poor*	Population taken from a 2-year longitudinal study of quality of life; prevalent haemodialysis patients. N=140	Quality of life
Perlman et al (2005)[104]	Cross-sectional analysis of prospectively collected data *Fair*	CKD defined as a GFR ≤50 mL/min/1.73 m^2 (MDRD. N=222 (all variables available), 487 (Hb available).	Quality of life
Platinga et al (2007)[97]	Prospective cohort study	Patients initiating haemodialysis during 10/95 to 6/98.	Quality of life

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
	Fair	N=438	
Portolés et al (2007)[98]	Prospective cohort study *Fair*	A representative sample of prevalent haemodialysis patients ≥18 years who started treatment between January 1999 and March 2001. N=1428	Mortality
Robinson et al (2005)[99]	Prospective cohort study (DOPPS) *Fair*	Random selection of patients undergoing haemodialysis N=5517	Mortality
Stevens et al (2004)[101]	Prospective cohort study *Fair*	Prevalent dialysis patients (haemodialysis or peritoneal dialysis) in dialysis centres in British Columbia who were alive and on dialysis as of January 2000 and had calcium, phosphate and parathyroid hormone data entered between Jan and Mar 2000. N=515	Mortality
Turk et al (2004)[102]	Cross-sectional analysis of prospectively collected data *Poor*	Men aged 18-65 on haemodialysis for at least 3 months. N=148	Quality of life
Yen et al (2010)[103]	Prospective cohort study *Fair*	Maintenance haemodialysis patients. N=959	Mortality

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; Hb. Hb; HD, haemodialysis; MDRD, modification of diet in renal disease; PD, peritoneal dialysis

Anaemia as an independent risk factor for mortality

No studies assessed the association between **anaemia as defined by the World Health Organisation (WHO) and mortality**.

Four studies assessed the association between **various Hb levels and all-cause mortality**, as shown in Table 3.38.[92,93,95,99] In the study by Astor et al (2006),[92] the risk of mortality was assessed in subjects with chronic kidney disease (CKD) compared with those without CKD. This analysis was conducted in two separate populations: those with anemia (defined as a Hb level <12 g/dL for women and <13.5 g/dL for men) and those without anaemia. Thus, while this study does not specifically assess anaemia as an independent risk factor, this can be inferred by comparing the results in the two populations. In subjects with a glomerular filtration rate of 30-59 mL/min/1.73m^2 (often defined as moderate CKD) who also had anaemia, the risk of mortality compared with subjects without CKD was HR 3.49 (95% CI 2.38, 5.12; p<0.001). In subjects without anaemia the equivalent HR was 1.72 (95% CI 1.34, 2.20; p<0.001). This suggests that having anaemia confers a two-fold greater risk of mortality. In subjects with a glomerular filtration rate of 60-74 mL/min/1.73m^2 (often defined as mild CKD) who also had anaemia, the risk of mortality compared with subjects without CKD was HR 1.62 (95% CI 1.12, 2.35; p<0.05). In subjects without anaemia the equivalent HR was 1.02 (95% CI 0.87, 1.20; p≥0.05). This also suggests that having anaemia confers a greater risk of mortality. Finally, in subjects with a glomerular filtration rate of 75-

89 mL/min/1.73m^2 (often defined as very mild CKD) who also had anaemia, the risk of mortality compared with subjects without CKD was HR 1.11 (95% CI 0.80, 1.55; p≥0.05). In subjects without anaemia the equivalent HR was 0.93 (95% CI 0.83, 1.05; p≥0.05). These results suggest that anaemia does not increase the risk of mortality in this very mild CKD population. Although in some cases there was no significant difference in either the anaemia or non-anaemia groups, the authors note that "the excess risk of each end point associated with decreased kidney function…was >2-fold greater among individuals with anaemia than among individuals without anaemia".

The remaining three studies assessed the risk of mortality associated with anaemia/Hb levels in patients on dialysis. Avram et al (2003)[93] examined the association between a Hb level of <12 g/dL and mortality in both haemodialysis (HD) and peritoneal dialysis (PD) patients. In the overall population of HD patients (N=527), a low Hb level was independently associated with an increased risk of mortality (RR 2.13; P=0.008). However, stratification by diabetes status showed significant effect modification, with patients with diabetes showing no association between low Hb and mortality (RR 0.74; p=0.39) and patients without diabetes showing a significant association between low Hb and mortality (RR 4.53; P=0.003). A similar result was seen in patients with PD (RR 1.85, P=0.06; RR 1.15, P=0.81 and RR 2.02, P=0.07, respectively). Failure to reach statistical significance in this analysis may have been due to the small patient number (P=192). The authors conclude that enrolment Hb is a predictor of long-term survival in HD and PD patients. As noted in the Volkova et al (2006) review, diabetes was a possible effect modifier and wasn't adjusted for in the categorical analyses. However, diabetes was adjusted for in the continuous Hb level analysis, which will be presented below. This analysis showed that increasing Hb was significantly associated with a reduction in mortality risk in both haemodialysis and peritoneal dialysis patients.

In the previous two studies, the use of erythropoietin was not reported. In the study by Fort et al (2010)[95] erythropoietin use was reported in approximately 70% of the cohort. The use of erythropoietin was taken into account by using time-dependent Hb in the analysis, rather than single timepoint Hb, and adjustment for erythropoietin dose. In this newly dialysed population, a time-dependent Hb of ≤10 g/dL was an independent risk factor for mortality compared with a time-dependent Hb of 11.1-12.0 g/dL (HR 1.36; 95% CI 1.01, 1.86; P=0.048). There was no significant association between a Hb level of 10.2-11 g/dL and mortality. The analyses were repeated using baseline Hb (which showed no association between lower Hb and mortality) and 6-month Hb, which showed a significant increased risk of mortality for both Hb ≤10 g/dL (HR 2.32; 95% CI 1.73, 3.12) and 10.1-11.0 g/dL (HR 1.46; 95% CI 1.06, 2.01) compared with Hb 11.1-12.0 g/dL. The authors conclude that "higher Hb levels are associated with lower mortality in Spanish incident haemodialysis patients, regardless of ESA dose, iron deficiency, comorbidity, vascular access or malnutrition". The authors performed a number of sensitivity analyses which showed similar results with the following exceptions: (i) when patients who died within 6 months were excluded (N=177), the Hb ≤10 g/dL analysis failed to reach statistical significance; and (ii) when patients with or without previous CV history were assessed, there was no association between Hb and mortality in patients without previous CV history but there was in those with previous CV history.

Erythropoietin use was also reported the analysis of US patients in the DOPPS by Robinson et al (2005),[99] with 91.2% of subjects receiving at least some erythropoietin. The use of erythropoietin was accounted for in the analysis via including erythropoietin dose in the multivariate analysis; parenteral iron dose was also adjusted for. A 3-month lagged Hb level of <9 g/dL was shown to be significant associated with mortality compared with a level of 11-<12 g/dL. When the reference range was increased 11-<13 g/dL, all three Hb levels below the

reference range (<9 g/dL, 9-<10 g/dL and 10-<11 g/dL) were significantly associated with mortality. The analyses were repeated using 1- 3- and 6-month lagged Hb in a more restricted population (ie, those that had a full dataset for the 6-month lagged analyses) and results were similar, with lower Hb levels associated with an increased risk of mortality. The authors concluded that "our findings confirm the associations of Hb levels ≥11 g/dL with longer survival among maintenance HD patients, but show no additional survival advantage for patients with Hb levels ≥12 g/dL". The results were consistent across different lag-times and different reference ranges. They also looked at effect modification by health status and found no significant interactions.

Table 3.38 Question 1 (renal): Results for Level II evidence – all-cause mortality (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
RENAL									
ALL-CAUSE MORTALITY									
KIDNEY DISEASE									
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=793	Community-based middle-aged population <u>with anaemia</u>	Community US	GFR 30-59 mL/min/1.73 m2 + anaemia vs GFR ≥90 mL/min/1.73 m^2 + anaemia	Mortality (12 years)	NR	NR	HR 3.49 (2.38, 5.12) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 30-59 mL/min/1.73 m^2 is an independent risk factor for all-cause mortality in subjects with anaemia* P <0.001
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=6757	Community-based middle-aged population <u>without anaemia</u>	Community US	GFR 30-59 mL/min/1.73 m2 + no anaemia vs GFR ≥90 mL/min/1.73 m^2 + no anaemia	Mortality (12 years)	NR	NR	HR 1.72 (1.34, 2.20) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 30-59 mL/min/1.73 m^2 is an independent risk factor for all-cause mortality in subjects without anaemia* P <0.001
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=923	Community-based middle-aged population <u>with anaemia</u>	Community US	GFR 60-74 mL/min/1.73 m2 + anaemia vs GFR ≥90 mL/min/1.73 m^2 + anaemia	Mortality (12 years)	NR	NR	HR 1.62 (1.12, 2.35) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 60-74 mL/min/1.73 m^2 is an independent risk factor for all-cause mortality in subjects with anaemia* P<0.05
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=8389	Community-based middle-aged population <u>without anaemia</u>	Community US	GFR 60-74 mL/min/1.73 m2 + no anaemia vs GFR ≥90 mL/min/1.73 m^2 + no anaemia	Mortality (12 years)	NR	NR	HR 1.02 (0.87, 1.20) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 60-74 mL/min/1.73 m^2 is <u>not</u> an independent risk factor for all-cause mortality in subjects without anaemia* P ≥0.05
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=1130	Community-based middle-aged population <u>with anaemia</u>	Community US	GFR 75-89 mL/min/1.73 m^2 + anaemia vs GFR ≥90 mL/min/1.73 m^2 + anaemia	Mortality (12 years)	NR	NR	HR 1.11 (0.80, 1.55) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 75-89 mL/min/1.73 m^2 is <u>not</u> an independent risk factor for all-cause mortality in subjects with anaemia* P ≥0.05

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=11,257	Community-based middle-aged population <u>without anaemia</u>	Community US	GFR 75-89 mL/min/1.73 m^2 + no anaemia vs GFR ≥90 mL/min/1.73 m^2 + no anaemia	Mortality (12 years)	NR	NR	HR 0.93 (0.83, 1.05) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 75-89 mL/min/1.73 m^2 is <u>not</u> an independent risk factor for all-cause mortality in subjects without anaemia* P ≥0.05
DIALYSIS									
Avram 2003 Level II *Fair*	1 prospective cohort study N=527	Patients on <u>haemodialysis</u>	Hospital US	Hb <12 g/dL vs Hb ≥12 g/dL	Mortality (mean 4 years)	NR	NR	RR 2.13 Adjusted for age, gender, race and months on dialysis at enrolment.	*Hb <12 g/dL is an independent risk factor for increased mortality in haemodialysis patients* P=0.008
Avram 2003 Level II *Fair*	1 prospective cohort study N=280	Patients on <u>haemodialysis (non-diabetic patients only)</u>	Hospital US	Hb <12 g/dL vs Hb ≥12 g/dL	Mortality (mean 4 years)	NR	NR	RR 4.53 Adjusted for age, gender, race and months on dialysis at enrolment.	*Hb <12 g/dL is an independent risk factor for increased mortality in haemodialysis patients without diabetes* P=0.003
Avram 2003 Level II *Fair*	1 prospective cohort study N=249	Patients on <u>haemodialysis (diabetic patients only)</u>	Hospital US	Hb <12 g/dL vs Hb ≥12 g/dL	Mortality (mean 4 years)	NR	NR	RR 0.74 Adjusted for age, gender, race and months on dialysis at enrolment.	*Hb <12 g/dL is <u>not</u> an independent risk factor for increased mortality in haemodialysis patients with diabetes* P=0.39
Avram 2003 Level II *Fair*	1 prospective cohort study N=326	Patients on <u>peritoneal dialysis</u>	Hospital US	Hb <12 g/dL vs Hb ≥12 g/dL	Mortality (mean 4 years)	NR	NR	RR 1.85 Adjusted for age, gender, race and months on dialysis at enrolment.	*Hb <12 g/dL <u>may</u> be an independent risk factor for increased mortality in peritoneal dialysis patients* P=0.06
Avram 2003 Level II *Fair*	1 prospective cohort study N=192	Patients on <u>peritoneal dialysis (non-diabetic patients only)</u>	Hospital US	Hb <12 g/dL vs Hb ≥12 g/dL	Mortality (mean 4 years)	NR	NR	RR 2.02 Adjusted for age, gender, race and months on dialysis at enrolment.	*Hb <12 g/dL <u>may</u> be an independent risk factor for increased mortality in peritoneal dialysis patients* P=0.07
Avram 2003	1 prospective	Patients on <u>peritoneal</u>	Hospital	Hb <12 g/dL vs Hb	Mortality (mean 4	NR	NR	RR 1.15	*Hb <12 g/dL is <u>not</u> an*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Level II *Fair*	cohort study N=134	dialysis (diabetic patients only)	US	≥12 g/dL	years)	Adjusted for age, gender, race and months on dialysis at enrolment.			*independent risk factor for increased mortality in peritoneal dialysis patients* P=0.81
Fort 2010 Level II *Fair*	1 prospective cohort study N=NR	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	Time-dependent Hb ≤10 g/dL vs time-dependent Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 1.36 (1.01, 1.86)	*A time-dependent Hb level of ≤10 g/dL is an independent predictor of all-cause mortality compared with a time-dependent Hb level of 11.1-12.0 g/dL* P=0.048
						Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.			
Fort 2010 Level II *Fair*	1 prospective cohort study N=NR	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	Time-dependent Hb 10.1-11.0 g/dL vs time-dependent Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 1.03 (0.75, 1.42)	*A time-dependent Hb level of 10.1-11.0 g/dL is not an independent predictor of all-cause mortality compared with a time-dependent Hb level of 11.1-12.0 g/dL* P=0.83
						Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.			
Fort 2010 Level II *Fair*	1 prospective cohort study N=NR	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	Time-dependent Hb 12.1-13.0 g/dL vs time-dependent Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 0.93 (0.68, 1.26)	*A time-dependent Hb level of 12.1-13.0 g/dL is not an independent predictor of all-cause mortality compared with a time-dependent Hb level of 11.1-12.0 g/dL* P=0.63
						Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.			
Fort 2010 Level II *Fair*	1 prospective cohort study N=NR	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	Time-dependent Hb ≥13.0 g/dL vs time-dependent Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 0.69 (0.49, 0.97)	*A time-dependent Hb level of ≥13.0 g/dL is an independent predictor of a reduced risk of all-cause mortality compared with a time-dependent Hb level of 11.1-12.0 g/dL* P=0.03
						Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Fort 2010 Level II *Fair*	1 prospective cohort study N=NR	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	Baseline Hb ≤10 g/dL vs baseline Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 1.23 (0.92, 1.64) Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.	*A baseline Hb level of ≤10 g/dL is not an independent predictor of all-cause mortality compared with a baseline Hb level of 11.1-12.0 g/dL* P=NR
Fort 2010 Level II *Fair*	1 prospective cohort study N=NR	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	Baseline Hb 10.1-11.0 g/dL vs baseline Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 1.11 (0.81, 1.53) Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.	*A baseline Hb level of 10.1-11.0 g/dL is not an independent predictor of all-cause mortality compared with a baseline Hb level of 11.1-12.0 g/dL* P=NR
Fort 2010 Level II *Fair*	1 prospective cohort study N=NR	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	Baseline Hb 12.1-13.0 g/dL vs baseline Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 1.01 (0.68, 1.52) Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.	*A baseline Hb level of 12.1-13.0 g/dL is not an independent predictor of all-cause mortality compared with a baseline Hb level of 11.1-12.0 g/dL* P=NR
Fort 2010 Level II *Fair*	1 prospective cohort study N=NR	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	Baseline Hb ≥13.0 g/dL vs baseline Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 0.77 (0.44, 1.36) Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.	*A baseline Hb level of ≥13.0 g/dL is not an independent predictor of all-cause mortality compared with a baseline Hb level of 11.1-12.0 g/dL* P=NR
Fort 2010 Level II *Fair*	1 prospective cohort study N=897	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	6-month Hb ≤10 g/dL vs 6-month Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 2.32 (1.73, 3.12) Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.	*A 6-month Hb level of ≤10 g/dL is an independent predictor of all-cause mortality compared with a 6-month Hb level of 11.1-12.0 g/dL* P=NR

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Fort 2010 Level II *Fair*	1 prospective cohort study N=902	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	6-month Hb 10.1-11.0 g/dL vs 6-month Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 1.46 (1.06, 2.01) Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.	*A 6-month Hb level of 10.1-11.0 g/dL is an independent predictor of all-cause mortality compared with a 6-month Hb level of 11.1-12.0 g/dL* P=NR
Fort 2010 Level II *Fair*	1 prospective cohort study N=1063	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	6-month Hb 12.1-13.0 g/dL vs 6-month Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 0.94 (0.69, 1.29) Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.	*A 6-month Hb level of 12.1-13.0 g/dL is not an independent predictor of all-cause mortality compared with a 6-month Hb level of 11.1-12.0 g/dL* P=NR
Fort 2010 Level II *Fair*	1 prospective cohort study N=1086	Patients starting haemodialysis, who had received haemodialysis for ≤30 days	Hospital Spain	6-month Hb ≥13.0 g/dL vs 6-month Hb 11.1-12.0 g/dL	Mortality (mean 1.5 years)	NR	NR	HR 0.71 (0.51, 0.99) Adjusted for age, vascular access, Karnofsky score, ESA dose, albumin, neoplasia, cerebrovascular disease, peripheral vascular disease, cardiac arrhythmia, BMI.	*A 6-month Hb level of ≥13.0 g/dL is an independent predictor of a reduced risk of all-cause mortality compared with a 6-month Hb level of 11.1-12.0 g/dL* P=NR
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (total 3352)	Patients undergoing haemodialysis	Hospital US	3-month lagged Hb <9 g/dL vs Hb 11-<12 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.74 (1.24, 2.43) Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.	A Hb <9 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (total 3352)	Patients undergoing haemodialysis	Hospital US	3-month lagged Hb 9-<10 g/dL vs Hb 11-<12 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.25 (0.96, 1.63) Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.	A Hb 9-<10 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (total 3352)	Patients undergoing haemodialysis	Hospital US	3-month lagged Hb 10-<11 g/dL vs Hb 11-<12 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.22 (0.99, 1.49) Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.	A Hb 10-<11 g/dL is not an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (total 3352)	Patients undergoing haemodialysis	Hospital US	3-month lagged Hb <9 g/dL vs Hb 11-<13 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.80 (1.29, 2.49) Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.	A Hb <9 g/dL is an independent risk factor for mortality compared with a Hb 11-<13 g/dL P=NR
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (total 3352)	Patients undergoing haemodialysis	Hospital US	3-month lagged Hb 9-<10 g/dL vs Hb 11-<13 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.29 (1.01, 1.67) Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.	A Hb 9-<10 g/dL is an independent risk factor for mortality compared with a Hb 11-<13 g/dL P=NR
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (total 3352)	Patients undergoing haemodialysis	Hospital US	3-month Hb 10-<11 g/dL vs Hb 11-<13 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.26 (1.04, 1.52) Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.	A Hb 10-<11 g/dL is an independent risk factor for mortality compared with a Hb 11-<13 g/dL P=NR
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (total 2790)	Patients undergoing haemodialysis	Hospital US	1-month lagged Hb <9 g/dL vs Hb 11-<12 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.69 (1.14, 2.49) Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.	A Hb <9 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (total 2790)	Patients undergoing haemodialysis	Hospital US	1-month lagged Hb 9-<10 g/dL vs Hb 11-<12 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.46 (1.07, 2.00) Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.	A Hb 9-<10 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Robinson 2005	1 prospective	Patients	Hospital	1-month lagged Hb	Mortality (mean	NR	NR	HR 1.23 (0.97, 1.56)	A Hb 10-<11 g/dL is not

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Level II *Fair*	cohort study N=NR (total 2790)	undergoing <u>haemodialysis</u>	US	10-<11 g/dL vs Hb 11-<12 g/dL	13.4 months)	Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.			an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (<u>total 2790</u>)	Patients undergoing <u>haemodialysis</u>	Hospital US	<u>3-month</u> lagged Hb <9 g/dL vs Hb 11-<12 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.62 (1.09, 2.40)	A Hb <9 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
						Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.			
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (<u>total 2790</u>)	Patients undergoing <u>haemodialysis</u>	Hospital US	<u>3-month</u> lagged Hb 9-<10 g/dL vs Hb 11-<12 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.21 (0.90, 1.64)	A Hb 9-<10 g/dL is <u>not</u> an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
						Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.			
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (<u>total 2790</u>)	Patients undergoing <u>haemodialysis</u>	Hospital US	<u>3-month</u> lagged Hb 10-<11 g/dL vs Hb 11-<12 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.28 (1.02, 1.62)	A Hb 10-<11 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
						Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.			
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (total 2790)	Patients undergoing <u>haemodialysis</u>	Hospital US	<u>6-month</u> lagged Hb <9 g/dL vs Hb 11-<12 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.59 (1.06, 2.37)	A Hb <9 g/dL is an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
						Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.			
Robinson 2005 Level II *Fair*	1 prospective cohort study N=NR (total 2790)	Patients undergoing <u>haemodialysis</u>	Hospital US	<u>6-month</u> lagged Hb 9-<10 g/dL vs Hb 11-<12 g/dL	Mortality (mean 13.4 months)	NR	NR	HR 1.27 (0.95, 1.72)	A Hb 9-<10 g/dL is <u>not</u> an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR
						Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.			
Robinson 2005	1 prospective	Patients	Hospital	<u>6-month</u> lagged Hb	Mortality (mean	NR	NR	HR 1.21 (0.97, 1.50)	A Hb 10-<11 g/dL is <u>not</u>

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Level II *Fair*	cohort study N=NR (total 2790)	undergoing haemodialysis	US	10-<11 g/dL vs Hb 11-<12 g/dL	13.4 months)	Adjusted for variables shown to be associated with mortality in univariate analysis (P≤0.20) and then included in multivariate analysis using backward elimination (P≤0.10): sex, ESRD cause, atherosclerotic CVD, CHF, pulmonary illness, age, albumin, calcium-phosphate product, total cholesterol, creatinine, ferritin, PTH, WBC, EPO dose, parenteral iron dose, prescribed HD duration, post dialysis SBP, currently prescribed nutritional supplement and hospitalised days.			an independent risk factor for mortality compared with a Hb 11-<12 g/dL P=NR

BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval;; CVD, cardiovascular disease; DBP, diastolic blood pressure; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; ESRD, end stage renal disease; GFR, glomerular filtration rate; Hb, haemoglobin; HD, haemodialysis; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; NR, not reported; PTH, parathyroid hormone; RR, risk ratio; SBP, systolic blood pressure; US; United States of America; WBC, white blood cell

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Two studies assessed the association between **various Hb levels and cardiovascular mortality**, as shown in Table 3.39.[92,96] In the study by Astor et al (2006),[92] the risk of cardiovascular mortality was assessed in subjects with CKD compared with those without CKD. This analysis was conducted in two separate populations: those with anaemia (defined as a Hb level <12 g/dL for women and <13.5 g/dL for men) and those without anaemia. In subjects with a glomerular filtration rate of 30-59 mL/min/1.73m^2 (often defined as moderate CKD) who also had anaemia, the risk of mortality compared with subjects without CKD was HR 4.38 (95% CI 1.96, 9.79; p<0.001). In subjects without anaemia the equivalent HR was 2.67 (95% CI 1.71, 4.17; p<0.001). In subjects with a glomerular filtration rate of 60-74 mL/min/1.73m^2 (often defined as mild CKD) who also had anaemia, the risk of mortality compared with subjects without CKD was HR 2.78 (95% CI 1.30, 5.97; p<0.001). In subjects without anaemia the equivalent HR was 1.36 (95% CI 0.98, 1.89; p≥0.05). Finally, in subjects with a glomerular filtration rate of 75-89 mL/min/1.73m^2 (which can be defined as very mild CKD) who also had anaemia, the risk of mortality compared with subjects without CKD was HR 1.26 (95% CI 0.59, 2.69; p≥0.05). In subjects without anaemia the equivalent HR was 0.99 (95% CI 0.76, 1.31; p≥0.05). As mentioned previously, the authors note that "the excess risk of each end point associated with decreased kidney function…was >2-fold greater among individuals with anaemia than among individuals without anaemia".

Leeder et al (2006)[96] assessed the risk of coronary heart disease (CHD)-related death in residents of two postcode regions of the Blue Mountains in NSW, Australia. Presence of CKD was defined as a GFR <60 mL/min/1.73 m2 using three estimation methods: Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD) and Bjornsson. In addition, CKD was also estimated using serum creatinine (≥1.46 mg/dL in men and ≥1.26 mg/dL in women). Hb was categorised by quintiles, with the lowest quintile having a mean of 13.1 g/dL and the other quintiles having a mean of 15.2 g/dL. The lowest quintile Hb was an independent risk factor for cardiovascular mortality in subjects with CKD estimated using the Cockcroft-Gault (HR 1.49; 95% CI 1.08, 2.06) and Bjornsson (HR 1.57; 95% CI 1.12, 2.19) methods, and serum creatinine (HR 1.80; 95% CI 1.02, 3.18). There was no significant association between low Hb and cardiovascular mortality in subjects with CKD estimated using the MDRD. When CKD was defined as the lowest quintile using the Cockcroft-Gault method, the association remained significant. However, when stratified by gender, there remained a significant association in men (HR 2.32; 95% CI 1.29, 4.17) but not women (HR 1.82; 0.88, 3.78). The authors conclude that "low hemoglobin, even within the normal range, together with CKD increased the risk for CHD-related deaths".

Table 3.39 Question 1 (renal): Results for Level II evidence – cardiovascular mortality (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
RENAL									
CHD MORTALITY									
KIDNEY DISEASE									
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=793	Community-based middle-aged population with anaemia	Community US	GFR 30-59 mL/min/1.73 m2 + anaemia vs GFR ≥90 mL/min/1.73 m^2 + anaemia	CHD mortality (12 years)	NR	NR	HR 4.38 (1.96, 9.79) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 30-59 mL/min/1.73 m^2 is an independent risk factor for CHD mortality in subjects with anaemia* P <0.001
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=6757	Community-based middle-aged population without anaemia	Community US	GFR 30-59 mL/min/1.73 m2 + no anaemia vs GFR ≥90 mL/min/1.73 m^2 + no anaemia	CHD mortality (12 years)	NR	NR	HR 2.67 (1.71, 4.17) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 30-59 mL/min/1.73 m^2 is an independent risk factor for CHD mortality in subjects without anaemia* P <0.001
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=923	Community-based middle-aged population with anaemia	Community US	GFR 60-74 mL/min/1.73 m2 + anaemia vs GFR ≥90 mL/min/1.73 m^2 + anaemia	CHD mortality (12 years)	NR	NR	HR 2.78 (1.30, 5.97) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 60-74 mL/min/1.73 m^2 is an independent risk factor for CHD mortality in subjects with anaemia* P <0.001
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=8389	Community-based middle-aged population without anaemia	Community US	GFR 60-74 mL/min/1.73 m2 + no anaemia vs GFR ≥90 mL/min/1.73 m^2 + no anaemia	CHD mortality (12 years)	NR	NR	HR 1.36 (0.98, 1.89) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 60-74 mL/min/1.73 m^2 is not an independent risk factor for CHD mortality in subjects without anaemia* P ≥0.05
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=1130	Community-based middle-aged population with anaemia	Community US	GFR 75-89 mL/min/1.73 m^2 + anaemia vs GFR ≥90 mL/min/1.73 m^2 + anaemia	CHD mortality (12 years)	NR	NR	HR 1.26 (0.59, 2.69) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 75-89 mL/min/1.73 m^2 is not an independent risk factor for CHD mortality in subjects with anaemia* P ≥0.05

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Astor 2006 Level II *Fair*	1 prospective cohort study (ARIC) N=11,257	Community-based middle-aged population without anaemia	Community US	GFR 75-89 mL/min/1.73 m^2 + no anaemia vs GFR ≥90 mL/min/1.73 m^2 + no anaemia	CHD mortality (12 years)	NR	NR	HR 0.99 (0.76, 1.31) Adjusted for serum creatinine, age, gender, race, prevalent CHD, SBP, DBP, use of antihypertensive medication, diabetes mellitus, current smoking, BMI, LDL, HDL, triglycerides, fibrinogen and field centre.	*A GFR of 75-89 mL/min/1.73 m^2 is not an independent risk factor for CHD mortality in subjects without anaemia* P ≥0.05
Leeder 2006 Level II *Good*	1 prospective cohort study N=1639	Residents of two postcode areas in the Blue Mountains born before January 1, with CKD defined as GFR <60 mL/min/1.73 m^2 (Cockcroft-Gault method)	Community Australia	Lowest Hb quintile (mean 13.1 g/dL) vs other Hb quintiles (mean 15.2 g/dL)	CHD-related death[a] (mean 8.2 years)	64/352 (18.2)	115/1287 (8.9)	HR 1.49 (1.08, 2.06) Adjusted for age, gender, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total cholesterol and fibrinogen levels, BMI, diabetes and self-reported health status.	*The lowest quintile of Hb is an independent risk factor for CHD-related mortality compared with other Hb quintiles.* P=NR
Leeder 2006 Level II *Good*	1 prospective cohort study N=NR	Female residents of two postcode areas in the Blue Mountains born before January 1, with CKD defined as GFR <60 mL/min/1.73 m^2 (Cockcroft-Gault method)	Community Australia	Lowest Hb quintile (mean 13.1 g/dL) vs other Hb quintiles (mean 15.2 g/dL)	CHD-related death[a] (mean 8.2 years)	NR	NR	HR 1.82 (0.88, 3.78) Adjusted for age, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total cholesterol and fibrinogen levels, BMI, diabetes and self-reported health status.	*The lowest quintile of Hb is not an independent risk factor for CHD-related mortality compared with other Hb quintiles in women with the lowest quintile GFR.* P=NR
Leeder 2006 Level II *Good*	1 prospective cohort study N=NR	Male residents of two postcode areas in the Blue Mountains born before January 1, with CKD defined as GFR <60 mL/min/1.73 m^2 (Cockcroft-Gault method)	Community Australia	Lowest Hb quintile (mean 13.1 g/dL) vs other Hb quintiles (mean 15.2 g/dL)	CHD-related death[a] (mean 8.2 years)	NR	NR	HR 2.32 (1.29, 4.17) Adjusted for age, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total cholesterol and fibrinogen levels, BMI, diabetes and self-reported health status.	*The lowest quintile of Hb is an independent risk factor for CHD-related mortality compared with other Hb quintiles in women with the lowest quintile GFR.* P=NR
Leeder 2006 Level II *Good*	1 prospective cohort study N=NR	Residents of two postcode areas in the Blue Mountains born before January 1, with CKD defined as lowest quintile GFR (Cockcroft-Gault method)	Community Australia	Lowest Hb quintile (mean 13.1 g/dL) vs other Hb quintiles (mean 15.2 g/dL)	CHD-related death[a] (mean 8.2 years)	NR	NR	HR 2.07 (1.33, 3.22) Adjusted for age, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total cholesterol and fibrinogen levels, BMI, diabetes and self-reported health status.	*The lowest quintile of Hb is an independent risk factor for CHD-related mortality compared with other Hb quintiles.* P=NR

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Leeder 2006 Level II *Good*	1 prospective cohort study N=1427	Residents of two postcode areas in the Blue Mountains born before January 1, with CKD defined as GFR <60 mL/min/1.73 m^2 (abbreviated MDRD method)	Community Australia	Lowest Hb quintile (mean 13.1 g/dL) vs other Hb quintiles (mean 15.2 g/dL)	CHD-related death[a] (mean 8.2 years)	53/312 (17.0)	95/1115 (8.5)	HR 1.36 (0.95, 1.94) Adjusted for age, gender, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total cholesterol and fibrinogen levels, BMI, diabetes and self-reported health status.	*The lowest quintile of Hb is not an independent risk factor for CHD-related mortality compared with other Hb quintiles.* P=NR
Leeder 2006 Level II *Good*	1 prospective cohort study N=1258	Residents of two postcode areas in the Blue Mountains born before January 1, with CKD defined as GFR <60 mL/min/1.73 m^2 (Bjornsson method)	Community Australia	Lowest Hb quintile (mean 13.1 g/dL) vs other Hb quintiles (mean 15.2 g/dL)	CHD-related death[a] (mean 8.2 years)	63/299 (21.1)	102/959 (10.6)	HR 1.57 (1.12, 2.19) Adjusted for age, gender, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total cholesterol and fibrinogen levels, BMI, diabetes and self-reported health status.	*The lowest quintile of Hb is an independent risk factor for CHD-related mortality compared with other Hb quintiles.* P=NR
Leeder 2006 Level II *Good*	1 prospective cohort study N=294	Residents of two postcode areas in the Blue Mountains born before January 1, with CKD defined as high serum creatinine (≥1.46 mg/dL for men and ≥1.26 mg/dL for women)	Community Australia	Lowest Hb quintile (mean 13.1 g/dL) vs other Hb quintiles (mean 15.2 g/dL)	CHD-related death[a] (mean 8.2 years)	28/99 (28.3)	31/195 (15.9)	HR 1.80 (1.02, 3.18) Adjusted for age, gender, pre-existing CHD, smoking status, alcohol consumption, mean arterial BP, total cholesterol and fibrinogen levels, BMI, diabetes and self-reported health status.	*The lowest quintile of Hb is an independent risk factor for CHD-related mortality compared with other Hb quintiles.* P=NR

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval;; CKD, chronic kidney disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; Hb, haemoglobin; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; NR, not reported; SBP, systolic blood pressure; US; United States of America

[a] CHD-related death (death confirmed by cross-matching demographic information with Australian National Death Index [NDI] data). Cause of death collected from death certificates and defined using ICD-9 and ICD-10 codes.

Four studies assessed the association between **Hb as a continuous variable and all-cause mortality**, as shown in Table 3.40.[93,98,101,103] In the study by Avram et al (2003)[93], a 1 g/dL increment in Hb resulted in a 17% reduction in mortality risk for patients on haemodialysis, and a 15% reduction in mortality risk for patients on peritoneal dialysis. These results were obtained after adjusting for a number of factors including diabetes, which was shown in categorical analyses in the same study to be a significant effect modifier.

Portolés et al (2007)[98] assessed the association between Hb and mortality in a representative sample of prevalent haemodialysis patients treated between January 1999 and March 2001. Greater than 90% of included patients were receiving erythropoietin. A 1 g/dL increment in time-dependent Hb resulted in a 15% reduction in mortality risk. Similarly, a 1 g/dL increment in baseline Hb resulted in a 14% reduction in the risk of mortality. The authors conclude that "anaemia is an independent risk factor that can predict survival…after adjustment for comorbidity, time on HD, cause of CKD, type of HD access, albumin level and Kt/V".

The study by Stevens et al (2004)[101] examined the association between albumin, calcium, phosphate and parathyroid hormone levels and mortality in prevalent HD or PD patients who were alive as of January 2000 and who had calcium, phosphate and parathyroid hormone data entered between January and March 2000. This study included Hb as a potential predictor. When all patients were included in the analysis, there was a significant association between Hb (per 5 g/dL) and mortality when only age, gender, race, diabetes and dialysis type and duration were included in the model (RR 0.93; 95% CI 0.89, 0.97). However, when albumin, calcium, phosphate and parathyroid hormone were included in the model, statistical significance was lost. When populations were varied according to length of time on dialysis and analyses were adjusted for a number of variables including albumin, calcium, phosphate and parathyroid hormone, there was a significant association between Hb and mortality for those on dialysis <6 months (RR 0.88; 95% CI 0.78, 0.99), but not 6-18 months (RR 0.98; 95% CI 0.89, 1.01) or >18 months (RR 0.99; 95% CI 0.92, 1.06). As this study was not specifically aimed at assessing Hb, no specific comments regarding the associations between Hb and mortality were made by the authors.

Yen et al (2010)[103] assessed the association between body mass and mortality in maintenance HD patients. While Hb was shown to be significantly associated with mortality in univariate analysis, it was not included in the multivariate stepwise analysis. The authors make no comment on the Hb results, other than to note that erythropoietin use was highest in the subgroup of patients with the lowest Hb, those who were underweight.

Table 3.40 Question 1 (renal): Results for Level II evidence – mortality (Hb as a continuous variable)

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
RENAL									
ALL-CAUSE MORTALITY									
DIALYSIS									
Avram 2003 Level II *Fair*	1 prospective cohort study N=855	Patients on haemodialysis	Hospital US	1 g/dL increment in Hb	Mortality (mean 4 years)	NA	NA	OR 0.83 Adjusted for age, gender, race, diabetes and months on dialysis at enrolment.	*A 1 g/dL increment in Hb results in a 17% reduction in risk of mortality in patients on haemodialysis* P=0.002
Avram 2003 Level II *Fair*	1 prospective cohort study N=855	Patients on peritoneal dialysis	Hospital US	1 g/dL increment in Hb	Mortality (mean 4 years)	NA	NA	OR 0.85 Adjusted for age, gender, race, diabetes and months on dialysis at enrolment.	*A 1 g/dL increment in Hb results in a 15% reduction in risk of mortality in patients on peritoneal dialysis* P=0.02
Portolés 2007 Level II *Fair*	1 prospective cohort study N=1428	A representative sample of prevalent haemodialysis patients who started treatment between January 1999 and March 2001	Hospital Spain	1 g/dL increment in time-dependent Hb	Mortality (12 months)	NA	NA	OR 0.85 (0.75, 0.95) Adjusted for age, sex, time on HD, cause of CKD, previous CV morbidity, previous vascular access events, non-CV comorbidity, type of access, albumin level, compliance with HD targets (Kt/V, nPCR, TAC urea).	*A 1 g/dL increment in time-dependent Hb is significantly associated with a 15% decrease in mortality risk* P<0.005
Portolés 2007 Level II *Fair*	1 prospective cohort study N=1428	A representative sample of prevalent haemodialysis patients who started treatment between January 1999 and March 2001	Hospital Spain	1 g/dL increment in baseline Hb	Mortality (12 months)	NA	NA	OR 0.86 (0.76, 0.96) Adjusted for age, sex, time on HD, cause of CKD, previous CV morbidity, previous vascular access events, non-CV comorbidity, type of access, albumin level, compliance with HD targets (Kt/V, nPCR, TAC urea) and time-dependent Hb.	*A 1 g/dL increment in baseline Hb is significantly associated with a 14% decrease in mortality risk* P<0.02
Stevens 2004 Level II *Fair*	1 prospective cohort study N=515	Prevalent dialysis patients (haemodialysis or peritoneal dialysis) in dialysis centres in British Columbia who were alive and on dialysis as of January 2000 and had calcium, phosphate and parathyroid hormone data entered between Jan and Mar 2000	Hospital Canada	Hb (per 5 g/dL)	Mortality (median follow-up 32 months)	NA	NA	RR 0.93 (0.89, 0.97) Adjusted for age, gender, race, diabetes and dialysis type and duration.	*A 5 g/dL difference in Hb is significantly associated with a 7% reduction in mortality risk.* P<0.001

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Stevens 2004 Level II *Fair*	1 prospective cohort study N=515	Prevalent dialysis patients (haemodialysis or peritoneal dialysis) in dialysis centres in British Columbia who were alive and on dialysis as of January 2000 and had calcium, phosphate and parathyroid hormone data entered between Jan and Mar 2000	Hospital Canada	Hb (per 5 g/dL)	Mortality (median follow-up 32 months)	NA	NA	RR 0.97 (0.92, 1.02) Adjusted for age, gender, diabetes, dialysis type, dialysis duration, race, dialysis adequacy (PRU), albumin, calcium, phosphate, parathyroid hormone.	*A 5 g/dL difference in Hb is not significantly associated with a change in mortality risk when continuous values of mineral metabolism parameters are included in the model.* P=0.194
Stevens 2004 Level II *Fair*	1 prospective cohort study N=515	Prevalent dialysis patients (haemodialysis or peritoneal dialysis) in dialysis centres in British Columbia who were alive and on dialysis as of January 2000 and had calcium, phosphate and parathyroid hormone data entered between Jan and Mar 2000	Hospital Canada	Hb (per 5 g/dL)	Mortality (median follow-up 32 months)	NA	NA	RR 0.96 (0.91, 1.01) Adjusted for age, gender, diabetes, dialysis type, dialysis duration, race, dialysis adequacy (PRU), albumin, calcium and phosphate and parathyroid hormone (different combinations of different levels).	*A 5 g/dL difference in Hb is not significantly associated with a change in mortality risk when categories of mineral metabolism parameters are combined and included in the model.* P=0.097
Stevens 2004 Level II *Fair*	1 prospective cohort study N=125	Prevalent dialysis patients (haemodialysis or peritoneal dialysis) in dialysis centres in British Columbia who were alive and on dialysis as of January 2000 and had calcium, phosphate and parathyroid hormone data entered between Jan and Mar 2000; on dialysis for <6 months	Hospital Canada	Hb (per 5 g/dL)	Mortality (median follow-up 32 months)	NA	NA	RR 0.88 (0.78, 0.99) Adjusted for age, gender, diabetes, dialysis type, dialysis duration, race, dialysis adequacy (PRU), albumin, calcium and phosphate and parathyroid hormone (different combinations of different levels).	*A 5 g/dL difference in Hb is significantly associated with a 12% reduction in mortality risk in patients on dialysis <6 months when categories of mineral metabolism parameters are combined and included in the model* P=0.029
Stevens 2004	1 prospective cohort study	Prevalent dialysis patients (haemodialysis or	Hospital	Hb (per 5 g/dL)	Mortality (median follow-up 32	NA	NA	RR 0.98 (0.89, 1.01)	*A 5 g/dL difference in Hb is not significantly*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Level II *Fair*	N=117	peritoneal dialysis) in dialysis centres in British Columbia who were alive and on dialysis as of January 2000 and had calcium, phosphate and parathyroid hormone data entered between Jan and Mar 2000; on dialysis for 6-18 months	Canada		months)	Adjusted for age, gender, diabetes, dialysis type, dialysis duration, race, dialysis adequacy (PRU), albumin, calcium and phosphate and parathyroid hormone (different combinations of different levels).			*associated with a change in mortality risk in patients on dialysis 6-18 months when categories of mineral metabolism parameters are combined and included in the model.* P=0.710
Stevens 2004 Level II *Fair*	1 prospective cohort study N=117	Prevalent dialysis patients (haemodialysis or peritoneal dialysis) in dialysis centres in British Columbia who were alive and on dialysis as of January 2000 and had calcium, phosphate and parathyroid hormone data entered between Jan and Mar 2000; on dialysis for >18 months	Hospital Canada	Hb (per 5 g/dL)	Mortality (median follow-up 32 months)	NA	NA	RR 0.99 (0.92, 1.06)	*A 5 g/dL difference in Hb is not significantly associated with a change in mortality risk in patients on dialysis >18 months when categories of mineral metabolism parameters are combined and included in the model.* P=0.758
						Adjusted for age, gender, diabetes, dialysis type, dialysis duration, race, dialysis adequacy (PRU), albumin, calcium and phosphate and parathyroid hormone (different combinations of different levels).			
Yen 2010 Level II *Fair*	1 prospective cohort study N=959	Maintenance haemodialysis patients	Hospital Taiwan	1 g/dL increment in Hb	Mortality (3 years)	NA	NA	NR	*A 1 g/dL increment in Hb is not significantly associated with mortality* P=NR
						Variables considered if they were significant on univariate analysis and included age, BMI, previous CVD, diabetes, hypertension, haemodialysis duration, use of fistula, use of BCM dialyzer, nPCR, Hb, albumin, creatinine, Log ferritin, phosphate, Log iPTH, HDL, LDL, Log hsCRP and cardiothoracic ratio. Only variables <0.05 remained in model: age, diabetes, BMI, albumin, Log hsCRP, and cardiothoracic ratio. Hb excluded from model.			

BCM, body composition monitor; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; Hb, haemoglobin; HD, haemodialysis; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein; NA, not applicable; nPCR, normalised protein catabolic rate; NR, not reported; OR, odds ratio; PRU, percent reduction urea; RR, risk ratio; TAC, time-averaged concentration; US, United States of America

Anaemia as an independent risk factor for stroke/MI

One study assessed the association between **anaemia as defined by the WHO and stroke**, as shown in Table 3.41.[91] Based on data from the Atherosclerosis Risk in Communities (ARIC) study, the risk of mortality was assessed in subjects with CKD compared with those without CKD. This analysis was conducted in two separate populations: those with anemia and those without anaemia. CKD was defined according to a GFR of <60 mL/min/1.73m^2, estimated using the Cockcroft-Gault method. In subjects with CKD who also had anaemia, the risk of stroke compared with subjects without CKD was HR 5.43 (95% CI 2.04, 14.41; p<0.01). In subjects without anaemia the equivalent HR was 1.41 (95% CI 0.93, 2.14; p=0.1). In subjects with CKD who also had anaemia, the risk of ischaemic stroke compared with subjects without CKD was HR 10.34 (95% CI 1.00, 29.0; p=0.03). In subjects without anaemia the equivalent HR was not reported although it was noted that there was no significant association in this population. The authors note that a significant interaction was seen between CKD and anaemia for stroke (P=0.01). The authors conclude that "among middle-aged community-based persons, the combination of CKD and anemia was associated with a substantial increase in stroke risk, independent of other known risk factors for stroke".

No studies were identified which assessed the association between anaemia and myocardial infarction.

Table 3.41 Question 1 (renal): Results for Level II evidence – stroke (WHO or similar anaemia criteria)

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
RENAL									
STROKE									
KIDNEY DISEASE									
Abramson (2003) Level II *Fair*	1 prospective cohort study (ARIC) N=1262	Community-based middle-aged population <u>with anaemia</u>[c]	Community US	CKD + anaemia vs no CKD + anaemia	Stroke (9 years)	NR	NR	HR 5.43 (2.04, 14.41) Adjusted for age, gender, race, education, prevalent CHD, diabetes, SBP, DBP, HDL, LDL, carotid intima media thickness, current smoking.	*CKD is an independent risk factor for increased risk of stroke in subjects with anaemia* P <0.01
Abramson (2003) Level II *Fair*	1 prospective cohort study (ARIC) N=12,454	Community-based middle-aged population <u>without anaemia</u>	Community US	CKD + no anaemia vs no CKD + no anaemia	Stroke (9 years)	NR	NR	HR 1.41 (0.93, 2.14) Adjusted for age, gender, race, education, prevalent CHD, diabetes, SBP, DBP, HDL, LDL, carotid intima media thickness, current smoking.	*CKD is <u>not</u> an independent risk factor for increased risk of stroke in subjects without anaemia* P=0.1
Abramson (2003) Level II *Fair*	1 prospective cohort study (ARIC) N=1262	Community-based middle-aged population <u>with anaemia</u>[c]	Community US	CKD + anaemia vs no CKD + anaemia	Ischaemic stroke (9 years)	NR	NR	HR 10.34 (1.00, 29.0) Adjusted for age, gender, race, education, prevalent CHD, diabetes, SBP, DBP, HDL, LDL, carotid intima media thickness, current smoking.	*CKD is an independent risk factor for increased risk of ischaemic stroke in subjects with anaemia* P=0.03
Abramson (2003) Level II *Fair*	1 prospective cohort study (ARIC) N=12,454	Community-based middle-aged population <u>without anaemia</u>	Community US	CKD + no anaemia vs no CKD + no anaemia	Ischaemic stroke (9 years)	NR	NR	NR Adjusted for age, gender, race, education, prevalent CHD, diabetes, SBP, DBP, HDL, LDL, carotid intima media thickness, current smoking.	*CKD is <u>not</u> an independent risk factor for increased risk of ischaemic stroke in subjects without anaemia* P=NR

CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; NR, not reported; SBP, systolic blood pressure; US, United States of America

[a] Hb <13 g/dL in men and <12 g/dL in women.

Anaemia as an independent risk factor for functional/performance status

Two studies assessed the association between **various Hb levels and functional/performance status**, as shown in Table 3.42.[94,97] Both studies assessed quality of life using the Short-Form (SF)-36 survey. The study by Finkelstein et al (2009)[94] examined the association between different categories of Hb (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL and ≥13 g/dL) and different components and domains of the SF-36 in patients with CKD who were not on dialysis. The results of the analyses showed that Hb was significantly associated with the following component and domains of the SF-36: physical component summary (P=0.08), physical functioning (P=0.003), role physical (P=0.002), energy-fatigue (P=0.02), pain (P=0.015) and general health (P=0.049). Components and domains not showing with association between Hb included mental component summary (P=0.82), role emotional (P=0.18), social function (P=0.15) and emotional wellbeing (P=0.29). The authors conclude that "higher Hgb levels are associated with improved QofL domains of the KDQofL questionnaire [which includes the SF-36]". The most dramatic changes occurred between Hb levels <11 and 11-12 g/dL. Analyses were adjusted for erythropoietin therapy, and the interaction between Hb and erythropoietin was tested and shown to be non significant for all domains.

Plantinga et al (2007)[97] assessed the relationship between 6-month Hb levels and 1-year SF-36 in patients initiating haemodialysis between October 1995 and June 1998. Hb was dichotomised as follows: ≥11 g/dL and <11 g/dL. The results of the analyses showed that higher Hb was significantly associated with higher scores on the following component and domains of the SF-36: physical component summary, mental component summary, physical functioning, role physical, social functioning, bodily pain and mental health (all P<0.05). Components and domains not showing with association between Hb included role emotional, general health and vitality.

Table 3.42 Question 1 (renal): Results for Level II evidence – functional/performance status (other anaemia criteria, Hb levels or change in Hb levels)

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
RENAL									
QUALITY OF LIFE									
SF-36–PHYSICAL COMPONENT SUMMARY									
CKD									
Finkelstein 2009 Level II *Fair*	1 cross-sectional analysis of a prospective cohort study N=NR (up to 1186)	Patients with CKD (defined as a eGFR <60 mL/min/1.73m2 (MDRD)) stages 3-5 not on dialysis	Hospital US and Canada	Hb categories (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL)	SF-36 (physical component summary)	SF-36 scores across categories: 37.4, 39.9, 38.5, 41.0		NR	*Increasing Hb level is an independent risk factor for an increase in physical component summary score* P=0.008
						Adjusted for age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)			
Dialysis									
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	6 month Hb ≥11 g/dL vs 6 month Hb <11 g/dL	1-year SF-36 (physical component summary)	33.6 ± 10.6	32.0 ± 10.1	MD 1.56 (0.16, 2.96)	*Hb ≥11 g/dL is an independent predictor of greater physical component summary score compared with Hb <11 g/dL* P<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
SF-36–MENTAL COMPONENT SUMMARY									
CKD									
Finkelstein 2009 Level II *Fair*	1 cross-sectional analysis of a prospective cohort study N=NR (up to 1186)	Patients with CKD (defined as a eGFR <60 mL/min/1.73m2 (MDRD)) stages 3-5 not on dialysis	Hospital US and Canada	Hb categories (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL)	SF-36 (mental component summary)	SF-36 scores across categories: 49.7, 50.5, 50.0, 49.5		NR	*Increasing Hb level is not an independent risk factor for change in mental component summary score* P=0.82
						Adjusted for age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)			
Dialysis									
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	6 month Hb ≥11 g/dL vs 6 month Hb <11 g/dL	1-year SF-36 (mental component summary)	49.7 ± 10.9	46.8 ± 11.9	MD 2.49 (0.35, 4.62)	*Hb ≥11 g/dL is an independent predictor of greater mental component summary score compared with Hb <11 g/dL* P<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
SF-36–PHYSICAL FUNCTIONING									

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
CKD									
Finkelstein 2009 Level II *Fair*	1 cross-sectional analysis of a prospective cohort study N=NR (up to 1186)	Patients with CKD (defined as a eGFR <60 mL/min/1.73m2 (MDRD)) stages 3-5 not on dialysis	Hospital US and Canada	Hb categories (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL)	SF-36 (physical functioning)	SF-36 scores across categories: 51.2, 56.9, 53.1, 60.7		NR	*Increasing Hb level is an independent risk factor for an increase in physical functioning score* P=0.003
						Adjusted for age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)			
Dialysis									
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	6 month Hb ≥11 g/dL vs 6 month Hb <11 g/dL	1-year SF-36 (physical functioning)	47.4 ± 28.2	40.9 ± 29.0	MD 5.02 (1.44, 8.60)	*Hb ≥11 g/dL is an independent predictor of greater physical functioning score compared with Hb <11 g/dL* P<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
SF-36–ROLE PHYSICAL									
CKD									
Finkelstein 2009 Level II *Fair*	1 cross-sectional analysis of a prospective cohort study N=NR (up to 1186)	Patients with CKD (defined as a eGFR <60 mL/min/1.73m2 (MDRD)) stages 3-5 not on dialysis	Hospital US and Canada	Hb categories (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL)	SF-36 (role physical)	SF-36 scores across categories: 40.8, 51.7, 47.1, 56.9		NR	*Increasing Hb level is an independent risk factor for an increase in role-physical score* P=0.002
						Adjusted for age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)			
Dialysis									
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	6 month Hb ≥11 g/dL vs 6 month Hb <11 g/dL	1-year SF-36 (role physical)	30.9 ± 38.3	23.8 ± 34.4	MD 6.07 (0.69, 11.5)	*Hb ≥11 g/dL is an independent predictor of greater role physical score compared with Hb <11 g/dL* P<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
SF-36–ROLE EMOTIONAL									
CKD									
Finkelstein 2009 Level II *Fair*	1 cross-sectional analysis of a prospective cohort study N=NR (up to 1186)	Patients with CKD (defined as a eGFR <60 mL/min/1.73m2 (MDRD)) stages 3-5 not on dialysis	Hospital US and Canada	Hb categories (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL)	SF-36 (role emotional)	SF-36 scores across categories: 68.5, 73.4, 68.2, 75.6		NR	*Increasing Hb level is not an independent risk factor for change in role emotional score* *P=0.18*
						Adjusted for age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Dialysis									
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	6 month Hb ≥11 g/dL vs 6 month Hb <11 g/dL	1-year SF-36 (role emotional)	61.6 ± 43.6	51.8 ± 44.4	MD 9.99 (-0.64, 20.6)	*Hb ≥11 g/dL is not an independent predictor of greater role emotional score compared with Hb <11 g/dL* P=NR
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
SF-36–ENERGY-FATIGUE									
CKD									
Finkelstein 2009 Level II *Fair*	1 cross-sectional analysis of a prospective cohort study N=NR (up to 1186)	Patients with CKD (defined as a eGFR <60 mL/min/1.73m2 (MDRD)) stages 3-5 not on dialysis	Hospital US and Canada	Hb categories (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL)	SF-36 (energy-fatigue)	SF-36 scores across categories: 43.4, 48.8, 49.0, 50.1		NR	*Increasing Hb level is an independent risk factor for an increase in energy/fatigue score* P=0.02
						Adjusted for age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)			
SF-36–SOCIAL FUNCTION									
CKD									
Finkelstein 2009 Level II *Fair*	1 cross-sectional analysis of a prospective cohort study N=NR (up to 1186)	Patients with CKD (defined as a eGFR <60 mL/min/1.73m2 (MDRD)) stages 3-5 not on dialysis	Hospital US and Canada	Hb categories (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL)	SF-36 (social function)	SF-36 scores across categories: 71.7, 76.9, 72.8, 76.2		NR	*Increasing Hb level is not an independent risk factor for change in social function* P=0.15
						Adjusted for age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)			
Dialysis									
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	6 month Hb ≥11 g/dL vs 6 month Hb <11 g/dL	1-year SF-36 (social functioning)	66.8 ± 27.1	60.4 ± 28.4	MD 5.72 (0.33, 11.1)	*Hb ≥11 g/dL is an independent predictor of greater social functioning score compared with Hb <11 g/dL* P<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
SF-36–PAIN									
CKD									
Finkelstein 2009 Level II *Fair*	1 cross-sectional analysis of a prospective cohort study N=NR (up to 1186)	Patients with CKD (defined as a eGFR <60 mL/min/1.73m2 (MDRD)) stages 3-5 not on dialysis	Hospital US and Canada	Hb categories (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL)	SF-36 (pain)	SF-36 scores across categories: 67.4, 71.4, 63.7, 70.8		NR	*Increasing Hb level is an independent risk factor for an increase in pain score* P=0.015
						Adjusted for age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)			
Dialysis									

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	6 month Hb ≥11 g/dL vs 6 month Hb <11 g/dL	1-year SF-36 (bodily pain)	59.9 ± 26.3	53.0 ± 26.7	MD 6.16 (2.37, 9.96)	*Hb ≥11 g/dL is an independent predictor of greater bodily pain score compared with Hb <11 g/dL* P<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
SF-36–GENERAL HEALTH									
CKD									
Finkelstein 2009 Level II *Fair*	1 cross-sectional analysis of a prospective cohort study N=NR (up to 1186)	Patients with CKD (defined as a eGFR <60 mL/min/1.73m2 (MDRD)) stages 3-5 not on dialysis	Hospital US and Canada	Hb categories (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL)	SF-36 (general health)	SF-36 scores across categories: 44.9, 47.0, 45.9, 50.4		NR	*Increasing Hb level is an independent risk factor for an increase in general health score* P=0.049
						Adjusted for age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)			
Dialysis									
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	6 month Hb ≥11 g/dL vs 6 month Hb <11 g/dL	1-year SF-36 (general health)	45.3 ± 21.2	43.1 ± 21.5	MD 2.63 (-2.12, 7.38)	*Hb ≥11 g/dL is not an independent predictor of greater general health score compared with Hb <11 g/dL* P=NR
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
SF-36–EMOTIONAL WELLBEING									
CKD									
Finkelstein 2009 Level II *Fair*	1 cross-sectional analysis of a prospective cohort study N=NR (up to 1186)	Patients with CKD (defined as a eGFR <60 mL/min/1.73m2 (MDRD)) stages 3-5 not on dialysis	Hospital US and Canada	Hb categories (<11 g/dL, 11-<12 g/dL, 12-<13 g/dL, ≥13 g/dL)	SF-36 (emotional wellbeing)	SF-36 scores across categories: 73.0, 76.3, 73.9, 73.2		NR	*Increasing Hb level is not an independent risk factor for change in emotional wellbeing score* P=0.29
						Adjusted for age, CKD stage, albumin, diabetes, congestive heart failure, myocardial infarction, iron use, ESA use (± interaction between Hb and ESA)			
SF-36–MENTAL HEALTH									
Dialysis									
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	6 month Hb ≥11 g/dL vs 6 month Hb <11 g/dL	1-year SF-36 (mental health)	73.0 ± 19.0	66.2 ± 21.0	MD 5.12 (2.31, 7.93)	*Hb ≥11 g/dL is an independent predictor of greater mental health score compared with Hb <11 g/dL* P<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
SF-36–VITALITY									
Dialysis									
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	6 month Hb ≥11 g/dL vs 6 month Hb <11 g/dL	1-year SF-36 (vitality)	45.7 ± 21.1	43.4 ± 20.9	MD 2.39 (-0.51, 5.29) Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.	*Hb ≥11 g/dL is not an independent predictor of greater vitality score compared with Hb <11 g/dL* P=NR

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; MD, mean difference; MDRD, modification of diet for renal disease; NR, not reported; QoL, quality of life; SF-36, short form 36 question general health survey; US, United States of America.

Five studies assessed the association between **Hb as a continuous variable and functional/performance status**, as shown in Table 3.43.[97,100,102,104,105] Merkus et al (1997)[105] examined the association between Hb and the SF-36 in patients initiating HD or PD between October 1993 and April 1995. Hb was found to be significantly associated with role emotional, social functioning and vitality. The partial variance explained by Hb was very low, ranging from 1.7% for role emotional to 6.1% for social functioning. No other domains examined were associated with Hb. The authors conclude that 'multivariate analysis showed that a higher number of comorbid conditions, a lower Hb level, and a lower residual renal function (rGFR) were the most important independent explanatory factors for poorer quality of life". However, the authors note that the total explained variation by all identified characteristics was small.

The study by Mollaoglu et al (2004)[100] examined the relationship between depression and health-related quality of life in prevalent HD patients in Turkey. Hb was one of the variables also under consideration. Hb was not shown to be associated with either the mental component summary or the physical component summary. It should kept in mind that this was a very small study (N=140). The authors did not make any specific comments regarding the association between Hb and quality of life. Global Beck's Depression Inventory (BDI) was an independent predictor of both mental and physical component summaries in this population.

Perlman et al (2005)[104] assessed the association between a number of different risk factors (including Hb) and SF-36 in patients with CKD, defined as a GFR ≤50 mL/min/1.73m^2 estimated using the MDRD. A significant association was shown between anaemia and the following components and domains of the SF-36: physical component summary ($P<0.05$), mental component summary ($P<0.05$), physical function ($P<0.05$), role physical ($P<0.05$), role emotional ($P<0.05$), social function ($P<0.01$), general health ($P<0.05$), vitality ($P<0.05$) and mental health ($P<0.05$). The only domain not significantly associated with Hb was pain.

The study by Plantinga et al (2007)[97] assessed not only the association between Hb at 6 months and 1-year SF-36, but also the association between change in Hb from baseline to 6 months and 1-year SF-36. As noted previously, this study was conducted in patients initiating haemodialysis between October 1995 and June 1998. With regards to both 6-month Hb levels and change in Hb levels from baseline to 6 months, there was a significant association with both component summaries and all individual domains examined. The authors conclude that "hemodialysis patients who attain higher hemoglobin concentration at 6 months, especially >11 g/dL, have a better [quality of life] QOL at 1 year".

Turk et al (2004)[102] assessed the association between Hb and SF-36 in men aged 18-65 who had been on HD for at least 3 months. Hb was shown to be significantly associated with both the physical and mental component summaries in this population. The authors conclude that Hb level is an independent variable (along with erectile dysfunction) that predicts the physical and mental component scores of the SF-36.

