Patient Blood Management Guidelines: Module 2

Perioperative

Technical Report

Volume 1a

Review of the evidence (questions 1, 2 and 4–9)

Note

This volume presents the main body of evidence found by a systematic literature review on perioperative patient blood management. Volume 2a presents the related appendixes (Appendix A to Appendix E). These two volumes cover the background, foreground and generic research questions developed for this topic, with the exception of question 3, which is presented in Volumes 1b and 2b.

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Abbreviations and acronyms

AAA	abdominal aortic aneurysm
ACC	American College of Cardiology
ACHF	acute congestive heart failure
ACS	acute coronary syndrome
ACS	American College of Surgeons
ACT	anticoagulant therapy
ACS-NSQIP	American College of Surgeons – National Surgical Quality Improvement Program
ADL	activities of daily living
ADP	adenosine diphosphate
AE	adverse event/s
AF	atrial fibrillation
AHA	American Heart Association
AKI	acute kidney injury
AMI	acute myocardial infarction
AMI	Australasian Medical Index
ANZSBT	Australian and New Zealand Society of Blood Transfusion
APTT	activated partial thromboplastin time
APT	antiplatelet therapy
ARCBS	Australian Red Cross Blood Service
ATLS	Advanced Trauma Life Support
bid	twice daily (*bis in die*)
BCC	blood conservation coordinator
CABG	coronary artery bypass graft
CAD	coronary artery disease
CADTH	Canadian Agency for Drugs and Technologies in Health
CBS	Canadian Blood Service
CHF	congestive heart failure
CI	confidence interval
CICU	coronary intensive care unit
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COPES	Canadian Orthopaedic Perioperative Erythropoietin Study
CPB	cardiopulmonary bypass

CRG	Consumer/Clinical Reference Group
CUSUM	cumulative sum
CVA	cardiovascular accident
DASI	Duke Activity Status Index
DVT	deep vein thrombosis
EACA	epsilon-aminocaproic acid
ECC	extracorporeal circulation
EF	expiratory flow
EPO	erythropoietin
ESA	erythropoiesis-stimulating agents
EWG	Expert Working Group
Fe	Iron
FEV1	forced expiratory volume in one minute
FFP	Fresh frozen plasma
FIM	Functional Independence Measure
FIS	Fatigue Inventory Scale
FUWB	Fresh unrefrigerated whole blood
FWB	Fresh whole blood
GAR	Guidelines Assessment Register
GFR	glomerular filtration rate
GI	gastrointestinal
GpIIb/IIIa	glycoprotein IIb/IIIa
Hb	haemoglobin
Hct	haematocrit
HR	hazard ratio
HSCT	haematopoietic stem cell transplantation
HTA	health technology assessment
IABP	intra-aortic balloon pump
ICU	intensive care unit
INR	international normalised ratio
IQR	interquartile range
ITT	intention to treat
iv	intravenous
LMCA	left main coronary artery
LOF	loss of function

LOS	length of stay
MACE	major cardiovascular event
MD	mean difference
MI	myocardial infarction
MOF	multiple organ failure
NA	not applicable
N/A	not assessable
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NR	not reported
NS	not significant
NSAID/s	non-steroidal anti-inflammatory drug/s
od	once daily (*omne die*)
OLT	orthotopic liver transplantation
OPCAB	off-pump coronary cardiopulmonary artery bypass
OR	odds ratio
ORP	pooled odds ratio
OT	operating theatre
PICO	population, intervention, comparator, outcome
PPO	population, predictor, outcome
PRO	population, risk, outcome
PT	prothrombin time
PTR	prothrombin time ratio
QoL	quality of life
R^2	coefficient of determination
RBC/s	red blood cell/s
RCT	randomised controlled trial
rFVIIa	recombinant factor VIIa
RIS	rapid infusion system
RR	relative risk
RTI	respiratory tract infection
S	significant
SAE	serious adverse event

SBP	systolic blood pressure
sc	subcutaneous
SD	standard deviation
SE	standard error
TAE	thromboembolic adverse event
TBC	to be confirmed
TE	thromboembolic event
THJR	total hip joint replacement
THR	total hip replacement
tid	three times a day (*ter in die*)
TIVA	total intravenous anaesthesia
TKR	total knee replacement
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
VAS	visual analog scale
WHO	World Health Organization
WMD	weighted mean difference

1 Introduction

This document presents the methods and results relating to the findings from a systematic literature review on perioperative patient blood management. It is the second volume of a technical report produced as part of the development process for the *Patient blood management guidelines: Module 2 – Perioperative*, which is the second 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 questions 1, 2 and 4–9. Volume 2a of the technical report presents the related appendixes. Volumes 1b and 2b deal with question 3.

The document *Patient blood management guidelines: Module 2 – Perioperative* 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. A National Health and Medical Research Council (NHMRC) Guidelines Assessment Register (GAR) 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, NBA and NHMRC GAR experts.

Research questions were developed for each module throughout Phases I to III, except for the critical care module. The requirement for this module was not identified until after the initial systematic review for Phase I had commenced.

Questions 1–3 are specific to perioperative transfusion (i.e. to this module); questions 4–9 are relevant to all six modules of these guidelines.

- *Question 1* – In patients undergoing surgery, what is the effect of a multidisciplinary, multimodal, programmatic approach to perioperative patient blood management on patient outcomes?
  (Interventional question)

- *Question 2* – In patients undergoing surgery, what effect does the cessation and timing of cessation of medication that affects haemostasis have on morbidity, mortality and RBC transfusion?
  (Interventional question)

- *Question 3* – In patients undergoing surgery, what is the effect of perioperative strategies that minimise blood loss on morbidity, mortality and blood transfusion?
  (Interventional question)

- *Question 4* – In patients undergoing surgery, is anaemia an independent risk factor for adverse outcomes?
  (Aetiological question)

- *Question 5* – In patients undergoing surgery, what is the effect of red blood cell (RBC) transfusion on patient outcomes?
  (Interventional question)

- *Question 6* – In patients undergoing surgery, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion?
  (Interventional question)

- *Question 7* – In patients undergoing surgery, what is the effect of recombinant activated factor VII (rFVIIa) (prophylaxis or treatment) on morbidity, mortality and transfusion rate?
  (Interventional question)

- *Question 8* – In patients undergoing surgery, what is the effect of fresh frozen plasma (FFP), cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?
  (Interventional question)

- *Question 9* – In patients undergoing surgery, at what international normalised ratio (INR (prothrombin time/activated partial thromboplastin time [PT/ APTT]) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelet concentrates should patients be transfused to avoid risks of significant adverse events?
  (Prognostic question)

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 question developed for perioperative patient blood management was 'Does choice of anaesthetic agent or technique reduce blood loss and transfusion?'

2.1.2 Research question structure

Details of research question criteria are presented in **Appendix 1** of this volume. The pre-specified populations for the generic research questions presented in **Appendix 1** were intended to identify evidence relevant to both critical bleeding/massive transfusion and perioperative patient blood management modules. Various subgroups were pre-specified for population criteria, and this was intended to identify patient groups of particular importance for each research question (**Appendix 1** in this volume). During the review of the evidence for Generic Question 6, the CRG advised that evidence for an additional patient population (non-surgical invasive procedures and minimally invasive surgical procedures) would be necessary for the module. Therefore, additional literature searches were developed for Generic Question 6 to identify relevant studies (shown in **Appendix A**, Volume 2a).

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 evidence4. 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 2a). Publication cut-off points varied from 29 April 2009 to 30 June 2009, as shown

in Table 2.1.1, below. Any future searches undertaken to revise, reuse or update these searches should take 1 April 2009 as the start date, to ensure complete coverage of the date range.

Following a review of the search results by the CRG in November 2009, the terms for some searches (specific question 2 and generic question 6) were revised to ensure inclusion of appropriate patient populations. Table 2.1.1 shows the dates on which the revised searches were conducted. The cut-off date for these searches was 30 June 2009, to better align with previous cut-off dates.

Table 2.1.1 Search dates and cut-off points

	Conducted	With cut-off	Updated	With cut-off
Specific question 1				
EMBASE.com	4/06/2009	4/06/2009	–	–
Cochrane Library Database	12/06/2009	12/06/2009	–	–
PreMedline	15/06/2009	15/06/2009	–	–
CINAHL	11/06/2009	11/06/2009	–	–
AMI	11/06/2009	11/06/2009	–	–
BMJ Clinical Evidence	18/06/2009	18/06/2009	–	–
Specific question 2				
EMBASE.com	12/06/2009	12/06/2009	28/01/2010	30/06/2009
Cochrane Library Database	18/06/2009	18/06/2009	27/01/2010	30/06/2009
PreMedline	18/06/2009	18/06/2009	–	–
CINAHL	16/06/2009	16/06/2009	21/01/2010	30/06/2009
AMI	16/06/2009	16/06/2009	–	–
Specific question 3				
Searches by IMS Ltd.				
EMBASE.com	17/06/2009	17/06/2009	–	–
Cochrane Library Database	22/06/2009	22/06/2009	–	–
PreMedline	22/06/2009	22/06/2009	–	–
CINAHL	19/06/2009	19/06/2009	–	–
AMI	19/06/2009	19/06/2009	–	–
Searches by HTA Ltd.				
Intervention 1 (acute normovolemic haemodilution)				
Embase SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
Embase RCT	3/01/2010	30/06/2009	–	–
Cochrane RCT	3/01/2010	30/06/2009	–	–
Interventions 2–4 (cell salvage)				
EMBASE SR	22/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
Intervention 2 (intraoperative cell salvage)				
EMBASE RCT	3/01/2010	30/06/2009	–	–
Cochrane RCT	3/01/2010	30/06/2009	–	–
Intervention 3 (ANH and intraoperative cell salvage)				
EMBASE RCT	3/01/2010	30/06/2009	–	–
Cochrane RCT	3/01/2010	30/06/2009	–	–
EMBASE lower level evidence	11/02/2010	30/06/2009	–	–
Intervention 4 (postoperative cell salvage)				
EMBASE RCT	3/01/2010	30/06/2009	–	–
Cochrane RCT	3/01/2010	30/06/2009	–	–
Intervention 5 (induced hypotension)				

	Conducted	With cut-off	Updated	With cut-off
EMBASE SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
EMBASE RCT	4/01/2010	30/06/2009	–	–
Cochrane RCT	4/01/2010	30/06/2009	–	–
Intervention 6 (prevention of hypothermia)				
EMBASE SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/10/2009	30/06/2009	–	–
EMBASE RCT	5/01/2010	30/06/2009	–	–
Cochrane RCT	5/01/2010	30/06/2009	–	–
Intervention 7 (point-of-care testing)				
EMBASE SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
EMBASE RCT	2/02/2010	30/06/2009	–	–
Cochrane RCT	2/02/2010	30/06/2009	–	–
EMBASE lower level evidence	8/04/2010	30/06/2009	–	–
Intervention 8 (antifibrinolytics)				
EMBASE SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
EMBASE RCT (desmopressin)	16/02/2010	30/06/2009	–	–
Cochrane RCT	16/02/2010	30/06/2009	–	–
EMBASE RCT (aminocaproic and tranexamic acid)	24/02/2010	30/06/2009	–	–
Intervention 9 (patient positioning)				
EMBASE SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
EMBASE RCT	3/01/2009	30/06/2009	–	–
Cochrane RCT	3/01/2009	30/06/2009	–	–
Intervention 10 (autologous transfusion)				
EMBASE SR	22/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
EMBASE RCT	3/01/2010	30/06/2009	–	–
Cochrane RCT	3/01/2010	30/06/2009	–	–
Quality of life search (all interventions)				
EMBASE lower level evidence	14/02/2010	30/06/2009	–	–
Generic question 1				
EMBASE.com	29/04/2009	29/04/2009	–	–
Cochrane Library Database	14/05/2009	14/05/2009	–	–
PreMedline	14/05/2009	14/05/2009	–	–
CINAHL	14/05/2009	14/05/2009	–	–
AMI	26/06/2009	26/06/2009	–	–
Generic question 2				
EMBASE.com	13/05/2009	13/05/2009	–	–
Cochrane Library Database	13/05/2009	13/05/2009	–	–

	Conducted	With cut-off	Updated	With cut-off
PreMedline	18/05/2009	18/05/2009	–	–
CINAHL	28/05/2009	28/05/2009	–	–
AMI	11/06/2009	11/06/2009	–	–
Generic question 3				
EMBASE.com	27/05/2009	27/05/2009	–	–
Cochrane Library Database	21/05/2009	21/05/2009	–	–
PreMedline	28/05/2009	28/05/2009	–	–
CINAHL	14/05/2009	14/05/2009	–	–
AMI	14/05/2009	14/05/2009	–	–
Generic question 4				
EMBASE.com	24/06/2009	24/06/2009	–	–
Cochrane Library Database	24/06/2009	24/06/2009	–	–
PreMedline	24/06/2009	24/06/2009	–	–
CINAHL	23/06/2009	23/06/2009	–	–
Generic question 5				
EMBASE.com	25/06/2009	25/06/2009	–	–
Cochrane Library Database	25/06/2009	25/06/2009	–	–
PreMedline	25/06/2009	25/06/2009	–	–
CINAHL	26/06/2009	26/06/2009	–	–
AMI	30/06/2009	30/06/2009	–	–
Generic question 6				
EMBASE.com	28/06/2009	28/06/2009	4/01/2010	30/06/2009
Cochrane Library Database	28/06/2009	28/06/2009	4/01/2010	30/06/2009
PreMedline	28/06/2009	28/06/2009	–	–
CINAHL	30/06/2009	30/06/2009	6/01/2010	30/06/2009
AMI	30/06/2009	30/06/2009	6/01/2010	30/06/2009

AMI, Australasian Medical Index; CINAHL, Cumulative Index to Nursing and Allied Health Literature; EMBASE, Excerpta Medica Database; RCT, randomised controlled trial; SR, systematic review

Search strategies for primary and secondary databases were developed in consultation with a specialist search strategist. All strategies were based on the PICO, PPO or 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 2a).

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 2a).

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.

2.3 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 2a). Examples of reasons for exclusion in this circumstance include different systematic reviews reporting the same primary studies, and inadequate data reporting. In addition, there were late exclusions after an internal peer review and quality assurance process discovered studies that had been incorrectly included: Volume 2 Appendix B10.

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 2.4.1**). 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 evidence2 (**Table 2.4.2**). 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 2.4.1**.

Table 2.4.1 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)2.

[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 utilised. 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 2.4.2 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

Dimension	Definition
	the potential of each included study to adequately answer a particular research question and indicates the 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)2.

2.4.1 Quality appraisal

The methodological quality of the included studies was assessed using the criteria presented in **Appendix 3** of this volume5. 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 2a).

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 guidelines3. 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 2a).

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 recommendations2. Assessment of the body of evidence considers the dimensions of evidence of studies relevant to that recommendation (**Table 2.4.2**). 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.

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

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 2.5.1**). 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 2.5.1** were rated according to the matrix shown in **Table 2.5.2**. 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 2.5.1 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) (Table 2.4.1). 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).2

Table 2.5.2 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)2

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 (outlined in **Table 2.5.2)**. Definitions of the NHMRC grades of recommendations are presented in **Table 2.5.3**. 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 2.5.3 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)2.

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 2a).

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 Results of systematic review

3.1 Question 1

In patients undergoing surgery, what is the effect of a multidisciplinary, multimodal, programmatic approach to perioperative patient blood management on patient outcomes? (referred to as PO1)

3.1.1 Summary of evidence

Methods

Only studies that addressed both multimodal and multidisciplinary programmatic approaches to blood management were included for data extraction. There were seven studies included overall; four of these were identified from the systematic review process (see **Appendix C**, Volume 2a), and three were included following recommendation by the Clinical/Consumer Reference Group (CRG).

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for this research question.

While no published cost-effectiveness analysis on the use of a multidisciplinary, multimodal perioperative patient blood management program was identified in the literature search for this research question, two studies[29, 30] published information about program costs and savings.

Level I evidence

A Level I study[27] that examined the effect on patient outcomes of a multidisciplinary, multimodal, programmatic approach to perioperative patient blood management was identified from the literature search. The review included an opinion and proposed a series of recommendations related to the use of a multimodal, multidisciplinary approach to blood management. A description of the findings of the systematic review is included in **Table 3.1.1**.

Table 3.1.1 Summary of Level I evidence

Author	Study type Study quality	Population	Outcomes
Ferraris et al (2007)[27]	Systematic review *Poor*	Cardiac surgery patients	Recommendations for blood transfusion and blood conservation algorithms, prophylaxis, interventions to limit blood transfusion, indications for blood transfusion, causes of blood transfusion after cardiac operations and risks and benefits of blood transfusion

Results of Level I studies

Ferraris and colleagues[27] reviewed all available published evidence related to blood conservation during cardiac operations. Sources of evidence included randomised controlled

trials (RCTs), published observational information, and case reports. Methods from the American Heart Association/American College of Cardiology (AHA/ACC) *Manual for guideline writing committees* were used to identify the level of evidence available for each of the blood conservation interventions. After considering the level of evidence, recommendations were made regarding each intervention using the AHA/ACC classification scheme.

The review systematically addressed eight questions and made 57 recommendations concerning the use of a multimodal blood conservation program. Of the 57 recommendations, one directly addressed the use of a multidisciplinary, multimodal, programmatic approach to perioperative patient blood management. This recommendation stated that a multimodal approach to perioperative patient blood management, involving multiple stakeholders, institutional support and enforceable transfusion algorithms, supplemented with point-of-care testing and efficacious blood conservation interventions, reduces the need for, or limits, blood transfusions and provides optimal blood conservation for patients undergoing cardiac surgery. The stakeholders included in the recommendation were not described. Other recommendations described specific interventions that could comprise separate components of multidisciplinary, multimodal, programmatic approaches[27]. These recommendations are not discussed because they fell outside the scope of this research question.

The recommendation regarding implementation of a multidisciplinary, multimodal, programmatic approach was based on Level A evidence (regarded as multiple [3–5] population groups evaluated and general consistency of direction and magnitude of effect), as assigned by the authors[27]. The definitions of included population groups were not reported. Furthermore, there was no information presented that provided a clear link between this recommendation, its grade (Level A), and evidence for a multidisciplinary, multimodal, programmatic approach.

Level II evidence

No Level II evidence examining the effect of a multidisciplinary, multimodal programmatic approach to perioperative blood management was identified from the literature search.

Level III evidence

Five Level III studies were identified that compared patient outcomes before and after implementation of multidisciplinary, multimodal programs. All five were comparative studies with historical control groups. The main characteristics of the studies are summarised according to whether they involved cardiac[28–31] or noncardiac[28,30,32] surgery in **Table 3.1.2** and **Table 3.1.3**, respectively. Further details are presented in **Appendix F** (Volume 2). No quality of life outcomes were reported in the identified Level III studies.

Level IV evidence

One Level IV noncardiac study was identified (**Table 3.1.3**). This case report describes a multidisciplinary approach to a second reconstructive back surgery[33]. Results pertaining to quality of life were not reported in this Level IV study[33].

Table 3.1.2 Summary of Level III evidence: Cardiac surgery

Author Country	Study type Study quality	Population (N)	Intervention	Comparator	Outcomes
Freedman et al (2005)[28] Canada	Comparative study with historical control; outcomes compared pre- and post-multidisciplinary, multimodal program implementation Multicentre study (23 hospitals) *Poor*	CABG surgery patients (N=300 at each time point: baseline, 12, 18 and 24 months)	Introduction of a blood conservation program	Standard practice (before intervention)	LOS, infection rates, mortality
DeAnda et al (2006)[29] USA	Comparative study with historical control; outcomes compared pre- and post-multidisciplinary, multimodal program implementation Single centre study *Poor*	Cardiothoracic surgery patients (N=521, pre-multidisciplinary, multimodal program; 1996 to 1999; N=477, post-multidisciplinary, multimodal program, 1999 to 2003	Introduction of a blood conservation program	Standard practice (before intervention)	Postoperative haematocrit, transfusions rates, major adverse cardiac events
Freedman et al (2008)[30] Canada	Comparative study with historical control; outcomes compared pre- and post-multidisciplinary, multimodal program implementation Multicentre study (23 hospitals) *Poor*	CABG surgery patients (NR, if on- or off-pump CABG) (N=274 at baseline; 271 at 12 months; 294 at 18 months and 275 at 24 months)	Introduction of a blood conservation program	Standard practice (before intervention)	LOS, infection rates, mortality
Brevig et al (2009)[31] USA	Comparative study with historical control; outcomes compared pre- and post-multidisciplinary, multimodal program implementation Single centre study *Poor*	Cardiac surgery patients N=2531,2003 -07) N=530 (2003); 479 (2007)) CABG subgroup: (N=1617, 2003-07 N=377 (2003); 281 (2007))	A data driven, multidisciplinary effort to decrease allogeneic RBC transfusion in a community hospital. Numerous innovations in treatment protocols to be implemented and evaluated	Standard practice (before intervention)	Blood utilisation, mortality

Abbreviations: AAA, abdominal aortic aneurysm; CABG, coronary artery bypass surgery; CPB, cardiopulmonary bypass; LOS, length of stay; NR, not reported; RBC, red blood cell

Table 3.1.3 Summary of Level III and IV evidence: Noncardiac surgery

Author Country	Study type Study quality	Population (N)	Intervention	Comparator	Outcomes
Level III					
Bui et al (2002)[32] Canada	Comparative study with historical control; outcomes compared pre- and post-multidisciplinary, multimodal program implementation Single centre study *Poor*	Patients undergoing elective liver resection (N=151; between 1980 and 1999)	Minimal blood loss program	Standard practice (before intervention)	Blood loss, patients requiring transfusion, units of homologous blood transfusion, morbidity, mortality, complications
Freedman et al (2005)[28] Canada	Comparative study with historical control; outcomes compared pre- and post-multidisciplinary, multimodal program implementation Multicentre study (23 hospitals) *Poor*	Patients undergoing knee arthroplasty (N~1200 at each time point), or AAA surgery (N~300 at each time point) (baseline, 12, 18 and 24 months)	Introduction of a blood conservation program	Standard practice (before intervention)	LOS, infection rates, mortality
Freedman et al (2008)[30] Canada	Comparative study with historical control; outcomes compared pre- and post-multidisciplinary, multimodal program implementation *Poor*	Patients undergoing knee arthroplasty (N=1088 at baseline; 1137 at 12 months; 1078 at 18 months; 1127 at 24 months) or AAA surgery (N=287 at baseline; 292 at 12 months; 236 at 18 months; 232 at 24 months)	Introduction of a blood conservation program	Standard practice (before intervention)	LOS, infection rates, mortality
Level IV					
Bolan et al (2001)[33] USA	Case report *Poor*	Patient with von Willebrand disease and a history of heavy surgical bleeding N=1	Patient with von Willebrand disease, flatback syndrome, and a history of heavy surgical bleeding	NA	Estimated blood loss, replacement autologous RBC, replacement autologous plasma, replacement autologous plateletpheresis, Humate P use

Abbreviations: AAA, abdominal aortic aneurysm; LOS, length of stay; NA, not applicable; RBC, red blood cell

Results of Level III and IV studies

The results of the six Level III and IV included studies are presented in **Table 3.1.4** and **Table 3.1.5**, which represent outcomes after cardiac and noncardiac surgery respectively. No studies directly reported the effect on patient outcomes of a multidisciplinary, multimodal programmatic approach to perioperative blood management. Furthermore, because a multidisciplinary, multimodal approach was implemented as the overall intervention, it was not possible to determine whether any particular aspects of the overall intervention were more responsible for changing outcomes than others. However, a common feature of these studies was introduction of a coordinator[28,30,31] or committee[29] with responsibility for perioperative patient blood management.

For each included study, the clinical effectiveness of implementing multidisciplinary, multimodal programmatic approaches to perioperative blood management was investigated by comparing outcomes before and after program implementation. Each study detailed initiation of a patient blood management program designed to decrease blood use during surgery and reported effects on outcomes such as mortality, morbidity, and length of stay (LOS) measured during the duration of the study. The effect of the introduced treatment program was established by comparing measured outcomes among patients receiving care after initiation of the program with those receiving care before its initiation. Overall, study results showed that a multidisciplinary, multimodal approach could be beneficial in reducing blood utilisation in a perioperative setting.

Results of Level III cardiac studies

Results of the Level III evidence cardiac studies are presented in **Table 3.1.4**.

Table 3.1.4 Results for Level III evidence: Cardiac studies

Author	Outcome	Pre-Multidisciplinary, Multimodal Program Value	Post-Multidisciplinary, Multimodal Program Value	Statistical significance
DeAnda et al (2006)[29]	All patients transfused	1996 to 1999 (N=521) 79%	1999 to 2003 (N=477) 39%	<0.05
	RBC transfused	35%	16%	<0.05
	Preoperative Hb (g/dL)	12.2	12.2	NS
	ICU entry Hb (g/dL)	10.8	9.2	<0.05
	Discharge Hb (g/dL)	10.8	9.2	<0.05
	Any adverse outcome[a]	51.8%	33.5%	<0.05
	Myocardial infarction	0.5%	0.4%	NS
	Respiratory failure	9.7%	8.3%	NS
	Infection	5.9%	5.4%	NS
	Death	7.7%	7.3%	NS
	Balloon pump required	15%	6.1%	<0.05
	≥ 2 catecholamines	43.1%	23.3%	<0.05
	Renal failure	5.1%	2.8%	<0.05
	Re-operation for bleeding	4.8%	1.4%	<0.05
Freedman et al (2008)[30]	CABG patients[b] Proportion of patients who received transfusion with allogeneic RBC	Baseline (N=274) ~60%	24 month time point (N=275) ~43%	<0.0001
	CABG patients[b] Units of allogeneic blood per patient who received transfusion	~3.25	~2.75	<0.001
	CABG patients[b] Units of allogeneic blood per patient overall	~2.0	~1.2	<0.0001
	CABG patients Infection LOS (days) Death	 10.95% 10.78 (9.80, 11.76) 2.19%	 5.82% 7.81 (6.83, 8.76) 0.73%	 0.620 <0.001 0.1888
Brevig et al (2009)[31]	Incidence of RBC transfusion Observed Predicted OR	2003 (N=530) 43.2% 53.9% 0.6	2007 (N=479) 18% 52.9% 0.1	NR

Author	Outcome	Pre-Multidisciplinary, Multimodal Program Value	Post-Multidisciplinary, Multimodal Program Value	Statistical significance
	95% CI of OR	(0.6, 0.68)	(0.08, 0.14)	
	Units of RBC transfused Mean per recipient Mean per patient population	 3.3 1.4	 3.0 0.5	 NR NR
	Units of other blood products (mean per patient population) Platelets FFP Cryoprecipitate	CABG subgroup N=377 0 0 0	CABG subgroup N=281 0 0.007 0	 NR NR NR
	Discharge haematocrit	NA	28.8 ± 3.8	NR
	Mortality	0.8%	2.5%	0.452[c]

Abbreviations: CABG, coronary artery bypass graft; CI, confidence interval; Hb, haemoglobin; FFP, fresh frozen plasma; ICU, intensive care unit; LOS, length of stay; NA, not applicable; NR, not reported; NS, not significant; OR, odds ratio; RBC, red blood cell
[a] Any adverse outcome includes MI, respiratory failure, infection, death, balloon pump requirement, need for two or more catecholamines, renal failure and re-operation for bleeding [b] Data presented graphically. These values are estimates from the graphs. [c] χ^2 test

Three studies were identified that described patient outcomes associated with implementation of a multidisciplinary, multimodal perioperative blood conservation strategy for cardiac surgery. Each study reported the use of a different multidisciplinary, multimodal program.

DeAnda and colleagues[29] reported effects on patient outcomes of introducing a blood reduction program for perioperative management of patients undergoing cardiac surgery. The program was multimodal and multidisciplinary in its approach. The approach consisted of inception and implementation of a new treatment algorithm and transfusion guidelines for the cardiothoracic surgical service; establishment of a multidisciplinary team committed to reducing the use of blood in a cardiac surgery setting; and incorporation of a blood utilisation committee. The blood utilisation committee was responsible for reviewing transfusion events against established numerical triggers. The study results showed that implementing the committee and involving a multidisciplinary team in conjunction with a treatment algorithm led to significant reduction in use of blood products. When no detrimental effects were observed with use of the new algorithm, the program was expanded, enhanced and offered to the rest of the healthcare system. The results from this study are shown in **Table 3.1.4**.

Brevig and colleagues[31] reviewed a blood conservation initiative conducted between 2003 and 2007. This initiative was a data-driven, multidisciplinary effort to decrease allogeneic RBC transfusion in a community hospital. Numerous innovations in treatment protocols were implemented and evaluated. Clinical data from 2003 to 2007 were presented. Yearly review of outcomes led to evolution of clinical practice and lowered transfusion rates. Data were reported for all cardiac surgery. Additional data were reported separately for patients who

underwent coronary artery bypass graft (CABG) with cardiopulmonary bypass (CPB)[31] to compare specific patient characteristics and risk adjusted outcomes as RBC use decreased.

A total of 2531 consecutive cardiac surgeries from 2003 to 2007 were retrospectively evaluated. The Transfusion Risk Understanding Scoring Tool developed by Alghamdi and colleagues was chosen to calculate the predicted risk of transfusion[34]. Predictors included age, sex, weight, preoperative haemoglobin and creatinine levels, re-operation, urgency and type of operation. Preoperative anaemia, especially when combined with advanced age or chronic renal insufficiency, were reported as common indications for consulting a blood conservation coordinator. Although there are no agreed indications, each surgeon decided who of their patients would benefit from referral to a blood conservation coordinator. The blood conservation coordinator evaluations included fasting ferritin, transferrin, serum iron, and complete blood count to ensure that adequate iron stores were available for RBC production. Anaesthesia techniques and fluid administration were not standardised among cardiac anaesthesiologists. Typical anaesthetic agents used were midazolam, fentanyl citrate, isoflurane, propofol, and neuromuscular blockade. During the study period, aprotinin use was low. Those patients who did not receive aprotinin received aminocaproic acid, with dose ranging from 7.5 to 10.0 g, both as a loading dose and in the pump prime, at the discretion of the anaesthesiologist. All surgeons made concerted efforts to standardise surgical techniques and follow agreed protocols. Only patients who had high risk of blood transfusion, or who did not accept blood products, routinely had cell saver technology applied. When a cell saver was used, a portion of blood remaining in the cardiopulmonary bypass circuit was processed. Otherwise, all blood in the circuit was returned to the patient. In every case, the techniques used were vacuum-assisted venous drainage with dry 3/80 tubing, 10-foot arteriovenous loop, retrograde autologous prime, and drainage of saline prime from the cardioplegia circuit. Postoperative care was provided by the surgeons and physician assistants. Other subspecialists were consulted by surgeons as needed. The results of this study are shown in **Table 3.1.4**. Data are presented for outcomes in 2003 (before the multidisciplinary, multimodal program was implemented) and 2007 (following program implementation).

Freedman and colleagues[28,30] reported changes in blood management practice at 23 hospitals in Ontario, Canada, after a multidisciplinary transfusion program was implemented. The program aimed to enhance transfusion practice outside the blood transfusion laboratory, to promote blood conservation in surgical patients, and to reduce allogeneic RBC use. Part of the program involved establishing a transfusion coordinator role to manage the blood conservation program, collection and analysis of program data, education of patients, families and staff, and coordination of institutional and regional activities. Management of the blood conservation program included provision of ongoing support for the mission of the Provincial Blood Conservation Program at the hospital, liaison with personnel in relevant departments, enrolment of eligible patients in suitable programs, and liaison with staff to follow up the blood conservation strategy employed. These strategies ensured appropriate reporting of blood conservation to the transfusion review and monitoring of transfusion informed consent. The coordinator also liaised with the blood transfusion laboratory to collect appropriate data and facilitate referrals to appropriate services required (e.g. the

Canadian Blood Service's autologous program, host institutions autologous programs, and the epoietin assistance line). Detailed information was collected from a defined number of consecutive patients admitted for knee arthroplasty, abdominal aortic aneurysm (AAA) and CABG. Results from the most recent Freedman et al article[30] are shown in **Table 3.1.4** and **Table 3.1.5**.