Table 3.43 Question 1 (renal): Results for Level II evidence – functional/performance status (Hb as a continuous variable)

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
RENAL									
QUALITY OF LIFE									
SF-36–PHYSICAL COMPONENT SUMMARY									
CKD									
Perlman 2005 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=NR	CKD defined as a GFR ≤50 mL/min/1.73 m^2 (estimated by MDRD)	Hospital US	Hb	SF-36 (physical component summary)	NA	NA	1.1	*Hb level is significantly associated with physical component summary score* P <0.05
						Adjusted for age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.			
Dialysis									
Mollaoglu 2004 Level II Poor	Cross-sectional analysis of prospectively collected data N=140	Prevalent haemodialysis patients	Hospital Turkey	Hb	SF-36 (physical component summary)	NA	NA	0.0329	*Hb is not significantly associated with physical component summary score* P ≥0.05
						Adjusted for age, sex, serum albumin and BDI.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increment 6-month Hb	1-year SF-36 (physical component summary)	NA	NA	MD 0.92 (0.22, 1.62)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in physical component summary score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increase in Hb from baseline to 6 months	Change in SF-36 score from baseline to 1 year (physical component summary)	NA	NA	MD 0.64 (0.16, 1.11)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in physical component summary score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: age, race, sex, baseline comorbidity (Index of Coexistent Disease), albumin and creatinine.			
Turk 2004 Level II *Poor*	1 cross-sectional analysis of prospectively collected data N=148	Men aged 18-65 on haemodialysis for at least 3 months	Hospital Turkey	Hb g/dL	SF-36 (physical component summary)	NA	NA	NR	*Hb level is significantly associated with physical component summary score* *P=0.024*
						Adjusted for variables found significant in the univariate analyses: age, occupation, education level and erectile dysfunction score.			
SF-36–MENTAL COMPONENT SUMMARY									

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
CKD									
Perlman 2005 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=NR	CKD defined as a GFR ≤50 mL/min/1.73 m2 (estimated by MDRD)	Hospital US	Hb	SF-36 (mental component summary)	NA	NA	1.1	*Hb level is significantly associated with mental component summary score* P <0.05
						Adjusted for age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.			
Dialysis									
Mollaoglu 2004 Level II Poor	Cross-sectional analysis of prospectively collected data N=140	Prevalent haemodialysis patients	Hospital Turkey	Hb	SF-36 (mental component summary)	NA	NA	Regression coefficient 0.121	*Hb is not significantly associated with mental component summary score* P ≥0.05
						Adjusted for age, sex, serum albumin and BDI.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increment 6-month Hb	1-year SF-36 (mental component summary)	NA	NA	MD 1.42 (0.72, 2.12)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in mental component summary score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increase in Hb from baseline to 6 months	Change in SF-36 score from baseline to 1 year (mental component summary)	NA	NA	MD 0.80 (0.27, 1.33)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in mental component summary score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: age, race, sex, baseline comorbidity (Index of Coexistent Disease), albumin and creatinine.			
Turk 2004 Level II *Poor*	1 cross-sectional analysis of prospectively collected data N=148	Men aged 18-65 on haemodialysis for at least 3 months	Hospital Turkey	Hb g/dL	SF-36 (mental component summary)	NA	NA	NR	*Hb level is significantly associated with mental component summary score* *P=0.021*
						Adjusted for variables found significant in the univariate analyses: age, occupation, education level and erectile dysfunction score.			
SF-36–PHYSICAL FUNCTIONING									
CKD									
Perlman 2005 Level II	1 cross-sectional analysis of	CKD defined as a GFR ≤50 mL/min/1.73 m2	Hospital US	Hb	SF-36 (physical function)	NA	NA	Parameter estimate 2.3	*Hb level is significantly associated with physical*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Fair	prospectively collected data N=NR	(estimated by MDRD)				Adjusted for age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.			*function score* P <0.05
Dialysis									
Merkus 1997 Level II *Fair*	Cross-sectional analysis of prospectively collected data N=226	Adults started on chronic haemodialysis or peritoneal dialysis in 13 Dutch dialysis centres between October 1993 and April 1995	Hospital The Netherlands	Hb	SF-36 (physical functioning)	NA	NA	NR	*Hb is <u>not</u> significantly associated with physical functioning score* P=NR
						Variables shown to be P≤0.20 in univariate analysis were included in a multiple linear regression (forward stepwise selection strategy): age, employment status, primary kidney disease, no of comorbid conditions, nPCR/nPNA, residual GFR and dialysis modality.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients <u>initiating haemodialysis</u> during 10/95 to 6/98	Hospital US	1 g/dL increment 6-month Hb	1-year SF-36 (physical functioning)	NA	NA	MD 2.61 (0.51, 4.71)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in physical functioning score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients <u>initiating haemodialysis</u> during 10/95 to 6/98	Hospital US	1 g/dL increase in Hb from baseline to 6 months	Change in SF-36 score from baseline to 1 year (physical functioning)	NA	NA	MD 1.51 (0.39, 2.62)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in physical functioning score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: age, race, sex, baseline comorbidity (Index of Coexistent Disease), albumin and creatinine.			
SF-36–ROLE PHYSICAL									
CKD									
Perlman 2005 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=NR	<u>CKD</u> defined as a GFR ≤50 mL/min/1.73 m2 (estimated by MDRD)	Hospital US	Hb	SF-36 (physical role)	NA	NA	Parameter estimate 4.8	*Hb level is significantly associated with physical role score* P <0.05
						Adjusted for age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.			
Dialysis									
Merkus 1997 Level II *Fair*	Cross-sectional analysis of prospectively collected data N=226	Adults started on chronic haemodialysis or peritoneal dialysis in 13 Dutch dialysis centres between October 1993 and April 1995	Hospital The Netherlands	Hb	SF-36 (role physical)	NA	NA	NR	*Hb is <u>not</u> significantly associated with role physical score* P=NR
						Variables shown to be P≤0.20 in univariate analysis were included in a multiple linear regression (forward stepwise selection strategy): age, employment status, primary kidney disease, no of comorbid conditions, nPCR/nPNA, residual GFR and dialysis modality.			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increment 6-month Hb	1-year SF-36 (role physical)	NA	NA	MD 2.81 (0.37, 5.26)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in role physical score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increase in Hb from baseline to 6 months	Change in SF-36 score from baseline to 1 year (role physical)	NA	NA	MD 2.72 (1.03, 4.40)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in role physical score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: age, race, sex, baseline comorbidity (Index of Coexistent Disease), albumin and creatinine.			
SF-36–ROLE EMOTIONAL									
CKD									
Perlman 2005 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=NR	CKD defined as a GFR ≤50 mL/min/1.73 m2 (estimated by MDRD)	Hospital US	Hb	SF-36 (role emotional)	NA	NA	Parameter estimate 4.0	*Hb level is significantly associated with role emotional score* P <0.05
						Adjusted for age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.			
Dialysis									
Merkus 1997 Level II *Fair*	Cross-sectional analysis of prospectively collected data N=226	Adults started on chronic haemodialysis or peritoneal dialysis in 13 Dutch dialysis centres between October 1993 and April 1995	Hospital The Netherlands	Hb	SF-36 (role emotional)	NA	NA	Regression coefficient 0.13 Partial explained variance 1.7%	*Hb is significantly associated with role emotional score* P=NR
						Variables shown to be P≤0.20 in univariate analysis were included in a multiple linear regression (forward stepwise selection strategy): age, employment status, primary kidney disease, no of comorbid conditions, nPCR/nPNA, residual GFR and dialysis modality.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increment 6-month Hb	1-year SF-36 (role emotional)	NA	NA	MD 3.75 (2.28, 5.22)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in role emotional score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
Plantinga 2007	1 cross-sectional	Patients initiating	Hospital	1 g/dL increase in Hb	Change in SF-36	NA	NA	MD 3.06 (1.01, 5.10)	*A 1 g/dL increase in Hb*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Level II *Fair*	analysis of prospectively collected data N=438	haemodialysis during 10/95 to 6/98	US	from baseline to 6 months	score from baseline to 1 year (role emotional)	Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: age, race, sex, baseline comorbidity (Index of Coexistent Disease), albumin and creatinine.			*from baseline to 6 months is significantly associated with an increase in role emotional score* *P*<0.05
SF-36–SOCIAL FUNCTIONING									
CKD									
Perlman 2005 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=NR	CKD defined as a GFR ≤50 mL/min/1.73 m2 (estimated by MDRD)	Hospital US	Hb	SF-36 (social function)	NA	NA	Parameter estimate 4.1	*Hb level is significantly associated with social function score* P <0.01
						Adjusted for age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.			
Dialysis									
Merkus 1997 Level II *Fair*	Cross-sectional analysis of prospectively collected data N=226	Adults started on chronic haemodialysis or peritoneal dialysis in 13 Dutch dialysis centres between October 1993 and April 1995	Hospital The Netherlands	Hb	SF-36 (social functioning)	NA	NA	Regression coefficient 0.23 Partial explained variance 6.1%	*Hb is significantly associated with social functioning score* P=NR
						Variables shown to be P≤0.20 in univariate analysis were included in a multiple linear regression (forward stepwise selection strategy): age, employment status, primary kidney disease, no of comorbid conditions, nPCR/nPNA, residual GFR and dialysis modality.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increment 6-month Hb	1-year SF-36 (social functioning)	NA	NA	MD 2.60 (1.35, 3.85)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in social functioning score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increase in Hb from baseline to 6 months	Change in SF-36 score from baseline to 1 year (social functioning)	NA	NA	MD 2.56 (1.20, 3.92)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in social functioning score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: age, race, sex, baseline comorbidity (Index of Coexistent Disease), albumin and creatinine.			
SF-36–PAIN									
CKD									

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Perlman 2005 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=NR	CKD defined as a GFR ≤50 mL/min/1.73 m2 (estimated by MDRD)	Hospital US	Hb	SF-36 (pain)	NA	NA	Parameter estimate 2.3	*Hb level is not significantly associated with pain score* P = NR
						Adjusted for age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.			
Dialysis									
Merkus 1997 Level II *Fair*	Cross-sectional analysis of prospectively collected data N=226	Adults started on chronic haemodialysis or peritoneal dialysis in 13 Dutch dialysis centres between October 1993 and April 1995	Hospital The Netherlands	Hb	SF-36 (bodily pain)	NA	NA	NR	*Hb is not significantly associated with bodily pain score* P=NR
						Variables shown to be P≤0.20 in univariate analysis were included in a multiple linear regression (forward stepwise selection strategy): age, employment status, primary kidney disease, no of comorbid conditions, nPCR/nPNA, residual GFR and dialysis modality.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increment 6-month Hb	1-year SF-36 (bodily pain)	NA	NA	MD 3.12 (0.94, 5.29)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in bodily pain score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increase in Hb from baseline to 6 months	Change in SF-36 score from baseline to 1 year (bodily pain)	NA	NA	MD 1.57 (0.20, 2.94)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in bodily pain score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: age, race, sex, baseline comorbidity (Index of Coexistent Disease), albumin and creatinine.			
SF-36–GENERAL HEALTH									
CKD									
Perlman 2005 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=NR	CKD defined as a GFR ≤50 mL/min/1.73 m2 (estimated by MDRD)	Hospital US	Hb	SF-36 (general health)	NA	NA	Parameter estimate 2.0	*Hb level is significantly associated with general health score* P <0.05
						Adjusted for age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Dialysis									
Merkus 1997 Level II *Fair*	Cross-sectional analysis of prospectively collected data N=226	Adults started on chronic haemodialysis or peritoneal dialysis in 13 Dutch dialysis centres between October 1993 and April 1995	Hospital The Netherlands	Hb	SF-36 (general health perceptions)	NA	NA	NR	*Hb is not significantly associated with general health perceptions score* P=NR
						Variables shown to be P≤0.20 in univariate analysis were included in a multiple linear regression (forward stepwise selection strategy): age, employment status, primary kidney disease, no of comorbid conditions, nPCR/nPNA, residual GFR and dialysis modality.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increment 6-month Hb	1-year SF-36 (general health)	NA	NA	MD 5.28 (2.38, 8.18)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in general health score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increase in Hb from baseline to 6 months	Change in SF-36 score from baseline to 1 year (general health)	NA	NA	MD 1.33 (0.41, 2.26)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in general health score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: age, race, sex, baseline comorbidity (Index of Coexistent Disease), albumin and creatinine.			
SF-36–VITALITY									
CKD									
Perlman 2005 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=NR	CKD defined as a GFR ≤50 mL/min/1.73 m2 (estimated by MDRD)	Hospital US	Hb	SF-36 (vitality)	NA	NA	Parameter estimate 2.3	*Hb level is significantly associated with vitality score* P <0.05
						Adjusted for age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Dialysis									
Merkus 1997 Level II *Fair*	Cross-sectional analysis of prospectively collected data N=226	Adults started on chronic haemodialysis or peritoneal dialysis in 13 Dutch dialysis centres between October 1993 and April 1995	Hospital The Netherlands	Hb	SF-36 (vitality)	NA	NA	Regression coefficient 0.15 Partial explained variance 2.5%	*Hb is significantly associated with vitality score* P=NR
						Variables shown to be P≤0.20 in univariate analysis were included in a multiple linear regression (forward stepwise selection strategy): age, employment status, primary kidney disease, no of comorbid conditions, nPCR/nPNA, residual GFR and dialysis modality.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increment 6-month Hb	1-year SF-36 (vitality)	NA	NA	MD 2.44 (1.10, 3.78)	*A 1 g/dL increment in 6-month Hb is significantly associated with an increase in vitality score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increase in Hb from baseline to 6 months	Change in SF-36 score from baseline to 1 year (vitality)	NA	NA	MD 1.59 (0.55, 2.62)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in vitality score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: age, race, sex, baseline comorbidity (Index of Coexistent Disease), albumin and creatinine.			
SF-36–MENTAL HEALTH									
CKD									
Perlman 2005 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=NR	CKD defined as a GFR ≤50 mL/min/1.73 m2 (estimated by MDRD)	Hospital US	Hb	SF-36 (mental health)	NA	NA	Parameter estimate 1.6	*Hb level is significantly associated with mental health score* P <0.05
						Adjusted for age, sex, race, diabetes, CAD, HTN, marital status, GFR stage 3, GFR stage 4, albumin, CHF, BMI, education.			
Dialysis									
Merkus 1997 Level II *Fair*	Cross-sectional analysis of prospectively collected data N=226	Adults started on chronic haemodialysis or peritoneal dialysis in 13 Dutch dialysis centres between October 1993 and April 1995	Hospital The Netherlands	Hb	SF-36 (mental health)	NA	NA	NR	*Hb is not significantly associated with mental health score* P=NR
						Variables shown to be P≤0.20 in univariate analysis were included in a multiple linear regression (forward stepwise selection strategy): age, employment status, primary kidney disease, no of comorbid conditions, nPCR/nPNA, residual GFR and dialysis modality.			
Plantinga 2007	1 cross-sectional	Patients initiating	Hospital	1 g/dL increment 6-	1-year SF-36	NA	NA	MD 1.90 (0.27, 3.52)	*A 1 g/dL increment in 6-*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Score ± SD	Score ± SD	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Level II *Fair*	analysis of prospectively collected data N=438	haemodialysis during 10/95 to 6/98	US	month Hb	(mental health)	Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: baseline QoL score, age, race, sex, Index of Coexistent Disease, albumin and creatinine.			*month Hb is significantly associated with an increase in mental health score* *P*<0.05
Plantinga 2007 Level II *Fair*	1 cross-sectional analysis of prospectively collected data N=438	Patients initiating haemodialysis during 10/95 to 6/98	Hospital US	1 g/dL increase in Hb from baseline to 6 months	Change in SF-36 score from baseline to 1 year (mental health)	NA	NA	MD 1.13 (0.21, 2.04)	*A 1 g/dL increase in Hb from baseline to 6 months is significantly associated with an increase in mental health score* *P*<0.05
						Adjusted for variables that had a significant association with both Hb at 6 months and QoL at 12 months, or due to prior evidence of association with QoL: age, race, sex, baseline comorbidity (Index of Coexistent Disease), albumin and creatinine.			

BDI, Beck depression index; BMI, body mass index; CAD; coronary artery disease; CHF, congestive heart failure; CI, confidence interval; GFR, glomerular filtration rate; Hb, haemoglobin; HTN, hypertension; MD, mean difference; MDRD, modification of diet for renal disease; NA, not applicable; NR, not reported; nPCR, normalised protein catabolic rate; nPNA, normalised protein nitrogen appearance; QoL, quality of life; SD, standard deviation; SF-36, short form 36-question general health survey; US, United States of America.

3.2 Question 2

Question 2 (Intervention)

In medical patients, what is the effect of RBC (allogeneic) transfusion on patient outcomes?

3.2.1 Medical population

Evidence statements – medical population		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.1	In medical patients, the effect of a restrictive versus liberal RBC transfusion strategy on mortality is uncertain. (See evidence matrix EM2.A in Volume 2 of the technical report)	√	√√	X	√	√√
ES, evidence statement; RBC, red blood cell √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – medical population	
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.

PP3	Direct evidence is not available in general medical patients.[a] Evidence from other patient groups and CRG consensus suggests that, with a: • **Hb concentration <70 g/L**, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. • **Hb concentration of 70–100 g/L**, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. • **Hb concentration >100 g/L**, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. **a** Recommendations and practice points for medical patients in a critical care setting will be found in the *Patient Blood Management Guidelines: Module 4 – Critical Care*.[3] Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.
PP4	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.
ACS, acute coronary syndrome; CHF, chronic heart failure; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; PP, practice point; RBC, red blood cell	

3.2.2 Acute coronary syndrome

Evidence statements – acute coronary syndrome		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.2	In ACS patients with a Hb concentration >100 g/L, RBC transfusion may be associated with a higher risk of mortality, proportional to Hb concentration. (See evidence matrix EM2.B in Volume 2 of the technical report)	√	√√	√√	√√√	√√√
ES2.3	In ACS patients with an *admission* Hb concentration <100 g/L, RBC transfusion may be associated with a lower risk of mortality. (See evidence matrix EM2.B in Volume 2 of the technical report)	X	√√	√	√√√	√

Evidence statements – acute coronary syndrome		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.4	In ACS patients with a *nadir* Hb concentration <80 g/L, RBC transfusion may be associated with a lower risk of mortality. (See evidence matrix EM2.B in Volume 2 of the technical report)	√	√√	X	√√√	√√√
ES2.5	In ACS patients with a *nadir* Hb concentration of 80–100 g/L, RBC transfusion is not associated with an altered mortality risk. (See evidence matrix EM2.B in Volume 2 of the technical report)	√	√√	NA	√√√	√√√
ES2.6	In patients with ACS, RBC transfusion may be associated with an increased risk of recurrence (up to 6 months) of MI. (See evidence matrix EM2.C in Volume 2 of the technical report)	√	NA	√√	√√	√√√
ACS, acute coronary syndrome; ES, evidence statement; Hb, haemoglobin; MI, myocardial infarction; RBC, red blood cell √√√=A; √√=B; √=C; X=D; NA, not applicable						

Recommendation – acute coronary syndrome	
R1 Grade C	In ACS patients with a Hb concentration >100 g/L, RBC transfusion may not be recommended because of an association with increased mortality.
Practice points – acute coronary syndrome	
PP5	In patients with ACS and a Hb concentration <80 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. (See PP1 and PP2.)
PP6	In patients with ACS and a Hb concentration of 80–100 g/L, the effect of RBC transfusion on mortality is uncertain and may be associated with an increased risk of recurrence of MI. Any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits. (See PP1 and PP2.)
ACS, acute coronary syndrome; Hb, haemoglobin; MI, myocardial infarction; PP, practice point; R, recommendation; RBC, red blood cell	

3.2.3 Heart failure

Evidence statements – heart failure		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.7	In patients with heart failure, the effect of RBC transfusion on the risk of mortality is uncertain. (See evidence matrix EM2.D in Volume 2 of the technical report)	√	NA	NA	√√	√√
ES, evidence statement; RBC, red blood cell √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice point – heart failure	
PP7	In all patients with heart failure, there is an increased risk of transfusion-associated circulatory overload. This needs to be considered in all transfusion decisions. Where indicated, transfusion should be of a single unit of RBC followed by reassessment of clinical efficacy and fluid status. For further guidance on how to manage patients with heart failure, refer to general medical or ACS sections, as appropriate (R1, R3, PP3–PP6).
ACS, acute coronary syndrome; CHF, chronic heart failure; PP, practice point; RBC, red blood cell	

3.2.4 Cancer

Evidence statements – cancer		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES2.8	In patients with cancer, RBC transfusion may be associated with an increased risk of in-hospital mortality. (See evidence matrix EM2.E in Volume 2 of the technical report)	√	NA	√	√√√	√√
ES2.9	In patients with cancer, RBC transfusion may be associated with an increased risk of in-hospital venous and arterial thromboembolic events. (See evidence matrix EM2.F in Volume 2 of the technical report)	√	NA	√	√√√	√√
ES, evidence statement; RBC, red blood cell √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – cancer	
PP8	In patients with cancer, the aetiology of anaemia is often multifactorial; where appropriate, reversible causes should be identified and treated.
PP9	There is a lack of specific evidence relating to the effects of RBC transfusion in patients with cancer. Any decision to transfuse should be based on the need to relieve clinical signs and symptoms of anaemia. When treating patients with cancer, refer also to the general medical points PP1–PP4.
PP, practice point; RBC, red blood cell	

3.2.5 Acute upper gastrointestinal blood loss

Evidence statements – acute upper gastrointestinal blood loss		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.10	In patients with acute upper gastrointestinal blood loss, the effect of a restrictive versus liberal RBC transfusion strategy on mortality is uncertain. (See evidence matrix EM2.G in Volume 2 of the technical report)	X	NA	NA	√√√	X
ES2.11	In patients with acute upper gastrointestinal blood loss, the effect of RBC transfusion on mortality is uncertain. (See evidence matrix EM2.H in Volume 2 of the technical report)	√	NA	NA	√√√	√
ES, evidence statement; RBC, red blood cell √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – acute upper gastrointestinal blood loss	
PP10	In well-compensated patients with acute upper gastrointestinal blood loss that is non-critical, there is no evidence to favour a liberal transfusion policy. Therefore, a more restrictive approach may be appropriate. There are no data to support a specific Hb treatment target in these patients.
PP11	For critically bleeding patients, refer to *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion* (2011).[110]
Hb, haemoglobin; PP, practice point	

3.2.6 Summary of evidence

Five different populations were considered for this question: (i) a mixed/general population; (ii) patients with acute coronary syndrome (ACS), (iii) patients with heart failure, (iv) patients with cancer and (v) patients with upper gastrointestinal blood loss. These were the populations that were included in relevant studies identified via the literature search.

As this is an intervention question, the levels of evidence are as follows: Level I – a systematic review of two or more Level II studies; Level II – a randomised controlled trial (RCT); Level III-1 – a pseudorandomised trial; Level III-2 – a comparative study with concurrent controls (including non-randomised, experimental trials, cohort studies, case-control studies and interrupted time series with a control group); Level III-3 – a comparative study without concurrent controls (including historical control studies, two or more single arm studies, interrupted time series without a parallel control group); and Level IV – case series with either post-test or pre-test/post-test outcomes.

For this review, only evidence down to Level III-2 was considered. In addition, for Level III evidence, only studies which included ≥500 subjects and adjusted for potential confounding variables using multivariate analysis were included; studies in which only univariate analyses were undertaken were excluded. The studies included for this question identified potential confounding variables in various ways. In some cases, variables have been identified which have been shown to be associated with blood transfusion or the specified outcome in previous studies, while in other cases a wide range of variables have been examined using univariate analysis and those shown to be associated with blood transfusion or the outcome have been included in the analysis. In some studies, all potential confounding variables have been included in the multivariate analysis, while in other studies different methods have been used (eg, backwards or forwards stepwise regression) to include only those variables which are shown to be independent predictors in the analysis.

There were two different comparisons made in this review: (1) transfusion versus no transfusion; and (2) restrictive transfusion versus liberal transfusion. As it is not considered ethical to withhold blood transfusion, RCTs were not available for the transfusion versus no transfusion comparison; the evidence for this comparison came from observational studies (Level III) only. Proof of causation can only be determined using a randomised, controlled trial. Thus, while the results of these adjusted Level III study analyses indicate whether or not blood transfusion is an independent risk factor for specific outcomes, they do not prove that blood transfusion *causes* these outcomes.

MEDICAL POPULATION

While the aim of this review is to assess the effect of allogeneic RBC transfusion on adverse outcomes specifically in *medical* patients, there is a large amount of evidence available in other populations, in particular in the surgical and critical care settings. Thus, studies which assessed the effect of allogeneic RBC transfusion across a wide population (including medical) were considered eligible for assessment. Of the adverse outcomes specified for this question, three are covered for this wide population: mortality, thromboembolic events and transfusion-related adverse events.

Methods

There were two studies identified for this population from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified one systematic review of Level II evidence (RCT) examining the effect of RBC transfusion in a mixed population from medical, critical care and surgical settings.

Level II evidence

The literature search did not identify any Level II studies relevant to this population.

Level III evidence

The literature search did not identify any Level III studies relevant to this population.

Level IV evidence

Level IV evidence was not searched for this question.

Results

Level I evidence

One Level I study was identified which assessed the efficacy and safety of restrictive versus liberal RBC transfusion in a mixed population which included medical, critical care and surgical patients. This study by Carless et al (2002)[111] was a Cochrane review with the literature updated to August 2009. The review assessed data from 17 RCTs including a total of 3746 patients. Only three of the included studies were in a medical population (two in gastrointestinal haemorrhage and one in leukaemia); the remaining studies were in surgical patients (eight studies), critical care (5 studies) and paediatric critical care (one study). Of the three medical studies included in Carless et al (2010), only one was considered eligible for inclusion in this review.[112] The remaining two medical studies were excluded for being available as an abstract only (Colomo et al 2008) and for assessing the wrong outcomes (Webert et al 2008). Thus, while the Carless review provides a comprehensive assessment of the efficacy and safety of restrictive versus liberal RBC transfusion in a broad population, its generalisability to the medical population needs to be considered.

Table 3.44 Question 1 (Medical): Characteristics and quality of Level I evidence

Level I evidence			
Author	Study type *Study quality*	Population	Outcomes
Carless et al (2010)[111]	Systematic review of 17 RCTs *Good*	Any (2 GI haemorrhage, 1 leukaemia, 8 surgery, 5 critical care and 1 paediatric critical care)	Mortality Thromboembolic events Transfusion-related adverse events

GI, gastrointestinal; RCT, randomised controlled trial.

The effect of liberal versus restrictive RBC transfusion on mortality

One Level I study assessed the effect of a restrictive versus liberal RBC transfusion strategy on mortality in a mixed population, as shown in Table 3.45The authors note that there was a variation in the thresholds used in the individual studies for the restrictive and liberal

transfusion strategies. For restrictive transfusion, the majority of trials used a Hb threshold of between 7.0 g/dL and 9.0 g/dL, while two studies specified Hct levels of 25% or 30%. The definition of liberal transfusion varied to a greater degree and included transfusion in all in some trials, transfusion sufficient to maintain a Hb of ≥9, 10 or 12 g/dL in most studies, and Hct 32% in two trials.

The study by Carless et al (2010)[111] showed no difference between the two strategies for all mortality outcomes with the exception of in-hospital mortality, where restrictive transfusion resulted in 22% less mortality than liberal transfusion. The results for 30-day mortality also suggested a possible reduction in mortality for restrictive transfusion, although this failed to reach statistical significance. The Blair 1986 study was included in the 30-day mortality and hospital mortality analyses; the Colomo study was included in the unspecified follow-up period analysis. Based on their review, which includes an assessment of harms as well, the authors' conclude that "the existing evidence supports the use of restrictive transfusion triggers in patients who are free of serious cardiac disease". When considering the results of this study, it is important to keep in mind that the analyses are driven by the results of studies conducted in the surgical and critical care settings, and that these may not be generalisable to a medical population.

Table 3.45 Question 2 (Medical): Results for Level I evidence – mortality

Study Level of evidence[a] *Quality* *(Level I/Level II)*	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity[b]
LEVEL I EVIDENCE									
Any population (includes critical care and surgical)									
Carless 2010 Level I Good/fair	2 RCTs N=821	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	<15-day mortality	1/408 (0.2)	3/413 (0.7)	RR 0.44 (0.006, 2.96)	No difference P=0.40 No heterogeneity (Phet=0.84; I^2=0%)
Carless 2010 Level I Good/fair	9 RCTs N=2461	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	30-day mortality	113/1226 (9.2)	134/1235 (10.9)	RR 0.83 (0.66, 1.05)	No difference P=0.12 No heterogeneity (Phet=0.65; I^2=0%)
Carless 2010 Level I Good/fair	2 RCTs N=922	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	60-day mortality	100/460 (21.7)	113/462 (24.5)	RR 1.09 (0.46, 2.60)	No difference P=0.85 Moderate heterogeneity (Phet=0.19; I^2=42%)
Carless 2010 Level I Good/poor	1 RCT N=69	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	120-day mortality	13/33 (39.4)	11/36 (30.6)	RR 1.29 (0.67, 2.47)	No difference P=NR Not applicable (Phet=NA)
Carless 2010 Level I Good/fair	4 RCTs N=1409	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Hospital mortality	96/701 (13.7)	126/708 (17.8)	RR 0.78 (0.62, 0.98)	Favours restrictive transfusion P=0.031 No heterogeneity (Phet=0.53; I^2=0%)
Carless 2010 Level I Good/fair	3 RCTs N=736	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	ICU mortality	19/373 (5.1)	15/363 (4.1)	RR 1.15 (0.59, 2.23)	No difference P=0.68 No heterogeneity (Phet=0.52; I^2=0%)
Carless 2010 Level I Good/poor	1 RCT N=214	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Mortality (unspecified follow-up)	12/109 (11.0)	17/105 (16.2)	RR 0.68 (0.34, 1.35)	No difference P=NR Not applicable (Phet=NA)

CI, confidence interval; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio
Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.
[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

The effect of liberal versus restrictive RBC transfusion on thromboembolic events

One Level I study assessed the effect of RBC transfusion on MI/stroke and related cardiac and thromboembolic events. The study by Carless et al (2010)[111] showed a 24% reduction in the number of patients experiencing cardiac events (defined as MI, cardiac arrhythmias, cardiac arrest, pulmonary oedema and angina) when a restrictive RBC transfusion threshold is used. Analysis of MI showed no significant difference; however, the risk estimate was low (RR 0.50) so underpowering may have been an issue in this analysis. Analyses of stroke and thromboembolism also showed no significant difference between the use of restrictive and liberal transfusion thresholds, with RRs of 0.98 and 0.95, respectively. These analyses included data from surgical and critical care populations only.

Table 3.46 Question 2 (Medical): Results for Level I evidence – thromboembolic events

Study Level of evidence[a] Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneityb
LEVEL I EVIDENCE									
Any population (includes critical care and surgical)									
Carless 2010 Level I Good	5 RCTs N=1530	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Cardiac events	113/762 (14.8)	152/768 (19.8)	RR 0.76 (0.57, 1.00)	Favours restrictive transfusion P=0.049 Mild heterogeneity (Phet=0.30; I^2=18%)
Carless 2010 Level I Good	7 RCTs N=1868	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Myocardial infarction	7/931 (0.8)	16/937 (1.7)	RR 0.50 (0.21, 1.21)	No difference P=0.12 No heterogeneity (Phet=0.54; I^2=0%)
Carless 2010 Level I Good	3 RCTs N=242	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Stroke	2/122 (1.6)	2/120 (1.7)	RR 0.98 (0.17, 5.52)	No difference P=0.98 No heterogeneity (Phet=0.65; I2=0%)
Carless 2010 Level I Good	2 RCTs N=204	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Thromboembolism	2/102 (2.0)	2/102 (2.0)	RR 0.95 (0.14, 6.36)	No difference P=0.96 No heterogeneity (Phet=0.37; I2=0%)

CI, confidence interval; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

The effect of liberal versus restrictive RBC transfusion on transfusion-related adverse events

One Level I study assessed the effect of a restrictive RBC transfusion threshold on transfusion-related adverse events including pulmonary oedema, pneumonia and infection. The study by Carless et al (2010)[111] showed that a restrictive strategy significantly reduced the risk of infection (RR 0.76; 95% CI 0.60, 0.97). There was no significant difference for pneumonia or pulmonary oedema. However, the risk estimate for pulmonary oedema was low (RR 0.49) and the event rate was small (2.9% for restrictive versus 6.3% for liberal) suggesting that this analysis may have been underpowered.

Table 3.47 Question 2 (Medical): Results for Level I evidence – transfusion-related adverse events

Study Level of evidence[a] Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity[b]
LEVEL I EVIDENCE									
Any population (includes critical care and surgical)									
Carless 2010 Level I Good	4 RCTs N=1633	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Pulmonary oedema	24/818 (2.9)	51/815 (6.3)	RR 0.49 (0.18, 1.31)	No difference P=0.16 Mild heterogeneity (Phet=0.30; I^2=19%)
Carless 2010 Level I Good	4 RCTs N=1679	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Pneumonia	99/840 (11.8)	100/839 (11.9)	RR 1.00 (0.78, 1.29)	No difference P=0.98 No heterogeneity (Phet=0.68; I^2=0%)
Carless 2010 Level I Good	4 RCTs N=1788	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Infection	94/891 (10.5)	124/897 (13.8)	RR 0.76 (0.60, 0.97)	Favours restrictive transfusion P=0.029 No heterogeneity (Phet=0.43; I^2=0%)

CI, confidence interval; RCT, randomised controlled trial; RR, risk ratio

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25-50%; substantial heterogeneity I2 >50%.

ACUTE CORONARY SYNDROME

The term acute coronary syndrome refers to a range of acute myocardial ischaemic states. It encompasses unstable angina, non-ST segment elevation myocardial infarction (NSTE-ACS; ST segment elevation generally absent), and ST segment elevation infarction (STEMI; persistent ST segment elevation usually present).

Of the adverse outcomes specified for this question, two are covered for this population: mortality and MI.

Methods

There were 6 studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no Level I studies examining the effect of RBC transfusion in patients with ACS.

Level II evidence

The literature search identified no Level II studies examining the effect of RBC transfusion in patients with ACS.

Level III evidence

The literature search identified six Level III studies examining the effect of RBC transfusion in patients with ACS.

Level IV evidence

Level IV evidence was not searched for this question.

Results

Level III evidence

Six Level III-2 studies were included for this question: all six studies provided evidence for mortality and one provided evidence for thromboembolic events, as summarised in Table 3.48.[16,113-117]

Table 3.48 Question 2 (ACS): Characteristics and quality of Level III evidence

Author	Study type *Study quality*	Population	Outcomes
Level III evidence			
Alexander et al (2008)[113]	Retrospective cohort study *Fair*	Patients with NSTE-ACS presenting within 24 hours of their last symptoms (subgroups defined by nadir Hct) N=44,242	Mortality
Rao et al (2004)[114]	Cohort analysis of data from 3 RCTs *Good*	ACS N=24,112	Mortality
Sabatine et al (2005)[16]	Cohort analysis of data from 16 RCTs *Fair*	STEMI (subgroups defined by baseline Hb) and NSTE-ACS N=39,922	Mortality
Shishehbor et al (2009)[115]	Cohort analysis of data from a RCT *Good*	STEMI N=3,575	Mortality Thromboembolic events
Wu et al (2001)[116]	Retrospective cohort study *Fair*	Aged ≥65 years with confirmed acute MI (subgroups defined by Hct) N=78,974	Mortality
Yang et al (2005)[117]	Retrospective cohort study *Poor*	NSTE-ACS (excluding patients undergoing CABG) N=74,271	Mortality

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; Hb, haemoglobin; NSTE-ACS, non-ST segment elevation acute coronary syndrome; RCT, randomised controlled trial; STEMI, ST-segment elevation infarction; Hct, hematocrit; MI, myocardial infarction.

The effect of RBC transfusion on mortality

Four level III-2 studies assessed the **association between RBC transfusion and mortality in the overall ACS population**, as shown in Table 3.49.[16,114,115,117] The study by Rao et al (2004)[114] assessed the association between blood transfusion (whole blood or pRBCs) and 30-day mortality and 30-day mortality/MI in 24,112 patients with ACS who took part in three RCTs (GUSTO IIb, PURSUIT and PARAGON). Rao et al (2004)[114] performed two analyses on the whole population: (i) a Cox regression analysis which incorporated transfusion as a time-dependent covariate; and (ii) a landmark analysis in which they assessed transfusion as a time-fixed covariate, with the analysis divided into seven 24-hour periods. While the analyses were adjusted for a large number of potential confounding variables based on previously identified confounders and variables shown to be associated with propensity for bleeding and transfusion in regression analyses conducted specifically for their study, it is unclear if the treatments given in the RCTs were included in these considerations.

In the Cox regression analysis, blood transfusion was significantly and independently associated with 30-day mortality and 30-day mortality/MI (HR 3.94 and 2.92 respectively). In the landmark analysis, blood transfusion was significantly and independently associated with 30-day mortality during the third (49-72 hours) and fifth (97-120 hours) 24-hour periods. The ORs associated with these increased mortality risks were approximately 2.8 and 2.7, respectively.

The study by Sabatine et al (2005)[16] assessed the association between blood transfusion (whole blood or pRBCs) and 30-day cardiovascular mortality/MI/recurrent ischaemia in 39,922 patients diagnosed with NSTE-ACS. The results of the analysis showed that blood transfusion was an independent risk factor for 30-day cardiovascular mortality/MI/recurrent ischaemia (OR 1.54; 95% CI 1.14, 2.09).

Yang et al (2005)[117] assessed the effect of blood transfusion (non-autologous whole blood or pRBCs) on in-hospital mortality and in-hospital mortality/MI in patients with NSTE-ACS who did not undergo CABG while hospitalised. The median (25^{th}/75^{th} percentiles) nadir Hct in the transfused group was 26 (24, 26) and 35 (31, 39) in the non-transfused group.

Yang et al (2005)[117] found that blood transfusion was associated with a significantly increased risk of mortality (OR 1.67; 95% CI 1.48, 1.88) and mortality/MI (OR 1.44; 95% CI 1.30, 1.60). While this study did assess a large number of potential confounders, adjustment for Hct did not appear to have been carried out which, as will be shown by the following section, may have biased the results of the study.

The study by Shishehbor et al (2009) examined the association between blood transfusion (whole blood or pRBCs) and mortality in patients with STEMI (approximately 4% underwent CABG and 18% underwent PCI within 7 days of randomisation). Baseline and nadir Hb and Hct were significantly lower in the transfused group compared with the non-transfused group.

The analysis showed a large increase in the risk of 30-day, 60-day and 1-year mortality in those undergoing blood transfusion, with HRs ranging from 3.03 to 3.89 (N=up to 3575). In addition, they undertook and propensity score and matching analysis which included 958 subjects, which also showed a significant increased risk of 30-day, 60-day and 1-year mortality associated with blood transfusion (HR 5.44, 4.81 and 3.10, respectively). Only the matched propensity analysis was adjusted for nadir Hb.

Shishhebor et al (2009)[115] state that their study results support the results of Rao, although their analysis was based on data from the GUSTO trial, which was one of three RCTs included in the Rao study.

Table 3.49 Question 2 (ACS): Results for Level III evidence – mortality (all ACS patients)

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=24,112	NSTE-ACS	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	192/2401 (8.0)	669/21,711 (3.1)	HR 3.94 (3.26, 4.75)	Blood transfusion is significantly associated with increased 30-day mortality in patients with NSTE-ACS P=NR
						Cox-regression analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit.			
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=24,112	NSTE-ACS	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality/recurrent MI	702/2401 (29.2)	2176/21,711 (10.0)	HR 2.92 (2.55, 3.35)	Blood transfusion is significantly associated with increased 30-day mortality/recurrent MI in patients with NSTE-ACS P=NR
						Cox-regression analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit.			
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=20,688 at risk	NSTE-ACS	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality (first 24 hours)	NR	NR	NR	Blood transfusion is not significantly associated with 30-day mortality during the first 24 hours in patients with NSTE-ACS P=NR
						Landmark analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period.			

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=20,464 at risk	NSTE-ACS	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality (second 24 hours)	NR	NR	NR	Blood transfusion is not significantly associated with 30-day mortality during the second 24 hours in patients with NSTE-ACS P=NR
						Landmark analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period.			
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=20,256 at risk	NSTE-ACS	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality (third 24 hours)	NR	NR	NR	Blood transfusion is significantly associated with increased 30-day mortality during the third 24 hours in patients with NSTE-ACS P=NR
						Landmark analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period.			
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=20,013 at risk	NSTE-ACS	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality (fourth 24 hours)	NR	NR	NR	Blood transfusion is not significantly associated with 30-day mortality during the fourth 24 hours in patients with NSTE-ACS P=NR
						Landmark analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period.			

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=19,816 at risk	NSTE-ACS	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality (fifth 24 hours)	NR	NR	NR	Blood transfusion is significantly associated with increased 30-day mortality during the fifth 24 hours in patients with NSTE-ACS P=NR
						Landmark analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period.			
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=19,625 at risk	NSTE-ACS	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality (sixth 24 hours)	NR	NR	NR	Blood transfusion is not significantly associated with 30-day mortality during the sixth 24 hours in patients with NSTE-ACS P=NR
						Landmark analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period.			
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=19,450 at risk	NSTE-ACS	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality (seventh 24 hours)	NR	NR	NR	Blood transfusion is not significantly associated with 30-day mortality during the seventh 24 hours in patients with NSTE-ACS P=NR
						Landmark analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period.			

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
Sabatine 2005 Level III-2 Fair	1 prospective cohort study (analysis of data from 16 RCTs) N=14,503	NSTE-ACS	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day cardiovascular mortality/MI/recurrent ischaemia	NR	NR	OR 1.54 (1.14, 2.09) Adjusted for: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, β-blocker, angiotensin receptor blocker, or hypolipidemic use, index revascularisation, transfusion, transfusion and Hb interaction, bleeding and anterior location of index MI.	Whole or pRBC transfusion is significantly associated with increased 30-day cardiovascular mortality in patients with NSTE-ACS patients P=NR
Yang 2005 Level III-2 Poor	1 retrospective cohort study N=74,271	NSTE-ACS (excludes patients undergoing CABG)	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	In-hospital mortality	11.5%	3.8%	OR 1.67 (1.48, 1.88) Adjusted for: patient demographics (age, gender, BMI, race), cardiac risk factors (family history of CAD, hypertension, diabetes, current/recent smoker, hypercholesterolaemia), medical co-morbidities (renal insufficiency, previous MI, previous PCI, previous CABG, previous CHF, previous stroke), presenting characteristics (ST-segment depression, ST-segment elevation, positive cardiac marker, signs of CHF at presentation, HR, SBP) and socioeconomic status (insurance status).	Blood transfusion is significantly associated with in-increased hospital mortality in patients with NSTE-ACS who haven't undergone CABG while hospitalised P=NR
Yang 2005 Level III-2 Poor	1 retrospective cohort study N=74,271	NSTE-ACS (excludes patients undergoing CABG)	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	In-hospital mortality/MI	13.4%	5.8%	OR 1.44 (1.30, 1.60) Adjusted for: patient demographics (age, gender, BMI, race), cardiac risk factors (family history of CAD, hypertension, diabetes, current/recent smoker, hypercholesterolaemia), medical co-morbidities (renal insufficiency, previous MI, previous PCI, previous CABG, previous CHF, previous stroke), presenting characteristics (ST-segment depression, ST-segment elevation, positive cardiac marker, signs of CHF at presentation, HR, SBP) and socioeconomic status (insurance status).	Blood transfusion is significantly associated with increased in-hospital mortality/MI in patients with NSTE-ACS who haven't undergone CABG while hospitalised P=NR
Shishehbor 2009 Level III-2 Good	1 prospective cohort study (analysis of data from a RCT) N=3575	STEMI	Hospital Various (including Australia)	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	HR 3.89 (2.66, 5.68) Cox proportional hazards analysis adjusted for: age, gender, race, height, weight, country of origin, comorbidities including diabetes, hypertension, hypercholesterolaemia, smoking, COPD, chronic renal insufficiency, PAD, HF, stroke, cancer diagnosed in past 5 years, history of PCI and CABG, Killip class, family history of cardiac diseases and risk factors, medical therapy and interventions (ambulatory and in-hospital).	Blood transfusion is significantly associated with increased 30-day mortality in patients with STEMI P<0.001

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
Shishehbor 2009 Level III-2 Good	1 prospective cohort study (analysis of data from a RCT) N=3538	STEMI	Hospital Various (including Australia)	Whole or RBC transfusion vs no whole or RBC transfusion	6-month mortality	NR	NR	HR 3.63 (2.67, 4.95) Cox proportional hazards analysis adjusted for: age, gender, race, height, weight, country of origin, comorbidities including diabetes, hypertension, hypercholesterolaemia, smoking, COPD, chronic renal insufficiency, PAD, HF, stroke, cancer diagnosed in past 5 years, history of PCI and CABG, Killip class, family history of cardiac diseases and risk factors, medical therapy and interventions (ambulatory and in-hospital).	Blood transfusion is significantly associated with increased 6-month mortality in patients with STEMI P<0.001
Shishehbor 2009 Level III-2 Good	1 prospective cohort study (analysis of data from a RCT) N=3465	STEMI	Hospital Various (including Australia)	Whole or RBC transfusion vs no whole or RBC transfusion	1-year mortality	NR	NR	HR 3.03 (2.25, 4.08) Cox proportional hazards analysis adjusted for: age, gender, race, height, weight, country of origin, comorbidities including diabetes, hypertension, hypercholesterolaemia, smoking, COPD, chronic renal insufficiency, PAD, HF, stroke, cancer diagnosed in past 5 years, history of PCI and CABG, Killip class, family history of cardiac diseases and risk factors, medical therapy and interventions (ambulatory and in-hospital).	Blood transfusion is significantly associated with increased 6-month mortality in patients with STEMI P<0.001
Shishehbor 2009 Level III-2 Good	1 prospective cohort study (analysis of data from a RCT) N=943	STEMI	Hospital Various (including Australia)	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	HR 5.44 (3.21, 9.22) Propensity score and matching analysis adjusted for: age, gender, race, height, weight, country of origin, comorbidities including diabetes, hypertension, hypercholesterolaemia, smoking, COPD, chronic renal insufficiency, PAD, HF, stroke, cancer diagnosed in past 5 years, history of PCI and CABG, Killip class, family history of cardiac diseases and risk factors, medical therapy and interventions (ambulatory and in-hospital) and nadir Hb.	Blood transfusion is significantly associated with increased 30-day mortality in patients with STEMI P<0.001
Shishehbor 2009 Level III-2 Good	1 prospective cohort study (analysis of data from a RCT) N=958	STEMI	Hospital Various (including Australia)	Whole or RBC transfusion vs no whole or RBC transfusion	6-month mortality	NR	NR	HR 4.81 (3.00, 7.71) Propensity score and matching analysis adjusted for: age, gender, race, height, weight, country of origin, comorbidities including diabetes, hypertension, hypercholesterolaemia, smoking, COPD, chronic renal insufficiency, PAD, HF, stroke, cancer diagnosed in past 5 years, history of PCI and CABG, Killip class, family history of cardiac diseases and risk factors, medical therapy and interventions (ambulatory and in-hospital) and nadir Hb.	Blood transfusion is significantly associated with increased 6-month mortality in patients with STEMI P<0.001
Shishehbor 2009 Level III-2 Good	1 prospective cohort study (analysis of data from a RCT) N=958	STEMI	Hospital Various (including Australia)	Whole or RBC transfusion vs no whole or RBC transfusion	1-year mortality	NR	NR	HR 3.10 (2.18, 4.40) Propensity score and matching analysis adjusted for: age, gender, race, height, weight, country of origin, comorbidities including diabetes, hypertension, hypercholesterolaemia, smoking, COPD, chronic renal insufficiency, PAD, HF, stroke, cancer diagnosed in past 5 years, history of PCI and CABG, Killip class, family history of cardiac diseases and risk factors, medical therapy and interventions (ambulatory and in-hospital) and nadir Hb.	Blood transfusion is significantly associated with increased 1-year mortality in patients with STEMI P<0.001

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; NR, not reported; NSTE-ACS, non-ST segment elevation acute coronary syndrome; OR, odds ratio; RBC, red blood cell; RCT, randomised controlled trial; STEMI, ST-segment elevation infarction; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CAD, coronary artery disease; CHF, coronary heart failure; PVD, peripheral artery disease; PCI, percutaneous coronary intervention; CK, creatine kinase; ECG, electrocardiogram; ACEI, angiotensin converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease.

As shown in the previous section, the results of all four studies which assessed the association between blood transfusion and mortality in the overall population suggest that blood transfusion is associated with an increased risk of mortality.

Four Level III-2 studies assessed the association between blood transfusion and mortality, **stratified by Hct/Hb level**, as shown in Table 3.50.[16,113,114,116] The first of these was performed by Wu et al (2001),[116] who carried out two analyses of the association between blood transfusion (whole blood or pRBCs) and mortality in a population aged ≥65 years with confirmed acute MI: (i) including all patients and (ii) excluding patients who died within the first 48 hours. This second analysis was carried out in order to account for those patients who may have died before receiving a transfusion. The blood transfusion rate was 71.3% in those in the lowest admission Hct category (5.0-24.0%; N=380) and 1.6% in those in the highest admission Hct category (39.1-48.0%; N=44,699).

In the analysis including all subjects, Wu et al found that blood transfusion was associated with a reduction in mortality in patients with admission Hct levels of ≤33%, with the OR ranging from 0.22 to 0.69. Admission Hct >36% was associated with an increase in mortality (OR 1.38-1.46). A similar result was seen for the second analysis excluding those who died within the first 48 hours, with a decreased risk of mortality associated with blood transfusion seen in patients with an admission Hct of <30% (OR 0.36-0.75). The risk of mortality associated with blood transfusion in patients who survived at least 2 days with Hct >33% was not reported.

The study by Rao et al (2004)[114] examined the relationship between blood transfusion (whole blood or pRBCs) and 30-day mortality, stratified by nadir Hct in patients with ACS. The median nadir Hct (IQR) was 29.0 (24.6-35.2) in the transfused group (N=2401) and 37.6 (34.4-40.5) in the non-transfused group (N=21,711), while the baseline Hct was 39.9 (36.3-43.1) in the transfused group and 41.7 (38.8-44.5) in the non-transfused group. There was no significant association between blood transfusion and mortality at nadir Hct levels of 20% and 25%, but there was a large and significant association at nadir Hct levels of 30% and 35% (OR 168 and 292, respectively).

Rao et al (2004)[114] note the disparity between the results of their study and the Wu study; ie, blood transfusion in patients with lower admission Hct resulted in lower mortality in the Wu study, while blood transfusion in patients with a lower nadir Hct resulted in no significant difference in mortality risk in the Rao study. Rao presents a number of possible reasons for the discrepancy including: (i) the use of admission Hct in the Wu study compared with nadir Hct in the Rao study, which they state is a critical issue as "a fundamental problem facing clinicians is whether to use transfusion in patients who are otherwise stable but have developed anaemia [during hospitalisation] as a consequence of medications, procedures or both"; (ii) the difference in methods of data collections (i.e. Medicare claims database for Wu and RCTs for Rao, which had better data collection, particularly for bleeding and transfusion); (iii) the more restricted population in the Wu study which excluded patients <65 years, those with bleeding within 48 hours of admission and those who underwent open-heart surgery; and (iv) different statistical methods, with Rao carrying out analyses with transfusion as both a time-dependent variable and in a landmark analysis, which they consider minimised survivor bias.

Sabatine et al (2005)[16] analysed the relationship between blood transfusion (whole blood or pRBCs) and cardiovascular mortality, stratified by admission Hb level. In patients with STEMI and a Hb <12 g/dL, blood transfusion was significantly associated with a decreased risk of

cardiovascular mortality (OR 0.42; 95% CI 0.20, 0.89). In patients with STEMI and a Hb ≥12 g/dL, blood transfusion was associated with a potentially increased risk of cardiovascular mortality (OR 1.42), although this was not statistically significant.

The results of the Sabatine et al (2005)[16] study are consistent with those of the Wu study, where blood transfusion appears to be beneficial at a lower Hct/Hb. Sabatine et al note that the Wu and Rao studies had conflicting results. They state that in their study there was a reduction in cardiovascular mortality in STEMI patients with an admission Hb <12 g/dL who were transfused, but an increase in cardiovascular mortality/MI/recurrent ischaemia in patients with NSTE-ACS (not stratified by Hb) who were transfused.

Alexander et al (2008)[113] assessed the association between blood transfusion (non-autologous whole blood or pRBCs) and in-hospital mortality, stratified by different categories of nadir Hct. The transfusion rate was 79.2% in the Hct ≤24% group, 59.1% in the Hct 24.1-27.0% group, 21.8% in the Hct 27.1-30.0% group and 0.9% in the Hct >30% group.

After performing two adjusted analyses (the first adjusting for clinical factors and the second adjusting for clinical factors, baseline Hct and transfusion by nadir Hct interaction) they found no significant association between blood transfusion and mortality when the nadir Hct was ≤30% (although there was a trend towards reduced mortality), and a significant and independent association between blood transfusion and mortality when the nadir Hct was >30% (OR 2.89 and 3.47, respectively).

In their discussion Alexander et al (2008)[113] also state that two previous studies by Wu and Rao arrive at different conclusions, and note that the Wu study was performed exclusively in the elderly and did not consider the "effects of bleeding, baseline and nadir HCTs."

Table 3.50 Question 2 (ACS): Results for Level III evidence – mortality (stratified by Hct/Hb level)

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
Wu 2001 Level III-2 Fair	1 retrospective cohort study N=380	Aged ≥65 years with confirmed acute MI and admission Hct 5.0-24 %	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 0.22 (0.11, 0.45)	Blood transfusion is significantly associated with decreased 30-day mortality in elderly patients with AMI and a Hct 5.0-24.0% P=NR
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			
Wu 2001 Level III-2 Fair	1 retrospective cohort study N=838	Aged ≥65 years with confirmed acute MI and admission Hct 24.1-27%	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 0.48 (0.34, 0.69)	Blood transfusion is significantly associated with decreased 30-day mortality in elderly patients with AMI and a Hct 24.1-27.0% P=NR
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			
Wu 2001 Level III-2 Fair	1 retrospective cohort study N=2106	Aged ≥65 years with confirmed acute MI and admission Hct 27.1-30%	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 0.60 (0.47, 0.76)	Blood transfusion is significantly associated with decreased 30-day mortality in elderly patients with AMI and a Hct 27.1-30.0% P=NR
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			
Wu 2001	1 retrospective cohort	Aged ≥65 years with	Hospital	Whole or RBC	30-day mortality	NR	NR	OR 0.69 (0.53, 0.89)	Blood transfusion is

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			
Wu 2001 Level III-2 Fair	1 retrospective cohort study N=9885	Aged ≥65 years with confirmed acute MI and admission Hct 33.1-36%	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 1.13 (0.89, 1.44)	Blood transfusion is not associated with 30-day mortality in elderly patients with AMI and a Hct 33.1-36.0% P=NR
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			
Wu 2001 Level III-2 Fair	1 retrospective cohort study N=16,218	Aged ≥65 years with confirmed acute MI and admission Hct 36.1-39%	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 1.38 (1.05, 1.80)	Blood transfusion is significantly associated with increased 30-day mortality in elderly patients with AMI and a Hct 36.1-39.0% P=NR
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			
Wu 2001 Level III-2 Fair	1 retrospective cohort study N=44,699	Aged ≥65 years with confirmed acute MI and admission Hct 39.1-48%	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 1.46 (1.18, 1.81)	Blood transfusion is significantly associated with increased 30-day mortality in elderly patients with AMI and a Hct 39.1-48.0% P=NR
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			
Wu 2001	1 retrospective cohort	Aged ≥65 years with	Hospital	Whole or RBC	30-day mortality	NR	NR	OR 0.36 (0.15, 0.83)	Blood transfusion is

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			
Wu 2001 Level III-2 Fair	1 retrospective cohort study N=NR	Aged ≥65 years with confirmed acute MI and admission Hct 24.1-27%, excluding those who died in the first 48 hours	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 0.69 (0.47, 1.01)	Blood transfusion may be associated with decreased 30-day mortality in elderly patients with AMI and a Hct 24.1-27.0% P=NR
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			
Wu 2001 Level III-2 Fair	1 retrospective cohort study N=NR	Aged ≥65 years with confirmed acute MI and admission Hct 27.1-30%, excluding those who died in the first 48 hours	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 0.75 (0.58, 0.96)	Blood transfusion is significantly associated with decreased 30-day mortality in elderly patients with AMI and a Hct 27.1-30.0% P=NR
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			
Wu 2001 Level III-2 Fair	1 retrospective cohort study N=NR	Aged ≥65 years with confirmed acute MI and admission Hct 30.1-33%, excluding those who died in the first 48 hours	Hospital US	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 0.98 (0.76, 1.25)	Blood transfusion is not associated with 30-day mortality in elderly patients with AMI and a Hct 30.1-33.0% P=NR
						Adjusted for: APACHE II score, do-not-resuscitate order on admission, MI location, CHF, MAP, HR, renal insufficiency; primary reperfusion therapy, aspirin use on admission, beta-blocker use on admission and predictors of the use of blood transfusion.			

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=NR	ACS and nadir Hct 20%	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 1.59 (0.95, 2.66)	Blood transfusion is not significantly associated with 30-day mortality in patients with NSTE-ACS with a nadir Hct of 20% P=NR
						Logistic regression analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period plus nadir Hct.			
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=NR	ACS and nadir Hct 25%	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 1.13 (0.70, 1.82)	Blood transfusion is not significantly associated with 30-day mortality in patients with NSTE-ACS with a nadir Hct of 25% P=NR
						Logistic regression analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period plus nadir Hct.			
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=NR	ACS and nadir Hct 30%	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 168 (7.49, 3798)	Blood transfusion is significantly associated with increased 30-day mortality in patients with NSTE-ACS with a nadir Hct of 30% P=NR
						Logistic regression analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period plus nadir Hct.			

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
Rao 2004 Level III-2 Good	1 prospective cohort study (analysis of data from 3 RCTs) N=NR	ACS and nadir Hct 35%	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day mortality	NR	NR	OR 292 (10.3, 8274) Logistic regression analysis adjusted for: site, age, race, weight, diabetes mellitus, SBP, DBP, HR, time from symptom onset to hospitalisation, prior stroke, prior MI, gender, history of angina, hypertension, hyperlipidaemia, family history CAD, history of CHF, PVD, prior CABG, prior PCI, Killip class, baseline Hct, maximum CK ratio, chronic renal insufficiency, ST-segment elevation or depression on ECG, β-blocker use, calcium channel blocker use, nitrate use and current smoking, bleeding and transfusion propensity, nadir haematocrit plus bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period plus nadir Hct.	Blood transfusion is significantly associated with increased 30-day mortality in patients with NSTE-ACS with a nadir Hct of 35% P=NR
Sabatine 2005 Level III-2 Fair	1 prospective cohort study (analysis of data from 16 RCTs) N=1441	STEMI and admission Hb <12 g/dL	Hospital Various	Whole or RBC transfusion vs no whole or RBC transfusion	30-day cardiovascular mortality	NR	NR	OR 0.42 (0.20, 0.89) Adjusted for: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, β-blocker, angiotensin receptor blocker, or hypolipidemic use, index revascularisation, transfusion, transfusion and Hb interaction, bleeding and anterior location of index MI.	Whole or pRBC transfusion is significantly associated with decreased 30-day cardiovascular mortality in patients with STEMI with a Hb <12 g/dL P=NR
Sabatine 2005	1 prospective cohort study	STEMI and admission	Hospital	Whole or RBC	30-day cardiovascular	NR	NR	OR 1.42 (0.94, 2.17)	Whole or pRBC

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
						Adjusted for: age, gender, race, hypertension, diabetes, smoking history, creatinine clearance, prior MI, prior congestive heart failure, prior percutaneous coronary intervention, prior CABG, cerebrovascular disease, peripheral arterial disease, prior aspirin, β-blocker, ACEI, angiotensin receptor blocker, or hypolipidemic use, index hospitalisation aspirin, β-blocker, angiotensin receptor blocker, or hypolipidemic use, index revascularisation, transfusion, transfusion and Hb interaction, bleeding and anterior location of index MI.		
Alexander 2008 Level III-2 Fair	1 retrospective cohort study N=1633	NSTE-ACS presenting with 24 hours of their last symptoms with a nadir Hct <24%	Hospital US	Whole or packed RBCs vs no whole or packed RBCs	Mortality (in-hospital)	NR	NR	OR 0.75 (0.50, 1.12)	Transfusion is not significantly associated with in-hospital mortality in NSTE-ACS patients with a nadir HCT <24% P=NR
						Adjusted for: age, sex, BMI, race, family history of CAD, hypertension, diabetes, current/recent smoking status, hypercholesterolaemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, ECG changes (ST-segment depression, transient ST-segment elevation), positive cardiac markers, signs of CHF at presentation, heart rate and SBP at admission.			
Alexander 2008 Level III-2 Fair	1 retrospective cohort study N=1633	NSTE-ACS presenting with 24 hours of their last symptoms with a nadir Hct <24%	Hospital US	Whole or packed RBCs vs no whole or packed RBCs	Mortality (in-hospital)	NR	NR	OR 0.67 (0.45, 1.02)	Transfusion is not significantly associated with in-hospital mortality in NSTE-ACS patients with a nadir HCT <24% P=NR
						Adjusted for: age, sex, BMI, race, family history of CAD, hypertension, diabetes, current/recent smoking status, hypercholesterolaemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, ECG changes (ST-segment depression, transient ST-segment elevation), positive cardiac markers, signs of CHF at presentation, heart rate and SBP at admission and baseline HCT and transfusion by nadir HCT interaction.			
Alexander 2008 Level III-2 Fair	1 retrospective cohort study N=3263	NSTE-ACS presenting with 24 hours of their last symptoms with a nadir Hct 24.1–27%	Hospital US	Whole or packed RBCs vs no whole or packed RBCs	Mortality (in-hospital)	NR	NR	OR 1.01 (0.79, 1.28)	Transfusion is not significantly associated with in-hospital mortality in NSTE-ACS patients with a nadir HCT 24.1% to 27% P=NR
						Adjusted for: age, sex, BMI, race, family history of CAD, hypertension, diabetes, current/recent smoking status, hypercholesterolaemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, ECG changes (ST-segment depression, transient ST-segment elevation), positive cardiac markers, signs of CHF at presentation, heart rate and SBP at admission).			
Alexander 2008 Level III-2 Fair	1 retrospective cohort study N=3263	NSTE-ACS presenting with 24 hours of their last symptoms with a nadir Hct 24.1–27%	Hospital US	Whole or packed RBCs vs no whole or packed RBCs	Mortality (in-hospital)	NR	NR	OR 1.01 (0.79, 1.30)	Transfusion is not significantly associated with in-hospital mortality in NSTE-ACS patients with a nadir HCT 24.1% to 27% P=NR
						Adjusted for: age, sex, BMI, race, family history of CAD, hypertension, diabetes, current/recent smoking status, hypercholesterolaemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, ECG changes (ST-segment depression, transient ST-segment elevation), positive cardiac markers, signs of CHF at presentation, heart rate and SBP at admission) and baseline HCT and transfusion by nadir HCT interaction.			
Alexander 2008	1 retrospective cohort	NSTE-ACS presenting	Hospital	Whole or packed	Mortality (in-hospital)	NR	NR	OR 1.14 (0.90, 1.46)	Transfusion is not

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
Level III-2 Fair	study N=4919	with 24 hours of their last symptoms with a nadir Hct 27.1–30%	US	RBCs vs no whole or packed RBCs		Adjusted for: age, sex, BMI, race, family history of CAD, hypertension, diabetes, current/recent smoking status, hypercholesterolaemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, ECG changes (ST-segment depression, transient ST-segment elevation), positive cardiac markers, signs of CHF at presentation, heart rate and SBP at admission).			significantly associated with in-hospital mortality in NSTE-ACS patients with a nadir HCT 27.1% to 30% P=NR
Alexander 2008 Level III-2 Fair	1 retrospective cohort study N=4919	NSTE-ACS presenting with 24 hours of their last symptoms with a nadir Hct 27.1–30%	Hospital US	Whole or packed RBCs vs no whole or packed RBCs	Mortality (in-hospital)	NR	NR	OR 1.18 (0.92, 1.50)	Transfusion is not significantly associated with in-hospital mortality in NSTE-ACS patients with a nadir HCT 27.1% to 30% P=NR
						Adjusted for: age, sex, BMI, race, family history of CAD, hypertension, diabetes, current/recent smoking status, hypercholesterolaemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, ECG changes (ST-segment depression, transient ST-segment elevation), positive cardiac markers, signs of CHF at presentation, heart rate and SBP at admission) and baseline HCT and transfusion by nadir HCT interaction.			
Alexander 2008 Level III-2 Fair	1 retrospective cohort study N=34,427	NSTE-ACS presenting with 24 hours of their last symptoms with a nadir Hct >30%	Hospital US	Whole or packed RBCs vs no whole or packed RBCs	Mortality (in-hospital)	NR	NR	OR 2.89 (1.85, 4.51)	Transfusion is significantly associated with increased in-hospital mortality in NSTE-ACS patients with a nadir HCT >30% P=NR
						Adjusted for: age, sex, BMI, race, family history of CAD, hypertension, diabetes, current/recent smoking status, hypercholesterolaemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, ECG changes (ST-segment depression, transient ST-segment elevation), positive cardiac markers, signs of CHF at presentation, heart rate and SBP at admission).			
Alexander 2008 Level III-2 Fair	1 retrospective cohort study N=34,427	NSTE-ACS presenting with 24 hours of their last symptoms with a nadir Hct >30%	Hospital US	Whole or packed RBCs vs no whole or packed RBCs	Mortality (in-hospital)	NR	NR	OR 3.47 (2.30, 5.23)	Transfusion is significantly associated with increased in-hospital mortality in NSTE-ACS patients with a nadir HCT >30% P=NR
						Adjusted for: age, sex, BMI, race, family history of CAD, hypertension, diabetes, current/recent smoking status, hypercholesterolaemia, prior MI, prior PCI, prior CABG, prior CHF, prior stroke, renal insufficiency, ECG changes (ST-segment depression, transient ST-segment elevation), positive cardiac markers, signs of CHF at presentation, heart rate and SBP at admission) and baseline HCT and transfusion by nadir HCT interaction.			