Blood utilisation

Three studies[29–31] were identified that examined the effect of multimodal, multidisciplinary blood management approaches on blood utilisation for patients undergoing cardiac surgery. DeAnda[29], Brevig[31] and their respective colleagues reported the effect of program implementation for all cardiac patients undergoing transfusion; and Freedman et al[30] and Brevig[31] reported results for patients undergoing CABG.

DeAnda et al[29] showed that the use of a multimodal, multidisciplinary approach significantly reduced the numbers of patients transfused, from 79% pre-program to 39% post-program implementation ($p<0.05$) in cardiac patients. In line with this finding, RBC transfusions were also shown to decrease significantly from 35% pre-program to 16% post-program implementation ($p<0.05$). Similarly, Brevig et al[31] showed a significant reduction in the incidence of blood transfusion with the use of a multimodal, multidisciplinary blood management program. The predicted incidence of RBC transfusions for 2003 and 2007 was 53.9% and 52.9% respectively. However, the observed change in the incidence of blood transfusion was from 43.2% in 2003 (pre-program implementation) to 18% in 2007 (post-program implementation). The odds ratio (OR) for the likelihood of a RBC transfusion before program implementation in 2003 was 0.6 (95%CI: [0.46, 0.68]) (observed versus predicted RBC transfusion); following program implementation, the OR decreased to 0.1 (95%CI: [0.08, 0.14]) in 2007. A similar reduction in the incidence of RBC transfusion was reported in the CABG subgroup from 38.5% to 13.5% in 2003 and 2007. The likelihood of receiving a transfusion for a CABG procedures reduced from 60% to 10% over the same period: OR 2003 0.6(95% CI: [0.4, 0.7]) ; OR 2007 0.1(95%CI:[0.1, 0.2]. Consequently, the mean number of RBC units transfused per patient population decreased from 1.44 to 0.5, from 2003 to 2007. The overall decrease in the incidence of transfusion was accompanied by a small reduction in the mean number of units of blood transfused per patient (3.33 units pre-program versus 3.00 units post-program implementation).

In support of these findings, Freedman and colleagues[30] also showed a reduction in blood transfusion requirements after implementation of a multimodal, multidisciplinary blood management program specifically for patients undergoing CABG. The proportion of patients reported to receive allogeneic RBC transfusion decreased significantly, from approximately 60% to 43% ($p<0.0001$). The number of units of allogeneic blood transfused per patient who received transfusion was also shown to decrease from approximately 3.25 units to 2.75 units ($p<0.001$). Similarly, the number of units of allogeneic blood per patient overall was demonstrated to decrease significantly post-program implementation, from 2 units per patient to 1.2 units per patient ($p<0.001$). It is noteworthy that CABG patient groups were similar at both baseline and 24 month time points[30] (data not shown).

DeAnda et al[29] also reported pre- and postoperative haemoglobin levels. Although preoperative haemoglobin levels remained unchanged at 12.2 g/dL pre- and post-program implementation, haemoglobin levels at both intensive care entry and discharge decreased from 10.8 g/dL pre-program to 9.2 g/dL post-program implementation. Despite the use of blood conservation strategies, there was a modest decrease in haemoglobin levels. Furthermore, results reported by DeAnda et al indicated that there was no negative impact on clinical outcomes among patients in the study[29].

Mortality

Three studies reported mortality among patients undergoing cardiac surgery[29–31]. Of these, none reported statistically significant changes in mortality when comparing patients pre- and post-implementation of the blood management program. These results should be interpreted with caution because these studies were underpowered for mortality rates. DeAnda et al[29] reported decreased mortality (from 7.7% to 7.3%) after implementation of a multidisciplinary, multimodal perioperative blood management program. Freedman et al[30] also reported a non-significant decrease in mortality rates (2.19% to 0.73%) associated with implementation of a multimodal, multidisciplinary perioperative blood management program. In contrast, Brevig et al[31] reported an increased mortality rate (0.8% to 2.5%, pre- versus post-program implementation) in patients who underwent isolated CABG with CPB. Although this change was not statistically significant, it represents a threefold increase in mortality. The study authors reported that the mortality increase was confined to CABG patients who underwent RBC transfusion; five of seven patients who died underwent RBC transfusion either intraoperatively or early in the postoperative period. Cumulative sum (CUSUM) analysis showed that the reported increase in mortality for all CABG patients was limited to those who underwent RBC transfusion[31] (data not shown). It is possible that the five patients who died were at higher risk than other patients, which would explain the need for RBC transfusion.

In addition to underpowering, several variables could account for the difference in findings on the impact of multidisciplinary, multimodal program implementation on cardiac surgery mortality rates. Freedman et al[30] did not report the types of CABG surgery undergone by patients; nor did De Anda et al[29] report types of cardiothoracic surgery. The type of cardiac surgery might account for different findings concerning the impact of a multidisciplinary, multimodal program on mortality. There is also likely to be variation in patient blood management within the multidisciplinary, multimodal program. Freedman et al[30] conducted a multicentre study, whereas Brevig[31] and De Anda[29] and their respective colleagues conducted single centre investigations.

Therefore, given the difference in direction of effect on mortality rates and study heterogeneity, the effect of implementation of a multidisciplinary, multimodal program on mortality among cardiac surgery patients is unclear.

Adverse outcomes

DeAnda et al[29] identified significant decreases in adverse outcomes among patients undergoing some form of cardiac surgery. The authors found that adverse events, such as

use of balloon pumps or two or more catecholamines, renal failure, and the need for re-operation for bleeding were all significantly reduced after implementation of a multimodal, multidisciplinary perioperative blood management program.

Infection

Infection rates were measured in two studies that involved patients undergoing cardiac surgery. Both DeAnda et al[29] and Freedman et al[30] reported decreases in infection rates. DeAnda et al[29] showed a reduction in infection rates of 5.9% to 5.3%, pre- versus post-program implementation; and Freedman et al[30] reported a 10.95% to 5.82% reduction in infection rates pre- versus post-implementation. However, neither reduction was reported to be significant.

Length of stay in hospital

Freedman et al[30] measured the length of hospital stay among patients who underwent cardiac surgery. Length of stay was reported to be reduced significantly to 7.81 days post-implementation of a multimodal, multidisciplinary perioperative patient blood management program, from 10.78 days pre-program implementation ($p<0.001$).

Other reported adverse outcomes

Myocardial infarction (MI), respiratory failure, renal failure and re-operation for bleeding were assessed by DeAnda et al[29]. Although no significant changes were reported for either MI or respiratory failure with the implementation of a multimodal, multidisciplinary perioperative blood management program, re-operation for bleeding (4.8% versus 1.4%, $p<0.05$) and renal failure (5.1% versus 2.8%, $p<0.05$) were reported to be significantly decreased post-program implementation.

Cost Effectiveness

DeAndra et al[29] reported that no additional investment was required to implement the program. The authors developed a model of savings derived from units not transfused, which took into consideration savings resulting from fewer complications and reduced risks. A total savings of US$1.4M was derived from reductions in: units and cross matching (US$295K); fixed overhead (US$274K); and adverse event avoidance (US$863K). Freedman et al[30] estimated cost savings taking into account reduction in costs for units of blood avoided through fewer patients transfused and fewer units of blood transfused per patient, reduction in length of stay and reduced work in hospital blood transfusion laboratories and nursing units. The authors did not include costs associated with adverse event avoidance. Using an activity based analysis that included the cost of the program implementation (CAD$1.8M annually), the authors reported a total cost savings of CAD$14.95M.

Results of Level III and IV noncardiac studies

The results of Level III and IV noncardiac studies are presented in **Table 3.1.5**.

Table 3.1.5 Results for Level III and IV evidence: Noncardiac studies

Author	Outcome	Pre-multidisciplinary, multimodal program value	Post-multidisciplinary, multimodal program value	Statistical significance
Level III evidence				
Bui et al (2002)[32]		1980 to 1990 (N=49)	1991 to 1999 (N=102)	
	Mean no. of units homologous blood transfused	13.7 ± 1.8	2.3 ± 0.4	<0.001
	Mean no. of autologous blood transfused	0	0.72 ± 0.2	<0.001
	Mean total no. of units transfused	13.7 ± 1.8	3.0 ± 0.4	<0.001
	Patients receiving $\geq$1 units of homologous blood			
	Major resection	96.9%	29.5%	<0.001
	Minor resection	82.3%	19.5%	<0.001
	Total	91.8%	25.5%	<0.001
	Morbidity			
	Haemorrhage	8.2%	2.9%	0.159
	Bile leak	12.2%	11.8%	0.949
	Sepsis	23.6%	8.8%	<0.001
	Overall morbidity	57.1%	25.5%	<0.001
	Mortality	10.2%	4.9%	<0.0001
Freedman et al (2008)[30]		Baseline (N=1089)	24 month time point (N=1127)	
	Knee arthroplasty patients[a]			
	Proportion of patients who underwent allogeneic RBC transfusion	~25%	~18%	<0.0001
	Knee arthroplasty patients[a]			
	Number of units of allogeneic blood per patient who underwent transfusion	~2.0	~2.0	NS
	Knee arthroplasty patients[a]			
	Number of units of allogeneic blood per patient overall	~0.5	~0.3	<0.0001
	Knee arthroplasty patients			
	Infection	3.76%	2.04%	0.0730
	LOS (days)	7.16 (6.54, 7.47)	6.25 (5.64, 6.86)	0.0888
	Death	0.09%	0.18%	0.2142

Author	Outcome	Pre-multidisciplinary, multimodal program value	Post-multidisciplinary, multimodal program value	Statistical significance
		Baseline (N=287; AAA patients[a])	24 month time point (N=232; AAA patients[a])	
	AAA patients[a] Proportion of patients who underwent allogeneic RBC transfusion	~50%	~45%	<0.05
	AAA patients[a] Number of units of allogeneic blood per patient who underwent transfusion	~4.25	~3.8	NS
	AAA patients[a] Number of units of allogeneic blood per patient overall	~2.1	~1.8	NS
	AAA patients Infection LOS (days) Death	 9.76% 12.91 (10.56, 15.26) 2.44%	 11.64% 8.07 (5.45, 10.69) 1.29%	 0.8797 0.0576 0.1640
Level IV evidence				
Bolan et al (2001)[33]	Estimated blood loss Replacement autologous RBC Replacement autologous plasma Replacement autologous plateletpheresis product Humate P administered	–	 5 L 9 units 6 units 2 units 17,000 units	–

Abbreviations: AAA, abdominal aortic aneurysm; LOS, length of stay; NS, not significant; RBC, red blood cells
a Data presented graphically. These values are estimates from the graphs

Freedman et al[28,30] reported on AAA surgery and knee arthroplasty as well as cardiac surgery (**Table 3.1.5**). Patient groups were similar at baseline and 24-month time points[30] for both AAA and knee arthroscopy (data not shown).

Bui and collegues[32] analysed the impact of a systematic protocol aimed at reducing intraoperative blood loss and homologous blood transfusion associated with hepatic resection. Clinical data were collected from 151 elective liver resections performed between 1980 and 1999. Blood loss and anaesthesia data were collected retrospectively from the anaesthetic intraoperative patient record. Strategies implemented in 1991 included preoperative autologous blood donation, low central venous pressure anaesthesia, aprotinin administration, ultrasonic dissection, hepatic vascular inflow occlusion and a cell saver. The new strategy included developing a programmatic approach to liver resection that included cooperation and coordination between the anaesthetist and surgeon in both the preoperative (with autologous blood donation), and intraoperative period (with aprotinin

administration and maintenance of low central venous pressure). Results are reported in **Table 3.1.5**. Data are presented for two groups: pre-implementation of the multidisciplinary, multimodal program (1980 to 1990) and post-implementation (1991 to 1999). Patient groups pre- and post-implementation were similar in terms of demographics, indications for operation or scope of the resection[32] (data not shown).

Bolan and colleagues[33] described a case report on a multidisciplinary approach to repeat reconstructive back surgery for a patient with von Willebrand disease, flatback syndrome and a history of heavy surgical bleeding. Although this Level IV study was not comparative, it indicates how a multidisciplinary team can minimise blood loss. Bolan et al[33] describes a surgical procedure where anterior and posterior spine fusions were performed during a 14-hour period. Humate-P was administered perioperatively, based on assessment of baseline Factor VIII and von Willebrand factor levels, plasma volume, half-life of infused Humate-P and the anticipated risk and tolerance for bleeding.

Blood utilisation

Blood utilisation was measured by Freedman[30] , Bui[32] andBolan[33], and their respective colleagues. Bui et al[32] and Freedman et al[30] reported the change in homologous and autologous blood use. Freedman et al[30] reported in patients undergoing AAA surgery and knee arthroplasty and Bui et al[32] reported outcomes in patients undergoing liver resection.. Both Freedman et al[30] and Bui et al[32] reported significant decreases in blood utilisation.

Freedman et al[30] reported a significant reduction in the proportion of knee arthroplasty and AAA surgery patients who underwent allogeneic RBC transfusion ($p<0.001$ and $p<0.05$, respectively). The number of units of allogeneic blood per patient who underwent transfusion was not found to change significantly for both knee arthroplasty and AAA surgery patients, but the number of units of allogeneic blood per knee arthroplasty patient was reduced significantly overall from 5.0 to 3.0 units ($p<0.001$), and was reduced from 2.1 to 1.8 (not significant) in AAA surgery patients. Similarly, Bui et al[32] applied a multimodal, multidisciplinary approach and reported that the mean number of units of homologous blood transfused was reduced from 13.7 to 2.3 units ($p<0.001$). The mean number of autologous blood units administered increased significantly, from 0 to 0.72 units ($p<0.001$), and the mean total number of units of blood was reduced from 13.7 to 3.0 units ($p<0.001$).

Bolan et al[33] measured blood utilisation, but because this was a case study, comparison could not be made. It was reported that 5 L of blood was lost by a patient with von Willebrand disease, flatback syndrome and a history of heavy surgical bleeding during reconstructive back surgery. In this study, 9 units of replacement autologous RBC, 6 units of replacement autologous plasma, 2 units of replacement autologous plateletpheresis product and 17,000 units of antihaemophilic factor/von Willebrand factor complex were administered. This surgery was deemed a success by the study authors.

Mortality

Freedman[30and] Bui[32] and their respective colleagues, reported the effect of a perioperative multidisciplinary, multimodal program on mortality rates in noncardiac surgery. Like the

results for cardiac surgery, reported outcomes should be interpreted with caution. Neither study was powered for mortality rates.

Freedman et al[30] demonstrated no effect on mortality following the implementation of a patient blood management program. In contrast, Bui et al[32] reported a significant decrease in overall mortality associated with elective liver resection (from 10.2% to 4.9%. p<0.0001); however, the high rate of mortality in historical controls (10.2%) is noted.

Infection

Infection rates were measured in two studies. Freedman et al[30] measured the infection rate among both AAA surgery and knee arthroplasty patients. Infection rates increased from 9.76% to 11.64% (p<0.8797) among patients undergoing AAA surgery, and decreased from 3.76% to 2.04% (p<0.073) among knee surgery patients. Neither result was statistically significant. Bui et al[32] measured the rate of sepsis, which was found to decrease from 23.6% to 8.8% (p<0.001)—a statistically significant result.

Length of stay in hospital

Freedman et al[30] measured the mean length of stay for AAA surgery and knee arthroplasty patients. A decrease from 12.91 to 8.07 days (p<0.0576) was measured in AAA surgery patients. A decrease in length of stay from 7.16 to 6.25 days (p<0.088) was observed among knee arthroplasty patients. Neither result was statistically significant.

Other reported outcomes

Bui et al[32] measured several adverse outcomes. An overall morbidity reduction, from 57.1% to 25.5% (p<0.001) was measured. This was a significant result. Other adverse outcomes measured were haemorrhage rates and bile leakage. Haemorrhage rates decreased from 8.2% to 2.9% (p<0.159) and bile leakage was reduced from 12.2% to 11.8% (p<0.949). These were not found to be statistically significant.

Apart from Bolan et al[33], all studies compared outcomes of patients before and after implementation of multidisciplinary, multimodal programs, and found significant reductions in infection rates[32], length of stay in hospital[28,30], blood use[29–32], and morbidity[29,32].

Evidence statement

Box 3.1.1 outlines the evidence statement (PO1.1) for cardiac and noncardiac studies of the effect on patient outcomes of a multidisciplinary, multimodal, programmatic approach to perioperative patient blood management.

Box 3.1.1 PO1.1 Evidence statement for the effect of a multidisciplinary, multimodal programmatic approach to perioperative patient blood management on outcomes in cardiac and noncardiac surgery

Evidence base	Poor (D): One Level I study[27]; five Level III studies[28–32] and one Level IV study[33], all with a high level of bias
Consistency	Good (B): In general, consistent findings were made in all studies, but the measured outcomes differed slightly and there was some inconsistency in the direction of effect for mortality
Clinical impact	Good (B): A multidisciplinary, multimodal programmatic approach to perioperative blood management is associated with decreases in morbidity, blood loss, transfusion requirements and length of stay in hospital. The impact on mortality is unclear
Generalisability	Good (B): Population/s studied in the body of evidence are similar to the target population for the guidelines
Applicability	Satisfactory (C): Most studies were conducted in the USA. Because the health system is dissimilar from Australia's, applicability is reduced

Evidence statement PO1.1

A multidisciplinary, multimodal programmatic approach to perioperative blood management is associated with a reduction in transfusion requirements during cardiac or noncardiac surgery. The effect of such programs on morbidity and mortality is uncertain (Grade C)[29–33].

3.2 Question 2

In patients undergoing surgery, what effect does the cessation and timing of cessation of medication that affects haemostasis have on morbidity, mortality and RBC transfusion? (Referred to as PO2)

3.2.1 Cardiac surgery: Summary of evidence

In patients before undergoing cardiac surgery, what effect does the cessation and timing of cessation of medications that affect haemostasis have on morbidity, mortality, and transfusion requirements?

Methods

The systematic review process identified 13 studies that investigated the effect of cessation and timing of cessation the timing of haemostasis of antiplatelet medication (antiplatelet and/or anticoagulant therapy) on patient outcomes in cardiac surgery (coronary artery bypass graft surgery [CABG]). Study characteristics and results are summarised (see **Appendix C**, Volume 2). For the purpose of this research question, where antiplatelet and/or anticoagulant therapy is stopped in patients for a longer period before surgery than an alternative perioperative antiplatelet/anticoagulant management strategy, these patients are classified as having received the intervention (cessation of antiplatelet and/or anticoagulant therapy, including conversion to substitution therapy). Where the duration of ceasing antiplatelet and/or anticoagulant therapy before surgery is shorter, including continuation until surgery, these patients are classified as having received the comparator (not ceasing antiplatelet and/or anticoagulant therapy). Results are presented for different perioperative antiplatelet/anticoagulant management strategies. Evidence statements are presented for different perioperative management strategies. No relevant evidence was identified on the perioperative management of cardiac surgery patients who had been receiving warfarin, non-steroidal anti-inflammatory drugs (NSAIDs), statins, complementary medicines, vitamins or any other anticoagulants or antiplatelets. There was no relevant evidence identified concerning perioperative antiplatelet management strategies involving substitution therapy.

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for this research question.

No published cost-effectiveness analysis on the cessation and timing of cessation of medications that affect haemostasis was identified in the literature search for this research question.

Level I evidence

No relevant Level I evidence was identified.

Level II evidence

One Level II study in cardiac surgery was identified[35]. Characteristics of this study are summarised in **Table 3.2.1**. This study investigated the perioperative management of patients who had been receiving aspirin monotherapy before first-time elective CABG[35]. No quality of life data were reported in this study.

Level III evidence

Twelve Level III studies in cardiac surgery were identified. Characteristics of these studies are summarised in **Table 3.2.1**. Perioperative management strategies included patients who had been receiving aspirin[36–38,47] clopidogrel[39–41], or combination antiplatelet medication[42–46]. Studies in patients having off pump coronary artery surgery (OPCAB) provided documentation of the regime used for intraoperative administration of heparin[42–44] . It should be noted that all patients having CABG with cardiopulmonary bypass (CPB) routinely receive full heparinisation intraoperatively and this will have been assumed to have occurred in the patients undergoing CABG with CPB groups in the relevant studies [35-41,45-47] . In one study, it was recorded that patients also received subcutaneous heparin 5000 units the night before surgery[47] . In some studies received intraoperative heparin[42–44,47]. No quality of life data were reported by the included Level III studies.

Level IV evidence

Because higher level evidence is presented (Level II and III), non-comparative, Level IV evidence is not discussed. Excluded Level IV evidence is listed in **Appendix B**, Volume 2. No quality of life data were reported by the excluded Level IV studies.

Table 3.2.1 Summary of Level II and III studies

Author	Study type Study quality	Population	Intervention N	Comparator N	Outcomes
Aspirin monotherapy					
Ghaffarinejad et al (2007)[35]	RCT, single blinded (blinding details NR) *Fair*	Patients undergoing first time elective CABG (NR whether OPCAB or with CPB) Aprotinin prescribed for all patients during surgery	Aspirin therapy (regimen NR) stopped at least 7 days before surgery N=100	Aspirin until (regimen NR) surgery N=100	Mortality, morbidity, blood loss, transfusion requirements
Gerrah et al (2005)[36]	Prospective cohort *Fair*	Patients undergoing first time CABG, with CPB. Mixed population of elective and urgent[a] patients Details of other blood conservation strategies, including antifibrinolytic use NR	Aspirin therapy (100 mg daily) stopped at least 7 days before surgery N=18 (4 urgent cases)	Aspirin given daily until surgery N=14 (2 urgent cases)	Mortality, transfusion requirements, change in Hb, hospital and ICU LOS
Gulbins et al (2009)[37]	Retrospective cohort *Fair*	Patients undergoing elective and emergency CABG Patients underwent conservative CABG with ECC (on-pump CABG); revascularisation with OPCAB or re-do bypass grafting All patients received antifibrinolytic therapy with aprotinin during the study period	Aspirin therapy (regimen NR) stopped at least 5 days before surgery N=9504 (Emergencies=8.7% of all cases) CABG with ECC=84.6% OPCAB= 10.5% Re-do=4.9%	Aspirin until (regimen NR) day of surgery N=2519 (Emergencies=8.8% of all cases) CABG with ECC=89.4 OPCAB= 5.8% Re-do=4.8%	Mortality, morbidity, transfusion requirements, re-operation for bleeding, ICU LOS
Kamran et al (2008)[38]	Prospective cohort *Poor*	Patients undergoing primary isolated off-pump CABG Details of other blood conservation strategies, including antifibrinolytic use NR Unclear whether mixed population of	Aspirin therapy (regimen NR) stopped at least 5 days before surgery N=15	Aspirin until (regimen NR) day of surgery N=15	Blood loss, transfusion requirements, hospital and ICU LOS

		emergency/elective			
Weightman et al (2002)[47]	Retrospective cohort *Poor*	Patients who underwent first time CABG with CPB (emergent cases not included) All patients received unfractionated heparin, 5000 IU bid, s.c, starting the evening before surgery as DVT prophylaxis. Heparin reversed after CPB with protamine No patients received antifibrinolytic therapy	Aspirin discontinued 3–5 days before surgery N=255 Aspirin discontinued 6–7 days before surgery N=215 Aspirin discontinued >7 days before surgery N=187 (Aspirin regimen NR)	Aspirin continued until ≤2 days before surgery N=140 (Aspirin regimen NR)	Mortality, transfusion requirements, change in haemoglobin re-operation for bleeding, hospital LOS
Clopidogrel monotherapy					
Ascione et al (2005)[39]	Prospective cohort *Poor*	In-hospital referral patients undergoing first time CABG (On/off pump CABG proportions NR for patients whose clopidogrel regimen was stopped for reported durations) Emergency patients excluded Clopidogrel regimen: loading dose of 300 mg orally then 75 mg daily Details of other blood conservation strategies, including antifibrinolytic use NR	Clopidogrel stopped 2 to 5 days before surgery N=22	Clopidogrel stopped <2 days before surgery N=66	Mortality, transfusion requirements
Berger et al (2008)[40]	Retrospective, multicentre cohort *Fair*	Patients with diagnosis of ACS on admission, undergoing first time CABG On and off-pump CABG used Mixed group of urgent, elective and emergency patients Clopidogrel regimen included 75 mg daily maintenance dose ± 300 mg loading dose	Clopidogrel-naïve patients or stopped >5 days before surgery (proportion in each group NR) Cases: Urgent, emergency=7.0%; Urgent=65.1%; Elective=27.9% On pump CABG=72.5%	Clopidogrel stopped ≤5 days before surgery Cases: Urgent, emergency=12.1%; Urgent=68.8%; elective=19.1% On pump CABG=72.1%	Mortality, morbidity, blood loss, transfusion requirements, re-operation for bleeding, hospital and ICU LOS

		Antifibrinolytics used (intervention 55.7% patients; comparator 66.1%)	N=298	N=298	
Chu et al (2004)[41]	Prospective cohort *Fair*	Consecutive urgent or emergent CABG patients[b] (elective cases excluded) Aprotinin used intraoperatively	Clopidogrel stopped 5–8 days before surgery N=39 OPCAB=33% Clopidogrel discontinued >8 days before surgery N=232 OPCAB=17%	Clopidogrel stopped within 4 days of surgery N=41 OPCAB=22%	Mortality, morbidity, blood loss, transfusion requirements, re-operation for bleeding, hospital and ICU LOS, hospital readmission

Combination antiplatelet therapy					
Kang et al (2007)[45]	Retrospective cohort *Poor*	Patients undergoing isolated on-pump CABG Details of other blood conservation strategies, including antifibrinolytic use NR Unclear whether mixed population of emergency/elective Regimen: Clopidogrel loading dose of 300 mg, followed by a daily intake of 75 mg All patients received aspirin—either 325 mg or 81 mg. Unclear if/when aspirin stopped preoperatively	Clopidogrel not received within 7 days before surgery N=255	Clopidogrel continued to within 3 days of surgery N=25 Clopidogrel continued up to 4–7 days before surgery N=40	Mortality, blood loss, transfusion requirements, re-operation for bleeding, ICU LOS
Picker et al (2007)[46]	Retrospective cohort *Poor*	Patients who underwent first time elective CABG on CPB All patients received antifibrinolytic therapy with either high dose aprotinin or tranexamic acid. These therapies were administered intraoperatively in all cases and postoperatively only with bleeding complications	No APT/ACT 8 days before surgery N=40 APT/ACT regimen before surgery NR	APT/ACT continued until 1–7 days before surgery N=40 Various APT/ACT strategies: 11/40 aspirin only (100 mg daily); 28/40 aspirin and ticlopidine (250 mg daily) or clopidogrel (75 mg daily); 1/40 clopidogrel only	Mortality, morbidity, blood loss, transfusion requirements, change in Hb, re-operation for bleeding, hospital and ICU LOS
Kapetanakis et al (2006)[42]	Retrospective cohort *Fair*	Patients undergoing isolated off-pump CABG (emergent cases not included) Aspirin administered before surgery (regimen NR). Intraoperative anticoagulation: initial dose at 400 u/kg porcine heparin, with additional dosing during procedure to maintain target activated clotting time >480 seconds. (Details of heparin reversal NR) Details of other blood conservation strategies, including antifibrinolytic use NR	Clopidogrel-naïve or stopped ≥7 days before surgery (proportion in each group NR) N=1291 (18.7% urgent cases)	Clopidogrel regimen 75 mg daily within 7 days of surgery or patients received a 300 mg oral loading dose before PCI N=281 (31.7% urgent cases)	Mortality, morbidity, blood loss, transfusion requirements, re-operation for bleeding, hospital and ICU LOS

Shim et al (2007)[43]	Prospective cohort *Poor*	Patients who underwent elective, off-pump CABG Systematic heparinisation during anastomoses achieved with 150 U/kg of porcine heparin with additional doses to reach the target activated clotting time >300 seconds. Heparin activity was neutralised with protamine No patients received antifibrinolytics throughout the study period Cell salvage device used for all patients during surgery and salvaged blood re-infused before end of surgery	Aspirin and clopidogrel discontinued >6 days before surgery N=33 (100 mg aspirin and 75 mg clopidogrel, both oral, daily)	1. Aspirin and clopidogrel continued until 3–5 days before surgery N=50 2. Aspirin and clopidogrel continued within 3 days of surgery N=20 (100 mg aspirin and 75 mg clopidogrel, both oral, daily)	Blood loss, transfusion requirements, change in haematocrit, ICU LOS
Song et al (2008)[44]	Retrospective cohort *Poor*	Patients who underwent off-pump CABG (NR proportions of elective, emergent or urgent cases) Aspirin (100 mg daily) continued until surgery in all patients. Intraoperative heparin used: initial dose 1 mg/kg, additional dosing administered during the procedure to maintain a target activated clotting time of >350 seconds. Protamine used for half heparin reversal after surgery Details of other blood conservation strategies, including antifibrinolytic use NR	Surgery postponed ≥3 days before cessation of clopidogrel (75 mg daily) (period of cessation: mean=4.3 ± 1.2, range 3–7 days) N=102	Clopidogrel (75 mg daily) continued until immediately before surgery N=70	Mortality, morbidity, transfusion requirements, change in Hb re-operation for bleeding, ICU LOS

Abbreviations: ACS, acute coronary syndrome; ACT, anticoagulant therapy; APT, antiplatelet therapy; CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; DVT, deep vein thrombosis; ECC, extracorporeal circulation; Hb, haemoglobin; ICU, intensive care unit; IU, international units; LOS, length of stay; NR, not reported; OPCAB, off-pump cardiopulmonary artery bypass; PCI, percutaneous coronary intervention

[a]Urgent operation defined by study investigators as one performed within 48 hr from the time of admission or from catheterisation in patients with refractory angina

[b]Urgent patients were defined as those requiring revascularisation during the same hospital admission and emergent patients were defined as ICU or coronary care unit patients with intractable angina requiring imminent operative intervention

Aspirin monotherapy

There were five studies identified that compared outcomes among patients whose aspirin therapy was stopped before cardiac surgery with those who received aspirin until the day of surgery[35–38, 47]. In two studies, aspirin was stopped at least 7 days before surgery[35,36]; in two the other two studies, aspirin was stopped at least 5 days before surgery[37,38]; in another study, aspirin was stopped either 3-5 days, 6-7 days, or >7 days before surgery and compared with cessation <2 days[47]. Studies varied in terms of sample size, patient population, coronary artery bypass graft (CABG) techniques and the use of other blood conservation strategies. In a fair quality RCT conducted by Ghaffarinejad et al[35], the included population of elective patients only (determined by the RCT design), were administered an antifibrinolytic—aprotinin. It was unclear whether CABG was performed using cardiopulmonary bypass (CPB) or off-pump coronary artery bypass (OPCAB). In contrast, a large retrospective database review of approximately 12,000 patients by Gulbins et al[37] investigated patients who had undergone different types of CABG, including OPCAB and on-pump CABG with extracorporeal circulation (ECC). In this study, the patient population comprised approximately 9% emergency cases[37] . In a poor quality retrospective cohort study, Weightman et al[47] studied patients who underwent elective primary CABG with CPB, who also received preoperative subcutaneous heparin (5000 units pm on the night before surgery) and no antifibrinolytic therapy (**Table 3.2.1**).

Clopidogrel monotherapy

The impact of varying the timing of cessation of clopidogrel therapy was investigated by three studies[39–41] that differed in terms of sample size and patient populations (elective patients[39], a mixed population of elective, urgent and emergency patients[40]; elective or urgent patients[41]). Two studies[40, 41] involved a mixture of off pump coronary artery bypass (OPCAB) and CABG with CPB and the other study[39] did not record the type of surgery. Antifibrinolytic use was reported by two studies[40, 41] but it was unclear whether these or other blood conservation strategies were applied by the third study[39] (**Table 3.2.1**).

Combination antiplatelet therapy

There were five studies identified that investigated outcomes among CABG surgery patients who received combination antiplatelet and/or anticoagulant therapy before surgery[42-46]. Three of them involved patients having off pump coronary artery bypass (OPCAB). Kapetanakis et al[42], included only elective cases and did not report on the use of blood conservation methods including antifibrinolytics. Shim et al[43] studied elective OPCAB patients who had intraoperative cell salvage but did not receive antifibrinolytics and Song et al[44] reported on an OPCAB population but included no details of blood conservation, urgency status or antifibrinolytic therapy. Picker et al[46] reported on a patient population undergoing first-time elective CABG (with CPB) whose perioperative blood management included use of antifibrinolytics (either high dose aprotinin or tranexamic acid). The blood conservation approach used for CABG patients (with CPB) reported by Kang et al[45] was unclear, and it is uncertain whether the patient population included elective, emergency or urgent cases. Only Shim et al[43] investigated the impact of varying the timing of cessation of both aspirin and

clopidogrel. Aspirin was continued until surgery in the other studies, and the timing of clopidogrel cessation varied[42,44] (**Table 3.2.1**).