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; Hb, haemoglobin; Hct/HCT, haematocrit; NR, not reported; NSTE-ACS, non-ST segment elevation acute coronary syndrome; OR, odds ratio; RBC, red blood cell; RCT, randomised controlled trial; STEMI, ST-segment elevation infarction MI, myocardial infarction; AMI, acute myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CAD, coronary artery disease; CHF, coronary heart failure; PVD, peripheral artery disease; PCI, percutaneous coronary intervention; CK, creatine kinase; ECG, electrocardiogram; ACEI, angiotensin converting enzyme inhibitor; COPD, chronic obstructive pulmonary disease; MAP, mean arterial pressure; BMI, body mass index.

The effect of RBC transfusion on thromboembolic events

One Level III-2 study assessed the association between RBC transfusion and MI, as shown in Table 3.51. Shishehbor et al (2009)[115] examined the association between blood transfusion (whole blood or pRBCs) and MI in patients with STEMI. The median ± IQR nadir Hct in the patients who received transfusion was 25.1 ± 4.3 (N=307), and in patients who did not receive transfusion was 37.2 ± 5.1 (N=3268).

The results of the analysis showed that blood transfusion was significantly associated with 30-day (HR 3.44) and 6-month (HR 2.69) MI, but not 1-year MI.

Table 3.51 Question 2 (ACS) Results for Level III evidence – thromboembolic events

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Tranfused n/N (%)	Not transfused n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity
Shishehbor 2009 Level III-2 Good	1 prospective cohort study (analysis of data from a RCT) N=3575	STEMI	Hospital Various (including Australia)	Whole or RBC transfusion vs no whole or RBC transfusion	30-day MI	NR	NR	HR 3.44	Blood transfusion is significantly associated with increased 30-day MI in patients with STEMI P<0.001
						Cox proportional hazards analysis adjusted for: age, gender, race, height, weight, country of origin, comorbidities including diabetes, hypertension, hypercholesterolaemia, smoking, COPD, chronic renal insufficiency, PAD, HF, stroke, cancer diagnosed in past 5 years, history of PCI and CABG, Killip class, family history of cardiac diseases and risk factors, medical therapy and interventions (ambulatory and in-hospital).			
Shishehbor 2009 Level III-2 Good	1 prospective cohort study (analysis of data from a RCT) N=3538	STEMI	Hospital Various (including Australia)	Whole or RBC transfusion vs no whole or RBC transfusion	6-month MI	NR	NR	HR 2.69	Blood transfusion is is significantly associated with increased 6-month MI in patients with STEMI P<0.001
						Cox proportional hazards analysis adjusted for: age, gender, race, height, weight, country of origin, comorbidities including diabetes, hypertension, hypercholesterolaemia, smoking, COPD, chronic renal insufficiency, PAD, HF, stroke, cancer diagnosed in past 5 years, history of PCI and CABG, Killip class, family history of cardiac diseases and risk factors, medical therapy and interventions (ambulatory and in-hospital).			
Shishehbor 2009 Level III-2 Good	1 prospective cohort study (analysis of data from a RCT) N=3465	STEMI	Hospital Various (including Australia)	Whole or RBC transfusion vs no whole or RBC transfusion	1-year MI	NR	NR	NR	Blood transfusion is <u>not</u> is significantly associated with 6-month MI in patients with STEMI P=NR
						Cox proportional hazards analysis adjusted for: age, gender, race, height, weight, country of origin, comorbidities including diabetes, hypertension, hypercholesterolaemia, smoking, COPD, chronic renal insufficiency, PAD, HF, stroke, cancer diagnosed in past 5 years, history of PCI and CABG, Killip class, family history of cardiac diseases and risk factors, medical therapy and interventions (ambulatory and in-hospital).			

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ration; MI, myocardial infarction; NR, not reported; RBC, red blood cell; RCT, randomised controlled trial; STEMI, ST-segment elevation infarction.
Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

HEART FAILURE

Of the adverse outcomes specified for this question, only mortality is covered for this population.

Methods

There was one study identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no Level I studies examining the effect of RBC transfusion in patients with heart failure.

Level II evidence

The literature search identified no Level II studies examining the effect of RBC transfusion in patients with heart failure.

Level III evidence

The literature search identified one Level III study examining the effect of RBC transfusion in patients with heart failure.

Level IV evidence

Level IV evidence was not searched for this question.

Results

One Level III-2 study was included for this question.[118] The characteristics of this included study are summarised in Table 3.52.

Table 3.52 Question 2 (heart failure): Characteristics and quality of Level III evidence

Level III evidence			
Author	Study type *Study quality*	Population	Outcomes
Garty et al (2009)[118]	Prospective cohort study *Fair*	Patients with heart failure admitted to cardiology or internal medicine wards specifically with acute decompensated heart failure. N=2335	Mortality

The effect of RBC transfusion on mortality

One study assessed the association between blood transfusion (not further defined) and mortality, as shown in Table 3.53. Garty et al (2009)[118] examined the relationship between blood transfusion and mortality in 2335 hospitalised adults with acute decompensated heart failure. The mean ± SD nadir Hb was 8.7 g/dL ± 1.1 in the transfused group and 12.4 g/dL ± 1.9 in the non transfused group. The analysis was not adjusted for nadir Hb but was adjusted for propensity for blood transfusion.

The results of the analysis showed that blood transfusion was significantly associated with a reduction in 30-day mortality (OR 0.29; 95% CI 0.13, 0.64; p=0.02) and may be associated with reduced in-hospital mortality (OR 0.48; 95% CI 0.21, 1.11; p=0.08). Blood transfusion was not significantly associated with 1-year mortality (HR 0.74; 95% CI 0.50, 1.09) or 4-year mortality (HR 0.86; 95% CI 0.64, 1.14). The authors conclude that the patients included in this study who received blood transfusion had "worse clinical features and unadjusted outcomes, but BT per se seemed to be safe and perhaps even beneficial".

Table 3.53 Question 2 (heart failure): Results for Level III evidence – mortality

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Garty 2009 Level III-2 Fair	1 prospective cohort study N=2335	Acute decompensated heart failure	Hospital Israel	Blood transfusion vs no blood transfusion	In-hospital mortality	18/166 (10.8)	113/2169 (5.2)	OR 0.48 (0.21, 1.11)	Blood transfusion may be significantly associated with decreased in-hospital mortality in patients with ADHF P=0.08
						Adjusted for: age, sex, hypertension, diabetes mellitus, current smoking, concurrent ACS, heart rate, SBP, LVEF, eGFR and propensity for blood transfusion.			
Garty 2009 Level III-2 Fair	1 prospective cohort study N=2317	Acute decompensated heart failure	Hospital Israel	Blood transfusion vs no blood transfusion	30-day mortality	18/164 (11.0)	183/2153 (8.5)	OR 0.29 (0.13, 0.64)	Blood transfusion is significantly associated with decreased 30-day mortality in patients with ADHF P=0.02
						Adjusted for: age, sex, hypertension, diabetes mellitus, current smoking, concurrent ACS, heart rate, SBP, LVEF, eGFR and propensity for blood transfusion.			
Garty 2009 Level III-2 Fair	1 prospective cohort study N=2325	Acute decompensated heart failure	Hospital Israel	Blood transfusion vs no blood transfusion	1-year mortality	65/164 (39.6)	616/2161 (28.5)	HR 0.74 (0.50, 1.09)	Blood transfusion is not significantly associated with 1-year mortality in patients with ADHF P=0.12
						Adjusted for: age, sex, hypertension, diabetes mellitus, current smoking, concurrent ACS, heart rate, SBP, LVEF, eGFR and propensity for blood transfusion.			
Garty 2009 Level III-2 Fair	1 prospective cohort study N=2321	Acute decompensated heart failure	Hospital Israel	Blood transfusion vs no blood transfusion	4-year mortality	114/164 (69.5)	1284/2157 (59.5)	HR 0.86 (0.64, 1.14)	Blood transfusion is not significantly associated with 4-year mortality in patients with ADHF P=0.29
						Adjusted for: age, sex, hypertension, diabetes mellitus, current smoking, concurrent ACS, heart rate, SBP, LVEF, eGFR and propensity for blood transfusion.			

ADHF, acute decompensated heart failure; CI, confidence interval; HR, hazard ratio; NR, not reported; OR, odds ratio; US, United States of America;ACS, acute coronary syndrome; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.
Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

CANCER

Of the adverse outcomes specified for this question, two are covered for this population: mortality and thromboembolic events.

Methods

There was one study identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no Level I studies examining the effect of RBC transfusion in patients with cancer.

Level II evidence

The literature search identified no Level II studies examining the effect of RBC transfusion in patients with cancer.

Level III evidence

The literature search identified one Level III study examining the effect of RBC transfusion in patients with cancer.

Level IV evidence

Level IV evidence was not searched for this question.

Results

Level III evidence

One Level III-2 study was included for this question,[119] which assessed the association between RBC transfusion and mortality and thromboembolic events, as summarised in Table 3.54.

Table 3.54 Question 2 (cancer): Characteristics and quality of Level III evidence

Level III evidence			
Author	Study type *Study quality*	Population	Outcomes
Khorana et al (2008)[119]	Retrospective cohort study *Fair*	Adult patients with cancer admitted to one of 60 academic medical centres in the US N=503,185	Mortality Thromboembolic events

Due to the requirement that analyses were adjusted for multiple potential confounders, studies were limited to those including >500 subjects. This resulted in the exclusion of one study examining the influence of blood transfusion on survival in 130 patients undergoing radiotherapy for uterine cervical cancer.[120]

The effect of RBC transfusion on mortality

One study assessed the association between RBC transfusion and mortality, as shown in Table 3.55. The study by Khorana et al (2008)[119] examined the association between blood transfusion (pRBCs) and in-hospital mortality, in 503,185 hospitalised cancer patients. Approximately 12% of the included patients had undergone major oncologic surgery. This analysis showed that RBC transfusion was significantly associated with an increased risk of mortality (OR 1.34; 95% CI 1.29, 1.38) in hospitalised patients with cancer.

It should be noted that the excluded study by Santin et al (2002)[120] which included only 130 patients also showed a significant association between blood transfusion and mortality overall (RR 2.6; 95% CI 1.6, 4.0; P<0.001), when considering Stage-IIB patients only (RR 1.9; 95% CI 1.1, 3.3; P=0.013) and in stage-III patients only (RR 3.2; 95% CI 1.2, 8.7; P=0.022).

Table 3.55 Question 2 (cancer): Results for Level III evidence – mortality

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Khorana 2008 Level III-2 *Fair*	1 retrospective cohort study N=503,185	Adult patients with cancer admitted to one of 60 academic medical centres	Hospital US	RBC transfusion vs no RBC transfusion	In-hospital mortality	NR	NR	OR 1.34 (1.29, 1.38)	RBC transfusion is significantly associated with increased in-hospital mortality in hospitalised patients with cancer P=<0.001
						Adjusted for: age, gender, site or type of cancer, race/ethnicity, chemotherapy, venous catheters, and comorbidities including anaemia, infection, renal disease and lung disease.			

CI, confidence interval; NR, not reported; OR, odds ratio; RBC, red blood cell.
Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

The effect of RBC transfusion on thromboembolic events

One study assessed the association between RBC transfusion and thromboembolic events, as shown in Table 3.56. The study by Khorana et al (2008)[119] examined the association between blood transfusion (pRBCs) and VTE and ATE, in 503,185 hospitalised cancer patients. This analysis showed that RBC transfusion is significantly associated with an increased risk of VTE (OR 1.60; 95% CI 1.53, 1.67) and ATE (OR 1.53; 95% CI 1.46, 1.61) in hospitalised patients with cancer. In addition to RBC transfusion, a large number of other predictors of VTE were identified including age, gender, site or type of cancer, race, chemotherapy, use of venous catheter, platelet transfusion and comorbidities including anaemia, infection, renal disease and lung disease. The authors note that they were unable to identify patients concomitantly receiving outpatient ESA therapy, which is a potential confounding factor.

Table 3.56 Question 2 (cancer): Results for Level III evidence – thromboembolic events

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome	Results			
						Risk factor n/N (%)	No risk factor n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Khorana 2008 Level III-2 Fair	1 retrospective cohort study N=503,185	Adult patients with cancer admitted to one of 60 academic medical centres	Hospital US	RBC transfusion vs no RBC transfusion	In-hospital VTE	NR	NR	OR 1.60 (1.53, 1.67) Adjusted for: age, gender, site or type of cancer, race/ethnicity, chemotherapy, venous catheters, and comorbidities including anaemia, infection, renal disease and lung disease.	RBC transfusion is significantly associated with increased VTE in hospitalised patients with cancer P=<0.001
Khorana 2008 Level III-2 Fair	1 retrospective cohort study N=503,185	Adult patients with cancer admitted to one of 60 academic medical centres	Hospital US	RBC transfusion vs no RBC transfusion	In-hospital ATE	NR	NR	OR 1.53 (1.46, 1.61) Adjusted for: age, gender, site or type of cancer, race/ethnicity, chemotherapy, venous catheters, and comorbidities including anaemia, infection, renal disease and lung disease.	RBC transfusion is significantly associated with increased ATE in hospitalised patients with cancer P=<0.001

ATE, arterial thromboembolism; CI, confidence interval; NR, not reported; OR, odds ratio; RBC, red blood cell; VTE, venous thromboembolism.

ACUTE UPPER GASTROINTESTINAL BLOOD LOSS

Of the adverse outcomes specified for this question, only mortality is covered for this population.

Methods

There were three studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified one Level I study examining the effect of RBC transfusion on adverse outcomes in patients with upper gastrointestinal blood loss. This study by Jairath et al (2010)[121] included data from three trials, only one of which was eligible for inclusion in this review. As this study is already included in the Level II evidence below, the Jairath review will not be considered further.

Level II evidence

The literature search identified one Level II study examining the effect of RBC transfusion on adverse outcomes in patients with upper gastrointestinal blood loss.

Level III evidence

The literature search identified one Level III study examining the effect of RBC transfusion on adverse outcomes in patients with upper gastrointestinal blood loss.

Level IV evidence

Level IV evidence was not searched for this question.

Results

Level II evidence

One Level II study was included for this question; which provided evidence for mortality only.[112] The characteristics of this included study is summarised in Table 3.57. It should be noted that this study was small (N=50) and as such is unlikely to be sufficiently powered to detect a difference between treatment arms in mortality.

Table 3.57 Question 2 (acute GI haemorrhage): Characteristics and quality of Level II evidence

Level II evidence			
Author	Study type *Study quality*	Population	Outcomes
Blair et al (1986)[112]	RCT *Poor*	Patients with acute severe upper GI haemorrhage. N=50	Mortality

GI, gastrointestinal; RCT, randomised controlled trial.

The effect of RBC transfusion on mortality

One study assessed the effect of RBC transfusion on mortality, as shown in Table 3.58. In the study by Blair et al (1986)[112], the risk of mortality was assessed in patients with acute upper GI haemorrhage. Patients were randomised to one of two treatment arms: (i) blood transfusion within 24 hours of hospitalisation or (ii) no blood transfusion within 24 hours of hospitalisation. The exception to this was if patients had a Hb <8 g/dL or if shock persisted after initial resuscitation with Haemacel; this occurred in 6/24 patients in the transfusion arm and 5/26 patients in the no transfusion arm. Thus, the transfusion arm can be considered equivalent to a liberal transfusion threshold, while the no transfusion arm can be considered equivalent to a restrictive transfusion threshold.

The results of the analysis showed no significant difference in mortality between the two treatment arms; however, as mentioned previously this study was underpowered to detect a difference in mortality.

Table 3.58 Question 2 (acute upper GI blood loss): Results for Level II evidence – mortality

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						Restrictive blood transfusion n/N (%)	Liberal blood transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Blair 1986 Level II Poor	1 RCT N=50	Acute severe upper gastrointestinal haemorrhage	Hospital UK	Restrictive blood transfusion in first 24 hours vs liberal blood transfusion in first 24 hours	Mortality	0/26 (0)	2/24 (8.3)	NR	No difference P=NR

CI, confidence interval; NR, not reported; RCT, randomised controlled trial.

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Level III evidence

One Level III-2 study was included for this question which provided evidence for mortality only.[122] The characteristics of this included study are summarised in Table 3.59.

Table 3.59 Question 2 (acute upper GI blood loss): Characteristics and quality of Level III evidence

Level III evidence			
Author	Study type *Study quality*	Population	Outcomes
Hearnshaw et al (2010)[122]	Prospective cohort study *Good*	Patients with acute upper GI haemorrhage. N=4370	Mortality

The effect of RBC transfusion on mortality

One Level III study assessed the effect of RBC transfusion on mortality, as shown in Table 3.60. In the study by Hearnshaw et al (2010),[122] the risk of mortality relating to early RBC transfusion (within 12 hours of presentation) was assessed in patients with acute upper GI haemorrhage. Patients were identified from NHS (UK) hospitals who agreed to take part in the study and submitted data (82%). All patients included had undergone an upper GI endoscopy. RBC transfusion was defined as RBC transfusion within 12 hours of presentation. The mean ± SD admission Hb was 8.0 ± 2.16 in the early RBC transfusion group and 12 ± 2.54 in the no early RBC transfusion group.

The association between RBC within 12 hours and mortality was examined in the overall population (N=4370) and a number of patients subgroups including in-patients only, new admissions only, female or male only, excluding patients on varices and excluding patients on aspirin. The patient numbers for these subgroup analyses ranged from 722 to 3944. All analyses showed no significant association between RBC transfusion within 12 hours and mortality. However, the majority of analyses (except that in the excluding those on aspirin subgroup) resulted in an OR >1.25, suggesting that there may be an increased risk and that the analyses may have been underpowered to detect a significant association.

Table 3.60 Question 2 (acute upper GI blood loss): Results for Level III evidence – mortality

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						RBC transfusion n/N (%)	No RBC transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Hearnshaw 2010 Level III-2 Good	1 prospective cohort study N=4370	Acute upper gastrointestinal bleeding	Hospital UK	RBC transfusion within 12 hours vs no RBC transfusion within 12 hours	30-day mortality	NR	NR	OR 1.28 (0.94, 1.74) Adjusted for: Rockall Index (age, shock, comorbidity and major stigmata of recent haemorrhage) and baseline Hb	RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in patients with acute upper GI haemorrhage P=NR
Hearnshaw 2010 Level III-2 Good	1 prospective cohort study N=722	Acute upper gastrointestinal bleeding (<u>in-patients only</u>)	Hospital UK	RBC transfusion within 12 hours vs no RBC transfusion within 12 hours	30-day mortality	NR	NR	OR 1.33 (0.83, 2.13) Adjusted for: Rockall Index (age, shock, comorbidity and major stigmata of recent haemorrhage) and baseline Hb	RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in in-patients with acute upper GI haemorrhage P=NR
Hearnshaw 2010 Level III-2 Good	1 prospective cohort study N=3596	Acute upper gastrointestinal bleeding (<u>new admissions only</u>)	Hospital UK	RBC transfusion within 12 hours vs no RBC transfusion within 12 hours	30-day mortality	NR	NR	OR 1.40 (0.92, 2.13) Adjusted for: Rockall Index (age, shock, comorbidity and major stigmata of recent haemorrhage) and baseline Hb	RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in newly admitted patients with acute upper GI haemorrhage P=NR
Hearnshaw 2010 Level III-2 Good	1 prospective cohort study N=1714	Acute upper gastrointestinal bleeding (<u>female only</u>)	Hospital UK	RBC transfusion within 12 hours vs no RBC transfusion within 12 hours	30-day mortality	NR	NR	OR 1.29 (0.82, 2.03) Adjusted for: Rockall Index (age, shock, comorbidity and major stigmata of recent haemorrhage) and baseline Hb	RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in females with acute upper GI haemorrhage P=NR
Hearnshaw 2010 Level III-2 Good	1 prospective cohort study N=2727	Acute upper gastrointestinal bleeding (<u>male only</u>)	Hospital UK	RBC transfusion within 12 hours vs no RBC transfusion within 12 hours	30-day mortality	NR	NR	OR 1.31 (0.86, 2.02) Adjusted for: Rockall Index (age, shock, comorbidity and major stigmata of recent haemorrhage) and baseline Hb	RBC transfusion within 12 hours is <u>not</u> significantly associated with 30-day mortality in males with acute upper GI haemorrhage P=NR

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome (follow-up)	Results			
						RBC transfusion n/N (%)	No RBC transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*
Hearnshaw 2010 Level III-2 Good	1 prospective cohort study N=3944	Acute upper gastrointestinal bleeding (excluding patients with varices)	Hospital UK	RBC transfusion within 12 hours vs no RBC transfusion within 12 hours	30-day mortality	NR	NR	OR 1.26 (0.89, 1.79) Adjusted for: Rockall Index (age, shock, comorbidity and major stigmata of recent haemorrhage) and baseline Hb	RBC transfusion within 12 hours is not significantly associated with 30-day mortality in patients with acute upper GI haemorrhage excluding those with varices P=NR
Hearnshaw 2010 Level III-2 Good	1 prospective cohort study N=3036	Acute upper gastrointestinal bleeding (excluding patients on aspirin)	Hospital UK	RBC transfusion within 12 hours vs no RBC transfusion within 12 hours	30-day mortality	NR	NR	OR 1.10 (0.75, 1.61) Adjusted for: Rockall Index (age, shock, comorbidity and major stigmata of recent haemorrhage) and baseline Hb	RBC transfusion within 12 hours is not significantly associated with 30-day mortality in patients with acute upper GI haemorrhage excluding those with aspirin P=NR

CI, confidence interval; GI, gastrointestinal; NR, not reported; OR, odds ratio; RBC, red blood cell.

3.3 Question 3

Question 3 (Intervention)

In medical patients, what is the effect of non-transfusion interventions to increase Hb concentration on morbidity, mortality and need for RBC blood transfusion?

3.3.1 Non-transfusion interventions for patients with cancer

Evidence statements – cancer (erythropoiesis-stimulating agents)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.1	In anaemic adults with cancer, ESA therapy increases the risk of all-cause mortality; this effect appears to be greater in patients with a Hb concentration over 100 g/L. (See evidence matrix EM3.A in Volume 2 of the technical report)	√√	√√√	√√	√√√	√√√
ES3.2	In adult cancer patients with non chemotherapy-induced anaemia, ESA therapy increases the risk of all-cause mortality. (See evidence matrix EM3.A in Volume 2 of the technical report)	√√	√√√	√√	√√√	√√√
ES3.3	In adult cancer patients with chemotherapy-induced anaemia, the effect of ESA therapy on mortality is uncertain. (See evidence matrix EM3.A in Volume 2 of the technical report)	√√	√√√	X	√√√	√√√
ES3.4	In anaemic adults with cancer, ESA therapy reduces transfusion incidence and volume. (See evidence matrix EM3.B and EM3.C in Volume 2 of the technical report)	√√	√√	√√	√√√	√√√
ES3.5	In anaemic adults with cancer, ESA therapy increases the risk of thromboembolic events. (See evidence matrix EM3.D in Volume 2 of the technical report)	√√	√√√	√√	√√√	√√
ES3.6	In anaemic adults with cancer, ESA therapy may improve functional or performance status; however, the magnitude of this effect appears slight. (See evidence matrix EM3.E in Volume 2 of the technical report)	√	√	X	√√√	√√

Evidence statements – cancer (iron therapy)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.7	In anaemic adults with cancer receiving ESAs, the effect of IV iron versus oral or no iron on short-term mortality is uncertain. (See evidence matrix EM3.F in Volume 2 of the technical report)	√√	√√	NA	√√	√√
ES3.8	In adults with cancer-related anaemia receiving ESAs, IV iron may reduce the incidence of RBC transfusion. (See evidence matrix EM3.G in Volume 2 of the technical report)	√√	√√	√	√√	√
ES3.9	In anaemic patients with gynaecological cancer receiving chemotherapy, IV iron may reduce the incidence and volume of RBC transfusion. (See evidence matrix EM3.G in Volume 2 of the technical report)	√	NA	√√	√√√	√
ES3.10	In adults with chemotherapy-induced anaemia receiving ESAs, the effect of IV iron versus oral or no iron on the incidence of thromboembolic events is uncertain. (See evidence matrix EM3.H in Volume 2 of the technical report)	√√	√√	NA	√√	√
ES3.11	In adults with non-myeloid malignancies and chemotherapy-induced anaemia receiving ESAs, IV iron versus oral or no iron appears to have no effect on functional or performance status. (See evidence matrix EM3.I in Volume 2 of the technical report)	√	NA	NA	√√	√
ES3.12	In anaemic patients with gynaecological cancer receiving chemotherapy, the effect of IV iron versus oral iron on functional or performance status is uncertain. (See evidence matrix EM3.I in Volume 2 of the technical report)	√	NA	NA	√√√	√
ES, evidence statement; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; RBC, red blood cell √√√=A; √√=B; √=C; X=D; NA, not applicable						

Recommendation – cancer	
R2 Grade A	In cancer patients with anaemia, the *routine* use of ESAs is not recommended. If considered necessary, ESAs should be used with caution, balancing the increased risks of mortality and thromboembolic events against the reduced incidence and volume of transfusion.
Practice points – cancer	
PP8[a]	In patients with cancer, the aetiology of anaemia is often multifactorial; where appropriate, reversible causes should be identified and treated.
PP12	In anaemic patients with cancer receiving ESAs, evaluate iron status to guide adjuvant iron therapy.
a Repeated from Section 3.2.4, above ESA, erythropoiesis-stimulating agent; PP, practice point; R, recommendation	

3.3.2 ESAs vs no ESAs for anaemic patients with cancer

There were 19 Level I studies and five subsequently published Level II studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

From the 19 applicable Level I studies two systematic reviews of RCTs were selected as being the highest quality and most comprehensive reviews that had recently been conducted.[123,124] These two studies will form the basis of this review and will be updated with any Level II studies published subsequently. Both Level I studies evaluated the use of erythropoiesis stimulating agents (ESAs) in cancer patients with anaemia and the main characteristics of these reviews are summarised in Table 3.61.

The Tonelli et al (2009)[123] review compared the use of erythropoietin (EPO) or darbepoetin (DAR) with treatment without EPO or DAR. The review included 52 studies containing data from 12, 006 subjects. Of these studies, 19 had compulsory iron therapy in both study arms, 9 trials had iron therapy as required in either study arm, 1 trial had no iron therapy and 23 studies did not report the use of iron therapy. Data from this review will be used in the assessment of mortality, transfusion incidence, transfusion volume and functional and performance status outcomes. Tonelli et al (2009)[123] did not assess thromboembolic events as a separate outcome. For this outcome the earlier review from the Cochrane Collaboration by Bohlius et al (2006)[124] will be used. The Bohlius et al (2006)[124] review compared the use of EPO with treatment without EPO and assessed the proportion of subjects experiencing thromboembolic events as a separate category of adverse events. This review also had many studies that included iron therapy and many studies that did not report iron therapy. Data from this review will be updated with any studies included in Tonelli et al (2009)[123] that were not included in Bohlius et al (2006).[124] This will include studies that examined the use of DAR, which was excluded from Bohlius et al (2006).[124] Any data available from Level II studies published after Tonelli et al (2009)[123] will also be included.

Table 3.61 Characteristics and quality of Level I evidence

Level I evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Tonelli et al (2009)[123]	*Level I* Good	Adults with cancer-related anaemia 52 RCTs, N=12,006	EPO or DAR vs. no treatment or placebo	All-cause mortality, cardiovascular events and hypertension, QoL, blood transfusion incidence and volume, tumour response, adverse events.
Bohlius et al (2006)[124]	*Level I* Good	Cancer patients affected by, or at risk from, treatment-related anaemia	EPO vs. no treatment or placebo	Haematological response, blood transfusion incidence and volume, overall survival, tumour response, QoL, adverse events, predictors of response to EPO.

DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agents; Hb, haemoglobin; QoL, quality of life; RCT, randomised controlled trial

Level II evidence

A literature search was conducted to identify Level II evidence published after the literature search conducted in the Tonelli et al (2009)[123] systematic review.[a] Five studies were identified and the main characteristics of these studies are summarised in Table 3.62. Where the use of iron therapy was reported it has been included in the intervention. Four of the studies (Christodoulou et al [2009],[125] Hoskin et al [2009],[126] Pronzato et al [2010][127] and Tsuboi et al [2009][128]) compared treatment with EPO to treatment without EPO. One study, Hernandez et al (2009),[129] compared the use of DAR with treatment without DAR. Christodoulou et al (2009)[125] was conducted in Greece, Hoskin et al (2009)[126] was conducted in the United Kingdom and Tsuboi et al (2009)[128] was conducted in Japan. Hernandez et al (2009)[129] was conducted in multiple centres in Australia, New Zealand and North America and Pronzato et al (2010)[127] was conducted in six European countries. Preliminary results from the Pronzato et al (2010)[127] study had been published as a conference proceeding in 2002. This earlier version had been identified and included in the Tonelli et al (2009)[123] study, but did not appear in any of the meta-analyses shown in that review and updated here. It is possible that the preliminary data may have been included in the subgroup analyses in Tonelli et al (2009),[123] as the list of studies that contributed to these analyses was not provided.

[a] The literature search in Tonelli et al (2009) included papers published from 1950 to 2007.

Table 3.62 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Christodoulou et al (2009)[125]	*Level II* Poor	Adult cancer patients with solid tumours, Hb ≤120 g/L, concurrent chemotherapy (not high-dose), performance status ≤2 (WHO), life expectancy at least 3 months.	EPO-α All patients received daily 200mg elemental iron.	No treatment	QoL, blood transfusion incidence and volume, tumour response, overall survival.
Hernandez et al (2009)[129]	*Level II* Fair	Adult cancer patients with non-myeloid malignancy, Hb <110 g/L, scheduled for ≥12 weeks of chemotherapy	DAR Iron therapy recommended if : serum iron <500 µg/L, serum ferritin <10 ng/ mL, transferring saturation <20%	Placebo	QoL, blood transfusion incidence and volume, change in Hb concentration, adverse events.
Hoskin et al (2009)[126]	*Level II* Poor	Adult patients with squamous cell head and neck cancer, Hb <150 g/L, scheduled for radical radiotherapy.	EPO-α All patients received daily 200mg oral iron.	No treatment	Local disease-free survival, overall survival (at 1, 2 and 5 years), change from baseline in anaemia and fatigue.
Pronzato et al (2010)[127]	*Level II* Fair	Adult female patients with breast cancer, Hb ≤120 g/L, receiving chemotherapy for minimum 12 weeks, ECOG PS score 0–3, life expectancy 6 months, adequate renal, hepatic, and hematologic function.	EPO-α	Best standard care	QOL, hematologic response, tumour response, 6-month and 12-month overall survival rates.
Tsuboi et al (2009)[128]	*Level II* Fair	Patients aged 20 to 80 years, with lung cancer or malignant lymphoma, receiving chemotherapy with at least two cycles scheduled after the first study drug administration, Hb 80-110 g/L, an ECOG PS ≤2, life expectancy ≥3 months, adequate renal and liver function.	EPO Oral iron administered if serum iron saturation <15% or MCV <80 µm^3	Placebo	Changes in Hb concentration from baseline, QoL, blood transfusion incidence.

DAR, darbepoetin; EPO, erythropoietin; ECOG PS, Eastern Cooperative Oncology Group performance status; ESA, erythropoiesis stimulating agents; g, grams; Hb, haemoglobin; L, litre; QoL, quality of life; RCT, randomised controlled trial

The literature search also identified three studies[130-132] that contained socioeconomic data on the use of ESAs in cancer patients. The main characteristics of these studies are summarised in Table 3.63.

Table 3.63 Characteristics and quality of socioeconomic evidence

Level I evidence			
Study	Population Setting	Comparison	Outcomes
Borg et al (2008)[130]	Cancer patients with chemotherapy-related anaemia Sweden	EPO vs. RBC transfusion	Cost-effectiveness
Cremieux et al (1999)[131]	Cancer patients undergoing chemotherapy, N=4500 US	EPO vs. RBC transfusion	Cost-effectiveness
Roungrong et al (2008)[132]	Cancer patients with chemotherapy-induced anaemia Thailand	EPO vs. RBC transfusion	Cost-utility

EPO, erythropoietin; RBC, red blood cell; US, United States of America.

Results

Mortality

Mortality was reported as an outcome in the Tonelli et al (2009)[123] systematic review. Three RCTs published after Tonelli et al (2009) (Hernandez et al [2009],[129] Hoskin et al [2009][126] and Pronzato et al [2010][127]) also reported mortality as an outcome. Table 3.64 provides a summary of the results from these studies.

Tonelli et al (2009)[123] identified 28 RCTs (N=6525) that reported all-cause mortality as an outcome. A meta-analysis of the data from these RCTs found a significant increase in the risk of mortality with ESA treatment (RR 1.15; 95% CI: 1.03, 1.29). When the EPO and DAR interventions were analysed separately, only DAR treatment resulted in a significant increase in risk (RR 1.22; 95% CI: 1.01, 1.47). Tonelli et al (2009)[123] also analysed the risk of all-cause mortality in subject subgroups with a baseline Hb concentration of <100 g/L, 100-120 g/L or >120 g/L. There was a trend towards a higher relative risk of mortality in subjects with higher baseline Hb who received ESA treatment; however this effect was not statistically significant.

Hernandez et al (2009),[129] Hoskin et al (2009)[126] and Pronzato et al (2010)[127] all reported rates of mortality. In all of the studies the rates of mortality were similar in the two treatment groups; however, none of the studies provided a risk estimate for mortality.

A meta-analysis was conducted to update Tonelli et al (2009)[123] with the results from Hernandez et al (2009)[129] and Pronzato et al (2010)[127] (see Figure 3.1). Hoskin et al (2009)[126] had reported the mortality rate as a percentage of subjects affected. This could not be unambiguously converted to actual subject numbers so this study was excluded from the meta-analysis. After the addition of the Hernandez et al (2009)[129] and Pronzato et al (2010)[127] RCTs, the analysis still showed a significant increase in the risk of mortality in anaemic cancer patients treated with ESAs (RR 1.14; 95% CI: 1.02, 1.27).

Tonelli et al (2009)[123] also reported an increased risk of mortality with ESA treatment in patients whose anaemia is not related to chemotherapy (RR 1.22; 95% CI: 1.06, 1.40), but no significant increase in risk in patients with chemotherapy-related anaemia (RR 1.04; 95% CI:

0.86, 1.26) (see Table 3.64 and Figure 3.2). A study published by Bohlius et al (2009)[124] compared the association between the use of additional cancer therapies and mortality in patients treated or not treated with ESAs. The authors found that in patients receiving no additional therapy, ESA treatment was associated with a significant increase in mortality (HR 1.33; 95% CI: 1.06, 1.66). In patients receiving chemotherapy, radiotherapy or other therapies there was a trend towards increased mortality in patients treated with ESAs, but the findings did not reach significance.

Table 3.64 Results for ESAs vs no ESAs in cancer: all-cause mortality

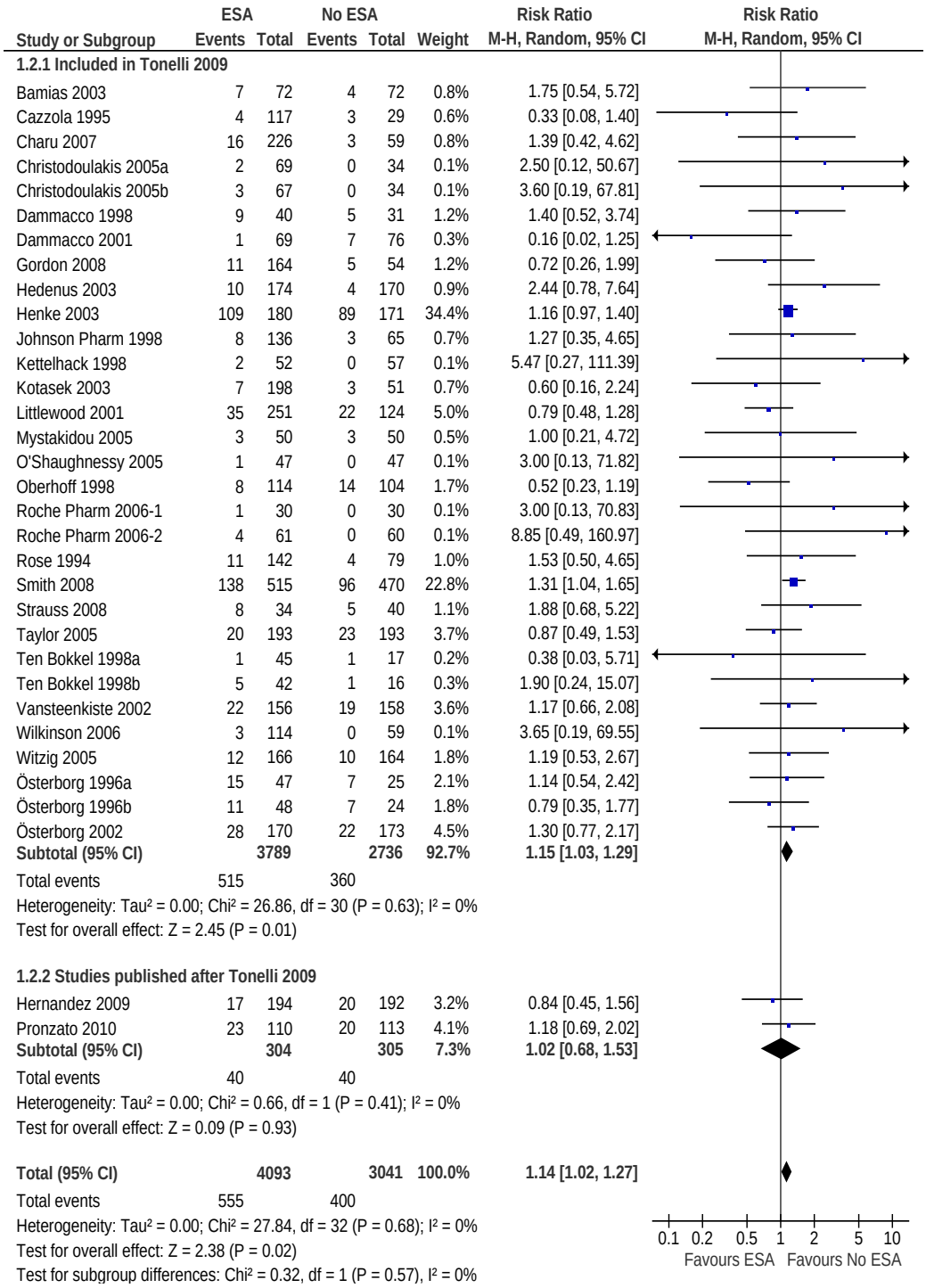
Study	Level of evidence *Quality*	No. of trials (sample size)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I2)
LEVEL I STUDIES										
Tonelli et al (2009)[123]	Level I *Good*	28 RCTs N=6525	Adults with cancer-related anaemia Hb <100 g/L	Multiple international centres	ESA vs. No ESA	All-cause mortality	NR	NR	Random effects RR 1.04 (0.81, 1.32)	*No significant difference* I^2=28%
			Adults with cancer-related anaemia Hb 100-120 g/L		ESA vs. No ESA		NR	NR	Random effects RR 1.16 (0.99, 1.36)	*No significant difference* I^2=0%
			Adults with cancer-related anaemia Hb >120 g/L		ESA vs. No ESA		NR	NR	Random effects RR 3.00 (0.13, 71.82)	*No significant difference* I^2=NA
			Adults with cancer-related anaemia		EPO vs. No EPO		291/2163	207/1581	Random effects RR 1.12 (0.97, 1.29)	*No significant difference* I^2=0%
					DAR vs. No DAR		224/1626	153/1155	Random effects RR 1.22 (1.01, 1.47)	*Favours no ESA treatment.* I^2=0%
			Adults with anaemia related to chemotherapy		ESA vs. No ESA		23/4273		RR 1.04 (0.86, 1.26)	*No significant difference*
			Adults with anaemia not related to chemotherapy		ESA vs. No ESA		8/2252		RR 1.22 (1.06, 1.40)	*Favours no ESA treatment.*
			Adults with cancer-related anaemia		ESA vs. No ESA		515/3789	360/2736	Random effects RR 1.15 (1.03, 1.29)	*Favours no ESA treatment.* I^2=0%

Study	Level of evidence *Quality*	No. of trials (sample size)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I2)
LEVEL II STUDIES										
Hernandez et al (2009)[129]	Level II *Fair*	1 RCT N=386	Adult patients with non-myeloid malignancy, Hb <110 g/L, scheduled for ≥12 weeks of chemotherapy	Conducted at 81 sites in Australia, New Zealand and North America	DAR vs. placebo Iron therapy recommended if : serum iron <500 µg/L, serum ferritin <10 ng/ mL, transferring saturation <20%	All-cause mortality	17/194	20/192	NR	P=NR
Hoskin et al (2009)[126]	Level II *Poor*	1 RCT N=282	Adult patients with squamous cell head and neck cancer, Hb <150 g/L, scheduled for radical radiotherapy.	Conducted at 21 sites in the United Kingdom	EPO-α vs. No treatment All patients received daily 200mg oral iron	All-cause mortality	53% [a]	50% [a]	NR	P=NR
Pronzato et al (2010)[127]	Level II *Fair*	1 RCT N=223	Adult female patients with breast cancer, Hb ≤120 g/L, receiving myelotoxic chemotherapy for a planned minimum of 12 weeks	Conducted at multiple sites in Italy, Spain, Portugal, Belgium, The Netherlands and the United Kingdom.	EPO-α vs. best standard care	All-cause mortality	23/110	20/113	NR	*No significant difference.*

CI, confidence interval; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; g, grams; Hb, haemoglobin; L, litre; NR, not reported; RCT, randomised controlled trial; RR, relative risk

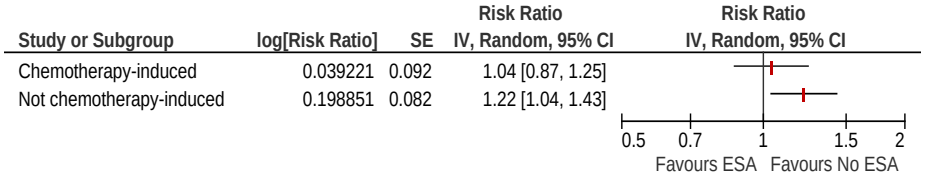
[a] The study by Hoskin et al (2009)[126] did not report patient numbers for mortality and these could not be calculated unambiguously *post hoc*.

Figure 3.1 Meta-analysis of ESAs vs no ESAs in cancer: all-cause mortality



Letters following publication dates indicate separate data sets within a single publication. Numbers following publication dates indicate separate publications published within a single year.

Figure 3.2 Analysis of ESAs vs. no ESAs in chemotherapy-induced anaemia and not chemotherapy-induced anaemia: all-cause mortality



The log of the risk ratio and standard error were calculated post hoc from the risk ratio and associated 95% confidence interval reported in Tonelli et al (2009)[123]. Differences in the bound of the 95% confidence interval are due to data conversion and calculation performed in Review Manager 5 software.

RBC transfusion incidence and volume

Tonelli et al (2009)[123] identified 26 RCTs (N=5321) that reported the proportion of subjects who received RBC transfusions. A meta-analysis of the data showed a significantly lower risk of transfusion in subjects who received ESA treatment (RR 0.64; 95% CI: 0.56, 0.73). The same effect was observed when the analysis was restricted to treatment with EPO (RR 0.65; 95% CI: 0.56, 0.75) or DAR (RR 0.58; 95% CI: 0.41, 0.83). Transfusion incidence was analysed by subgroups with a baseline Hb concentration of <100 g/L, 100-120 g/L or >120 g/L. The analysis found significant reductions in risk with ESA treatment in subjects with baseline Hb <100 g/L (RR 0.72; 95% CI: 0.62, 0.84) and 100-120 g/L (RR 0.57; 95% CI: 0.47, 0.69), but not in subjects with baseline Hb >120 g/L (RR 0.46; 95% CI: 0.11, 1.88).

The RCTs by Christodoulou et al (2009),[125] Hernandez et al (2009),[129] Pronzato et al (2010)[127] and Tsuboi et al (2009)[128] reported the proportion of patients requiring RBC transfusion. Christodoulou et al (2009)[125] and Hernandez et al (2009)[129] both reported a significantly lower rate of transfusion in subjects treated with ESAs (p=0.0035 and p=0.003, respectively). Tsuboi et al (2009)[128] and Pronzato et al (2010)[127] did not find a significant difference in transfusion rates, although Pronzato et al (2010)[127] did observe a trend towards lower transfusion rates with ESA treatment (see Table 3.65).

A meta-analysis was conducted to update Tonelli et al (2009)[123] with the data from Christodoulou et al (2009),[125] Tsuboi et al (2009)[128] and Pronzato et al (2010)[127] (see Figure 3.3). Hernandez et al (2009)[129] had reported the transfusion rate as a percentage of subjects affected. This could not be unambiguously converted to actual subject numbers so this study was excluded from the meta-analysis. After the addition of the three RCTs the analysis still showed a significantly reduced risk of transfusion in anaemic cancer patients treated with ESAs (RR 0.64; 95% CI: 0.56, 0.72).

Tonelli et al (2009)[123] identified 15 RCTs that reported mean transfusion volume. The meta-analysis found significantly lower transfusion volume in patients treated with ESAs (WMD -0.80 units; 95% CI: -0.99, -0.61). Christodoulou et al (2009)[125] reported a significantly lower mean transfusion volume in patients treated with EPO (difference: –0.37 units, p=0.003). Neither study provided sufficient data to allow an update of the Tonelli et al (2009)[123] meta-analysis.

Table 3.65 Results for ESAs vs no ESAs in cancer: RBC transfusion incidence and volume

Study	Level of evidence *Quality*	No. of trials (sample size)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I2)
TRANSFUSION INCIDENCE										
LEVEL I STUDIES										
Tonelli et al (2009)[123]	Level I *Good*	26 RCTs N=5321	Adults with cancer-related anaemia Hb <100 g/L	Multiple international centres	ESA vs. No ESA	Patients requiring transfusion	NR	NR	Random effects RR 0.72 (0.62–0.84)	*Favours ESA treatment* I^2=22%
			Adults with cancer-related anaemia Hb 100-120 g/L		ESA vs. No ESA		NR	NR	Random effects RR 0.57 (0.47–0.69)	*Favours ESA treatment* I^2=56%
			Adults with cancer-related anaemia Hb >120 g/L		ESA vs. No ESA		NR	NR	Random effects RR 0.46 (0.11–1.88)	*No significant difference* I^2=34%
			Adults with cancer-related anaemia		EPO vs. No EPO		579/2229	739/1892	Random effects RR 0.65 (0.56, 0.75)	*Favours EPO treatment* I^2=NR
					DAR vs. No DAR		128/653	213/547	Random effects RR 0.58 (0.41, 0.83)	*Favours DAR treatment* I^2=NR
					ESA vs. No ESA		707/2882	952/2439	Random effects RR 0.64 (0.56, 0.73)	*Favours ESA treatment* I^2=NR

Study	Level of evidence *Quality*	No. of trials (sample size)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I2)
LEVEL II STUDIES										
Christodoulou et al (2009)[125]	Level II *Poor*	1 RCT N=337	Adult patients with solid tumours, Hb ≤120 g/L, concurrent chemotherapy (not high-dose), performance status ≤2 (WHO), life expectancy at least 3 months.	Conducted at multiple centres in Greece	EPO-α vs. No treatment All patients received daily 200mg elemental iron.	Patients requiring transfusion	16/167	36/170	NR	*Favours EPO-α treatment* P=0.0035
Hernandez et al (2009)[129]	Level II *Fair*	1 RCT N=386	Adult patients with non-myeloid malignancy, Hb <110 g/L, scheduled for ≥12 weeks of chemotherapy.	Conducted at 81 sites in Australia, New Zealand and North America	DAR vs. placebo Iron therapy recommended if : serum iron <500 µg/L, serum ferritin <10 ng/ mL, transferring saturation <20%	Patients requiring transfusion (adjusted Kaplan-Meier estimate)[a]	30% N=193	47% N=193	Mean difference: -14.6% (-31.29, -4.6)	*Favours DAR treatment* P=0.003
Tsuboi et al (2009)[128]	Level II *Fair*	1 RCT N=117	Patients of age 20 to 80 years, with lung cancer or malignant lymphoma, receiving chemotherapy with at least two cycles scheduled after the first study drug administration, Hb 80-110 g/L, an Eastern Cooperative Oncology Group performance status (PS) ≤2, life expectancy ≥3 months as well as adequate renal and liver function.	Conducted at 11 centres in Japan	EPO vs. placebo Oral iron administered if serum iron saturation <15% or MCV <80 μm^3	Patients requiring transfusion	7/61	7/56	NR	*No significant difference* P=0.865
Pronzato et al (2010)[127]	Level II *Fair*	1 RCT N=223	Adult female patients with breast cancer, Hb ≤120 g/L, receiving myelotoxic chemotherapy for a planned minimum of 12 weeks	Conducted at multiple sites in Italy, Spain, Portugal, Belgium, The Netherlands and the United Kingdom.	EPO-α vs. best standard care	Patients requiring transfusion	8/107	18/109	NR	*No significant difference* P=0.059

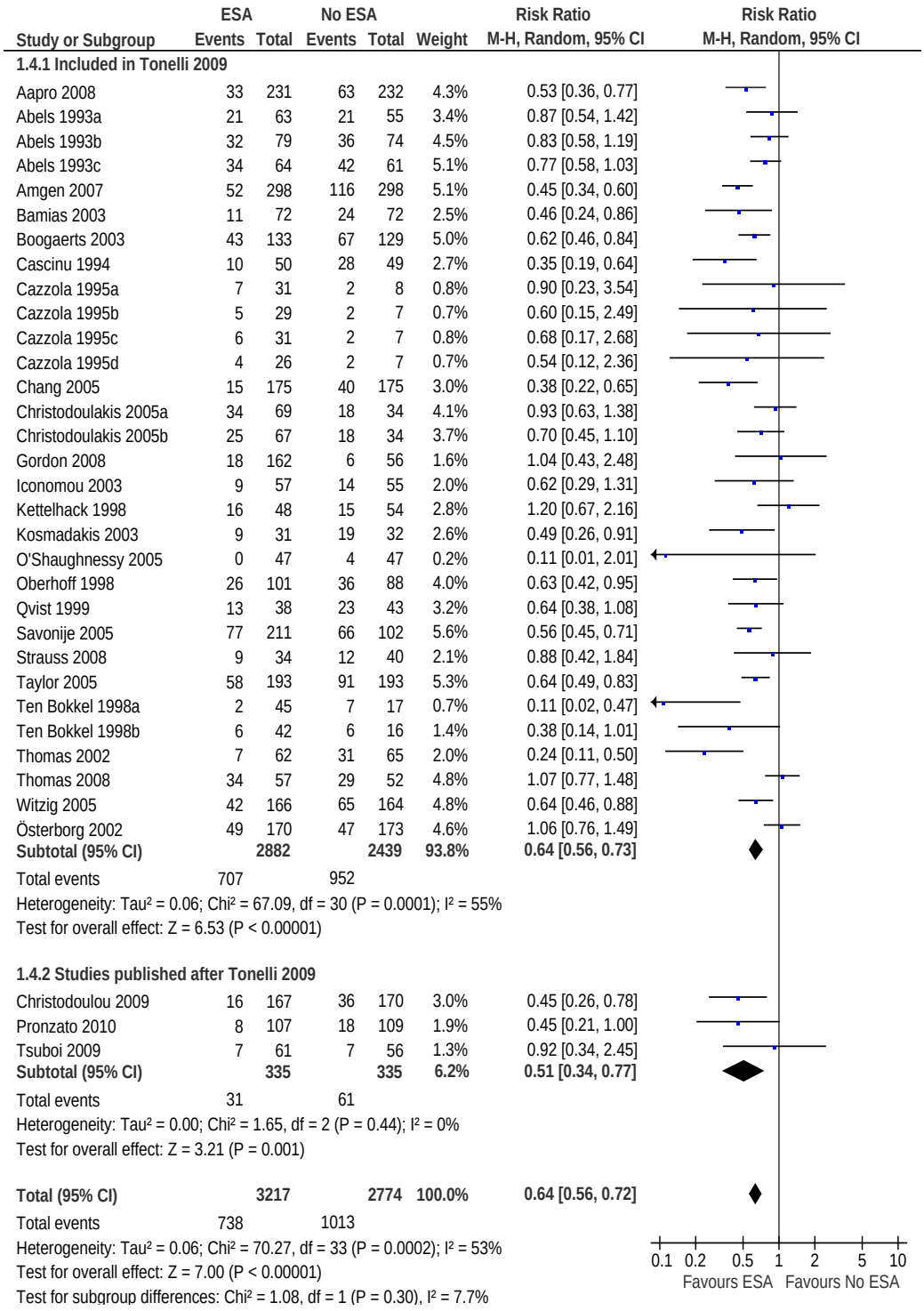
Study	Level of evidence *Quality*	No. of trials (sample size)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I2)
TRANSFUSION VOLUME										
LEVEL I STUDIES										
Tonelli et al (2009)[123]	Level I *Good*	15 RCTs N=NR	Adults with cancer-related anaemia	Multiple international centres	ESA vs. No ESA	Transfusion volume (units transfused per patient)	NR	NR	WMD -0.8 units (-0.99, -0.61)	*Favours ESA treatment* I^2=12%
LEVEL II STUDIES										
Christodoulou et al (2009)[125]	Level II *Poor*	1 RCT N=337	Adult patients with solid tumours, Hb ≤120 g/L, concurrent chemotherapy (not high-dose), performance status ≤2 (WHO), life expectancy at least 3 months.	Conducted at multiple centres in Greece	EPO-α vs. No treatment All patients received daily 200mg elemental iron.	Transfusion volume (units transfused per patient)	0.24 (SD=NR) N=16	0.61 (SD=NR) N=36	Difference: -0.37[b]	*Favours ESA treatment* P=0.003

CI, confidence interval; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; g, grams; Hb, haemoglobin; L, litre; NR, not reported; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation, WHO, World Health Organisation

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2<25%; moderate heterogeneity if I2 between 25%-50%; substantial heterogeneity if I2>50%.

[b] Difference calculated post hoc.

Figure 3.3 Meta-analysis of ESAs vs no ESAs in cancer: RBC transfusion incidence



Letters following publication dates indicate separate data sets within a single publication. Numbers following publication dates indicate separate publications published within a single year.

Thromboembolic events

The incidence of thromboembolic events was reported in 12 RCTs (N=1738) indentified by Bohlius et al (2006).[124] A meta-analysis of these studies found a trend towards increased risk of thromboembolic events with ESA treatment (RR 1.58; 95% CI: 0.94, 2.66), although this result was not significant. Tonelli et al (2009)[123] included 8 RCTs (N=2138) that reported thromboembolic events that were not included in Bohlius et al (2006).[124] The results from these studies were meta-analysed, and showed a significant increase in the risk of thromboembolic events with ESA treatment (RR 1.86; 95% CI 1.32, 2.64).

Hernandez et al (2009)[129] and Pronzato et al (2010)[127] reported the rate of embolism/thrombosis as a separate outcome. Both studies found higher rates of events in subjects treated with ESAs but did not report a risk estimate (see Table 3.66). Hoskin et al (2009)[126] and Tsuboi et al (2009)[128] reported the rate of all thromboembolic events as an outcome. Both studies reported low numbers of patients affected but did not provide a risk estimate.

The data from the additional studies from Tonelli et al (2009)[123] and from Hoskin et al (2009)[126] and Tsuboi et al (2009)[128] was used to update the meta-analysis from Bohlius et al (2006)[124] (see Figure 3.4). After the inclusion of the additional studies the analysis showed a significantly greater risk of thromboembolic events in anaemic cancer patients treated with ESAs (RR 1.73; 95%CI: 1.29, 2.31).

Table 3.66 Results for ESAs vs no ESAs in cancer: thromboembolic events

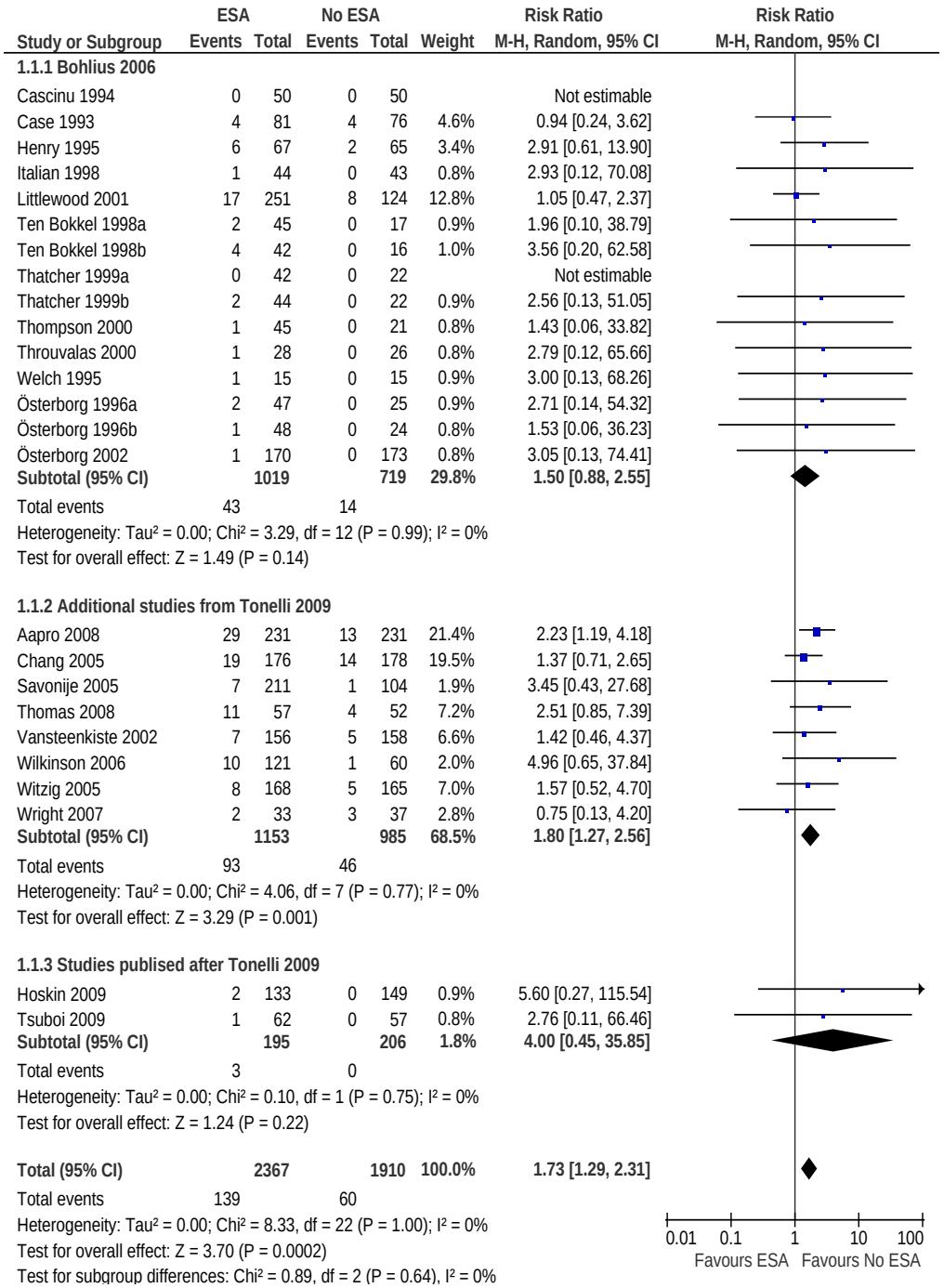
Study	Level of evidence *Quality*	No. of trials (sample size)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			
							Intervention n/N	Comparator n/N	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
ALL THROMBOEMBOLIC EVENTS (STROKE/MI/DVT/PE)										
LEVEL I STUDIES										
Bohlius et al (2006)[124]	Level I *Good*	12 RCTs N=1738	Cancer patients affected by, or at risk from, treatment-related anaemia	Multiple international centres	EPO vs. No EPO	All thromboembolic events	43/1019	14/719	Fixed effects RR 1.58 (0.94, 2.66)	Fixed effects *No significant difference* P=0.08 I^2=0.0%
LEVEL II STUDIES										
Additional studies from Tonelli et al (2009)[123]	*Level II*	8 RCTs N=2138	Adults with cancer-related anaemia	Multiple international centres	ESA vs. No ESA	All thromboembolic events	93/1153	46/985	Fixed effects RR 1.86 (1.32, 2.64) Random effects RR 1.80 (1.27, 2.56)	Fixed effects *Favours no treatment* P=0.0004 I^2=0% Random effects *Favours no treatment* P=0.001 I^2=0%
Hoskin et al (2009)[126]	Level II *Poor*	1 RCT N=282	Adult patients with squamous cell head and neck cancer, Hb <150 g/L, scheduled for radical radiotherapy.	Conducted at 21 sites in the United Kingdom	EPO-α vs. No treatment All patients received daily 200mg oral iron	All thromboembolic events	2/133	0/149	NR	P=NR

Study	Level of evidence *Quality*	No. of trials (sample size)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			
							Intervention n/N	Comparator n/N	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I^2)
Tsuboi et al (2009)[128]	Level II *Fair*	1 RCT N=117	Patients of age 20 to 80 years, with lung cancer or malignant lymphoma, receiving chemotherapy with at least two cycles scheduled after the first study drug administration, Hb 80-110 g/L, an Eastern Cooperative Oncology Group performance status (PS) ≤2, life expectancy ≥3 months as well as adequate renal and liver function.	Conducted at 11 centres in Japan	EPO vs. placebo Oral iron administered if serum iron saturation <15% or MCV <80 μm^3	All thromboembolic events	1/62	0/57	NR	P=NR
EMBOLISM AND THROMBOSIS (ARTERIAL AND VENOUS)										
LEVEL II STUDIES										
Hernandez et al (2009)[129]	Level II *Fair*	1 RCT N=386	Adult patients with non-myeloid malignancy, Hb <110 g/L, scheduled for ≥12 weeks of chemotherapy.	Conducted at 81 sites in Australia, New Zealand and North America	DAR vs. placebo Iron therapy recommended if : serum iron <500 μg/L, serum ferritin <10 ng/ mL, transferring saturation <20%	Embolism/thrombosis (arterial and venous) events	16/194	11/192	NR	P=NR
Pronzato et al (2010)[127]	Level II *Fair*	1 RCT N=223	Adult female patients with breast cancer, Hb ≤120 g/L, receiving myelotoxic chemotherapy for a planned minimum of 12 weeks	Conducted at multiple sites in Italy, Spain, Portugal, Belgium, The Netherlands and the United Kingdom.	EPO-α vs. best standard care	Venous thrombosis	8/109 (7.3%)	7/111 (6.3%)	NR	P=NR

: CI, confidence interval; DAR, darbepoetin; DVT, deep vein thrombosis; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; g, grams; Hb, haemoglobin; L, litre; MCV, mean corpuscular volume; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; RCT, randomised controlled trial; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.|

Figure 3.4 Meta-analysis of ESAs vs no ESAs in cancer: all thromboembolic events



Letters following publication dates indicate separate data sets within a single publication. Numbers following publication dates indicate separate publications published within a single year.

Functional/performance status

Functional/performance status, measured using FACT instruments, was reported in 13 studies identified by Tonelli et al (2009).[123] Meta-analysis of these studies showed a favourable score for patients treated with ESAs in the FACT-Anaemia (general) score (WMD 4.11; 95% CI: 2.00, 6.22), the FACT-Anaemia (subscale) score (WMD 3.90; 95% CI: 1.63, 6.16) and the FACT-Fatigue (subscale) score (WMD 3.00; 95% CI: 1.36, 4.64), but not for the FACT-Anaemia (total) score (WMD 14.66; 95% CI:–1.09, 30.41).

Hoskin et al (2009)[126] reported no difference in the scores for the FACT-Anaemia (total) score (p=0.915) or in its fatigue (p=0.966) and non-fatigue (p=0.299) component scores. The authors also found no difference in the FACT-fatigue (subscale) score (p=0.928). In contrast, Pronzato et al (2010)[127] reported a favourable difference in the scores of ESA-treated patients for the FACT-Anaemia (total) score (p=0.002) and for the fatigue (p=0.003) and non-fatigue (p=0.008) component scores. Tsuboi et al (2009)[128] found a favourable effect of ESA treatment on the FACT-Fatigue (subscale) for patients whose baseline score was >36 (p=0.016), but not for patients with a baseline score ≤36 (p=0.225) or for all patients (p=0.082). Hoskin et al (2009)[126] also reported results For the FACT-General scores and FACT-head and neck scores, however none of these showed a difference between ESA treatment and no ESA treatment (see Table 3.67).

The meta-analysis from Tonelli et al (2009) was updated with the results from Hoskin et al (2009)[126] and Tsuboi et al (2009)[128] (see Figure 3.5). The results from Pronzato et al (2010)[127] could not be added to the meta-analysis as they were expressed as % change, and actual changes in score were not provided. The addition of the two studies gave new results for change in FACT-Anaemia (total) score (WMD 11.41; 95% CI: -1.46, 24.29), which was not significant, and for the change in FACT-Fatigue (subscale) score (WMD 2.90; 95% CI: 1.45, 4.36), which showed a significant effect for ESA treatment. The analysis was repeated using a standardised mean difference analysis. This analysis showed that the total change in score across the four categories analysed showed a significantly favourable effect of treatment with ESAs in anaemic cancer patients (SMD 0.32; 95% CI: 0.21, 0.42).

Table 3.67 Results for ESAs vs no ESAs in cancer: functional and performance status

Study	Level of evidence *Quality*	No. of trials (sample size)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			
							Intervention mean change from baseline (SD)	Comparator mean change from baseline (SD)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I2)
FACT-Anaemia (total) score and subscale scores										
LEVEL I STUDIES										
Tonelli et al (2009)[123]	Level I *Good*	8 RCTs	Adults with cancer-related anaemia	Multiple international centres	ESA vs. No ESA	Change in FACT-Anaemia (total) score [a] N=526	NR	NR	WMD 14.66 (–1.09 to 30.41)	*No significant difference* P=NR
						Change in FACT-Anaemia (general) score N=709	NR	NR	WMD 4.11 (2.00 to 6.22)	*Favours ESA treatment* P=NR
						Change in FACT-Anaemia (subscale) score N=1420	NR	NR	WMD 3.90 (1.63 to 6.16)	*Favours ESA treatment* P=NR
LEVEL II STUDIES										
Hoskin et al (2009)[126]	Level II *Poor*	1 RCT N=282	Adult patients with squamous cell head and neck cancer, Hb <150 g/L, scheduled for radical radiotherapy.	Conducted at 21 sites in the United Kingdom	EPO-α vs. No treatment All patients received daily 200mg oral iron	Change in FACT-Anaemia (total) score [a]	-3.3 (26.41) N=151	-5.2 (27.43) N=149	NR	*No significant difference* P=0.915
						Change in total fatigue score	-2.6 (10.67) N=151	-2.6 (12.45) N=149	NR	*No significant difference* P=0.966
						Change in total non-fatigue score	-0.5 (3.68) N=151	-1.0 (4.00) N=149	NR	*No significant difference* P=0.299
Pronzato et al (2010)[127]	Level II *Fair*	1 RCT N=223	Adult female patients with breast cancer, Hb ≤120 g/L, receiving myelotoxic chemotherapy for a planned minimum of 12 weeks	Conducted at multiple sites in Italy, Spain, Portugal, Belgium, The Netherlands and the United Kingdom.	EPO-α vs. best standard care	Change in FACT-Anaemia (total) score [a]	14.2% N=70	-0.5% N=71	NR	*Favours ESA treatment* P=0.002
						Fatigue subscale	17.5% N=70	-0.9% N=71	NR	*Favours ESA treatment* P=0.003

Study	Level of evidence *Quality*	No. of trials (sample size)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			
							Intervention mean change from baseline (SD)	Comparator mean change from baseline (SD)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I2)
						Non-fatigue subscale	8.8% N=70	0.2% N=71	NR	*Favours ESA treatment* P=0.008
FACT-Fatigue subscale scores										
LEVEL I STUDIES										
Tonelli et al (2009)[123]	Level I *Good*	10 RCTs N=3169	Adults with cancer-related anaemia	Multiple international centres	ESA vs. No ESA	Change in FACT-Fatigue (subscale) score [b]	NR	NR	WMD 3.00 (1.36 to 4.64)	*Favours ESA treatment* P=NR
LEVEL II STUDIES										
Hoskin et al (2009)[126]	Level II *Poor*	1 RCT N=282	Adult patients with squamous cell head and neck cancer, Hb <150 g/L, scheduled for radical radiotherapy.	Conducted at 21 sites in the United Kingdom	EPO-α vs. No treatment All patients received daily 200mg oral iron	Change in FACT-Fatigue (subscale) score [b]	-3.1 (22.88) N=151	-4.4 (24.81) N=149		*No significant difference* P=0.982
Tsuboi et al (2009)[128]	Level II *Fair*	1 RCT N=117	Patients of age 20 to 80 years, with lung cancer or malignant lymphoma, receiving chemotherapy with at least two cycles scheduled after the first study drug administration, Hb 80-110 g/L, an Eastern Cooperative Oncology Group performance status (PS) ≤2, life expectancy ≥3 months as well as adequate renal and liver function.	Conducted at 11 centres in Japan	EPO vs. placebo Oral iron administered if serum iron saturation <15% or MCV <80 μm^3	Change in FACT-Fatigue (subscale) score [b] All subjects	-0.5 (9.4) N=61	-3.6 (9.0) N=53	NR	*No significant difference* P=0.082
						Change in FACT-Fatigue (subscale) score [b] Subjects with baseline score ≤36	2.1 (11.7) N=29	-1.3 (9.6) N=28	NR	*No significant difference* P=0.225
						Change in FACT-Fatigue (subscale) score [a] Subjects with baseline score >36	-2.9 (5.9) N=32	-7.9 (9.4) N=25	NR	*Favours ESA treatment* P=0.016
Other FACT scales										
LEVEL II STUDIES										
Hoskin et al (2009)[126]	Level II *Poor*	1 RCT N=282	Adult patients with squamous cell head and neck cancer, Hb <150 g/L,	Conducted at 21 sites in the United Kingdom	EPO-α vs. No treatment All patients received	Change in FACT-General total score	-1.2 (13.19) N=151	-2.4 (13.78) N=149	NR	*No significant difference* P=0.509

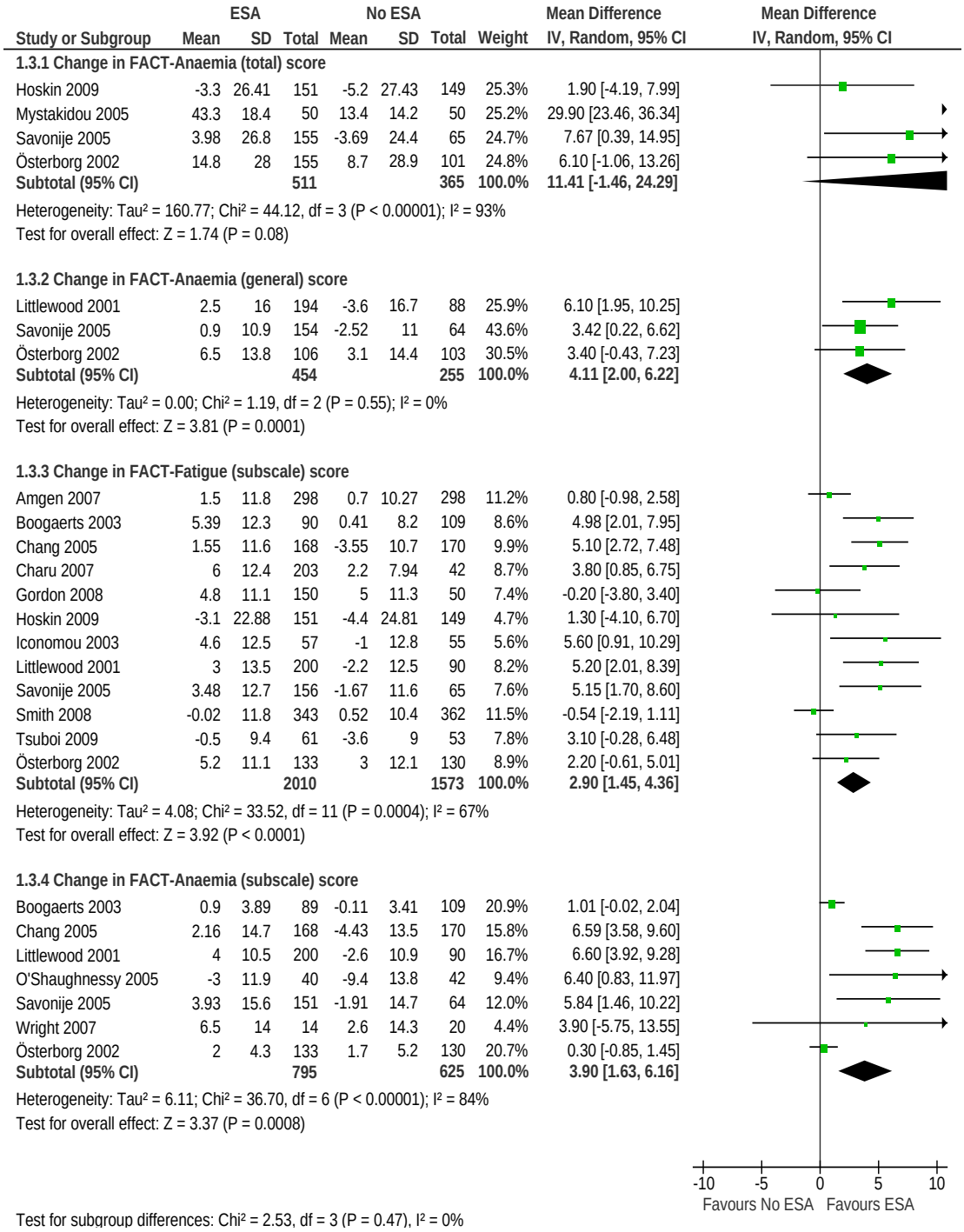
Study	Level of evidence *Quality*	No. of trials (sample size)	Patient population / Surgical procedure	Setting	Intervention	Outcome	Results			
							Intervention mean change from baseline (SD)	Comparator mean change from baseline (SD)	Risk estimate (95% CI)	Significance P-value Heterogeneity P value (I2)
			scheduled for radical radiotherapy.		daily 200mg oral iron	Change in physical well-being score	-1.1 (5.32) N=151	-1.5 (5.55) N=149	NR	*No significant difference* P=0.500
						Change in social/family well-being score	0.1 (3.93) N=151	-0.6 (3.64) N=149	NR	*No significant difference* P=0.097
						Change in emotional well-being score	1.3 (3.90) N=151	1.3 (3.87) N=149	NR	*No significant difference* P=0.994
						Change in functional well-being score	-1.2 (5.93) N=151	-1.7 (5.79) N=149	NR	*No significant difference* P=0.471
						Change in total FACT-head&neck score	-4.6 (19.69) N=151	-6.4 (18.82) N=149	NR	*No significant difference* P=0.475
						Change in FACT-head&neck (subscale) score	-2.5 (7.66) N=151	-3.4 (7.17) N=149	NR	*No significant difference* P=0.318

CI, confidence interval; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; FACT, Functional Assessment of Cancer Therapy; g, grams; Hb, haemoglobin; L, litre; NR, not reported; RCT, randomised controlled trial; RR, relative risk; WMD, weighted mean difference

[a] Score range 1-100

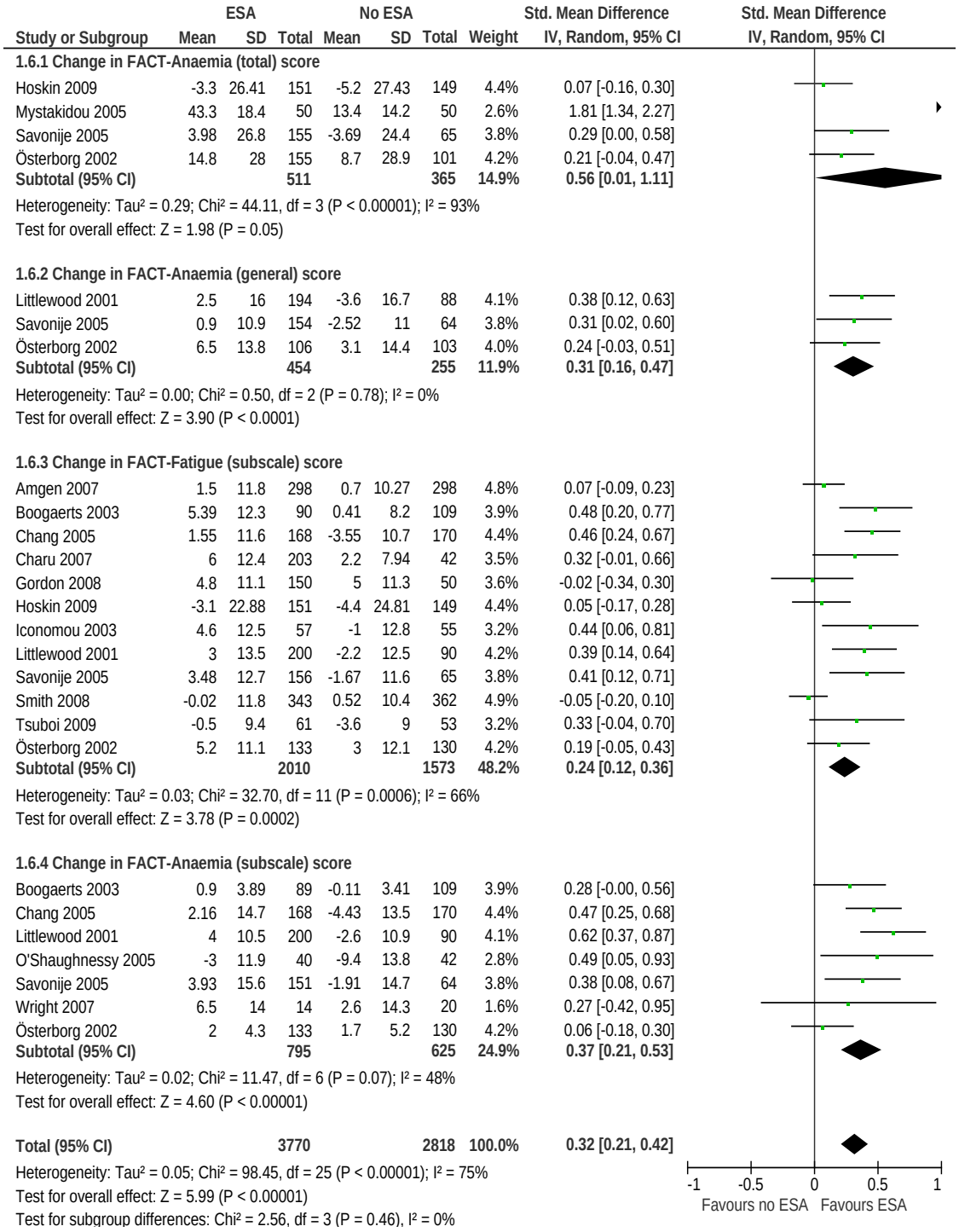
[b] Score range 0-52

Figure 3.5 Mean difference meta-analysis of ESAs vs no ESAs in cancer: functional and performance status



Letters following publication dates indicate separate data sets within a single publication. Numbers following publication dates indicate separate publications published within a single year.

Figure 3.6 Standardised mean difference meta-analysis of ESAs vs no ESAs in cancer: functional and performance status



Letters following publication dates indicate separate data sets within a single publication. Numbers following publication dates indicate separate publications published within a single year.

Socioeconomic data

Three studies were identified that presented socioeconomic data for the use of ESAs in cancer patients. The results from these studies are summarised in Table 3.68. The study by Roungrong et al (2008)[132] was carried out in Thailand and examined the cost-effectiveness of the use of EPO in cancer patients with chemotherapy induced anaemia compared to the use of RBC transfusion. The authors reported that the incremental cost-effectiveness ratio for EPO compared to transfusion was 3.7 and 2.7 million Baht per QALY for patients with a Hb concentration of <80 g/L or 80-90 g/L, respectively. For patients with a Hb concentration of 90-100 g/L the cost-effectiveness of EPO was reduced. Borg et al (2008)[130] used a Markov model to assess the cost-effectiveness of EPO compared to RBC transfusion in patients with chemotherapy-induced anaemia. The authors found that the cost per QALY for EPO compared to transfusion was €24700 when using an Hb target of 100 g/L. Approximately two thirds of the EPO cost was offset by reductions in transfusion costs. When using a higher Hb target of 130 g/L the cost per QALY increased to €39800, supporting a lower target Hb concentration of 120 g/L. The Cremieux et al (1999)[131] study performed economic modelling using data from three US clinical trials involving cancer patients. The study found that EPO was cost effective compared to standard care, with the same level of effectiveness resulting from $US1 spent on standard care achieved with only $US0.81 of EPO care.

Table 3.68 Results for ESAs vs RBC transfusion in cancer: socioeconomic studies

Study	Patient population / Surgical procedure	Setting	Intervention	Model used	Outcome		Hb target/level (g/L)	Cost
Studies reporting costs per QALY								
Borg et al (2008)[130]	Cancer patients with chemotherapy related anaemia	Sweden	EPO vs. RBC transfusion	Markov model	Relative cost per QALY		Hb target 100	€24700
							Hb target 120	€39800
Roungrong et al (2008)[132]	Cancer patients with chemotherapy induced anaemia	Thailand	EPO vs. RBC transfusion	Markov model	Incremental cost-effectiveness ratio (Baht/QALY)		Hb level <80	3.8 million Baht
							Hb level 80-90	2.7 million Baht
							Hb level 90-100	Reduced cost-effectiveness
Other studies								
Cremieux et al (1999)[131]	Anaemic cancer patients undergoing chemotherapy	US	EPO vs. RBC transfusion	Cost-effectiveness model	Relative cost effectiveness	Standard care	NR	US$1
						EPO	NR	US$0.81

Abbreviations:; EPO, erythropoietin; g, grams; L, litre; RBC, red blood cell; US, United States of America.

3.3.3 IV iron for anaemic patients with cancer

Methods

There were five Level II studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

No Level I evidence evaluating the use of iron therapy in anaemic patients with cancer was identified.

Level II evidence

The literature search identified Five RCTs[133-137] that evaluated the use of IV iron therapy in anaemic patients with cancer. All of the studies compared IV iron with either oral iron or no iron therapy. Participants received adjuvant darbepoetin in three of the studies[133,134,136], and adjuvant erythropoietin in one of the studies.[137] The main characteristics of the trials are summarised in Table 3.69.

Table 3.69 Characteristics and quality of Level II evidence

Level II evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Auerbach et al (2010)[133]	RCT *Good*	Non-myeloid cancer patients with anaemia (Hb ≤100 g/L), and ≥8 additional weeks of planned chemotherapy N=243	DAR (300 μg or 500 μg every 3 weeks) and IV iron (400 μg every 3 weeks) for 15 weeks vs DAR with oral or no iron	Mortality Blood transfusion Thromboembolic events
Bastit et al (2008)[134]	RCT *Fair*	Non-myeloid cancer patients with anaemia (Hb <110 g/L) N=398	200 mg IV iron and 500 μg DAR every 3 weeks for 16 weeks vs DAR with oral or no iron	Mortality Blood transfusion Thromboembolic events Functional/performance status
Dangsuwan et al (2010)[135]	RCT *Fair*	Gynaecologic cancer patients with anaemia (Hb <100 g/L) who underwent primary surgery and were receiving platinum based chemotherapy. N=44	200 mg IV iron vs 600 mg/day oral iron	Blood transfusion Functional/performance status
Hedenus et al (2007)[137]	RCT *Poor*	Adults with a diagnosis of clinically stable lymphoproliferative malignancy (indolent non-Hodgkin's lymphoma, chronic lymphocytic leukaemia or multiple myeloma) not requiring chemotherapy or blood transfusions, and an Hb concentration of 90 to 110 g/L N=67	Subcutaneous EPO 30 000 IU once weekly for 16 weeks plus IV iron (100 mg once weekly from weeks 0 to 6 followed by 100 mg every second week from weeks 8 to 14)	Mortality

Level II evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Pedrazzoli et al (2008)[136]	RCT *Fair*	Breast, colorectal, lung, or gynaecologic cancer patients with anaemia (Hb ≤110 g/L) and scheduled to receive12 additional weeks of chemotherapy. N=149	DAR (150 g/week) for 12 weeks plus IV iron (125 mg/week) for the first 6 weeks vs DAR alone	Mortality Blood transfusion Thromboembolic events

DAR, darbepoetin; EPO, erythropoietin; Hb, haemoglobin; IU, International Units; IV, intravenous; RCT, randomised controlled trial

Results

Mortality

Four of the RCTs[133,134,136,137] that evaluated the use of IV iron in cancer patients reported mortality as an outcome. Table 3.70 provides a summary of these results.

All of the studies found no significant difference in mortality between patients treated with IV iron compared with patients who received oral or no iron therapy. When the results from the four RCTs were meta-analysed (Figure 3.10) there was still no significant difference in mortality between cancer patients treated with IV iron and patients who received oral iron or no iron therapy (RR 0.93; 95% CI: 0.49, 1.77). The studies were not powered to detect a significant difference in mortality.

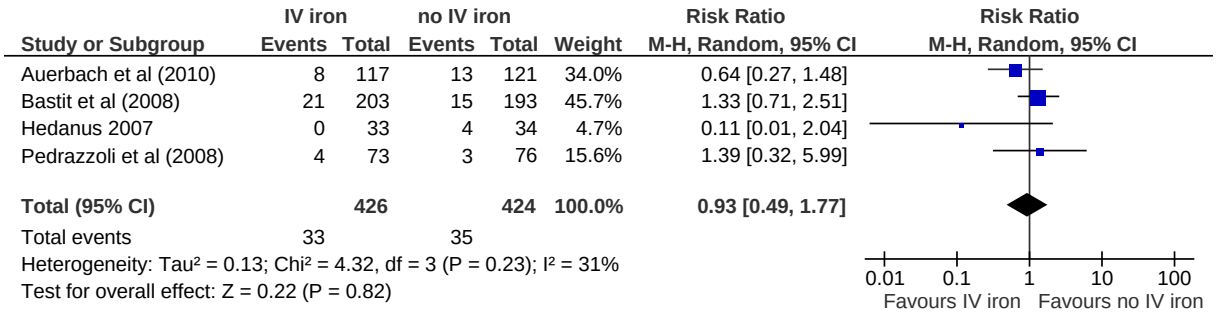
Table 3.70 Results for IV iron in cancer (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity* P-value (I^2)
LEVEL II STUDIES								
Auerbach et al (2010)[133] *Good*	Non-myeloid cancer patients with anaemia	DAR plus IV iron vs DAR with oral or no iron	15 weeks	Mortality, n/N (%) (N=238)	8/117 (7)	13/121 (11)	RR 0.64 (0.27, 1.48)[a]	*No significant difference* P=0.29[a]
Bastit et al (2008)[134] *Fair*	Non-myeloid cancer patients with anaemia	DAR plus IV iron vs DAR with oral or no iron	16 weeks	Mortality, n/N (%) (N=396)	21/203 (10)	15/193 (8)	RR 1.33 (0.71, 2.51)[a]	*No significant difference* P=0.38[a]
Hedenus et al (2007)[137] *Poor*	Anaemic patients with lymphoproliferative malignancies	EPO plus IV iron vs EPO alone	16 weeks	Mortality, n/N (%) (N=67)	0/33 (0.0)	4/34 (11.8)	RR 0.11 (0.01, 2.04)[a]	*No significant difference* P=0.14[a]
Pedrazzoli et al (2008)[136] *Fair*	Cancer patients with anaemia	DAR plus IV iron vs DAR alone	12 weeks	Mortality, n/N (%) (N=149)	4/73 (5.5)	3/76 (3.9)	RR 1.39 (0.32, 5.99)[a]	*No significant difference* P=0.66[a]

CI, confidence interval; EPO, erythropoietin; DAR, darbepoetin; IV, intravenous; RR, relative risk

[a] Calculated for the purpose of this systematic review using Review manager.

Figure 3.7 Meta-analysis of IV iron in cancer (mortality)



Blood transfusion

Table 3.71 provides a summary of the RBC transfusion outcomes reported in the RCTs that evaluated the use of IV iron in anaemic patients with cancer. Bastit et al (2008)[134] and Dangsuwan et al (2010)[135] found that patients treated with IV iron had a significantly lower incidence of RBC transfusion and a significantly lower median RBC transfusion volume compared with patients who did not receive IV iron. Pedrazzoli et al (2008)[136] found no significant difference in transfusion incidence between DAR and IV iron compared with DAR alone. The treatment arms in Auerbach et al (2010)[133] had similar incidences of RBC transfusion (P=NR).

Table 3.71 Results for IV iron in cancer (blood transfusion)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity* P-value (I^2)
LEVEL II STUDIES								
Auerbach et al (2010)[133] *Good*	Non-myeloid cancer patients with anaemia	DAR plus IV iron vs DAR alone	15 weeks	Kaplan-Meier percentage mean (95% CI) RBC transfusion incidence (N=238)	28 (20, 37)	30 (23, 39)	NR	NR
Bastit et al (2008)[134] *Fair*	Non-myeloid cancer patients with anaemia	DAR plus IV iron vs DAR with oral or no iron	16 weeks	Kaplan-Meier proportion of patients receiving a RBC transfusion, % (N=396)	16	25	NR	*Favours IV iron* P=0.038
Dangsuwan et al (2010)[135] *Fair*	Gynaecologic cancer patients with anaemia	IV vs oral iron	Consecutive cycle of chemotherapy	Incidence of RBC transfusion in consecutive cycle of chemotherapy, n/N (%) (N=44)	5/22 (22.7)	14/22 (63.6)	NR	*Favours IV iron* P<0.05
				Median (range) volume of RBCs transfused, units (N=44)	0 (0 to 2)	1 (0 to 2)	NR	*Favours IV iron* P=0.01
Pedrazzoli et al (2008)[136] *Fair*	Cancer patients with anaemia	DAR plus IV iron vs DAR alone	12 weeks	Incidence of RBC transfusion, n/N (%) (N=149)	2/73 (2.7)	5/76 (6.6)	RR 0.42 (0.08, 2.08)[a]	P=0.29[a]

CHF, chronic heart failure; CI, confidence interval; IV, intravenous; NR, not reported; RR, relative risk

[a] Calculated for the purpose of this systematic review using Review manager.

Thromboembolic events

Table 3.72 summarises the incidence of thromboembolic events in studies evaluating IV iron use cancer patients with anaemia. None of the studies found a significant difference in the incidence of myocardial infarction, stroke, or overall thromboembolic events between patients treated with IV iron plus darbepoetin compared with darbepoetin with oral iron or no iron therapy. When the results from the RCTs were meta-analysed there was still no significant difference between IV iron and treatment without IV iron in the incidence of thromboembolic events (RR 0.95; 95% CI: 0.54, 1.65; Figure 3.8) or myocardial infarction (RR 0.41; 95% CI 0.10, 1.64; Figure 3.9).

Figure 3.8 Meta-analysis of IV iron in cancer (thromboembolic events)

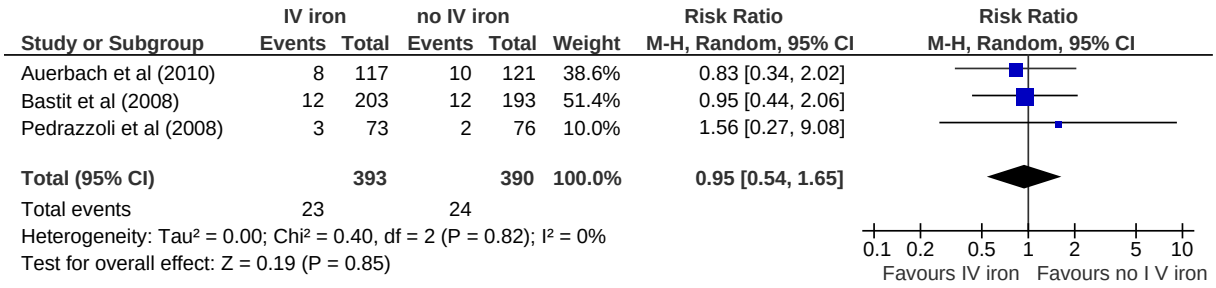


Figure 3.9 Meta-analysis of IV iron in cancer (myocardial infarction)

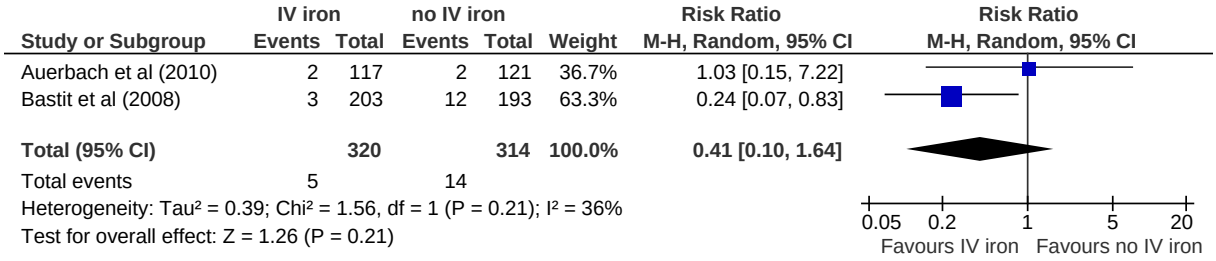


Table 3.72 Results for IV iron in cancer (thromboembolic events)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Auerbach et al (2010)[133] *Good*	Non-myeloid cancer patients with anaemia	DAR plus IV iron vs DAR alone	15 weeks	Thromboembolic events, n/N (%) (N=238)	8/117 (7)	10/121 (8)	RR 0.83 (0.34, 2.02)[a]	*No significant difference* P=0.68[a]
				MI/artery disorders, n/N (%) (N=238)	2/117 (2)	2/121 (2)	RR 1.03 (0.15, 7.22)[a]	*No significant difference* P=0.97[a]
				Stroke, n/N (%) (N=238)	1/117 (1)	0/121 (0)	RR 3.10 (0.13, 75.38)[a]	*No significant difference* P=0.49[a]
Bastit et al (2008)[134] *Fair*	Non-myeloid cancer patients with anaemia	DAR plus IV iron vs DAR with oral or no iron	16 weeks	Thromboembolic events, n/N (%) (N=396)	12/203 (6)	12/193 (6)	RR 0.95 (0.44, 2.06)[a]	*No significant difference* P=0.90[a]
				MI, ischemic and coronary artery disease, n/N (%) (N=396)	3/203 (1)	1/193 (1)	RR 2.85 (0.30, 27.19)[a]	*No significant difference* P=0.36[a]
				Stroke, n/N (%) (N=396)	0/203 (0)	0/193 (0)	NA	NA
Pedrazzoli et al (2008)[136] *Fair*	Cancer patients with anaemia	DAR plus IV iron vs DAR alone	12 weeks	Thromboembolic events, n/N (%) (N=149)	3/73 (4.1)	2/76 (2.6)	RR 1.56 (0.27, 9.08)[a]	*No significant difference* P=0.62[a]

CI, confidence interval; DAR, darbepoetin; IV, intravenous; MI, myocardial infarction; NA, not applicable; RR, relative risk

[a] Calculated for the purpose of this systematic review using Review manager.

Functional/performance status

Two of the studies[134,135] evaluating the use of IV iron in anaemic patients with cancer reported change in Functional Assessment of Cancer Therapy (FACT) score as an outcome. Neither study found a significant difference between patients treated with IV iron and those who received oral or no iron therapy (Table 3.73).

Table 3.73 Results for IV iron in cancer (functional/performance status)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Bastit et al (2008)[134] *Fair*	Non-myeloid cancer patients with anaemia	DAR plus IV iron vs DAR with oral or no iron	16 weeks	Mean (SD) FACT-F score at baseline (N=396)	30.85 (11.16)	32.98 (11.24)	NR	NR
				Mean (95% CI) adjusted change in FACT-Fatigue score from baseline at follow-up (N=396)	2.40 (0.84, 3.95)	2.17 (0.65, 3.69)	NR	*No significant difference* P>0.05
				Kaplan-Meier proportion (95% CI) of patients with a clinically meaningful increase in FACT-Fatigue score (≥3 points), % (N=396	76 (67, 84)	67 (56, 78)	NR	*No significant difference* P>0.05
Dangsuwan et al (2010)[135] *Fair*	Gynaecologic cancer patients with anaemia	IV vs oral iron	Consecutive cycle of chemotherapy	Median (range) FACT-anaemia score at baseline (N=44)	118.2 (83.5 to 153.0)	123.8 (97.0 to 165.6)	NR	*No significant difference* P>0.05
				Median (range) FACT-anaemia score after treatment (N=44)	123.7 (87.0 to 151.0)	125.8 (98.1 to 165.0)	NR	*No significant difference* P>0.05
				Median (range) change in FACT-anaemia score from baseline (N=44)	1.7 (−9.2 to 16.8)	0.5 (−19.0 to 18.5)	NR	*No significant difference* P>0.05

CI, confidence interval; DAR, darbepoetin; FACT, Functional Assessment of Cancer Therapy; IV, intravenous; NR, not reported; SD, standard deviation

3.3.4 Non-transfusion interventions for patients with chronic heart failure

Evidence statements – chronic heart failure (erythropoiesis-stimulating agents)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.13	In anaemic patients with CHF, the effect of ESAs on mortality is uncertain. (See evidence matrix EM3.J in Volume 2 of the technical report)	√√√	X	X	√√	√√√
ES3.14	In anaemic patients with CHF, the effect of ESAs on transfusion requirements is uncertain. (See evidence matrix EM3.K in Volume 2 of the technical report)	X	NA	X	X	√√
ES3.15	In anaemic patients with CHF, the effect of ESAs on the incidence of thromboembolic events is uncertain. (See evidence matrix EM3.L in Volume 2 of the technical report)	√√√	√√	NA	√	√√
ES3.16	In anaemic patients with CHF, ESAs may improve functional or performance status compared with no ESAs. (See evidence matrix EM3.M in Volume 2 of the technical report)	√√√	√	√	√	√√
Evidence statements – chronic heart failure (iron therapy)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.17	In CHF patients with iron deficiency, the effect of IV iron on mortality is uncertain. (See evidence matrix EM3.N in Volume 2 of the technical report)	√√	√√	NA	√√	√√
ES3.18	In CHF patients (NYHA functional classes II or III) with iron deficiency (absolute and functional), IV iron improves functional or performance status, independent of Hb concentration. (See evidence matrix EM3.O in Volume 2 of the technical report)	√√	√√	√√	√√	√√

CHF, chronic heart failure; ES, evidence statement; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; NYHA, New York Heart Association
√√√=A; √√=B; √=C; X=D; NA, not applicable

Recommendation – chronic heart failure	
R3 Grade B	In patients with CHF, identification and treatment of iron deficiency (absolute and functional) is recommended to improve functional or performance status. This is consistent with the 2011 update to the *Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia, 2006.*[138] Note: The studies reviewed only included patients treated with IV iron, and of NYHA functional classes II or III.
CHF, chronic heart failure; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; NYHA, New York Heart Association; R, recommendation	

3.3.5 ESAs vs standard care for anaemic patients with chronic heart failure

Methods

There were six Level I studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

There were six systematic reviews of RCTs that evaluated the use of ESAs in patients with anaemia of chronic heart failure (CHF). The main characteristics of these reviews are summarised in Table 3.74.

Five of the systematic reviews (Desai et al [2010],[139] Jin et al [2010],[140] Lawler et al [2010],[141] Ngo et al [2010],[142] Tehrani et al [2009][143]) compared the use of any ESA with treatment without ESAs, the other review (Van der Meer et al [2009][144]) compared EPO with treatment without EPO. Desai et al (2010)[139] included a subpopulation (N=1347) of CHF patients from the Pfeffer et al (2009)[145] trial, which randomised 4044 patients with type 2 diabetes mellitus, CKD, and anaemia (Hb≤11.0 g/dL) to treatment with DAR or placebo.

Table 3.74 Characteristics and quality of Level I evidence

Level I evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Desai et al (2010)[139]	Systematic review *Good*	Anaemic adults with CHF N=2039	ESA vs no ESA	Mortality Adverse events (heart failure)
Jin et al (2010)[140]	Systematic review *Good*	Anaemic adults with CHF N=678	ESA vs no ESA	Mortality Functional/performance status

Level I evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Lawler et al (2010)[141]	Systematic review *Fair*	Anaemic adults with CHF N=747	ESA vs no ESA	Mortality Thromboembolic events Functional/performance status Hospitalisation for HF
Ngo et al (2010)[142]	Systematic review *Good*	Anaemic adults with CHF N=794	ESAs vs no ESAs	Mortality Thromboembolic events Functional/performance status
Tehrani et al (2009)[143]	Systematic review *Fair*	Anaemic adults with CHF N=663	ESAs vs no ESAs	Exercise duration NYHA functional classification Exercise tolerance
Van der Meer et al (2009)[144]	Systematic review *Fair*	Anaemic adults with CHF N=650	EPO vs no EPO	Mortality Hospitalisation for HF Thromboembolic events

CHF, chronic heart failure; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agents; Hb, haemoglobin; HF, heart failure; NYHA, New York Heart Association; QoL, quality of life; RBC, red blood cell

Level II evidence

A literature search was conducted to identify Level II evidence published after the literature search conducted in the Desai et al (2010)[139] systematic review[a]. No Level II evidence was identified.

Results

Mortality

The systematic reviews by Desai et al (2010)[139] and Ngo et al (2010)[142] both evaluate the impact of ESAs on mortality (Table 3.75). Ngo et al (2010) found that ESAs significantly reduce mortality (5.9% vs 10.4%; 95% CI 0.61; 95% CI 0.37, 0.99); Desai et al (2010) found no significant difference between treatment arms (21.9% vs 23.2%; RR 1.03; 95% CI 0.89, 1.21). Desai et al (2010)[139] included a subpopulation (N=1347) of CHF patients from the Pfeffer et al (2009)[145] trial, which randomised 4044 patients with type 2 diabetes mellitus, CKD, and anaemia (Hb≤11.0 g/dL) to treatment with DAR or placebo. Furthermore, two studies not discussed in Desai et al (2010) (Palazzuoli et al [2006] and the unpublished results from Kourea et al [2008] were included in the Ngo et al (2010) meta-analysis for mortality. Silverberg et al (2001) was included in the Ngo et al (2010) meta-analysis, but was excluded from Desai et al (2010) due to concerns regarding the lack of blinding, lack of placebo control, and potential confounding by concomitant administration of IV iron to ESA-administered patients. Desai et al (2010) identified one RCTthat was published after the literature search conducted for Ngo et al (2010).

[a] The literature search in Desai et al (2010) included papers published from 1966 to September 2009.

Table 3.75 Results for ESAs vs no ESAs in CHF (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL I STUDIES								
Desai et al (2010)[139] *Good*	Anaemic adults with CHF	ESA vs no ESA	3-24 months	Mortality, n/N (%) 9 trials (N=2039)	224/1023 (21.9)	236/1016 (23.2)	RR 1.03 (0.89, 1.21)	*No significant difference* P=0.68 *No significant heterogeneity*[a] P*het*=0.21 (I^2=NR)
Ngo et al (2010)[142] *Good*	Anaemic adults with CHF	ESA vs no ESA	2-12 months	Mortality, n/N (%) 10 studies (N=764)	25/426 (5.9)	35/338 (10.4)	RR 0.61 (0.37, 0.99)	*Favours ESA* P=0.045 *No significant heterogeneity*[a] P*het*=0.67 (I^2=0.0%)

CHF, chronic heart failure; CI, confidence interval; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; NR, not reported; OR, odds ratio; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Blood transfusion

Klapholz et al (2009)[146] present a pooled analysis of the unpublished incidence rates of RBC transfusion (Table 3.76). However, Klapholz et al (2009. did not report the results of the individual studies, only the pooled outcomes. The incidence of RBC transfusion was similar for patients treated with DAR compared with those who did not receive DAR (6.4% vs 9.5%; P=NR).

Table 3.76 Results for ESAs vs no ESAs in CHF (blood transfusion)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
POOLED ANALYSIS OF LEVEL II STUDIES								
Klapholz et al (2009)[146] *Poor*	Anaemic adults with CHF	DAR vs no DAR	NR	RBC transfusion incidence, n/N (%) 3 trials (N=514)	18/283 (6.4)	22/231 (9.5)	NR	NR

CI, confidence interval; CHF, chronic heart failure; DAR, darbepoetin; NR, not reported; RBC, red blood cell;

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Thromboembolic events

The Ngo et al (2010)[142] systematic review reported the incidence of thromboembolic events and CHF-related hospitalisations for patients treated with ESAs compared with patients not treated with ESAs (Table 3.77). There was no significant difference between ESA and no ESA for the incidence of stroke (1.8% vs 1.3%; RR 1.57; 95% CI 0.52, 4.70), myocardial infarction (2.2% vs 3.7%; RR 0.69; 95% CI 0.31, 1.55), or other thromboembolic events (1.0% vs 1.8%; RR 0.65; 95% CI 0.22, 1.88).

Table 3.77 Results for ESAs vs no ESAs in CHF (thromboembolic events)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL I STUDIES								
Ngo et al (2010)[142] *Good*	Anaemic adults with CHF	ESA vs no ESA	2-12 months	Stroke, n/N (%) 8 studies (N=700)	7/389 (1.8)	4/311 (1.3)	RR 1.57 (0.52, 4.70)	*No significant difference* P=0.42 *No significant heterogeneity*[a] P*het*=0.86 (I^2=0.0%)
				MI, n/N (%) 9 studies (N=732)	9/410 (2.2)	12/322 (3.7)	RR 0.69 (0.31, 1.55)	*No significant difference* P=0.37 *No significant heterogeneity*[a] P*het*=0.94 (I^2=0.0%)
				Other thromboembolic events, n/N (%) 9 studies (N=741)	4/410 (1.0)	6/331 (1.8)	RR 0.65 (0.22, 1.88)	*No significant difference* P=0.42 *No significant heterogeneity*[a] P*het*=0.59 (I^2=0.0%)

CI, confidence interval; CHF, chronic heart failure; ESA, erythropoiesis stimulating agent; HF, heart failure; MI, myocardial infarction; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Functional/performance status

Ngo et al (2010)[142] found that ESAs, compared with control, significantly improve Six-Minute Walk Test (6MWT) distance (MD 69.33 m; 95% CI 16.99, 121.67) and NYHA functional class (MD -0.73; 95% CI -1.11, -0.36) (Table 3.78).

Table 3.78 Results for ESAs vs no ESAs in CHF (functional/performance status)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL I STUDIES								
Ngo et al (2010)[142] *Good*	Anaemic adults with CHF	ESA vs no ESA	2-12 months	6MWT distance, m 4 studies (N=261)	NR	NR	MD 69.33 (16.99, 121.67)	*Favours ESA* P=0.0094 *Substantial heterogeneity*[a] P*het*=0.02 (I^2=70%)
				NYHA functional class improvement 8 studies (N=657)	NR	NR	MD -0.73 (-1.11, -0.36)	*Favours ESA* P=0.00013 *Substantial heterogeneity*[a] P*het*<0.001 (I^2=95%)

6MWT, six-minute walk test; CI, confidence interval; CHF, chronic heart failure; DAR, darbepoetin; ESA, erythropoiesis stimulating agent; MD, mean difference; NR, not reported; NYHA, New York Heart Association; RR, relative risk;

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

3.3.6 IV iron for chronic heart failure patients with iron deficiency

Methods

There were two Level II studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

No Level I evidence evaluating the use of iron therapy in patients with CHF was identified.

Level II evidence

Two RCTs (Anker et al [2009][147] and Okonko et al [2008][148]) evaluating the use of iron therapy in patients with CHF were identified. Both RCTs compared IV iron with treatment without IV iron in CFH patients with of New York Heart Association (NYHA) class II or III. The main characteristics of these trials are summarised in **Table 3.79**.

Table 3.79 Characteristics and quality of Level II evidence

Level II evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Anker et al (2009)[147]	RCT *Good*	Ambulatory patients who had CHF of NYHA class II or III, a left ventricular ejection fraction of 40% or less (for patients in NYHA class II) or 45% or less (for patients in NYHA class III), a Hb concentration at the screening visit between 95 and 135 g/L, and iron deficiency (ferritin <100 µg/L or between 100 µg/l and 299 µg/l when TSAT <20%). N=459	200 mg IV iron[a] vs placebo for 24 weeks.	Mortality Thromboembolic events Functional/performance status
Okonko et al (2008)[148]	RCT *Poor*	Patients with CHF (NYHA class II or III), exercise limitation (pVO_2/kg ≤18 mL/kg/min), ferritin <100 µg/l or between 100 µg/l and 300 µg/l with TSAT <20%, and LVEF ≤45%. N=35	16 weeks of IV iron (200 mg weekly until ferritin >500 ng/ mL, 200 mg monthly thereafter) vs standard care	Mortality Functional/performance status

CHF, chronic heart failure; Hb, haemoglobin; IV, intravenous; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RCT, randomised controlled trial; TSAT, transferring saturation

[a] Weekly during the correction phase and then every 4 weeks during the maintenance phase, which started at week 8 or week 12, depending on the required iron-repletion dose.

Results

Mortality

Both RCTs that evaluated the use of IV iron therapy in CHF patients[147,148] reported mortality as an outcome (Table 3.80). Neither study found a significant difference in mortality between treatment arms. When the results from the two RCTs were meta-analysed (Figure 3.10) there

was still no significant difference in mortality between anaemic patients with CHF treated with IV iron and CHF patients who did not receive IV iron (RR 0.73; 95% CI: 0.22, 2.41). The studies were not powered to detect a significant difference in mortality.

Table 3.80 Results for IV iron in CHF (mortality)

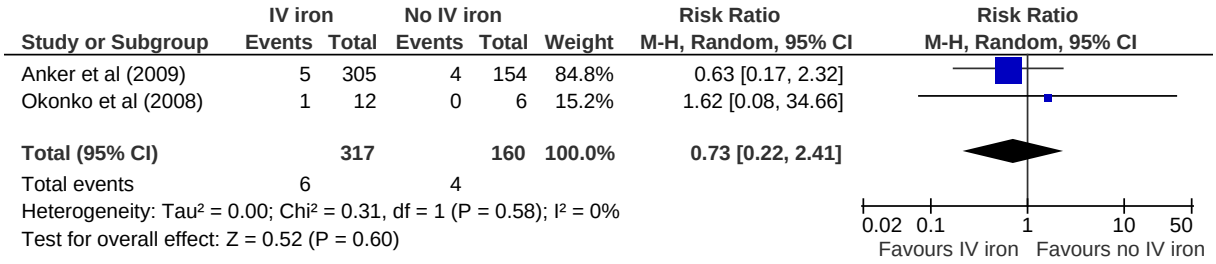
Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity* P-value (I^2)
LEVEL II STUDIES								
Anker et al (2009)[147] *Good*	CHF patients with iron deficiency	IV iron vs placebo	24 weeks	Mortality, n/N (%) (N=459)	5/305 (1.6)	4/154 (2.6)	NR	*No significant difference* P=0.47
				Mortality due to cardiovascular causes, n/N (%) (N=459)	4/305 (1.3)	4/154 (2.6)	NR	*No significant difference* P=0.31
Okonko et al (2008)[148] *Poor*	CHF patients with iron deficiency	IV iron vs standard care	16 weeks	Mortality, n/N (%)	1/24 (4.2)	0/11 (0.0)	RR 1.44 (0.06, 32.80)[a]	*No significant difference* P=0.82
				Mortality (patients with anaemia at baseline)[b], n/N (%) (N=18)	1/12 (8.3)	0/6 (0.0)	RR 1.62 (0.08, 34.66)[a]	*No significant difference* P=0.76[b]

CHF, chronic heart failure; CI, confidence interval; IV, intravenous; NR, not reported; RR, relative risk

[a] Calculated for the purpose of this systematic review using Review manager.

[b] Hb <125 g/L.

Figure 3.10 Meta-analysis of IV iron in CHF (mortality)



Blood transfusion

Neither of the studies reported the incidence or volume of blood transfusion.

Thromboembolic events.

Table 3.81 summarises the incidence of thromboembolic events in studies that evaluate IV iron use CHF patients with iron deficiency. Anker et al (2009)[147] found that CHF patients treated with IV iron had a significantly lower incidence of cardiac disorder and severe cardiac disorder compared with placebo-treated patients (P<0.01). There was no significant difference between IV iron and placebo in the rates of hospitalisation for any cardiovascular cause, vascular disorders, or severe vascular disorders. Okonko et al (2008)[148] did not reported thromboembolic events as an outcome.

Table 3.81 Results for IV iron in CHF (thromboembolic events)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Anker et al (2009)[147] *Good*	CHF patients with iron deficiency	IV iron vs placebo	24 weeks	Hospitalisation for any cardiovascular cause, n/N (%) (N=459)	16/305 (5.2)	18/154 (11.7)	NR	*No significant difference* P=0.30
				Cardiac disorder[a], n/N (%) (N=459)	46/305 (15.1)	49/154 (31.8)	NR	*Favours IV iron* P<0.01
				Cardiac disorder[a] (SAEs), n/N (%) (N=459)	12/305 (3.9)	23/154 (14.9)	NR	*Favours IV iron* P<0.01
				Vascular disorder[b], n/N (%) (N=459)	24/305 (7.9)	13/154 (8.4)	NR	*No significant difference* P>0.05
				Vascular disorder[b] (SAEs), n/N (%) (N=459)	3/305 (1.0)	1/154 (0.6)	NR	*No significant difference* P>0.05

CHF, chronic heart failure; CI, confidence interval; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified; NR, not reported; SAEs, serious adverse events

[a] As defined by MedDRA. Includes: cardiac arrhythmias; cardiac disorder signs and symptoms; cardiac neoplasms; cardiac valve disorders; congenital cardiac disorders; coronary artery disorders; endocardial disorders; heart failures; myocardial disorders; pericardial disorders.

[b] As defined by MedDRA. Includes: aneurysms and artery dissections; arteriosclerosis, stenosis, vascular insufficiency and necrosis; decreased and non-specific blood pressure disorders and shock; embolism and thrombosis; lymphatic vessel disorders; vascular disorders NEC; vascular haemorrhagic disorders; vascular hypertensive disorders; vascular inflammations; vascular injuries; venous varices.

Functional/performance status

Table 3.82 presents the functional/performance status results reported in the RCTs that assessed the use of IV iron in CHF patients with iron deficiency. Anker et al (2009)[147] found that a significantly greater proportion of patients treated with IV iron had an improvement in the Self-Reported Patient Global Assessment (73.7% vs 52.9%; OR 2.49; 95% CI 1.66, 3.74) and NYHA functional class (OR 2.40; 95% CI 1.55, 3.71) at follow-up compared with the placebo-treated patients. Subgroup analyses found no significant interaction between improvement in either Patient Global Assessment or NYHA and baseline Hb concentration, baseline ferrite concentration, baseline estimated GFR, age, gender, NYHA class, baseline median left ventricular ejection fraction (LVEF), heart failure type, presence of diabetes, or median BMI.

IV iron-treated patients in Anker et al (2009) also had a significantly greater improvement from baseline in the 6 Minute Walk Test (6MWT) distance, EQ-5D score, and Kansas City Cardiomyopathy Questionnaire score, compared with placebo-treated patients (P<0.001).

CHF patients treated with IV iron in Okonko et al (2008)[148] demonstrated a significantly greater improvement in NYHA functional class from baseline compared with patients treated with placebo (P=0.048). There was no significant difference between treatment arms for improvement in exercise duration.

Table 3.82 Results for IV iron in CHF (functional/performance status)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Anker et al (2009)[147] *Good*	CHF patients with iron deficiency	IV iron vs placebo	24 weeks	Patients with an improvement in Self-Reported Patient Global Assessment at follow-up, n/N (%) (N=459)	224/304 (73.7)	82/155 (52.9)	OR 2.49 (1.66, 3.74)[a]	*Favours IV iron* P<0.0001
					Subgroup analyses found no significant interaction between improvement in Patient Global Assessment and baseline Hb concentration (≤120 or >120 g/L), baseline ferrite concentration (≤39 or >39 µg/L), baseline estimated GFR (<60 or ≥60 mL/min/1.73 m^2 of body-surface area), age (≤69.7 or >69.7 years), gender, NYHA class, baseline median LVEF (≤33% or >33%), heart failure type (non-ischemic or ischemic), presence of diabetes, median BMI (≤27.37 or >27.37).			
				Patients with an improvement in NYHA functional class at follow-up, n/N (%) (N=459)	NR	NR	OR 2.40 (1.55, 3.71)	*Favours IV iron* P<0.001
					Subgroup analyses found no significant interaction between improvement in NYHA functional class and baseline Hb concentration (≤120 or >120 g/L), baseline ferrite concentration (≤39 or >39 µg/L), baseline estimated GFR (<60 or ≥60 mL/min/1.73 m^2 of body-surface area), age (≤69.7 or >69.7 years), gender, NYHA class, baseline median LVEF (≤33% or >33%), heart failure type (non-ischemic or ischemic), presence of diabetes, median BMI (≤27.37 or >27.37).			
				Mean (SD) 6MWT distance at baseline, m (N=458)	274 (6)	269 (9)	NR	NR
				Mean (SD) change in 6MWT distance from baseline at follow-up, m (N=402)	NR	NR	Mean (SD) study-treatment effect: 35 (8)	*Favours IV iron* P<0.001
				Mean (SD) EQ-5D score at baseline (N=447)	54 (1)	54 (1)	NR	NR
				Mean (SD) change in EQ-5D score from baseline at follow-up (N=431)	NR	NR	Mean (SD) study-treatment effect: 7 (2)	*Favours IV iron* P<0.001
				Mean (SD) Kansas City Cardiomyopathy Questionnaire score at baseline (N=448)	52 (1)	53 (1)	NR	NR

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
				Mean (SD) change in Kansas City Cardiomyopathy Questionnaire score from baseline at follow-up (N=431)	NR	NR	Mean (SD) study-treatment effect: 7 (2)	*Favours IV iron* P<0.001
Okonko et al (2008)[148] *Poor*	CHF patients with iron d	IV iron vs standard care	16 weeks	Baseline mean (SD) absolute peak Vo_2, mL/min (N=35)	1053 (321)	1201 (330)	NR	NR
				Mean (SD) change in absolute peak Vo_2, mL/min (N=35)	75 (156)	-21 (210)	Treatment effect 96 (-12, 205)	*No significant difference* P=0.08
				Baseline mean (SD) absolute peak Vo_2 (anaemic patients)[b], mL/min (N=18)	880 (259)	1224 (314)	NR	NR
				Mean (SD) change in absolute peak Vo_2 (anaemic patients)[b], mL/min (N=18)	158 (182)	-46 (116)	Treatment effect 204 (31 to 378)	*Favours IV iron* P=0.02
				Baseline mean (SD) peak Vo_2/kg, mL/kg/min (N=35)	13.9 (2.7)	14.2 (3)	NR	NR
				Mean (SD) change in absolute peak Vo_2/kg, mL/kg/min (N=35)	1.5 (2.7)	-0.7 (1.4)	Treatment effect 2.2 (0.5, 4.0)	*Favours IV iron* P=0.01
				Baseline mean (SD) peak Vo_2/kg (anaemic patients)[b], mL/kg/min (N=18)	12.9 (2.8)	14.7 (3.6)	NR	NR

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
				Mean (SD) change in absolute peak Vo_2/kg (anaemic patients)[b], mL/kg/min (N=18)	2.8 (3.2)	-1.1 (0.9)	Treatment effect 3.9 (1.1, 6.8)	*Favours IV iron* P=0.009
				Baseline mean (SD) NYHA functional class (N=35)	2.5 (0.5)	2.4 (0.5)	NR	NR
				Mean (SD) change in NYHA functional class from baseline (N=35)	-0.4 (0.6)	0.2 (0.4)	Treatment effect -0.6 (-0.9, -0.2)	*Favours IV iron* P=0.007
				Baseline mean (SD) NYHA functional class (anaemic patients)[b] (N=18)	2.4 (0.5)	2.5 (0.5)	NR	NR
				Mean (SD) change in NYHA functional class from baseline (anaemic patients)[b] (N=18)	-0.3 (0.5)	0.2 (0.4)	Treatment effect -0.5 (-1.0, 0)	*Favours IV iron* P=0.048
				Mean (SD) change in patient global assessment score (N=35)	1.5 (1.2)	-0.2 (1.6)	Treatment effect 1.7 (0.7, 2.6)	*Favours IV iron* P=0.002
				Baseline mean (SD) MLHFQ score (N=35)	41 (22)	46 (18)	NR	NR
				Mean (SD) change in MLHFQ	-10 (18)	3 (19)	Treatment effect -13 (-26, 1)	*No significant difference* P=0.07
				Baseline mean (SD) exercise duration[c], s (N=35)	476 (185)	501 (179)	NR	NR
				Mean (SD) change in exercise duration from baseline[c], s (N=35)	45 (84)	-15 (109)	Treatment effect 60 (-6, 126)	*No significant difference* P=0.08

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
				Baseline mean (SD) exercise duration[c] (anaemic patients)[b], s (N=18)	441 (188)	506 (71)	NR	NR
				Mean (SD) change in exercise duration from baseline[c] (anaemic patients)[b], s (N=18)	63 (97)	20 (114)	Treatment effect 43 (-66, 153)	*No significant difference* P=0.41

6MWT, six-minute walk test; BMI, body mass index; CHF, chronic heart failure; CI, confidence interval; GFR, glomerular filtration rate; IV, intravenous; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NR, not reported; NYHA, New York Heart Association; OR, odds ratio; SD, standard deviation; Vo_2, oxygen consumption

[a] Calculated for the purpose of this systematic review using Review manager.

[b] Hb <120 g/L.

[c] Exercise testing was performed on a treadmill using a modified Naughton or modified Bruce protocol depending on the physician's judgement.

3.3.7 Non-transfusion interventions for patients with chronic kidney disease

Evidence statements – chronic kidney disease (erythropoiesis-stimulating agents)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.19	In anaemic patients with CKD, the effect of ESA therapy to a Hb target of 100–110 g/L on mortality is uncertain compared with no ESA therapy. (See evidence matrix EM3.P in Volume 2 of the technical report)	√√	√√√	NA	√√	√√√
ES3.20	In anaemic patients with non dialysis-dependent CKD, type 2 diabetes and a history of malignant condition at baseline, ESAs increase the incidence of mortality attributable to cancer. (See evidence matrix EM3.P in Volume 2 of the technical report)	√√	NA	√√√	√√√	√√√
ES3.21	In anaemic patients with CKD, ESA therapy to a Hb target of 100–110 g/L reduces RBC transfusion incidence compared with no ESA therapy. (See evidence matrix EM3.Q in Volume 2 of the technical report)	√√	√√	√√√	√√	√√√
ES3.22	In anaemic patients with CKD, targeting a Hb concentration above 130 g/L with ESA therapy increases the incidence of stroke and other thromboembolic events. The effect of targeting lower Hb concentrations is uncertain. (See evidence matrix EM3.R in Volume 2 of the technical report)	√√	√√	√√	√√	√√√
ES3.23	In anaemic patients with CKD, ESA therapy to a Hb target of 100–110 g/L does not appear to affect the incidence of MI. (See evidence matrix EM3.R in Volume 2 of the technical report)	√√	√√	√√	√√	√√√
ES3.24	In nondiabetic dialysis patients, compared to no treatment, ESA therapy targeted to a Hb ≥95 g/L may reduce fatigue and improve physical functioning. (See evidence matrix EM3.S in Volume 2 of the technical report)	√√	√	√	√√	√√√
ES3.25	In anaemic patients with non dialysis-dependent CKD, ESA therapy to a Hb target of 100–110 g/L may reduce fatigue, but has little impact on physical functioning. (See evidence matrix EM3.S in Volume 2 of the technical report)	√√	√	√	√√	√√√

Evidence statements – chronic kidney disease (iron therapy)		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES3.26	In anaemic patients with CKD receiving ESAs, the effect of IV iron on mortality is uncertain. (See evidence matrix EM3.T in Volume 2 of the technical report)	√	√√	NA	√√	√√
ES3.27	In anaemic patients with CKD on dialysis and receiving ESAs, IV iron may reduce the need for an anaemia intervention.[a] (See evidence matrix EM3.U in Volume 2 of the technical report)	X	NA	√	√√√	√√
ES3.28	In anaemic patients with non dialysis-dependent CKD, the effect of IV iron on RBC transfusion requirement is uncertain. (See evidence matrix EM3.U in Volume 2 of the technical report)	X	NA	X	√√	√√
ES3.29	In anaemic patients with non dialysis-dependent CKD, IV iron therapy may improve functional or performance status compared to oral iron therapy. (See evidence matrix EM3.V in Volume 2 of the technical report)	√√	√√	X	√√	√√
CKD, chronic kidney disease; ES, evidence statement; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; MI, myocardial infarction; RBC, red blood cell √√√=A; √√=B; √=C; X=D; NA, not applicable						

[a] Anaemia intervention defined as either: an increase in ESA dose, non-protocol IV iron or RBC transfusion, resulting in non-completion of study.