In addition to differences in the timing of cessation of anticoagulant therapy and/or antiplatelet therapy, studies varied according to the type of CABG (on versus off-pump), the category of included patients (elective/emergency/urgent), and the use of other blood management strategies. Studies also varied from small sample sizes[36,38,39,43] to large retrospective database reviews[37,41]. The limited number of relevant studies and variation in characteristics impact on the generalisability and applicability of reported results to the guidelines' target population. This should be taken into account when considering the findings of included studies. A major limitation of all included cohort studies was that reasons for stopping anticoagulant therapy and/or antiplatelet therapy in some patients and continuing in others were generally not clear. It was assumed that timing of cessation of antiplatelet therapy and/or anticoagulant therapy could have been influenced by the nature of CABG surgery, that is, elective, emergency or urgent surgeries.

Results of studies on aspirin monotherapy

Results of the studies[35–38, 47] (one Level II and four Level III studies) that investigated the perioperative management of CABG patients who had been receiving aspirin therapy alone are presented in **Table 3.2.2**.

Mortality

Mortality outcomes were reported in one RCT[35] and three cohort studies[36,37, 47]. No deaths were reported in the studies that compared cessation of aspirin at least 7 days before CABG with continuing aspirin therapy until the day of surgery[35,36]. In a large retrospective database review, outcomes among patients who ceased aspirin at least 5 days before surgery was compared with those who continued on aspirin until the day of surgery[37]. Although there was some variation in in-hospital mortality about the type of CABG performed (on- or off-pump, re-do), there were no significant differences in in-hospital mortality between patients who ceased aspirin before surgery and those who continued receiving aspirin until the day of surgery. (**Table 3.2.2**). The results of this study however, should be interpreted with caution because of the likelihood of selection bias. In the study by Weightman[47], variation of the timing of aspirin cessation did not have a statistically significant effect on mortality. Cessation of aspirin up to 2 days before surgery resulted in increased mortality compared with patients whose aspirin dose was ceased 3 to 5 days or 6 to 7 days prior: 2.1% vs.1.6%, respectively[47]. However, in patients whose aspirin was ceased 6 to 7 days before, mortality was 2.8%[47] (**Table 4.2.2**).

Morbidity

Ghaffarinejad[35], Gulbins[37] and their respective colleagues also investigated the effect of varying the timing of aspirin cessation on morbidity outcomes. Compared with patients who received aspirin until surgery, the frequency of myocardial infarction (MI) was not significantly affected (keeping in mind that the studies were not adequately powered for this outcome) regardless of whether aspirin was stopped at least seven days[35] or at least five

days[37] before surgery. However it should be noted that the studies were not adequately powered for this outcome. Timing of aspirin cessation had no effect on the frequency of pericardial effusions[37] (**Table 3.2.2**). This study however, was not sufficiently powered to detect a difference between the two groups.

Blood loss

There were three studies identified that reported blood loss[35,37,38]. Ghaffarinejad et al[35] conducted an RCT that reported a significant increase in postoperative blood loss when aspirin was continued until surgery compared with ceasing administration at least 7 days prior: 608 ± 359.7 mL vs. 483 ± 251.5 mL, respectively (mean ± SD, p=0.005). In contrast, Gulbins et al[37] reported that postoperative blood loss was slightly decreased when aspirin was continued until surgery compared with ceasing the dose at least 5 days prior: 834 ± 781 mL vs. 902 ± 811 mL, respectively (all CABG patients, mean ± SD, p<0.05). Although based on a small sample size (N=30) Kamran et al[38] reported similar findings: that blood loss was significantly lower during the second postoperative hour, and between 28 to 76 hours postoperatively, when aspirin was continued until surgery when compared with stopping the administration at least 5 days before surgery: 45 ± 23.3 mL versus 60.3 ± 60.1 mL, respectively (mean ± SD, p=0.004) for the second postoperative hour; and 32.0 ± 68.68 mL versus 102.8 ± 106.8 mL, respectively (mean ± SD, p=0.043) for the period from 28 to 76 hours post surgery[38] (**Table 3.2.2**). It is also of dubious clinical relevance to set out to measure postoperative blood loss in such arbitrary time frames as used in this study.

Although these three studies reported varying results that were statistically significant, the broad and overlapping standard deviation values suggest that there was effectively no difference between patient groups in terms of blood loss. Mean blood loss values plus or minus twice the standard deviation do not represent reasonable estimates of 95% confidence intervals (CI), which indicates that the blood loss data sets in each study are skewed. Based on these studies no definitive conclusions can be made.

Transfusion requirements

Intraoperative transfusion requirements were reported by three studies[37,38,47]. Gulbins et al[37] reported that timing of cessation of aspirin did not affect requirements for intraoperative transfusion of red blood cells. RBC transfusion requirements for all CABG patients who continued aspirin until surgery were in 0.23 ± 1 packages (mean ± SD). In patients who ceased therapy at least 5 days prior, transfusion requirements were 0.3 ± 1.1 (mean ± SD, p<0.05). Similarly, Kamran et al[38] found that intraoperative transfusion requirements were comparable for RBC, fresh frozen plasma (FFP) and platelets, regardless of when aspirin therapy was stopped before surgery. Weightman et al[47] reported a statistically significant increase in the volume of platelets, RBC and FFP in patients who received aspirin until up to 2 days before surgery when compared with patients whose aspirin therapy was discontinued more than 7 days before surgery (p<0.05, for all three comparisons). However, the wide standard deviation values indicate that the data set is skewed, and no reliable conclusion can be made from these results. (**Table 3.2.2**).

Postoperative transfusion requirements were reported by three studies[35–37]. Data reported by Ghaffarinejad et al[35] suggests that transfusion requirements are increased when aspirin is given until the day of surgery. For example, RBC requirements were 1.32 ± 0.97 (units, mean ± SD) when aspirin was given until surgery; whereas RBC requirements were 0.94 ± 1.02 (units, mean ± SD, p=0.008) when aspirin was stopped at least 7 days prior. Gulbins et al[37] reported a similar, statistically significant result for postoperative RBC transfusion. In contrast, Gerrah et al[36] found no statistically significant difference in either plasma or RBC postoperative transfusion requirements when cessation of aspirin therapy was varied. Overall, given the wide standard deviation values reported for mean transfusion requirements in each of these studies, there seems to be no difference in either intra- or postoperative transfusion requirements when the timing of aspirin cessation is varied. No definitive conclusions can be made because of the wide standard deviation values and skewed nature of the transfusion data sets (**Table 3.2.2**).

Change in haemoglobin

Haemoglobin levels at hospital discharge were reported by one study[36]. There was no significant difference in haemoglobin levels between patients who received aspirin until surgery and those whose aspirin therapy stopped at least 7 days prior: 11.2 ± 1.5 g/dL versus 11.3 ± 1.4 g/dL (mean ± SD, p=0.8). Preoperative haemoglobin levels were also similar in both groups of patients. Although this result suggests that timing of cessation of aspirin therapy does not impact haemoglobin levels, the standard deviation values indicate that the haemoglobin data sets are skewed and no definitive conclusions can be drawn from this finding. In another study[47], haemoglobin levels were reported on day 0, on admission to ICU and on postoperative day 3. There were no differences between the groups receiving aspirin between 3-5 days, 6-7 days, >7 days or <2 days before surgery (**Table 3.2.2**).

Re-operation for bleeding

Two studies, Gulbins et al[37] and Weightman et al[47] reported on re-operation for bleeding rates. In one, there was no difference in re-operation for bleeding between patients whose aspirin therapy continued until surgery and those whose aspirin therapy was stopped at least 5 days before surgery: 2.1% vs. 2.2% respectively (p value not reported) [37]. In the other, the frequency of re-operation for bleeding was not affected when aspirin was continued up until <2 days (4.3%) before CABG's, compared to cessation 3-5 days (3.1%), 6-7 days (5.5%) or >7 days (2.7%) prior to surgery (**Table 3.2.2**).

Hospital length of stay

Three studies compared hospital length of stay when timing of cessation of aspirin therapy was varied[36,38, 47]. Hospital length of stay was not significantly different when aspirin was ceased before surgery or continued until the day of surgery. Gerrah et al[36] reported a hospital length of stay of 7.6 ± 2.3 days (mean ± SD) for patients who stopped aspirin and 7.2 ± 2 days (mean ± SD, p=0.6) for those who continued until surgery. Kamran et al[38] also found that hospital length of stay (ward days) was not different between treatment groups: 2.3 ± 0.48 days (mean ± SD) for both patients who ceased aspirin and those who continued until surgery. Weightman et al[47], found no difference in hospital length of stay whether or not

aspirin was ceased 3-5 days (8.2), 6-7 days (7.6), >7 days (8.3) compared to continuation up until <2 days prior to surgery (7.8) (**Table 3.2.2**). Hospital LOS often depends on hospital or local policies and is therefore not a very sensitive indicator of poor outcomes.

Intensive care unit length of stay

Intensive care unit (ICU) length of stay was reported in three studies[36–38]. Data reported by Gerrah et al[36] suggests that there was a slight significant reduction in ICU length of stay when aspirin was taken until the day of surgery: 1.85 ± 0.7 days (mean ± SD) vs. 2.5 ± 0.9 days (mean ± SD) in patients who stopped aspirin at least 5 days before surgery. However, there is little difference in ICU length of stay between patients who stopped or continued aspirin therapy in the studies by Gulbins et al[37] and Kamran et al[38] (**Table 3.2.2**).

Summary of key findings

Overall, results from the studies that investigated the effect of varying the timing of aspirin cessation indicate that the effect on patient outcomes remains uncertain when aspirin is continued until the day of surgery. Mortality, morbidity (MI and pericardial effusion), hospital length of stay and ICU length of stay were similar regardless of the timing of aspirin cessation. However, the studies were not powered to detect a difference. Blood loss (postoperative) and transfusion requirements (intraoperative and postoperative) were also similar despite analyses that claim statistical significance. Nevertheless, reported standard deviation values for these data show wide variation in results for both parameters. Definitive conclusions can therefore not be made with respect to the effect of varying timing of cessation of aspirin therapy on these outcomes.

Table 3.2.2 Results of studies in patients receiving aspirin monotherapy

Author	Outcome	Intervention N	Comparator N	Statistical significance
Level II				
Ghaffarinejad et al (2007)[35]		Aspirin ceased at least 7 days before surgery N=100	Aspirin until surgery N=100	
	Mortality (in-hospital, proportion)	0%	0%	NA
	Morbidity[a,b] (proportion)	Definite MI=3% Probable MI=8%	Definite MI=0% Probable MI=5%	p=0.24 p=0.56
	Blood loss (postoperative, mL, mean ± SD)	483 ± 251.5	608 ± 359.7	p=0.005
	Transfusion requirements (postoperative, units, mean ± SD)	Platelet transfusion=0.28 ± 0.84 FFP=1.46 ± 1.64 RBC=0.94 ± 1.02	Platelet transfusion=0.45 ± 1.32 FFP=2 ± 1.84 RBC=1.32 ± 0.97	p=0.25 p=0.03 p=0.008
Level III				
Gerrah et al (2005)[36]		Aspirin ceased at least 7 days before surgery N=18	Aspirin daily until surgery N=14	
	Mortality (proportion)	0%	0%	NA
	Transfusion requirements (postoperative, units, mean ± SD)	Plasma=1.0 ± 1.5 RBC=1.9 ± 1.4	Plasma=0.8 ± 1.2 RBC=1.5 ± 1.22	p=0.7 p=0.5
	Haemoglobin (preoperative, g/dL, mean ± SD)	13.3 ± 1.4	12.8 ± 1.3	p=0.4
	Haemoglobin (at hospital discharge, g/dL, mean ± SD)	11.3 ± 1.4	11.2 ± 1.5	p=0.8
	Hospital LOS (days, mean ± SD,)	7.6 ± 2.3	7.2 ± 2	p=0.6
	ICU LOS (days, mean ± SD)	2.5 ± 0.9	1.85 ± 0.7	p=0.04

Author	Outcome	Intervention N	Comparator N	Statistical significance
Gulbins et al (2009)[37]		Aspirin ceased at least 5 days before surgery N=9504	Aspirin until day of surgery N=2519	
	Mortality (in-hospital, proportion for each type of CABG)	On-pump CABG (ACB with ECC)=1.9% OPCAB=1.8% Re-do=3.6%	On-pump CABG (ACB with ECC)=1.7% OPCAB=2.1% Re-do=4.1%	p values for intervention vs. comparator NR
	Morbidity (proportion)	Perioperative infarction ACB with ECC=1.8% OPCAB=2% Re-do=3.6% Pericardial effusion All CABG patients: 1.8%	Perioperative infarction ACB with ECC=2% OPCAB=0.7% Re-do=6.6% Pericardial effusion All CABG patients: 1.8%	p values for intervention vs. comparator NR
	Blood loss (chest drainage, postoperative) (mL, mean ± SD)	ACB with ECC=856 ± 717 OPCAB=851 ± 696 Re-do=1005 ± 1198 All CABG patients=902 ± 811	ACB with ECC=781 ± 776 OPCAB=774 ± 694 Re-do=970 ± 1021 All CABG patients=834 ± 781	p<0.05 (all CABG patients)

Author	Outcome	Intervention N	Comparator N	Statistical significance
	Transfusion requirements (RBC packages, mean ± SD)	Intraoperative ACB with ECC=0.3 ± 1 OPCAB=0.3 ± 1.4 Redo=0.6 ± 1.3 All CABG patients=0.3 ± 1.1 Postoperative ACB with ECC=0.8 ± 2.7 OPCAB=0.7 ± 2.6 Re-do=2 ± 3.9 All CABG patients=0.88 ± 2.7	Intraoperative ACB with ECC=0.2 ± 1.0 OPCAB=0.14 ± 0.6 Re-do=0.74 ± 2.2 All CABG patients=0.23 ± 1 Postoperative ACB with ECC=0.9 ± 2.8 OPCAB=0.7 ± 2.5 Re-do=2.4 ± 5.6 All CABG patients=1.01 ± 2.9	Intraoperative p<0.05 (All CABG patients) Postoperative p<0.05 (All CABG patients)
	Re-operation for bleeding (%)	2.2%	2.1%	p value NR
	ICU LOS (days, mean ± SD)	ACB with ECC=3.8 ± 6 OPCAB=3.9 ± 5.3 Re-do=5.7 ± 8	ACB with ECC=3.4 ± 4.7 OPCAB=2.7 ± 2.5 Re-do=5.9 ± 9.3	p value NR

Author	Outcome	Intervention N	Comparator N	Statistical significance
Kamran et al (2008)[38]		Aspirin ceased at least 5 days before surgery N=15	Aspirin until day of surgery N=15	
	Blood loss (postoperative, mL, mean ± SD)	1st hour=125 ± 128 2nd hour=60.3 ± 60.1 3rd hour=48.0 ± 43.2 Next 24 hours=619.3 ± 392.0 28 to 76 hours=102.8 ± 106.8	1st hour=88 ± 63 2nd hour=45 ± 23.3 3rd hour=47.0 ± 35.0 Next 24 hours=392.3 ± 333.5 28 to 76 hours=32.0 ± 68.68	1st hour, p=0.074 2nd hour; p=0.004 3rd hour, p=0.48 Next 24 hours, p=0.23 28 to 76 hours, p=0.043
	Transfusion requirements (intraoperative, pints, mean ± SD)	RBC=1.7 ± 1.7 FFP=0.4 ± 0.5 Platelets=0.13 ± 0.35	RBC=1.1 ± 1.2 FFP=0.13 ± 0.35 Platelets=0.06 ± 0.25	p values NR
	Hospital LOS (ward days, mean ± SD)	3.3 ± 0.48	3.3 ± 0.48	NS
	ICU LOS (days, mean ± SD)	2.4 ± 0.63	2.2 ± 0.88	NS
Weightman et al (2002)[47]		Aspirin discontinued 3–5 days before surgery. N=255 Aspirin discontinued 6–7 days before surgery. N=215 Aspirin discontinued >7 days before surgery. N=187 Unfractionated heparin started evening before surgery	Aspirin continued until ≤2 days before surgery. Unfractionated heparin started the evening before surgery. N=140	
	Mortality	1. =1.6% 2. =2.8% 3. =1.6%	2.1%	NS

Author	Outcome	Intervention N	Comparator N	Statistical significance
	Transfusion requirements, platelets (units, mean ± SD)	1. =1.6 ± 4.0 2. =1.5 ± 3.4 3. =0.9 ± 2.4	2.7 ± 6.0	p<0.05 (comparator vs. group 3)
	Transfusion requirements, RBC (units, mean ± SD)	1. =1.5 ± 2.0 2. =1.6 ± 2.8 3. =1.3 ± 1.9	2.2 ± 3.8	p<0.05 (comparator vs. group 3)
	Transfusion requirements, FFP (units, mean ± SD)	1. =0.8 ± 2.1 2. =0.9 ± 3.1 3. =0.6 ± 1.5	1.4 ± 3.1	p<0.05 (comparator vs. group 3)
	Haemoglobin, day 0 (g/dL, mean ± SD)	1. =14.3 ± 1.4 2. =14.3 ± 1.2 3. =14.2 ± 1.3	14.2 ± 1.4	NS
	Haemoglobin, admission to ICU (g/dL, mean ± SD)	1. =10.1 ± 1.5 2. =10.1 ± 1.4 3. =10.1 ± 1.4	10.0 ± 1.4	NS
	Haemoglobin, postoperative day 3 (g/dL, mean ± SD)	1. =11.0 ± 1.4 2. =11.0 ± 1.3 3. =11.0 ± 1.4	10.8 ± 1.4	NS
	Re-operation for bleeding (proportion)	1. =3.1 % 2. =5.5 % 3. =2.7 %	4.3 %	NS
	Hospital LOS (days, mean ± SD)	1. =8.2 ± 8 2. =7.6 ± 3 3. =8.3 ± 6	7.8 ± 4	NS

Abbreviations: ACB with ECC, isolated coronary bypass grafting with extracorporeal circulation; ACS, acute coronary syndrome; ACT, anticoagulant therapy; APT, antiplatelet therapy; CABG, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; DVT, deep vein thrombosis; ECC, extracorporeal circulation; FFP, fresh frozen plasma; ICU, intensive care unit; IU, international units; LOS, length of stay; MI, myocardial infarction; NA, not applicable; NR, not

reported; OPCAB, off-pump cardiopulmonary artery bypass; SD, standard deviation; RBC, red blood cells
[a] Definite MI=a new QS on ECG and a new RWMA on echo with or without CK-MB >30 IU/L) (RWMA = regional wall motion abnormality; CK-MB=cardiac enzyme marker)
[b] Probable MI=defined as CK-MB >30 IU/L, with a new QS on ECG or a new RWMA on echo

Results of studies on clopidogrel monotherapy

Results from Level III studies[39–41] that investigated the impact of timing of cessation of clopidogrel monotherapy are presented in **Table 3.2.3**. Results from the prospective cohort study by Ascione et al[39] represent a subgroup analysis of 473 in-hospital referrals for first-time CABG. This subgroup analysis was not pre-specified, but was adjusted for variation in baseline characteristics. Statistical methods applied by Berger et al[40] were also planned to adjust for variables, enabling the relationship between timing of clopidogrel cessation in patients with acute coronary syndromes (ACS) and outcomes after CABG to be better understood. Logistic regression analysis was applied to adjust for potential confounders, and propensity score analysis was applied to adjust for variation in baseline and clinical factors[40]. Chu et al[41] restricted inclusion criteria to urgent or emergency cases to assess outcomes in patients who were under the effects of clopidogrel after cessation at different time periods before surgery (**Table 3.2.3**).

Mortality

Ascione et al[39] compared outcomes in CABG patients who stopped clopidogrel less than 2 days before surgery with patients who stopped therapy 2 to 5 days before surgery. Compared with no therapy, the likelihood of in-hospital mortality was greatly increased when clopidogrel was stopped less than 2 days before surgery versus cessation 2 to 5 days prior: OR=21.7 (95% CI: [2.93, 160]) vs. 2.52 (95% CI: [0.34,18.8]), respectively (p<0.0001). Berger et al[40] compared outcomes among CABG patients who stopped clopidogrel up to 5 days before surgery with those who stopped more than 5 days before surgery, or were clopidogrel-naïve. In this study, in-hospital and postoperative mortality did not differ significantly when the timing of clopidogrel cessation was varied. In urgent or emergency CABG[41], stopping clopidogrel closer to the time of surgery had no significant effect on mortality (**Table 3.2.3**).

Morbidity

Berger et al[40] reported several morbidity outcomes. Although the frequency of several complications was slightly increased in patients whose clopidogrel therapy was stopped up to 5 days before surgery, the only statistically significant difference was in the number of patients who required inotropes: 34.2% of patients who stopped clopidogrel up to 5 days before surgery vs. 24.5% of patients who were clopidogrel-naïve or stopped therapy more than 5 days before surgery (p=0.009). In urgent or emergency CABG[41], stopping clopidogrel closer to the time of surgery had no significant impact on various complications, apart form a slight trend towards increased incidence of stroke and MI (**Table 3.2.3**).

Blood loss

The unadjusted analysis reported by Berger et al[40] showed that blood loss was not affected by the timing of cessation of clopidogrel therapy. In contrast, a propensity score analysis which was performed to control for confounding, showed that exposure to clopidogrel within 5 days of surgery greatly increased the likelihood of bleeding: OR=1.82 (95% CI: [1.11, 3.01]) (p=0.02) (**Table 3.2.3**).

Transfusion requirements

Ascione et al[39] reported that requirements for RBC and clotting factors were significantly increased ($p<0.05$) when clopidogrel therapy was stopped less than 2 days before surgery; however, no data were reported in support of this assertion. In the unadjusted results reported by Berger et al[40], there was a significant increase in the number of patients who required postoperative transfusion (RBC, platelets, FFP and cryoprecipitate combined) in the group exposed to clopidogrel within 5 days of surgery, than clopidogrel-naïve patients or those who stopped therapy more than 5 days before surgery: 50% vs. 35.6% ($p<0.001$). Although intraoperative transfusion requirements were also increased in the group who received clopidogrel within 5 days of surgery, this was not statistically significant. Berger et al[40] reported a statistically significant increase in the amount of blood products (intraoperative and postoperative combined) used for patients who stopped clopidogrel less than 5 days before surgery: 4.90 ± 7.90 units (mean ± SD) vs. 2.03 ± 3.75 units (mean ± SD) in clopidogrel-naïve patients or those who stopped therapy more than 5 days before surgery ($p<0.001$). The standard deviation values show that the data set is skewed. In urgent or emergency CABG[41], stopping clopidogrel closer to the time of surgery increased both the number of patients requiring transfusions and the volume of blood products transfused. Chu et al[41] also applied logistic regression analysis—stopping clopidogrel within 4 days of surgery increased the likelihood of transfusion in comparison with stopping 5 to 8 days before, or more than 8 days prior: OR=4.22 (95% CI: [1.79, 9.95]) ($p=0.001$) (**Table 3.2.3**).

Re-operation for bleeding

In the unadjusted analysis, Berger et al[40] found that stopping clopidogrel within 5 days of surgery increased the likelihood of re-operation for bleeding: 4.7% of patients underwent re-operation when exposed to clopidogrel within 5 days of CABG surgery, whereas 1.3% required re-operation if patients were clopidogrel-naïve or clopidogrel was stopped more than 5 days before surgery ($p=0.017$). This result was reflected in the analyses that adjusted for potential confounders: propensity score analysis and logistic regression analysis both showed that cessation of clopidogrel within 5 days of CABG surgery was associated with an increased risk of re-operation for bleeding: OR=9.80, (95% CI: [2.18, 43.95]) ($p<0.01$) and OR=4.60 (95% CI: [1.55, 14.55) ($p=0.009$) respectively. Berger et al[40] also reported the incidence of the composite outcome of re-operation or major bleeding and showed that the risk of this composite outcome decreased with each day between exposure to clopidogrel and CABG surgery (data were presented graphically and could not be extracted). In urgent or emergency CABG[41], stopping clopidogrel closer to the time of surgery increased the frequency of re-operation for bleeding (**Table 3.2.3**).

Hospital length of stay

In the unadjusted analysis, Berger et al[40] found no significant difference in hospital length of stay between study groups. In comparison, the propensity score analysis showed that cessation of clopidogrel within 5 days of surgery could result in an increased hospital length of stay: OR=1.47 (95% CI: [1.00, 2.165]) ($p=0.05$). In urgent or emergency CABG[41], stopping clopidogrel closer to the time of surgery increased hospital length of stay (**Table 3.2.3**).

Intensive care unit length of stay

There was no significant difference in intensive care unit (ICU) length of stay between treatment groups in the study by Berger et al[40]. In a logistic regression analysis, Chu et al[41] found that stopping clopidogrel within 4 days of surgery increased the likelihood of increased ICU length of stay in comparison with stopping 5 to 8 days before, or more than 8 days before surgery: OR=3.14 (95% CI: [1.40, 7.04]) (p=0.006) (**Table 3.2.3**).

Hospital readmission

There was no significant difference in the rates of hospital readmission between treatment groups in the study by Berger et al[40]. In urgent or emergency CABG[41], stopping clopidogrel closer to the time of surgery had no effect on hospital readmission (**Table 3.2.3**).

Summary of key findings

Evidence for the effect of varying cessation of clopidogrel monotherapy on patient outcomes in CABG surgery is limited to the three studies discussed[39–41]. The effect of cessation of clopidogrel within 2 to 5 days of surgery compared with stopping clopidogrel more than 5 days before surgery is uncertain[39,40]. This may be due to the poor quality of available evidence and studies not being powered to detect a difference between groups for this outcome. Cessation of clopidogrel within 5 days of surgery was associated with an increased risk of blood loss, transfusion requirements, re-operation for bleeding and increased hospital length of stay. Although there was a trend to increased frequency of complications, a statistically significant difference was only reported for an increased requirement of inotropes[40]. In patients who require urgent or emergency CABG[41], stopping clopidogrel closer to the time of surgery (within four days) had no significant effect on mortality or morbidity. However, transfusion requirements, re-operation for bleeding, hospital and ICU length of stay and hospital readmission were all adversely affected.

- Timing of cessation did not affect hospital or ICU length of stay.
- Timing of cessation had no effect on re-operation for bleeding
- The effect of varying timing of cessation on mortality is unclear.

Cessation closer to surgery appears to increase transfusion requirements. It is uncertain whether this effect is genuine because of weaknesses in statistical methods.

Table 3.2.3 Results of studies in patients receiving clopidogrel monotherapy

Author	Outcome	Intervention N	Comparator N	Statistical significance
Ascione et al (2005)[39]		Clopidogrel stopped 2–5 days before surgery N=22	Clopidogrel stopped <2 days before surgery N=66	
	Mortality (in-hospital, OR, 95% CI vs. no therapy)	2.52 (0.34,18.8)	21.7 (2.93, 160)	p<0.0001
Berger et al (2008)[40]		Clopidogrel-naïve or stopped >5 days before surgery N=298	Clopidogrel stopped ≤5 days before surgery N=298	
	Mortality, in-hospital (proportion)	0.3%	1.3%	p=0.373
	Mortality, postoperative (proportion)	0%	1.0%	p=0.249
	Morbidity (proportion)	AF=18.8% Infection=5.7% Ischaemic CVA=1.0% Haemorrhagic CVA=0% Haemodynamic instability=8.4% Inotropes needed=24.5% Mediastinitis=0% Cardiac arrest=0.7%	AF=23.5% Infection=7.4% Ischaemic CVA=1.7% Haemorrhagic CVA=0% Haemodynamic instability=12.4% Inotropes needed=34.2% Mediastinitis=0.7% Cardiac arrest=1.3%	AF, p=0.160 Infection, p=0.408 Ischaemic CVA, p=0.725 Haemorrhagic CVA, NA Haemodynamic instability, p=0.107 Inotropes needed, p=0.009 Mediastinitis=0.157 Cardiac arrest, p=0.686
	Blood loss (mL, mean ± SD)	557.2 ± 339.01	668.3 ± 515.50	p=0.026
	Transfusion requirements[a] (intraoperative and postoperative combined, units, mean ± SD)	2.03 ± 3.75	4.90 ± 7.90	p<0.001
	Transfusion requirements[a] preoperative(proportion)	1.3%	1.7%	p=0.751
	Transfusion requirements[a] intraoperative (proportion)	32.2%	43%	p=0.751
	Transfusion requirements[a], postoperative (proportion)	35.6%	50%	p<0.001

Author	Outcome	Intervention N	Comparator N	Statistical significance
	Re-operation for bleeding	1.3%	4.7%	p=0.017
	Hospital LOS (days, mean ± SD)	6.3 ± 3.87	7.2 ± 5.53	p=0.054
	ICU LOS (days, mean ± SD)	2.4 ± 2.52	2.7 ± 3.17	p=0.059
	Hospital readmission (proportion)	8.1%	9.1%	p=0.670
Chu et al (2004)[41]		1. Clopidogrel stopped 5–8 days before operation N=39; OPCAB=33% 2. Clopidogrel discontinued >8 days before operation N=232; OPCAB=17%	Clopidogrel stopped within 4 days of operation N=41; OPCAB=22%	
	Mortality (proportion)	1. =0%; 2. =4.5%	2.4%	p=0.63
	Morbidity (proportion)	Mediastinitis 1. =0%; 2. =2.1% MI 1. = 0%; 2. =3.9% Respiratory failure 1. =0%; 2. =9.5% Renal failure requiring dialysis 1. =0%; 2. =0.4% Wound infection 1. =7.7%; 2. =6.9% Stroke: 1. =5.1%; 2. =3.0%	Mediastinitis=0% MI=4.9% Respiratory failure=12.2% Renal failure requiring dialysis=2.4% Wound infection=4.9% Stroke=9.8%	Mediastinitis p=0.89 MI p=0.43 Respiratory failure p=0.07 Renal failure requiring dialysis p=0.35 Wound infection p=0.84 Stroke p=0.09
	Transfusion requirements (proportion)	1. =35.9%; 2. =42.2%	75.6%	p<0.0001
	Transfusion requirements, total[a] (units, mean±SD)	1. =1.2 ± 2.0; 2. =2.6 ± 5.7	12.2 ± 2.0	p<0.001
	Re-operation for bleeding	1. =2.6%; 2. =1.7%	14.6%	p=0.002
	Hospital LOS (days, median)	1. =7; 2. =7	9	p=0.018
	Hospital readmission, within 30 days (proportion)	1. =9.8%; 2. =10.8%	7.7%	p=0.89

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CVA, cerebrovascular accident; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; NR, not reported; NS, not significant; OR, odds ratio; SD, standard deviation

[a] Includes platelets, RBC, FFP and cryoprecipitate

Results of studies on combination antiplatelet medication

Results of five Level III studies[42-46] that reported on the perioperative management of patients who received combination antiplatelet medication (without intraoperative heparin) are presented in **Table 3.2.4**. Patients underwent off pump coronary artery surgery (OPCAB)[42-44] and CABG with cardiopulmonary bypass (CPB)[45,46]. The studies also varied in the timing of administration and cessation of combination antiplatelet therapy (APT). Kapetanakis et al[42] compared patients (all of whom had aspirin) who were either clopidogrel naive or had it ceased >7 days before surgery, with patients who either received 75 mg of clopidogrel within 7 days of surgery or received a loading dose of 300 mg before percutaneous coronary intervention (PCI). Shim etal[43] studied patients who had aspirin and clopidogrel discontinued >6 days before surgery compared to those who had these drugs continued either between 3-5 days before surgery or within 3 days of surgery. Song et al[44] compared patients (all of whom continued aspirin 100 mg until the day of surgery) who either had surgery postponed until >3 days after cessation of clopidogrel or continued clopidogrel until immediately before surgery. The other two studies were both studies reported outcomes in patients who underwent isolated CABG with CPB[45,46]. Kang and colleagues[45] reported that clopidogrel was continued to within 3 days of surgery (comparator #1), continued for 4 to 7 days before surgery (comparator #2), or not received within 7 days of surgery. All patients in this study received aspirin, but it was not clear whether (or when) aspirin was stopped before surgery. Picker et al[46] compared patients who did not receive combination antiplatelet medication during the 8 days before surgery with those who had continuation of combination antiplatelet therapy (APT) until 1 to 7 days before surgery. The latter group comprised patients who received either aspirin or clopidogrel alone or combinations of aspirin and clopidogrel or aspirin and ticlopidine. Patients who received combined APT therapy constituted 70% of the study population. Results were not reported separately for the different perioperative APT therapies used in this group (**Table 3.2.4**).

Mortality

Mortality data were reported by four studies[42,44-46]. In an unadjusted analysis, Kapetanakis and colleagues[42] found that cessation of clopidogrel within 7 days of surgery did not affect operative mortality in patients who continued to receive aspirin until the day of surgery. Propensity matched pair analysis and logistic regression analysis had similar findings: OR=0.9 (95% CI: [0.24, 3.62]) (p=0.92) and OR=1.0 (95% CI: [0.32, 3.28]) (p=0.98). Given the wide confidence intervals for these outcomes, no definitive conclusions can be made. Song et al[44] also investigated the effect of varying the timing of cessation of clopidogrel in CABG patients who received aspirin until surgery. Both propensity matched pair analysis and unadjusted analysis (data not shown) showed that continuation of clopidogrel until immediately before surgery did not result in statistically significant increases in operative mortality (note the inadequate power of the study)[44]. The effects on mortality with continuation of clopidogrel until close to[42] or immediately before[44] surgery is unclear as the studies were not powered to detect a difference[42,44].

Picker and colleagues[46] reported 30-day mortality of 2.5% in patients whose combination antiplatelet therapy (APT) therapy was continued until surgery. There were no deaths in the

group of patients who did not receive APT therapy during the 8 days before surgery. It was not reported whether this result was statistically significant although it should be kept in mind that the size of the study was small. Kang et al[45] reported increased operative mortality in patients who continued clopidogrel within 3 days before surgery in comparison with patients who did not receive clopidogrel within 7 days before surgery: 8.0% vs. 3.1%, respectively. Although this result was not statistically significant (p=0.193), this represents a greater than twofold increase in mortality. There were no deaths in the group who continued clopidogrel 4 to 7 days before surgery[45] (**Table 3.2.4**).

Morbidity

Morbidity data were reported by two studies where patients underwent off-pump coronary artery surgery (OPCAB), with aspirin continued until surgery, and the timing of cessation of clopidogrel therapy varied[42,44] (**Table 3.2.4**). In their analysis (unadjusted), Kapetanakis et al[42] found that cessation of clopidogrel therapy within 7 days of OPCAB had no significant impact on the incidence of postoperative stroke or MI. In a propensity matched score analysis by Song et al[44], continuation of clopidogrel until immediately before surgery did not significantly increase the incidence of a variety of postoperative complications (**Table 4.2.4**). Similar results were found in an unadjusted analysis[44] (data not shown). Both studies reported that continuation of anticoagulant therapy[42,44] until close to[42] or immediately before[44] OPCAB does not increase postoperative complications.

Picker et al[46] reported complications that included pneumonia and MI. There were no instances of pneumonia in patients who did not receive APT during the 8 days before surgery, but MI was reported for 7.5% of these patients. In the group where APT was continued until surgery, pneumonia was reported in 2.5% of patients and there were no cases of MI. It was not reported whether this result was statistically significant although it should be kept in mind that the size of the study was small (**Table 3.2.4**).

Blood loss

In their analysis (unadjusted), Kapetanakis et al[42] found that intraoperative blood loss was similar when clopidogrel therapy was ceased within 7 days of off pump coronary artery surgery (OPCAB) or stopped 7 or more days before surgery: 400 mL (100–3400 mL) vs. 400 (100–2000 mL), respectively (median values, minimum to maximum) (p=0.02, Wilcoxon rank sum test for variables with non normal distribution). Similarly, in a propensity matched pair analysis, Song et al[44] also found that continuation of clopidogrel until immediately before surgery had no effect on either intra- or postoperative blood loss when compared with patients who ceased clopidogrel 3 days or more before surgery. Shim et al[43] found that stopping both clopidogrel and aspirin closer to surgery did not result in a significant increase in intraoperative blood loss. Note that this was recorded as the amount of blood reinfused from a cell salvage device that was used intraoperatively. Shim et al[43] also reported blood loss during the first 24 hours in ICU. Timing of clopidogrel and aspirin cessation did not significantly impact on the volume of blood loss. Although Shim et al[43] suggested that both intra- and postoperative blood loss is not affected by the timing of clopidogrel and aspirin cessation, the wide standard deviation values reported indicate that the data set is skewed,

and that a different statistical analysis (appropriate for skewed data distribution) would have been more appropriate (**Table 3.2.4**).

These studies suggest that continuation of aspirin and clopidogrel until close to the time of off-pump coronary artery surgery (OPCAB) does not increase intraoperative[42–44] or postoperative[43,44] blood loss. However, no definitive conclusions can be made because of the absence of appropriate statistical analysis in one study[43].

Results reported by Picker and colleagues[46] suggest a trend toward increased postoperative blood loss in patients (CABG with CPB) whose APT continued until surgery: 940 ± 861 mL (mean ± SD) vs. 412 ± 590 mL (mean ± SD) in patients who had no APT during the 8 days before surgery. Data reported by Kang et al[45] (CABG with CPB) suggests that the timing of cessation of clopidogrel therapy has no effect on postoperative blood loss (**Table 3.2.4**).

Transfusion requirements

In their unadjusted analysis Kapetanakis et al[42] reported significant increases in transfusion requirements when clopidogrel was continued to within 7 days of surgery. The unadjusted analysis showed that more patients required intraoperative RBC transfusion, and postoperative transfusions of platelets, FFP and RBC ($p<0.01$ for all comparisons). The propensity matched pair analysis also showed that stopping clopidogrel therapy within 7 days of surgery increased the likelihood for requiring platelets or blood transfusion: OR=2.3 (95% CI: [1.48, 3.71]) ($p<0.01$) and OR=2.7 (95% CI: [1.86, 3.92) ($p<0.01$), respectively. Despite the increased likelihood of platelet and blood transfusion, there was not a significant increase in the possibility of receiving multiple units of blood when clopidogrel was continued closer to the time of surgery. Logistic regression analysis also showed that clopidogrel within 7 days of surgery increased the likelihood of requiring platelets or RBC transfusion, but found a significant increase in the possibility of receiving multiple units of blood (Table 4.2.4). In contrast to Kapetanakis[42], Shim[43], Song[44] and their respective colleagues, found that continuing combination antiplatelet therapies until closer to the time of OPCAB surgery did not significantly increase transfusion requirements (**Table 4.2.4**). It is likely that variation in antiplatelet therapy regimens, sample size, patient populations and statistical analyses are the most likely explanations for the differences in findings.

In one of the studies of patients having CABG with CPB, when clopidogrel was continued to within 3 days of surgery there was an increase in blood transfusion requirements compared with patients who did not receive clopidogrel within 7 days before surgery[45]: 5.8 ± 9.4 units (mean ± SD) vs. 3.4 ± 4.1 units (mean ± SD). Although this was reported to be statistically significant ($p=0.027$), no reliable conclusions can be made from this finding given the wide standard deviation values. In the other study of patients having CABG with CPB, Picker et al[46] also reported that cessation of APT closer to the time of surgery increased transfusion requirements (FFP, platelets, and RBC) (**Table 3.2.4**). No statistical analysis was reported and given the wide standard deviation values, no firm conclusions can be made from this result.

Importantly however, in all of these mostly retrospective cohort studies, it is likely that the decision to transfuse blood components, especially platelets, was based on the fact that the

patients in the group who received clopidogrel within 7 days of surgery would have been deemed to "need" platelets. The results are therefore not valid. This challenging question could only be answered using prospective, blinded, randomly controlled trials in which the transfusion trigger for each blood component was predefined.

Change in haemoglobin

In the propensity matched pair analysis, Song et al[44] reported a slight decrease in haemoglobin level on the first day post-surgery among patients who continued clopidogrel until immediately before surgery compared patients whose surgery was postponed 3 or more days before surgery: 8.8 ± 1.2 g/dL (mean ± SD) vs. 9.1 ± 1.2 g/dL (mean ± SD) (p=0.046). Although this result was statistically significant, it is unlikely to be clinically meaningful. In another study, variation in the timing of APT cessation had no effect on haemoglobin levels from baseline to discharge[46] (**Table 3.2.4**).

Re-operation for bleeding

There were two studies identified that investigated the impact of varying cessation of timing of combination antiplatelet therapies on the frequency of re-operation for bleeding after off pump coronary artery surgery (OPCAB)[42,44,] Kapetanakis et al[42] reported that continuation of clopidogrel until within 7 days of surgery was associated with an increased risk of re-operation for bleeding: in patients who had clopidogrel within 7 days of surgery the incidence of re-operation for bleeding was 6.4% vs. 1.4% in patients who were clopidogrel-naïve or stopped 7 or more days before CABG (p<0.01). Propensity matched pair analysis and logistic regression analysis supported this finding: these analyses both demonstrated that likelihood of re-operation for bleeding is increased when clopidogrel is continued closer to the time of CABG surgery: OR=3.9 (95% CI: [1.42, 10.46]) (p<0.01) and OR=5.1 (95% CI: [2.47, 10.47]) (p<0.01), respectively. In contrast, Song et al[44] reported that the frequency of re-operation for bleeding was not affected when clopidogrel was continued to immediately before OPCAB (**Table 4.2.4**).

Variation in APT regimens, patient populations and statistical analyses are the most likely explanations for the differences in findings between Kapetanakis et al[42] and Song et al[44] .Song et al[44] adjusted for variation in baseline patient characteristics only, whereas Kapetanakis et al[42] performed three different analyses. Therefore, it is reasonable to assume that findings reported by Kapetanakis et al[43] are the most reliable, and that continuation of clopidogrel until within 7 days of surgery is associated with an increased risk of re-operation for bleeding in patients who undergo OPCAB.

In patients who underwent CABG with CPB, Picker et al[46] reported that re-operation for bleeding was more common in patients who continued APT until 1 to 7 days before surgery: 20% vs. 7.5% in patients who had no APT during the 8 days before surgery. This result was not statistically significant (p=0.190). Similarly, Kang et al[45] found there was a trend toward increased re-operation for bleeding in patients who continued clopidogrel until 7 days before surgery (**Table 3.2.4**). It was not reported whether this result was statistically significant.

Hospital length of stay

Two studies assessed the impact of varying the timing of cessation of combination antiplatelet therapies in OPCAB [42,43.] Hospital length of stay was not affected by the timing of cessation of antiplatelet therapies (**Table 4.2.4**). Findings were similar regardless of whether clopidogrel was stopped at the same time as aspirin[42], or clopidogrel was stopped but aspirin continued until surgery[43].

In one study of patients having CABG with CPB, variation in the timing of cessation of APT had no effect on hospital length of stay[46] (**Table 3.2.4**).

Intensive care unit length of stay

Three studies assessed the impact of varying the timing of cessation of clopidogrel (with[43] or without[42,44] aspirin cessation) in OPCAB patients. In these studies, ICU length of stay was not affected by the timing of cessation of antiplatelet therapies (**Table 4.2.4**).

Similarly, variation in the timing of cessation of APT had no effect on ICU length of stay in patients undergoing CABG with CPB[45,46] (**Table 3.2.4**).

Summary of key findings

Results are summarised by the two different combination antiplatelet strategies investigated in the studies involving patients having OPCAB surgery discussed above:

1. Aspirin not ceased, and timing of clopidogrel cessation varied [42,44]
    - Timing of clopidogrel cessation did not affect mortality[42,44], morbidity[42,44], hospital[42] or ICU length of stay[42,44], intraoperative[42,44] or postoperative[44] blood loss.
    - Continuation of clopidogrel until closer to surgery increased the likelihood of transfusion and re-operation for bleeding in one study[42] but had no effect in another[44]. Postoperative haemoglobin levels were slightly decreased when clopidogrel was continued until surgery[44].
2. Timing of both clopidogrel and aspirin cessation varied [43].
    - The effect of varying the timing of cessation on intraoperative and postoperative blood loss is unclear because of to the absence of appropriate statistical analysis.
    - Timing of cessation did not affect transfusion requirements, but cell salvage was used intraoperatively.
    - Timing of cessation did not affect hospital or ICU length of stay.

Cessation of combined antiplatelet therapy (APT) closer to the time of CABG surgery with CPB does not appear to increase morbidity, blood loss, transfusion requirements, and hospital or ICU length of stay. However, definitive conclusions could not be made because of the absence of appropriate statistical analysis[45,46] and data separation[46]. Results regarding the effect of varying the timing of cessation on mortality were inconsistent; increases were reported in two comparisons[45,46] and no effect was reported in another[45]. There is a trend

toward increased re-operation for bleeding, but this was not statistically significant. These conclusions are based on only two studies that varied regarding use of intraoperative antifibrinolytic therapy (**Table 3.2.4**).

Therefore, it is uncertain whether these findings also apply to the guidelines' target population.

Table 3.2.4 Results of studies in patients receiving combination antiplatelet medication

Author	Outcome	Intervention N	Comparator N	Statistical significance
Kang et al (2007)[45]		Clopidogrel not received within 7 days before surgery N=255	1. Clopidogrel continued to within 3 days of surgery, N=25 2. Clopidogrel continued 4–7 days before surgery, N=40	
	Mortality (operative, proportion)	3.1%	1. =8.0% 2. =0.0%	p=0.193 (Comparator 1 vs. intervention)
	Blood loss (chest tube output, mL, mean ± SD)	1720 ± 1258	1. =1811 ± 1223 2. =1596 ± 1238	p=0.775 (Comparator 1 vs. intervention)
	Blood transfusion requirements (units, mean ± SD)	3.4 ± 4.1	1. =5.8 ± 9.4 2. =2.8 ± 3.5	p=0.027 (Comparator 1 vs. intervention)
	Re-operation for bleeding (proportion)	4.3%	1. =8.0% 2. =5.0%	p=0.41 (Comparator 1 vs. intervention)
	ICU LOS (hours, mean ± SD)	52.1 ± 77.9	1. =49.5 ± 63.5 2. =43.6 ± 39.3	p=0.786 (Comparator 1 vs. intervention)

Author	Outcome	Intervention N	Comparator N	Statistical significance
Picker et al (2007)[46]		No APT 8 days before surgery N=40	APT continued until 1–7 days before surgery N=40	
	Mortality (30 day, proportion)	0	2.5%	NR
	Morbidity (proportion)	Pneumonia=0% MI=7.5%	Pneumonia=2.5% MI=0%	NR
	Blood loss (chest tube, at 12 hours postoperative, mL, mean ± SD)	412 ± 590	940 ± 861	NR
	Transfusion requirements, FFP (units, mean ± SD)	1.3 ± 2.5	4.9 ± 6.4	NR
	Transfusion requirements, platelets (units, mean ± SD)	0.1 ± 0.2	1.5 ± 1.3	NR
	Transfusion requirements, RBC (units, mean ± SD)	1.5 ± 2.9	4.5 ± 4.9	NR
	Haemoglobin, baseline (g/dL, mean ± SD)	13.5 ± 1.5	14.0 ± 1.7	NR
	Haemoglobin, discharge (g/dL, mean ± SD)	12.2 ± 1.5	11.9 ± 1.6	NR
	Re-operation for bleeding (proportion)	7.5%	20%	p=0.190, NS
	Hospital LOS (days, mean ± SD)	10.4 ± 2.3	11.6 ± 3.9	NR
	ICU LOS (days, mean ± SD)	1.7 ± 1.4	1.7 ± 1.3	NR

Author	Outcome	Intervention N	Comparator N	Statistical significance
Kapetanakis et al (2006)[42]		Clopidogrel-naïve or stopped ≥7 days before surgery. Aspirin given before surgery. Intraoperative heparin treatment N=1291	Clopidogrel regimen of 75 mg daily within 7 days of surgery or patients received a 300 mg oral loading dose before PCI. Aspirin given before surgery. Intraoperative heparin treatment N=281	
	Mortality, operative (proportion)	1.4%	1.4%	p=1.00
	Morbidity, postoperative stroke (proportion)	1.6%	2.1%	p=0.44
	Morbidity, postoperative MI (proportion)	0.6%	1.4%	p=0.25
	Blood loss, intraoperative (mL, median, min to max)	400 (100–2000)	400 (100–3400)	p=0.02
	Transfusion requirements			
	Intraoperative, platelets (proportion)	1.0%	3.2%	p<0.01
	Intraoperative, platelets, amount (mL, median, min to max)	300 (200–300)	300 (270–600)	p=0.13
	Intraoperative, FFP (proportion)	1.0%	1.8%	p=0.21
	Intraoperative, FFP, amount (mL, median, min to max)	400 (350–750)	400 (100–3400)	p=0.15
	Intraoperative, RBC (proportion)	16.0%	22.1%	p<0.01
	Intraoperative, RBC, amount (mL, median, min to max)	500 (250–1500)	500 (250–1250)	p=0.56
	Postoperative, platelets (proportion)	9.1%	19.6%,	p<0.01
	Postoperative, FFP (proportion)	7.5%	12.1%	p <0.01
	Postoperative, RBC (proportion)	34.4%	55.9%	p<0.01
	Postoperative, RBC, amount (mL, median,	500 (250–2500)	500 (250–3250)	p<0.01

Author	Outcome	Intervention N	Comparator N	Statistical significance
	min to max)			
	Re-operation for bleeding (proportion)	1.4%	6.4%	p<0.01
	Hospital LOS (days, median, min to max)	4 (1–79)	5 (1–62)	p=0.03
	ICU LOS (days, median, min to max)	1 (0–30)	1 (1–28)	p=0.30
		Propensity matched pair analysis (278 pairs, n=556): Clopidogrel regimen of 75 mg daily within 7 days of surgery or patients received a 300 mg oral loading dose of clopidogrel before PCI vs. clopidogrel-naïve or stopped ≥7 days before surgery		
	Mortality, operative (OR, 95% CI)	0.9 (0.24, 3.62)		p=0.92
	Transfusion requirements, received platelets (OR, 95% CI)	2.3 (1.48, 3.71)		p<0.01
	Transfusion requirements, received blood transfusion (OR, 95% CI)	2.7 (1.86, 3.92)		p<0.01
	Transfusion requirements, received multiple units of blood (OR, 95% CI)	1.5 (0.91, 2.52)		p=0.11
	Re-operation for bleeding (OR, 95% CI)	3.9 (1.42, 10.46)		p<0.01
		Logistic regression analysis: Clopidogrel regimen of 75 mg daily within 7 days of surgery or patients received a 300 mg oral loading dose before PCI vs. clopidogrel-naïve or stopped ≥ 7 days before surgery		
	Mortality, operative (OR, 95% CI)	1.0 (0.31, 3.28)		p<0.01
	Transfusion requirements, received platelets (OR, 95% CI)	2.5 (1.77, 3.66)		p<0.01
	Transfusion requirements, received blood transfusion (OR, 95% CI)	2.6 (1.94, 3.6)		p<0.01
	Transfusion requirements, received multiple units of blood (OR, 95% CI)	1.6 (1.07, 2.48)		p=0.02

Author	Outcome	Intervention N	Comparator N	Statistical significance
	Re-operation for bleeding (OR, 95% CI)	5.1 (2.47, 10.47)		p<0.01
Shim et al (2007)[43]		Aspirin and clopidogrel discontinued >6 days before surgery N=33	1. Aspirin and clopidogrel continued until 3 to 5 days before surgery. N=50 2. Aspirin and clopidogrel continued within 3 days of surgery. N=20	
	Blood loss, intraoperative (mL, mean ± SD)	265 ± 146	1. =330 ± 191 2. =323 ± 187	p=0.174 (comparison across all patient groups)
	Blood loss, during first 24 hours in ICU (mL, mean ± SD)	756 ± 408	1. =729 ± 485 2. =627 ± 257	p=0.425 (comparison across all patient groups)
	Transfusion requirements, intraoperative (proportion)	39%	1. =48% 2. =26%	p=0.255 (comparison across all patient groups)
	Transfusion requirements, during first 24 hours in ICU (proportion)	42%	1. =42% 2. =25%	p=0.368 (comparison across all patient groups)
	Transfusion requirements, RBC, intraoperative (units, mean ± SD)	0.4 ± 0.5	1. =0.5 ± 0.5 2. =0.3 ± 0.4	p=0.260 (comparison across all patient groups)
	Transfusion requirements, during first 24 hr in ICU (units, mean ± SD)	0.4 ± 0.7	1. =0.7 ± 1.0 2. =0.6 ± 1.0	p=0.512 (comparison across all patient groups)
	Transfusion requirements, FFP/platelets, intraoperative	0	1. =0 2. =0	NA
	Transfusion requirements, FFP, postoperative	10 units in 4 patients	1. =13 units in 4 patients 2. =2 units in one patients	NR

Author	Outcome	Intervention N	Comparator N	Statistical significance
	Transfusion requirements, platelets, postoperative	None	1. =8 units in 1 patient 2. =8 units in 1 patient	NR
	Haematocrit, preoperative (%, mean ± SD)	35.9 ± 5.7	1. =37.3 ± 5.3 2. =39.4 ± 4.5	p=0.063 (intergroup comparison)
	Haematocrit, postoperative (%, mean ± SD)	25.9 ± 2.5	1. =24.8 ± 3.3 2.= 24.1 ± 2.7	p=0.092 (intergroup comparison)
	Hospital LOS, postoperative (days, mean ± SD)	12.9 ± 7.0	1. =11.0 ± 4.1 2. =10.1 ± 2.2	p=0.174 (intergroup comparison)
	ICU LOS (days, mean ± SD)	2.9 ± 0.7	1. =2.8 ± 0.6 2. =2.7 ± 0.7	p=0.595 (intergroup comparison)
Song et al (2008)[44]		Surgery postponed ≥ 3 days before cessation of clopidogrel (period of cessation: mean=4.3 ± 1.2, range 3–7 days) N=70 (propensity matched score analysis)	Clopidogrel continued until immediately before surgery N=70 (propensity matched score analysis)	
	Mortality, operative (proportion)	0%	1.4%	p=0.41
	Morbidity (proportion)	Perioperative MI=1.4% Coronary spasm=0% Respiratory failure=0% Pneumonia=1.0% Renal failure=1.0% Hepatic failure=1.0% Mediastinitis=0%	Perioperative MI=1.4% Coronary spasm=0% Respiratory failure=1.4% Pneumonia=0% Renal failures=0% Hepatic failure=0% Mediastinitis=1.4%	p=1.0 for perioperative MI; p=0.41 for all other morbidity outcomes
	Blood loss, intraoperative (mL, mean ± SD)	273.8 ± 138.6	303.3 ± 149.5	p=0.842
	Blood loss, postoperative (mL, mean ± SD)	673.2 ± 452.4	601.4 ± 312.6	p=0.616

Author	Outcome	Intervention N	Comparator N	Statistical significance
	Transfusion requirements, platelets, perioperative (proportion)	7.1%	2.9%	p=0.441
	Transfusion requirements, RBC, perioperative (proportion)	33.3%	34.3%	p=1.000
	Transfusion requirements, RBC (units, mean ± SD)	0.5 ± 0.4	0.4 ± 0.3	p=0.624
	Haemoglobin level, preoperative (g/dL, mean ± SD)	12.7 ± 1.8	12.7 ± 1.8	NA
	Haemoglobin level, first day post-surgery (g/dL, mean ± SD)	9.1 ± 1.2	8.8 ± 1.2	p=0.046
	Re-operation for bleeding (proportion)	1.4%	1.4%	p=1.00
	ICU LOS (h, mean ± SD)	52.8 ± 19.6	53.0 ± 52.8	p=0.955

Abbreviations: APT/ACT; antiplatelet therapy/anticoagulation therapy; FFP, fresh frozen plasma; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; NR, not reported; NS, not significant; OR, odds ratio; RBC, red blood cell; SD, standard deviation

Evidence statements

Cardiac surgery

Evidence statements are presented for each of the perioperative management strategies discussed:

- aspirin monotherapy
- clopidogrel monotherapy
- combination antiplatelet medication.

Two evidence statements are presented relating to studies investigating combination antiplatelet medication: one for patients undergoing coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CPB), and another for patients undergoing off-pump CABG (OPCAB). Details of intraoperative administration of heparin was documented in the three studies[42–44] involving patients that underwent off-pump coronary artery surgery (OPCAB); however, it should be noted that all patients who undergo CABG with CPB routinely receive full heparinisation and this may not be explicitly stated in every study.

Aspirin monotherapy

Box 3.2.1 outlines the evidence statement (PO2.1) for the perioperative management of coronary artery bypass graft patients who are receiving aspirin monotherapy.

Box 3.2.1 PO2.1 Evidence statement for perioperative management of coronary artery bypass graft patients receiving aspirin monotherapy

Evidence base	Good (B): One Level II study[35] with a moderate risk of bias; two Level III studies[36,37] with a moderate risk of bias; and two Level III studies with a high risk of bias[38,47]
Consistency	Satisfactory (C): Most studies were consistent. Inconsistency can be explained by differences in study quality
Clinical impact	Poor (D): Slight clinical impact. The impact of the timing of cessation of aspirin therapy on mortality, morbidity (myocardial infarction and pericardial effusion), hospital and intensive care unit length of stay, blood loss and transfusion requirements is uncertain. The reduction in blood loss is not considered clinically meaningful.
Generalisability	Excellent (A): All studies were in coronary artery bypass surgery populations with or without cardiopulmonary bypass.
Applicability	Satisfactory (C): One included study from Europe[37] and one from Australia[47]. There are differences between the healthcare systems of Australia and New Zealand and other included studies[35,36,38]

Evidence statement PO2.1

In patients undergoing coronary atery bypass surgery, the effect of continuing aspirin monotherapy until the day of surgery on mortality[35,36], morbidity[35,37] (myocardial infarction and pericardial effusion), ICU LOS[37,38], hospital LOS[36,38,47], perioperative blood loss and transfusion requirement is uncertain (Grade C)[35–38,47].

Clopidogrel monotherapy

Box 3.2.2 outlines the evidence statement (PO2.2) for the perioperative management of coronary artery bypass graft patients who are receiving clopidogrel monotherapy.

Box 3.2.2 PO2.2 Evidence statement for perioperative management of coronary artery bypass graft patients receiving clopidogrel monotherapy

Evidence base	Poor (D): Three Level III studies: two with a moderate risk of bias[40,41] and one with a high risk of bias[39]
Consistency	Satisfactory (C): Some conflicting findings: mortality was increased in one study[39], but unaffected in others[40,41]. There were also some differences in morbidity findings[40,41]. Inconsistencies may be explained due to study quality, selection bias and a lack of power
Clinical impact	Good (B): Substantial clinical impact. Stopping clopidogrel closer to the time of surgery has negative consequences, including increased transfusion requirements and re-operation for bleeding
Generalisability	Excellent (A): Study populations are the same as the target population
Applicability	Good (B): One study was performed in the UK[39]; one in Canada[41], and another in the USA[40] where the healthcare system has some differences to Australia/NZ

Evidence statement PO2.2

In patients undergoing coronary artery bypass surgery there may be an increased risk of bleeding, transfusion requirement and re-operation for bleeding if clopidogrelis not ceased at least 5 days before surgery. The impact on morbidity and mortality is uncertain (Grade C)[39–41].

Combination antiplatelet medication: patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass

Box 3.2.3 outlines the evidence statement (PO2.3) for the perioperative management of patients undergoing coronary artery bypass graft with cardiopulmonary bypass who are receiving combination antiplatelet medication.

Box 3.2.3 PO2.3 Evidence statement for perioperative management of patients undergoing coronary artery bypass graft with cardiopulmonary bypass, receiving combination antiplatelet medication

Evidence base	Poor (D): Two Level III studies with a high risk of bias[45,46]
Consistency	Satisfactory (C): Results are fairly similar across the studies
Clinical impact	Good (B): There is substantial clinical impact
Generalisability	Excellent (A): Study population is the same as the target population
Applicability	Satisfactory (C): One study was performed in the USA where the healthcare system has some differences to Australia/NZ[45]. One study was performed in Germany[46]

Evidence statement PO2.3

In patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass who are receiving combination antiplatelet medication, the continuation of clopidogrel up until the time of surgery may be associated with an increase in volume of transfusion; however, the available evidence is poor (Grade D)[45,46].

Combination antiplatelet medication: patients undergoing off-pump coronary artery bypass graft surgery

Box 3.2.4 outlines the evidence statement (PO2.4) for perioperative management of patients undergoing off-pump coronary artery bypass graft surgery who are receiving combination antiplatelet medication. Patients in these studies received intraoperative heparin.

Box 3.2.4 PO2.4 Evidence statement for perioperative management of patients undergoing off-pump coronary artery bypass graft receiving combination antiplatelet medication

Evidence base	Poor (D): Three Level III studies, one with a moderate risk of bias[42] and two with a high risk of bias[43,44]
Consistency	Satisfactory (C): Consistent evidence for most outcomes, inconsistent finding for intraoperative blood loss, transfusion and re-operation for bleeding. Explained by inter-study heterogeneity and variation in statistical analyses
Clinical impact	Good (B): Timing of combination anti-platelet cessation does not have negative consequences for the majority of relevant outcomes. However, there , may be an increased likelihood of intraoperative blood loss, transfusion requirement and re-operation for bleeding
Generalisability	Excellent (A): All study populations were off-pump surgery.
Applicability	Satisfactory (C): Two studies were from Korea[43,44] the other from the USA[42]. Healthcare systems in both countries differ from the Australian and New Zealand healthcare systems

Evidence statement PO2.4

In patients undergoing off-pump coronary artery bypass graft surgery who are receiving combination antiplatelet therapy, the effect of continuing clopidogrel within the 7-day period before surgery may be associated with an increased likelihood of red blood cell transfusion and re-operation for bleeding(Grade C)[42–44]. The effect on on mortality[42,44], ICU LOS[42,44] or hospital LOS[42,43]is uncertain (Grade C)[42–44].

3.2.2 Noncardiac surgery or invasive procedures: Summary of evidence

In patients undergoing noncardiac surgery or an invasive procedure, what effect does the cessation and timing of cessation of medications that affect haemostasis have on morbidity, mortality, and red blood cell transfusion?

Methods

The systematic review process identified 13 studies investigating the effect of the timing of haemostasis medication (antiplatelet and/or anticoagulant therapy) on patient outcomes in a variety of noncardiac surgeries and invasive procedures (see **Appendix C**, Volume 2). Study characteristics and results are summarised. The intervention and comparator were defined as previously described for patients undergoing cardiac surgery. Results are presented for different perioperative management strategies.

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for this research question.

No cost-effectiveness studies relevant to this research question were identified in the literature search.

Level I evidence

Three systematic reviews were identified by the literature search[48–50]. The first was a fair quality review specifically on the perioperative management of patients receiving aspirin[48]; the second was a fair quality systematic review on the perioperative management of patients receiving oral anticoagulants (the majority of studies investigating warfarin)[49], and the third was a good quality review of studies of patients receiving warfarin undergoing dental surgery[50]. The characteristics of these three studies are presented in **Table 3.2.5**.

Level II evidence

Four Level II studies that were not included in the previous systematic reviews were identified by the literature search[52,56–58]. Characteristics of these studies are summarised in **Table 3.2.6**. One study investigated NSAIDs in orthopaedic surgery[52], two studies investigated warfarin therapy in minor dental surgery[56,57], and one investigated warfarin therapy in patients undergoing coronary angiography[58]. For further details see **Appendix F** (Volume 2).

Level III evidence

Six Level III studies in noncardiac surgery or invasive procedures were identified[51,53–55,59,60]. Characteristics of these studies are summarised in **Table 3.2.6**. Perioperative management strategies included patients who had been receiving aspirin[51], NSAIDs[53,54], clopidogrel[55], or warfarin with or without bridging therapy[59,60].