Recommendations – chronic kidney disease	
R4 Grade B	In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to avoid RBC transfusion, after consideration of risks and benefits for the individual patient (Grade B). Note: The CARI guidelines recommend 100-115 g/L.
R5 Grade C	In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to relieve fatigue, after consideration of risks and benefits for the individual patient (Grade C). Note: The CARI guidelines recommend 100-115 g/L.
R6 Grade B	In anaemic patients with CKD, ESA therapy to a Hb target of over 130 g/L is not recommended because of increased morbidity.
R7 Grade B	In anaemic patients with non dialysis-dependent CKD, type 2 diabetes and a history of malignancy, the *routine* use of ESAs is not recommended because of the increased risk of cancer-related mortality.
Practice points – chronic kidney disease	
PP13	ESA use is less effective in patients who have absolute or functional iron deficiency.
PP14	For comprehensive information about ESA and iron therapy in patients with CKD, refer to CARI iron guidelines.[149]
CARI, Caring for Australasians with Renal Impairment; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; MI, myocardial infarction; PP, practice point; R, recommendation; RBC, red blood cell	

3.3.8 ESAs vs no ESAs for anaemic patients with chronic kidney disease

Methods

There were four Level I studies and three subsequently published Level II studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

There were four systematic reviews of randomised controlled trials (RCTs) that evaluated the use of erythropoiesis stimulating agents (ESAs) in patients with anaemia of chronic kidney disease (CKD).[150-153] The main characteristics of these reviews are summarised in Table 3.83.

Three of the systematic reviews compared the use of any ESA with treatment without ESAs and the other systematic review compared erythropoietin (EPO) with standard care. Cody et al (2005)[152] and Gandra et al (2010)[150] evaluated ESAs in pre-dialysis CKD patients. Johansen et al (2010)[153] evaluated ESAs in end-stage renal disease patients who were on dialysis. Tonelli et al (2008)[151] included studies which assessed both on- and pre-dialysis CKD and only included studies which used low-to-intermediate Hb targets.[a]

Table 3.83 Characteristics and quality of Level I evidence

Level I evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Gandra et al (2010)[150]	Systematic review *Fair*	Anaemic adults with pre-dialysis CKD N=159	ESA vs no ESA	Functional/performance status
Johansen et al (2010)[153]	Systematic review *Fair*	Anaemic adults with on-dialysis ESRD N=767	ESA vs no ESA	Functional/performance status
Tonelli et al (2008)[151]	Systematic review *Good*	Anaemic adults with CKD (on-dialysis or pre-dialysis) N=1553 (ESA vs no ESA)	ESA (low-to-intermediate Hb target) vs no ESA	Mortality Thromboembolic events RBC transfusion Functional/ performance status Cost effectiveness
Cody et al (2005)[152]	Systematic review *Good*	Anaemic adults with pre-dialysis CKD N=461	EPO vs standard care	Mortality RBC transfusion Functional/performance status

CKD, chronic kidney disease; CV, cardiovascular; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agents; ESRD, end-stage renal disease; Hb, haemoglobin; QoL, quality of life; RBC, red blood cell

Only reviews that compared ESAs with no ESA treatment were eligible for inclusion. Therefore, Strippoli et al (2006),[154] which compared Hb targets rather than comparing treatment with no treatment, was excluded. Similarly, when discussing the results from Tonelli et al (2008),[151] only the studies defined by the review as comparing "ESA vs no ESA", rather than comparing "high vs intermediate/low target Hb protocols", were eligible for inclusion.

Level II evidence

A literature search was conducted to identify Level II evidence published after the literature search conducted in the Tonelli et al (2008)[151] systematic review.[b] Three studies were identified and the main characteristics of these studies are summarised in Table 3.84. Two of

[a] Tonelli et al (2008) also reported studies that compared high vs intermediate/low target Hb protocols; however, these studies are outside of the scope for this guideline review.

[b] The literature search in Tonelli et al (2008) included papers published from 1966 to 2006.

the RCTs[155,156] compared EPO with standard care and the other RCT[145] compared darbepoetin (DAR) with placebo. One study[145] was in anaemic adults with type 2 diabetes and CKD who had not yet commenced dialysis; the other two studies[155,156] were in adults with anaemia of CKD who had not yet commenced dialysis.

Pfeffer et al (2009)[145] was a multicentre study conducted at 623 sites in 24 countries, including Australia. The other two RCTs were conducted in Italy[155] and the UK. [156]

Table 3.84 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Pfeffer et al (2009)[145]	RCT *Good*	Anaemic adults with type 2 diabetes and pre-dialysis CKD N=4047	SC DAR[a] (Hb maintained at 13.0 g/dL)	Placebo (unless Hb <9.0 g/dL, at which point EPO could be administered to maintain their Hb concentration ≥9.0 g/dL)	Mortality RBC transfusion Thromboembolic events Functional/performance status
Cianciaruso et al (2008)[155]	RCT *Good*	Anaemic adults with pre-dialysis CKD N=94	SC EPO once weekly (Hb concentration between 12 to 14 g/dL ± 0.5 g/dL and not exceeding 14 g/dL) Oral or IV iron supplementation	No EPO (unless Hb ≤9.0 g/dL, at which point EPO could be administered to maintain their Hb concentration between 9.0 and 10.5 g/dL) Oral or IV iron supplementation	AEs Functional/performance status
Macdougall et al (2007)[156]	RCT *Fair*	Anaemic adults with pre-dialysis CKD N=197	SC EPO twice weekly (Hb maintained at 11.0 ± 1.0 g/dL)	No EPO (unless Hb ≤9.0 g/dL, at which point EPO could be administered to maintain their Hb concentration at 11.0 ± 1.0 g/dL)	Mortality Functional/performance status

CKD, chronic kidney disease; DAR, darbepoetin; EPO, erythropoietin; Hb, haemoglobin; RBC, red blood cells; SC, subcutaneous

Results

Mortality

Mortality was reported in the Tonelli et al (2008)[151] and Cody et al (2005)[152] systematic reviews. Two RCTs[145,156] published after the Tonelli et al (2008)[151] literature search also reported mortality as an outcome. Table 3.85 provides a summary of these results.

Tonelli et al (2008)[151] identified seven RCTs (N=1048) that compared the incidence of mortality between subjects treated with and without ESAs for anaemia of CKD. There was no significant difference between treatment arms for pre-dialysis patients (2 trials; relative risk [RR] 0.35; 95% CI: 0.05, 2.30), peritoneal dialysis patients (1 trial; RR 1.90; 95% CI: 0.18, 20.49), haemodialysis patients (4 trials; RR 0.71; 95% CI: 0.39, 1.31), or all CKD patients (7 trials; RR 0.71; 95% CI: 0.40, 1.24). There was, however, a significantly lower incidence of cardiovascular mortality in CKD patients treated with ESAs compared with those who were

not treated with ESAs (3 trials; RR 0.15; 95% CI: 0.03, 0.69). Of the 12 cases of cardiovascular mortality in the comparator arms of the RCTs, 9 occurred in 1 study[157] of 181 haemodialysis patients with a follow-up of 1 year. The other two studies that reported cardiovascular mortality had lengths of follow-up of 36 weeks (Kuriyama et al 1997) and ≤26 weeks (Bahlmann et al 1991).

Cody et al (2005)[152] identified three RCTs (N=168) that compared EPO with treatment without EPO on mortality in CKD patients who had not yet commenced dialysis. There was no significant difference in mortality between treatment arms (RR 0.60; 95% CI: 0.13, 2.88).

The RCT conducted by Macdougall et al (2007)[156] found no significant difference between EPO and no EPO in mortality (1.6% vs 3.8%; RR 0.41; 95% CI; 0.05, 3.46) and median length of time to dialysis or death (36.3 months vs 27.3 months; P=0.351) in pre-dialysis CKD patients. Pfeffer et al (2009)[145] found that in pre-dialysis CKD patients with type 2 diabetes there was no significant difference in mortality (20.5% vs 19.5%; hazard ratio [HR] 1.05; 95% CI: 0.92, 1.21) or deaths attributable to cancer (1.9% vs 1.2%; P=0.08) between patients treated with DAR and those who received placebo. Among the patients with a history of malignant condition at baseline, however, those treated with DAR had a significantly greater incidence of death attributable to cancer (7.4% vs 0.6%; P=0.0002).

A meta-analysis was conducted in order to update Tonelli et al (2008)[151] with the results from Macdougall et al (2007)[156] and Pfeffer et al (2009)[145] (see Figure 3.11). After the addition of the two RCTs, there was still no significant difference in the mortality rates of CKD patients treated with and without ESAs (9 trials; RR 1.03; 95% CI: 0.91, 1.16).

Table 3.85 Results for ESAs vs no ESAs in CKD (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity* P-value (I^2)
LEVEL I STUDIES								
Cody et al (2005)[152] *Good*	Anaemic adults with pre-dialysis CKD	EPO vs no EPO	8-48 weeks	Mortality, n/N (%) 3 studies (N=168)	3/94 (3.2)	3/74 (4.1)	RR 0.60 (0.13, 2.88)	*No significant difference* P=0.52 *No significant heterogeneity*[a] P*het*=0.60 (I^2=0.0)
Tonelli et al (2008)[151] *Good*	Anaemic adults with CKD (on-dialysis or pre-dialysis)	ESA vs no ESA	12 weeks to 1 year	All-cause mortality[b], n/N (%) 7 studies (N=1048)	19/575 (3.3)	26/473 (5.5)	RR 0.71 (0.40, 1.24)	*No significant difference* P=0.23 *No significant heterogeneity*[a] P*het*=0.80 (I^2=0)
				All-cause mortality (pre-dialysis patients), n/N (%) 2 studies (N=156)	1/85 (1.2)	3/71 (4.2)	RR 0.35 (0.05, 2.30)	*No significant difference* P=0.27 *No significant heterogeneity*[a] P*het*=0.93 (I^2=0)
				All-cause mortality (peritoneal dialysis patients), n/N (%) 1 study (N=152)	2/78 (2.6)	1/74 (1.4)	RR 1.90 (0.18, 20.49)	*No significant difference* P=0.60
				All-cause mortality (haemodialysis patients), n/N (%) 4 studies (N=740)	16/412 (3.9)	22/328 (6.7)	RR 0.71 (0.39, 1.31)	*No significant difference* P=0.28 *No significant heterogeneity*[a] P*het*=0.60 (I^2=0)
				Cardiovascular mortality[c], n/N (%) 3 studies (N=564)	1/286 (0.3)	12/278 (4.3)[d]	RR 0.15 (0.03, 0.69)	*Favours ESA* P=0.01 *No significant heterogeneity*[a] P*het*=0.84 (I^2=0)
				Cardiovascular mortality (pre-dialysis CKD patients), n/N (%) 1 study (N=73)	0/42 (0.0)	2/31 (6.5)	RR 0.15 (0.01, 2.99)	*No significant difference* P=0.21

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity* P-value (I^2)
				Cardiovascular mortality (haemodialysis patients), n/N (%) 2 studies (N=491)	1/244 (0.4)	10/247 (4.0)	RR 0.16 (0.03, 0.88)	*Favours ESA* P=0.03 *No significant heterogeneity*[a] P*het*=0.55 (I^2=0)
LEVEL II STUDIES								
Macdougall et al (2007)[156] *Fair*	Anaemic adults with pre-dialysis CKD	EPO vs no EPO	3 years[e]	Mortality, n/N (%) (N=196)	1/64 (1.6)	5/132 (3.8)[f]	RR 0.41 (0.05, 3.46)[g]	*No significant difference* P=0.41[g]
				Median length of time to dialysis or death, months (N=196)	36.3	27.3	NR	*No significant difference* P=0.351[h]
Pfeffer et al (2009)[145] *Good*	Anaemic adults with type 2 diabetes and pre-dialysis CKD	DAR vs placebo	4 years	Mortality, n/N (%) (N=4038)	412/2012 (20.5)	395/2026 (19.5)	HR 1.05 (0.92, 1.21)	*No significant difference* P=0.48
				Deaths attributable to cancer, n/N (%) (N=4038)	39/2012 (1.9)	25/2026 (1.2)	NR	*No significant difference* P=0.08[h]
				Deaths among patients with a history of a malignant condition at baseline, n/N (%) (N=348)	60/188 (31.9)	37/160 (23.1)	NR	*No significant difference* P=0.13[h]
				Deaths attributable to cancer among patients with a history of malignant condition at baseline, n/N (%) (N=348)	14/188 (7.4)	1/160 (0.6)	NR	*Favours placebo* P=0.0002[h]
				Death from cardiovascular causes, n/N (%) (N=4038)	259/2012 (12.9)	250/2026 (12.3)	HR 1.05 (0.88, 1.25)	*No significant difference* P=0.61

CI, confidence interval; CKD, chronic kidney disease; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; DAR, darbepoetin; HR, hazard ratio; NR, not reported; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

[b] In the one trial (N=362) that accrued at least one year of follow-up, the pooled RR was significantly lower (RR [95% CI] 0.11 [0.01, 0.87]) with ESA.

[c] In the one trial (N=362) that accrued at least one year of follow-up, the pooled RR was significantly lower (RR [95% CI] 0.11 [0.01, 0.87]) with ESA.

[d] Nine of the mortality cases occurred in Klinkmann 1993[157] (N=181).

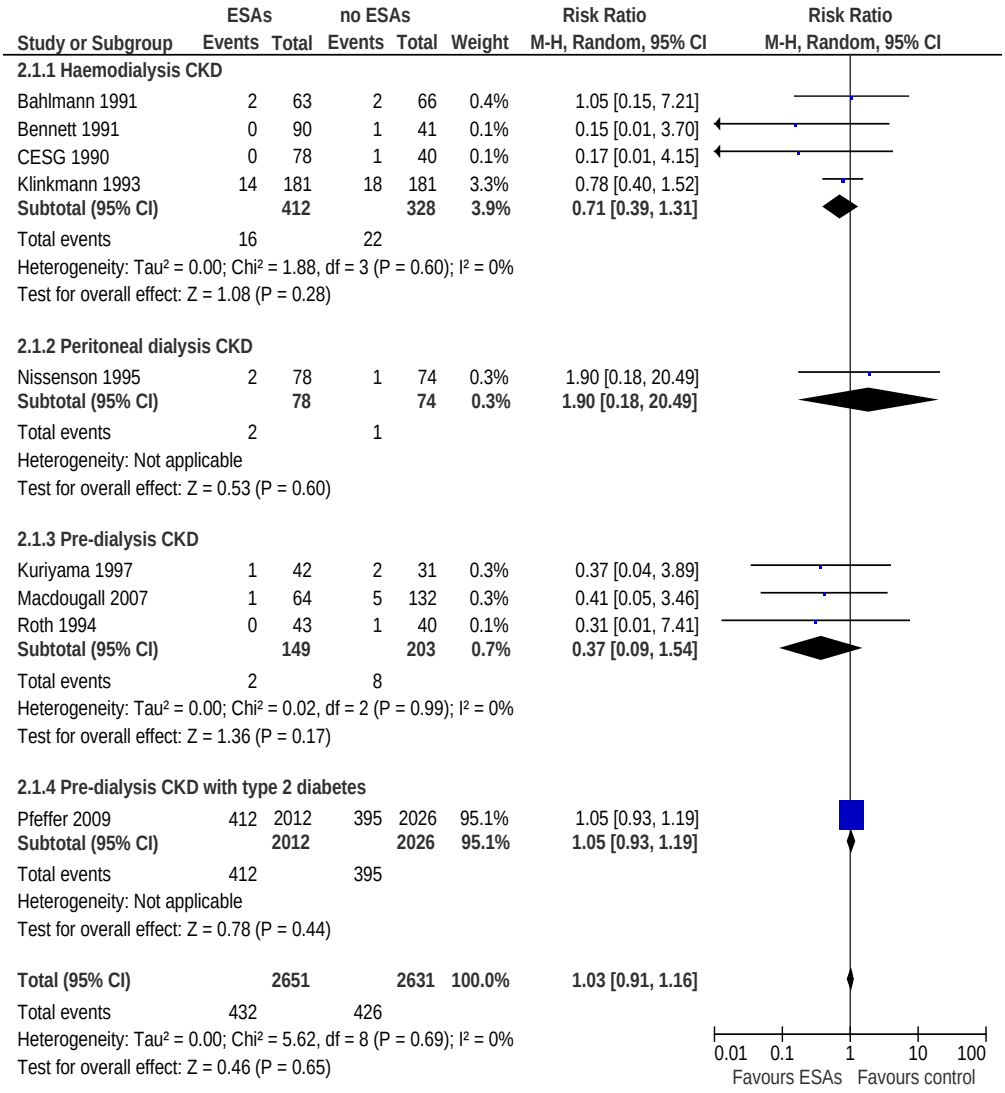
[e] Or until renal replacement/death.

[f] Excludes one patient who received dialysis before death.

[g] Calculated for the purpose of this systematic review using Review manager.

[h] Log rank test.

Figure 3.11 Meta-analysis of ESAs vs no ESAs in CKD (mortality)



Blood transfusion

Red blood cell (RBC) transfusion incidence was reported in the Tonelli et al (2008)[151] and Cody et al (2005)[152] systematic reviews. One RCT published after the Tonelli et al (2008)[151] literature search also reported RBC transfusion as an outcome (Pfeffer et al [2009][145]). No studies reported the volume of blood transfused. Table 3.86 provides a summary of these results.

Cody et al (2005)[152] found that the incidence of RBC transfusions was significantly lower in pre-dialysis CKD patients who received EPO compared with those who did not (3 trials; RR 0.32; 95% CI: 0.12, 0.83).

The results from Cody et al (2005)[152] were not consistent with the results from Tonelli et al (2008),[151] which found that ESAs, compared with treatment without ESAs, did not significantly reduce the incidence of RBC transfusion in pre-dialysis CKD patients (1 trial; RR 0.41; 95% CI: 0.14, 1.24) but did significantly reduce the incidence of RBC transfusion for CKD

patients on haemodialysis (2 trials; RR 0.09; 95% CI: 0.03, 0.32). Two of the three RCTs reported in Cody et al (2005)[152] were excluded from Tonelli et al (2008)[151] because they had a sample size of less than 30. Similarly, two of the three RCTs reported in Tonelli et al (2008)[151] were excluded from the Cody et al (2005)[152] review because they were conducted in patients undergoing haemodialysis.

The RCT conducted by Pfeffer et al (2009)[145] found that DAR compared with placebo significantly reduced the incidence of RBC transfusion (14.8% vs 24.5%; HR 0.56; 95% CI: 0.49, 0.65).

Table 3.86 Results for ESAs vs no ESAs in CKD (blood transfusion)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL I STUDIES								
Cody et al (2005)[152] *Good*	Anaemic adults with pre-dialysis CKD	EPO vs no EPO	8-48 weeks	RBC transfusion incidence, n/N (%) 3 studies (N=111)	4/61 (6.6)	13/50 (26.0)	RR 0.32 (0.12, 0.83)	*Favours EPO* P=0.020 *No significant heterogeneity*[a] P*het*=0.60 (I^2=0.0%)
Tonelli et al (2008)[151] *Good*	Anaemic adults with CKD (on-dialysis or pre-dialysis)	ESA vs no ESA	≤26-48 weeks	RBC transfusion incidence (pre-dialysis CKD), n/N (%) 1 study (N=83)	4/43 (9.3)	9/40 (22.5)	RR 0.41 (0.14, 1.24)	*No significant difference* P=0.11
				RBC transfusion incidence (haemodialysis), n/N (%) 2 studies (N=217)	7/131 (5.3)	51/86 (59.3)	RR 0.09 (0.03, 0.32)	*Favours ESA* P=0.0001 *Substantial heterogeneity*[a] P*het*=0.13 (I^2=56.2%)
LEVEL II STUDIES								
Pfeffer et al (2009)[145] *Good*	Anaemic adults with type 2 diabetes and pre-dialysis CKD	DAR vs placebo	4 years	RBC transfusion incidence, n/N (%) (N=4038)	297/2012 (14.8)	496/2026 (24.5)	HR 0.56 (0.49, 0.65)	*Favours DAR* P<0.001

CI, confidence interval; CKD, chronic kidney disease; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; HR, hazard ratio; RBC, red blood cell; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Thromboembolic events

The incidence of thromboembolic events was reported in the Tonelli et al (2008)[151] systematic review. One RCT (Pfeffer et al [2009][145]) published after the Tonelli et al (2008)[151] literature search also reported the incidence of thromboembolic events. Table 3.87 provides a summary of these results.

Tonelli et al (2008)[151] found no significant difference between CKD patients treated with or without ESAs in the incidence of myocardial infarction (2 trials; RR 0.56; 95% CI: 0.12, 2.62), stroke (1 trial; RR 0.35; 95% CI: 0.01, 8.41), and vascular access thrombosis (1 trial; RR 5.64, 95% CI: 0.75, 42.16).

In Pfeffer et al (2009),[145] anaemic patients with type 2 diabetes and pre-dialysis CKD randomised to DAR had a significantly greater incidence of stroke (5.0% vs 2.6%; HR 1.92; 95% CI: 1.38, 2.68), venous thromboembolic events (2.0% vs 1.1%; P=0.02), and arterial thromboembolic events (8.9% vs 7.1%; P=0.04) compared with patients who received placebo. There was no significant difference between the DAR and placebo treatment arms in the incidence of myocardial infarction (6.2% vs 6.4%; HR 0.96; 95% CI 0.75, 1.22).

Meta-analyses were conducted to update Tonelli et al (2008)[151] with the results from Pfeffer et al (2009).[145] Overall, no significant difference between ESAs and no ESAs was found for the incidence of MI (5.6% vs 5.9%; RR 0.96; 95% CI 0.75, 1.21; Figure 3.12), stroke (4.9% vs 2.6%; RR 1.76; 95% CI 0.84, 3.68; Figure 3.13), or other thromboembolic events (11.0% vs 8.1%; RR 1.91; 95% CI 0.55, 6.64; Figure 3.14).

Table 3.87 Results for ESAs vs no ESAs in CKD (thromboembolic events)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL I STUDIES								
Tonelli et al (2008)[151] *Good*	Anaemic adults with CKD (on-dialysis or pre-dialysis)	ESA vs no ESA	48 weeks to 1 year	MI, n/N (%) 2 studies (N=445)	2/224 (0.9)	4/221 (1.8)	RR 0.56 (0.12, 2.62)	*No significant difference* P=0.46 *No significant heterogeneity*[a] P*het*=0.68 (I^2=0)
			≤26 weeks	Stroke, n/N (%) 1 study (N=129)	0/63 (0.0)	1/66 (1.5)	RR 0.35 (0.01, 8.41)	*No significant difference* P=0.52
			26 weeks	Vascular access thrombosis 1 study (N=118)	11/78 (14.1)	1/40 (2.5)	RR 5.64 (0.75, 42.16)	*No significant difference* P>0.05
LEVEL II STUDIES								
Pfeffer et al (2009)[145] *Good*	Anaemic adults with type 2 diabetes and pre-dialysis CKD	DAR vs placebo	4 years	MI, n/N (%) (N=4038)	124/2012 (6.2)	129/2026 (6.4)	HR 0.96 (0.75, 1.22)	*No significant difference* P=0.73
				Stroke, n/N (%) (N=4038)	101/22012 (5.0)	53/2026 (2.6)	HR 1.92 (1.38, 2.68)	*Favours placebo* P<0.001
				Venous thromboembolic events, n/N (%) (N=4038)	41/2012 (2.0)	23/2026 (1.1)	NR	*Favours placebo* P=0.02
				Arterial thromboembolic events[b], n/N (%) (N=4038)	178/2012 (8.9)	144/2026 (7.1)	NR	*Favours placebo* P=0.04

CI, confidence interval; CKD, chronic kidney disease; DAR, darbepoetin; ESA; erythropoiesis stimulating agent; HR, hazard ratio; MI, myocardial infarction; NR, not reported; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.|

[b] Some of which were adjudicated as cardiovascular events

Figure 3.12 Meta-analysis of ESAs vs no ESAs in CKD (MI)

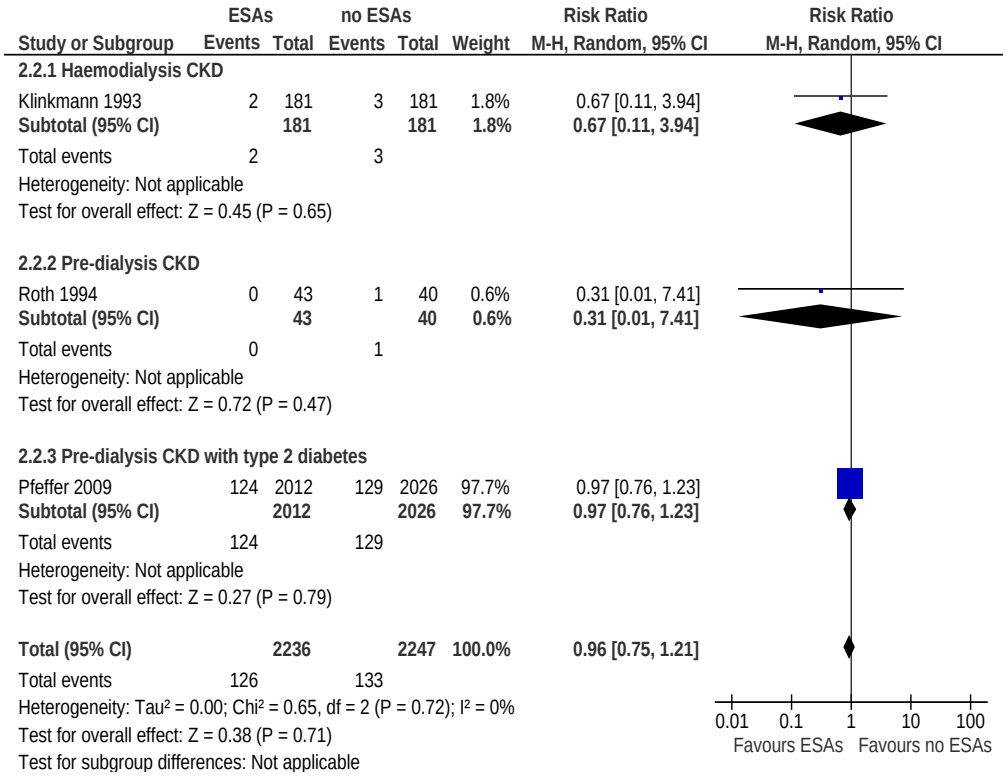


Figure 3.13 Meta-analysis of ESAs vs no ESAs in CKD (stroke)

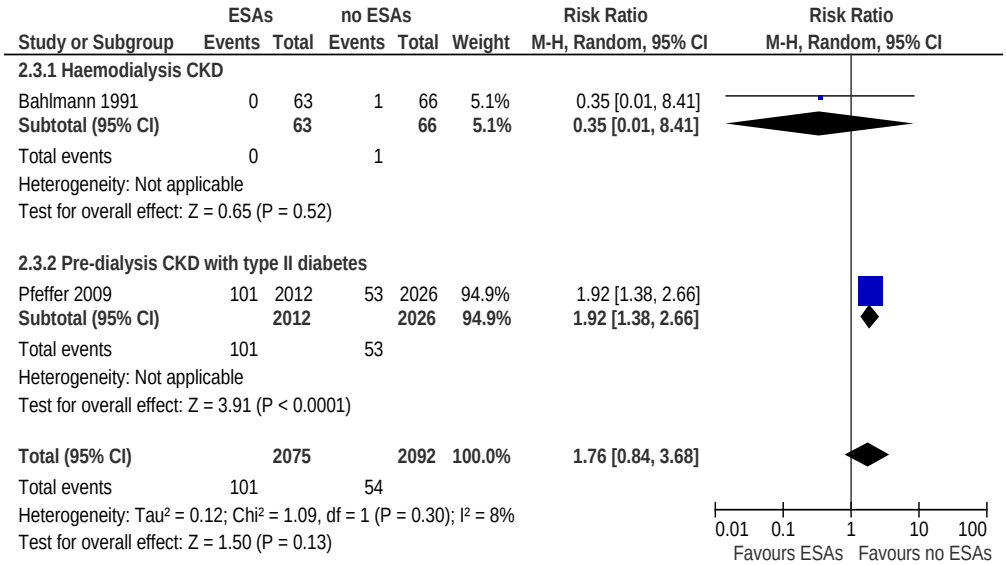
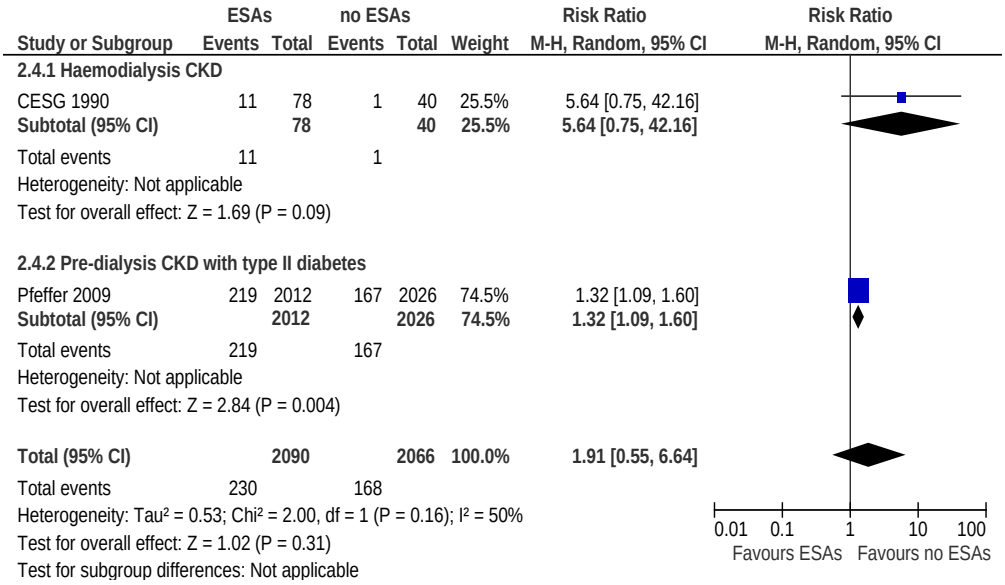


Figure 3.14 Meta-analysis of ESAs vs no ESAs in CKD (other thromboembolic events)



Functional/performance status

Functional/performance status was reported in the Tonelli et al (2008)[151] systematic review. All three RCTs published after the Tonelli et al (2008)[151] literature search also reported functional/performance status as an outcome (Cianciaruso et al [2008][155]; Macdougall et al [2007][156]; Pfeffer et al [2009][145]). Table 3.88 provides a summary of these results.

Tonelli et al (2008)[151] reported the results of one trial (Churchill et al[1990][158]), which found that haemodialysis patients treated with EPO experienced a significantly greater improvement in quality of life (Kidney Disease Questionnaire [KDQ]–fatigue) compared with control (MD 1.10; 95% CI: 0.76, 1.44). Keown et al (2010)[159] reported a reanalysis of the data from the CESG trial reported in Tonelli et al (2008).[151] The reanalysis confirmed using a repeated measures approach on an intention to treat (ITT) population that there was a statistically significant improvement in the KDQ symptom of fatigue when dialysis patients were treated with EPO compared with control.

Four RCTs[145,155,156] published after the Tonelli et al (2008)[151] literature search reported functional/performance status as an outcome. Cianciaruso et al (2008)[155] found no significant difference in pre-dialysis patients between EPO and control in the proportion of individuals who had a decline in New York Heart Association (NYHA) status (5.4% vs 2.4%; P=0.609) or in Canadian Cardiovascular Society (CCS) status (0.0% vs 4.9%; P=0.495). Macdougall et al (2007)[156] found no significant difference between EPO and control in the six-minute walk test (6MWT; P=0.954) in pre-dialysis CKD patients. In Pfeffer et al (2009)[145], pre-dialysis CKD patients with type 2 diabetes treated with DAR had a significantly greater improvement in Functional Assessment of Cancer Therapy (FACT)-Fatigue score from baseline compared with placebo (P<0.001); and there was significantly more patients in the DAR group with an increase of three or more points on the FACT-Fatigue score (54.7% vs 49.5%; P=0.002). Pfeffer et al (2009)[145] found no significant difference between treatment arms in mean changes to SF-36 (Short Form Health Survey) energy (P=0.20) and physical functioning scores (P=0.51).

Table 3.88 Results for ESAs vs no ESAs in CKD (functional/performance status)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL I STUDIES								
Tonelli et al (2008)[151] *Good*	Anaemic adults with CKD (on-dialysis or pre-dialysis)	ESA vs no ESA	26 weeks	Change in KDQ–fatigue (0 low to 100 high) 1 study (N=98)	NR	NR	WMD 1.10 (0.76, 1.44)	*Favours ESA* P<0.001
LEVEL II STUDIES								
Cianciaruso et al (2008)[155] *Good*	Anaemic adults with pre-dialysis CKD	EPO vs no EPO	1 year	Decline in NYHA status at follow-up, n/N (%) (N=78)	2/37 (5.4)	1/41 (2.4)	NR	*No significant difference* P=0.609
				Decline in CCS status at follow-up, n/N (%) (N=78)	0/37 (0.0)	2/41 (4.9)	NR	*No significant difference* P=0.495
Macdougall et al (2007)[156] *Fair*	Anaemic adults with pre-dialysis CKD	EPO vs no EPO	3 years[d]	Mean (SD) 6MWT distance (at the last recorded exercise test), m (N=196)	419.3 (124.4)	420.5 (129.0)	NR	*No significant difference* P=0.954
				Mean (SD) worst result for 6MWT, m (N=196)	395.8 (110.5)	408.4 (127.8)	NR	*No significant difference* P=0.526
Pfeffer et al (2009)[145] *Good*	Anaemic adults with type 2 diabetes and pre-dialysis CKD	DAR vs placebo	25 weeks	Mean (SD) baseline FACT-Fatigue score (N=3531)	30.2 (NR)	30.4 (NR)	NR	NR
				Mean (SD) change in FACT-Fatigue score from baseline at follow-up (N=3531)	4.2 (10.5)	2.8 (10.3)	NR	*Favours DAR* P<0.001
				Patients with an increase of 3 or more points[e] on the FACT-Fatigue score, n/N (%) (N=3531)	963/1762 (54.7)	875/1769 (49.5)	NR	*Favours DAR* P=0.002

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
			NR	Mean (SD) change in SF-36 (energy; 0 low to 100 high) (N=2295)	2.6 (9.9)	2.1 (9.7)	NR	*No significant difference* P=0.20
				Mean (SD) change in SF-36 (physical functioning; 0 low to 100 high) (N=2295)	1.3 (9.2)	1.1 (8.8)	NR	*No significant difference* P=0.51

CCS, Canadian Cardiovascular Society; 6MWT, six-minute walk test; CI, confidence interval; CKD, chronic kidney disease; DAR, darbepoetin; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; FACT, Functional Assessment of Cancer Therapy; HRQL, health related quality of life; KDQ, Kidney Disease Questionnaire; NR, not reported; NYHA, New York Heart Association; SD, standard deviation; SF, Short Form Health Survey; SF-36, Short Form (36) Health Survey; SIP, Sickness Impact Profile; WMD, weighted mean difference

[a] Quality of life was assessed by asking participants to: (i) "rate your energy level during the past week"; (ii) "judge your ability to do work during the previous week"; (iii) "rate your overall quality of life during the past week".

[b] A standardised exercise test was performed using a bicycle ergometer.

[c] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

[d] Or until renal replacement/death.

[e] Considered to be clinically meaningful.

3.3.9 IV iron for anaemic patients with chronic kidney disease

Methods

There was one Level I study and five Level II studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

There was one systematic review of randomised controlled trials (RCTs) that evaluated the use of iron therapy (parenteral and/or oral) in anaemic patients with chronic kidney disease. The characteristics of the review by Rozen-Zvi et al (2008)[160] are summarised in Table 3.89.

Rozen-Zvi et al (2008)[160] compared the use of IV versus oral iron supplementation in anaemic patients with chronic kidney disease (CKD; stages III to V). The review included studies assessing iron therapy in pre- and on-dialysis patients, treated with or without ESA treatment.

Rozen-Zvi et al (2008)[160] reported insufficient detail to provide the basis for a systematic review update. Therefore the individual trials from Rozen-Zvi et al (2008)[160] were retrieved. Three of the studies identified by Rozen-Zvi et al (2008)[160] met eligibility criteria for these guidelines (Stoves et al [2001],[161] Van Wyck et al [2005],[162] Agarwal et al [2006][163]).

Table 3.89 Characteristics and quality of Level I evidence

Level I evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Rozen-Zvi et al (2008)[160]	Systematic Review *Fair*	Anaemic and non-anaemic adults with CKD (on-dialysis or pre-dialysis), with or without ESA treatment N=1197	IV vs Oral	Mortality RBC transfusion Functional/performance status

CKD, chronic kidney disease; ESA, erythropoiesis stimulating agents; IV, intravenous; RBC, red blood cell

Level II evidence

A literature search was conducted to identify Level II evidence comparing IV vs oral iron published after the Rozen-Zvi et al (2008)[160] systematic review[a]. One study was identified (Provenzano et al [2009][164]).

Additionally, a literature search was conducted to identify Level II evidence (published from January 1985 to July 2010) comparing any form of iron therapy to treatment without iron therapy. The search identified one study (Singh et al [2006][165]).

The main characteristics of the five eligible RCTs, including the three eligible RCTs identified by Rozen-Zvi et al (2008)[160] are summarised in Table 3.90. Stoves et al (2001)[161] was a single centre study conducted in the UK. The other RCTs were multicentre studies conducted in the

[a] The literature search in Rozen-Zvi et al (2008) included papers published from January 1966 to January 2008

USA (Agarwal et al [2006],[163] Provenzano et al [2009],[164] Van Wyck et al [2005][162]) and international sites (Singh et al [2006][165]).

Table 3.90 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
IV vs oral iron					
Agarwal et al (2006)[163]	RCT *Fair*	Anaemic, iron-deficient adults with pre-dialysis CKD, no ESA treatment N=89	IV Iron sucrose, 250mg over 1hr, weekly	Oral Ferrous sulphate, 325mg, t.d.s.	Functional/ performance status
Provenzano et al (2009)[164]	RCT *Fair*	Anaemic, iron-deficient adults with on-dialysis CKD, with ESA treatment N=230	IV Two ferumoxytol injections during dialysis treatments (every 5± 3 days) + EPO	Oral Elemental iron, 200mg, daily + EPO	Mortality
Stoves et al (2001)[161]	RCT *Poor*	Anaemic adults with pre-dialysis PRI, with ESA treatment N=45	IV Iron sucrose, 300mg over 2 hrs, monthly + EPO, twice weekly (Hb concentration between 120 to 140 g/L)	Oral Ferrous sulphate, 200mg, t.d.s. + EPO, twice weekly (Hb concentration between 120 to 140 g/L)	Mortality
Van Wyck et al (2005)[162]	RCT *Poor*	Anaemic, iron-deficient adults with pre-dialysis CKD, with ESA or no ESA treatment N=188	IV Iron sucrose, 1000mg over 14 days as: a) 500mg infusion over 3.5-4 hrs from days 1-and 14 b) 200mg undiluted injection over 2-5min for 5 days between day 0 -14. + ESA or no ESA	Oral Ferrous sulphate, 325mg, t.d.s. + ESA or no ESA	RBC transfusion Functional/ performance status

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
IV iron vs no iron therapy					
Singh et al (2006)[165]	RCT *Poor*	Anaemic adults with on-dialysis CKD (peritoneal), with ESA treatment N=126	IV 1g of iron sucrose divided into 3 doses over 28 days. (300mg over 1.5 hrs on days 1 and 15, 400mg over 2.5hrs on day 29.) + ESA	No iron supplementation + ESA	RBC transfusion

CKD, chronic kidney disease; ESA, erythropoiesis stimulating agents; EPO, erythropoietin; Hb, haemoglobin; IV, intravenous; PRI, progressive renal insufficiency; RBC, red blood cell RCT, randomised controlled trials; t.d.s, three times a day

Results

Mortality

Two RCTs[161,164] reported mortality as an outcome (Table 3.91). Provenzano et al (2009)[164] reported no significant difference between IV and oral iron (0.9% vs 2.6%; RR 0.35; 95% CI; 0.04, 3.27). Stoves et al (2001)[161] reported a single death in the IV arm and found no significant difference in mortality between IV and oral treatments (4.5% vs 0%; RR 3.13; 95% CI; 0.13, 72.99).

A meta-analysis was conducted with the results from Provenzano et al (2009)[164] and Stoves et al (2001),[161] see Figure 3.15. The meta-analysis showed no significant difference in the mortality rates of CKD patients treated with IV compared with oral iron therapy (2 trials; RR 0.78; 95% CI: 0.10, 6.28).

Figure 3.15 Meta-analysis of IV vs oral iron in anaemic patients with chronic kidney disease (mortality)

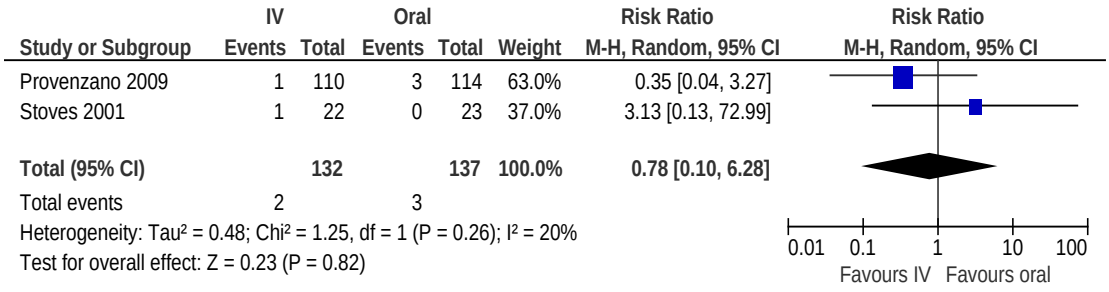


Table 3.91 Results for IV iron in anaemic patients with chronic kidney disease (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity* P-value (I^2)
LEVEL II STUDIES								
Provenzano et al (2009)[164] *Fair*	Anaemic, iron-deficient adults with on-dialysis CKD, with ESA treatment	IV iron vs oral iron	5 weeks	Mortality, n/N (%) (N=214)	1/110 (0.9)	3/114 (2.6)	RR 0.35 (0.04, 3.27)[a]	*No significant difference* P=0.35
Stoves et al (2001)[161] *Poor*	Anaemic adults with pre-dialysis CKD, with ESA treatment	IV iron vs oral iron	6 months	Mortality, n/N (%) (N=45)	1/22 (4.5)	0/23 (0.0)	RR 3.13 (0.13, 72.99)[a]	*No significant difference* P=0.48

CI, confidence interval; CKD, chronic kidney disease; IV, intravenous; NR, not reported; RR, relative risk; ESA, erythropoiesis stimulating agents

[a] Calculated for the purpose of this systematic review using Review manager.

Blood transfusion

Although none of the included studies reported transfusion incidence, two of the included RCTs[162,165] reported the proportion of patients requiring an anaemia intervention. Anaemia intervention was defined as either: an increase in ESA dose, initiation of non-protocol IV iron or initiation of RBC transfusion. Table 3.92 provides a summary of these results.

The RCT conducted by Van Wyck et al (2005)[162] found no significant difference between IV and oral iron therapy (8.8% vs 8.8%; RR 1.00; 95% CI; 0.39, 2.55). While Singh et al (2006)[165] found IV therapy significantly reduced the incidence of anaemia intervention compared to no iron supplementation, and hence RBC transfusion (1.3% vs 10.9%; RR 0.12; 95% CI: 0.10, 1.02).

A meta-analysis was conducted with the results from Singh et al (2006)[165] and Van Wyck et al (2005)[162] (see Figure 3.16). The meta-analysis showed that there was still no significant difference in the mortality rates of CKD patients treated with IV or oral iron therapy (2 trials; RR 0.43; 95% CI: 0.06, 3.36).

Figure 3.16 Meta-analysis of IV iron in anaemic patients with chronic kidney disease (patients requiring an anaemia intervention)

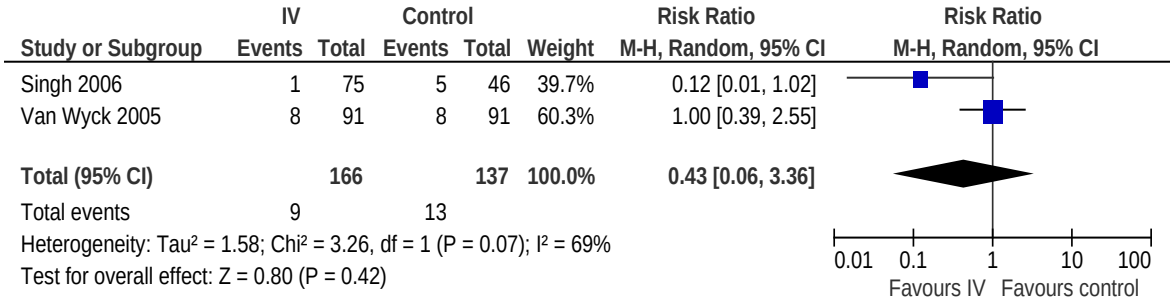


Table 3.92 Results for IV iron in anaemic patients with chronic kidney disease (blood transfusion)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Singh et al (2006)[165] *Poor*	Anaemic adults with on-dialysis CKD, with ESA treatment	IV iron vs no iron supplementation	12 weeks	Anaemia intervention[a] incidence, n/N (%) (N=121)	1/75 (1.3)	5/46 (10.9)	RR 0.12 (0.10, 1.02)[b]	*Favours IV* P=0.05[b]
Van Wyck et al (2005)[162] *Poor*	Anaemic, iron-deficient adults with pre-dialysis CKD, with ESA or no ESA treatment	IV iron vs oral iron	8 weeks	Anaemia intervention[a] incidence, n/N (%) (N=182)	8/91 (8.8)	8/91 (8.8)	RR 1.00 (0.39, 2.55)[b]	*No significant difference* P=1.00[b]

CI, confidence interval; CKD, chronic kidney disease; ESA, erythropoiesis stimulating agents; RBC, red blood cell; RR, relative risk

[a] Anaemia intervention defined as either: an increase in ESA dose, non-protocol IV iron or RBC transfusion, resulting in non-completion of study.

[b] Calculated for the purpose of this systematic review using Review manager.

Thromboembolic events

None of the included studies reported the incidence of thromboembolic events.

Functional/performance status

Two of the included RCTs[163,162] reported functional/performance status (Table 3.93**)**. Agarwal et al (2006)[163] found that patients treated with IV iron therapy experienced significantly greater improvements in quality of life (Kidney Disease Quality of Life Questionnaire [KDQOL]) compared to patients treated with oral iron therapy. These improvements were restricted to two measures of KDQOL: Symptoms of Kidney Disease (3.0 % vs -2.7 %, P=0.025) and Effect of Kidney Disease (2.7 % vs -2.3 %, P=0.048). No significant differences between the treatment groups were reported in the other measures (SF-12 physical health composite, SF-12 mental health composite and Burden of KD). Van Wyck et al (2005)[162] found no significant differences in the SF-36 scores between the IV and oral treatment arms.

Table 3.93 Results for IV iron in anaemic patients with chronic kidney disease (functional/performance status)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Agarwal et al (2006)[163] *Good*	Anaemic, iron-deficient adults with pre-dialysis CKD, no ESA treatment	IV iron vs oral iron	4-6 weeks	Mean (SD) KDQOL change from baseline to day 43 or termination, %				
				SF-12 physical health composite (N=75)	4.8 (8.6)[a]	0.7 (8.6)	NR	*No significant difference* P=0.080
				SF-12 mental health composite (N=75)	3.3 (9.8)	-0.8 (15.1)	NR	*No significant difference* P=0.114
				Burden of KD (N=75)	6.4 (19.6)	-3.6 (25.9)	NR	*No significant difference* P=0.056
				Symptoms of KD (N=75)	3.0 (11.6)	-2.7 (17.5)	NR	*Favours IV* P=0.025
				Effects of KD (N=75)	2.7 (14.5)	-2.3 (13.13)	NR	*Favours IV* P=0.048
Van Wyck et al (2005)[162] *Poor*	Anaemic, iron-deficient adults with pre-dialysis CKD, with ESA or no ESA treatment	IV iron vs oral iron	8 weeks	Mean (SD) SF-36[b] change from baseline to day 56, m (N=182)	NR	NR	NR	*No significant difference*

Chronic Kidney Disease, CKD; KDQOL, Kidney Disease Quality of Life; NR, not reported; KD, Kidney Disease; IV, intravenous; SD, standard deviation; SF, Short Form Health Survey; SF-12, Short Form (12) Health Survey; SF-36, Short Form (36) Health Survey NS, no significant difference

[a] Significant with-in group change, p <0.01.

[b] SF-36 included health concept categories of: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health.

3.3.10 Non-transfusion interventions for elderly patients with anaemia

Evidence statements – community-dwelling elderly		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.30	In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on mortality is uncertain. (See evidence matrix EM3.W in Volume 2 of the technical report)	√	NA	NA	√	√√
ES3.31	In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on thromboembolic events is uncertain. (See evidence matrix EM3.X in Volume 2 of the technical report)	√	NA	NA	√	√√
ES3.32	In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on functional or performance status is uncertain. (See evidence matrix EM3.Y in Volume 2 of the technical report)	√	NA	X	√	√√
ES, evidence statement; ESA, erythropoiesis-stimulating agent √√√=A; √√=B; √=C; X=D; NA, not applicable						

ESAs vs no ESAs for elderly patients with anaemia

Methods

There was one Level II study identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic review of RCTs that evaluated the use of ESAs in elderly patients with anaemia.

Level II evidence

The literature search identified one RCT that evaluated the use of ESAs in elderly patients with anaemia (Agnihotri et al [2007][166]). The main characteristics of this study are summarised in Table 3.94. Agnihotri et al (2007) was a 32-week, randomised, double-blind, placebo-controlled crossover trial. Ambulatory, community-dwelling adults aged 65 years and older with Hb of 11.5 g/dL or less for more than 3 months were randomised to once-weekly injection of placebo or EPO for 15 weeks (Phase I) and were then crossed over to the other treatment for the remainder of the trial (Phase II).

Table 3.94 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Agnihotri et al (2007)[166]	Cross-over RCT *Fair*	Ambulatory, community-dwelling adults aged ≥65 years with Hb ≤11.5 g/dL for more than 3 months N=62	SC EPO once weekly (target Hb 13.0 to 13.9 g/dL) Patients received oral iron therapy if serum ferritin was <20 ng/ mL or transferring saturation was <15%	Matched placebo Patients received oral iron therapy if serum ferritin was <20 ng/ mL or transferring saturation was <15%	Mortality Thromboembolic events Functional/performance status

EPO, erythropoietin; Hb, haemoglobin; RCT, randomised controlled trial; SC, subcutaneous

Results

Mortality

Agnihotri et al (2007)[166] found no significant difference in mortality between EPO and placebo in either phase of the cross-over trial (Table 3.95). In Phase I there was one death in the EPO treatment arm and one death in the placebo arm. There were no deaths in Phase II. None of the deaths were considered to be treatment related.

Table 3.95 Results for ESAs vs no ESAs in elderly patients with anaemia (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Agnihotri et al (2007)[166] *Fair*	Elderly patients with anaemia	EPO vs placebo	16 weeks for each phase	Mortality, n/N (%)	Phase I 1/32 (3.1)[a] Phase II 0/24 (0.0)	Phase I 1/26 (3.8)[a] Phase II 0/30 (0.0)	Phase I RR 0.81 (0.05, 12.37)[b] Phase II NA	Phase I *No significant difference* *P=0.88*[b] Phase II NA

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; NA, not applicable; RR, relative risk

[a] Not considered to be treatment related.

[b] Calculated for the purpose of this systematic review using Review Manager.

Blood transfusion

Agnihotri et al (2007)[166] did not report either the incidence or volume of blood transfusion.

Thromboembolic events

In Phase I of Agnihotri et al (2007)[166] there was one case of DVT and one case of stroke in the placebo treatment arm and no thromboembolic events in the EPO arm (Table 3.96). In Phase II there was one case of pulmonary embolism in the EPO arm and no thromboembolic events in the placebo arm. There were no significant differences in the incidences of DVT, pulmonary embolism, or stroke between EPO and placebo in either phase of the study.

Table 3.96 Results for ESAs vs no ESAs in elderly patients with anaemia (thromboembolic events)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Agnihotri et al (2007)[166] *Fair*	Elderly patients with anaemia	EPO vs placebo	16 weeks for each phase	DVT, n/N (%)	Phase I 0/32 (0.0) Phase II 0/24 (0.0)	Phase I 1/26 (3.8) Phase II 0/30 (0.0)	Phase I RR 0.27 (0.01, 6.43)[b] Phase II NA	Phase I *No significant difference* P=0.43[b] Phase II NA
				Pulmonary embolism, n/N (%)	Phase I 0/32 (0.0) Phase II 1/24 (4.2)	Phase I 0/26 (0.0) Phase II 0/30 (0.0)	Phase I NA Phase II RR 3.72 (0.16, 87.42)[b]	Phase I NA Phase II *No significant difference* P=0.41[b]
				Stroke, n/N (%)	Phase I 0/32 (0.0) Phase II 0/24 (0.0)[a]	Phase I 1/26 (3.8) Phase II 0/30 (0)	Phase I RR 0.27 (0.01, 6.43)[b] Phase II NA	Phase I *No significant difference* P=0.42[b] Phase II NA

CI, confidence interval; DVT, deep vein thrombosis; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; NA, not applicable; RR, relative risk

[a] Was determined to be due to underlying pre-existing atrial fibrillation (last study Hb 11.0 g/dL).

[b] Calculated for the purpose of this systematic review using Review Manager.

Functional/performance status

In Agnihotri et al (2007),[166] treatment with EPO led to a significantly greater improvement compared with control in FACIT–anaemia (including both the fatigue and anaemia subscales) but not FACT score or the Timed Up and Go (TUG) test (Table 3.97).

Table 3.97 Results for ESAs vs no ESAs in elderly patients with anaemia (functional/performance status)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Agnihotri et al (2007)[166] *Fair*	Elderly patients with anaemia	EPO vs placebo	16 weeks for each phase	Mean (SE) FACIT–anaemia (fatigue subscale; 0 low to 52 high) at follow-up	Phase I 41.9 (1.0) Phase II 43.4 (2.3)	Phase I 36.4 (1.1) Phase II 33.8 (2.0)	NR	Phase I *Favours EPO* P<0.001 Phase II *Favours EPO* P=0.01
				Mean (SE) FACIT–anaemia (anaemia subscale; 0 low to 80 high) at follow-up	Phase I 62.3 (1.2) Phase II 64.3 (2.8)	Phase I 56.3 (1.4) Phase II 53.6 (2.4)	NR	Phase I *Favours EPO* P=0.002 Phase II *Favours EPO* P=0.02
				Mean (SE) FACIT–anaemia (total; 0 low to 188 high) at follow-up	Phase I 146.8 (2.6) Phase II 152.2 (5.3)	Phase I 137.9 (2.9) Phase II 132 (4.6)	NR	Phase I *Favours EPO* P=0.03 Phase II *Favours EPO* P=0.02
				FACT–general (0 low to 108 high) at follow-up	Phase I 85.1 (1.5) Phase II 87.9 (2.9)	Phase I 81.6 (1.6) Phase II 78.4 (2.4)	NR	Phase I *No significant difference* P=0.13 Phase II *Favours EPO* P=0.04
				Mean (SE) TUG test (<20 sec normal), sec	Phase I 27.9 (2.8) Phase II 23.8 (1.7)	Phase I 27.9 (3.2) Phase II 24.5 (1.5)	NR	Phase I *No significant difference* P=0.99 Phase II *No significant difference* P=0.80

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; FACIT, Functional Assessment of Chronic Illness Therapy; FACT, Functional Assessment of Cancer Therapy; NR, not reported; RR, relative risk; SE, standard error; TUG, Timed Up and Go

3.3.11 Non-transfusion interventions for patients with hepatitis C

Evidence statements – hepatitis C virus
In patients with HCV who are receiving combination therapy and have developed anaemia, the effect of ESAs on mortality is uncertain. (C, NA, NA, B, B)
In patients with HCV who are receiving combination therapy and have developed anaemia, the effect of ESAs on transfusion requirements is unknown. (no evidence)
In patients with HCV who are receiving combination therapy and have developed anaemia, the effect of ESAs on thromboembolic events is uncertain. (C, NA, NA, B, B)
In patients with HCV who are receiving combination therapy and have developed anaemia, ESAs may improve quality of life compared with no ESAs. (C, C, D, B, B)

ESAs vs standard care for anaemic patients with hepatitis C

Methods

There were three Level II studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

The CRG considered that there was insufficient evidence on which to base evidence-based recommendations and practice points. Therefore this population will not be discussed in the Module 3 Guideline.

The evidence identified during the systematic review is shown below for completion.

Level I evidence

No Level I evidence evaluating the use of ESAs in patients with hepatitis C was identified.

Level II evidence

Two RCTs that assessed the use of ESAs in hepatitis C virus (HCV)-infected patients on combination therapy were identified (Afdhal et al [2004][167]; Dieterich et al [2003][168]). Both studies assessed the impact of EPO on quality of life. Afdhal et al (2004)[167] also assessed the impact of EPO on thromboembolic events and mortality. Table 3.98 provides a summary of the main characteristics of these RCTs.

ESAs help to maintain treatment (ribavirin) in patients with some genotypes. But this was not specifically addressed in the guideline development.

Table 3.98 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type *Study quality*	Population N	Intervention	Comparator	Outcomes
Afdhal et al (2004)[167]	RCT *Fair*	HCV-infected patients on combination therapy who developed anaemia N=185	EPO once weekly	Placebo	QoL Thromboembolic events Mortality
Dieterich et al (2003)[168]	RCT *Poor*	HCV-infected patients on combination therapy who developed anaemia N=64	EPO once weekly	Standard care	QoL

EPO, erythropoietin; HCV, hepatitis C virus; QoL, quality of life; RCT, randomised controlled trial

Results

Mortality

One RCT[167] that assessed ESAs in HCV-infected patients reported mortality as an outcome (Table 3.99). The study found no significant difference between EPO and placebo (1.1% vs 0.0%; RR 2.97; 95% CI 0.12, 71.93).

Table 3.99 Results for ESAs vs no ESAs in patients with HCV (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Afdhal et al (2004)[167] *Fair*	HCV-infected patients on combination therapy who developed anaemia	EPO vs placebo	8 weeks[a]	Mortality, n/N (%) N=185	1/93 (1.1)[b]	0/92 (0.0)	RR 2.97 (0.12, 71.93)[c]	*No significant difference* P=0.50[c]

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agents; HCV, hepatitis C virus; RR, relative risk

[a] There was an 8-week double-blind phase followed by an 8-week open-label phase (where both arms received EPO).

[b] Patient died with pneumonia, renal failure, and hepatic failure.

[c] Calculated for the purpose of this systematic review using Review Manager.

Blood transfusion

None of the identified studies reported the incidence or volume of blood transfusion.

Thromboembolic events

One RCT[167] that assessed ESAs in HCV-infected patients reported the incidence of thromboembolic events (Table 3.100). The study found no significant difference between EPO and placebo in cerebrovascular disorder/cerebral thrombosis (1.1% vs 0.0%; RR 2.97; 95% CI 0.12, 71.93).

Table 3.100 Results for ESAs vs no ESAs in HCV (thromboembolic events)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Afdhal et al (2004)[167] *Fair*	HCV-infected patients on combination therapy who developed anaemia	EPO vs placebo	8 weeks[a]	Cerebrovascular disorder/cerebral thrombosis, n/N (%) (N=185)	1/93 (1.1)	0/92 (0.0)	RR 2.97 (0.12, 71.93)[c]	*No significant difference* P=0.50[c]

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agents; HCV, hepatitis C virus; RR, relative risk

[a] There was an 8-week double-blind phase followed by an 8-week open-label phase (where both arms received EPO).

[b] Patient died with pneumonia, renal failure, and hepatic failure.

[c] Calculated for the purpose of this systematic review using Review Manager.

Functional/performance status

Both Afdhal et al (2004)[167] and Dieterich et al (2003)[168] reported functional/performance status as an outcome (Table 3.101). EPO significantly improved SF-36 (physical functioning, physical and emotional role, bodily pain, vitality, social functioning, and mental health; not general health subscale) scores compared with control in Afdhal et al (2004)[167] but did not improve SF-12 (physical and mental components) in Dieterich et al (2003).[168]

Table 3.101 Results for ESAs vs no ESAs in HCV (functional/performance status)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Afdhal et al (2004)[167] *Fair*	HCV-infected patients on combination therapy who developed anaemia	EPO vs placebo	8 weeks[a]	Mean (SD) change in SF-36 (physical functioning; 0 low to 100 high) score from baseline at follow-up N=185	9.7 (NR)	4.3 (NR)	NR	*Favours EPO* P<0.05
				Mean (SD) change in SF-36 (role physical; 0 low to 100 high) score from baseline at follow-up N=185	10 (NR)	0.7 (NR)	NR	*Favours EPO* P<0.05
				Mean (SD) change in SF-36 (bodily pain; 0 low to 100 high) score from baseline at follow-up N=185	8.4 (NR)	4.2 (NR)	NR	*Favours EPO* P<0.05
				Mean (SD) change in SF-36 (general health; 0 low to 100 high) score from baseline at follow-up N=185	2.7 (NR)	1.1 (NR)	NR	*No significant difference* P>0.05
				Mean (SD) change in SF-36 (vitality; 0 low to 100 high) score from baseline at follow-up N=185	15.2 (NR)	4.1 (NR)	NR	*Favours EPO* P<0.05
				Mean (SD) change in SF-36 (social functioning; 0 low to 100 high) score from baseline at follow-up N=185	12 (NR)	2.6 (NR)	NR	*Favours EPO* P<0.05

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
				Mean (SD) change in SF-36 (role emotional; 0 low to 100 high) score from baseline at follow-up N=185	6.2 (NR)	-3.3 (NR)	NR	*Favours EPO* P<0.05
				Mean (SD) change in SF-36 (mental health; 0 low to 100 high) score from baseline at follow-up N=185	5.6 (NR)	0.1 (NR)	NR	*Favours EPO* P<0.05
Dieterich et al (2003)[168] *Poor*	HCV-infected patients on combination therapy who developed anaemia	EPO vs standard care	16 weeks	Mean (SD) improvement in SF-12 (physical component; 0 low to 100 high) from baseline N=64	4.9 (9.1)	2.0 (10.8)	MD 2.9 (-2.1, 7.9)[c]	*No significant difference* P=0.248[c]
				Mean (SD) improvement in SF-12 (mental component; 0 low to 100 high) from baseline N=64	2.7 (10.1)	0.1 (7.7)	MD 2.6 (-2.0, 7.2)[c]	*No significant difference* P=0.263[c]

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agents; HCV, hepatitis C virus; MD, mean difference; NR, not reported; SD, standard deviation; SF-12, Short Form (12) Health Survey; SF-36, Short Form (36) Health Survey

[a] There was an 8-week double-blind phase followed by an 8-week open-label phase (where both arms received EPO).