Level IV evidence

Because higher level (Levels I, II and III) evidence is presented, non-comparative Level IV evidence is not discussed. Excluded Level IV evidence is listed in **Appendix B**, Volume 2.

Table 3.2.5 Summary of Level I studies

Level I Evidence					
Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Aspirin therapy					
Burger et al (2005)[48]	Systematic review of RCTs and observational studies (36) *Fair*	Patients undergoing surgery or other invasive procedure	Aspirin therapy stopped before procedure	Aspirin therapy continued until procedure	Cardiovascular event including bleeding risk
Warfarin therapy					
Dunn et al (2003)[49]	Systematic review of RCTs and observational studies (31) *Fair*	Patients undergoing dental procedures, cutaneous surgery, cataract surgery, genitourinary surgery and other invasive procedures	Pre- and/or perioperative anticoagulation therapy stopped before procedure	Anticoagulation therapy continued until procedure	Event rates including haemorrhagic events and thromboembolic events
Nematullah et al (2009)[50]	Systematic review of RCTs (5) *Good*	Patients undergoing dental surgery	Warfarin therapy stopped before surgery	Warfarin continued until surgery	Clinically significant nonmajor bleeding and minor bleeding

Abbreviations: RCT, randomised controlled trial

Table 3.2.6 Summary of Level II and III studies

Author	Study type Study quality	Population	Intervention N	Comparator N	Outcomes
Aspirin therapy					
Krishnan et al (2008)[51]	Prospective cohort *Fair*	Patients requiring dental extractions	Aspirin ceased 1–10 days before surgery N=25	Aspirin until surgery N=32	Clinically significant bleeding defined as: continued beyond 12 hours of the operative procedure; caused a patient to call or return to the dental office or emergency department; resulted in the development of a large haematoma within the soft tissues; and required a blood transfusion.
NSAID therapy					
Slappendel et al (2002)[52]	RCT (double-blind) *Good*	Patients undergoing their first elective total hip replacement for coxarthrosis during spinal anaesthesia. Patients receiving NSAIDs before the study were excluded.	Placebo for 2 weeks before surgery N=19	Ibuprofen for 2 weeks before surgery N=17	total blood loss (determined by taking into account the amount in the suction bottles, the weight of the surgical sponges and the irrigation fluid used), blood loss during surgery, blood loss in the 24 hours after surgery
Robinson et al (1993)[53]	Prospective cohort *Fair*	Patients undergoing cemented primary total hip arthroplasties performed for osteoarthritis	No NSAID therapy N=75 (52 general anaesthesia; 23 spinal anaesthesia)	NSAID therapy (for at least 6 months) continued until surgery N=85 (55 general anaesthesia; 30 spinal anaesthesia)	Operative blood loss assessed by swab weighing and suction and theatre drape loss, and the subsequent 24-hour postoperative loss was assessed by the suction drainage over this period.
An et al (1991)[54]	Retrospective cohort *Fair*	Patients who underwent total hip arthroplasty	No aspirin or NSAID therapy or discontinuation at least 2 weeks before surgery N=90	Aspirin or NSAIDs until surgery N=55	Intraoperative blood loss (determined by the volume of blood in suction apparatus and the weight of the sponges with blood), postoperative blood loss (determined by the amount of suction or drainage for 48

					hours after the operation), haemoglobin drop.
Clopidogrel therapy					
Ozao-Choy et al (2008)[55]	Retrospective cohort *Fair*	Patients taking clopidogrel who underwent general surgery	Clopidogrel ceased 7 or more days before surgery N=22	Clopidogrel within the 6 days before surgery N=28	Primary outcomes included blood loss in the first 24 hours and transfusion requirements. Secondary outcomes included deaths, myocardial infarction, stroke, respiratory failure, renal failure, wound infections, and ICU and hospital stay.
Warfarin therapy					
Devani et al (1998)[56]	RCT, (blinding details NR) *Poor*	Patients undergoing dental extractions	Warfarin ceased 2 days before surgery N=32	Warfarin until surgery N=33	Bleeding
Campbell et al (2000)[57]	RCT, (blinding details NR) *Poor*	Patients undergoing dentoalveolar surgery procedures	Warfarin ceased 72-96 hours before surgery N=13	Warfarin until surgery N=12	Blood loss
El-Jack et al (2006)[58]	RCT, (blinding details NR) *Fair*	Patients requiring transfemoral coronary angiography	Warfarin ceased at least 48 hours before angiography N=31	Warfarin until angiography and INR 2-3 N=30	Incidence of vascular access site complication (any groin haematoma, bleeding that caused a significant decrease in Hb (>5 g/dL) or required transfusion, or arteriovenous fistula or pseudo aneurysm formation
Wysokinski et al (2008)[59]	Prospective cohort *Good*	Patients receiving long-term anticoagulation therapy referred for periprocedural management (patients were to undergo general surgeries or invasive procedures)	Warfarin ceased 4–5 days before surgery or procedure N=164	Warfarin ceased 4–5 days before surgery or procedure and bridged with IV heparin or LMWH N=181	The primary efficacy end point was symptomatic arterial venous TE occurring from 5 days before to 90 days after the procedure or surgery. Arterial TE was defined as ischaemic stroke, TIA, amaurosis fugax, unstable angina, myocardial infarction, or other peripheral artery TE.

					The primary safety endpoint was major bleeding defined as overt bleeding plus a haemoglobin decrease of 2 g/dL or more after the procedure or transfusion of 2 units or more of PRBCs, or intracranial, intraspinal, intraocular, retroperitoneal, pericardial or fatal bleeding. Minor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding.
McLemore et al (2006)[60]	Retrospective cohort *Fair*	Patients undergoing open inguinal herniography	Warfarin ceased before surgery (timing of cessation not reported) N=54	Warfarin until surgery N=19 Warfarin ceased before surgery with anticoagulation bridge N=15	Length of stay and post-operative complications within 30 days of the operation.

Abbreviations: Hb, haemoglobin; ICU, intensive care unit; LMWH, low molecular weight heparin; NR, not reported; PRBC, packed red blood cells; RCT, randomised controlled trial; TIA, transient ischaemic attack; TE,thrombotic event.

Aspirin therapy

One systematic review[48] as well as one study published since the publication of this review[51], compared outcomes among patients whose aspirin therapy was stopped before noncardiac surgery or invasive procedure with those whose aspirin therapy was continued. The systematic review by Burger and colleagues[48] identified Level II and III studies of aspirin discontinuation versus aspirin continuation in a number of different surgeries and procedures including spinal and epidural anaesthesia; oral surgery, biopsy, ophthalmology, orthopaedic surgery, urology and vascular surgery. The timing of cessation of aspirin was not reported in the meta-analysis. In the prospective cohort study by Krishnan and colleagues[51], aspirin continuation was compared with aspirin discontinuation in patients undergoing dental surgery. Aspirin therapy was ceased 1–10 days before surgery.

NSAID therapy

Three studies were identified investigating the effect of NSAID therapy on bleeding outcomes in surgery[52–54]. In a double-blind randomised control trial[52], patients not currently on NSAID therapy were randomised to receive either placebo or ibuprofen for 2 weeks before surgery. A prospective cohort study was identified comparing outcomes among patients who had been receiving NSAID therapy for 6 months and continuing therapy until surgery with patients who were not on NSAID therapy[53]. The third study was a retrospective cohort study comparing outcomes among patients who were not receiving aspirin or NSAID therapy or discontinued therapy at least 2 weeks before surgery with patients continuing aspirin or NSAID therapy until surgery[54].

Clopidogrel therapy

One retrospective cohort study was identified comparing outcomes among patients discontinuing clopidogrel therapy more than 7 days before general surgery with patients who continued therapy within 6 days of beginning surgery[55].

Warfarin therapy

Seven studies were identified investigating the effect on patient outcomes of discontinuing warfarin before surgery or procedure with discontinuing warfarin and receiving bridging anticoagulant therapy or continuing warfarin until surgery or procedure[49,50,56–60]. Two of these studies were systematic reviews[49,50]. The review by Dunn and colleagues[49] identified Level II and III studies on the effect of continuing versus discontinuing oral anticoagulants in different surgeries and invasive procedures. While these studies were not specific for warfarin therapy, the majority of the studies included were studies on warfarin. The review by Nematullah et al[50] identified Level II studies on the use of warfarin in patients undergoing dental surgery. A further 5 studies not included in either systematic review were also identified[56–60]. These included 2 RCTs in dental surgery comparing warfarin therapy ceasing 2 or more days before surgery with warfarin therapy continuing until surgery[56,57]. A further RCT was identified comparing patients who ceased warfarin 2 or more days before transfemoral coronary angiography compared with patients who continued warfarin until the procedure[58]. The remaining 2 studies were level III studies investigating warfarin cessation before surgery

or procedure with patients who discontinued warfarin but received bridging therapy[59,60] or patients who continued warfarin therapy[59].

Results of studies on aspirin therapy

The evidence base for aspirin therapy comprises one systematic review[48] and one prospective cohort study[51]. Their results are presented in **Table 3.2.7** and **Table 3.2.8** respectively. In the meta-analysis by Burger and colleagues,[48] they found that continuation of aspirin until the surgery or procedure increased the bleeding rate by a factor of 1.5, however it did not lead to a higher level of the severity of bleeding or bleeding complications. The possible exception to this was in intracranial surgery and possibly transurethral prostatectomy. In a further prospective cohort study identified by the current systematic review process, continuation of aspirin in patients undergoing dental extractions did not result in an increase in bleeding time or in bleeding complications compared with patients discontinuing aspirin 1–10 days before surgery[51].

Overall, the authors of the meta-analysis conclude that aspirin should only be ceased before noncardiac surgery or invasive procedures if it may cause bleeding risks with increased mortality or sequels comparable with the observed cardiovascular risks after aspirin withdrawal[48].

Table 3.2.7 Results of Level I studies in patients receiving aspirin therapy and undergoing noncardiac surgery or invasive procedures

Study	Number of included studies	Results and conclusion
Burger et al (2005)[48]	41 studies (10 randomised, 19 prospective cohort and 12 retrospective cohort) in 49,590 patients (14,981 on aspirin and 34,609 controls)	Clinical studies comparing periprocedural bleeding risks with and without aspirin Summarising all studies, aspirin multiplied baseline bleeding rate by a factor of 1.5. Mortalities, possibly caused by bleeding, occurred only after transurethral prostatectomy. Spinal and epidural anaesthesia In three studies, no spinal haematomas occurred in patients on aspirin. Dermatology Six studies which after a meta-analysis showed a 2.4 increased risk of aspirin related bleeding complications in dermatological procedures (p=0.006). No study showed significance alone. Oral surgical procedures (dental extractions) One RCT involving 39 patients. No significant increase in bleeding complications with aspirin continuation. Biopsy In 3 studies (pancreas transplant biopsy, transbronchial biopsy and core needle breast biopsy) bleeding complications were not related to aspirin. Endoscopy In 4 studies with slightly conflicting results, it was concluded that aspirin was not related to bleeding complications. Ophthalmology In 5 studies aspirin did not significantly increase bleeding complications (OR: 2.7; p=0.88). Orthopaedic surgery In a total of 7 studies, 2 studies found that aspirin use was indicative of a blood transfusion. However, the other studies found no relationship of aspirin use with bleeding complications. Urology In the meta-analysis of 6 studies, aspirin increased the risk of transfusion after biopsy by a factor of 2.7. There were also 2 deaths in patients on low-dose aspirin.
		The authors concluded that perioperative continuation of low-dose aspirin increases the frequency of procedural bleeding. However, with possible exceptions like in intracranial surgery and prostatectomy, low-dose aspirin neither increases the level of the severity of bleeding complications nor the perioperative mortality because of bleeding complications. Discontinuation of low-dose aspirin on the other hand, increases perioperative cardiovascular risks with life-threatening sequels. Therefore, aspirin should only be discontinued perioperatively if aspirin's known or assumed perioperative bleeding risks are expected to be similar or more severe than the observed cardiovascular risks after aspirin withdrawal.

Table 3.2.8 Results of Level III studies in patients receiving aspirin therapy

Author	*Outcome*	*Intervention N*	*Comparator N*	*Statistical significance*
Level III				
Krishnan et al (2008)[51]		Aspirin ceased 1-10 days before surgery N=25	Aspirin until surgery N=32	
	Bleeding time (minutes)	3 ± 2.75	2.75 ± 1.63	NS
	Clotting time (minutes)	5.07 ± 1.63	4.87 ± 1.07	NS
	Prolonged bleeding	0%	0%	NA

Abbreviations: NA, not applicable; NS, not significant

NSAID therapy

The evidence base for NSAID therapy comprises one randomised controlled trial[52], one prospective cohort study[53] and one retrospective cohort study[54]. The results of these studies are presented in **Table 3.2.9**. All three studies demonstrated that blood loss during and after surgery was greater in patients not ceasing NSAID therapy before surgery compared with patients not receiving NSAID therapy or ceasing therapy at least 2 weeks before surgery. While NSAID therapy did not affect haemoglobin levels[53,54], it appears to affect transfusion requirements, with more blood being transfused in patients on NSAID therapy compared with patients who did not receive NSAID therapy[53].

Table 3.2.9 Results of Level II and III studies on perioperative management of patients receiving NSAID therapy

Author	Outcome	Intervention N	Comparator N	Statistical significance
Level II				
Slappendel et al (2002)[52]		Placebo for 2 weeks before surgery N=19	Ibuprofen for 2 weeks before surgery N=17	
	Blood loss during surgery (mL)	416 ± 203	700 ± 367	p<0.01
	Blood loss 24 h after surgery (mL)	380 ± 169	461 ± 312	NS
	Total blood loss (mL)	796 ± 337	1,161 ± 472	p<0.05
Level III				
Robinson et al (1993)[53]		No NSAID therapy N=52[a]	NSAID therapy until surgery N=55[a]	
	Blood loss during surgery (mL)	372 ± 144	682 ± 148	p<0.01
	Blood loss 24 h after surgery (mL)	428 ± 179	672 ± 185	p<0.01
	Total blood loss (mL)	800	1,354	p<0.01
	Mean fall in Hb (g/dL)	-1.2	-0.8	NS
	Mean no. blood units transfused	2.2	3.9	p<0.01

Author	Outcome	Intervention N	Comparator N	Statistical significance
An et al (1991)[54]		No aspirin/ NSAIDs or therapy ceased at least 2 weeks before surgery N=90	Aspirin/ NSAIDs continued until surgery N=50	
	Blood loss during surgery (cm^3)	481	499	NS
	Blood loss 24 h after surgery (cm^3)	600	772	p=0.005
	Mean fall in Hb (g/dL)	3.36	3.46	NS
	Blood transfusion (cm^3)	644	532	NS

Abbreviations: Hb, haemoglobin; NSAID, nonsteroidal antiinflammatory drug
[a]Results shown are for patients receiving general anaesthesia. Results for patients receiving spinal anaesthesia were similar.

Clopidogrel therapy

Only one study was identified investigating the cessation of clopidogrel in patients undergoing noncardiac surgery or invasive procedures[55] and the results of this study are presented in **Table 3.2.10**. All the patients in this cohort underwent major general surgery procedures. While a larger proportion of patients who took their last dose of clopidogrel within 1 week of surgery had significant bleeding after surgery requiring a blood transfusion compared with patients who ceased clopidogrel therapy 7 days or more before surgery, there was no significant differences between the groups in operative or post-operative transfusions, hospital stay, ICU stay, late complications or mortality. The study was a small study however, and was not powered to detect differences in mortality and morbidity. The authors conclude that the results suggest that for nonelective general surgery procedures where outcomes depend on timely surgery, clopidogrel taken within 6 days before surgery should not be a reason to delay surgery.

Table 3.2.10 Results of Level III studies on perioperative management of patients receiving clopidogrel therapy

Author	*Outcome*	*Intervention N*	*Comparator N*	*Statistical significance*
Level III				
Ozao-Choy et al (2008)[55]		Clopidogrel ceased 7 or more days before surgery N=22	Clopidogrel within the 6 days before surgery N=28	
	Blood transfusion in OR	27.0%	10.7%	p=0.12
	Platelet transfusion in OR	0.0%	4.0%	p=0.56
	FFP transfusion in OR	9.0%	0.0%	p=0.18
	ICU stay	19.0%	24.0%	p=0.41
	Post-operative transfusion	18.0%	21.0%	p=0.53
	Late complications	9.0%	14.2%	p=0.45
	Re-operation	0.0%	0.0%	p=1.00
	Hospital stay	14.18 ± 19.0	8.61 ± 6.8	p=0.09
	Mortality	9.0%	4.0%	p=0.42
	Significant bleeding requiring transfusion within 1 week	9.5%	21.4%	NR

Abbreviations: ICU, intensive care unit; FFP, fresh frozen plasma; OR: operating room;

Warfarin therapy

Seven studies were identified by the systematic review process, comparing the discontinuation of warfarin therapy before surgery or procedure with continuing warfarin therapy until surgery or procedure or receiving bridging therapy until surgery or procedure[49,50,55–60]. The evidence base included two systematic reviews[49,50] as well as three RCTs[56–58], one prospective cohort[59] and one retrospective cohort[60] study which were not included in the published reviews. The results for the systematic reviews and the Level II and III studies are presented in **Table 3.2.11** and **Table 3.2.12** respectively.

The analysis performed by Dunn and colleagues[49] found that arterial thromboembolism and stroke rates for patients undergoing all types of surgery and invasive procedures were not higher for patients discontinuing warfarin without bridging therapy compared with patients continuing warfarin therapy or receiving heparin bridging therapy. The analysis also found that major bleeding was rare in patients undergoing dental procedures, arthrocentesis, cataract surgery and upper endoscopy or colonoscopy with or without biopsy. The authors concluded that warfarin therapy does not need to be withheld for patients undergoing these procedures. This was further supported by the meta-analysis by Nematullah and colleagues[50] as well as the two RCTs in dental surgery[56,57], which all found no increase in bleeding between patients ceasing warfarin therapy before the procedure or continuing therapy until surgery. The remaining RCT by El-Jack and colleagues[58], also found no increase in haematoma

formation with continuing warfarin therapy in patients undergoing transfemoral coronary angiography, compared with patients who had their warfarin therapy withheld.

Although it appears that warfarin therapy does not need to be discontinued before the above mentioned procedures, the analysis by Dunn and colleagues[49] found no evidence for the safe continuation of warfarin therapy in other surgeries or procedures. The authors of this review concluded that for other invasive and surgical procedures, warfarin needs to be withheld and the decision whether to pursue an aggressive strategy of perioperative administration of intravenous heparin or subcutaneous LMWH should be individualised based on an estimation of the patient's risks of thromboembolism and bleeding and the patient's preference. Since the publication of this review, a further two studies were identified which investigated the cessation of warfarin therapy with either its continuation or heparin bridging therapy in different surgeries and procedures. In a study by Wysokinski and colleagues[59], the cessation of warfarin was compared with the cessation of warfarin with LMWH bridging therapy in patients undergoing general surgery or invasive procedures. The study found no difference in TE event rate between the two groups. While the group receiving bridging therapy had more minor and major bleeding episodes, this was not significantly different from the group ceasing warfarin therapy. A further smaller study by McLemore and colleagues[60] investigated warfarin cessation with either warfarin continuation or LMWH bridging therapy in patients undergoing surgery for inguinal hernia repair. The results demonstrated no significant difference in mortality or morbidity outcomes between any of the treatment groups, but patients receiving bridging therapy had a significantly longer hospital stay than patients in the other two groups.

Table 3.2.11 Results of Level I studies in patients receiving warfarin therapy

Level I Evidence		
Study	Number of included studies	Results and conclusions
Dunn et al (2003)[49]	31 studies in noncardiac surgery or invasive procedures	Thromboembolic events Overall, for studies reporting thromboembolic events, 29 events occurred among 1868 patients receiving long-term oral anticoagulation and undergoing surgery or invasive procedures (1.6%; 95% CI: 1.0%, 2.1%). Continued oral anticoagulation: 1/237 (0.4%; 95% CI: 0.0%, 2.3%) Discontinued oral anticoagulation: 6/996 (0.6%; 95% CI: 0.0%, 1.1%) Discontinued warfarin with bridging: 0/26 (0.0%; 95% CI: 0.0%, 13.2%) Major bleeding events Major bleeding while receiving therapeutic oral anticoagulants was rare for dental procedures (4/2,014; 0.2%), arthrocentesis (0/32; 0.0%), cataract surgery (0/203; 0.0%), and upper endoscopy or colonoscopy with or without biopsy (0/111; 0.0%) Bleeding was noted in 2 studies involving cutaneous surgery,
		The authors concluded that most patients can undergo dental procedures, joint and soft tissue injections and arthrocentesis, cataract surgery and upper endoscopy or colonoscopy with or without biopsy without alteration of their anticoagulation regimen. For other invasive and surgical procedures, oral anticoagulation needs to be withheld, and the decision whether to pursue an aggressive strategy of perioperative administration of intravenous heparin or subcutaneous low molecular weight heparin needs to be individualised.
Nematullah et al (2009)[50]	5 RCTs (a total of 553 patients) in patients undergoing elective dental surgical procedures (extractions) and taking warfarin	Compared with interrupting warfarin therapy (either partial or complete), perioperative continuation of warfarin with patients' usual dose was not associated with an increased risk of clinically significant nonmajor bleeding (RR: 0.71; 95% CI: 0.39, 1.28; p=0.65) or an increased risk of minor bleeding (RR: 1.19; 95% CI: 0.90, 1.58; p=0.22).
		The authors conclude that continuing the regular dose of warfarin therapy does not seem to confer an increased risk of bleeding compared with discontinuing or modifying the warfarin dose for patients undergoing minor dental procedures.

Abbreviations: CI, confidence interval; RCT, randomised controlled trial; RR, relative risk

Table 3.2.12 Results of Level II and III studies in patients receiving warfarin therapy

Author	Outcome	Intervention N	Comparator N	Statistical significance
Level II				
Devani et al (1998)[56]		Warfarin ceased 2 days before surgery N=32	Warfarin until surgery N=33	
	Bleeding (30 min after surgery)	0%	0%	NA
	Bleeding (24 h after surgery)	0%	0%	NA
	Oozing	1/32 (3.2%)	1/33 (3.0%)	NS
Campbell et al (2000)[57]		Warfarin ceased 72-96 hours before surgery N=13	Warfarin until surgery N=12	
	Serious postoperative bleeding	0%	0%	NA
	Blood loss (mL/unit of surgery)	1.4	2.2	p=0.15
El-Jack et al (2006)[58]		Warfarin ceased at least 48 hours before angiography N=31	Warfarin until angiography and INR 2-3 N=30	
	Haematoma formation	2/31 (6.5%)	3/30 (10%)	NS
Level III				
Wysokinski et al (2008)[59]		Warfarin ceased 4–5 days before surgery or procedure N=164	Warfarin ceased 4–5 days before surgery or procedure and bridged with IV heparin or LMWH N=181	
	TE events	2/182 (1.2%)	2/204 (1.0%)	NS
	Major bleeding	4/182 (2.3%)	6/204 (3.0%)	NS
	Minor bleeding	2/182 (1.1%)	9/204 (4.6%)	NS

Author	Outcome	Intervention N	Comparator N	Statistical significance
McLemore et al (2006)[60]		Warfarin ceased before surgery (timing of cessation not reported) N=54	Warfarin until surgery N=19 Warfarin ceased before surgery with anticoagulation bridge N=15	
	LOS (days)	0.54 ± 1.1	0.72 ± 1.6 3.3 ± 3.3	p<0.0001
	Surgical site haematoma	2%	11% 13%	NS
	Surgical site infection	2%	0% 0%	NS
	Seroma	2%	5% 0%	NS
	Urinary retention	4%	5% 13%	NS
	UTI	0%	5% 0%	NS
	Arrhythmia	2%	5% 7%	NS
	Pneumonia	0%	0% 0%	NS
	Other	1%	11% 0%	NS

Abbreviations: INR, international normalised ratio; LMWH, low molecular weight heparin; LOS, length of stay; NA, not applicable; NS, not significant; TE, thrombotic event; UTI, urinary tract infection

Evidence statements

Noncardiac surgery or invasive procedures

Evidence statements are presented for each of the perioperative management strategies discussed:

- aspirin therapy
- NSAID therapy
- clopidogrel therapy
- warfarin therapy.

Aspirin therapy

Box 3.2.5 outlines the evidence statement (PO2.5) for the perioperative management of patients undergoing noncardiac surgery or invasive procedures who are receiving aspirin therapy.

Box 3.2.5 PO2.5 Evidence statement for perioperative management of patients undergoing noncardiac surgery or invasive procedures receiving aspirin therapy

Evidence base	Satisfactory (C): One systematic review made up mostly of Level III studies with a moderate risk of bias[48] and one Level III study with a moderate risk of bias[51]
Consistency	Good (B): Results are generally consistent
Clinical impact	Satisfactory (C): Moderate clinical impact. Overall study and sample size is relatively large and the evidence comes from a range of different procedures. In most cases, low dose aspirin use increased the frequency of bleeding, although this was not reflected in the severity of bleeding or bleeding complications (with the possible exception of intracranial surgery and prostatectomy). The trade-off in bleeding risk and cardiovascular risk should be considered.
Generalisability	Good (B): The studies included a range of different noncardiac surgeries and invasive procedures and is generalisable to this patient population
Applicability	Good (B): The results of these studies are most likely applicable to the Australian healthcare system

Evidence statement PO2.5

In patients undergoing noncardiac surgery or invasive procedures, the effect of continuing aspirin therapy on morbidity, and mortality and transfusion is uncertain, given the heterogeneity of the populations studied[48,51] (Grade C)

NSAID therapy

Box 3.2.6 outlines the evidence statement (PO2.6) for the perioperative management of patients undergoing noncardiac surgery or invasive procedures who are receiving NSAID therapy.

Box 3.2.6 PO2.6 Evidence statement for perioperative management of patients undergoing noncardiac surgery or invasive procedures receiving NSAID therapy

Evidence base	Good (B): One Level II study with a low risk of bias[52] and two Level III studies with a moderate risk of bias[53,54]
Consistency	Good (B): Results are consistent
Clinical impact	Satisfactory (C): Moderate clinical impact.
Generalisability	Good (B): All studies were performed in orthopaedic patients may be generalisable to orthopaedic patient populations
Applicability	Good (B): One study was conducted in the USA, one in the UK, and the other in the Netherlands

Evidence statement PO2.6

In patients undergoing orthopaedic surgery receiving NSAID therapy, blood loss and transfusion requirements are increased when NSAID therapy is continued until the day of surgery[52–54] (Grade C). There was insufficient evidence to determine the effect of the timing of cessation of NSAID therapy.

Clopidogrel therapy

Box 3.2.7 outlines the evidence statement (PO2.7) for the perioperative management of patients undergoing noncardiac surgery or invasive procedures who are receiving clopidogrel therapy.

Box 3.2.7 PO2.7 Evidence statement for perioperative management of patients undergoing noncardiac surgery or invasive procedures receiving clopidogrel therapy

Evidence base	Poor (D): One Level III study with a moderate risk of bias[55]
Consistency	Not applicable (NA): Only one study
Clinical impact	Poor (D): This is a small study with slight or restricted clinical impact
Generalisability	Good (B): The study included patients undergoing a range of different noncardiac surgeries and is probably generalisable to this patient population
Applicability	Satisfactory (C): The study was from the USA

Evidence statement PO2.7

In patients undergoing noncardiac surgery, the effect of continuing clopidogrel on morbidity, mortality and transfusion is uncertain[55] (Grade D).

Warfarin therapy

Box 3.2.8 outlines the evidence statement (PO2.8) for the perioperative management of patients undergoing noncardiac surgery or invasive procedures who are receiving warfarin therapy.

Box 3.2.8 PO2.8 Evidence statement for perioperative management of patients undergoing noncardiac surgery or invasive procedures receiving warfarin therapy

Evidence base	Excellent (A): One Level I study[50] and one Level III study[59] with a low risk of bias; one Level I study[49] and one Level II study[58] with a moderate risk of bias; and two Level II studies[56,57] with a high risk of bias
Consistency	Good (B): Studies are generally all consistent
Clinical impact	Good (B): Overall there was a substantial clinical impact
Generalisability	Excellent (A): The results are directly generalisable to patients undergoing noncardiac surgery or invasive procedures
Applicability	Good (B): Results of the included studies are most likely applicable to the Australian healthcare system

Evidence statement PO2.8

In patients undergoing minor dental procedures, arthrocentesis, cataract surgery, upper gastrointestinal endoscopy or colonoscopy with or without biopsy, morbidity and mortality are unaffected when warfarin is continued[49,50,56–59] (Grade B). In patients undergoing more complex procedures, the effect on mortality and morbidity is unclear when warfarin is continued or when bridging therapy is administered[49] (Grade B).

3.3 Question 3

In patients undergoing surgery, what is the effect of perioperative strategies that minimise blood loss on morbidity, mortality, and blood transfusion? (Referred to as PO3)

The body of evidence found by the systematic literature review for Question 3 is presented in a **separate** technical report.

3.4 Question 4

In patients undergoing surgery, is anaemia an independent risk factor for adverse outcomes? (Referred to as GN1)

3.4.1 Summary of evidence

Methods

The systematic review process identified 49 studies (see **Appendix C**, Volume 2).

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for this research question.

Level I evidence

No Level I evidence was identified for cardiac surgery by the literature search.

One fair quality systematic review of all study types was identified for noncardiac surgery[61] by the literature search. This review included literature searched to February 2003, and identified 31 studies. The review investigated both the prevalence of anaemia in surgery and the impact of anaemia on a range of clinical, functional, and quality of life outcomes in surgery. The review included results from nine orthopaedic surgical procedures, one lung carcinoma study, two colorectal surgery studies, and one mixed noncardiac surgery study. The characteristics and quality of this systematic review are presented in **Table 3.4.1**. For further details see **Appendix F** (Volume 2).

Table 3.4.1 Summary of Level I evidence: Noncardiac surgery

Level I Evidence			
Study	Study type (number of included studies) Study quality	Population	Outcomes
Shander et al (2004)[61]	Systematic review of all studies (13—prevalence) (20—outcomes) *Fair*	Surgical patients with and without anaemia	Prevalence of anaemia Clinical (morbidity, mortality, hospitalisation, transfusion requirements, disease progression, responsiveness to therapy, adherence to therapy, adverse events) Functional (functional status, cognitive function, exercise tolerance, psychosocial/sexual function, cardiac function/morphology, and quality of life) Satisfaction (patient satisfaction with care) Economic (direct and indirect costs)

The results of the existing systematic review are summarised in **Table 3.4.2**. The review did not attempt to combine the results of individual studies in any way. The review concluded that, although there was a suggestion that lower haemoglobin levels were associated with decreased survival, it was not a universal finding of all studies. Because of the paucity of data, the review could make no conclusions regarding the effect of anaemia on other outcomes. The review did find that most studies identified found that haemoglobin or haematocrit level was a significant predictor of risk of transfusion.

Table 3.4.2 Results of Level I evidence: Noncardiac surgery

Level I Evidence		
Study	Number of included studies	Results and conclusion
Shander et al (2004)[61]	20 studies investigating outcomes (no information was given on the level of evidence of each study or the quality)	Mortality: Nine studies investigated the effect of anaemia on mortality. There was some suggestion that lower haemoglobin levels are associated with decreased survival rates, although this was not found universally Morbidity and functional outcomes: Five studies examined morbidity and five studies examined signs, symptoms and physiologic measures or functional outcomes. No conclusions could be drawn on the effect of anaemia on any of these outcomes because of the lack of data Risk of transfusion: A total of 20 studies addressed the impact of anaemia on risk for and volume of transfusions. Many of these studies found that haemoglobin or haematocrit level were predictors of risk of transfusion

Level II evidence

There were 17 Level II studies identified that investigated the relationship of anaemia as an adverse outcome in patients undergoing surgery: 10 involved cardiac surgery,[62–71] and eight involved noncardiac surgery[63,72–78]. One study investigated both cardiac and noncardiac surgery patients and is reported in both sections[63]. The main characteristics of Level II studies identified by the literature search are summarised in **Table 3.4.3** for cardiac surgery, and in **Table 3.4.4** for noncardiac surgery. For further details see **Appendix F** (Volume 2).