[b] Patient died with pneumonia, renal failure, and hepatic failure.

[c] Calculated for the purpose of this systematic review using Instat.

3.3.12 Non-transfusion interventions for patients with HIV or AIDS

Evidence statements – HIV or AIDS
In anaemic patients with HIV, the effect of ESAs on mortality is uncertain. (C, NA, NA, C, C)
In HIV patients with anaemia, the effect of ESAs on transfusion requirements is uncertain. (C, NA, D, C, C)
In HIV patients with anaemia, the effect of ESAs on thromboembolic events is unknown. (no evidence)
In anaemic patients with HIV, the effect of ESAs on functional or performance status is uncertain. (D, NA, D, C, C)

ESAs vs no ESAs for anaemic patients with HIV or AIDS

Methods

There was one Level I study identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

The CRG considered that there was insufficient evidence on which to base evidence-based recommendations and practice points. Therefore this population will not be discussed in the Module 3 Guideline.

The evidence identified during the systematic review is shown below for completion.

Level I evidence

The literature search identified one systematic review[169] that evaluated the use of ESAs in anaemic patients with HIV or AIDS (Table 3.102).

Table 3.102 Characteristics and quality of Level I evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Marti-Carvajal et al (2007)[169]	SR *Good*	Anaemic (Hb <12 g/dL in men and <11 g/dL in women) patients with HIV or AIDS N=129[a]	EPO[b]	Any other intervention for anaemia or placebo	Mortality RBC transfusion incidence and volume Functional/performance status

AIDS, acquired immune deficiency syndrome; EPO, erythropoietin; Hb, haemoglobin; HIV, human immunodeficiency virus; RBC, red blood cell; SR, systematic review
[a] This figure does not include the results from Grossman et al (2003)[170] or Rendo et al (2001)[171]. Grossman et al (2003) compared two different treatment frequencies of EPO. Rendo et al (2001)[171] was a study in paediatric patients.
[b] Marti-Carvajal et al (2007)[169] also evaluated other treatments for anaemia, including androgen replacement, vitamin B_{12} therapy, and darbepoetin alfa.

Level II evidence

The Marti-Carvajal et al (2007)[169] systematic review identified two RCTs[172] that evaluated the use of ESAs vs no ESAs in anaemic adults with HIV or AIDs (Table 3.103).

Table 3.103 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type *Study quality*	Population N	Intervention	Comparator	Outcomes
Fischl et al (1990)[172]	RCT *Fair*	Adults with a clinical diagnosis of AIDS treated with zidovudine. Baseline haematocrit of ≤0.30 and either transfusion dependent or a ≥15% decline in haematocrit since zidovudine initiation. N=63	IV EPO thrice weekly (target haematocrit 0.38 to 0.40)	Placebo	Mortality RBC transfusion incidence and volume
Sulkowski et al (2005)[173]	RCT *Poor*	Anaemic (<12 g/dL or a >2 g/dL decrease in Hb after pegylated interferon alfa plus ribavirin) patients with HIV/AIDS treated with zidovudine	IV EPO thrice weekly (target haematocrit 0.38 to 0.40)	Standard care	Functional status

AIDS, acquired immune deficiency syndrome; EPO, erythropoietin; Hb, haemoglobin; HIV, human immunodeficiency virus; IV, intravenous; RBC, red blood cell; RCT, randomised controlled trial

Results

Mortality

Marti-Carvajal et al (2007)[169] identified one RCT[172] assessing EPO against placebo that reported mortality as an outcome (Table 3.104). This RCT found no significant difference between treatment arms (0% vs 5.9%; RR 0.23; 95% CI 0.01, 4.67).

Table 3.104 Results for ESAs vs no ESAs in anaemic patients with HIV or AIDS (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value *Heterogeneity* P-value (I^2)
LEVEL II STUDIES								
Fischl et al (1990)[172] *Fair*	Anaemic patients with HIV or AIDS	EPO vs placebo	12 weeks	Mortality, n/N (%) 1 trial (N=63)	0/29 (0%)	2/34 (5.9%)	RR 0.23 (0.01, 4.67)	*No significant difference* P=0.34

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; NA, not applicable; RR, relative risk

[a] Not considered to be treatment related.

Blood transfusion

Marti-Carvajal et al (2007)[169] identified one RCT[172] that assessed EPO against placebo that reported allogeneic blood transfusion as an outcome (Table 3.105). For patients with endogenous EPO less than or equal to 500 IU/L, treatment with EPO significantly reduced the incidence and volume of blood transfused compared with control. There was no significant difference between EPO and control in the incidence and volume of blood transfused for the overall population.

Table 3.105 Results for ESAs vs no ESAs in anaemic patients with HIV or AIDS (blood transfusion)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value *Heterogeneity* P-value (I^2)
LEVEL II STUDIES								
Fischl et al (1990)[172] *Fair*	Anaemic patients with HIV or AIDS	EPO vs placebo	12 weeks	Incidence of allogeneic blood transfusion, n/N (%) 1 trial (N=63)	11/29 (37.9)	21/34 (61.8)	NR	*No significant difference* P>0.05
				Incidence of allogeneic blood transfusion (patients with endogenous EPO ≤500 IU/L), n/N (%) 1 trial (N=63)	5/NR (NR)	17/NR (NR)	NR	*Favours EPO* P<0.05
				Mean (SD) volume of RBC or whole blood transfused, units 1 trial (N=63)	1.48 (NR)	2.58 (NR)	NR	*No significant difference* P>0.05
				Mean (SD) volume of RBC or whole blood transfused (patients with endogenous EPO ≤500 IU/L), units 1 trial (N=63)	0.84 (NR)	2.74 (NR)	NR	*Favours EPO* P<0.05

AIDS, acquired immune deficiency syndrome; CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; HIV, human immunodeficiency virus; IU, international units; NR, not reported; RBC, red blood cells; RR, relative risk; SD, standard deviation

[a] Not considered to be treatment related.

Thromboembolic events

None of the identified studies reported the incidence of thromboembolic events.

Functional/performance status

Marti-Carvajal et al (2007)[169] identified one RCT[173] assessing EPO against placebo that reported functional or performance status as an outcome (Table 3.106). This RCT reported a greater improvement for patients treated with EPO compared with placebo in both the physical component (mean [SD] 6.0 [1.8] vs 2.2 [1.2]; p=NR) and mental component (mean [SD] 2.3 [2.0] vs 0.1 [1.5]; p=NR) of the SF-12.

Table 3.106 Results for ESAs vs no ESAs in anaemic patients with HIV or AIDS (functional/performance status)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value *Heterogeneity* P-value (I^2)
LEVEL II STUDIES								
Sulkowski et al (2005)[173] *Poor*	Anaemic patients with HIV or AIDS	EPO vs placebo	16 weeks	Mean (SD) change in SF-12 (physical component; 0 low to 100 high) score from baseline at follow-up 1 trial (N=66)	6.0 (1.8)	2.2 (1.2)	NR	NR
				Change in SF-12 (mental component; 0 low to 100 high) score from baseline at follow-up 1 trial (N=66)	2.3 (2.0)	0.1 (1.5)	NR	NR

AIDS, acquired immune deficiency syndrome; CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; HIV, human immunodeficiency virus; NR, not reported; SF-12, Short Form (12) Health Survey

[a] Not considered to be treatment related.

3.3.13 Non-transfusion interventions for patients with inflammatory bowel disease

Evidence statements – inflammatory bowel disease		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.33	In IBD patients with iron deficiency anaemia, the effect of IV iron versus oral iron on mortality is uncertain. (See evidence matrix EM3.AF in Volume 2 of the technical report)	√	NA	NA	√√	√√
ES3.34	In IBD patients with iron deficiency anaemia, it is uncertain whether there is any difference between the effects of IV iron and oral iron on functional or performance status. (See evidence matrix EM3.AG in Volume 2 of the technical report)	√	NA	X	√√	√√
ES, evidence statement; IBD, inflammatory bowel disease; IV, intravenous √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice point – inflammatory bowel disease	
PP15	In patients with IBD, determine the cause of anaemia and treat reversible causes. IV iron may be required in patients who are intolerant of oral iron, or to avoid aggravation of intestinal inflammation.
IBD, inflammatory bowel disease; IV, intravenous; PP, practice point	

3.3.14 IV iron for anaemic patients with inflammatory bowel disease

Methods

There were two Level II studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

No Level I evidence evaluating the use of iron therapy in patients with inflammatory bowel disease (IBD) was identified.

Level II evidence

Two RCTs[174,175] evaluating the use of iron therapy in patients with IBD were identified. The main characteristics of these trials are summarised in Table 3.107.

Table 3.107 Characteristics and quality of Level II evidence

Level II evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Kulnigg et al (2008)[174]	RCT *Fair*	Patients with either Crohn's disease or ulcerative colitis and iron deficiency anaemia (defined by Hb ≤100 g/L and TSAT <20% or serum ferritin <100 µg/L) N=200	IV iron (maximum 1,000 mg per infusion) at 1-week intervals until the patient's calculated total iron deficit was reached. vs Oral iron (100 mg b.i.d.) for 12 weeks	Mortality Functional/performance status
Schroder et al (2005)[175]	RCT *Poor*	Patients with IBD and iron deficiency anaemia (Hb ≤1.05 g/L for females and Hb ≤1.10 g/L for males; TSAT ≤20% and/or serum ferritin concentrations ≤20 µg/L). N=46	IV iron (single 7 mg/kg body weight dose, followed by five 200 mg infusions for the following 5 weeks) vs oral iron (100 to 200 mg/day for 6 weeks).	Functional/performance status

Hb, haemoglobin; IBD, inflammatory bowel disease; IV, intravenous; RCT, randomised controlled trial; TSAT, transferrin saturation

[a] Weekly during the correction phase and then every 4 weeks during the maintenance phase, which started at week 8 or week 12, depending on the required iron-repletion dose.

Results

Mortality

Table 3.108 presents the mortality results from the RCTs that compared IV with oral iron in IBD patients with iron deficiency anaemia. Kulnigg et al (2008)[174] found no significant difference in mortality between IV and oral iron (0.7% vs 0.0%; RR 1.39; 95% CI 0.06, 33.69), but the study was not powered to detect a difference in mortality. Schroder et al (2005)[175] did not report mortality.

Table 3.108 Results for IV iron in IBD (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity* P-value (I^2)
LEVEL II STUDIES								
Kulnigg et al (2008)[174] *Fair*	Crohn's disease or ulcerative colitis with iron deficiency anaemia	IV iron vs oral iron	12 weeks	Mortality, n/N (%) (N=200)	1/137 (0.7)	0/63 (0.0)	RR 1.39 (0.06, 33.69)[a]	*No significant difference* P=0.84[a]

CI, confidence interval; IBD, inflammatory bowel disease; IV, intravenous; RR, relative risk

[a] Calculated for the purpose of this systematic review using Review manager.

Blood transfusion

Neither of the studies reported the incidence or volume of blood transfusion.

Thromboembolic events

Neither of the studies reported the incidence of thromboembolic events.

Functional/performance status

Table 3.109 presents the functional/performance status results reported in the RCTs that compared IV iron with oral iron in IBD patients with iron deficiency anaemia. Patients treated with IV iron in Kulnigg et al (2008)[174] had a greater improvement in SF-36 from baseline at follow-up compared with patients treated with oral iron (median 14.1 vs 8.6; P=NR). In Schroder et al (2005)[175] there were similar improvements from baseline at follow-up for IV iron compared with oral iron for Crohn's Disease Activity Index (CDAI), Colitis Activity Index (CAI), and SF-36 (P=NR). Kulnigg et al (2008) and Schroder et al (2005) provided insufficient detail to determine whether the treatment effect on this outcome was statistically significant.

Table 3.109 Results for IV iron in IBD (functional/performance status)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Kulnigg et al (2008)[174] *Fair*	Crohn's disease or ulcerative colitis with iron deficiency anaemia	IV iron vs oral iron	12 weeks	Median (range) SF-36 score at baseline (N=196)	93.5 (54 to 134)	91.2 (50 to 136)	NR	NR
				Median (range) SF-36 score at follow-up (N=196)	110.3 (48 to 143)	108.3 (45 to 137)	NR	NR
				Median change in SF-36 score from baseline at follow-up (N=196)	14.1	8.6	NR	NR
Schroder et al (2005)[175] *Poor*	IBD with iron deficiency anaemia	IV iron vs oral iron	6 weeks	Median (range) CDAI at baseline (N=29)	217 (46 to 417)	281 (71 to 423)	NR	NR
				Median (range) CDAI at follow-up (N=29)	74 (23 to 279)	78 (0 to 353)	NR	NR
				Median (range) CAI at baseline (N=17)	11 (7 to 19)	8 (4 to 11)	NR	NR
				Median (range) CAI at follow-up (N=17)	5 (1 to 9)	3 (0 to 5)	NR	NR
				Median (range) SF-36 score at baseline (N=NR)	104.5 (95.0 to 113.5)	111.0 (105.0 to 116.5)	NR	NR
				Median (range) SF-36 score at follow-up (N=NR)	108.0 (100.0 to 116.5)	116.0 (108.0 to 120.0)	NR	NR

CAI, Colitis Activity Index; CDAI, Crohn's Disease Activity Index; CI, confidence interval; IBD, inflammatory bowel disease; IV, intravenous; NR, not reported; SF-36, Short Form (36)

3.3.15 Non-transfusion interventions for patients with myelodysplastic syndrome

Evidence statements – myelodysplastic syndrome		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.35	In anaemic patients with MDS, the effect of ESAs on mortality is uncertain. (See evidence matrix EM3.AH in Volume 2 of the technical report)	X	√√	X	√√	√
ES3.36	In anaemic patients with MDS receiving GM-CSF, ESAs may reduce transfusion incidence compared with no ESAs. (See evidence matrix EM3.AI in Volume 2 of the technical report)	X	NA	√	√√	√√
ES3.37	In anaemic patients with MDS, the effect of ESAs on thromboembolic events is uncertain. (See evidence matrix EM3.AJ in Volume 2 of the technical report)	X	√√√	NA	√√	√
ES3.38	In anaemic patients with MDS, the effect of ESAs on functional or performance status is uncertain. (See evidence matrix EM3.AK in Volume 2 of the technical report)	X	NA	NA	√√	√

ES, evidence statement; ESA, erythropoiesis-stimulating agent; GM-CSF, granulocyte macrophage colony-stimulating factor; MDS, myelodysplastic syndrome
√√√=A; √√=B; √=C; X=D; NA, not applicable

3.3.16 ESAs vs standard care for anaemic patients with myelodysplastic syndrome

Methods

There were three Level II studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

No Level I evidence evaluating the use of ESAs in patients with myelodysplastic syndrome (MDS) was identified.

Level II evidence

Three RCTs that assessed the use of ESAs in anaemic patients with MDS were identified[176-178]. Table 3.110 provides a summary of the main characteristics of these RCTs.

Table 3.110 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Greenberg et al (2009)[176]	RCT *Poor*	Patients with MDS (RA, RARS, RAEB, or non-proliferative chronic myelomonocyte leukaemia according to the FAB group criteria) N=110	EPO daily (with or without G-CSF) for 4 months[a]	Placebo	Functional/performance status Mortality
Thompson et al (2000)[177]	RCT *Poor*	Patients with MDS (RA, RARS, or RAEB)	EPO plus GM-CSF	Placebo plus GM-CSF	Mortality RBC transfusion incidence and volume Thromboembolic events (stroke)
Ferrini et al (1998)[178]	RCT *Poor*	Patients with low-risk MDS (RA, RARS, or RAEB with bone marrow blast cells<10) N=87	EPO for 8 weeks	Placebo for 8 weeks	RBC transfusion incidence Thromboembolic events (stroke)

DAR, darbepoetin; FAB, French-American-British; MDS, myelodysplastic syndrome; NYHA, New York Heart Association; RA, refractory anaemia; RAS, refractory anaemia with ringed sideroblasts; RAEB, refractory anaemia with excess of blasts; RCT, randomised controlled trial

[a] For non-responders, G-CSF (1 μg/kg/day) was added. Patients who did not respond after addition of G-CSF received increased EPO doses

Results

Mortality

Two of the RCTs[176,177] that assessed the use of ESAs in MDS patients reported mortality as an outcome (Table 3.111). In Greenberg et al (2009),[176] there was no significant difference in mortality between EPO and standard care for the total study population (71.7% vs 84.2%; HR 0.77; 95% CI 0.48, 1.24); however, RARS (refractory anaemia with ring sideroblasts) MDS patients treated with EPO had a significantly lower mortality (60.0% vs 88.2%; HR 0.41; 95% CI 0.18, 0.96). No significant differences were found between treatment arms for subgroup analyses of mortality by gender, age, or MDS subtypes other than RARS. Thompson et al (2000)[177] found no significant difference in mortality between EPO and granulocyte macrophage colony-stimulating factor (GM-CSF) combination therapy and GM-CSF monotherapy (6.7% vs 0.0%; RR 3.35; 95% CI 0.18, 62.03).

Figure 3.17 presents a meta-analysis of mortality in MDS patients treated with ESAs compared with control. There was no significant difference between treatment arms (41.8% vs 61.5%; RR 0.89; 0.72, 1.10). MDS is a heterogeneous condition and disease subtype or baseline EPO concentration may influence mortality outcome.

Table 3.111 Results for ESAs vs no ESAs in MDS (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Greenberg et al (2009)[176] *Poor*	Patients with anaemia of MDS	EPO vs standard care	1 year	Mortality, n/N (%) N=110	38/53 (71.7)	48/57 (84.2)	HR 0.77 (0.48, 1.24)	*No significant difference* P=0.28
				Mortality (male), n/N (%) N=69	25/33 (75.8)	33/36 (91.7)	HR 0.63 (0.34, 1.17)	*No significant difference* P=0.14
				Mortality (female), n/N (%) N=41	13/20 (65.0)	15/21 (71.4)	HR 0.77 (0.28, 2.14)	*No significant difference* P=0.62
				Mortality (age<65 years), n/N (%) N=17	5/10 (50.0)	4/7 (57.1)	HR 1.00 (0.13, 7.51)	*No significant difference* P=1.00
				Mortality (RA MDS) N=42	14/20 (70.0)	17/22 (77.3)	HR 0.84 (0.40, 1.80)	*No significant difference* P=0.66
				Mortality (RARS MDS) N=37	12/20 (60.0)	15/17 (88.2)	HR 0.41 (0.18, 0.96)	*Favours EPO* P=0.041
				Mortality (RAEB MDS) N=29	11/12 (91.7)	15/17 (88.2)	HR 1.54 (0.55, 4.33)	*No significant difference* P=0.41
				Mortality (patients with no previous transfusion support) N=42	14/21 (66.7)	14/21 (66.7)	HR 0.72 (0.31, 1.64)	*No significant difference* P=0.43
				Mortality (patients with previous transfusion support) N=67	24/32 (75.0)	33/35 (94.3)	HR 0.67 (0.36, 1.26)	*No significant difference* P=0.22
				Mortality (EPO<200 mU/ mL) N=76	25/38 (65.8)	31/38 (81.6)	HR 0.71 (0.39, 1.28)	*No significant difference* P=0.25
				Mortality (EPO≥200 mU/ mL) N=33	13/15 (86.7)	16/18 (88.9)	HR 0.87 (0.37, 2.02)	*No significant difference* P=0.74

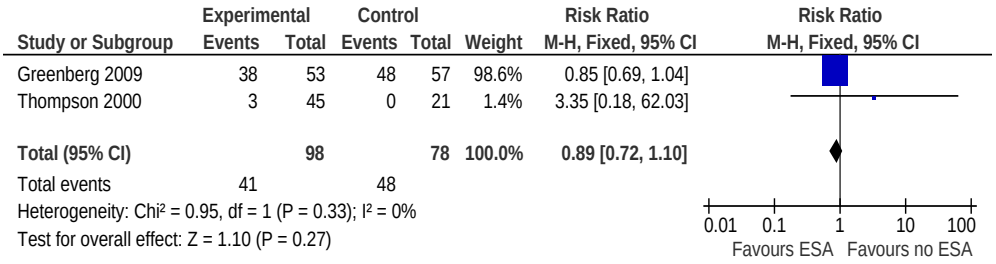
Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
				Mortality (lower risk IPSS[a] score) N=91	29/43 (67.4)	41/48 (85.4)	HR 0.73 (0.43, 1.25)	*No significant difference* P=0.25
				Mortality (higher risk IPSS[a] score) N=18	9/9 (100.0)	7/9 (77.8)	HR 1.46 (0.12, 17.08)	*No significant difference* P=0.76
Thompson et al (2000)[177] *Poor*	Patients with anaemia of MDS	EPO plus GM-CSF	Placebo plus GM-CSF	Mortality, n/N (%) N=66	3/45 (6.7)	0/21 (0.0)	RR 3.35 (0.18, 62.03)[b]	*No significant difference* P=0.42[b]

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; GM-CSF, granulocyte macrophage colony-stimulating factor ; Hb, haemoglobin; HR, hazard ratio; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; RA, refractory anaemia; RAEB, refractory anaemia with excess blasts; RARS, refractory anaemia with ring sideroblasts; RR, relative risk

[a] Takes into account age, white blood cell count, Hb levels, peripheral blood blast percentage and constitutional symptoms.

[b] Calculated for the purpose of this systematic review using Review Manager.

Figure 3.17 Meta-analysis of ESAs vs no ESAs in MDS (mortality)



Blood transfusion

One RCT (Thompson et al [2000][177]) reported RBC transfusion incidence and volume as clinical outcomes (Table 3.112). Overall, there was no significant difference in RBC transfusion incidence between patients treated with EPO plus GM-CSF compared with patients treated with placebo and GM-CSF (76% vs 90%; RR 0.84; 95% CI 0.67, 1.04). EPO plus GM-CSF did, on the other hand, significantly reduce RBC transfusion incidence compared with GM-CSF plus placebo in patients with baseline endogenous EPO less than or equal to 500 mU/ mL (60% vs 92%; RR 0.65; 95% CI 0.46, 0.94). There was no significant difference in the mean units of RBCs transfused between treatment arms, either overall or for patients with baseline endogenous EPO less than or equal to 500 mU/ mL.

Table 3.112 Results for ESAs vs no ESAs in MDS (blood transfusion)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Thompson et al (2000)[177] *Poor*	Patients with anaemia of MDS	EPO plus GM-CSF	Placebo plus GM-CSF	RBC transfusion incidence, n/N (%) (N=66)	34/45 (76)	19/21 (90)	RR 0.84 (0.67, 1.04)[a]	*No significant difference* P=0.10[a]
				RBC transfusion incidence (baseline endogenous EPO≤500 mU/ mL), n/N (%) (N=37)	15/25 (60)	11/12 (92)	RR 0.65 (0.46, 0.94)[a]	*Favours EPO* P=0.02[a]
				RBC transfusion incidence (baseline endogenous EPO>500), n/N (%) (N=29)	19/20 (95)	8/9 (89)	RR 1.07 (0.83, 1.37)[a]	*No significant difference* P=0.60[a]
				Mean (SD) units of RBCs transfused during Months 2 and 3 (N=66)	7.6 (NR)	9.1 (NR)	NR	*No significant difference* P>0.05
				Mean (SD) units of RBCs transfused during Months 2 and 3 (baseline endogenous EPO≤500 mU/ mL)	5.9 (NR)	9.5 (NR)	NR	*No significant difference* P=0.09
				Mean (SD) units of RBCs transfused during Months 2 and 3 (baseline endogenous EPO>500 mU/ mL)	9.7 (NR)	8.6 (NR)	NR	*No significant difference* P=0.62

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; GM-CSF, granulocyte macrophage colony-stimulating factor; MDS, myelodysplastic syndrome; NR, not reported; RBC, red blood cell; RR, relative risk; SD, standard deviation

[a] Calculated for the purpose of this systematic review using Review Manager.

Thromboembolic events

None of the RCTs found any effect of ESAs on the incidence of thromboembolic events in patients with anaemia of MDS (Table 3.113). Greenberg et al (2009)[176] reported no significant difference between EPO and standard care for the incidence of DVT (1.8% vs 0.0%; RR 2.79; 95% CI 0.12, 67.10). There was no significant difference between treatment arms in the incidence of stroke as reported in Thompson et al (2000)[177] (2.2% vs 0%; RR 1.43; 95% CI 0.06, 33.82) and Ferrini et al (1998)[178] (2.3% vs 0%; RR 2.93; 95% CI 0.12, 70.08).

Figure 3.18 presents a meta-analysis for the impact of ESAs on the incidence of stroke in adults with anaemia of MDS. The pooled results did not demonstrate a significant difference in incidence between patients who did and did not receive EPO (2.2% vs 0.0%; RR 2.05; 95% CI 0.22, 19.23).

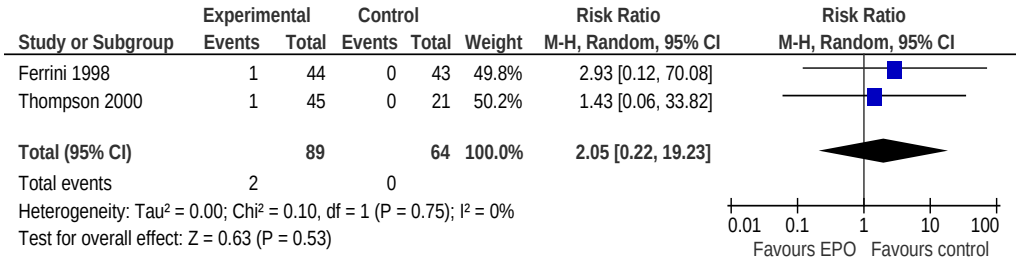
Table 3.113 Results for ESAs vs no ESAs in MDS (thromboembolic events)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Greenberg et al (2009)[176] *Poor*	Patients with anaemia of MDS	EPO vs standard care	1 year	DVT, n/N (%) (N=110)	1/57 (1.8)	0/53 (0.0)	RR 2.79 (0.12, 67.10)	*No significant difference* P=0.53
Thompson et al (2000)[177] *Poor*	Patients with anaemia of MDS	EPO plus GM-CSF	Placebo plus GM-CSF	Stroke, n/N (%) (N=66)	1/45 (2.2)	0/21 (0.0)	RR 1.43 (0.06, 33.82)	*No significant difference* P=0.82
Ferrini et al (1998)[178] *Poor*	Patients with anaemia of MDS	EPO vs placebo	8 weeks	Stroke, n/N (%) (N=87)	1/44 (2.3)	0/43 (0.0)	RR 2.93 (0.12, 70.08)	*No significant difference* P=0.51

CI, confidence interval; DVT, deep vein thrombosis; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; MDS, myelodysplastic syndrome; NA, not applicable; NR, not reported; RR, relative risk; VTE, venous thromboembolism

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Figure 3.18 Meta-analysis of ESAs vs no ESAs in MDS (stroke)



Functional/performance status

Greenberg et al (2009)[176] found no significant difference in FACT subscale and fatigue scores between EPO and standard care (P>0.05; Table 3.114). However, treatment with EPO was associated with erythroid response, and patients with erythroid response at 4 months had a significant improvement from baseline in physical (P=0.007), emotional (P=0.02), and functional (P=0.005) well-being, as well as fatigue (P=0.02) and overall QoL (P=0.02).

Table 3.114 Results for ESA vs no ESA in MDS (functional/performance status)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
LEVEL II STUDIES								
Greenberg et al (2009)[176] *Poor*	Patients with anaemia of MDS	EPO vs standard care	4 months	FACT subscale and fatigue scores (at 4 months follow-up) N=84	NR	NR	NR	*No significant difference* P>0.05
				FACT score (patients who had an erythroid response at 4 months) N=23	Significant improvement from baseline in physical (P=0.007), emotional (P=0.02), and functional (P=0.005) well-being, as well as fatigue (P=0.02) and overall QoL (P=0.02; 2-way analysis of variance)			

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agents; FACT, Functional Assessment of Cancer Therapy; MDS, myelodysplastic syndrome; NR, not reported; QoL, quality of life
a Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

3.4 Question 4

Question 4 (Intervention)

In medical patients, what is the effect of fresh frozen plasma, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?

3.4.1 Fresh frozen plasma

Evidence statements – fresh frozen plasma		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES4.1	In patients with acute pancreatitis, the effect of FFP on mortality is uncertain. (See evidence matrix EM4.A in Volume 2 of the technical report)	X	√	NA	X	X
ES4.2	In patients with acute pancreatitis, the effect of FFP on bleeding events is uncertain. (See evidence matrix EM4.B in Volume 2 of the technical report)	X	√	NA	X	X
ES4.3	In patients with liver disease, the effect of FFP on mortality is uncertain. (See evidence matrix EM4.C in Volume 2 of the technical report)	X	NA	NA	√	√
ES4.4	In patients with liver disease, the effect of FFP on bleeding events is uncertain. (See evidence matrix EM4.D in Volume 2 of the technical report)	X	NA	NA	X	√
ES, evidence statement; FFP, fresh frozen plasma √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – fresh frozen plasma	
PP16	The *routine* use of FFP in medical patients with coagulopathy (including those with liver impairment) is not supported. Tests for coagulation correlate poorly with bleeding risk in liver impairment. The underlying causes of coagulopathy should be assessed. Where FFP transfusion is considered necessary, the risks and benefits should be considered for each patient, and expert guidance sought.
PP17	For guidance on the use of FFP in specific patient groups, refer to: • *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion* (2011)[110]

	• *Patient Blood Management Guidelines: Module 2 – Perioperative* (2012)[179] • *Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis* (2004)[180] • AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au) • *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant* (2004).[181]
AHCDO, Australian Haemophilia Centre Directors' Organisation; FFP, fresh frozen plasma; PP, practice point	

Summary of the evidence

Plasma transfusion is a therapeutic intervention used in a range of clinical scenarios, including critical bleeding and massive transfusion, surgery, warfarin reversal in patients with and without severe bleeding, liver disease, coagulation factor deficiencies, and thrombotic thrombocytopenic purpura (TTP). In the current systematic review (Murad et al 2010) [182], only studies that compared plasma transfusion to an infusion of a non-haemostatic solution were included. For example, an RCT in cirrhosis/hepatitis by Mannucci et al (1976) [183] was excluded because it used infusion of prothrombin complex in the control arm. Studies in a perioperative setting or critical bleeding/massive transfusion setting were also excluded, as these have been covered in other modules of the PBM guidelines.

As this is an intervention question, the levels of evidence are as follows: Level I – a systematic review of two or more Level II studies; Level II – an RCT; Level III – (I) a pseudo-RCT, (II) a comparative study with concurrent controls and (III) a comparative study without concurrent controls; and Level IV – case series with either post-test or pre-test/post-test outcomes. For this question, the search was limited to studies that could be categorised as Level II or above.

The literature search identified no systematic reviews that specifically addressed the PICO criteria specified in the Research Protocol. A number of systematic reviews assessed the effect of plasma transfusion on morbidity and mortality;[182,184-186] however, the reviews included studies that were not RCTs, studies that were not in eligible populations, and studies that included ineligible comparators. Through searching the reference lists of these reviews, three Level II studies comparing treatment with FFP with no FFP were identified. An updated literature search was undertaken to identify any studies published since the most recent review was undertaken.[a] The updated literature search identified no new eligible RCTs.

The included studies assessed the use of FFP in the following populations: acute pancreatitis, and liver disease.

FFP VS NO FFP FOR PATIENTS WITH ACUTE PANCREATITIS

Methods

There were two studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

[a] The literature search in Murad et al (2010) included papers published until August 2009

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews examining FFP vs no FFP in patients with acute pancreatitis.

Level II evidence

There were two studies identified from the systematic review and hand searching process (see Appendix C, Volume 2). The main characteristics of these studies are summarised in **Table 3.84**. Both studies were fair quality RCTs in which patients with acute pancreatitis were randomised to receive FFP or a similar volume of colloid control as part of their intravenous fluid therapy. At eight units daily, the dose of FFP used in the more recent study[187] was four times greater than the dose used in the in the earlier study.[188]

Table 3.115 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Leese et al (1987)[188]	RCT *Fair*	Patients with severe acute pancreatitis and no coagulopathy N=202	FFP 2 units daily for 3 days (total 400 mL/day)	Albumin	Mortality Gastrointestinal haemorrhage
Leese et al (1991)[187]	RCT *Fair*	Patients with severe acute pancreatitis N=72	FFP 8 units daily for 3 days (total 400 mL/day)	2000 mL daily of human albumin solution as colloid control.	Mortality Gastrointestinal haemorrhage

FFP, fresh frozen plasma; RCT, randomised controlled trial

Results

Mortality

Mortality was reported in the both of the included studies.[187,188] **Table 3.85** provides a summary of these results. Neither study observed a significant difference between study arms in terms of mortality. This is not surprising, given that both studies were underpowered to measure the effect of treatment on mortality.

Table 3.116 Results for FFP vs. no FFP in acute pancreatitis (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
LEVEL II STUDIES										
Leese (1987)[188]	Level II *Fair*	N=202	Patients with severe acute pancreatitis and no coagulopathy	UK hospital	FFP vs albumin	Mortality	8/99 (8)	9/99 (9)	0.97 (0.38-2.42)	*No significant effect* P=1
Leese (1991)[187]	Level II *Fair*	N=72	Patients with severe acute pancreatitis	UK hospital	FFP vs albumin	Mortality	7/36 (19)	6/36 (17)	1.17 (0.43-3.13)	*No significant effect* P=0.76

CI, confidence interval; FFP, fresh frozen plasma; UK, United Kingdom

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

Bleeding events

The incidence of gastrointestinal haemorrhage was reported in the both of the included studies.[187,188] **Table 3.86** provides a summary of these results. Neither study observed a significant difference between study arms in terms of bleeding events. This is not surprising, given that both studies were inadequately powered to detect significant differences between study arms.

Table 3.117 Results for FFP vs. no FFP in acute pancreatitis (bleeding events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
LEVEL II STUDIES										
Leese (1987)[188]	Level II *Fair*	N=202	Patients with severe acute pancreatitis and no coagulopathy	UK hospital	FFP vs albumin	Gastrointestinal haemorrhage	1/99	4/99	0.25 (0.03-2.2)	*No significant effect* P=0.21
Leese (1991)[187]	Level II *Fair*	N=72	Patients with severe acute pancreatitis	UK hospital	FFP vs albumin	Gastrointestinal haemorrhage	0/36 (0)	1/36 (3)	0.33 (0.01-7.92)	*No significant effect* P=0.50

CI, confidence interval; FFP, fresh frozen plasma; UK, United Kingdom

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

Transfusion related serious adverse events

There were no RCTs reporting the incidence of transfusion-related SAEs in patients with acute pancreatitis receiving plasma transfusions.

FFP VS NO FFP FOR PATIENTS WITH LIVER DISEASE

Methods

There was one study identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews examining FFP vs no FFP in patients with liver disease.

Level II evidence

There was one eligible study identified from the systematic review and hand searching process (see Appendix C, Volume 2). The main characteristics of this study are summarised in Table 3.118. The study by Gazzard et al (1975)[189] was a poor quality RCT that compared the clinical effectiveness of FFP with a control group given no FFP. The study population consisted of 20 patients with liver disease due to paracetamol overdosage (as shown by a prothrombin time ratio of more than 2.2). The 20 patients were randomly allocated to supportive therapy only or to treatment with FFP (300 mL every 6 hours) until the prothrombin time ratio had fallen to less than 1.4. For both groups, if at any time, the prothrombin time ratio rose to 7.0 or more, the dose of FFP was increased to 600 mL.

The small size of this study was not optimal to detect any clinically or statistically significant differences in clinical outcomes between the two groups. Furthermore, any details about randomisation, allocation of concealment and analysis were not reported.

Table 3.118 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Gazzard et al (1975)[189]	RCT *Poor*	Patients with severe coagulation defects following paracetamol overdose, as shown by a prothrombin time ratio >2.2. N=20	FFP 300 mL/6 h (600 mL if prothrombin time ratio >7)	No FFP (unless prothrombin time ratio >7)	Mortality

FFP, fresh frozen plasma; RCT, randomised controlled trial

Results

Mortality

Mortality was reported in the study by Gazzard et al (1975).[189] Table 3.119 provides a summary of these results. The study did not detect a significant difference between study arms in terms of mortality. This is not surprising, given the study was underpowered to measure the effect of treatment on mortality.

Table 3.119 Results for FFP vs. no FFP in patients with liver disease (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
LEVEL II STUDIES										
Gazzard (1975) [189]	Level II *Poor*	N=20	Patients with prothrombin time ratio >2.2 due to paracetamol overdose.	Single site in the UK	FFP 300 mL/6 h (600 mL if prothrombin time ratio >7) vs. no FFP (unless prothrombin time ratio >7)	Mortality	1/10 (10)	2/10 (20)	0.5 (0.1 - 4.7)	*No significant effect* P=1

CI, confidence interval; FFP, fresh frozen plasma; UK, United Kingdom

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

Bleeding events

Evidence of bleeding was reported in the study by Gazzard et al (1975).[189] Table 3.120 provides a summary of these results. Neither study arm reported any instances of bleeding events. With only 20 patients in both arms, the study was most probably underpowered to detect differences for this outcome.

Table 3.120 Results for FFP vs. no FFP in in liver disease (bleeding events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* P-value
LEVEL II STUDIES										
Gazzard (1975) [189]	Level II *Poor*	N=20	Patients with prothrombin time ratio >2.2 due to paracetamol overdose.	Single site in the UK	FFP 300 mL/6 h (600 mL if prothrombin time ratio >7) vs. no FFP (unless prothrombin time ratio >7)	Bleeding events	0/10 (0)	0/10 (0)	NE	*No significant effect*

CI, confidence interval; FFP, fresh frozen plasma; UK, United Kingdom

Transfusion related serious adverse events

There were no RCTs reporting the incidence of transfusion-related SAEs in patients with liver disease receiving plasma transfusions.

3.4.2 Fibrinogen and cryoprecipitate

Evidence statements – fibrinogen and cryoprecipitate	
ES4.5	In medical patients, no relevant studies were found reporting the effect of fibrinogen replacement, using cryoprecipitate or fibrinogen concentrate on mortality, bleeding events and transfusion-related serious adverse events.
ES, evidence statement	

Practice points – fibrinogen and cryoprecipitate	
PP18	The *routine* use of cryoprecipitate or fibrinogen concentrate in medical patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified; where transfusion is considered necessary, the risks and benefits should be considered for each patient. Specialist opinion is advised for the management of DIC.
PP19	For guidance on the use of cryoprecipitate or fibrinogen concentrate in specific patient groups, refer to: • *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion* (2011)[110] • AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au).
AHCDO, Australian Haemophilia Centre Directors' Organisation; DIC, disseminated intravascular coagulation; PP, practice point	

Summary of the evidence

Cryoprecipitate is prepared from controlled thawing of FFP; it contains factors VIII and XIII, fibrinogen and fibronectin. Some plasma fractionators now produce fibrinogen concentrates, which have the benefits of improved viral safety profile and defined dose in a small infusion volume. Fibrinogen concentrate is now licensed in Australia for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia. There is limited experience with the use of the product for the treatment of congenital dysfibrinogenaemia.

The objective of the current systematic review was to identify and review clinical studies comparing fibrinogen or cryoprecipitate transfusion with no fibrinogen or cryoprecipitate transfusion. Studies in a perioperative setting or critical bleeding/massive transfusion setting were excluded.

As this is an intervention question, the levels of evidence are as follows: Level I – a systematic review of two or more Level II studies; Level II – an RCT; Level III – (I) a pseudo-RCT, (II) a

comparative study with concurrent controls and (III) a comparative study without concurrent controls; and Level IV – case series with either post-test or pre-test/post-test outcomes. For this question, the search included all studies that could be categorised as Level II or above.

The literature search identified no Level I-IV that specifically addressed the PICO criteria specified in the Research Protocol. The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

3.4.3 Platelet transfusion

Evidence statements – platelet transfusion		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES4.6	In patients with haematological malignancies receiving chemotherapy, the effect of prophylactic platelet transfusion on mortality is uncertain. (See evidence matrix EM4.E in Volume 2 of the technical report)	X	√√	√	√√	√
ES4.7	In patients with haematological malignancies receiving chemotherapy, the effect of prophylactic platelet transfusion on bleeding events is uncertain. (See evidence matrix EM4.F in Volume 2 of the technical report)	X	√√	NA	√	√
ES4.8	Platelet transfusions are associated with transfusion-related adverse events that can range from mild to serious. (See evidence matrix EM4.G in Volume 2 of the technical report)	X	√√	√√	√√	√
ES4.9	In a broad population of hospitalised cancer patients, platelet transfusion may be associated with increased mortality, but causation has not been established. (See evidence matrix EM4.H in Volume 2 of the technical report)	X	NA	√√	√√	√√
ES4.10	In a broad population of hospitalised cancer patients, platelet transfusion may be associated with increased risk of thromboembolic events, but causation has not been established. (See evidence matrix EM4.I in Volume 2 of the technical report)	X	NA	√	√√	√√
ES4.11	In patients receiving chemotherapy and prophylactic platelet transfusion, the effect of platelet dose on mortality is uncertain. (See evidence matrix EM4.J in Volume 2 of the technical report)	√√	NA	NA	√√√	√√

Evidence statements – platelet transfusion		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES4.12	In patients receiving chemotherapy and prophylactic platelet transfusion, platelet dose has no effect on bleeding events defined as mild or greater (WHO grade 2 or above). (See evidence matrix EM4.K in Volume 2 of the technical report)	√√	√√	X	√√√	√√
ES4.13	In patients receiving chemotherapy and prophylactic platelet transfusion, platelet dose does not appear to affect the incidence of transfusion-related adverse events. (See evidence matrix EM4.L in Volume 2 of the technical report)	√√	√	√	√√√	√√√
ES, evidence statement; WHO, World Health Organization √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice points – platelet concentrates	
PP20	Platelet transfusion may be indicated for the prevention and treatment of haemorrhage in patients with thrombocytopenia or platelet function defects. Platelet transfusions are not indicated in all causes of thrombocytopenia, and may be contraindicated in certain conditions (e.g. TTP and HIT). Thus, the cause of the thrombocytopenia should be established and expert opinion sought.
PP21	In patients with chronic failure of platelet production (e.g. myelodysplasia or aplastic anaemia), a specific threshold for transfusion may not be appropriate. These patients are best managed on an individual basis, in consultation with a relevant expert.[190] Long-term prophylactic platelet transfusions may be best avoided because of the risk of complications (e.g. alloimmunisation and platelet refractoriness). Therapeutic platelet transfusions could be considered for treatment of bleeding.
HIT, heparin-induced thrombocytopaenia; PP, practice point; TTP, thrombotic thrombocytopenic purpura	

Summary of the evidence

Platelet transfusion is a therapeutic intervention used for the prevention and treatment of bleeding in patients with thrombocytopenia. The objective of the current systematic review was to identify and review clinical studies comparing (i) the use of prophylactic transfusion and therapeutic transfusion strategies, and (ii) the use of different platelet transfusion doses. Studies in a perioperative setting or critical bleeding/massive transfusion setting were excluded.

As this is an intervention question, the levels of evidence are as follows: Level I – a systematic review of two or more Level II studies; Level II – an RCT; Level III – (I) a pseudo-randomised RCT, (II) a comparative study with concurrent controls and (III) a comparative study without concurrent controls; and Level IV – case series with either post-test or pre-test/post-test outcomes. For this question, the search included all studies that could be categorised as Level III or above and Level IV case series with more than 500 patients.

The literature search identified no systematic reviews that specifically addressed the PICO criteria specified in the Research Protocol. A number of systematic reviews assessed the effect of platelet transfusion on morbidity and mortality (Stanworth et al 2004a; Cid and Lozano 2007) [185,191]; however the reviews included studies that were not in eligible populations, and studies that included ineligible comparators. Through searching the reference lists of these reviews, two eligible Level II studies were identified. An updated literature search was undertaken to identify any studies published since the most comprehensive and recent review was undertaken.[a] The updated literature search identified no new eligible RCTs, but did identify one additional Level III study and four additional Level IV studies with more than 500 patients.

[a] The literature search in Stanworth et al (2004a) included citations published from 1980-2002

The included studies were all in patients with cancer, and the majority of studies related to patients with thrombocytopenia as a result of chemotherapy or stem cell transplantation. Results for the broad population of patients with cancer, and patients with haematological malignancies undergoing chemotherapy are presented separately.

The CRG requested that populations of special interest included patients receiving treatment with anti-fibrinolytic or anti-platelet therapy. The literature search found no Level I-IV evidence in these populations.

PROPHYLACTIC PLATELET TRANSFUSION IN PATIENTS WITH CANCER (INCLUDING PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES RECEIVING CHEMOTHERAPY)

Methods

There were six studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews comparing prophylactic and therapeutic platelet transfusion in patients with chemotherapy and/or stem cell transplantation.

Level II evidence

There were two poor quality RCTs identified from the systematic review and hand searching process (see Appendix C, Volume 2). The main characteristics of these studies are summarised in Table 3.121.

The paper by Solomon et al (1978) [192] was a published letter reporting the results of a study of thrombocytopenic adult patients with acute lymphoblastic leukaemia who were randomised to receive prophylactic platelet transfusions (when platelet count <20 x 10^9/L with clinically significant bleeding) or specifically indicated transfusions (when clinically significant bleeding or platelet count <20 x 10^9/L was preceded by a decline in platelet count of ≥50% in the preceding 24 hours). In the study by Higby et al (1974) [193], 18 patients with thrombocytopenia and acute leukaemia were randomised to receive either platelets or platelet-poor plasma as a prophylaxis against bleeding. Both of the aforementioned studies were inadequately powered to detect any clinically or statistically significant differences in clinical outcomes between the study arms. Furthermore, due to their age they are likely to be of limited applicability to current Australian clinical practice.

It should be noted that the definitions of prophylactic and therapeutic transfusions vary between studies.

Table 3.121 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Solomon et al (1978) [192]	RCT *Poor*	Previously untreated adult patients with acute lymphoblastic with thrombocytopenia induced by induction chemotherapy. N=31	Prophylactic platelet transfusion (when platelet count <20 x 10^9/L with clinically significant bleeding)	Specifically indicated transfusion (transfusion administered when clinically significant bleeding or platelet count <20 x 109/L was preceded by a decline in platelet count of ≥50% in the preceding 24 hours	All deaths within one month/course Bleeding deaths within 1 month
Higby et al (1974) [193]	RCT *Poor*	Adult afebrile thrombocytopenic patients with acute myelocytic leukaemia, without evidence of bleeding or haemolysis. Significant thrombocytopenia was defined as having a platelet count <30 x 10^9/L	Prophylactic platelet transfusion (~3 x10^{11} platelets / square metre)	Therapeutic plasma infusion (platelet poor)	Major bleeding events

RCT, randomised controlled trial

Level III evidence

There literature search identified one poor quality Level III study, the main characteristics of which are summarised in Table 3.122**.**

The paper by Khorana et al (2008)[119] was a retrospective cohort study investigating the associations between transfusions and venous thromboembolism, arterial thromboembolism, and mortality in hospitalised patients with cancer using the discharge database of the University Health System Consortium, which included 504,208 hospitalisations of patients with cancer between 1995 and 2003 at 60 US medical centres. Variables associated with a higher risk of mortality or thromboembolism were identified using multivariate logistic regression. Although this study provides low level (Level III-2) evidence, it is extremely large and well powered to detect rare events such as mortality and thromboembolism.

It should be noted that the analyses reported in this study included any hospitalised patients with cancer, including a large proportion who were not receiving chemotherapy. Therefore, the results for this population are presented separately to the Level II and Level IV evidence pertaining to patients with haematological malignancies receiving chemotherapy.

Table 3.122 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Khorana et al (2008) [119]	Level III-2 *Fair*	Hospitalised patients with cancer N=504 208	Blood transfusions, including platelet transfusion	No transfusion	Mortality and thromboembolism

Level IV evidence

There literature search identified four poor quality Level IV studies that included more 500 patients. The main characteristics of these studies are summarised in Table 3.121**.**

The study by Slichter (1997)[194] was a multi-institutional, randomised, blinded trial to determine whether the use of platelets from which leukocytes had been removed by a filter or that had been treated with ultraviolet B irradiation would prevent the formation of antiplatelet alloantibodies and refractoriness to platelet transfusions. Although the study presents comparative data for different methods of platelet preparation, the data presented here are the pooled results across all study arms.

The study by McCullough et al (2004)[195] was a transfusion trial of platelets photochemically treated (PCT) for pathogen inactivation using the synthetic psoralen amotosalen HCl. Patients with thrombocytopenia were rando mLy assigned to receive either PCT or conventional (control) platelets for up to 28 days. The primary end point was the proportion of patients with World Health Organization (WHO) grade 2 bleeding during the period of platelet support. As was the case for the study by Slichter (1997), the results presented here reflect the overall rate of post-transfusion reaction in across all study arms.

The study by Heim et al (2008)[196] was a prospective single-centre study in which 9923 mainly prophylactic PLT transfusions given to 672 patients treated for haematologic malignancies between 1997 and 2004. The study by Osselaer et al (2008)[197] was also a prospective cohort study investigating the safety and characteristics of a system of pathogen inactivation (the INTERCEPT process).

The Level IV studies presented here provide data on the incidence of outcomes, but no comparative data. Two of the studies were relatively good-quality RCTs (Slichter 1997 and McCullough et al 2004); however in the context of the PICO criteria posed in this question they represent poor quality evidence.

Table 3.123 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Slichter, 1997[194]	Level IV *Poor*	Patients who were receiving induction chemotherapy for acute myeloid leukemia.	Four types of PLT transfusion, including: unmodified, pooled PLT concentrates from random donors (control); filtered, pooled PLT concentrates from random donors (F-PC); ultraviolet B–irradiated, pooled PLT concentrates from random donors (UVB-PC); or filtered platelets obtained by apheresis from single random donors (F-AP). In the current analysis, the study arms have been pooled	N/A	Incidence of severe platelet-transfusion reactions
McCullough et al 2004 [195]	Level IV *Poor*	Patients with thrombocytopenia requiring platelet transfusion support and were at least 6 years of age [a]. Only 3.4% of patients were aged less than 16.	Platelets photochemically treated for pathogen inactivation using the synthetic psoralen amotosalen HCl and control platelets. In the current analysis, the study arms have been pooled	N/A	Any grade 2 bleeding Any grade 3-4 bleeding Transfusion related adverse events Death
Heim et al 2008[196]	Level IV *Poor*	Patients with malignant or nonmalignant hematologic diseases in need of prophylactic or therapeutic PLT transfusions and patients with nonhematologic malignancies being treated with myeloablative chemotherapy or with HSCT.	Platelet transfusion	N/A	Post-transfusion reactions in patients who had no fever before transfusion Fever in patients who had no fever before transfusion
Osselaer et al 2008[197]	Level IV *Poor*	Patients in intensive and non-intensive locations receiving PLT transfusion. Haematooncology diseases with or without chemotherapy and/or stem cell transplant constituted 58.1% of the primary diagnoses among the transfused patient population.	Photochemically treated (INTERCEPT) platelet transfusion	N/A	Any transfusion related adverse event Transfusion related serious adverse event

HSCT, hematopoietic stem cell transplantation; PLT, platelet

[a] The underlying diagnoses of participants were: acute leukaemia, chronic leukaemia, lymphoma, myelodysplasia, plasma cell dyscrasia, non-haematopoeitic solid tumour and other.

Results

Mortality

Mortality was reported in one Level II study by Solomon et al (1978)[192] and one Level IV study by McCullough et al (2004).[195] Table 3.124 provides a summary of these results.

The RCT by Solomon et al (1978)[192] study observed no significant difference between study arms for the outcome of mortality; however with only 31 patients the study was inadequately powered to detect any clinically or statistically significant differences in clinical outcomes between the study arms. The Level IV study by McCullough et al (2004)[195] did not report any comparative data, but observed a mortality rate of 4.3% in patients receiving platelet transfusions.

Table 3.124 Results for prophylactic platelet transfusion in patients with haematological malignancies receiving chemotherapy (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
LEVEL II STUDIES										
Solomon (1978) [192]	Level II *Poor*	N=31	Adult patients with acute lymphoblastic leukaemia	USA	Prophylactic platelet transfusion vs. Specifically indicated transfusion	All deaths within one month/course	3/17	2/12	1.06 (0.21, 5.40)	*No significant effect* P=0.95
						Bleeding deaths within one month/course	2/17	0/12	3.61 (0.19, 69.09)	*No significant effect* P=0.39
LEVEL IV STUDIES										
McCullough (2004) [195]	Level IV *Poor*	N=645	Patients ≥6 years of age with thrombocytopenia requiring transfusion support. The underlying diagnoses of participants were: AL, CLL, lymphoma, myelodysplasia, plasma cell dyscrasia, non-haematopoeitic solid tumour and other.	Numerous sites in the USA	Platelet transfusion	Mortality rate	28/645 (4.3%)	NA	NA	NA

AL, acute leukaemia; CLL, chronic lymphocytic leukaemia; CI, confidence interval; USA, United States of America

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

Bleeding events

One Level II study (Higby et al 1974)[193] and one Level IV study (McCullough et al 2004)[195] reported the incidence of bleeding events. Table 3.125 provides a summary of these results.

Higby et al (1974) found a trend towards reduced risk of major bleeding events in patients receiving prophylactic platelet transfusion; however the difference between study arms was non-significant (p=0.08).[193]

The Level IV study by McCullough et al (2004)[195] did not report any comparative data, but found an incidence rate of 58.0% for grade 2 bleeding and 5.1% for grade 3-4 bleeding.

Table 3.125 Results for prophylactic platelet transfusion in patients with haematological malignancies receiving chemotherapy (bleeding events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
LEVEL II STUDIES										
Higby (1974)[193]	Level II *Poor*	N=21	Adult afebrile patients with acute myelocytic leukaemia, without evidence of bleeding or haemolysis. Significant thrombocytopenia was defined as having a platelet count <30 x 10^9/L	USA	Prophylactic platelet transfusion (~3 x10^{11} platelets / square metre) vs. platelet poor	Major bleeding events	3/12 (%)	6/9 (%)	0.38 (0.13, 1.11)	*Favours intervention* P=0.08
LEVEL IV STUDIES										
McCullough (2004)[195]	Level IV *Poor*	N=645	Patients ≥6 years of age with thrombocytopenia requiring transfusion support. The underlying diagnoses of participants were: AL, CLL, lymphoma, myelodysplasia, plasma cell dyscrasia, non-haematopoeitic solid tumour and other.	Numerous sites in the USA	Platelet transfusion	Any grade 2 bleeding	374/645 cases (58.0%)	NA	NA	NA
						Any grade 3-4 bleeding	33/645 cases (5.1%)	NA	NA	NA

CI, confidence interval; USA, United States of America

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

Transfusion related serious adverse events

Four Level IV studies reported the incidence of transfusion related adverse events in patients receiving platelet transfusions. These results are presented in Table 3.126.

Heim et al (2008) reported an incidence rate of 7.5% for post-transfusion reactions in patients without fever before transfusion, and 6.9% for fever in patients who had no fever before transfusion.[196] These rates are per transfusion, rather than per patient. McCullough et al (2004) reported that the incidence of transfusion related adverse events in patients receiving transfusion was 27.9%. [195] This rate was similar to that reported by Slichter (1997),[194] where 22% of patients receiving any type of platelet transfusion had severe platelet-transfusion reactions. The results of these two studies differ markedly to those reported by Osselaer et al (2008),[197] where the transfusion related adverse event rate was 4.9% (per patient) and 0.8% (per transfusion). The rate of transfusion related serious adverse events in the study by Osselaer (2008) was relatively low, at 0.2% (per patient and per transfusion). This difference may be accounted for by the different populations included in the studies or differences in the clinical safety of the interventions. The study by Osselaer et al (2008) assessed the characteristics of the INTERCEPT pathogen inactivation system, in a population where a large proportion of patients were not oncological.[197]

Table 3.126 Results for prophylactic platelet transfusion in patients with haematological malignancies receiving chemotherapy (transfusion-related adverse events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* P-value
LEVEL IV STUDIES										
Heim (2008)[196]	Level IV *Poor*	N=672 patients; 9923 transfusions	Patients with malignant or nonmalignant hematologic diseases receiving platelet transfusions and patients with nonhematologic malignancies being treated with myeloablative chemotherapy or HSCT.	Single centre Switzerland	Platelet transfusion	Post-transfusion reactions in patients who had no fever before transfusion	753/9,923 cases (7.5% of all transfusions)	NA	NA	*NA*
						Fever in patients who had no fever before transfusion	682/9,923 cases (6.9% of all transfusions)	NA	NA	*NA*
McCullough (2004)[195]	Level IV *Poor*	N=645	Patients ≥6 years of age with thrombocytopenia requiring transfusion support. The underlying diagnoses of participants were: AL, CLL, lymphoma, myelodysplasia, plasma cell dyscrasia, non-haematopoeitic solid tumour and other.	Numerous sites in the USA	Platelet transfusion	Transfusion-related adverse events	180/645 (27.9%)	NA	NA	*NA*
Osselaer (2008)[197]	Level IV *Poor*	N=651 patients; 5106 transfusions	Patients with haematooncology diseases, surgical patients, critical care patients and outpatients.	Multiple centres Belgium, Norway, Spain and Italy.	Platelet transfusion (photochemically treated)	Any transfusion related adverse event	42/5106 (0.8%) transfusions 32/651(4.9%) patients	NA	NA	*NA*
						Transfusion related serious adverse event	1/5106 (0.2%) transfusions 1/651 (0.2%) patients	NA	NA	*NA*
Slichter (1997)[194]	Level IV *Poor*	N=530	Patients who were receiving induction chemotherapy for acute myeloid leukemia.	Multiple centres USA	Platelet transfusion (4 types compared)	Incidence of severe platelet-transfusion reactions	114/530 patients (22%) 160[a] transfusions (2.0%)	NA	NA	*NA*

Mortality

Mortality was reported in the Level III study by Khorana et al (2008).[119] Table 3.127 provides a summary of these results.

This large multivariate analysis found that platelet transfusion is significantly and independently associated with in-hospital mortality with a relative risk of 2.40 (95% CI: 2.27, 2.52; P<0.001). The study controlled for a range of variables in the analysis, including cancer type, age, sex, race/ethnicity, and clinical variables that were statistically significantly associated with risk of event in the full model. It should be noted that this type of study design does not establish causality.

Table 3.127 Results for prophylactic platelet transfusion in patients with cancer (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
						Bleeding deaths within one month/course	2/17	0/12	3.61 (0.19, 69.09)	*No significant effect* P=0.39
LEVEL III STUDIES										
Khorana (2008)[119]	Level III-2 *Fair*	N=504208	Hospitalised cancer patients. More than one third of patients were aged over 65 years.	60 centres USA	Platelet transfusion vs. No transfusion	In-hospital mortality	NR	NR	2.40 (2.27, 2.52)	*Platelet transfusion is significantly and independently associated with in-hospital mortality* P<0.001

AL, acute leukaemia; CLL, chronic lymphocytic leukaemia; CI, confidence interval; USA, United States of America

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

Transfusion related serious adverse events

One Level III study reported the incidence of transfusion related adverse events in patients receiving platelet transfusions (Khorana et al 2008).[119] The results of this study are presented in Table 3.128.

This large multivariate analysis found that platelet transfusion is significantly and independently associated with venous and arterial thromboembolism. The relative risk of venous thromboembolism was 1.20 (95% CI: 1.11, 1.29; P<0.001) while the relative risk for arterial thromboembolism was 1.55 (95% CI: 1.40, 1.71; P<0.001). The study controlled for a range of variables in the analysis, including cancer type, age, sex, race/ethnicity, and clinical variables that were statistically significantly associated with risk of event in the full model. It should be noted that this type of study design does not establish causality.

Table 3.128 Results for prophylactic platelet transfusion in patients with cancer (transfusion-related adverse events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
LEVEL III STUDIES										
Khorana (2008)[119]	Level III-2 *Fair*	N=504208	Hospitalised cancer patients. More than one third of patients were aged over 65 years.	60 centres USA	Platelet transfusion vs. No transfusion	Venous thromboembolism (VTE)	NR	NR	1.20 (1.11,1.29)	*Platelet transfusion is significantly and independently associated with VTE* P<0.001
						Arterial thromboembolism (ATE)	NR	NR	1.55 (1.40-1.71)	*Platelet transfusion is significantly and independently associated with VTE* P<0.001

PLATELET DOSE IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES RECEIVING CHEMOTHERAPY

Methods

There were five studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews comparing high dose and low dose platelet transfusion in patients with chemotherapy and/or stem cell transplantation.

Level II evidence

There were two good quality RCTs (Slichter et al 2010, Heddle et al 2009) [198,199], two fair quality RCTs (Tinmouth et al 2004, Goodnough et al 2001) [200,201] and one poor quality RCT (Sensebé et al 2005)[202] identified from the systematic review and hand searching process. The main characteristics of these studies are summarised in Table 3.129. The paper by Slichter et al (2010)[198] reports the results of a large multicentre RCT to determine the optimal prophylactic platelet dose in patients with hypoproliferative thrombocytopenia related to patients undergoing stem cell transplants or chemotherapy. The primary endpoint of the study was to compare three different platelet doses in terms of the incidence of WHO grade 2 bleeding events. The other good quality study by Heddle et al (2009)[199] had the same primary outcome. This was a multicentre prospective RCT undertaken in various sites across Canada, Norway and the US. Patients were eligible if they were thrombocytopenic and were likely to require at least 6 prophylactic platelet transfusions during their period of chemotherapy-induced thrombocytopenia

The study by Tinmouth et al (2004)[200] was a fair quality RCT in which patients with acute leukaemia or undergoing autologous transplantation were randomly assigned to receive low-dose (3 units) or standard-dose (5 units) prophylactic PLT transfusions. Using a sequential Bayesian design, the difference in major bleeding events was determined. The numbers of platelets in each study arm were not reported. The other fair quality study reported by

Goodnough et al (2001)[201] was designed to determine whether platelets harvested from healthy donors treated with thrombopoietin could provide larger increases in platelet counts and thereby delay time to next platelet transfusion compared to routinely available platelets given to thrombocytopenic patients. Since the study reported the median number of platelets transfused in each study arm, it was considered eligible for inclusion in the current systematic review.

There was one poor quality study by Sensebé et al (2005)[202] that assessed the comparative efficacy of transfusion strategies with different platelet targets.

The definitions of thrombocytopenia and the assessed dose ranges vary widely between studies.

Table 3.129 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Slichter et al (2010) [198]	RCT *Good*	Patients undergoing hematopoietic stem-cell transplantation or chemotherapy for hematologic cancers or solid tumours with platelet counts ≤10 x 10^{11}/L for 5 days or more.	Low dose: 1.1 x1011 platelets/ m2/ transfusion vs. Medium dose: 2.2 x1011 platelets/ m2/ transfusion vs. High dose: 4.4 x1011 platelets/ m2/ transfusion		Death from haemorrhage ≥1 Episode of bleeding of WHO grade 2 or higher Serious adverse events Adverse event occurring during or ≤4 hr after a transfusion
Heddle et al (2009) [199]	RCT *Good*	Adults with chemotherapy-induced thrombocytopenia requiring prophylactic platelet transfusion (platelet count <10 x 10^9/L for a minimum of 10 days)	Standard dose prophylactic platelet transfusion (3-6 x 10^{11} platelets/product)	Low dose prophylactic platelet transfusion (1.5-3 x 10^{11} platelets/product)	Occurrence of a WHO grade 2 or higher bleed
Tinmouth et al 2004 [200]	RCT *Fair*	Patients undergoing ASCT or induction chemotherapy for acute myelogenous leukaemia or acute lymphoblastic leukaemia	Low dose platelets (3 whole-blood derived platelet units) Exact number of platelets not reported	Standard dose (5 whole-blood derived platelet units) Exact number of platelets not reported	Major bleeds Minor bleeds
Goodnough et al 2001 [201]	RCT *Fair*	Patients with chemotherapy induced thrombocytopenia (platelet count <25 x 109/L)	Platelets derived from donors treated with placebo, PEG-rHuMGDF 1 mg/kg and PEG-rHuMGDF 3 mg/kg. Median platelets in each study arm: 3.4 x 1011 platelets for the placebo 5.7 x 1011 platelets for the PEG-rHuMGDF 1 mg/kg 11.0 x 1011 platelets for the PEG-rHuMGDF 3 mg/kg		Afebrile transfusion reaction
Sensebé et al 2005 [202]	RCT *Poor*	Patients who had not undergone transfusion who had acute leukaemia undergoing first-line treatment or ASCT	Single platelet dose (target 0.5 x 10^{11}/10 kg)	Double dose (target 1.0 x 10^{11}/10 kg)	Incidence of haemorrhage

ASCT, autologous stem cell transplantation; PEG-rHuMGDF, peglycated recombinant human megakaryocyte growth and development factor; RCT, randomised controlled trial; WHO, World Health Organisation

Results

Mortality

Mortality was only reported in one study by Slichter et al (2010).[198] Table 3.130 provides a summary of these results. The study found no significant difference between any of the assessed platelet doses for the outcome of mortality. Since the event rate was low, it is likely that the study was underpowered to detect differences between study arms for this outcome.

Table 3.130 Results for platelet dose in patients with haematological malignancies receiving chemotherapy (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
LEVEL II STUDIES										
Slichter et al (2010) [198]	Level II *Good*	N=1271	Patients undergoing hematopoietic stem-cell transplantation or chemotherapy for hematologic cancers or solid tumours with platelet counts ≤10 x 10^{11}/L for 5 days or more.	A number of sites in the USA	Low dose: 1.1 x10^{11} platelets/ m^2/ transfusion vs. Medium dose: 2.2 x10^{11} platelets/ m^2/ transfusion vs. High dose: 4.4 x10^{11} platelets/ m^2/ transfusion	Death from haemorrhage (low dose vs medium dose)	0/417 (0)	0/423 (0)	NE	NE
						Death from haemorrhage (medium dose vs high dose)	0/423 (0)	1/432(0)	0.34 (0.01, 8.33)	*No significant effect* P=0.51
						Death from haemorrhage (low dose vs high dose)	0/417 (0)	1/432 (0)	0.35 (0.01, 8.45)	*No significant effect* P=0.51

CI, confidence interval; USA, United States of America

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

Bleeding events

Two good quality studies (Slichter et al 2010, Heddle et al 2009)[198,199] one fair quality study (Tinmouth et al 2004)[200] and one poor quality study (Sensebé et al 2005)[202] reported the incidence of bleeding events in patients receiving different doses of platelets. These results are summarised in Table 3.131**.**

For the incidence of bleeding events with a WHO grade ≥2, the large multicentre RCT by Slichter et al (2010) found no significant difference between study arms in any of the dose comparisons presented.[198] For the same outcome, the study by Heddle et al (2009) reported similar results (RR 0.95; 95% CI 0.67, 1.36; p=0.78).[199] The fair quality study by Tinmouth et al (2004) found that there was a higher risk of experiencing a minor bleed in patients receiving 3 platelet units compared to 5 platelet units (RR 0.49; 95% CI 0.26, 0.91; p=0.02).[200] This difference remained significant in the subgroup of patients with acute leukaemia, but not recipients of autologous transplants. The same study found no significant difference between different platelet doses for the incidence of major bleeds.

The poor quality study by Sensebé et al (2005) found no effect of platelet dose on the incidence of haemorrhage; however it is likely that the study was underpowered to detect significant differences for this outcome.[202]

Table 3.131 Results for platelet dose in patients with haematological malignancies receiving chemotherapy (bleeding events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value *Heterogeneity* [b] P-value (I^2)
LEVEL II STUDIES										
Slichter (2010) [198]	Level II *Good*	N=1271	Patients undergoing hematopoietic stem-cell transplantation or chemotherapy with platelet counts ≤10 x 10^{11}/L for 5 days or more.	A number of sites in the USA	Low dose: 1.1 x10^{11} platelets/ m^2/ transfusion vs. Medium dose: 2.2 x10^{11} platelets/ m^2/ transfusion vs. High dose: 4.4 x10^{11} platelets/ m^2/ transfusion	≥1 Episode of bleeding of grade 2 or higher (low dose vs medium dose)	71/417 (17) (LOW)	69/423 (16) (MEDIUM)	1.04 (0.77, 1.41)	*No significant effect* P=0.78
						≥1 Episode of bleeding of grade 2 or higher (medium dose vs high dose)	69/423 (16)	70/432 (16)	1.01 (0.74, 1.36)	*No significant effect* P=0.97
						≥1 Episode of bleeding of grade 2 or higher (low dose vs high dose)	71/417 (17)	70/432 (16)	1.05 (0.78, 1.42)	*No significant effect* P=0.75
Heddle (2009)[199]	Level II *Good*	N=129	Adults with chemotherapy-induced thrombocytopenia requiring prophylactic platelet transfusion.	3 Canadian sites, 1 Norwegian site, and 2 sites in the United States.	Standard dose (3-6 x 10^{11} platelets/product) vs. Low dose (1.5-3 x 10^{11} platelets/product)	Occurrence of a WHO grade 2 or higher bleed	30/58 (51.7)	30/61 (49.2)	0.95 (0.67, 1.36)	No significant effect P=0.78

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value *Heterogeneity* [b] P-value (I^2)
Tinmouth (2004) [200]	Level II *Fair*	N=111	Patients undergoing ASCT or induction chemotherapy for acute myelogenous leukaemia or acute lymphoblastic leukaemia.	One hospital in Canada	Low dose platelets (3 whole-blood derived platelet units) vs. Standard dose (5 whole-blood derived platelet units)	Patients with major bleeds All patients	6/56 (10.7)	4/55 (7.3)	1.47 (0.44, 4.94)	*No significant effect* P=0.53
						Patients with major bleeds Acute leukaemia	4/17 (23.5)	4/17 (23.5)	1.00 (0.30, 3.36)	*No significant effect* P=1.00
						Patients with major bleeds Autologous PBPC transplant	2/39 (5.1)	0/38 (0)	4.88 (0.24, 98.32)	*No significant effect* P=0.30
						Patients with minor bleeds All patients	11/56 (19.6)	22/55 (40.0)	0.49 (0.26, 0.91)	Favours low dose P=0.02
						Patients with minor bleeds Acute leukaemia	6/17 (35.3)	13/17 (76.5)	0.46 (0.23, 0.93)	Favours low dose P=0.03
						Patients with minor bleeds Autologous PBPC transplant	5/39 (12.8)	9/38 (23.7)	0.54 (0.20, 1.47)	*No significant effect* P=0.23
Sensebé (2005) [202]	Level II *Poor*	N=96	Patients who had not undergone transfusion who had acute leukaemia undergoing first-line treatment or ASCT.	One hospital in France	Single platelet dose (target 0.5 x 1011/10 kg) vs. Double dose (target 1.0 x 10^{11}/10 kg)	Incidence of haemorrhage	5/50	9/51	0.57 (0.20, 1.57)	No significant effect P=0.28

ASCT, autologous stem cell transplantation; CI, confidence interval; PBPC, peripheral blood progenitor cell; USA, United States of America; WHO, World Health Organisation

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

Transfusion related serious adverse events

One good quality study (Slichter et al 2010)[198] and one fair quality study (Goodnough et al 2001)[201] reported the incidence of bleeding events in patients receiving different platelet doses. These results are summarised in Table 3.132.

The study by Slichter et al (2010) reported no significant difference in the incidence of serious adverse events, or adverse events occurring during or ≤4 hours after transfusion, for any of the assessed dose comparisons.[198] Similarly, the study by Goodnough et al (2001) found no significant difference between study arms in the incidence of febrile transfusion reactions, although it should be noted that this study was probably inadequately powered to detect significant differences for this outcome.[201]

In both studies, the overall rate of serious adverse events was relatively high.

Table 3.132 Results for platelet dose in patients with haematological malignancies receiving chemotherapy (transfusion-related SAEs)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
LEVEL II STUDIES										
Slichter (2010) [198]	Level II *Good*	N=1271	Patients undergoing hematopoietic stem-cell transplantation or chemotherapy for hematologic cancers or solid tumours with platelet counts ≤10 x 10^{11}/L for 5 days or more.	A number of sites in the USA	Low dose: 1.1 x10^{11} platelets/ m^2/ transfusion vs. Medium dose: 2.2 x10^{11} platelets/ m^2/ transfusion vs. High dose: 4.4 x10^{11} platelets/ m^2/ transfusion	Serious adverse events (low dose vs medium dose)	35/417 (8)	27/423 (6)	1.31 (0.81, 2.13)	*No significant effect* P=0.27
						Serious adverse events (medium dose vs high dose)	27/423 (6)	36/432 (8)	0.77 (0.47, 1.24)	*No significant effect* P=0.28
						Serious adverse events (low dose vs high dose)	35/417 (8)	36/432 (8)	1.01 (0.65, 1.57)	*No significant effect* P=0.97
						Adverse event occurring during or ≤4 hr after a transfusion (low dose vs medium dose)	193/417 (46)	181/423 (43)	1.08 (0.93, 1.26)	*No significant effect* P=0.31
						Adverse event occurring during or ≤4 hr after a transfusion (medium dose vs high dose)	181/423 (43)	205/432 (47)	0.90 (0.78, 1.05)	*No significant effect* P=0.17
						Adverse event occurring during or ≤4 hr after a transfusion (low dose vs high dose)	193/417 (46)	205/432 (47)	0.98 (0.85, 1.13)	*No significant effect* P=0.73
Goodnough (2001) [201]	Level II *Fair*	N=120	Patients with chemotherapy induced thrombocytopenia (platelet count <25 x 10^9/L).	Five centres in the USA	- 3.4 x 10^{11} platelets for the placebo - 5.7 x 10^{11} platelets for the PEG-rHuMGDF 1 mg/kg - 11.0 x 10^{11} platelets for the PEG-rHuMGDF 3 mg/kg	Febrile transfusion reaction (placebo vs both treated arms)	7/83 (8.4)	14/83 (16.9)	0.50 (0.21, 1.18)	*No significant effect* P=0.11

CI, confidence interval; PEG-rHuMGDF, peglycated recombinant human megakaryocyte growth and development factor; SAE, serious adverse event; USA, United States of America

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

3.5 Question 5

Question 5 (Intervention/prognostic)

In medical patients, at what INR (or PT/APTT) for fresh frozen plasma, fibrinogen level for cryoprecipitate, platelet count for platelets concentrates should patients be transfused to avoid risks of significant adverse events?

3.5.1 Platelet count and prophylactic platelet transfusion in patients undergoing chemotherapy and haematopoietic stem cell transplantation

Evidence statements – chemotherapy and haematopoietic stem cell transplantation		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES5.9	In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to the effect on mortality – the difference between a prophylactic platelet transfusion trigger of <10 × 10^9/L without risk factors or <20 × 10^9/L plus risk factors versus a higher trigger is uncertain. The effect at lower values is unknown. (See evidence matrix EM5.A in Volume 2 of the technical report)	√√	√√	X	√√	√√
ES5.10	In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to major bleeding events – there is no difference between a prophylactic platelet transfusion trigger of <10 × 10^9/L without risk factors or <20 × 10^9/L plus risk factors and a higher trigger. The effect at lower values is unknown. (See evidence matrix EM5.B in Volume 2 of the technical report)	√√	√√√	X	√√	√√
ES5.11	In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to RBC transfusion – there is no difference between a prophylactic platelet transfusion trigger of <10 × 10^9/L without risk factors or <20 × 10^9/L plus risk factors and a higher trigger. The effect at lower values is unknown. (See evidence matrix EM5.C in Volume 2 of the technical report)	√√	√√√	X	√√	√√

ES, evidence statement
√√√=A; √√=B; √=C; X=D; NA, not applicable

Recommendation – chemotherapy and haematopoietic stem cell transplantation	
R8 Grade B	In patients undergoing chemotherapy and haematopoietic stem cell transplantation, the recommended strategy for prophylactic use of platelets is transfusion at a platelet count of $<10 \times 10^9$/L in the absence of risk factors, and at $<20 \times 10^9$/L in the presence of risk factors.
Practice point – chemotherapy and haematopoietic stem cell transplantation	
PP22	In patients undergoing chemotherapy and haematopoietic stem cell transplantation, there is no evidence to support: • a lower trigger for prophylactic platelet transfusion for patients with risk factors (e.g. fever, minor bleeding) • a strategy of therapeutic-only platelet transfusions (i.e. for treatment of clinically significant bleeding). Further research to determine the safety and efficacy of a lower platelet transfusion trigger is underway.
PP, practice point; R, recommendation	

When the foreground questions for each module were originally defined, Question 5 was classified as a prognostic question. It was anticipated that the best evidence to answer the question would come from large cohort studies where the results are stratified according to baseline INR/fibrinogen/PLT count. At subsequent CRG meetings it was agreed that Question 5 could also be characterised as an intervention question, whereby the comparator intervention would be the use of a different transfusion trigger. The best evidence to answer this question would come from RCTs, while lower levels of evidence could include comparative studies of identical cohorts or retrospective studies of institutions where the implementation of new guidelines has resulted in a change in policy regarding transfusion triggers.

As a result, it was decided that this question would be approached in the first instance as an intervention question, and if relevant RCT evidence was not available, it would be subsequently treated as a prognostic question. Of the three interventions considered in the clinical question, only platelet transfusions had good-quality RCT evidence. For cryoprecipitate and fresh frozen plasma (FFP), the evidence included in the systematic review primarily consists of cohort studies in which patients are stratified by INR (or PT/APTT) or fibrinogen at baseline.

3.5.2 Prophylactic platelet transfusion with one trigger level vs another trigger level

Summary of the evidence

Platelet transfusion is a therapeutic intervention used for the prevention and treatment of bleeding in patients with thrombocytopenia. The objective of the current systematic review was to identify and review clinical studies reporting the platelet counts at which patients should receive platelet transfusions in order to avoid risks of significant adverse events.

Studies in a peri-operative setting or critical bleeding/massive transfusion setting were excluded.

As discussed above, this question was initially treated as an intervention question comparing different transfusion triggers. The levels of evidence are as follows: Level I – a systematic review of two or more Level II studies; Level II – an RCT; Level III – (I) a pseudo-randomised RCT, (II) a comparative study with concurrent controls and (III) a comparative study without concurrent controls; and Level IV – case series with either post-test or pre-test/post-test outcomes.

There was one systematic review of RCTs that evaluated the optimal use of platelet transfusion for the prevention of haemorrhage (prophylactic platelet transfusion) in patients with haematological malignancies undergoing chemotherapy or stem cell transplantation (Stanworth et al 2004b)[a].[203] The review included RCTs involving transfusions of platelet concentrates, prepared either from individual units of whole blood or by apheresis, and given prophylactically to prevent bleeding in patients with haematological malignancies. Various comparisons were undertaken in the review, including prophylactic platelet transfusion with one trigger level vs prophylactic platelet transfusion with another trigger level.

An updated literature search was undertaken to identify any publications published since the review by Stanworth et al (2004b).[203] The updated literature search included all studies published after 1970. The search identified three RCTs that had already been included in the systematic review by Stanworth et al (2004b) and one new eligible RCT. The current systematic review includes data extracted from the primary publications for the four RCTs, and does not present results reported in the systematic review by Stanworth et al (2004b).[203]

All of the included studies were in patients with thrombocytopenia as a result of chemotherapy or stem cell transplantation.

PATIENTS UNDERGOING CHEMOTHERAPY AND HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Methods

The literature search identified four eligible RCTs.

The literature search identified one study reporting relevant socioeconomic outcomes (Diedrich et al 2005) and no studies pertaining to Australia's Indigenous population.

Level I evidence

There was one systematic review of randomised controlled trials (RCTs) that evaluated the optimal use of platelet transfusion for the prevention of haemorrhage (prophylactic platelet transfusion) in patients with haematological malignancies undergoing chemotherapy or stem cell transplantation (Stanworth et al 2004b).[203] Since the data presented in the current review were extracted from the primary publications for the eligible RCTs, the results of this systematic review are not discussed further.

[a] The literature search in Stanworth et al (2004b) included citations published from 1980 to 2002

Level II evidence

The literature search identified one good quality study, two studies of fair quality, and one poor quality study.

Level III evidence

Due to the identification of Level II evidence, the literature was not searched for Level III evidence.

Level IV evidence

Due to the identification of Level II evidence, the literature was not searched for Level IV evidence.

Results

Level II evidence

There was one good quality study, two studies of fair quality, and one poor quality study identified from the literature search. The main characteristics of these studies are summarised in Table 3.133.

The studies by Rebulla et al (1997),[204] Heckman et al (1997)[205] and Zumberg et al (2002)[206] assessed the effects of a transfusion trigger of 10 x 10^9/L compared to 20 x 10^9/L; however, the criteria for patients requiring rescue transfusion differed between all three studies. The study by Diedrich et al (2005)[207] had the same restrictive transfusion trigger of 10 x 10^9/L in the intervention arm; however, the transfusion threshold in the control arm (30 x 10^9/L) was higher than that in the other three studies.

The paper by Rebulla et al (1997)[204] reported the results of a relatively large, good quality RCT in newly diagnosed patients with acute myeloid leukaemia (A ML) receiving induction therapy. The primary objective of this study was to measure frequency and severity of haemorrhage, with secondary objectives of numbers of platelet and red cell transfusions, rates of complete remission and mortality rates. Therapeutic transfusions for bleeding were allowed in both arms of the study, independently of platelet count, but details of the definition of a therapeutic transfusion were not provided. The study had very few protocol violations compared with other studies of platelet triggers.

Heckman (1997)[205] was a fair quality RCT in patients undergoing induction therapy for acute leukaemia. The study reported a high rate of protocol deviations for the use of platelet transfusions: 38% and 15% of patients in the intervention and control arms respectively. The authors state that these violations were generally minor.

Diedrich et al (2005)[207] was a fair quality RCT in patients undergoing allogeneic haematopoietic progenitor cell transplantation. The study population included patients with a range of malignancies, although the majority were patients with acute leukaemia or chronic leukaemia. The results are broadly generalisable to similar patients in Australia; however it should be noted that the study population included about 30% of patients aged 18 years or less. The primary outcome in this study was the frequency of haemorrhage. The trial also included a comparison of the costs associated with each transfusion strategy.

The study by Zumberg et al (2002)[206] included patients older than 2 years who underwent an allogeneic, matched unrelated donor, syngeneic, or autologous bone marrow transplant. The trial population therefore included some children; however the exact numbers were not

provided. The primary objective of the study was to compare the number of prophylactic and therapeutic transfusions and the incidence of minor and major bleeding in the two study arms. The results are generally applicable to the Australian setting; however, it should be noted that the patterns of haematopoietic stem cell transplantation may have changed since the trial was undertaken, with fewer autologous transplantations for breast cancer and a larger number of nonmyeloblative transplantations. The trial had a high rate of protocol violations, with 49% of the transfusions in the lower trigger arm and 21% of transfusions in the higher trigger arm being given above the assigned trigger level.

It should be further noted that it is unclear if any of these studies were adequately powered to detect differences in the main outcomes of interest. Zumberg (2002) was the only study that clearly reported their power calculation, but it was not designed to test equivalence; the target number (which was not actually met) was based on detecting a difference in platelet transfusions of 25%.

Table 3.133 Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Rebulla (1997) [204]	RCT *Good*	Patients with a diagnosis of acute myeloid leukaemia, hospital admission for the first course of induction chemotherapy, and aged between 16 and 70 years. N=255	Platelet count <10 x 10^9/L or 10-20 x 10^9/L when the body temperature exceeded 38°C, in the presence of fresh minor or major bleeding, or if invasive procedures were necessary.	Platelet count <20 x 10^9/L.	Mortality rates Frequency and severity of haemorrhage Numbers of platelet and red-cell transfusions
Heckman (1997) [205]	RCT *Fair*	Previously untreated adult patients with acute lymphoblastic with thrombocytopenia induced by induction chemotherapy. N=78	Platelet transfusion threshold of <10 x 109/L	Platelet transfusion threshold of <20 x 109/L	Mean RBC transfusions

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Diedrich (2005) [207]	RCT *Fair*	Patients undergoing allogeneic haematopoietic progenitor cell transplantation N=166	Prophylactic platelet transfusions when morning platelet counts decreased to below 10 x 10^9/L	Prophylactic platelet transfusions when morning platelet counts decreased to below 30 x 10^9/L	Survival (3 years) Subsequent RBC transfusion at 30 days Subsequent RBC transfusion at 60 days Median cost (USD) during first 2 months
Zumberg (2002) [206]	RCT *Poor*	Patients undergoing allogeneic, matched unrelated donor (MUD), syngeneic, or autologous bone marrow transplant. N=159	Prophylactic platelet transfusions when morning platelet counts decreased to below 10 x 10^9/L	Prophylactic platelet transfusions when morning platelet counts decreased to below 20 x 10^9/L	Mortality (100 days) Mean number of packed RBC transfusions Number of bleeding days per patient Major bleeding events

RBC, red blood cell; RCT, randomised controlled trial; USD, United States dollars

Results

Mortality

Mortality was reported in the studies by Rebulla et al (1997),[204] Diedrich et al (2005)[207] and Zumberg et al (2002).[206] Table 3.134 provides a summary of these results. None of the included studies observed a significant difference between study arms for the outcome of mortality. Nor were there any significant trends in favour of restrictive transfusion compared to standard of care, or vice versa. It should be noted that some of the studies may have been inadequately powered to detect any clinically or statistically significant differences in mortality between the study arms.

Table 3.134 Results for prophylactic platelet transfusion with one trigger level vs prophylactic platelet transfusion with another trigger level in patients undergoing chemotherapy and haematopoietic stem cell transplantation (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
LEVEL II STUDIES										
Rebulla (1997) [204]	Level II *Good*	N=255	Patients with a diagnosis of acute myeloid leukaemia, hospital admission for the first course of induction chemotherapy, and aged between 16 and 70 years.	21 haematology centres in Italy	Prophylactic platelet transfusion vs. Specifically indicated transfusion	Death	18/144 (13)	9/132 (7)	1.83 (0.85, 3.94)	*No significant difference* P=0.12
Diedrich (2005) [207]	Level II *Fair*	N=166	Patients undergoing allogeneic haematopoietic progenitor cell transplantation	Single hospital in Sweden	Prophylactic platelet transfusions when morning platelet counts decreased to below 10 x 10^9/L vs Prophylactic platelet transfusions when morning platelet counts decreased to below 30 x 10^9/L	Mortality (3 years)	20/79 (25)	26/87 (30)	NR	*No significant difference*
Zumberg (2002) [206]	Level II *Poor*	N=159	Patients undergoing allogeneic, matched unrelated donor (MUD), syngeneic, or autologous bone marrow transplant.	Single hospital in USA	Prophylactic platelet transfusions when morning platelet counts decreased to below 10 x 10^9/L vs Prophylactic platelet transfusions when morning platelet counts decreased to below 20 x 10^9/L	Mortality (note that none of the deaths were attributable to bleeding)	8/78 (10)	5/81 (6)	NR	*No significant difference*

CI, confidence interval; NR, not reported; USA, United States of America

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

Bleeding events

Bleeding events were reported in the studies by Rebulla et al (1997) [204], Diedrich et al (2005) [207], and Zumberg et al (2002) [206]. Table 3.135 provides a summary of these results. None of the included studies observed a significant difference between study arms for the outcome of bleeding events. Nor were there any significant trends in favour of restrictive transfusion compared to standard of care, or vice versa. It should be noted that studies had varying criteria for rescue transfusion and there were high rates of protocol violations in most cases. The exception to this was the study by Rebulla et al (1997), which had relatively low rates of protocol violations.

Table 3.135 Results for prophylactic platelet transfusion with one trigger level vs prophylactic platelet transfusion with another trigger level in patients undergoing chemotherapy and haematopoietic stem cell transplantation (bleeding events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value
LEVEL II STUDIES										
Rebulla (1997) [204]	Level II *Good*	N=255	Patients with a diagnosis of acute myeloid leukaemia, hospital admission for the first course of induction chemotherapy, and aged between 16 and 70 years.	21 haematology centres in Italy	Morning platelet count <10 x 10^9/L or 10-20 x 10^9/L when the body temperature exceeded 38°C, in the presence of fresh minor or major bleeding, or if invasive procedures were necessary. vs Morning platelet count <20 x 10^9/L	Patients with major bleeding episodes	29/144 (20)	24/132 (18)	1.11 (0.68, 1.80)	*No significant difference* P=0.68
Diedrich (2005) [207]	Level II *Fair*	N=166	Patients undergoing allogeneic haematopoietic progenitor cell transplantation	Single hospital in Sweden	Prophylactic platelet transfusions when morning platelet counts decreased to below 10 x 10^9/L vs Prophylactic platelet transfusions when morning platelet counts decreased to below 30 x 10^9/L	Bleeding (WHO Grades 2-4)	14/79 (18)	13/87 (15)	NR	*No significant difference*
Zumberg (2002) [206]	Level II *Poor*	N=159	Patients undergoing allogeneic, matched unrelated donor (MUD), syngeneic, or autologous bone marrow transplant.	Single hospital in USA	Prophylactic platelet transfusions when morning platelet counts decreased to below 10 x 10^9/L vs Prophylactic platelet transfusions when morning platelet counts decreased to below 20 x 10^9/L	Major bleeding events	11/78 (14)	14/81 (17)	NR	*No significant difference*
						Number of bleeding days per patient	11.4 (78)	11.4 (81)	NR	*No significant difference* P=0.99

CI, confidence interval; NR, not reported; USA, United States of America

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

RBC transfusion

RBC transfusion outcomes were reported in the studies by Rebulla et al (1997) [204], Heckman et al (1997) [205], Diedrich et al (2005) [207] and Zumberg et al (2002) [206]. Table 3.136 provides a summary of these results. None of the included studies observed a significant difference between study arms in terms of the mean number of RBC units transfused, or the mean number of RBC transfusions. Nor were there any significant trends in favour of restrictive transfusion compared to the control arm, or vice versa.

Table 3.136 Results for prophylactic platelet transfusion with one trigger level vs prophylactic platelet transfusion with another trigger level in patients undergoing chemotherapy and haematopoietic stem cell transplantation (RBC transfusion)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value *Heterogeneity* [b] P-value (I^2)
LEVEL II STUDIES										
Rebulla (1997) [204]	Level II *Good*	N=255	Patients with a diagnosis of acute myeloid leukaemia, hospital admission for the first course of induction chemotherapy, and aged between 16 and 70 years.	21 haematology centres in Italy	Morning platelet count <10 x 10^9/L or 10-20 x 10^9/L when the body temperature exceeded 38°C, in the presence of fresh minor or major bleeding, or if invasive procedures were necessary. vs Morning platelet count <20 x 10^9/L	Number of RBC units transfused	9.57± 5.18 (135)	9.07± 4.58 (120)	0.50 (-0.70, 1.70)	*No significant difference* P=0.41
Heckman (1997) [205]	Level II *Fair*	N=78	Adults more than 17 years of age who were receiving induction for acute leukaemia, mainly myeloid, either newly presenting or in relapse	Single site in the USA	Platelet transfusion threshold of <10 x 109/L vs Platelet transfusion threshold of <20 x 10^9/L	Mean RBC transfusions	12.2 ± 6.9 (37)	10.7 ± 5.1 (41)	1.5 (-1.22, 4.22)	*No significant difference* P=0.28
Diedrich (2005) [207]	Level II *Fair*	N=166	Patients undergoing allogeneic haematopoietic progenitor cell transplantation	Single hospital in Sweden	Prophylactic platelet transfusions when morning platelet counts decreased to below 10 x 10^9/L vs Prophylactic platelet transfusions when morning platelet counts decreased to below 30 x 10^9/L	Subsequent RBC transfusion at 30 days (range)	4 (0-26)	4 (0-31)	NR	No significant difference
						Subsequent RBC transfusion at 60 days (range)	5 (0-40)	6 (0-44)	NR	No significant difference

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value *Heterogeneity* [b] P-value (I^2)
Zumberg (2002) [206]	Level II *Poor*	N=159	Patients undergoing allogeneic, matched unrelated donor (MUD), syngeneic, or autologous bone marrow transplant.	Single hospital in USA	Prophylactic platelet transfusions when morning platelet counts decreased to below 10 x 10^9/L vs Prophylactic platelet transfusions when morning platelet counts decreased to below 20 x 10^9/L	Mean number of packed RBC transfusions	6.0	5.9	NR	*No significant difference* P=0.93

CI, confidence interval; RBC, red blood cell; USA, United States of America

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

Costs

The mean cost of therapy was only reported in one study by Diedrich et al (2005).[207] Table 3.137 provides a summary of these results. The study found a mean difference of $2,400 between study arms, in favour of a restrictive transfusion policy. This was largely attributable to a difference between study arms in terms of the number of platelet transfusions administered. The statistical significance of this finding was not reported. It should also be noted that due to differences in reporting and costs at different institutions, the applicability of these data to an Australian setting is uncertain.

Table 3.137 Results for prophylactic platelet transfusion with one trigger level vs prophylactic platelet transfusion with another trigger level in patients undergoing chemotherapy and haematopoietic stem cell transplantation (costs)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Mean difference	*Significance* [a] P-value
LEVEL II STUDIES										
Diedrich (2005) [207]	Level II *Fair*	N=166	Patients undergoing allogeneic haematopoietic progenitor cell transplantation	Single hospital in Sweden	Prophylactic platelet transfusions when morning platelet counts decreased to below 10 x 10^9/L vs Prophylactic platelet transfusions when morning platelet counts decreased to below 30 x 10^9/L	Median cost (USD) during first 2 months (range)	$1,600 ($0-$22,400)	$4,000 ($0-$32,400)	$2,400	NR

NR, not reported; USD, United States dollars

3.5.3 Risk of adverse events associated with different INR (or PT/aPTT) levels

Evidence statements – coagulation parameters and transfusion		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES5.1	In patients with liver disease, an elevated INR/PT/APTT level is independently associated with an increased risk of mortality. (See evidence matrix EM5.D in Volume 2 of the technical report)	√	√√	√√	√√	√√
ES5.2	In patients with acute leukaemia, INR/PT/APTT levels may be independently associated with mortality. (See evidence matrix EM5.E in Volume 2 of the technical report)	√	NA	√	√√	√√
ES5.3	In patients with acute promyelocytic leukaemia, the independent association between INR/PT/APTT levels and bleeding events is uncertain. (See evidence matrix EM5.F in Volume 2 of the technical report)	√	NA	X	√√√	√√
ES5.4	In heparinised patients with ACS receiving standard-dose reteplase or half-dose reteplase and full-dose abciximab, subtherapeutic peak APTT levels may be associated with an increased risk of mortality. (See evidence matrix EM5.G in Volume 2 of the technical report)	√√	NA	√	√√	√√
ES5.5	In heparinised patients with ACS receiving standard-dose reteplase or half-dose reteplase and full-dose abciximab, supratherapeutic peak APTT levels may be associated with an increased risk of moderate-to-severe bleeding. (See evidence matrix EM5.H in Volume 2 of the technical report)	√√	NA	√	√√	√√
ACS, acute coronary syndrome; APTT, activated partial thromboplastin time; ES, evidence statement; INR, international normalised ratio; PT, prothrombin time √√√=A; √√=B; √=C; X=D; NA, not applicable						

Summary of the evidence

Transfusion of fresh frozen plasma (FFP) is a therapeutic intervention used in a range of clinical scenarios, including critical bleeding and massive transfusion, surgery, warfarin reversal in patients with and without severe bleeding, liver disease, coagulation factor deficiencies, and thrombotic thrombocytopenic purpura (TTP). The objective of the current systematic review was to identify and review clinical studies reporting the INR (or PT/aPTT) levels at which patients should receive plasma transfusions in order to avoid risks of significant adverse events. Studies in a perioperative setting or critical bleeding/massive transfusion setting were excluded. As described in the Research Protocol, studies in which

patients were receiving oral anti-coagulation (OAC) were also excluded, as OAC reversal was considered outside the scope of the current guidelines.

As discussed previously, this question was initially treated as an intervention question comparing different transfusion triggers; however, if relevant RCT evidence was not available, it would be subsequently treated as a prognostic question. Since literature search did not identify any relevant RCTs with different triggers for FFP transfusion, the evidence included in the systematic review primarily consists of cohort studies in which patients are stratified by INR (or PT/APTT) at baseline. To minimise the risk of confounding, only studies which have adjusted for potential confounding variables using multivariate analysis, have been included in this analysis; studies in which only univariate analyses have been undertaken have been excluded. Since FFP transfusion is itself, a major confounding variable, studies in which patients received plasma transfusions were excluded.

There were no systematic reviews of evidence in this area, so the literature search included all studies published after 1970.

The search identified studies in three distinct population groups: patients with liver disease, patients with acute leukaemia, and patients with acute coronary syndromes receiving antifibrinolytic and/or antiplatelet therapy.

PATIENTS WITH LIVER DISEASE

Methods

The literature search identified two eligible prospective cohort studies and two retrospective cohort studies in patients with liver disease.

The literature search identified no socioeconomic literature, or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no Level I evidence examining prognostic markers in patients with liver disease.

Level II evidence

The literature search identified two Level II studies examining prognostic markers in patients with liver disease.

Level III evidence

The literature search identified two Level III studies examining prognostic markers in patients with liver disease.

Level IV evidence

Due to the identification of Level II and Level III evidence, Level IV evidence was not included in the systematic review.

Results

Level II evidence

The literature search identified two Level II studies examining prognostic markers in patients with liver disease. The main characteristics of these studies are summarised in Table 3.138.

The study by Garden et al (1985) [208] was a fair quality prospective cohort study in 70 patients with acute variceal haemorrhage. The final analysis included data from 100 hospital admissions in the study cohort. For the majority of patients, variceal bleeding was caused by cirrhosis or hepatitis. The multivariate analysis assessed the association between a range of risk factors (including prothrombin ratio) and admission mortality, defined as death in hospital within 30 days of admission. The study is relatively old, and is therefore likely to have limited applicability to current standard of care in Australia. It should also be noted that the study did not stratify patients by different prothrombin time thresholds, but rather reported the association between absolute prothrombin ratio and admission mortality.

The study by Violi et al (1995) [209] was a poor quality prospective cohort study in 165 patients with cirrhosis, hospitalised for diagnosis or worsening of liver failure. The study used multivariate analysis to identify risk factors for mortality, and to predict which patients were better candidates for liver transplantation. Unlike the study by Garden et al (1985), this study stratified patients according to their baseline aPTT levels, and levels of prothrombin activity. At 2 years, the follow up period for this study was much longer than that for the study by Garden et al (1985).

Table 3.138 Characteristics and quality of Level II evidence

Level II evidence			
Study	Study type Study quality	Population N	Outcomes
Garden (1985) [208]	Prospective cohort study *Fair*	Patients with acute variceal haemorrhage N=70 (100 admissions)	Admission mortality, defined as death in hospital within 30 days of admission.
Violi (1995) [209]	Prospective cohort study *Poor*	Patients with cirrhosis, hospitalised for diagnosis or worsening of liver failure. N=102	Survival

Level III evidence

The literature search identified two Level III-3 studies examining prognostic markers in patients with liver disease. The main characteristics of these studies are summarised in Table 3.139.

The paper by Le Moine et al (1992) [210] reports the results of a good quality retrospective cohort study in 102 patients with a diagnosis of parenchymal cirrhosis. Cirrhosis was alcoholic in origin in the majority of cases. The study used multivariate analysis to identify risk factors for mortality as a result of liver failure or exsanguination. The study assessed a broad range of prognostic markers including prothrombin time; however, it should be noted that patients were not stratified according to their baseline prothrombin time. The length of follow-up in this study was 6 weeks.

The study by Krige et al (2009) [211] was a fair quality study in 310 patients with acute esophageal variceal bleeding from alcohol related cirrhosis. The study used multivariate analysis to assess the association between a range of risk factors (including INR) and variceal

rebleeding and death. Although the study was published relatively recently, it should be noted that the analysis included data collected from patients over a 26 year period. Results from older patients may have limited applicability to the current Australian healthcare setting.

Table 3.139 Characteristics and quality of Level III evidence

Level III evidence			
Study	Study type Study quality	Population N	Outcomes
Le Moine (1992) [210]	Retrospective cohort study *Good*	Patients with a diagnosis of parenchymal cirrhosis, Cirrhosis was of alcoholic origin in 62% of the cases. N=102	Survival or death as a result of liver failure or exsanguination
Krige (2009) [211]	Retrospective cohort study *Fair*	Adult patients with endoscopically proven acute esophageal variceal bleeding from alcohol-related cirrhosis who were treated with injection sclerotherapy. N=310	Variceal rebleeding Death

Results

Mortality

Mortality and/or survival was reported in the studies by Garden et al (1985), Violi et al (1995), Le Moine et al (1992) and Krige et al (2009).[208-211] Table 3.140 provides a summary of the results.

The trials measured a range of coagulation parameters, including absolute prothrombin ratio (PR), prothrombin time, partial thromboplastin time (aPPT) and international normalised ratio (INR). There was also some variation between studies in how the results were reported, with one study reporting the mean difference in the absolute prothrombin ratio in patients who survived and those who died (Garden et al, 1985)[208], another reporting a regression coefficient for prothrombin time (Le Moine et al, 1992)[210] and another reporting relative risk (Krige et al 2009). All of the included studies, with the exception of one poor quality prospective cohort study (Violi et al, 1995)[209] found that coagulopathy was an independent risk factor for mortality. In the study by Violi et al (1995), aPTT and prothrombin time were associated with survival in the univariate analysis but not in the multivariate analysis.[209] The studies by Garden et al (1985) and Le Moine et al (1992) did not stratify patients according to their baseline clotting parameters; however, the study by Krige et al (2009) reported that an INR ≥2.3 was an independent risk factor for mortality (P=0.003).

Table 3.140 Results for INR (or PT/APTT) level and risk of adverse events in patients with liver disease (mortality/survival)

Study	Level of evidence *Quality*	Sample size included in analysis	Patient population	Setting Location	Risk factors assessed	Outcome	Results			
							Risk factor definition	No risk factor definition	Relative Risk (95% CI)	Significance P-value
LEVEL II STUDIES										
Garden (1985) [208]	Level II Fair	N=70 (100 admissions)	Patients with acute variceal haemorrhage	Single site in Scotland	Prothrombin ratio, age, sex, cause and duration of liver disease, time since first variceal haemorrhage, presence of ascites, encephalopathy, bilirubin, alanine aminotransferase, alkaline phosphatase, urea, creatinine, total protein, kaolin cephalin clotting ratio, thrombin ratio, Hb, white cell count, platelet count.	Admission mortality	Absolute prothrombin ratio (the study does not report different prothrombin time thresholds)		*Mean difference* *0.5*	*The prothrombin ratio at admission is an independent predictor of admission mortality.* *P<0.001*
Violi (1995) [209]	Level II *Poor*	N=165	Patients with cirrhosis, hospitalised for diagnosis or worsening of liver failure.	Single site in Italy	Fibrinogen, prothrombin activity, aPTT, factor VII, prekallikrein, grade of liver disease, D-dimer, albumin, bilirubin, age.	Survival	aPTT <1.3 mg/dL, 2.0-3.4 mg/dL, 1.3-1.9 mg/dL, >3.4 mg/dL Prothrombin activity <28 sec, 28-30 sec, 31-36 sec,>36 sec		*No significant association* aPTT and prothrombin activity were associated with survival in the univariate analysis but not in the multivariate analysis.	

Study	Level of evidence *Quality*	Sample size included in analysis	Patient population	Setting Location	Risk factors assessed	Outcome	Results			
							Risk factor definition	No risk factor definition	Relative Risk (95% CI)	Significance P-value
LEVEL III-3 STUDIES										
Le Moine (1992) [210]	Level III-3 *Good*	N=102	Patients with a diagnosis of parenchymal cirrhosis, Cirrhosis was of alcoholic origin in 62% of the cases.	Single site in the Belgium	Prothrombin time, sex, aetiology of cirrhosis, activity of alcoholism, duration of liver disease from initial diagnosis, degree of ascites, degree of encephalopathy, extra-hepatic infection, previous non-surgical haemostatic procedures before admission if referred from other hospitals, source of variceal bleeding, staging of oesophageal varices and presence of blood in stomach, systolic blood pressure, heart rate, Hb, albumin, aspartate aminotransferase, alanine aminotransferase, bilirubin, the number of blood units transfused within 72 hours of admission, the amount of polidocanol injected per patient during the first sclerotherapy session, Child-Pugh score, and serum creatinin.	Mortality related to liver disease	Prothrombin time (absolute value in %)		Regression co-efficient (SE) 0.102 (0.037)	*The value of the prothrombin time at admission is associated with mortality related to liver disease.* P<0.01
Krige (2009) [211]	Level III-3 *Fair*	N=310	Adult patients with acute esophageal variceal bleeding from alcohol-related cirrhosis who were treated with injection sclerotherapy.	Single site in South Africa	Tested variables included albumin level (<25 vs.>25 g/L), total bilirubin level (<51 vs. >51 lmol/l), ascites (nil and mild vs. moderate and severe), and encephalopathy (nil and mild vs. moderate and severe). The categorical variables included gender, age (<60 years vs.>60 years), pitressin, and theneed for balloon tube tamponade.	Mortality	INR ≥2.3	INR ≤2.3	4.93 (1.70, 14.24)	*An INR ≥2.3 is significantly associated with an increased risk of death* P=0.003

aPTT, activated partial thromboplastin time; CI, confidence interval; INR, international normalisation ratio; PT, prothrombin time; SE, standard error

Bleeding events

The literature search did not identify any studies reporting whether coagulopathy is an independent risk factor for bleeding events in patients with liver disease.

RBC transfusions

The literature search did not identify any studies reporting whether coagulopathy is an independent risk factor for RBC transfusion in patients with liver disease.

PATIENTS WITH ACUTE LEUKAEMIA

Methods

The literature search identified two eligible retrospective cohort studies in patients with acute leukaemia.

The literature search identified no socioeconomic literature, or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no Level I evidence examining prognostic markers in patients with acute leukaemia.

Level II evidence

The literature search identified no Level II evidence examining prognostic markers in patients with acute leukaemia.

Level III evidence

The literature search identified two Level III studies examining prognostic markers in patients with acute leukaemia.

Level IV evidence

Due to the identification of Level III evidence, Level IV evidence was not included in the systematic review.

Results

Level III evidence

The literature search identified two Level III-3 studies examining prognostic markers in patients with acute leukaemia. The main characteristics of these studies are summarised in Table 3.141.

The paper by Kim et al (2006) [212] reports the results of large, good quality retrospective cohort study including 792 patients with leukaemia diagnosed between July 1989 and March 2003. The study used multivariate analysis to examine the association between various risk factors (including a range of coagulation parameters) and fatal intracranial haemorrhage (FICH).

The study by Dally et al (2005) [213] was a fair quality retrospective study in patients with acute promyelocytic leukaemia (APL) receiving induction therapy. For a rare disease with high mortality, the cohort size is relatively large and well-powered. The outcomes measured included severe haemorrhagic and thrombotic events. Severe bleeding included any bleeding to vital organs (intracranial bleeding and diffuse alveolar haemorrhage) or significant bleeding necessitating transfusion (severe vaginal bleeding and intraabdominal haemorrhage).

Table 3.141 Characteristics and quality of Level III evidence

Level III evidence			
Study	Study type Study quality	Population N	Outcomes
Kim (2006) [212]	Retrospective cohort study *Good*	Patients with acute leukaemia. N=792	Fatal intracranial haemorrhage (FICH)
Dally (2005) [213]	Retrospective cohort study *Fair*	Patients with acute promyelocytic leukaemia (APL) receiving induction therapy. N=34	Severe hemorrhagic and thrombotic events

Results

Mortality

Only one study in patients with acute leukaemia reported the association between coagulation parameters and mortality. This good quality Level III-3 study by Kim et al (2006) reported the relative risk of experiencing FICH, in patients with INR ≥1.5 compared to those with INR <1.5.[212] The results of this study are presented in Table 3.142. The study found that a high INR is an independent risk factor for FICH in patients with acute leukaemia (RR 3.29; 95% CI 1.25, 8.69). The study also found that aPTT is not an independent risk factor for FICH.

Table 3.142 Results for INR (or PT/APTT) level and risk of adverse events in patients with acute leukaemia (mortality)

Study	Level of evidence *Quality*	Sample size included in analysis	Patient population	Setting Location	Risk factors assessed	Outcome	Results			
							Risk factor definition	No risk factor definition	Relative Risk (95% CI)	Significance P-value
LEVEL III STUDIES										
Kim (2006) [212]	Level III-3 *Good*	N=792	Acute leukaemia	Single site in Korea	Plasma fibrinogen: <250 vs ≥250 mg/dl, prothrombin time (PT): <1.5 vs ≥1.5 INR, activated partial thromboplastim time (aPTT): <48 vs ≥48 s, APL vs acute leukemia other than APL, hemorrhage score (0 vs ≥1), ALL vs non-ALL, gender (male vs female), age (<40 vs ≥40 years), white blood cell (WBC) counts (<50 000 vs ≥50 000/mm3), platelets (<35 000 vs ≥35 000/mm3), peripheral blood blasts (<70 vs ≥70%), performance status (<70 vs ≥70%), performance of induction chemotherapy (done vs not done) and presence of fever (none vs present).	Fatal intracranial haemorrhage	INR ≥1.5	INR <1.5	3.29 (1.25-8.67)	*INR is an independent risk factor for fatal intracranial haemorrhage* P=0.016
							aPTT ≥38s	aPTT <38s	2.26 (0.99-5.21)	*There is a trend towards aPTT being an independent risk factor for fatal intracranial haemorrhage* P=0.054

APL, acute promyelocytic leukaemia; aPTT, activated partial thromboplastin time; CI, confidence interval; INR, international normalisation ratio; PT, prothrombin time; WBC, white blood cell

Bleeding events

Only one study in patients with acute leukaemia reported the association between coagulation parameters and bleeding events. This fair quality Level III-3 study by Dally et al (2005) reported the relative risk of experiencing severe bleeding, in patients with PT ≥60% compared to those with PT <60%.[213] The results, presented in Table 3.143, found that a high PT or aPTT level is not an independent risk factor for severe bleeding in patients with promyelocytic leukaemia.

Table 3.143 Results for INR (or PT/APTT) level and risk of adverse events in patients with acute leukaemia (bleeding events)

Study	Level of evidence *Quality*	Sample size included in analysis	Patient population	Setting Location	Risk factors assessed	Outcome	Results			
							Risk factor definition	No risk factor definition	Odds ratio (95% CI)	Significance P-value
LEVEL III STUDIES										
Dally (2005) [213]	Level III-3 *Fair*	N=34	Acute promyelocytic leukaemia	Single site in Israel	Prothrombin time (PT) partial thromboplastin time (aPTT), fibrinogen level, platelets and white blood cells.	Severe bleeding	PT <60%[a]	PT ≥60% [a]	2.6 (0.15, 43.5)	*Prothrombin time is not an independent risk factor for bleeding complications* P=0.505
							aPTT ≥27 s	aPTT <27 s	NR	*Partial thromboplastin time is not an independent risk factor for bleeding complications*

aPTT, activated partial thromboplastin time; CI, confidence interval; INR, international normalisation ratio; NR, not reported; PT prothrombin time

[a] Note that >60% is defined as normal for that laboratory

RBC transfusions

The literature search did not identify any studies reporting whether coagulopathy is an independent risk factor for RBC transfusion in patients with acute leukaemia.

PATIENTS WITH ACUTE CORONARY SYNDROMES RECEIVING ANTIFIBRINOLYTIC OR ANTIPLATELET THERAPY

Methods

The literature search identified one eligible prospective cohort study in patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy.

The literature search identified no socioeconomic literature, or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no Level I evidence examining prognostic markers in patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy.

Level II evidence

The literature search identified one Level II study examining prognostic markers in patients acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy.

Level III evidence

Due to the identification of Level II evidence, Level III evidence was not included in the systematic review.

Level IV evidence

Due to the identification of Level II evidence, Level IV evidence was not included in the systematic review.

Results

Level II evidence

The literature search identified one Level II study examining prognostic markers in patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy. The main characteristics of this study are summarised in Table 3.144.

This was a large prospective cohort analysis based on RCT data (Nallamothu, 2005).[214] The RCT on which the analysis is based included patients in the first 6 h of evolving ST-segment elevation myocardial infarction who were rando mLy assigned standard-dose reteplase or half-dose reteplase and full-dose abciximab. Reteplase is an anti-fibrinolytic, and abciximab is an antiplatelet agent. Both study arms were also treated with intravenous unfractionated heparin (UFH). A lower dose of UFH in the combination therapy group was used to compensate for the anticoagulant effect of abciximab. The primary endpoint of the analysis was overall 30-day mortality. Additional endpoints assessed at 7 days or discharge (whichever occurred first) included moderate to severe bleeding, intracerebral haemorrhage, and reinfarction. Although this was a multivariate analysis, the authors note that the results may be confounded by greater use of UFH in patients receiving reteplase only.

Table 3.144 Characteristics and quality of Level II evidence

Level III evidence			
Study	Study type Study quality	Population N	Outcomes
Nallamothu (2005) [214]	Prospective cohort study *Fair*	Patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy N=11,420	30-day mortality Severe bleeding

Results

Mortality

Only one study in patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy reported the association between coagulation parameters and mortality. This fair quality Level II study by Nallamothu et al (2005) reported the relative risk of experiencing 30-day mortality in patients who were stratified according to their peak aPTT levels (<50, 50–70, >70 s). [214]The results of this study are presented in Table 3.145. The study found that in patients with peak aPTT levels <50 s, increased aPTT levels are associated with a decreased risk of mortality. The relative risk for each one second increase in peak aPTT in patients with peak aPTT <50 seconds was 0.94 (95% CI 0.92, 0.91), when compared with a peak aPTT level of 50 seconds. It should also be noted that the correlations observed are based on peak aPTT levels, and may have been different had aPTT levels been assessed at a specific time point.

Table 3.145 Results for INR (or PT/APTT) level and risk of adverse events in patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy (mortality)

Study	Level of evidence *Quality*	Sample size included in analysis	Patient population	Setting Location	Risk factors assessed	Outcome	Results			
							Risk factor definition	No risk factor definition	Relative Risk (95% CI)	Significance P-value
LEVEL III STUDIES										
Nallamothu (2005) [214]	Level II *Fair*	11,420	Patients in the first 6 h of evolving ST-segment elevation myocardial infarction who were rando mLy assigned standard-dose reteplase or half-dose reteplase and full-dose abciximab.	820 hospitals in 20 countries (including Australia)	Peak activated partial thromboplastin time (aPTT) levels. For moderate-to-severe bleeding, intracerebral haemorrhage, and reinfarction, the analyses were adjusted for age, gender, and weight. In the analysis of 30-day mortality, the analyses were adjusted for age, gender, myocardial infarction, the use of nitrates in <48 h, blood pressure, pulse, Killip classification, infarct location, and time to reperfusion therapy.	30-day mortality (<50 s) 30-day mortality (50–70 s) 30-day mortality (>70 s)	Patients were stratified by treatment assignment and peak aPTT levels (<50, 50–70, >70 s)		0.94 (0.92-0.95) for each 1s increase in peak aPTT <50s when compared with a peak aPTT level of 50s.	*In patients with peak aPTT levels <50 s, increased aPTT levels are associated with a decreased risk of mortality.* P<0.001
									NR	*There is no association between peak aPTT levels and mortality risk at 30 days, for patients with peak aPTT levels 50–70 s* P=0.461
									NR	*There is no association between peak aPTT levels and mortality risk at 30 days, for patients with peak aPTT levels 50–70 s* P=0.260

aPTT, activated partial thromboplastin time; CI, confidence interval; INR, international normalisation ratio; NR, not reported; PT, prothrombin time

Bleeding events

Only one study in patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy reported the association between coagulation parameters and bleeding events. This fair quality Level II study by Nallamothu et al (2005) reported the relative risk of experiencing bleeding events in patients who were stratified according to their peak aPTT levels (<50, 50–70, >70 s).[214] The results of this study are presented in Table 3.146. The study found that in patients with peak aPTT levels >70 s, increased aPTT levels are associated with an increased risk of moderate-to-severe bleeding. The risk was observed to be greater in patients receiving combination therapy.

Table 3.146 Results for INR (or PT/APTT) level and risk of adverse events in patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy (bleeding events)

Study	Level of evidence *Quality*	Sample size included in analysis	Patient population	Setting Location	Risk factors assessed	Outcome	Results			
							Risk factor definition	No risk factor definition	Relative Risk (95% CI)	Significance P-value
LEVEL III STUDIES										
Nallamothu (2005) [214]	Level II *Fair*	11,420	Patients in the first 6 h of evolving ST-segment elevation myocardial infarction who were rando mLy assigned standard-dose reteplase or half-dose reteplase and full-dose abciximab.	820 hospitals in 20 countries (including Australia)	Peak activated partial thromboplastin time (aPTT) levels. For moderate-to-severe bleeding, intracerebral haemorrhage, and reinfarction, the analyses were adjusted for age, gender, and weight. In the analysis of 30-day mortality, the analyses were adjusted for age, gender, myocardial infarction, the use of nitrates in <48 h, blood pressure, pulse, Killip classification, infarct location, and time to reperfusion therapy.	Severe bleeding	Patients were stratified by treatment assignment and peak aPTT levels (<50, 50–70, >70 s)		NR	In patients with peak aPTT levels >70 s, increased aPTT levels are associated with an increased risk of moderate-to-severe bleeding. The risk is greater in patients receiving combination therapy. P<0.001 (combination therapy) P<0.004 (reteplase therapy)

aPTT, activated partial thromboplastin time; CI, confidence interval; INR, international normalisation ratio; NR, not reported; PT, prothrombin time

RBC transfusions

The literature search did not identify any studies reporting whether coagulopathy is an independent risk factor for RBC transfusion in patients with acute coronary syndromes receiving antifibrinolytic or antiplatelet therapy.

3.5.4 Fibrinogen level and cryoprecipitate or fibrinogen concentrate

Evidence statements – fibrinogen level and cryoprecipitate or fibrinogen concentrate		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES5.6	In patients with liver disease, an independent association between fibrinogen levels and mortality is uncertain. (See evidence matrix EM5.I in Volume 2 of the technical report)	X	NA	X	√√	√√
ES5.7	In patients with acute leukaemia, the independent association between fibrinogen levels and mortality is uncertain. (See evidence matrix EM5.J in Volume 2 of the technical report)	√	NA	X	√√	√
ES5.8	In patients with acute promyelocytic leukaemia, the independent association between fibrinogen levels and bleeding events is uncertain. (See evidence matrix EM5.K in Volume 2 of the technical report)	√	NA	X	√√√	√√
ES, evidence statement √√√=A; √√=B; √=C; X=D; NA, not applicable						

Summary of the evidence

Fibrinogen, also known as Factor I, is synthesized in the liver and circulates in the blood with a normal plasma concentration of 250 to 400 mg/dL. Fibrinogen concentrates or cryoprecipitate may be transfused in patients with congenital fibrinogen deficiency (afibrinogenemia), or those with an acquired deficiency. Acquired deficiency may occur as a result of haemodilution, severe blood loss, during some phases of disseminated intravascular coagulation (DIC) and in sepsis. The objective of the current systematic review was to identify and review clinical studies reporting the fibrinogen levels at which patients should receive cryoprecipitate in order to avoid risks of significant adverse events. Studies in a perioperative setting or critical bleeding/massive transfusion setting were excluded.

As discussed previously, this question was initially treated as an intervention question comparing different transfusion triggers; however, if relevant RCT evidence was not available, it would be subsequently treated as a prognostic question. Since literature search did not identify any relevant RCTs with different triggers for cryoprecipitate transfusion, the evidence included in the systematic review primarily consists of cohort studies in which patients are stratified by fibrinogen level at baseline. To minimise the risk of confounding,

only studies which have adjusted for potential confounding variables using multivariate analysis, have been included in this analysis; studies in which only univariate analyses have been undertaken have been excluded. Since cryoprecipitate transfusion is itself, a major confounding variable, studies in which patients received these transfusions were excluded.

There were no systematic reviews of evidence in this area, so the literature search included all studies published after 1970.

The search identified studies in three distinct population groups: patients with liver disease and patients with acute leukaemia.

PATIENTS WITH LIVER DISEASE

Methods

The literature search identified one eligible prospective cohort study in patients with liver disease.

The literature search identified no socioeconomic literature, or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no Level I evidence examining prognostic markers in patients with liver disease.

Level II evidence

The literature search identified no Level II studies examining prognostic markers in patients with liver disease.

Level III evidence

The literature search identified one Level III studies examining prognostic markers in patients with liver disease.

Level IV evidence

Due to the identification of Level III evidence, Level IV evidence was not included in the systematic review.

Results

Level II evidence

The literature search identified one Level II study examining prognostic markers in patients with liver disease. The main characteristics of this study are summarised in Table 3.147.

The study by Violi et al (1995) [209] was a poor quality prospective cohort study in 165 patients with cirrhosis, hospitalised for diagnosis or worsening of liver failure. The study used multivariate analysis to identify risk factors for mortality, and to predict which patients were better candidates for liver transplantation. The study stratified patients according to their baseline fibrinogen levels.

Table 3.147 Characteristics and quality of Level II evidence

Level II evidence			
Study	Study type Study quality	Population N	Outcomes
Violi (1995) [209]	Prospective cohort study *Poor*	Patients with cirrhosis, hospitalised for diagnosis or worsening of liver failure. N=165	Survival

Results

Mortality

Mortality and/or survival were only reported in the study by Violi et al (1995).[209] Table 3.148 provides a summary of the results.

In the study by Violi et al (1995), fibrinogen level was associated with survival in the univariate analysis but not in the multivariate analysis.

Table 3.148 Results for fibrinogen level and risk of adverse events in patients with liver disease (survival)

Study	Level of evidence *Quality*	Sample size included in analysis	Patient population	Setting Location	Risk factors assessed	Outcome	Results			
							Risk factor definition	No risk factor definition	Relative Risk (95% CI)	Significance P-value
LEVEL II STUDIES										
Violi (1995) [209]	Level II *Poor*	N=165	Patients with cirrhosis, hospitalised for diagnosis or worsening of liver failure.	Single site in Italy	Fibrinogen, prothrombin activity, aPTT, factor VII, prekallikrein, grade of liver disease, D-dimer, albumin, bilirubin, age.	Survival	Fibrinogen >254 mg/dL, 254-196 mg/dL,195-143 mg/dL, <143 mg/dL		*No significant association* Fibrinogen was associated with survival in the univariate analysis but not in the multivariate analysis.	

aPTT, activated partial thromboplastin time; CI, confidence interval

Bleeding events

The literature search did not identify any studies reporting whether fibrinogen levels are an independent risk factor for bleeding events in patients with liver disease.

RBC transfusions

The literature search did not identify any studies reporting whether fibrinogen levels are an independent risk factor for RBC transfusion in patients with liver disease.

PATIENTS WITH ACUTE LEUKAEMIA

Methods

The literature search identified two eligible retrospective cohort studies in patients with acute leukaemia.

The literature search identified no socioeconomic literature, or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no Level I evidence examining prognostic markers in patients with acute leukaemia.

Level II evidence

The literature search identified no Level II evidence examining prognostic markers in patients with acute leukaemia.

Level III evidence

The literature search identified two Level III studies examining prognostic markers in patients with acute leukaemia.

Level IV evidence

Due to the identification of Level III evidence, Level IV evidence was not included in the systematic review.

Results

Level III evidence

The literature search identified two Level III-3 studies examining prognostic markers in patients with acute leukaemia. The main characteristics of these studies are summarised in Table 3.149.

The paper by Kim et al (2006) [212] reports the results of large, good quality retrospective cohort study including 792 patients with leukaemia diagnosed between July 1989 and March 2003. The study used multivariate analysis to examine the association between various risk factors (including a range of coagulation parameters) and fatal intracranial haemorrhage (FICH).

The study by Dally et al (2005) [213] was a small, fair quality retrospective study in patients with acute promyelocytic leukaemia (APL) receiving induction therapy. The outcomes measured included severe haemorrhagic and thrombotic events. Severe bleeding included any bleeding to vital organs (intracranial bleeding and diffuse alveolar haemorrhage) or significant bleeding necessitating transfusion (severe vaginal bleeding and intraabdominal

haemorrhage). This small retrospective cohort study is unlikely to be adequately powered to properly ascertain the influence of various prognostic markers on bleeding. It should be further noted that the study only adjusted for a small number of clinical parameters.

Table 3.149 Characteristics and quality of Level III evidence

Level III evidence			
Study	Study type Study quality	Population N	Outcomes
Kim (2006) [212]	Retrospective cohort study *Good*	Patients with acute leukaemia. N=792	Fatal intracranial haemorrhage (FICH)
Dally (2005) [213]	Retrospective cohort study *Fair*	Patients with acute promyelocytic leukaemia (APL) receiving induction therapy. N=34	Severe hemorrhagic and thrombotic events

Results

Mortality

Only one study in patients with acute leukaemia reported the association between fibrinogen levels and mortality. This good quality Level III-3 study by Kim et al (2006) reported the relative risk of experiencing FICH, in patients with serum fibrinogen <250 mg/dL compared to those with serum fibrinogen ≥250 mg/dL. [212]The results of this study are presented in Table 3.150. The study found that in the univariate analysis, plasma fibrinogen was not significantly associated with FICH.