Table 3.4.3 Summary of Level II evidence: Cardiac surgery

Author	Study type Study quality	Population N	Outcomes
DeFoe et al (2001)[62]	Prospective cohort study *Good*	Patients undergoing isolated CABG surgery N=6980	Use of intraoperative or postoperative IABP, intra- or postoperative stroke, return to bypass, return to surgery for postoperative haemorrhage, in-hospital death
Gombotz et al (2007)[63]	Prospective, multicentre cohort study *Good*	Patients undergoing THR, TKR, hemicolectomy, or CABG N=3793	Intra- and postoperative amounts of allogeneic and autologous blood components transfused, prevalence of preoperative anaemia, calculated perioperative RBC loss, lowest measured Hb
Koch et al (2003)[64]	Prospective cohort study *Good*	Patients undergoing CABG N=2417	Postoperative survival time, and 30 day, 6 month and 5 year mortality

Author	Study type Study quality	Population N	Outcomes
Kulier et al (2007)[65]	Prospective, multicentre cohort study *Good*	Patients undergoing CABG surgery with cardiopulmonary bypass N=4804	Fatal and non-fatal outcomes occurring after surgery and during the index hospitalisation were classified as cardiac events (MI, CHF, or death from cardiac causes) or noncardiac events: 1. cerebral events (encephalopathy, stroke, or death from cerebral causes) 2. renal events (renal dysfunction or failure, death from renal causes) 3. gastrointestinal events (ischaemia or infarction, death from gastrointestinal causes) 4. other (infectious, pulmonary) Composite outcome was defined as any of all adverse outcomes, cardiac and noncardiac, including in-hospital mortality
Lee et al (2007)[66]	Prospective cohort study *Fair*	Patients with medically refractory angina receiving coronary stenting for unprotected LMCA disease N=76	Repeated PCI and/or CABG, cardiovascular mortality, total mortality (outcomes were assessed over a follow-up period of 2–94 months)
Parr et al (2003)[67]	Prospective cohort study *Good*	Patients undergoing cardiac surgery with CPB N=600	Risk of receiving >2 units RBC
Rady et al (1998)[68]	Prospective cohort study *Good*	Patients aged ≥75 years undergoing cardiac surgery N=1157	Morbidity—cardiac dysfunction (low cardiac output syndrome) or postoperative MI, postoperative cardiac arrhythmias, pulmonary dysfunction, protracted weaning from ventricular support if the duration of mechanical ventilation was >3 days, renal dysfunction, gastrointestinal dysfunction, hepatic dysfunction, coagulopathy, nosocomial infection, neurologic dysfunction Mortality—death during hospitalisation for surgery, regardless of LOS or within 30 days of surgery if the patient had been discharged from the hospital. ICU LOS
Surgenor et al (2006)[69]	Prospective cohort study *Fair*	Patients undergoing isolated CABG procedures N=8004	Risk of LOF defined as needing intraoperative IABP, return to CPB after initial separation, or ≥ 2 inotropes at 48 hours postoperatively
Swenne et al (2004)[70]	Prospective cohort study *Poor*	Patients undergoing CABG surgery with or without a preoperative diagnosis of diabetes mellitus N=396	Risk of infection

Author	Study type Study quality	Population N	Outcomes
Zindrou et al (2002)[71]	Prospective cohort study *Good*	Patients undergoing isolated CABG N=2059	Mortality—patients who died in hospital (patients who died after hospital discharge were not included in the analysis)

Abbreviations: CABG, coronary artery bypass graft; CHF, congestive heart failure; CPB; cardiopulmonary bypass; Hb, haemoglobin; IABP, intra-aortic balloon pump; ICU, intensive care unit; LMCA, left main coronary artery; LOF, loss of function; LOS, length of stay; MI, myocardial infarction; PCI, percutaneous coronary intervention; RBC, red blood cells; THR, total hip replacement; TKR, total knee replacement

Within the group of cardiac studies, seven were considered of good quality[62–65,67,68,71], two fair[66,69], and the other of poor[70] quality. All were prospective cohort studies.

Table 3.4.4 Summary of Level II evidence: Noncardiac surgery

Author	Study type Study quality	Population N	Outcomes
Conlon et al (2008)[72]	Prospective cohort study *Good*	Patients aged >65 years, scheduled for primary elective unilateral hip arthroplasty N=87	Quality of life via the SF-36 and FACT anaemia
Foss et al (2008)[73]	Prospective cohort study *Good*	Patients undergoing hip fracture surgery N=510	Complications, LOS and 30-day mortality. Complication was defined as the postoperative presence in any patient of: CVA, delirium, AMI or unstable angina, ACHF, new onset arrhythmia, pneumonia, respiratory insufficiency, gastric or duodenal ulceration, renal dysfunction, septicaemia, pulmonary embolism, DVT or wound infection
Gombotz et al (2007)[63]	Prospective, multicentre cohort study *Good*	Patients undergoing THR, TKR, hemicolectomy, or CABG N=3793	Intra- and postoperative amounts of allogeneic and autologous blood components transfused, prevalence of preoperative anaemia, calculated perioperative RBC loss, lowest measured Hb
Halm et al (2004)[74]	Prospective cohort study *Good*	Patients undergoing surgery for hip fracture N=550	Death, readmission, and functional mobility 60 days after hospital discharge (measured using the FIM)
Meltomaa et al (2000)[75]	Prospective cohort study *Fair*	Patients undergoing hysterectomy for benign conditions N=687	Incidences and risk factors for infections
Myers et al (2004)[76]	Prospective cohort study *Poor*	Patients undergoing elective primary hip arthroplasties N=225	Postoperative complications including blood transfusion, UTI, RTI, and hospital LOS

Author	Study type Study quality	Population N	Outcomes
Wallis et al (2005)[77]	Prospective cohort study *Poor*	Patients undergoing first time elective unilateral hip arthroplasty N=30	QoL using the SF-36
Wolters et al (1997)[78]	Prospective cohort study *Good*	Patients undergoing general surgery N=6304	Postoperative complications including pulmonary complications, cardiac complications, wound infection and UTI. Postoperative mortality included all deaths in hospital

Abbreviations: ACHF, acute congestive heart failure; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CVA, cardiovascular accident; DVT, deep vein thrombosis; FIM, functional index measure; Hb, haemoglobin; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; QoL, quality of life; RBC, red blood cell; RTI, respiratory tract infection; THR, total hip replacement; TKR, total knee replacement; UTI, urinary tract infection

Five of the included noncardiac surgery studies were characterised as providing good quality evidence[63,72–74,78], one provided fair quality evidence[75] and two were deemed to be poor quality[76,77]. All were prospective cohort studies. Six studies included orthopaedic surgical patients[63,72–74,76,77], one focused on general surgical patients[78] and one considered patients undergoing gynaecological surgery[75].

The results for Level II cardiac and noncardiac surgery are summarised in **Table 3.4.5** and **Table 3.4.6** respectively.

Table 3.4.5 Results of Level II evidence: Cardiac surgery

Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
DeFoe et al (2001)[62]	In-hospital mortality	%	Hct <19%	Intraoperative	3.90%	p<0.001[b]
			Hct 19–20%		3.30%	
			Hct 21–22%		2.80%	
			Hct 23–24%		1.50%	
			Hct ≥25%		1.60%	
	Intra- or postoperative IABP	%	Hct <19%	Intraoperative	6.10%	p<0.001[b]
			Hct ≥25%		3.60%	
	Return to bypass	%	Hct <19%	Intraoperative	7.50%	p<0.001[b]
			Hct ≥25%		3.80%	
Gombotz et al (2007)[63] (cardiac outcomes)	Risk of RBC transfusion	OR (95% CI)	Hb ≤13 g/dL men	Preoperative	0.69 (0.63, 0.75)	S
			Hb ≤12 g/dL women	Postoperative	1.52 (1.35, 1.70)	S
Koch et al (2003)[64]	1 month mortality	HR	NR	Preoperative	1.6	p=0.279
	6 month mortality				1.9	p=0.050
	Last follow-up mortality				1.5	p=0.01

Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
Kulier et al (2007)[65]	Cardiac outcomes	OR (95% CI)	Hb 13–14 g/dL	Preoperative	0.97 (0.91, 1.04)	p=0.398[b]
			Hb 12–13 g/dL		0.95 (0.84, 1.07)	
			Hb 11–12 g/dL		0.92 (0.77, 1.11)	
			Hb 10–11 g/dL		0.90 (0.70, 1.15)	
			Hb <10 g/dL		0.87 (0.64, 1.19)	
	Noncardiac outcomes	OR (95% CI)	Hb 13–14 g/dL		1.14 (1.06, 1.24)	p<0.001[b]
			Hb 12–13 g/dL		1.31 (1.12, 1.53)	
			Hb 11–12 g/dL		1.49 (1.18, 1.89)	
			Hb 10–11 g/dL		1.71 (1.25, 2.34)	
			Hb <10 g/dL		1.95 (1.32, 2.90)	
Lee et al (2007)[66]	Repeated PCI and/or CABG	OR (95% CI)	Hb ≤13 g/dL men Hb ≤11 g/dL women	NR	NR[c]	p=0.8[d]
	Cardiovascular mortality	OR (95% CI)			NR[c]	p=0.27[d]
	Total mortality	OR (95% CI)			NR[c]	p=0.22[d]
Parr et al (2003)[67]	Risk of >2 U RBC transfusion	OR (95% CI)	Increase Hct%	Preoperative	0.48 (0.38, 0.62)	S
Rady et al (1998)[68]	Morbidity	OR (95% CI)	Hb <10 g/dL or Hct <30%	Postoperative (late)[e]	5.80 (3.25, 11.18)	p<0.001
	Mortality	OR (95% CI)			1.92 (1.0, 3.63)	p=0.05
Surgenor et al (2006)[69]	Low-operative heart failure	OR (95% CI)	Hct <35	Preoperative	1.05 (0.8, 1.36)	p=0.738
			Hct 35–40		0.96 (0.78, 1.18)	p=0.701
			Nadir Hct		0.90 (0.82, 0.98)	p=0.016

Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
Swenne et al (2004)[70]	Any leg wound infection Late leg wound infection Superficial sternal wound	OR (95% CI)	Hb <14 g/dL	Preoperative	1.36 (0.75, 2.46)[f] 2.91 (0.95, 8.89)[f] 4.16 (1.80, 9.62)[g]	p=0.312 p=0.061 p=0.001
Zindrou et al (2002)[71]	Mortality	OR (95% CI)	Hb ≤10 g/dL	Preoperative	3.17 (1.24, 8.08)	p=0.016

Abbreviations: CABG, coronary bypass graft; CI, confidence interval; Hb, haemoglobin; Hct, haematocrit; HR, hazard ratio; IABP, intra-aortic balloon pump; ICU, intensive care unit; NS, not significant; OR, odds ratio; PCI, percutaneous coronary intervention; RBC, red blood cell; S, significant

[a] In some instances, authors did not provide specific statistical data, but reported outcomes as 'significant' or 'not significant'. If no information was available on significance, significance was determined from the 95% confidence intervals

[b] Represents the p-value for the trend for the outcome

[c] None of the outcomes were significant in the univariate analysis and therefore were not entered into the multivariable model

[d] The p-values represent statistical significance from the univariate analysis

[e] Early anaemia was defined as occurring within 2 days of surgery and late anaemia was defined as occurring after 2 days. The 2-day cut-off for anaemia was determined from a regression equation of the likelihood of morbidity against the length of stay in the ICU

[f] Corrected for sex

[g] Corrected for BMI (kg/m^2), diabetes, sex, age, postoperative haemoglobin concentrations day one, cardiopulmonary by-pass time and re-operation on sternum

Table 3.4.6 Results of Level II evidence: Noncardiac surgery

Level II evidence						
Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
Conlon et al (2008)[72]	SF-36	Correlation	Increasing Hb level	Day 8 postoperative	0.47[b]	p<0.0005
	FACT-anaemia				0.47[b]	p<0.0005
Foss et al (2008)[73]	Ability to walk on third postoperative day	OR (95% CI)	Hb <10 g/dL	Day 1 postoperative	0.41 (0.23, 0.73)	p=0.002
Gombotz et al (2007)[63] (noncardiac outcomes)	Risk of RBC transfusion in THR	OR (95% CI)	Hb ≤13 g/dL men Hb ≤12 g/dL women	Preoperative	0.65 (0.60, 0.70)	S
				Postoperative	1.5 (1.38, 1.64)	S
	Risk of RBC transfusion in TKR	OR (95% CI)	Hb ≤13 g/dL men Hb ≤12 g/dL women	Preoperative	0.68 (0.63, 0.73)	S
				Postoperative	1.49 (1.35, 1.64)	S
Halm et al (2004)[74]	Mortality	OR (95% CI)	Hb <12 g/dL	Preoperative[c]	0.65 (0.48, 0.89)	p<0.01
				Postoperative[c]	1.29 (0.86, 1.94)	p<0.05
	Readmission			Preoperative[c]	0.86 (0.74, 1.00)	p<0.05
				Postoperative[c]	0.78 (0.64, 0.95)	p<0.01
	Mobility score	β correlation		Preoperative[c]	0.05 (–0.15, 0.24)	NS
				Postoperative[c]	0.15 (–0.09, 0.38)	NS
	LOS			Preoperative[c]	–0.76 (–1.04, –0.47)	p<0.05
				Postoperative[c]	–0.76 (–1.68, 0.35)	NS
Meltomaa et al (2000)[75]	Risk of infection	OR (95% CI)	NR	Postoperative	2.7 (1.5, 4.7)	p<0.001

Level II evidence						
Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
Myers et al (2004)[76]	Blood transfusion UTI RTI Hospital LOS	Rates anaemia vs. no anaemia Days anaemia vs. no anaemia	Hb <12.5 g/dL men, Hb <11.5 g/dL women	Preoperative	71% vs. 10.5% 28% vs. 14% 14% vs. 12% 18 days vs. 11 days	p<0.001 p=0.039 p=0.55 NR
Wallis et al (2005)[77]	SF-36	Correlation	Increasing Hb level	Post- and preoperative	None[d]	NS
Wolters et al (1997)[78]	Postoperative complications	OR (95% CI)	Hb <10 g/dL	Preoperative	1.23 (1.03, 1.48)	S

Abbreviations: CI, confidence interval; LOS, length of stay; Hb, haemoglobin; NR, not reported; NS, not significant; OR, odds ratio; RBC, red blood cell; RTI, respiratory tract infection; S, significant; THR, total hip replacement; TKR, total knee replacement; UTI, urinary tract infection

[a] In some instances, authors did not provide specific statistical data, but reported outcomes as 'significant' or 'not significant'. If no information was available on significance, significance was determined from the 95% confidence intervals

[b] Correlation after adjustment for age, presence of significant cardiovascular disease and transfusion

[c] Adjusted for prefracture characteristics (mobility, age, sex, nursing home resident, dementia, and paid help at home), clinical status on admission, discharge status and blood transfusion

[d] The study found no correlation between the QoL scores and Hb either preoperatively or postoperatively

Mortality

There were five studies identified that investigated mortality in patients undergoing some form of cardiac surgery[62,64,66,68,71]. Of these, four found that preoperative, intraoperative or postoperative anaemia was a significant predictor of mortality in patients undergoing cardiac surgery[62,64,68,71]. Lee and colleagues[66] did not find anaemia to be a significant predictor for mortality, but the number of patients and total number of deaths in this study was small. Only one prospective cohort study was identified that investigated the effect of anaemia on mortality in patients undergoing noncardiac surgery[74]. This study found that anaemia was a significant predictor of mortality in patients undergoing surgery for hip fracture.

Morbidity

A total of five studies investigated the effect of anaemia on some form of morbidity in patients undergoing cardiac surgery[65,66,69–71]. Lee et al[66] found that repeated percutaneous coronary intervention (PCI) and/or coronary artery bypass graft (CABG) were not significantly related to anaemia. In accordance with this finding, Surgenor et al[69] found that the risk of low-operative heart failure was not associated with preoperative anaemia. Kulier et al[65] found that while cardiac outcomes were not significantly associated with preoperative anaemia, noncardiac outcomes were. The remaining two studies found that preoperative anaemia was a significant predictor of sternal wound/operative site infections, cardiac infections[70] and intraoperative anaemia was found to be a significant predictor of use of intra- and postoperative intra-aortic balloon pump (IABP) interventions as well as return to bypass[62].

Five studies investigated the effect of anaemia on the risk of morbidity in patients undergoing noncardiac surgery[73–76,78]. Among patients undergoing surgery for hip fracture, Foss et al[73] found that postoperative anaemia had a significant negative impact on a patient's ability to walk; and Halm et al[74] reported that preoperative anaemia had no significant effect on mobility. Myers and colleagues[76] reported that preoperative anaemia was not significantly associated with respiratory tract infection (RTI), but was a significant predictor of urinary tract infection (UTI). Meltomaa et al[75] found that postoperative anaemia was a significant predictor of infection in patients undergoing hysterectomy. Wolters and colleagues[78] reported that preoperative anaemia was found to be a significant predictor of postoperative complications among general surgery patients.

Quality of life

Only two prospective cohort studies investigated the effect of anaemia on quality of life; both were conducted among patients undergoing surgery for hip fracture[72,77]. In the most recent study, Conlon and colleagues[72] found that increasing postoperative levels of haemoglobin resulted in better scores using the SF-36 and the FACT-anaemia instruments. In contrast, Wallis et al[77] found no correlation between pre- or postoperative haemoglobin levels and SF-36 scores. No quality of life studies were found in relation to cardiac surgery.

Risk of transfusion

Anaemia as a risk factor for blood transfusion was investigated in one by a cardiac surgery study[67], one in noncardiac surgery study[76], and one study conducted in both cardiac and general surgery patients[63]. The studies found that both preoperative[67,63,76] and postoperative[63] anaemia were significantly associated with transfusion.

Resource use

Only two studies investigated resource use, and both were conducted in patients undergoing noncardiac surgery. Halm et al[74] found that both pre- and postoperative anaemia was a significant predictor of hospital readmissions. This group also found that there was a significant correlation between preoperative anaemia and hospital length of stay. Myers et al[76] reported that patients with preoperative anaemia remained in hospital for longer periods.

No studies examining resource use were found in relation to cardiac surgery.

Level III evidence

Level III evidence was investigated to support the findings of the Level II studies. The main characteristics of Level III studies identified by the literature search are summarised in **Table 3.4.7** for cardiac surgery and in **Table 3.4.8** for noncardiac surgery. For further details see **Appendix F** (Volume 2).

The results for cardiac and noncardiac surgery are summarised in **Table 3.4.9** and **Table 3.4.10** respectively.

Table 3.4.7 Summary of Level III evidence: Cardiac surgery

Author	Study type Study quality	Population N	Outcomes
Bell et al (2008)[79]	Retrospective cohort study *Good*	Patients undergoing CABG only procedures with CPB	30-day operative mortality and 30-day operative morbidity including endocarditis, renal failure requiring dialysis, mediastinitis, re-operation for bleeding, mechanical ventilator used postoperatively >48 hours, repeat cardiac surgery, stroke, coma >24 hours, cardiac arrest requiring cardiopulmonary resuscitation
Cladellas et al (2006)[80]	Retrospective cohort study *Good*	Patients undergoing elective valve replacement N=201	30-day mortality, 30-day MACE
Fang et al (1997)[81]	Retrospective cohort study *Good*	Patients undergoing CABG surgery N=2738	Postoperative in-hospital mortality

Author	Study type Study quality	Population N	Outcomes
Ferraris et al (1996)[82]	Retrospective cohort study *Fair*	Patients undergoing CABG surgery N=938 N=385 (anaemic subgroup)	Hospital mortality, hospital LOS, serious postoperative morbidity (defined as postoperative MI, stroke, pulmonary failure, renal failure necessitating dialysis, postoperative cardiogenic shock necessitating left ventricular assist device or IABP, sepsis, or mediastinitis)
Habib et al (2003)[83]	Retrospective cohort study *Fair*	Patients undergoing cardiac surgery with CPB N=5000	Complications, operative mortality defined as in-hospital death or <30 days out of hospital death, ICU and hospital LOS
Habib et al (2005)[84]	Retrospective cohort study *Good*	Adult CABG with CPB patients; no preoperative renal failure N=1760	Post cardiopulmonary acute renal failure
Higgins et al (1992)[85]	Retrospective cohort study *Good*	Patients undergoing CABG surgery	Mortality defined as death during hospitalisation for surgery, regardless of LOS, or within 30 days of hospital discharge, morbidity (cardiac complication, prolonged ventilation, CNS complication, oliguric or anuric renal failure, serious infection, death)
Karkouti et al (2009)[86]	Prospective cohort study *Fair*	Patients undergoing cardiac surgery from 7 hospitals N=3500	Development of acute kidney injury
Karkouti et al (2008a)[87]	Retrospective cohort study *Fair*	Patients undergoing cardiac surgery from 7 hospitals N=3500	*Composite outcome of in-hospital mortality, stroke, or acute kidney failure*
Karkouti et al (2008b)[88]	Retrospective cohort study *Fair*	Patients undergoing cardiac surgery with CPB N=10,179	Composite outcome of in-hospital mortality, stroke, or acute kidney failure
Karkouti et (2005)[89]	Retrospective cohort study *Fair*	Patients undergoing cardiac surgery with CPB N=10,949	Perioperative stroke
Litmathe et al (2003)[90]	Retrospective cohort study *Fair*	Patients undergoing CABG N=400	Risk of transfusion
McKechnie et al (2004)[91]	Retrospective cohort study *Good*	Patients undergoing PCI at 18 hospitals N=48,851	In-hospital mortality, in-hospital cerebrovascular event, in-hospital post-procedural MI, and a combined end point of MACE including all 3 endpoints

Author	Study type Study quality	Population N	Outcomes
Reinecke et al (2003)[92]	Retrospective cohort study *Fair*	Male patients undergoing elective PCI N=689	In-hospital mortality, long-term mortality

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CNS, central nervous system; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; ICU, intensive care unit; LOS, length of stay; MACE, major cardiac event; MI, myocardial infarction; PCI, percutaneous coronary intervention

Table 3.4.8 Summary of Level III evidence: Noncardiac surgery

Author	Study type Study quality	Population N	Outcomes
Beattie et al (2009)[93]	Retrospective cohort study *Good*	Noncardiac surgery patients including vascular and oncology surgery in head and neck, urology, and thoracic, hepatobiliary, general and gynaecologic procedures N=7679	Mortality within 90 days of the index surgery
Carson et al (2002)[94]	Retrospective cohort study *Fair*	Patients aged $\geq$18 years undergoing surgery who declined blood transfusion because of religious reasons N=2083	30-day mortality, composite outcome of 30-day mortality or in-hospital 30-day morbidity (defined as MI, arrhythmia, CHF, or infection)
Dunkelgrun et al (2008)[95]	Retrospective cohort study *Good*	Patients undergoing elective noncardiac open vascular surgery with known or suspected CAD N=1363	Cardiac death (acute MI, cardiac arrhythmias, CHF) and composite outcome of MACE—defined as non-fatal MI and cardiac death. Both outcomes were measured at 30 days and 5 years
Gruson et al (2002)[96]	Retrospective cohort study *Fair*	Patients who had sustained an operatively treated hip fracture N=395	Postoperative medical complications, in-hospital mortality, hospital LOS, hospital discharge status, place of residence at one year, and mortality and recovery of ambulatory ability and ADL status at 3, 6 and 12 months after surgery
Lawrence et al (2003)[97]	Retrospective cohort study *Poor*	Patients $\geq$60 years undergoing hip fracture repair at 20 academic and community hospitals N=5793	Distance walked at time of discharge
Lunn and Elwood (1970)[98]	Retrospective cohort study *Poor*	Patients undergoing surgery N=1584	Complications, postoperative hospital LOS, mortality following surgery but before hospital discharge

Author	Study type Study quality	Population N	Outcomes
Marcantonio et al (1998)[99]	Retrospective cohort study *Poor*	Female patients undergoing major elective noncardiac surgery N=1341	Postoperative delirium
Rogers et (2007a)[100]	Retrospective cohort study *Fair*	Patients from 128 Veterans Affairs' medical centres and 14 private-sector hospitals who underwent major general or vascular procedures N=184,120	Postoperative venous thromboembolic events
Stoller et al (1994)[101]	Retrospective cohort study *Fair*	Patients undergoing percutaneous nephrolithotomy N=96	Risk of transfusion
Saleh et al (2007)[102]	Retrospective cohort study *Poor*	Patients undergoing elective orthopaedic procedures N=1322	Risk of transfusion
Wu et al (2007)[103]	Retrospective cohort study *Good*	Veterans aged $\geq$ 65 years undergoing major noncardiac surgery N=310,311	30-day postoperative mortality, combined outcome of 30-day mortality or cardiac events

Abbreviations: ADL, activities of daily living; CAD, coronary artery disease; CHF, congestive heart failure; LOS, length of stay; MACE, major adverse cardiac event; MI, myocardial infarction

Table 3.4.9 Results of Level III evidence: Cardiac surgery

Level III evidence						
Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
Bell et al (2008)[79]	30-day mortality 30-day postoperative morbidity	OR (95% CI)	Hb <10 g/dL	Preoperative	1.29 (0.99, 1.68) 1.20 (1.02, 1,43)	p=0.0641 p=0.033
Cladellas et al (2006)[80]	Mortality MACE MACE (after EUROscore adjustment)	OR (95% CI)	Hb <12 g/dL	Preoperative	3.23 (1.09, 9.55) 5.18 (2.18, 12.3) 4.67 (2.14, 10.36)	p=0.033 p<0.001 p<0.001
Fang et al (1997)[81]	Mortality	OR (95% CI)	Lowest Hct Hct <15%	Intraoperative	3.987 2.7	p=0.0001 p<0.001
Ferraris et al (1996)[82]	Operative mortality Serious postoperative morbidity Hospital LOS ≥8.4 days	OR (95% CI)	Age/RBCVOL	Preoperative	NR[b] 13.7 (6.7, 27.7) 2.6 (1.9, 3.4)	NS S S
Habib et al (2003)[83]	Operative mortality Cardiac ICU >2 days Postoperative hospital stay >8 days 0–6 year mortality	OR (95% CI) RR (95% CI)	Hct continuous	Intraoperative	0.86 (0.82, 0.92) 0.97 (0.96, 0.98) 0.95 (0.93, 0.98) 0.95 (0.92, 0.98)	p<0.001 p<0.001 p<0.001 p=0.001
Habib et al (2005)[84]	Acute renal failure	Coefficient[c]	Lowest Hct Hct 20–24 Hct <20	Intraoperative	0.93 (0.88, 0.98) 1.80 (0.94, 3.44) 2.46 (1.32, 4.56)	p=0.007 p=0.074 p=0.004

Level III evidence						
Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
Higgins et al (1992)[85]	Morbidity Mortality	OR (95% CI)	Hct ≤34	Preoperative	1.57 (1.20, 2.04) 2.68 (1.71, 4.20)	p=0.001 p<0.0001
Karkouti et al (2009)[86]	AKI, >25% decrease in GFR or dialysis	OR (95% CI)	Hb 12–13.9 g/dL Hb 10–11.9 g/dL Hb <10 g/dL	Preoperative	1.23 (1.07, 1.49) 1.63 (1.25, 2.12) 1.99 (1.29, 3.08)	S S S
	AKI, >50% decrease in GFR or dialysis		Hb 12–13.9 g/dL Hb 10–11.9 g/dL Hb ≤10 g/dL		1.06 (0.73, 1.54) 1.65 (1.07, 2.54) 2.94 (1.66, 5.23)	NS S S
	AKI, >75% decrease in GFR or dialysis		Hb 12–13.9 g/dL Hb 10–11.9 g/dL Hb <10 g/dL		1.00 (0.58, 1.67) 1.82 (1.04, 3.17) 1.83 (0.84, 3.95)	NS S NS
Karkouti et al (2008a)[87]	Adverse outcome	OR (95% CI)	Hb <12.5 g/dL	Preoperative	2.0 (1.4, 2.8)	p<0.0001
Karkouti et al (2008b)[88]	Adverse outcome	OR (95% CI)	Hb <7 g/dL <50% decrease from baseline	Lowest intraoperative Intraoperative	1.15 (0.84, 1.56) 1.53 (1.12, 2.08)	p=0.4 p=0.007
Karkouti et al (2005)[89]	Perioperative stroke	OR (95% CI)	+1% decrease Hb ≤12 g/dL	Intraoperative	1.10 (1.04, 1.18) 45%	S
Litmathe et al (2003)[90]	Risk of RBC transfusion	OR (95% CI)	Hb <11 g/dL	Preoperative	2.1 (1.6, 3.0)	p=0.0001

Level III evidence						
Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
McKechnie et al (2004)[91]	In-hospital mortality MI MACE	OR (95% CI)	Hb ≤13 g/dL men Hb ≤12 g/dL women	Preoperative	2.29 (1.79, 2.92) 1.34 (1.05, 1.72) 1.2 (1.05, 1.34)	p<0.0001 p=0.02 p<0.01
Reinecke et al (2003)[92]	Mortality	OR (95% CI)	Hb ≤12.9 g/dL	Preoperative	4.09 (1.52, 11.05)	p=0.008 (compared with Hb 14.6–15.2)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; GFR, glomerular filtration rate; Hb, haemoglobin; Hct, haematocrit; MACE, major cardiovascular event; MI, myocardial infarction; NS, not significant; OR, odds ratio; RBC, red blood cell; S, significant; RBCVOL, red blood cell volume

[a] In some instances authors did not provide specific statistical data, but reported outcomes as 'significant' or 'not significant'. Significance was determined from 95% confidence intervals if significance was not specified

[b] Only significant multivariate predictors were reported

[c] Correlation after adjustment for age, presence of significant cardiovascular disease and transfusion

Table 3.4.10 Results of Level III evidence: Noncardiac surgery

Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
Beattie et al (2009)[93]	90-day mortality	OR (95% CI)	Hb ≤ 13 g/dL men Hb ≤12 g/dL women	Preoperative	2.36 (1.57. 3.41)	p<0.0001
Carson et al (2002)[94]	Mortality	OR (95% CI)	+1 g/dL increase in Hb	Postoperative	2.1 (1.7, 2.6)	S
			Hb 1.1–2 g/dL		100%	p<0.01
			Hb 2.1–3 g/dL		54.20%	
			Hb 3.1–4 g/dL		25%	
			Hb 4.1–5 g/dL		34.40%	
			Hb 5.1–6 g/dL		9.30%	
			Hb 6.1–7 g/dL		8.90%	
			Hb 7.1–8 g/dL		0%	
	Mortality or morbidity		Hb 1.1–2 g/dL		100%	p<0.01
			Hb 2.1–3 g/dL		91.70%	
			Hb 3.1–4 g/dL		52.60%	
			Hb 4.1–5 g/dL		57.70%	
			Hb 5.1–6 g/dL		28.60%	
			Hb 6.1–7 g/dL		22%	
			Hb 7.1–8 g/dL		9.40%	

Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
Dunkelgrun et al (2008)[95]	30-day MACE	OR (95% CI)	Mild: Hb 12.2–13.0 g/dL men, 11.2–12.0 g/dL women	Preoperative	1.8 (0.8, 4.1)[b]	NS
			Moderate:11.0–12.1 g/dL men, 10.2–11.1 g/dL women		2.3 (1.1, 5.4)[b]	S
			Severe: 7.2–11.0 g/dL men, 7.5–10.1 g/dL women		4.7 (2.6, 10.9)[b]	S
	5 year MACE	HR (95% CI)	Mild: Hb 12.2–13.0 g/dL men, 11.2–12.0 g/dL women		2.4 (1.5, 4.2)[b]	S
			Moderate: 11.0–12.1 g/dL men, 10.2–11.1 g/dL women		3.6 (2.4, 5.6)[b]	S
			Severe: 7.2–11.0 g/dL men, 7.5–10.1 g/dL women		6.1 (4.1, 9.1)[b]	S
Gruson et al (2002)[96]	3 month mortality	OR (95% CI)	Hb ≤13 g/dL men, Hb ≤12 g/dL women	Preoperative	1.4 (0.5, 4.2)	NS
	6 month mortality				2.9 (1.2, 7.3)	p=0.02
	12 month mortality				2.6 (1.2, 5.5)	p=0.01
	Increased hospital LOS	Correlation			NR	p<0.01
Lawrence et al (2003)[97]	Distance walked at time of discharge	Feet (95% CI)	Hb 7 g/dL	Postoperative	56 (42, 70)	p<0.001
			Hb 8 g/dL		61 (54, 68)	
			Hb 9 g/dL		67 (64, 70)	
			Hb 10 g/dL		74 (72, 77)	
			Hb 11 g/dL		83 (80, 85)	
			Hb 12 g/dL		92 (87, 96)	

Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
Lunn and Elwood (1970)[98]	Postoperative complications (men)	Rates	Hb <10 g/dL	Preoperative	15.90%	p<0.01
			Hb ≥10 g/dL		5.70%	
	Postoperative complications (women)		Hb <10 g/dL		5.90%	p>0.7
			Hb ≥10 g/dL		6.80%	
	Mortality (men)		Hb <10 g/dL		15.30%	p<0.01
			Hb ≥10 g/dL		2.90%	
	Mortality (women)		Hb <10 g/dL		19%	p<0.01
			Hb ≥10 g/dL		2.10%	
Marcantonio et al (1998)[99]	Development of delirium	OR (95% CI)	Hct <30%	Postoperative	1.7 (1.1, 2.7)	p=0.03
Rogers et (2007a)[100]	Venous thromboembolism	OR (95% CI)	Hct ≤38%	Preoperative	1.32 (1.09, 1.60)	p=0.004
Stoller et al (1994)[101]	Transfusion	Rates	Hb >12 g/dL	Preoperative	14%	p<0.05
Saleh et al (2007)[102]	Transfusion	OR (95% CI)	Hb 11.1–13.0 g/dL	Preoperative	2.42 (1.69, 3.48)	p<0.001
			Hb ≤11 g/dL		13.92 (7.77, 24.90)	p<0.001

Author	Outcome	Risk measure	Definition of anaemia	Time of haemoglobin measurement	Risk	Statistical significance[a]
Wu et al (2007)[103]	30-day mortality and cardiac event rate	OR (95% CI)	Hct <18	Preoperative	2.41 (1.55, 3.73)	S
			Hct 18–20.9		1.52 (1.12, 2.07)	S
			Hct 21–23.9		1.11 (0.93, 1.34)	NS
			Hct 24–26.9		1.27 (1.13, 1.44)	S
			Hct 27–29.9		1.25 (1.13, 1.38)	S
			Hct 30–32.9		1.19 (1.08, 1.31)	S
			Hct 33–35.9		1.2 (1.09, 1.32)	S
			Hct 36–38.9		1.12 (1.03, 1.23)	S
			Hct 39–41.9		1.10 (1.01, 1.20)	S
			Hct 42–44.9		1.06 (0.97, 1.17)	NS
			+1% decrease		1.02 (1.01, 1.05)	S

Abbreviations: CI, confidence interval; Hb, haemoglobin; Hct, haematocrit; NR, not reported; NS, not significant; OR odds ratio; S, significant; SE, standard error; LOS, length of stay

[a] In some instances, authors did not provide specific statistical data, but reported outcomes as 'significant' or 'not significant'

[b] Adjustments were made for anaemia, GFR, heart failure, age, sex, type of vascular surgery, diabetes mellitus, hypertension, coronary heart disease, stroke, and chronic obstructive pulmonary disease

Mortality

There were eight studies identified that investigated anaemia as a risk factor for mortality in patients undergoing cardiac surgery[79–83,85,91,92]. Most found that either pre- or intraoperative anaemia was a significant risk factor for mortality in the cardiac surgery population[80,81,83,91,92]. A study by Bell and colleagues[79] found that preoperative anaemia was not a significant predictor of 30-day mortality. Ferraris et al[82] found that preoperative anaemia combined with age was not a significant predictor of operative mortality.

There were five studies identified that investigated the effect of anaemia on mortality in a noncardiac surgery patient population[93,94,96,98, 103]. Although Gruson et al[96] found that preoperative anaemia was not a significant risk factor for three month mortality, it was reported to be a significant risk factor for longer term mortality (6 and 12 month mortality). Beattie and colleagues[93] found preoperative anaemia to be a significant predictor of 90-day mortality. Carson et al[94] studied a patient population who refused blood transfusion on the basis of religious belief, and also found that as the postoperative haemoglobin level decreased, the proportion of patients dying increased. No patients with a haemoglobin level greater than 7 g/dL were reported to have died.

Morbidity

There were nine studies identified in patients undergoing cardiac surgery that investigated the effect of anaemia on different morbidity outcomes[79,80,82,85–87,89,91,92]. Of these, four found preoperative anaemia to be a significant predictor of postoperative morbidity[79,82,85,87]. Other studies reported that preoperative anaemia was a significant risk factor for morbidity outcomes including acute kidney injury[86], major adverse cardiac events[80,91] and myocardial infarction[91]. Intraoperative anaemia was found to be a predictor of acute renal failure[86] and perioperative stroke[89]. Karkouti and colleagues[878] reported that the difference in haemoglobin level from baseline was a predictor for adverse outcomes.

In patients undergoing noncardiac surgery, anaemia was investigated as a risk factor for morbidity outcomes in six studies[94,95,9798,99,100,103]. It was reported that preoperative anaemia was a significant predictor of morbidity outcomes such as mortality and cardiac event rate[103], and the development of venous thromboembolism[100]. Lawrence et al[97] found that postoperative anaemia had a significant effect on the distance walked at discharge in patients undergoing hip fracture surgery; and Marcantonio et al[99] reported that postoperative anaemia was a significant risk factor for development of delirium. In the study by Carson et al[94] of surgery patients refusing blood transfusion, it was found that patients with postoperative anaemia had greater morbidity. Although there were no deaths among patients with haemoglobin levels above 7 g/dL, these patients still experienced significant morbidity.

Quality of life

There were no Level III studies identified that investigated anaemia on quality of life in surgical patients for either cardiac or noncardiac populations.

Risk of transfusion

Anaemia as a risk factor for blood transfusion was investigated by one study in cardiac surgery[90] and two noncardiac surgery studies[101,102]. All studies reported that preoperative anaemia was a significant risk factor for transfusion.

Resource use

A total of three studies investigated the effect of anaemia and hospital length of stay[82,83,96]. In cardiac surgery it was found that preoperative[82] and intraoperative anaemia[83] were significant predictors of hospital length of stay. Preoperative anaemia was a significant predictor of increased hospital length of stay in patients undergoing noncardiac surgery. Gruson et al[96] showed a significant relationship between preoperative anaemia and hospital length of stay.

Level IV evidence

Six Level IV studies were identified. Given the quantity of higher level evidence, data were not extracted from these studies, which are listed in **Appendix B**, Volume 2. No quality of life data were reported in these Level IV studies.

Evidence statements

As GN Q1 was a risk question which did not test an intervention, no actions or recommendations have been developed from the evidence generated. Interventions are considered in later questions.

Box 3.4.1 outlines the evidence statement (GN1.1) for morbidity and mortality in patients with preoperative anaemia undergoing cardiac surgery.

Box 3.4.1 GN1.1 Evidence statement for the impact of preoperative anaemia on morbidity and mortality in patients undergoing cardiac surgery

Evidence base	Good (B): One good quality Level II[65] study, and three good quality[79,80,85] and three fair quality[82, 86, 87,]Level III studies for morbidity; two good quality Level II[64,71] studies, and three good quality[79,80,85] Level III studies for mortality
Consistency	Good (B): A relationship between anaemia and mortality was consistent; the relationship between morbidity and anaemia was mostly consistent
Clinical impact	Satisfactory (C): Overall study and sample size is large but there was some discrepancy around the definition of mortality
Generalisability	Good (B): All study results were from patients undergoing cardiac surgery
Applicability	Satisfactory (C): Seven studies included sites from the USA, three included sites from Europe, two included sites from Canada and one from Asia.

Evidence statement GN1.1

In patients undergoing cardiac surgery, preoperative anaemia is associated with an increased risk of morbidity and mortality (Grade B)[64,65,71,79,80,82,85, 86,87].

Box 3.4.2 outlines the evidence statement (GN1.2) on the impact of preoperative anaemia on likelihood of transfusion in cardiac patients.

Box 3.4.2 GN1.2 Evidence statement for the impact of preoperative anaemia on likelihood of transfusion in patients undergoing cardiac surgery

Evidence base	Good (B): Two good quality[63,67] Level II studies; one fair quality[90] Level III study
Consistency	Excellent (A): All consistent
Clinical impact	Good (B): Substantial clinical impact
Generalisability	Good (B): Can be applied to cardiac patients; need to take into consideration the procedure being completed
Applicability	Satisfactory (C): One study was from the USA, and two from Europe

Evidence statement GN1.2

In patients undergoing cardiac surgery, preoperative anaemia is associated with an increased likelihood of transfusion (Grade B)[63,67,90].

Box 3.4.3 outlines the evidence statement (GN1.3) for the impact of pre- and intraoperative anaemia on length of stay in patients undergoing cardiac surgery.

Box 3.4.3 GN1.3 Evidence statement for the impact of pre- and intraoperative anaemia on length of stay in patients undergoing cardiac surgery

Evidence base	Poor (D): Two fair quality Level III studies[82,83]
Consistency	Satisfactory: (C): Some inconsistency, reflecting genuine uncertainty around the question
Clinical impact	Poor (D): Slight or restricted clinical impact
Generalisability	Satisfactory (C): May be applied to all cardiac surgical patients
Applicability	Satisfactory (C): Both studies were conducted in the USA

Evidence statement GN1.3

In patients undergoing cardiac surgery, preoperative and intraoperative anaemia are associated with increased hospital length of stay (Grade D)[82,83].

Box 3.4.4 outlines the evidence statement (GN1.4) for mortality and morbidity outcomes in patients with intraoperative anaemia undergoing cardiac surgery.

Box 3.4.4 GN1.4 Evidence statement for the impact of intraoperative anaemia on mortality and morbidity in patients undergoing cardiac surgery

Evidence base	Satisfactory (C): One good quality[62] Level II study; two good quality[84,81] and one fair quality[83,88] Level III study
Consistency	Good (B): The studies showed a relationship between intraoperative anaemia and mortality and morbidity
Clinical impact	Satisfactory (C): Overall there was a moderate clinical impact
Generalisability	Good (B):All studies were performed in cardiac surgery patients
Applicability	Satisfactory (C): All studies were conducted in the USA.

Evidence statement GN1.4

In patients undergoing cardiac surgery, an intraoperative/operative haematocrit level below 20% is associated with an increased risk of morbidity and mortality (Grade C)[62,83,84,8188].

Box 3.4.5 outlines the evidence statement (GN1.5) for mortality and morbidity in patients with preoperative anaemia undergoing noncardiac surgery.

Box 3.4.5 GN1.5 Evidence statement for the impact of preoperative anaemia on mortality and morbidity in patients undergoing noncardiac surgery

Evidence base	Good (B): One good quality[74] Level II study, two good quality,[93,103] one fair quality[99] and one poor quality Level III study[98] for mortality. Two good quality[74,78] and one poor quality[76] Level II study, and two good quality[103, 95], three fair quality[94,96],[100]and two poor quality[97,98] Level III studies for morbidity
Consistency	Good (B): Mortality results consistent; some consistency among morbidity results
Clinical impact	Satisfactory (C): Reasonable samples; however, each applies to different outcomes for morbidity, and there is a question around the definition of mortality
Generalisability	Good (B): The results are generalisable to some extent, given they are from preoperative populations. The results, however, may depend on the type of surgery undergone
Applicability	Satisfactory (C): Seven studies were conducted in the USA, two in the UK, and one each inCanada, Germany and the Netherlands.

Evidence statement GN1.5

In patients undergoing noncardiac surgery, preoperative anaemia is associated with an increased risk of postoperative morbidity and mortality (Grade B)[74,76,78,93, 95,96,98,100,103].

Box 3.4.6 outlines the evidence statement (GN1.6) for the impact of preoperative anaemia on length of stay and likelihood of transfusion in patients undergoing noncardiac surgery.

Box 3.4.6 GN1.6 Evidence statement for the impact of preoperative anaemia on length of stay and likelihood of transfusion in patients undergoing noncardiac surgery

Evidence base	Satisfactory (C): One good quality[74] and one poor quality[76] Level II study, and one fair quality[96] Level III study for length of stay. One good quality Level II[63], and one fair quality[101] and one poor quality[102] Level III study for likelihood of transfusion
Consistency	Excellent (A): All results were consistent
Clinical impact	Good (B): Good sample size
Generalisability	Poor (D): Not directly generalisable
Applicability	Satisfactory (C): Three studies were conducted in the USA, and three in Europe

Evidence statement GN1.6

In patients undergoing noncardiac surgery, preoperative anaemia is associated with an increased likelihood of transfusion and increased hospital length of stay (Grade C)[63,74,76,96,101,102].

Box 3.4.7 outlines the evidence statement (GN1.7a) for mortality in patients with postoperative anaemia undergoing noncardiac surgery.

Box 3.4.7 GN1.7a Evidence statement for the impact of postoperative anaemia on mortality in patients undergoing noncardiac surgery

Evidence base	Good (B): One good quality[74] Level II study, and one fair quality[94] Level III study
Consistency	Good (B): Both All studies report a link with intraoperative anaemia and mortality outcomes
Clinical impact	Satisfactory (C): The review demonstrates moderate clinical impact
Generalisability	Poor (D): Main study is from a hip fracture population, which is not generalisable to the noncardiac perioperative population
Applicability	Satisfactory (C): Two studies were conducted in the USA

Evidence Statement GN1.7a

In patients undergoing noncardiac surgery, postoperative anaemia is associated with an increased risk of mortality (Grade C) [74,94].

Box 3.4.8 outlines the evidence statement (GN1.7b) for morbidity in patients with postoperative anaemia undergoing noncardiac surgery.

Box 3.4.8 GN1.7b Evidence statement for the impact of postoperative anaemia on morbidity outcomes in patients undergoing noncardiac surgery

Evidence base	Good (B): Three good quality[72–74], one fair quality[75] and one poor quality[77] Level II study; one fair quality[94] and two poor quality[97]98,[99]102 Level III studies
Consistency	Good (B): All studies report a link between intraoperative anaemia and morbidity outcomes; however, the outcomes differ
Clinical impact	Satisfactory (C): Reasonable samples however they each apply to different outcomes
Generalisability	Satisfactory (C): Studies are made up of differing types of noncardiac surgeries
Applicability	Satisfactory (C): Four studies were conducted in the USA, two in the UK, and in Denmark

Evidence statement GN1.7a

In patients undergoing noncardiac surgery, postoperative anaemia is associated with an increased risk of morbidity (Grade B) [72–75,77,94,97,99]

Evidence statement GN1.7

In patients undergoing noncardiac surgery, postoperative anaemia is associated with an increased risk of morbidity (Grade B)[72–75,77,94,97,99]102103 and mortality (Grade C)[74,94]98.

Box 3.4.9 outlines the evidence statement (GN1.8) on the impact of postoperative anaemia on likelihood of transfusion in patients undergoing noncardiac surgery.

Box 3.4.9 GN1.8 Evidence statement for the impact of postoperative anaemia on likelihood of transfusion in patients undergoing noncardiac surgery

Evidence base	Satisfactory (C): One good quality[63] Level II study
Consistency	Not applicable (NA): Only one study
Clinical impact	Satisfactory (C): Moderate clinical impact
Generalisability	Satisfactory (C): Numerous types of noncardiac surgery included
Applicability	Satisfactory (C): The study was conducted in Austria

Evidence statement GN1.8

In patients undergoing noncardiac surgery, postoperative anaemia is associated with an increased likelihood of transfusion (Grade C)[63].

3.5 Question 5

In patients undergoing surgery, what is the effect of red blood cell (RBC) transfusion on patient outcomes? (Referred to as GN2)

3.5.1 Effect of red blood cell transfusion: Summary of evidence

Methods

A total of 44 studies[104–145] were identified from the systematic review process (see **Appendix C** in Volume 2). These included two studies that investigated the cost of perioperative red blood cell transfusion[139,140], and five studies that compared liberal with restrictive red blood cell transfusion protocols[141–145].

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for this research question.

No published cost-effectiveness analyses on the effect of RBC transfusion on patient outcomes were identified in the literature search for this research question.

Results pertaining to liberal versus restrictive transfusion are presented separately in the second part of this chapter (*Effect of liberal versus restrictive red blood cell transfusion protocols*).

Level I evidence

No existing systematic reviews examining the effect of RBC transfusion on patient outcomes in a perioperative patient population were identified by the literature search.

Level II evidence

No Level II evidence examining the effect of RBC transfusion on patient outcomes in a perioperative patient population was identified by the literature search.

Level III evidence

Of the 37 Level III studies identified, 21 pertain to cardiac surgery, and 16 to noncardiac surgery; the main characteristics of these studies are summarised in **Table 3.5.1** and **Table 3.5.2** respectively. (See **Appendix F** in Volume 2 for further details). Because the studies could not control who did or did not receive the intervention (RBC transfusion), the highest grading they could receive was 'fair'.

Table 3.5.1 Summary of Level III evidence for RBC transfusion: Cardiac surgery

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Surgenor et al (2009)[104]	Retrospective cohort study *Fair*	Patients undergoing CABG, valve or CABG/valve surgery over a	RBC transfusion N=3254	No RBC transfusion N=5825	Mortality

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
		4 year period N=9079			
Hortal et al (2009)[105]	Prospective cohort study *Fair*	Patients undergoing major heart surgery in Europe who developed suspicion of VAP N=986	RBC transfusion N=NR	No RBC transfusion N=NR	VAP
Cislaghi et al (2009)[106]	Prospective cohort study *Fair*	Cardiac surgery patients admitted to ICU over a 6 year period N=5123	RBC transfusion N=NR	No RBC transfusion N=NR	Prolonged mechanical ventilation
Scott et al (2008)[107]	Retrospective cohort study *Fair*	Patients undergoing primary CABG at a tertiary care heart centre over a 3 year period N=1746	RBC transfusion N=1069	No RBC transfusion N=677	Mortality, extubation and LOS
Ranucci et al (2008a)[108]	Retrospective case–control study *Fair*	Patients who have undergone surgical re-exploration for postoperative bleeding after cardiac operations and propensity matched controls N=464	RBC transfusion N=NR	No RBC transfusion N=NR	Morbidity (low cardiac output, acute renal failure, sepsis), hospital mortality
Murphy et al (2007)[109]	Retrospective cohort study *Fair*	Patients undergoing cardiac surgery N=8724	RBC transfusion N=4909	No RBC transfusion N=3689	Risk of infection, ischaemic outcome, cost increase, hospital LOS, mortality
Rogers et al (2007b)[110]	Retrospective cohort study *Fair*	Adult patients who underwent primary CABG surgery, primary valve replacement surgery or both N=380	RBC transfusion N=326	No RBC transfusion N=54	Infection
Koch et al (2006a)[111]	Retrospective cohort study	Patients undergoing	RBC transfusion	No RBC transfusion	All cause mortality

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
	Fair	isolated CABG over a 7.5 year period N=10,289	N=5233	N=5056	
Surgenor et al (2006)[69]	Prospective cohort study *Fair*	Patients undergoing isolated CABG over a 9 year period N=8004	RBC transfusion N=1802	No RBC transfusion N=6208	Low operative heart failure
Koch et al (2006b)[112]	Retrospective cohort study *Fair*	Patients undergoing isolated CABG over a 7.5 year period N=11,963	RBC transfusion N=5812	No RBC transfusion N=6151	In-hospital mortality and morbidity
Koch et al (2006c)[113]	Retrospective cohort study *Fair*	Patients undergoing isolated CABG over a 3 year period N=5841	RBC transfusion in ICU N=1360	No RBC transfusion N=4481	Postoperative AF
Koch et al (2006d)[114]	Retrospective cohort study *Fair*	Patients undergoing isolated CABG, isolated valve repair or replacement, or a combination of both over a 4 year period N=7321	RBC transfusion N=4195	No RBC transfusion N=3126	QoL using DASI
El Solh et al (2006)[115]	Case–control study *Fair*	Patients were elderly who developed pneumonia post-cardiac surgery. Controls were matched for age, sex, type of surgery, FEV_1 and EF N=146	RBC transfusion N=NR	No RBC transfusion N=NR	Pneumonia
Augoustides et al (2006)[116]	Retrospective cohort study *Fair*	Adults undergoing thoracic aortic surgery requiring	RBC transfusion N=NR	No RBC transfusion N=NR	Mortality

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
		deep hypothermic circulatory arrest N=144			
Banbury et al (2006)[117]	Retrospective cohort study *Fair*	Patients undergoing cardiovascular surgery over a 5 year period N=15,592	RBC transfusion N=8539	No RBC transfusion N=7053	Septicaemia, bacteraemia, superficial and deep sternal wound infection
Kuduvalli et al (2005)[118]	Retrospective cohort study *Fair*	Patients undergoing isolated CABG over a 3 year period N=3024	RBC transfusion N=940	No RBC transfusion N=2084	30-day and 1-year mortality
Olsen et al (2003)[119]	Retrospective cohort study *Fair*	Patients undergoing CABG over 3.5 year period N=1980	Intraoperative RBC transfusion N=691 Postoperative RBC transfusion N=1332	No intraoperative RBC transfusion N=1289 No postoperative RBC transfusion N=648	Leg harvest site infection
Bucerius et al (2003)[120]	Prospective cohort study *Fair*	Patients undergoing cardiac surgery over a 5 year period N=16,184	RBC transfusion N=NR	No RBC transfusion N=NR	Perioperative stroke
Chelemer et al (2002)[121]	Prospective cohort *Fair*	Patients undergoing primary isolated CABG surgery over a 7 month period N=605	RBC transfusion N=271	No RBC transfusion N=262	Bacterial infection
Engoren et al (2002)[122]	Retrospective cohort study *Fair*	Patients who underwent first time isolated CABG with CPB over a 3.5 year period N=1953	RBC transfusion N=659	No RBC transfusion N=1266	Long-term survival
Leal-Noval et al (2001)[123]	Prospective cohort study	Patients undergoing	RBC transfusion	No RBC transfusion	Infection, mortality, ICU LOS

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
	Fair	cardiac surgery N=738	N=592	N=146	

Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass graft; DASI, Duke Activity Status Index; EF, expiratory flow; FEV_1, forced expiratory volume in one minute; ICU, intensive care unit; LOS, length of stay; NR, not reported; QoL, quality of life; RBC, red blood cell; VAP, ventilator-associated pneumonia

Table 3.5.2 Summary of Level III evidence for RBC transfusion: Noncardiac surgery

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Soleimani et al (2009)[124]	Prospective cohort study *Poor*	Patients with BPH who were candidates for either open prostatectomy or TURP	RBC transfusion N=NR	No RBC transfusion N=NR	Erectile dysfunction
Garcia-Alvarez et al (2009)[125]	Prospective cohort study *Fair*	Patients with displaced sub-capital hip fracture undergoing Thompson hip hemi-arthroplasty N=290	RBC transfusion N=120	No RBC transfusion N=170	Infection
Fuks et al (2009)[126]	Prospective cohort study *Fair*	Patients undergoing pancreatico-duodenectomy N=680	RBC transfusion N=NR	No RBC transfusion N=NR	Development of pancreatic fistula
Bursi et al (2009)[127]	Retrospective cohort study *Fair*	Patients undergoing elective major vascular surgery N=359	Perioperative RBC transfusion N=95	No perioperative RBC transfusion N=264	30-day mortality, 30-day MI, combined outcome of 30-day mortality or 30-day MI
Bernard et al (2009)[128]	Prospective cohort study *Fair*	Patients undergoing major surgical procedures in 121 hospitals as part of ACS-NSQIP N=125,177	Intra- or postoperative RBC transfusion N=4788	No RBC transfusion N=120,389	Infection, morbidity and mortality
Silva et al (2008)[129]	Prospective cohort study *Fair*	Patients undergoing general surgery who need blood transfusion N=80	Differing units of RBC transfusion N=80	None	Mortality

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Johnson et al (2008)[130]	Retrospective cohort study *Fair*	Patients who underwent surgery for popliteal artery aneurysms N=537	RBC transfusion N=NR	No RBC transfusion N=NR	Operative morbidity and mortality, early amputation
Engoren et al (2008)[131]	Retrospective cohort study *Poor*	Patients undergoing surgery for hip fracture N=229	RBC transfusion N=90	No RBC transfusion N=139	Mortality
Rogers et al (2007a)[100]	Retrospective cohort study *Fair*	Patients undergoing major general or vascular surgery over a 2 year period N=184,120	RBC transfusion N=NR	No RBC transfusion N=NR	Venous thromboembolism
Ruttinger et al (2007)[132]	Retrospective cohort study *Fair*	Surgical patients who required intensive care over a 12 year period N=3037	RBC transfusion N=1792	No RBC transfusion N=1245	Mortality
BuSaba et al (2007)[133]	Prospective cohort study *Fair*	Patients undergoing head and neck operations over a 2 year period N=3050)	RBC transfusion N=NR	No RBC transfusion N=NR	Prolonged hospital LOS
Weber et al (2005a)[134]	Prospective cohort study *Fair*	Patients undergoing THR over a 1-year period N=444	RBC transfusion N=92	No RBC transfusion N=352	Wound healing disturbances, hospital LOS
Halm et al (2003)[135]	Prospective cohort study *Fair*	Patients undergoing surgery for hip fracture at 4 hospitals N=551	RBC transfusion N=300	No RBC transfusion N=251	Mortality, readmission, mobility (using the FIM)
Dunne et al (2002)[136]	Retrospective cohort study *Fair*	Patients undergoing noncardiac surgery N=6301	RBC transfusion N=NR	No RBC transfusion N=NR	Postoperative pneumonia, 30-day mortality, hospital LOS

Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Chang et al (2000)[137]	Prospective cohort study *Fair*	Patients undergoing colorectal surgery at 11 centres in Canada N=1349	RBC transfusion N=282	No RBC transfusion N=1067	Infection
Carson et al (1998a)[138]	Retrospective cohort study *Fair*	Patients aged ≥ 60 years undergoing hip fracture surgery at 20 hospitals in the USA over a 10 year period N=8787	RBC transfusion N=3699	No RBC transfusion N=5088	30- and 90-day mortality

Abbreviations: ACS-NSQIP, American College of Surgeons–National Surgical Quality Improvement Program; BPH, benign prostatic hyperplasia; CABG, coronary bypass graft surgery; DASI, Duke Activity Status Index; FEV_1, forced expiratory volume in one minute; FIM, functional independence measure; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; NR, not reported; RBC, red blood cell; THR, total hip replacement; TURP, transurethral prostatectomy; VAP, ventilator-associated pneumonia

There were 37 Level III studies identified that examined the effect of RBC transfusion on patient outcomes in a perioperative patient population. The evidence base comprised 16 prospective cohort studies, 20 retrospective cohort studies, and one case–control study. Of the 37 studies, 21 specifically investigated cardiac surgery—mostly coronary artery bypass graft surgery (CABG). Results from the cardiac surgery studies are presented in **Table 3.5.3**, and those from the noncardiac studies in **Table 3.5.4**.

Table 3.5.3 Results of Level III evidence for RBC transfusion: Cardiac surgery

Study	Outcome	Units RBC Transfused	Transfusion	No Transfusion	OR (95% CI)	Statistical significance
Surgenor et al (2009)[104]	6 month mortality (HR, 95% CI)	Any	NR	NR	1.67 (1.21, 2.28)	p=0.002
	5 year mortality (HR, 95% CI)	Any	NR	NR	1.16 (1.01, 1.33)	p=0.035
Hortal et al (2009)[105]	VAP (risk per unit transfused)	Each unit	NR	NR	1.08 (1.04, 1.13)	p<0.001
Cislaghi et al (2009)[106]	Prolonged mechanical ventilation	>4 units	NR	NR	5.43 (3.63, 8.07)	<0.0001
Scott et al (2008)[107]	Mortality (correlation coefficient)	NR	33/1,069 (3.1)	0/677 (0.0)	0.383	p<0.001
	Time to extubation (h, correlation coefficient)	NR	8.0 ± 7.5	4.3 ± 4.6	0.259	p<0.001
	Prolonged LOS (days, correlation coefficient)	NR	7.2 ± 6.8	4.3 ± 2.0	0.434	p<0.001
	ICU LOS (days, correlation coefficient)	NR	1.6 ± 1.6	1.2 ± 0.7	0.209	p<0.001
Ranucci et al (2008a)[108]	Low cardiac output	Increasing RBC units	NR	NR	1.14 (1.04, 1.25)	p=0.003
	Acute renal failure	Increasing RBC units	NR	NR	1.10 (1.02, 1.19)	p=0.012
	Sepsis	Increasing RBC units	NR	NR	1.11 (1.03, 1.21)	p=0.008
	Hospital mortality	Increasing RBC units	NR	NR	1.08 (1.01, 1.16)	p=0.031
Murphy et al (2007)[109]	30-day mortality (HR [95% CI])	Any	NR	NR	6.69 (3.66, 15.1)	p<0.0001
	Infection	Any	NR	NR	3.73 (2.32, 5.07)	S
	Ischaemic outcome	Any	NR	NR	4.05 (2.63, 5.70)	S
	Relative increase in cost	Any	NR	NR	1.42 (1.37, 1.46)	S
	ICU discharge (HR [95% CI])	Any	NR	NR	0.69 (0.65, 0.72)	p<0.0001
	Hospital discharge (HR [95% CI])	Any	NR	NR	0.63 (0.60, 0.67)	p<0.0001
Rogers et al (2007b)[110]	Infection	Any	NR	NR	4.4 (1.5, 13.2)	p=0.009
Koch et al (2006a)[111]	All cause mortality (HR [SE])	Increasing RBC units	NR	NR	0.074 (0.016)	p<0.0001

Study	Outcome	Units RBC Transfused	Transfusion	No Transfusion	OR (95% CI)	Statistical significance
Surgenor et al (2006)[69]	Low operative heart failure	1–2 units	223/1802 (12.4)	422/6208 (6.8)	1.27 (1.00, 1.61)	p=0.047
Koch et al (2006b)[112]	In-hospital mortality	Any	178/5812 (3.07)	3/6151 (0.05)	1.77 (1.67, 1.87)	p<0.0001
	Renal morbidity	Each unit	105/5812 (1.81)	0/6151 (0.0)	2.06 (1.87, 2.27)	p<0.0001
	Prolonged ventilatory support	Each unit	531/5812 (9.14)	27/6151 (0.44)	1.79 (1.72, 1.86)	p<0.0001
	Serious postoperative infection	Each unit	292/5812 (5.03)	15/6151 (0.24)	1.76 (1.68, 1.84)	p<0.0001
	Cardiac morbidity	Each unit	176/5812 (3.03)	3/6151 (0.05)	1.55 (1.47, 1.63)	p<0.0001
	Neurologic morbidity	Each unit	140/5812 (2.41)	23/6151 (0.37)	1.37 (1.30, 1.44)	p<0.0001
	Overall morbidity	Each unit	717/5812 (12.33)	59/6151 (0.96)	1.73 (1.67, 1.80)	p<0.0001
Koch et al (2006c)[113]	Atrial fibrillation in on-pump population	Any	NR	NR	1.18 (1.14, 1.23)	p<0.0001
	Atrial fibrillation in off-pump population	Any	NR	NR	1.25 (1.16, 1.34)	p<0.0001
Koch et al (2006d)[114]	Quality of life using DASI	Any	NR	NR	0.89 (0.87, 0.92)	p<0.0001
El Solh et al (2006)[115]	Risk of pneumonia	≥4 units	NR	NR	2.8 (1.2, 6.3)	p=0.01
Augoustides et al (2006)[116]	Mortality	Any	NR	NR	NR	NS
Banbury et al (2006)[117]	Septicaemia/bacteraemia (coefficient [SD])	Increasing RBC units	NR	NR	0.23 (0.0210)	p<0.0001
	Superficial sternal wound infection	Increasing RBC units	NR	NR	0.029 (0.0087)	p=0.0008
	Deep sternal wound infection	Increasing RBC units	NR	NR	0.12 (0.023)	p<0.0001
Kuduvalli et al (2005)[118]	30-day mortality (HR [95% CI])	Any	NR	NR	1.88 (1.23, 3.00)	p<0.01
Olsen et al (2003)[119]	Total leg infections	≥5 units	18/135 (13.3)	58/1141 (5.1)	2.8 (1.5, 5.0)	p=0.001
	Confirmed leg infections	≥5 units	NR	NR	3.1 (1.7, 5.7)	p<0.001
Bucerius et al (2003)[120]	Perioperative stroke	High transfusion requirement	NR	NR	6.04 (5.05, 7.23)	p<0.0001