Table 3.150 Results for fibrinogen level and risk of adverse events in patients with acute leukaemia (mortality)

Study	Level of evidence *Quality*	Sample size included in analysis	Patient population	Setting Location	Risk factors assessed	Outcome	Results			
							Risk factor definition	No risk factor definition	Relative Risk (95% CI)	Significance P-value
LEVEL III STUDIES										
Kim (2006) [212]	Level III-3 *Good*	N=792	Acute leukaemia	Single site in Korea	Plasma fibrinogen: <250 vs ≥250 mg/dl, prothrombin time (PT): <1.5 vs ≥1.5 INR, activated partial thromboplastim time (aPTT): <48 vs ≥48 s, APL vs acute leukemia other than APL, hemorrhage score (0 vs ≥1), ALL vs non-ALL, gender (male vs female), age (<40 vs ≥40 years), white blood cell (WBC) counts (<50 000 vs ≥50 000/mm3), platelets (<35 000 vs ≥35 000/mm3), peripheral blood blasts (<70 vs ≥70%), performance status (<70 vs ≥70%), performance of induction chemotherapy (done vs not done) and presence of fever (none vs present).	Fatal intracranial haemorrhage	Serum fibrinogen <250 mg/dL	Serum fibrinogen ≥250 mg/dL	*No significant association* In the univariate analysis, plasma fibrinogen was not significantly associated with FICH.	

aPTT, activated partial thromboplastin time; CI, confidence interval; FICH, fatal intracranial haemorrhage; PT, prothrombin time; WBC, white blood cell

Bleeding events

Only one study in patients with acute leukaemia reported the association between fibrinogen levels and bleeding events. This fair quality Level III-3 study by Dally et al (2005) reported the relative risk of experiencing severe bleeding, in patients with fibrinogen levels <160 mg/dL compared to those with fibrinogen levels ≥160 mg/dL.[213] The results, presented in Table 3.151, found that fibrinogen is not an independent risk factor for bleeding complications in patients with promyelocytic leukaemia.

Table 3.151 Results for fibrinogen level and risk of adverse events in patients with acute leukaemia (bleeding events)

Study	Level of evidence *Quality*	Sample size included in analysis	Patient population	Setting Location	Risk factors assessed	Outcome	Results			
							Risk factor definition	No risk factor definition	Relative Risk (95% CI)	Significance P-value
LEVEL III STUDIES										
Dally (2005) [213]	Level III-3 *Fair*	N=34	Acute promyelocytic leukaemia	Single site in Israel	Prothrombin time (PT) partial thromboplastin time (aPTT), fibrinogen level, platelets and white blood cells.	Severe bleeding	Fibrinogen <160/mg/dL	Fibrinogen ≥160/mg/dL	1.3 (0.09, 18.8)	*Fibrinogen is not an independent risk factor for bleeding complications* P=0.843

aPTT, activated partial thromboplastin time; CI, confidence interval; PT, prothrombin time

RBC transfusions

The literature search did not identify any studies reporting whether fibrinogen level is an independent risk factor for RBC transfusion in patients with acute leukaemia.

3.6 Question 6: Triggers for RBC transfusion in chronically transfused patients

Question 6 (prognostic)

In specific regularly and chronically transfused patients, at what Hb threshold should patients be transfused to avoid adverse outcomes?

3.6.1 Thalassaemia

Evidence statements – thalassaemia		**Evidence**	**Consistency**	**Clinical impact**	**Generalisability**	**Applicability**
ES6.1	In patients with thalassaemia, the effect of the pretransfusion Hb threshold on mortality is uncertain. (See evidence matrix EM6.A in Volume 2 of the technical report)	X	NA	√	√√√	X
ES6.2	In patients with thalassaemia, a pretransfusion Hb concentration of 90–100 g/L may reduce transfusion volume, compared to 100–120 g/L. (See evidence matrix EM6.B in Volume 2 of the technical report)	√	√	√	√√	√√
ES, evidence statement; Hb, haemoglobin √√√=A; √√=B; √=C; X=D; NA, not applicable						

Practice point – thalassaemia	
PP23	In patients with thalassaemia, the evidence does not support any change to the current practice of maintaining a pretransfusion Hb concentration of 90–100 g/L, with transfusions at about monthly intervals.
Hb, haemoglobin; PP, practice point	

Thalasaemias are inherited blood diseases in which there is reduced production or no production of one of the globin chains of the Hb molecule. Sickle cell diseases, which are caused by impaired globin functioning, were specifically excluded from this question.

Methods

There were four studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews examining the prognostic value of pre-transfusion Hb in patients with thalassaemia.

Level II evidence

The literature search identified two Level II studies examining the prognostic value of pre-transfusion Hb in patients with thalassaemia. The main characteristics of these studies are summarised in Table 3.152.

Table 3.152 Question 6 (Thalassaemia): Characteristics and quality of Level II evidence

Level II evidence			
Author	Study type Study quality	Population	Outcomes
Masera et al (1982) [215]	Prospective cohort study *Poor*	Patients (aged 6-14 years) with a diagnosis of β-thalassaemia. All paitents splenectomised. N=11	Transfusion volume
Torcharus et al (1993) [216]	Prospective cohort study *Poor*	Patients (aged 2-13 years) with a diagnosis of β-thalassaemia or HbE.	Transfusion volume

Level III evidence

The literature search identified two Level III studies examining the prognostic value of pre-transfusion Hb in patients with thalassaemia. The main characteristics of these studies are summarised in Table 3.153.

Table 3.153 Question 6 (Thalassaemia): Characteristics and quality of Level III evidence

Level III evidence			
Author	Study type Study quality	Population	Outcomes
Cazzola et al (1997) [217]	Retrospective cohort crossover study *Fair*	Patients with a diagnosis of β-thalassaemia aged 16-30 years. N=32	Transfusion volume
Roudbari et al (2008) [218]	Retrospective cohort study *Fair*	Patients diagnosed with β-thalassaemia N = 578	Survival

Level IV evidence

The literature search identified no Level IV studies examining the prognostic value of pre-transfusion Hb in patients with thalassaemia.

Results

Pre-transfusion Hb level as a predictor of survival

One study, Roudbari (2008) [218], reported survival in thalassaemia patients with differing pre-transfusion Hb levels (Table 3.154). Roudbari et al (2008) reported that subjects with a pre-transfusion Hb level >90 g/L had significantly longer mean survival than subjects whose pre-transfusion Hb level was ≤90 g/L (33.5 years vs. 26.1 years, p=0.002). Roudbari et al(2008) also examined pre-transfusion Hb as a continuous variable. The authors reported that a 10 g/L increase in pre-transfusion Hb resulted in a 33% reduction in the risk of mortality (OR 0.67; 95% CI 0.47, 0.93; p=0.018).

Table 3.154 Question 6 (Thalassaemia) – mortality/Survival

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome *Analysis type*	Results			
						Risk factor	No risk factor	Risk estimate (95% CI)	*Significance* P-value
THALASSAEMIA									
ALL PATIENTS									
Hb as a categorical variable									
Roudbari et al (2008) [218] Level III-3 *Poor*	1 retrospective cohort study N=578	Patients diagnosed with β-thalassaemia	Treatment centre Iran	Pre-transfusion Hb >90 g/L vs. Pre-transfusion Hb ≤90 g/L	Survival (mean±SE, years) *Univariate*	33.5±2.04	26.1±1.56	NR	*Favours pre-transfusion Hb >90 g/L* P=0.002
Hb as a continuous variable									
Roudbari et al (2008) [218] Level III-3 *Poor*	1 retrospective cohort study N=578	Patients diagnosed with β-thalassaemia	Treatment centre Iran	Pre-transfusion Hb increase of 10 g/L	Survival *Multivariate*	NR Adjusted for: transfusion frequency, type of blood transfused, serum ferritin, comorbidities.		OR=0.67 (0.47, 0.93)	*A 10 g/L increase in Hb results in a 33% decrease in the risk of death.* P=0.018

CI, confidence interval; g, grams; Hb, haemoglobin; L, litre; NR, not reported; OR, odds ratio; SE, standard error.

Pre-transfusion Hb level as a predictor of RBC transfusion volume

Three studies (Cazzola et al (1997) [217], Masera et al (1982) [215] and Torcharus et al (1993) [216]) investigated the relationship between pre-transfusion Hb levels and transfusion volume (Table 3.155).

Cazzola et al (1997) [217] studied thalassaemia patients aged 16 to 30 years and reported the mean transfusion volume in patients with pre-transfusion Hb of 100-120 g/L compared to patients with pre-transfusion Hb of 90-100 g/L. A pretransfusion Hb level of 90-100 g/L was associated with a significantly lower mean transfusion volume compared to a level of 100-120 g/L (104 mL/kg/year vs. 137 mL/kg/year, $p<0.0001$). The same effect was observed when the study population was split into splenectomised and non-splenectomised subgroups ($p<0.0001$ in both subgroups).

The study by Masera et al (1982) [215] examined splenectomised thalassaemia patients aged 6 to 14 years. The study compared subjects on two transfusion regimens with mean pre-transfusion Hb levels of 102 g/L and 123 g/L. In the first five months of treatment subjects with a mean pre-transfusion Hb level of 123 g/L had a significantly greater mean transfusion volume compared to subjects with a mean pre-transfusion Hb level of 102 g/L (20.3 mL/kg/month vs. 16.7 mL/kg/month, $p<0.01$). After five months of treatment there was no significant difference in transfusion volume between the two groups.

Torcharus et al (1993) [216] also studied children with thalassaemia (ages 2 to 13 years). The authors report that patients with pretransfusion Hb level of >80 g/L had a higher mean transfusion volume (208.4 mL/kg/year) than subjects with a mean pre-transfusion Hb of 60-70 g/L (175 mL/kg/year).

Table 3.155 Question 6 (Thalassaemia) – transfusion volume

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Risk factor	Outcome	Results			
						Risk factor	No risk factor	Risk estimate (95% CI)	*Significance* P-value
THALASSAEMIA									
ALL PATIENTS									
Cazzola et al (1997) [217] Level III-3 *Fair*	1 retrospective crossover cohort study N=32	Patients with a diagnosis of β-thalassaemia aged 16-30 years.	Hospital Italy	Hyper-transfusion (pre-transfusion Hb 100-120 g/L) vs. moderate transfusion (pre-transfusion Hb 90-100 g/L)	Transfusion volume (mean±SD, mL/kg/year) All patients, N=32	137±26	104±23	NR	*A moderate transfusion regimen results in lower transfusion volume compared to hyper-transfusion.* P<0.0001
					Transfusion volume (mean±SD, mL/kg/year) Splenectomised patients, N=NR	124±18	93±14	NR	*A moderate transfusion regimen results in lower transfusion volume compared to hyper-transfusion.* P<0.0001
					Transfusion volume (mean±SD, mL/kg/year) Not splenectomised patients, N=NR	162±21	126±22	NR	*A moderate transfusion regimen results in lower transfusion volume compared to hyper-transfusion.* P<0.0001
CHILD PATIENTS									
Masera et al (1982) [215] Level II *Poor*	1 prospective cohort study N=11	Child patients (aged 6-14 years) with a diagnosis of β-thalassaemia. All paitents splenectomised.	Outpatient clinic Italy	Standard transfusion (mean pre-transfusion Hb 102 g/L) vs. supertransfusion (mean pre-transfusion Hb 123 g/L, up to 5 months treatment)	Transfusion volume (mean, mL/kg/month)	16.71±2.0	20.30±3.5	NR	*A standard transfusion regimen results in lower transfusion volume compared to up to 5 months of supertransfusion.* P<0.01
				Standard transfusion (mean pre-transfusion Hb 102 g/L) vs. supertransfusion (mean pre-transfusion Hb 123 g/L, more than 5 months of treatment)	Transfusion volume (mean, mL/kg/month)	16.71±2.0	16.53±2.0	NR	*A standard transfusion regimen shows no significant difference in transfusion volume compared to over 5 months of supertransfusion.* P=Not significant
Torcharus et al (1993) [216] Level II *Poor*	1 prospective cohort study N=18	Child patients (aged 2-13 years) with a diagnosis of β-thalassaemia or HbE.	Hospital Thailand	Hyper-transfusion (pre-transfusion Hb >80 g/L) vs. Standard transfusion (pre-transfusion Hb 60-70 g/L)	Transfusion volume (mean, mL/kg/year)	208.4±67	175±45	NR	*A standard transfusion regimen results in lower transfusion volume compared to hyper-transfusion* P=NR

CI, confidence interval; g, grams; Hb, haemoglobin; kg, kilogram; L, litre; mL, millilitre; NR, not reported; SD, standard deviation

Pre-transfusion Hb level as a predictor of transfusion incidence

No studies were identified that investigated an association between pre-transfusion Hb levels and transfusion incidence in thalassaemia patients.

Pre-transfusion Hb level as a predictor of functional and performance status

No studies were identified that investigated an association between pre-transfusion Hb levels and functional and performance status in thalassaemia patients.

Pre-transfusion Hb level as a predictor of arterial thromboembolic events

No studies were identified that investigated an association between pre-transfusion Hb levels and the incidence of arterial thromboembolic events in thalassaemia patients.

3.6.2 Myelodysplasia

Evidence statements – myelodysplasia	
ES6.3	In patients with myelodysplasia, no studies were found reporting the effect of the pretransfusion Hb threshold on mortality, transfusion incidence, transfusion volume, thromboembolic events and functional or performance status.
ES, evidence statement	

Practice point – myelodysplasia	
PP24	In patients with myelodysplasia who are regularly and chronically transfused, there is no evidence to guide particular Hb thresholds. Decisions around appropriate triggers and frequency of transfusion need to be individualised, taking into account anaemia-related symptoms, functional or performance status, and the patient's response to previous transfusions.
Hb, haemoglobin; PP, practice point	

Myelodysplasia, also known as myelodysplastic syndrome, is a collection of conditions involving impaired production of myeloid cells. In 2008 the World Health Organization created a new classification of myelodysplastic-myeloproliferative disease for chronic myelomonocytic leukaemia (CMML). Studies conducted with CMML patients have been included in this question under myelodysplasia because of the significant overlap between the two categories.

Methods

There were no studies identified from the systematic review and hand searching process that examined the prognostic value of the Hb level in patients with myelodysplasia. (see Appendix C, Volume 2).

The literature search identified 19 studies that have been included in this report to provide background information on myelodysplasia.

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified one systematic review examining the Hb level in patients with myelodysplasia. The main characteristics of the systematic review are shown in Table 3.156.

Table 3.156 Question 6 (Myelodysplasia): Characteristics and quality of Level I evidence

Level I evidence			
Author	Study type Study quality	Population	Outcomes
Pinchon et al (2009) [219]	Systematic review *Fair*	Studies repoting health-realted quality of life where at least 50% of subjects had a diagnosis of MDS N = 1234	Functional/Performance status

CM ML, chronic myelomonocytic leukaemia

Pinchon et al (2009) [219] provided insufficient detail of the outcomes from the individual trials for the purposes of this systematic review. Consequently the individual studies identified in the Pinchon et al (2009) review were retrieved and assessed for eligibility for inclusion as lower level evidence.

Level II evidence

The review of the studies identified in Pinchon et al (2009) did not identify any studies suitable for inclusion as Level II evidence. [219] One study, Jansen 2003, has been included in this report to give background information about functional and performance status in myelodysplasia patients.[220] The study was a good quality prospective cross sectional survey that that identified Hb level as a prognostic factor by multivariate analysis. This study was also identified in the literature search.

The literature search did not identify any Level II studies that investigated the pre-transfusion Hb level in myelodysplasia. The literature search identified one Level II study examining the prognostic value of the Hb level at diagnosis in patients with myelodysplasia. [221] The main characteristics of this study are summarised in Table 3.157.

Table 3.157 Question 6 (Myelodysplasia): Characteristics and quality of Level II evidence

Background Level II evidence			
Author	Study type Study quality	Population	Outcomes
Michaux and Martiat (1991) [221]	Prospective cohort study *Fair*	Adults with a diagnosis of CM ML N = 100	Survival
Jansen et al (2003) [220]	Prospective cross-sectional survey *Fair*	Adults with a diagnosis of MDS (includes 5 CM ML patients) N = 50	Functional/Performance status

CM ML, chronic myelomonocytic leukaemia; MDS, myelodysplastic syndrome

Level III evidence

The literature search did not identify any Level III studies that investigated the pre-transfusion Hb level in myelodysplasia. The literature search identified 16 Level III studies examining the prognostic value of the Hb level at the time of presentation or diagnosis in patients with myelodysplasia. These studies have been included here to provide background information on myelodysplasia. The main characteristics of these studies are summarised in Table 3.158.

Table 3.158 Question 6 (Myelodysplasia): Characteristics and quality of Level III evidence

Background Level III evidence			
Author	Study type Study quality	Population	Outcomes
Aul et al (1992) [222]	Retrospective cohort study *Fair*	Patients (age 17 to 90 years) with a diagnosis of MDS N=232	Survival
Breccia et al (2009) [223]	Retrospective cohort study *Fair*	Adults with a diagnosis of MDS, RAEB-2 subtype N = 98	Survival
Catalano et al (1996) [224]	Retrospective cohort study *Poor*	Adults with a diagnosis of CM ML N=77	Survival
Demirkan et al (2008) [225]	Retrospective cohort study *Fair*	Adults with a diagnosis of CM ML N=37	Survival
Fenaux et al (1988) [226]	Retrospective cohort study *Fair*	Adults with a diagnosis of CM ML N=107	Survival
Garcia et al (1988) [227]	Retrospective cohort study *Fair*	Adults with a diagnosis of MDS N=107	Survival
Germing et al (1998) [228]	Retrospective cohort study *Fair*	Adults with a diagnosis of CM ML (includes 81 patients with the MDS subtype of CM ML) N=158	Survival
Gonzales-Medina et al (2002) [229]	Retrospective cohort study *Fair*	Adults with a diagnosis of CM ML N=49	Survival
Guerci et al (1995) [230]	Retrospective cohort study *Fair*	Adults with a diagnosis of RAEB N=91	Survival
Kao et al (2008) [231]	Retrospective cohort study *Poor*	Adults with a diagnosis of primary MDS N=815	Survival
Onida et al (2002) [232]	Retrospective cohort study *Good*	Adults with a diagnosis of CM ML N=213	Survival
Riccardi et al (1988) [233]	Retrospective cohort study *Fair*	Patients with a diagnosis of MDS N=72	Survival
Sanz et al (1995) [234]	Retrospective cohort study *Fair*	Adults with a diagnosis of MDS (includes 9 patients with therapy-related MDS) N=368	Survival
Solal-Celigny et al (1984) [235]	Retrospective cohort study *Fair*	Adults with a diagnosis of CM ML N=35	Survival

Background Level III evidence			
Author	Study type Study quality	Population	Outcomes
Takahashi et al (1990) [236]	Retrospective cohort study *Poor*	Adults with a diagnosis of primary MDS N=124	Survival
Tefferi et al (1989) [237]	Retrospective cohort study *Fair*	Adults with a diagnosis of CM ML N=41	Survival

CM ML, chronic myelomonocytic leukaemia; MDS, myelodysplastic syndrome; RAEB, refractory anaemia with excess blasts

Level IV evidence

The literature search identified no Level IV studies examining the prognostic value of pre-transfusion Hb in patients with myelodysplasia.

Results

Hb level as a predictor of survival

No Level I to Level IV studies were identified that investigated the association between the pre-transfusion Hb level and survival in patients with MDS

Seventeen studies were identified that examined the association between Hb level at diagnosis and survival in patients with MDS (Table 3.159). These studies have been included in this report to provide background information on myelodysplasia.

For this prognostic factor only studies that used a multivariate analysis of the survival data were included. The studies by Garcia et al (1988) and Sanz et al (1995) shared one common institution and have overlap in their study periods.[227,234] It is likely that these two studies contain data from the same patients. The studies by Garcia et al (1988) and Riccardi et al (1988) did not specify the direction of the association between Hb level and survival.[227,233] For these studies it was assumed that a lower Hb level at diagnosis was associated with shorter survival, as this was the association observed in all other studies.

One Level II study by the Michaux and Martiat (1991) [221] compared survival in patients with Hb levels at diagnosis of >100 g/L compared to levels ≤100 g/L. The authors report a hazards ration for Hb ≥100 g/L of 0.40 (p=0.003), indicating the a Hb level of <100 g/L at diagnosis is an independent predictor of shorter survival.

Ten of the identified Level III studies assessed Hb level as a categorical variable. Two studies by Gonzales-Medina et al (2002) and Onida et al (2002) analysed survival in CM ML patients with Hb levels at diagnosis of <120 g/L compared to ≥120 g/L. Gonzales-Medina et al (2002) found that a Hb level <120 g/L at diagnosis was not a significant predictor of survival.[229] In contrast, Onida et al (2002) reported a hazards ratio of 1.8 (95% CI 1.2, 2.8; p<0.01) for Hb level at diagnosis of <120 g/L.

The studies by Breccia et al (2009), Demirkan et al (2008), Guerci et al (1995), Kao et al (2008) and Tefferi et al (1989) used multivariate analysis to compare survival in MDS patients with Hb levels at diagnosis of <100 g/L and ≥100 g/L.[223,225,230-232,237] Four of these studies found that a Hb level <100 g/L was significantly associated with shorter survival. The Demirkan et al (2008) study reported a hazards ratio of 2.4 (p=0.03) for a Hb level at diagnosis of <100 g/L compared to a level ≥100 g/L.[225] The Guerci et al (1995) study reported

a relative risk for mortality of 1.97 (95% CI 1.11, 3.49; p=0.04) for Hb <100 g/L compared to Hb ≥100 g/L at presentation.[230] Breccia et al (2008) and Kao et al (2008) also reported significant association s between survival and Hb levels at diagnosis of <100 g/L.[223,231] In contrast, Tefferi et al (2009) found that a Hb level below 100 g/L at diagnosis was not a significant predictor of survival in CM ML patients.[237]

Germing et al (1998) found that CM ML patients with a Hb level at diagnosis ≤90 g/L had significantly shorter survival than those with Hb levels >90 g/L (p=0.003).[228] The same effect was observed when the analysis was restricted to CM ML patients with the MDS disease subtype (p=0.002). Catalano et al (1996) reported a hazards ratio of 0.15 (p=0.01) for survival in CM ML patients with a Hb level at diagnosis of >88 g/L compared to patients with levels of ≤88 g/L.[224] The study by Garcia et al (1988) found that MDS patients with a Hb level at diagnosis of <70 g/L has significantly shorter median survival than subjects with Hb levels >70 g/L (p=0.017).

Six of the identified studies assessed the association between survival and Hb level at diagnosis as a continuous variable. The studies by Aul et al (1992), Garcia et al (1988), Riccardi et al (1988), Sanz et al (1995) and Takahashi et al (1990) all found that a higher Hb level at diagnosis was significantly associated with improved survival in MDS patients.[222,227,233,234,236] The study by Solal-Celigny et al (1984) found that the Hb level at diagnosis was not a significant predictor of survival in CM ML patients.[235]

In addition to the studies shown in Table 3.159, the study by Fenaux et al (1988) examined survival in 107 CM ML patients. The study separated paietns into those whose survived for <1 year and those who survived for ≥1 year. The authors found that the mean Hb at diagnosis was significantly lower in patients who survived <1 year compared to patients who survived ≥1 year (85 g/L vs. 108 g/L; p<0.005). The analysis was repeated with patients who survived 12-42 months compared to patients who survived >42 months, however no significant difference was found.[226]

Table 3.159 Question 6 (Myelodysplasia) – mortality/survival

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome *Analysis type*	Results			
						Risk factor	No risk factor	Risk estimate (95% CI)	*Significance* P-value
MYELODYSPLASIA									
Level II studies									
Michaux and Martiat1991 [218] Level II *Fair*	Prospective cohort study N=100	Adults diagnosed with CM ML	16 centres France, Belgium and Germany	Hb level at presentation Hb >100 g/L vs. Hb ≤100 g/L	Survival *Multivariate*	NR	NR	HR=0.40	*Hb level at diagnosis ≤100 g/L is an independent predictor of survival* P=0.003
						Adjusted for: Platelet count, splenomegaly, PB promyelocytes plus myelocytes plus metamyelocytes and PB blasts.			
Level III studies									
Hb as a categorical variable									
Gonzales-Medina et al (2002) [226] Level III-3 *Fair*	Retrospective cohort study N=49	Adults with a diagnosis of CM ML	Hospital Spain	Hb level at diagnosis Hb <120 g/L vs. Hb ≥120 g/L	Survival *Multivariate*	NR	NR	NR	*Hb level at diagnosis <120 g/L is not a significant independent predictor of survival.* P=NS
						Adjusted for: PB leukocytes, PB monocytes, PB myeloid precursors and blasts, LDH levels, BM blast % and BM myelodysplasia.			
Onida et al (2002) [229] Level III-3 *Good*	Retrospective cohort study N=213	Adults with a diagnosis of CM ML	Hospital US	Hb level at admission Hb <120 g/L vs. Hb ≥120 g/L	Survival *Multivariate*	NR	NR	HR=1.8 (1.2, 2.8)	*Hb level <120 g/L at admission is associated with shorter survival.* P<0.01
						Adjusted for: Platelets, PB IMCs, WBC count, absolute monocyte count, absolute lymphocyte count, BM blast %, BM erythroid %, serum LDH and cytogenetics.			
Breccia et al (2009) [223] Level III-3 *Fair*	Retrospective cohort study N=98	Adults with a diagnosis of MDS, RAEB-2 subtype	Hospital Italy	Hb level at diagnosis Hb <100 g/L vs. Hb ≥100 g/L	Survival *Multivariate*	NR	NR	CI: 0.40-2.79	*Hb level at diagnosis <100 g/L is associated with shorter survival.* P=0.0001
						Adjusted for: age, platelet count, bone marrow blastosis %, complex karyotype.			
Demirkan et al (2008) [225] Level III-3 *Fair*	Retrospective cohort study N=37	Adults diagnosed with CM ML	Hospital Turkey	Hb level at presentation Hb <100 g/L vs. Hb ≥100 g/L	Survival *Multivariate*	NR	NR	HR=2.4	*Hb at presentation <100 g/L is associated with reduced survival.* P=0.03
						Adjusted for: Platelet count, lymphocyte count and bone marrow blast count.			
Guerci et al (1995) [230] Level III-3 *Fair*	Retrospective cohort study N=91	Adults with a diagnosis of RAEB	Hospital France	Hb level at presentation Hb <100 g/L vs. Hb ≥100 g/L	Survival *Multivariate*	NR	NR	RR=1.97 (1.11, 3.49)	*Hb level below 100 g/L at presentation is associated with greater risk of death.* P=0.018
						Adjusted for: age, sex, blast cell %, platelet count, WBC count, absolute neutrophil count, peripheral blast cell (%).			
Kao et al (2008) [231] Level III-3 *Poor*	Retrospective cohort study with databse of subjects from seven studies N=815	Adults with a diagnosis of primary MDS with IPSS scores of Int-1 or Int-2	Various	Hb level at presentation Hb <100 g/L vs. Hb ≥100 g/L	Survival *Multivariate*	NR	NR	NR	*Hb level at presentation >100 g/L is associated with improved survival.* P=Significant
						Adjusted for: platelet count, absolute neutrophil count, IPSS score.			
Tefferi et al (1989)	Retrospective	Adults diagnosed with	Hospital	Hb level at	Survival	NR	NR	NR	*Hb level at diagnosis is not a*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome *Analysis type*	Results			
						Risk factor	No risk factor	Risk estimate (95% CI)	*Significance* P-value
[237] Level III-3 *Fair*	cohort study N=41	CM ML	US	diagnosis Hb <100 g/L vs. Hb ≥100 g/L	*Multivariate*	Adjusted for: BM blast % and "modified Bournemouth score".			*significant independent predictor of survival.* P=NS
Germing et al (1998) [228] Level III-3 *Fair*	Retrospective cohort study N=158	Adults diagnosed with CM ML N=158	Hospital Germany	Hb level at diagnosis Hb ≤90 g/L vs. Hb >90 g/L	Survival *Multivariate*	NR	NR	Exp(B)=0.50 (0.32, 0.79)	*Hb level at diagnosis >90 g/L is associated with improved survival in CM ML patients.* P=0.003
						Adjusted for: Monocyte count, LDH level and PB blast count.			
		Adults diagnosed with MDS subtype of CM ML N=81	Hospital Germany	Hb level at diagnosis Hb ≤90 g/L vs. Hb >90 g/L	Survival *Multivariate*	NR	NR	Exp(B)=0.32 (0.17, 0.59)	*Hb level at diagnosis >90 g/L is associated with improved survival in MDS-CM ML patients.* P=0.002
						Adjusted for: Monocyte count, LDH level and PB blast count.			
Catalano et al (1996) [224] Level III-3 *Poor*	Retrospective cohort study N=77	Adults with a diagnosis of CM ML (includes 4 patients with BM blasts of 20-30%)	5 hospitals Italy	Hb level at diagnosis Hb>88 g/L vs. Hb ≤88 g/L	Survival *Multivariate*	NR	NR	RR=0.15	*Hb level at diagnosis >88 g/L is associated with improved survival.* P=0.01
						Adjusted for: WBC count, platelet count, neutrophils, monocytes, promyelocytes, myelocytes, PB blasts, BM erythroid %, BM myeloid %, BM monocyte %, BM blats %, LDH, AST, creatinine and γ-globulin levels.			
Garcia et al (1988) [a 227] Level III-3 *Fair*	Retrospective cohort study N=107	Adults with a diagnosis of MDS	Hospital Spain	Hb level at diagnosis Hb <70 g/L vs. Hb >70 g/L	Survival *Multivariate*	NR	NR	NR	*Hb level at diagnosis <70 g/L is associated with shorter survival.* [c] P=0.017
						Adjusted for: age, systemic symptoms, platelet count, circulating blasts, circulating myeloid precursors, circulating erythroblasts, bone marrow cellularity, blasts I, blasts II, dyserythropoiesis, dysgranulopoiesis, MDS subtype.			
Hb as a continuous variable									
Aul et al (1992) [222] Level III-3 *Fair*	Retrospective cohort study N=232	Patients (age 17 to 90 years) with a diagnosis of MDS	43 hospitals Germany	Hb level at diagnosis	Survival *Multivariate*	NR	NR	NR	*Higher Hb level at diagnosis is associated with improved survival.* P=0.003
						Adjusted for: age, sex, platelet and leukocyte counts, LDH activity, bone marrow blast cells (%), peripheral blast cells (%), degree of dysgranulopoiesis, MDS subtype.			
Garcia et al (1988) [a 227] Level III-3 *Fair*	Retrospective cohort study N=107	Adults with a diagnosis of MDS	Hospital Spain	Hb level at diagnosis	Survival *Multivariate*	NR	NR	NR	*Higher Hb level at diagnosis is associated with improved survival.* P=0.011
						Adjusted for: age, systemic symptoms, platelet count, circulating blasts, circulating myeloid precursors, circulating erythroblasts, bone marrow cellularity, blasts I, blasts II, dyserythropoiesis, dysgranulopoiesis, MDS subtype.			
Riccardi et al (1988) [233] Level III-3 *Fair*	Retrospective cohort study N=72	Patients with a diagnosis of MDS	Hospital Italy	Hb level at diagnosis	Survival *Multiple regression*	Standardised coefficient (β) = +0.42		NR	*Higher Hb level at diagnosis is associated with improved survival.* [b] P<0.05
						Adjusted for: BM cellularity, BL blast %, erythroid/myeloid ratio and age.			
Sanz et al (1995) [a 234]	Retrospective cohort study	Adults with a diagnosis of MDS	Three hospitals	Hb level at presentation	Survival *Multivariate*	NR	NR	NR	*Higher Hb levels at presentation are associated*

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Risk factor	Outcome *Analysis type*	Results			
						Risk factor	No risk factor	Risk estimate (95% CI)	*Significance* P-value
Level III-3 *Fair*	N=368	(includes 9 patients with therapy-related MDS)	Spain			Adjusted for: Total bone marrow blasts (%), age, sex, platelets, neutrophils, immature myeloid precursors, nucleated RBC, blast cells, bone marrow dyserythropoiesis, bone marrow dysgranulopoiesis, bone marrow dysthrombopoiesis, WBC count, haemorrhages, systemic symptoms, interval first symptom to diagnosis, serum creatinine, serum uric acid, serum biliribulin, serum GPT, serum LDH, FAB classification.			*with improved survival.* P=0.0008
Solal-Celigny et al (1984) [235] Level III-3 *Poor*	Retrospective cohort study N=35	Adults with a diagnosis of CM ML	Hospital France	Hb level at diagnosis	Survival *Multivariate*	NR	NR	NR	*Hb level at diagnosis is not a significant predictor of survival.* P=NS
						Adjusted for: WBC, monocytosis, platelet count, PB blast %, BM blast %, serum IgG, blood lysozyme levels.			
Takahashi et al (1990) [236] Level III-3 *Poor*	Retrospective cohort study N=124	Adults with a diagnosis of MDS	Hospital Japan	Hb level at diagnosis	Survival *Multivariate*	NR	NR	F value for testing regression co-efficient = 2.21184	*Higher Hb level at diagnosis is associated with improved survival.* P=Significant
						Adjusted for: age, marrow erythroblasts (%), marrow lymphocytes (%), netrophil alkaline phosphatase score, marrow CFU, marrow granulocytes with atypia (%),Morphological dyserythropoiesis (%) , Morphological dysgranulopoiesis (%), Morphological dysmegakaryopoiesis (%).			

[a] The patients in the study by Garcia may also be included in the study by Sanz

[b] The direction of the relationship between Hb level and survival was assumed based on the results of the univariate analysis in the same study.

[c] For the multivariate analysis it was assumed that binary categories for Hb were the same as were reported in the univariate analysis and that lower Hb was associated with shorter survival.

AST, aspartate transaminase; BM, bone marrow; CFU, colony forming units; CI, confidence interval; CM ML, chronic myelomonocytic leukaemia;; FAB, French–American–British; g, grams; GPT, glutamic pyruvic transaminase; g, grams; Hb, haemoglobin; ; IMC, immature myeloid cell; IPSS, International Prognostic Scoring System; L, litre; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; NR, not reported; PB, peripheral blood; RAEB, refractory anaemia with an excess of blasts; RBC, red blood cell; RR, relative risk; US, the United States of America; WBC, white blood cell.

Pre-transfusion Hb level as a predictor of functional and performance status

No Level I to Level IV studies were identified that investigated an association between pre-transfusion Hb levels and functional and performance status in MDS patients.

One study, Jansen 2003 [220], has been included in this report to give background information about functional and performance status in myelodysplasia patients. The study was a good quality prospective cross sectional survey that that used a multivariate analysis of the study data. This study was also identified in the literature search.

The study by Jansen (2003) analyses the association between Hb level 24 hours prior to testing and the outcome of functional and performance status testing. In the time between Hb measurement and testing no transfusions were allowed. The study was a prospective hospital-based survey of 50 adult MDS patients using the EuroQOL 5D visual analogue scale (EQ-5D VAS) and SF-36 instruments (Table 3.160). The authors report that Hb level may be associated with EQ-5D VAS score (p=0.05). They also report that Hb level is significantly associated with the Physical functioning (p=0.00), Role physical (p=0.02), Vitality (p=0.02) and Physical sum score (p=0.01) scales of the SF-36 instrument. No significant association was found for the Bodily pain (p=0.58), General health (p=0.29), Mental health (p=0.52), Role emotional (p=0.13), Social functioning (p=0.22) and Mental sum score (p=0.54) SF-36 scales.

Table 3.160 Question 6 (Myelodysplasia) – functional and performance status

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population	Setting Location	Analysis	Outcome	Results			
						Risk factor	No risk factor	Risk estimate (95% CI)	*Significance* P-value
MYELODYSPLASIA									
ADULT PATIENTS									
Hb as a continuous variable									
Jansen 2003 [220] Level II *Fair*	Prospective cross-sectional survey N=50	Adults with a diagnosis of MDS (includes 5 CM ML patients)	Four hospitals The Netherlands	Multivariate Adjusted for: Age, sex, MDS subtype, hospital. Hb level was measured 24 hours prior to the survey and no transfusions were allowed between Hb measurement and the time of the survey.	EQ-5D [b] visual analogue scale	Hb level		NR	*Hb level may be correlated with EQ-5D VAS score.* P=0.05
					SF-36 [b] Bodily pain	Hb level		NR	*Hb level is not correlated with SF-36 bodily pain score.* P=0.58
					SF-36 [b] Physical functioning	Hb level		NR	*Hb level is correlated with SF-36 physical functioning score* P=0.00
					SF-36 [b] Role physical	Hb level		NR	*Hb level is correlated with SF-36 role physical score.* P=0.02
					SF-36 [b] General health	Hb level		NR	*Hb level is not correlated with SF-36 general health score.* P=0.29
					SF-36 [b] Physical sum score	Hb level		NR	*Hb level is correlated with SF-36 physical sum score.* P=0.01
					SF-36 [b] Mental health	Hb level		NR	*Hb level is not correlated with SF-36 mental health score.* P=0.52
					SF-36 [b] Role emotional	Hb level		NR	*Hb level is not correlated with SF-36 role emotional score.* P=0.13
					SF-36 [b] Social functioning	Hb level		NR	*Hb level is not correlated with SF-36 social functioning score.* P=0.22
					SF-36 [b] Vitality	Hb level		NR	*Hb level is correlated with SF-36 vitality score* P=0.02
					SF-36 [b] Mental sum score	Hb level		NR	*Hb level is not correlated with SF-36 mental sum score.* P=0.54

BFI, Brief Fatigue Inventory; BMI, body mass index; CI, confidence interval; CM ML, chronic myelomonocytic leukaemia; EQ-5D, EuroQOL 5D; FACT-An, Functional Assessment of Cancer Therapy-Anemia; g, grams; Hb, haemoglobin; MDS, myelodysplastic syndrome; NR, not reported; QOL, quality of life; SF-36, 36-question Short Form Health Survey; VAS, visual analogue scale.
b Scale has a score range of 1-100.

Pre-transfusion Hb level as a predictor of arterial thromboembolic events

No studies were identified that investigated an association between pre-transfusion Hb levels and the incidence of arterial thromboembolic events in MDS patients.

Pre-transfusion Hb level as a predictor of RBC transfusion incidence

No studies were identified that investigated an association between pre-transfusion Hb levels and transfusion incidence in MDS patients.

Pre-transfusion Hb level as a predictor of RBC transfusion volume

No studies were identified that investigated an association between pre-transfusion Hb levels and transfusion volume in MDS patients

4 Appendixes

4.1 Appendix 1 – Research question structure

The structure of the foreground research questions for medical patient blood management is presented in **Table 4.1.1** (generic questions relevant to all modules of the patient blood management guidelines) and **Note:** The CRG consider that the cardiac, elderly/geriatric and chronic transfusion (chronic anaemia) subgroups are the most important to identify. The cardiac (heart failure and ACS) and elderly populations need to be addressed in question 1 or 2. The elderly population needs to be addressed in question 3. The chronic transfusion subgroup is addressed in specific question 1.

Note: The CRG consider that for question 5 studies of platelet transfusion in bleeding patients receiving anti-platelet or anti-fibrinolytic therapies should be searched for up to Level II evidence. All studies of cryoprecipitate and fibrinogen will be searched for up to Level II evidence.
Note: The CRG decided that question 6 should be answered using interventional studies comparing different transfusion triggers.

Abbreviations: ACS, acute coronary syndrome; ADL, Activities of Daily Living; AE, adverse event; APTT, partial thromboplastin time; AQoL, Assessment of Quality of Life; ASTH, Australasian Society of Thrombosis and Haemostasis; DASI, Duke Activity Status Index; BM, bone marrow; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; EQ5D, EuroQoL 5D; ESA, erythropoiesis stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; FFP, fresh frozen plasma; GP, general practitioner; Hb, haemoglobin; Hct, haematocrit; HIV, human immunodeficiency virus; HUI, Health Utilities Index; IADL, Instrumental Activities of Daily Living; IM, intramuscular; INR, international normalised ratio; IV, intravenous; MI, myocardial infarction; 6MWT, 6-min Walk Test; MQoL, McGill Quality of Life Questionnaire; NHP, Nottingham Health Profile; OS, overall survival; PE, pulmonary embolism; PFS, progression-free survival; PT, prothrombin time; QWB, Quality of Well-Being; RBC, red blood cell; SAE, serious adverse event; SF-12, 12-item Short Form Health Survey; SF-36, 36-question Short Form Health Survey; SR, systematic review; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related immunomodulation.
[a] Within malignant haematology subgroup, consider high dose chemo/transplant patients as a subpopulation.
[b] Within renal subgroup, consider non-end stage renal failure as a subpopulation.
[c] Consider geriatrics without comorbidities.
[d] Within gastro subgroup, consider patients excluded from the TRICC trial (i.e., patients with significant, ongoing bleeding who are not acutely compromised).
[e] Only common, validated functional and performance status instruments will be included: AQoL, Barthel ADL, 15D, DASI, ECOG, EQ-5D, FACIT, HUI2, HUI3, IADL, Karnofsky, Katz ADL, 6MWT, MQoL, NHP, QWB, RAND-36, SF-12, SF-36. Disease-specific quality of life instruments will not be included.
[f] These additional outcomes will only be addressed if the specified subgroup falls out of the literature. The literature search will not be conducted to specifically look for this subgroup.
[g] Chronic anaemia includes chronic regular transfusion/transfusion-dependant patients.
[h] Other transfusion-related SAEs includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions.
[i] The cardiothoracic subgroup was covered in the Peri-operative module. Any relevant studies identified in the Peri-operative module will be carried over to this module.
[j] Will require CRG expertise to identify 'true' vs. functional' iron deficiency.
[k] Trial-based definitions of thromboembolic events will be recorded in the Technical Report.
[l] Consider subgroup of cardiac patients who have received fibrinolytics and antiplatelet agents.
[m] Refers to prophylactic vs. therapeutic use

Table 4.1.2. (question specific to the medical patient blood management guidelines)**.** As the generic research questions were designed to identify evidence relevant to all modules, **Note:** The CRG consider that the cardiac, elderly/geriatric and chronic transfusion (chronic anaemia) subgroups are the most important to identify. The cardiac (heart failure and ACS) and elderly populations need to be addressed in question 1 or 2. The elderly population needs to be addressed in question 3. The chronic transfusion subgroup is addressed in specific question 1.

Note: The CRG consider that for question 5 studies of platelet transfusion in bleeding patients receiving anti-platelet or anti-fibrinolytic therapies should be searched for up to Level II evidence. All studies of cryoprecipitate and fibrinogen will be searched for up to Level II evidence.
Note: The CRG decided that question 6 should be answered using interventional studies comparing different transfusion triggers.

Abbreviations: ACS, acute coronary syndrome; ADL, Activities of Daily Living; AE, adverse event; APTT, partial thromboplastin time; AQoL, Assessment of Quality of Life; ASTH, Australasian Society of Thrombosis and Haemostasis; DASI, Duke Activity Status Index; BM, bone marrow; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; EQ5D, EuroQoL 5D; ESA, erythropoiesis stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; FFP, fresh frozen plasma; GP, general practitioner; Hb, haemoglobin; Hct, haematocrit; HIV, human immunodeficiency virus; HUI, Health Utilities Index; IADL, Instrumental Activities of Daily Living; IM, intramuscular; INR, international normalised ratio; IV, intravenous; MI, myocardial infarction; 6MWT, 6-min Walk Test; MQoL, McGill Quality of Life Questionnaire; NHP, Nottingham Health Profile; OS, overall survival; PE, pulmonary embolism; PFS, progression-free survival; PT, prothrombin time; QWB, Quality of Well-Being; RBC, red blood cell; SAE, serious adverse event; SF-12, 12-item Short Form Health Survey; SF-36, 36-question Short Form Health Survey; SR, systematic review; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related immunomodulation.
[a] Within malignant haematology subgroup, consider high dose chemo/transplant patients as a subpopulation.
[b] Within renal subgroup, consider non-end stage renal failure as a subpopulation.
[c] Consider geriatrics without comorbidities.
[d] Within gastro subgroup, consider patients excluded from the TRICC trial (i.e., patients with significant, ongoing bleeding who are not acutely compromised).
[e] Only common, validated functional and performance status instruments will be included: AQoL, Barthel ADL, 15D, DASI, ECOG, EQ-5D, FACIT, HUI2, HUI3, IADL, Karnofsky, Katz ADL, 6MWT, MQoL, NHP, QWB, RAND-36, SF-12, SF-36. Disease-specific quality of life instruments will not be included.
[f] These additional outcomes will only be addressed if the specified subgroup falls out of the literature. The literature search will not be conducted to specifically look for this subgroup.
[g] Chronic anaemia includes chronic regular transfusion/transfusion-dependant patients.
[h] Other transfusion-related SAEs includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions.
[i] The cardiothoracic subgroup was covered in the Peri-operative module. Any relevant studies identified in the Peri-operative module will be carried over to this module.
[j] Will require CRG expertise to identify 'true' vs. functional' iron deficiency.
[k] Trial-based definitions of thromboembolic events will be recorded in the Technical Report.
[l] Consider subgroup of cardiac patients who have received fibrinolytics and antiplatelet agents.
[m] Refers to prophylactic vs. therapeutic use

Table 4.1.2 specifies subgroups relevant to the medical module's population.

Table 4.1.1 Structure of generic questions

1. Is anaemia an independent risk factor for adverse outcomes? [Aetiology question]			
Population	Risk factor	Comparison	Outcomes (primary, unless specified)
All patients Subgroups: • Cardiac (including heart failure & ACS) • Cerebrovascular disease • Oncology • Radiotherapy patients • Malignant haematology[a] • Non-malignant haematology • Respiratory • Renal[b] • Elderly (aged ≥65 years)[c] • Palliative care • Chronic anaemia • Other conditions (neurology, gastro[d], rheumatology, HIV) Stratify by: • Age (≥16 yrs only) • Indigenous/non-indigenous	• Anaemia • Anaemia by Hb level	• No anaemia • Another level of anaemia	• mortality • MI/stroke • functional/performance status[e] • other morbidity specific to particular subgroup (see below)[f] <u>Cardiac subgroup</u>: • reinfarction/arrhythmias/ composite outcomes

2. What is the effect of RBC (allogeneic) transfusion on patient outcomes? *Intervention vs. Comparator = (1) vs. (1), (2) vs. (2)* [Intervention question]			
Population	Intervention	Comparison	Outcomes (primary, unless specified)
All patients Subgroups: • ACS • Cardiac • Cerebrovascular disease • Oncology • Radiotherapy patients • Malignant haematology[a] • Non-malignant haematology • Respiratory • Renal[b] • Elderly • Palliative care • Chronic anaemia[g] • Other conditions (neurology, gastro[d], rheumatology, HIV) Stratify by: • Anaemia status according to Hb level • Age • Indigenous/non-indigenous	1. RBC (allogeneic) transfusion (including dose) 2. Restrictive transfusion (e.g. Hb trigger of <70 g/L and maintained between 70 and 90 g/L)	1. No transfusion (or alternative doses) 2. Liberal transfusion (e.g. Hb trigger of <100 g/L and maintain between 100 and 120 g/L	• mortality • MI/stroke •functional/performance status[e] • transfusion-related SAEs (TACO, TRALI, other[h])

3. What is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion? [Intervention question]			
Population	**Intervention**	**Comparison**	**Outcomes** (primary, unless specified)
All patients Subgroups: • ACS • Cardiac[i] • Cerebrovascular disease • Oncology • Radiotherapy patients • Malignant haematology[a] • Non-malignant haematology • Respiratory • Renal[b] • Elderly • Palliative care • Chronic anaemia • Other conditions (neurology, gastro[d], rheumatology, HIV) Stratify: • By level and type of anaemia/baseline Hb[j] • Indigenous/non-indigenous	1. ESAs 2. Oral and/or parenteral iron therapy (IV or IM) 3. Combination of these Nb. Look at all dose regimens reported in relevant studies	No intervention or any active head-to-head (e.g., 1 vs. 2, 1 vs. 3, 2 vs. 3)	• mortality • transfusion frequency • transfusion volume (in transfused patients only) • thromboembolic events (stroke, MI, DVT, PE)[k] *Secondary outcomes* • functional/performance status[e]

4. What is the effect of fresh frozen plasma, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? *Intervention vs. Comparator = (1) vs. (1), (2) vs. (2), etc* [Intervention question]			
Population	Intervention	Comparison	Outcomes (primary, unless specified)
All patients Subgroups: • ACS • Cardiac[l] • Cerebrovascular disease • Intracranial/ocular bleeding • Oncology • Malignant haematology[a] • Non-malignant haematology • Respiratory • Renal[b] • Elderly • Palliative care • Chronic anaemia • Gastro[d], hepatic failure • Other conditions (neurology, rheumatology, HIV) Stratify by: • Bleeding/non-bleeding[m] <u>Cardiology and intracranial bleeding subgroups:</u> • Antiplatelet therapy	1. FFP 2. Cryoprecipitate 3. Platelet transfusion 4. Fibrinogen concentrate	1. No FFP 2. No cryoprecipitate 3. No platelet transfusion or different platelet dose 4. No fibrinogen concentrate	• mortality • bleeding events (major and minor) • transfusion-related SAEs (TACO, TRALI, other[h])

5. At what INR (or PT/APTT) for fresh frozen plasma, fibrinogen level for cryoprecipitate, platelet count for platelets concentrates should patients be transfused to avoid risks of significant adverse events? [Prognostic question]			
Population	**Predictor**	**Comparison**	**Outcomes** (primary, unless specified)
All patients Subgroups: • ACS • Cardiac patients who have received fibrinolytics or antiplatelet agents • Cardiac • Cerebrovascular disease • Intracranial/ocular bleeding • Oncology • Malignant haematology[a] • Non-malignant haematology • Respiratory • Renal[b] • Elderly • Palliative care • Chronic anaemia • Gastro[d], hepatic failure • Other conditions (neurology, rheumatology, HIV) Stratify by: • Bleeding/non-bleeding[m]	1. INR (PT/APTT) threshold 2. Fibrinogen level 3. Platelets level	No comparator needed	• mortality • bleeding in previously non-bleeding patients (dichotomous) • subsequent RBC transfusion incidence/volume (in bleeding patients only)

Note: The CRG consider that the cardiac, elderly/geriatric and chronic transfusion (chronic anaemia) subgroups are the most important to identify. The cardiac (heart failure and ACS) and elderly populations need to be addressed in question 1 or 2. The elderly population needs to be addressed in question 3. The chronic transfusion subgroup is addressed in specific question 1.
Note: The CRG consider that for question 5 studies of platelet transfusion in bleeding patients receiving anti-platelet or anti-fibrinolytic therapies should be searched for up to Level II evidence. All studies of cryoprecipitate and fibrinogen will be searched for up to Level II evidence.
Note: The CRG decided that question 6 should be answered using interventional studies comparing different transfusion triggers.

Abbreviations: ACS, acute coronary syndrome; ADL, Activities of Daily Living; AE, adverse event; APTT, partial thromboplastin time; AQoL, Assessment of Quality of Life; ASTH, Australasian Society of Thrombosis and Haemostasis; DASI, Duke Activity Status Index; BM, bone marrow; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; EQ5D, EuroQoL 5D; ESA, erythropoiesis stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; FFP, fresh frozen plasma; GP, general practitioner; Hb, haemoglobin; Hct, haematocrit; HIV, human immunodeficiency virus; HUI, Health Utilities Index; IADL, Instrumental Activities of Daily Living; IM, intramuscular; INR, international normalised ratio; IV, intravenous; MI, myocardial infarction; 6MWT, 6-min Walk Test; MQoL, McGill Quality of Life Questionnaire; NHP, Nottingham Health Profile; OS, overall survival; PE, pulmonary embolism; PFS, progression-free survival; PT, prothrombin time; QWB, Quality of Well-Being; RBC, red blood cell; SAE, serious adverse event; SF-12, 12-item Short Form Health Survey; SF-36, 36-question Short Form Health Survey; SR, systematic review; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related immunomodulation.
[a] Within malignant haematology subgroup, consider high dose chemo/transplant patients as a subpopulation.
[b] Within renal subgroup, consider non-end stage renal failure as a subpopulation.
[c] Consider geriatrics without comorbidities.
[d] Within gastro subgroup, consider patients excluded from the TRICC trial (i.e., patients with significant, ongoing bleeding who are not acutely compromised).
[e] Only common, validated functional and performance status instruments will be included: AQoL, Barthel ADL, 15D, DASI, ECOG, EQ-5D, FACIT, HUI2, HUI3, IADL, Karnofsky, Katz ADL, 6MWT, MQoL, NHP, QWB, RAND-36, SF-12, SF-36. Disease-specific quality of life instruments will not be included.
[f] These additional outcomes will only be addressed if the specified subgroup falls out of the literature. The literature search will not be conducted to specifically look for this subgroup.
[g] Chronic anaemia includes chronic regular transfusion/transfusion-dependant patients.
[h] Other transfusion-related SAEs includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions.
[i] The cardiothoracic subgroup was covered in the Peri-operative module. Any relevant studies identified in the Peri-operative module will be carried over to this module.
[j] Will require CRG expertise to identify 'true' vs. functional' iron deficiency.
[k] Trial-based definitions of thromboembolic events will be recorded in the Technical Report.
[l] Consider subgroup of cardiac patients who have received fibrinolytics and antiplatelet agents.
[m] Refers to prophylactic vs. therapeutic use

Table 4.1.2 Structure of research question specific to medical patient blood management

6. In specific regularly and chronically transfused patients, at what haemoglobin threshold should patients be transfused to avoid adverse outcomes? [Prognostic question]			
Population	Predictor	Comparison	Outcomes (primary, unless specified)
Regularly and chronically transfused patients (not limited to adults) Subgroups: • Thalassaemia (not sickle cell anaemia) • Myelodysplasia Stratify by: • Age (including children)	Hb threshold (however reported)		•mortality/survival •functional/performance status[a] •arterial thromboembolic events (stroke/MI)[b] *Secondary outcomes:* •transfusion incidence •transfusion volume

4.2 Appendix 2. Quality assessment

Each included study was assessed using the quality criteria for the relevant study type, as shown below. Studies were considered:

- good quality, with a low risk of bias, if they met all, or all but one, of the criteria
- fair quality, with a medium risk of bias, if they did not meet two or three criteria
- poor quality, with a high risk of bias, if they did not meet four or more criteria.

4.2.1 Systematic reviews

Study type:				Systematic review	
Citation:					
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
				Were the databases searched reported?	III
				Was more than one database searched?	III
				Were search terms reported?	IV
				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
				Were inclusion/exclusion criteria reported?	II
				Was the inclusion criteria applied in an unbiased way?	III
				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
				Was the quality of the studies reported?	III
				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
				Were the characteristics of the individual studies reported?	III
				Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
				Was a test for heterogeneity applied?	III-IV
				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Systematic review:	
				Included studies:	

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

[a] Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

[b] Error categories as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (eg, good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

[c] Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality. For quality assessment of systematic reviews, this should include a statement regarding the methodological quality of the studies included in the systematic review.

[d]Quality ratings are good, fair or poor.

Source of quality criteria: NHMRC (2000)[5]

4.2.2 Randomised controlled trials

Study type:				Randomised controlled trial	
Citation:					
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
				Was the method of randomisation reported?	III
				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
				Was a method of allocation concealment reported?	III
				Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
				Were baseline patient characteristics and demographics reported?	III
				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
				Was loss to follow-up reported?	II
				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
				Was outcome assessment blinded to treatment allocation?	III
				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
				Were the methods used for comparing results between treatment arms appropriate?	III
				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
				Were subgroup analyses reported?	III-IV
				Were subgroup analyses appropriate?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]					

[a] Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).
[b] Error categories as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (eg, good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
[c] Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality.
[d] Quality ratings are good, fair or poor.
Source of quality criteria: NHMRC (2000)[5]

4.2.3 Cohort studies

Study type:				Cohort study	
Citation:					
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
				Was loss to follow-up and exclusions from analysis reported?	II
				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
				Was outcome assessment blinded to exposure status?	III
				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
				Was follow-up long enough for outcomes to occur?	III
Comments:					
Quality rating: [Good/Fair/Poor]					

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

[a] Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

[b] Error categories as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (eg, good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

[c] Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality.

[d] Quality ratings are good, fair or poor.

Source of quality criteria: NHMRC (2000)[5]

4.3 Appendix 3. NHMRC evidence statement form

Key question(s):		**Evidence table ref:**
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some **unknown** factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guidelines?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Evidence statement matrix

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account

Component	Rating	Description
Evidence base		
Consistency		
Clinical impact		
Generalisability		
Applicability		

Indicate any dissenting opinions

Recommendation *What recommendation(s) does the guidelines development group draw from this evidence? Use action statements where possible*	**Grade** of recommendation	

IMPLEMENTATION OF RECOMMENDATION

Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines

Will this recommendation result in changes in usual care?	**YES**	**NO**
Are there any resource implications associated with implementing this recommendation?	**YES**	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**YES**	**NO**
Are the guidelines development group aware of any barriers to the implementation of this recommendation?	**YES**	**NO**

4.4 Appendix 4. Facilitated group discussion for development of practice points

4.4.1 Background

Often, there are insufficient high-quality data in the contemporary clinical literature to produce clinical guidelines with an evidence-based recommendation. Thus, there remains a role for expert opinion and consensus in guidelines development. The use of expert opinion as a form of 'evidence' requires a formal consensus development process among the guidelines developers, with rigorous rules that will lead to the same attributes of validity, reliability and applicability demanded for more rigorous evidence-based practice methodology.

4.4.2 Role of the clinical/consumer reference group

The CRG provided expert opinion for the development of practice points relevant to the recommendation being considered under the consensus process.

The consensus process was followed only for recommendations where:

- the systematic review found no Level I to IV evidence to address the relevant clinical question, or where recommendations developed by the systematic review process were ranked with a Grade D (poor) quality evidence base
- the CRG determined that additional clinical practice guidance is required for recommendations developed by the systematic review process that are graded above D.

Applying the consensus process to recommendations with Grade D (poor) evidence could result in:

- the rejection of the recommendation
- the confirmation of the recommendation
- the development of a "practice point" to supplement the recommendation, or
- rejection of the recommendation and the development of a practice point on its own.

4.4.3 Chair of CRG meetings

The Chair of CRG meetings facilitated and guided the process of reaching a consensus decision on practice points. Specifically, the Chair's role was to:

- assist the CRG in defining decisions that need to be made
- help the CRG through the stages of reaching an agreement
- keep the meeting moving
- focus discussion to the point at hand
- ensure everyone has the opportunity to participate
- test whether consensus has been reached.

The Chair helped to direct the consensus process, not its content, and did not make decisions for the CRG.

4.4.4 Pre-meeting process

Before CRG meetings, the systematic reviewer/technical writer distributed draft versions of the results of the systematic review. Where evidence was not found or the body of evidence was graded D, this was indicated in the draft report to highlight the need for the consensus process to develop practice points. In addition:

- A consensus response template and a list of numbered Grade D evidence statements for clinical questions for which no evidence could be found was developed by the systematic reviewer/technical writer and distributed to the CRG/NBA members and the systematic review expert 2 weeks in advance of the meeting in which a decision was required, using the evidence statement format proposed in the research protocol for Phase I.
- The CRG/NBA members and the systematic review expert were asked to consider and rate proposals taking into account the research literature, clinical opinion and expertise and the realities of the relevant healthcare settings.
- The completed consensus templates were sent to the systematic reviewer/technical writer a few days before the CRG meeting date for consolidation.
- The systematic reviewer/technical writer collated all responses and distributed the results 2 days before the meeting. These were then reviewed and deliberated on at the face-to-face consensus meeting.

4.4.5 Development of practice points: overview of consensus decision-making process

The process outlined below was used to develop practice points through consensus.

4.4.6 Stage 1 – Introduction

- **Describe the process.** The Chair described the consensus process, participants' roles and responsibilities, ground rules and guiding principles.
- **State where there was a need for practice point development.** The Chair described where evidence was not found or was inadequate to develop recommendations above Grade D, or where a practice point might be required to supplement recommendations.

4.4.7 Stage 2 – Open discussion

- **Clarify the practice point.** The Chair opened the floor to a general discussion and suggestions for practice point content. This time was not used for raising objections or concerns but for suggesting content for the practice point. Suggestions were recorded in the relevant section of the draft results report.
- **State concerns.** When the CRG was satisfied that the practice point was complete, the Chair provided an opportunity for concerns or issues to be raised.

4.4.8 Stage 3 – Resolve concerns

- **Review concerns.** The group reviewed any concerns raised. If the concerns were many and the time was short, the discussion on practice point development was carried over to a later meeting.
- **Resolve concerns.** The Chair had the first option to resolve the listed concerns by:

- clarifying the wording of the practice point
- changing the wording of the practice point or adding a practice point to supplement the recommendation
- explaining why the recommendation as stated was not in conflict with the group's values
- see whether those with concerns would stand aside (i.e. "have concerns, but can live with them").

4.4.9 Stage 4 – First call for consensus

- When all concerns had been resolved, the Chair called for consensus.

4.4.10 Stage 5 – Consideration of group principles and values and second call for consensus

- When concerns had been adequately discussed but remain unresolved, the group assessed how the unresolved concerns related to group principles and values.
- After considering these principles, the Chair made one of the following conclusions:
  - the member withdrew the concern, consensus was reached and a practice point could be made (or a Grade D evidence-based recommendation could be confirmed)
  - the member stood aside so a practice point could be made (or Grade D evidence-based recommendation could be confirmed), and the differing schools of thought were documented
  - the member was not willing to withdraw the concern or stand aside, and the CRG declared itself blocked—the recommendation or practice point was not accepted.

4.4.11 Guiding principles and values

These principles and values were used through the development of consensus-based practice points:

- Consensus is reached when all members of the CRG strongly agree or agree with the practice point. Consensus is not achieved on the basis of a "majority".
- The opinions of all members of the group are equally valid and important, notwithstanding that some members may have discipline-specific expert opinion.
- Where consensus is not reached (one or more members disagree or strongly disagree with the practice point), the dissenting members are allowed to present their case. This may be done immediately in the current meeting, or be carried over to the subsequent meeting to allow the members to succinctly formulate their concerns or provide other documentation or research.
- Issues of semantics, language or content, while recognised as important, should preferably not absorb discussion time within CRG meetings.
- CRG members are respectfully asked to reflect on their own values and conflicts of interests, and be mindful of the extent to which these may influence their opinions.

4.4.12 Ground rules

- Members agree to take turns speaking and not interrupt each other.

- Members agree to call each other by their first names, not “he” or “she”.
- Members agree not to blame, attack or engage in put-downs, and will ask questions of each other for the purposes of gaining clarity and understanding.
- Members agree to stay away from establishing hard positions and express themselves in terms of personal needs and interests and the outcomes that they wish to realise.
- Members agree to listen respectfully and to try sincerely to understand the other person’s needs and interests.
- Members recognise that, even when they do not agree, each of them is entitled to their own perspective.
- Members will not dwell on things that did not work in the past, but instead will focus on the future they would like to create.
- Members agree to make a conscious, sincere effort to refrain from unproductive argument, venting or narration, and agree to use their time during the meeting to work toward what they perceive to be the fairest and most constructive agreement possible.
- Members will speak up when something is not working for them during the consensus process.
- Members will request a break when they need to.
- Members will point out when they feel the Chair is not being impartial as to person and neutral as to result.
- CRG members not present at the meeting will have the opportunity to provide feedback via email when developed practice points are circulated to the entire CRG after the meeting.

4.4.13 Post-meeting process

After the CRG meeting, the systematic reviewers/technical writers consolidated the outcomes from the meeting and circulated the results of the consensus process (all resultant practice points) to all members of the CRG, the NBA and the systematic review expert (including members who were not present at the meeting), together with a consensus response template.

All CRG/NBA members and the systematic review expert were asked to consider all resultant practice points and to provide any additional concerns or suggestions for amendments to these.

The completed consensus templates and all responses were sent to the systematic reviewers for consolidation.

The systematic reviewers/technical writers collated all responses and distributed the results 2 days before the following CRG–NBA consensus meeting. These were then reviewed and amended as appropriate, and consensus for each of the practice points was ratified at the face-to-face consensus meeting.

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