Study	Outcome	Units RBC Transfused	Transfusion	No Transfusion	OR (95% CI)	Statistical significance
Chelemer et al (2002)[121]	Bacterial infection	1–2 units	NR	NR	2.11 (0.97, 5.59)	p=0.06
		3–5 units	NR	NR	6.67 (2.60, 17.12)	p<0.001
		≥6 units	NR	NR	10.27 (2.66, 39.71)	p=0.001
Engoren et al (2002)[122]	5 year mortality (risk ratio [95% CI])	Any	99/659 (15.0)	82/1266 (6.5)	1.7 (1.4, 2.0)	p=0.001
		Intraoperative	20/164 (12.2)	82/1266 (6.5)	1.2 (0.6, 1.7)	p=0.534
		Postoperative	33/303 (10.9)	82/1266 (6.5)	1.6 (1.2, 2.0)	p=0.029
		Both	46/192 (24.0)	82/1266 (6.5)	2.4 (2.0, 2.8)	p<0.001
Leal-Noval et al (2001)[123]	Severe postoperative infection	≥4 units	NR	NR	2.0 (1.0, 4.0)	p=0.042
	Pneumonia	≥4 units	NR	NR	2.6 (1.1, 5.8)	p=0.016
	Mortality	Any	79/592 (13.3)	13/146 (8.9)	NR	p<0.01
	ICU LOS (days)	Any	6.1 days	3.7 days	NR	p<0.01

Abbreviations: CI, confidence interval; DASI, Duke Activity Status Index; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay; NR, not reported; NS, not significant; OR, odds ratio; RBC, red blood cell; S, significant; SD, standard deviation; SE, standard error; VAP, ventilator-associated pneumonia

Table 3.5.4 Results of Level III evidence for RBC transfusion: Noncardiac surgery

Study	Outcome	Units RBC transfused	Transfusion	No transfusion	OR (95% CI)	Statistical significance
Garcia-Alvarez et al (2009)[125]	Superficial wound infection	Any	NR	NR	1.96 (1.05, 3.62)	p<0.05
	UTI	Any	NR	NR	1.76 (1.08, 2.89)	p<0.05
	Pneumonia	Any	NR	NR	2.85 (1.21, 6.69)	p<0.05
Fuks et al (2009)[126]	Grade C pancreatic fistula	Any	NR	NR	1.72 (0.10, 28.75)	p=0.70
		>2 units	NR	NR	1.98 (0.09, 4.79)	p=0.65
Bursi et al (2009)[127]	30-day mortality (HR, [95% CI])	3 (2–4); median, 25th to 75th percentile	16/95 (16.8)	4/264 (1.5)	5.38 (1.45, 20.0)	p=0.012
	MI (HR, [95% CI])	3 (2–4); median, 25th to 75th percentile	20/95 (21.1)	18/264 (6.8)	2.23 (0.98, 5.09)	p=0.056
	MI or mortality (HR, [95% CI])	3 (2–4); median, 25th to 75th percentile	26/95 (27.4)	19/264 (7.2)	3.07 (1.43, 6.59)	p=0.004
Bernard et al (2009)[128]	Surgical site infection	1 U intraoperatively 2 U intraoperatively 3–4 U intraoperatively 5–9 U intraoperatively 10+ U intraoperatively >4 U postoperatively	208/1343 (15.5) 381/1903 (38.1) 207/977 (21.2) 75/412 (18.2) 35/153 (22.9) 110/575 (19.1)	5,779/120,389 (4.8)	1.02 1.25 1.19 0.94 1.21 1.19	p>0.05 p<0.05 p<0.05 p<0.05 p<0.05 p<0.05
	UTI	1 U intraoperatively 2 U intraoperatively 3–4 U intraoperatively 5–9 U intraoperatively 10+ U intraoperatively >4 U postoperatively	89/1343 (6.6) 120/1903 (6.31) 84/977 (8.6) 33/412 (8.0) 12/153 (7.8) 59/575 (10.3)	1,685/120,389 (1.4)	1.12 1.04 1.33 1.17 1.03 1.73	p<0.05 p<0.05 p<0.05 p<0.05 p<0.05 p<0.05

Study	Outcome	Units RBC transfused	Transfusion	No transfusion	OR (95% CI)	Statistical significance
	Pneumonia	1 U intraoperatively 2 U intraoperatively 3–4 U intraoperatively 5–9 U intraoperatively 10+ U intraoperatively >4 U postoperatively	130/1343 (9.7) 204/1903 (10.7) 139/977 (14.2) 66/412 (16.0) 38/153 (24.4) 141/575 (24.5)	1,685/120,389 (1.4)	1.24 1.25 1.41 1.64 2.80 2.71	p<0.05 p<0.05 p<0.05 p<0.05 p<0.05 p<0.05
	Sepsis or septic shock	1 U intraoperatively 2 U intraoperatively 3–4 U intraoperatively 5–9 U intraoperatively 10+ U intraoperatively >4 U postoperatively	263/1343 (19.6) 466/1903 (24.5) 284/977 (29.1) 123/412 (29.9) 57/153 (37.3) 250/575 (43.5)	3852/120,389 (3.2)	1.29 1.53 1.62 1.64 2.29 3.39	p<0.05 p<0.05 p<0.05 p<0.05 p<0.05 p<0.05
	Morbidity	1 U intraoperatively 2 U intraoperatively 3–4 U intraoperatively 5–9 U intraoperatively 10+ U intraoperatively >4 U postoperatively	568/1,343 (42.3) 912/1,903 (47.9) 556/977 (56.9) 242/412 (58.7) 106/153 (69.3) 428/575 (74.4)	11,437/120,389 (9.5)	1.23 1.40 1.68 1.81 2.89 4.80	p<0.05 p<0.05 p<0.05 p<0.05 p<0.05 p<0.05
	Mortality	1 U intraoperatively 2 U intraoperatively 3–4 U intraoperatively 5–9 U intraoperatively 10+ U intraoperatively >4 U postoperatively	136/1343 (10.1) 194/1903 (10.2) 150/977 (15.4) 67/412 (16.3) 45/153 (29.4) 153/575 (26.6)	1204/120,389 (1.0)	1.32 1.38 1.97 2.17 9.93 2.65	p<0.05 p<0.05 p<0.05 p<0.05 p<0.05 p<0.05
Silva et al (2008)[129]	Mortality	Increasing RBC units	NR	NR	2.22 (1.10, 4.46)	p=0.026
Johnson et al (2008)[130]	Morbidity and mortality	≥1 unit	NR	NR	4.5 (2.3, 8.9)	p=0.0002
	Early amputation	≥1 unit	NR	NR	7.2 (1.3, 40.4)	NS
Engoren et al (2008)[131]	Mortality (RR [95% CI])	Any	31/90 (34.4)	28/139 (20.1)	3.76 (1.22, 11.63)	p=0.02

Study	Outcome	Units RBC transfused	Transfusion	No transfusion	OR (95% CI)	Statistical significance
Rogers et al (2007a)[100]	Venous thromboembolism	>4 units	NR	NR	1.61 (1.03, 2.51)	p=0.037
Ruttinger et al (2007)[132]	Mortality in the ICU	1–2 units	NR	NR	0.68 (0.35, 1.28)	p=0.261
		3–4 units	NR	NR	1.11 (0.52, 2.39)	p=0.793
		5–8 units	NR	NR	1.16 (0.60, 2.26)	p=0.660
		>8 units	NR	NR	0.74 (0.36, 1.51)	p=0.406
	ICU LOS	Any	NR	NR	1.50 (1.36, 1.66)	p<0.0001
BuSaba et al (2007)[133]	Prolonged hospital LOS	Any	NR	NR	1.20 (1.10, 1.31)	p<0.0001
Weber et al (2005a)[134]	Wound healing disturbances	Any	29/92 (31)	63/352 (18)	2.1 (1.2, 3.5)	p=0.03
	Hospital LOS (coefficient [95% CI])	Any	12.3 days	9.8 days	2.2 (1.3, 3.1)	p<0.001
	1-year mortality	Any	NR	NR	1.67 (1.01, 2.89)	p=0.049
Halm et al (2003)[135]	Mortality	Any	14/300 (4.7)	7/251 (2.8)	1.74 (0.51, 5.94)	NS
	Readmission	Any	49/300 (16.4)	44/251 (17.7)	0.54 (0.30, 0.97)	S
	FIM score (coefficient [95% CI])	Any	19/300 (6.2)	17/251 (6.9)	0.27 (–0.47, 1.01)	NS
Dunne et al (2002)[136]	Mortality	Any intraoperatively	NR	NR	1.08 (1.04, 1.13)	p<0.001
		>4 units	NR	NR	2.84 (2.07, 3.89)	p<0.001
	Risk of infection	Any intraoperatively	NR	NR	1.06 (1.01, 1.11)	p<0.01
		>4 units	NR	NR	9.28 (5.74, 15.00)	p<0.001
	Hospital LOS (coefficient [SE])	Any intraoperatively	NR	NR	0.54 (0.10)	p<0.001
		>4 units	NR	NR	7.39 (0.82)	p<0.001

Study	Outcome	Units RBC transfused	Transfusion	No transfusion	OR (95% CI)	Statistical significance
Chang et al (2000)[137]	Postoperative infection (total)	Any	73/282 (25.9)	152/1067 (14.2)	1.18 (1.05, 1.33)	p=0.007
	Wound infection	Any	63/282 (22.3)	144/1067 (13.5)	1.13 (1.01, 1.54)	p=0.04
	Intra-abdominal infection	Any	10/282 (3.5)	8/1067 (0.7)	1.17 (0.995, 1.379)	p=0.058
Carson et al (1998a)[138]	30-day mortality	Preoperative	NR	NR	1.24 (0.81, 1.90)	NS
	30-day mortality	Postoperative	NR	NR	0.96 (0.74, 1.26)	NS
	90-day mortality (HR [95% CI])	Postoperative	NR	NR	1.08 (0.90, 1.29)	NS

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; NR, not reported; NS, not significant; OR, odds ratio; RBC, red blood cell; RR, relative risk; S, significant; UTI, urinary tract infection

Mortality

Ten studies investigated the effect of RBC transfusion on short and long-term mortality in patients undergoing cardiac surgery[104,107–109,111,112,116,118,122,123]. Of these, seven studies found that RBC transfusion was a significant predictor of short-term mortality[107–109,111,112,118,123], with the odds of death increasing with increasing units of blood transfused[108,111]. In contrast, Augoustides and colleagues[116] found that, although RBC transfusion was a univariate predictor of mortality in patients undergoing thoracic aortic surgery, it was not a significant multivariate predictor. Three studies investigated longer-term mortality[104,118,122]. The evidence showed that RBC transfusion was a significant predictor of 6-month[104], 1-year[118] and 5-year mortality[122]. Engoren and colleagues[122] found that postoperative transfusion correlated with higher 5-year mortality, but intraoperative transfusion did not.

Eight studies investigated the effect of RBC transfusion on mortality in patients undergoing noncardiac surgery[127–129,131,132,135,136,138]. Results from these studies conflict somewhat. Five studies found that RBC transfusion was significantly associated with a higher risk of mortality[127–129,131,136]; increasing units of blood transfused increased the odds of death[128,129]. In contrast, three studies found that RBC transfusion was not a significant predictor of mortality[132,135,137].

Morbidity

There were 14 studies identified that investigated the effect of RBC transfusion on different morbidity outcomes in patients undergoing cardiac surgery[105–110,112–114,117,119–121,123]. Infection was the most common morbidity outcome considered; 10 studies investigated infection outcomes, including wound infection, sepsis and pneumonia[105,108–110,112,114,117,119,121,123]. All 10 studies found that RBC transfusion was a significant predictor of infection, and the odds of infection increased with increasing units of blood transfused. Other outcomes investigated included cardiac[108,109,112,113,120]; renal[108,112], respiratory[112] and neurologic morbidities[112]. All studies found that RBC transfusion was a significant predictor of morbidity and that the morbidity risk increased with increasing units of RBC transfused.

Nine studies investigated the effect of RBC transfusion on different morbidity outcomes in patients undergoing noncardiac surgery[124–126,128,130,100,134,136,137]. The most common morbidity outcome investigated was infection; five studies found that RBC transfusion was a significant predictor for development of infection, including wound and infections, sepsis and pneumonia[125,128,134,136,137]. Johnson and colleagues[130] found that RBC transfusion was a significant predictor of a combined mortality and morbidity outcome. Others reported that RBC transfusion was a significant predictor for development of venous thromboembolism in patients undergoing major vascular surgery[100]. However, RBC transfusion was not a significant risk factor for development of erectile dysfunction in patients undergoing prostatectomy[124], for development of grade C pancreatic fistula in patients undergoing pancreatico-duodenectomy[126], or for early amputation in patients undergoing surgery for popliteal artery aneurysm[130].

Quality of life

One study was identified that investigated quality of life in patients undergoing cardiac surgery[114]. This study measured quality of life using the Duke Activity Status Index (DASI). It was found that RBC transfusion was associated with a negative impact on health-related quality of life after cardiac surgery that extended well beyond initial hospitalisation. Reduction in functional recovery was related to increasing units of transfused red blood cells in a dose dependant fashion.

No studies were found that investigated RBC transfusion and quality of life in patients undergoing noncardiac surgery.

Resource use

Three studies investigated the effect of RBC transfusion on resource use in cardiac surgery patients[107,109,123] and five studies investigated resource use in patients undergoing noncardiac surgery[132–136]. In both groups of surgical patients, RBC transfusion was associated with significantly longer hospital and ICU lengths of stay[107,109,123,132–134,136] and increased risk of hospital readmission in patients undergoing surgery for hip fracture[135].

Level IV evidence

No Level IV evidence was identified that examined the impact of RBC transfusion on patient outcomes.

Other evidence

Two studies investigated the cost of RBC transfusions[139,140] (**Table 3.5.5**). There is currently no system for grading economic studies, so a quality rating is not presented.

Table 3.5.5 Summary of other evidence on RBC transfusion: economic studies

Study	Study type	Methodology	Outcomes
Glenngard et al (2005)[139]	Economic study	The analysis was based on information from interviews with hospital staff and from published data	Cost of transfusion one allogeneic RBC unit (€)
Lubarsky et al (1994)[140]	Economic study	A cost manager computer program to determine total unit cost for all products and services provided for patient care within the Duke University Medical Centre for 1991–1992	Cost of transfusion one allogeneic RBC unit (US$)

Glenngard and colleagues[139] found that in Sweden, the cost of one unit of transfused filtered RBC in surgical patients was €373 for the first unit, and €329 for subsequent units, (2003 prices). Lubarsky et al[140] reported that the cost of one unit of transfused RBC for elective surgery patients was US$151.20 for the first unit, and US$139.77 for subsequent units, (1992 prices in the USA) (**Table 3.5.6**). Results are unlikely to be applicable to the Australian setting; both studies were performed outside Australia and one was conducted 16 years ago.

Table 3.5.6 Results of other evidence on RBC transfusion: economic studies

Study	Country	Results and conclusion
Glenngard et al (2005)[139]	Sweden	In Sweden, the societal cost of one unit of transfused filtered RBC was estimated to be €373 for the first unit and €329 for subsequent units in surgery patients (2003 prices)
Lubarsky et al (1994)[140]	USA	In the USA, the total cost for the first unit of RBC was US$151.20 and US$139.77 for subsequent units in elective surgery patients (1992 prices)

Evidence statements

Box 3.5.1 outlines the evidence statement (GN2.1a) for mortality outcomes in patients undergoing cardiac surgery.

Box 3.5.1 GN2.1a Evidence statement for the impact of RBC transfusion on patient outcomes: mortality and dose-dependent relationship with RBC transfusion in patients undergoing cardiac surgery

Evidence base	Satisfactory (C): Nine Level III studies with a moderate risk of bias[104,107–109,111,112,118,122,123]
Consistency	Good (B): All but one study showed that RBC transfusion was associated with a risk of mortality. Two studies reported a dose-dependent relationship between RBC transfusion and mortality [128,129]
Clinical impact	Satisfactory (C): Overall sample size was quite large with significant effects on mortality. Proving a direct effect of RBC transfusion on mortality is, however, difficult
Generalisability	Good (B): All studies involved patients undergoing cardiac surgery; however, there was no control over who received RBC transfusion and who did not
Applicability	Good (B): Of the nine studies, four were performed in the USA, three in the UK, and one each in Italy and Spain. Although the UK and Australian healthcare systems are similar, the USA healthcare system is different from Australia's

Box 3.5.2 outlines the evidence statement (GN2.1b) for morbidity outcomes in patients undergoing cardiac surgery.

Box 3.5.2 GN2.1b Evidence statement for the impact of RBC transfusion on patient outcomes: morbidity and dose-dependent relationship with RBC transfusion in patients undergoing cardiac surgery

Evidence base	Satisfactory (C): 14 Level III studies with a moderate risk of bias[105–112,117,119–121,123]
Consistency	Excellent (A): All studies showed that RBC transfusion was a significant predictor of morbidity outcomes, and that the relationship between RBC transfusion and morbidity was dose-dependent (that is, depended on the number of units of red blood cells transfused)
Clinical impact	Good (B): Overall sample size was very large, with significant effects on morbidity outcomes, especially infection. Proving a direct effect of RBC transfusion and morbidity, however, is difficult
Generalisability	Good (B): All studies involved patients undergoing cardiac surgery. There was no control over who received RBC transfusion and who did not
Applicability	Satisfactory (C): Of the 14 studies, eight were performed in the USA, two in Italy, and one each in Germany, Spain and the UK; the remaining study was conducted in a number of European countries. The healthcare system in the USA is quite different from that in Australia

Evidence statement GN2.1

In patients undergoing cardiac surgery, red blood cell transfusion is independently associated with increased morbidity (Grade B)[105–112,117,119–121,123] and mortality (Grade C)[104,107–109,111,112,118,122,123]. These relationships are dose-dependent (morbidity [Grade B][105–112,117,119–121,123] and mortality [Grade C][108,111]).

Box 3.5.3 outlines the evidence statement (GN2.2) for hospital and intensive care unit (ICU) length of stay in patients undergoing cardiac surgery.

Box 3.5.3 GN2.2 Evidence statement for the impact of RBC transfusion on hospital and intensive care unit length of stay in patients undergoing cardiac surgery

Evidence base	Satisfactory (C): Three Level III studies with a moderate risk of bias[107,109,123]
Consistency	Excellent (A): All studies showed that RBC transfusion was a significant predictor for increased hospital or ICU length of stay
Clinical impact	Satisfactory (C): The studies reported a moderate clinical impact
Generalisability	Excellent (A): All studies were performed in a perioperative patient population undergoing cardiac surgery
Applicability	Satisfactory (C): One study was conducted in Spain, one in the UK, and the other in the USA. The healthcare system in the USA is quite different from Australia's

Evidence statement GN2.2

In patients undergoing cardiac surgery, red blood cell transfusion is independently associated with increased intensive care unit and hospital length of stay (Grade C)[107,109,123].

Box 3.5.4 outlines the evidence statement (GN2.3) for RBC transfusion and quality of life among patients undergoing cardiac surgery.

Box 3.5.4 GN2.3 Evidence statement for the impact of RBC transfusion on quality of life in patients undergoing cardiac surgery

Evidence base	Poor (D): One Level III study with a moderate risk of bias[114]
Consistency	Not applicable (NA): One study provided the evidence
Clinical impact	Satisfactory (C): Although the sample size in this study was quite large, the clinical impact of this outcome was not clear
Generalisability	Satisfactory (C): The study was performed in a cardiac surgery population. There was no control over who received RBC transfusion and who did not
Applicability	Good (C: The study was performed in the USA

Evidence statement GN2.3

In patients undergoing cardiac surgery, there is insufficient evidence to determine the effect of red blood cell transfusion on quality of life (Grade D)[114].

Box 3.5.5 outlines the evidence statement (GN2.4a) for mortality outcomes in patients undergoing noncardiac surgery.

Box 3.5.5 GN2.4a Evidence statement for the impact of RBC transfusion on mortality in patients undergoing noncardiac surgery

Evidence base	Satisfactory (C): Nine Level III studies with a moderate risk of bias[127–131,132,135,136,138]
Consistency	Satisfactory (C): Most studies showed that RBC transfusion was associated with a risk of mortality. Two studies reported a dose-dependent relationship between mortality and RBC transfusions in noncardiac surgery patients
Clinical impact	Satisfactory (C): Overall sample size was quite large, and significant effects on mortality were reported. Proving a direct effect of RBC transfusion and mortality is, however, difficult
Generalisability	Good (B): All studies included patients undergoing noncardiac surgery, and a variety of surgeries were performed. However, there was no control over who received RBC transfusion and who did not
Applicability	Satisfactory (C): Of the nine studies, six were performed in the USA, and one each in UK, Germany and Brazil.

Box 3.5.6 outlines the evidence statement (GN2.4b) for morbidity outcomes in patients undergoing noncardiac surgery.

Box 3.5.6 GN2.4b Evidence statement for the impact of RBC transfusion on morbidity in patients undergoing noncardiac surgery

Evidence base	Satisfactory (C): Nine Level III studies with a moderate risk of bias[124–126,128,130,100,134,136,137]
Consistency	Good (B): The majority of studies showed that RBC transfusion was a significant predictor of morbidity outcomes. In those studies that did not report a significant effect, morbidity outcomes were obscure and related specifically to the condition for which the surgery was performed
Clinical impact	Good (B): Overall sample size was very large with significant effects on morbidity reported, especially for infection. Proving a direct effect of RBC transfusion on morbidity is, however, difficult
Generalisability	Good (B): All studies included patients undergoing noncardiac surgery and a variety of surgeries were performed. There was no control over who underwent RBC transfusion and who did not
Applicability	Satisfactory (C): Of the nine studies, four were performed in the USA, and one each in Iran, Spain, France, the Netherlands, and Canada

Evidence statement GN2.4

In patients undergoing noncardiac surgery, red blood cell transfusion is independently associated with increased morbidity (Grade C)[124–126,128,130,100,134,136,137] and mortality (Grade C)[127–131,132,135,136,138]. These relationships are dose dependent (Grade C)[128,129].

Box 3.5.7 outlines the evidence statement (GN2.5) for hospital and intensive care unit length of stay in patients undergoing noncardiac surgery.

Box 3.5.7 GN2.5 Evidence statement for the impact of RBC transfusion on hospital and intensive care unit length of stay in patients undergoing noncardiac surgery

Evidence base	Satisfactory (C): Four Level III studies with a moderate risk of bias[132–134,136]
Consistency	Excellent (A): All studies showed that RBC transfusion was independently associated with increased hospital or intensive care unit lengths of stay
Clinical impact	Satisfactory (C): The studies reported a moderate clinical impact
Generalisability	Good (B): All studies were performed in perioperative patient populations with a good mix of patients
Applicability	Satisfactory (C): Two studies were conducted in the USA, and one each in Germany and the Netherlands

Evidence statement GN2.5

In patients undergoing noncardiac surgery, red blood cell transfusion is independently associated with increased intensive care unit length of stay (Grade C)[132]and hospital length of stay (Grade C)[132–134,136].

3.5.2 Effect of liberal versus restrictive red blood cell transfusion protocols: Summary of evidence

Methods

Five Level II studies investigating the effect of a restrictive transfusion strategy on patient outcomes in a perioperative population[141–145] were identified through the systematic review process (see **Appendix F** in Volume 2).

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for this research question.

No published cost-effectiveness analyses on the effect of restrictive versus liberal RBC transfusion protocols on patient outcomes were identified in the literature search for this research question.

Level I evidence

No existing systematic reviews examining the effect of a restrictive transfusion strategy in a perioperative patient population were identified by the current systematic literature review.

Level II evidence

Five randomised controlled trials (RCTs) were identified by the systematic literature review. Of these, one[141] investigated the effect of a restrictive transfusion strategy in patients undergoing cardiac surgery; the main characteristics of this study are summarised in **Table 3.5.7**. The four remaining studies[142–145] investigated the effect of a restrictive transfusion strategy in noncardiac surgery; the main characteristics of these studies are summarised in **Table 3.5.8**.

Table 3.5.7 Summary of Level II evidence for a restrictive transfusion strategy: Cardiac surgery

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Bracey et al (1999)[141]	RCT *Fair*	Patients who underwent first-time, elective CABG surgery N=428	Patients receiving restrictive blood transfusion strategy of Hb <8 g/dL N=212	Patients receiving liberal blood transfusion strategy of Hb <9 g/dL N=216	Transfusion incidence, duration of mechanical ventilation, ICU LOS, hospital LOS, morbidity and mortality

Abbreviations: CABG, coronary artery bypass graft; Hb, haemoglobin; ICU, intensive care unit; LOS, length of stay; RCT, randomised controlled trial

Table 3.5.8 Summary of Level II evidence for a restrictive transfusion strategy: Noncardiac surgery

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Bush et al (1997)[142]	RCT *Good*	Patients undergoing elective aortic or infra-inguinal arterial reconstruction N=99	Patients receiving restrictive blood transfusion strategy of Hb <9 g/dL N=50	Patients receiving liberal blood transfusion strategy of Hb <10 g/dL N=49	Myocardial ischaemia, myocardial infarction, death and ICU and hospital LOS
Grover et al (2006)[143]	RCT *Fair*	Patients undergoing elective hip and knee replacement surgery N=260	Patients receiving restrictive blood transfusion strategy of Hb <8 g/dL N=109	Patients receiving liberal blood transfusion strategy of Hb <10 g/dL N=109	Silent ischaemia, blood loss, Hb concentration, transfusion rate, LOS, AEs and new infections
Carson et al (1998b)[144]	RCT *Fair*	Patients presenting for hip fracture repair with a Hb <10 g/dL in the immediate post operative period N=80	Patients receiving a restrictive blood transfusion strategy of Hb <8 g/dL N=40	Patients receiving a liberal blood transfusion strategy of Hb <10 g/dL N=40	Death within 60 days or inability to walk 10 feet within 60 days, 30-day and 60-day mortality, in-hospital myocardial infarction, thromboembolism, stroke and pneumonia
Foss et al (2009)[145]	RCT *Good*	Patients with hip fracture N=120	Patients receiving a restrictive blood transfusion strategy of Hb <8 g/dL N=60	Patients receiving a liberal blood transfusion strategy of Hb <10 g/dL N=60	Cumulated ambulation score, LOS, cardiac complications, infectious complications and mortality

Abbreviations: AE, adverse event; Hb, haemoglobin; LOS, length of stay; RCT, randomised controlled trial

The definitions of restrictive and liberal transfusion strategies varied among studies, but most applied a cut-off of 8 g/dL[141,143–145] for the restrictive strategy and 10 g/dL[142–145] for the liberal strategy. Of the five Level II studies, one included cardiac surgery patients[141], three included orthopaedic patients[143–145] and one included vascular noncardiac surgery patients[142]. The results of the five Level II studies are presented in **Table 3.5.9** for cardiac surgery and **Table 3.5.10** for noncardiac surgery.

Table 3.5.9 Results of Level II evidence for a restrictive transfusion strategy: Cardiac surgery

Study	Outcome	Restrictive Strategy	Liberal Strategy	OR (95% CI)	Statistical significance
Bracey et al (1999)[141]	Transfusion rate, units (mean ± SD)	2.0 ± 2.2	2.5 ± 2.6	NR	p=0.04
	Hospital LOS days (mean ± SD)	7.5 ± 2.9	7.9 ± 4.9	NR	NS
	Mortality, n/N (%)	3/212 (1.4%)	6/216 (2.7%)	NR	p=0.321
	Atrial arrhythmia, n/N (%)	30/212 (14%)	40/216 (19%)	NR	NS
	Ventricular arrhythmia, n/N (%)	13/212 (6%)	9/216 (4%)	NR	NS
	MI, n/N (%)	1/212 (0.5%)	0/216 (0%)	NR	NS
	Neurologic deficit, n/N (%)	11/212 (5%)	9/216 (4%)	NR	NS
	Pulmonary complications, n/N (%)	57/212 (27%)	64/216 (30%)	NR	NS
	Renal failure, n/N (%)	8/212 (4%)	5/216 (2%)	NR	NS
	Infection, n/N (%)	5/212 (2%)	3/216 (1%)	NR	NS

Abbreviations: ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; NR, not reported; NS, not significant; OR, odds ratio; SD, standard deviation

Table 3.5.10 Results of Level II evidence for a restrictive transfusion : Noncardiac surgery

Study	Outcome	Restrictive Strategy	Liberal Strategy	OR (95% CI)	Statistical significance
Bush et al (1997)[142]	Mortality, n/N (%)	4/48 (8%)	4/47 (9%)	NR	NS
	Transfusion rate, units (mean ± SD)	2.8 ± 3.1	3.7 ± 3.5	NR	p=0.19
	Cardiac morbidity, n/N (%)	8/48 (16%)	8/49 (16%)	NR	NS
	ICU LOS, days (mean ± SD)	4 ± 8	4 ± 4	NR	NS
	Hospital LOS, days (mean ± SD)	11 ± 9	10 ± 6	NR	NS
	MI rate, n/N (%)	2/48 (4%)	1/49 (2%)	NR	p=0.99
Grover et al (2006)[143]	Silent ischaemia, n/N (%)	21/109 (19%)	26/109 (24%)	MD: –4.6% (–15.5, 6.0%)	p=0.41
	DVT, n/N (%)	4/109 (4%)	5/109 (4.6%)	NR	NS
	PE, n/N (%)	1/109 (1%)	2/109 (2%)	NR	NS

Study	Outcome	Restrictive Strategy	Liberal Strategy	OR (95% CI)	Statistical significance
	MI, n/N (%)	1/109 (1%)	0/109 (0%)	NR	NS
	Chest infection, n/N (%)	3/109 (3%)	2/109 (2%)	NR	NS
	Wound infection, n/N (%)	2/109 (2%)	2/109 (2%)	NR	NS
	Mortality, n/N (%)	1/109 (1%)	0/109 (0%)	NR	NS
	Hospital LOS, median days (range)	7.3 (5–11)	7.5 (5–13)	NR	NS
Carson et al (1998b)[144]	Transfusion rate, median (range)	0 units (0–6)	2 units (0–4)	NR	p<0.001
	Death or inability to walk, n/N (%)	16/42 (39.0%)	19/42 (45.2%)	RR: 0.9 (0.5, 1.4)	p=0.57
	60-day mortality, n/N (%)	5/42 (11.9%)	2/42 (4.8%)	RR: 2.5 (0.5, 12.2)	p=0.43
	MI rate, n/N (%)	0/42 (0%)	0/42 (0%)	NR	NS
	Stroke, n/N (%)	1/42 (2.4%)	0/42	NR	NS
	Pneumonia, n/N (%)	2/42 (4.8%)	0/42 (0%)	NR	NS
	Thromboembolism, n/N (%)	0/42 (0%)	1/42 (0%)	NR	NS
	Hospital LOS, days (mean ± SD)	6.4 ± 3.4	6.3 ± 3.4	NR	NS
Foss et al (2009)[145]	Need for transfusion, n/N (%)	22/60 (37%)	44/60 (74%)	NR	p<0.01
	Transfusion rate, median	2 units	1 unit	NR	p<0.0001
	CAS rehabilitation score, median (range)	9 (9–13)	9 (9–15)	NR	p=0.46
	Any cardiovascular event, n/N (%)	6/60 (10%)	1/60 (2%)	NR	p=0.05
	Any infectious complication, n/N (%)	6/60 (10%)	11/60 (18%)	NR	p=0.19
	Thromboembolic event, n/N (%)	1/60 (2%)	2/60 (3%)	NR	p=0.56
	30-day mortality, n/N (%)	5/60 (8%)	0/60 (0%)	NR	p=0.02
	Hospital LOS, days (mean ± SD)	17.0 ± 12.9	18.4 ± 14.4	NR	p=0.61
	Hospital readmission in 30 days, n/N (%)	9/60 (15%)	11/60 (18%)	NR	p=0.31

Abbreviations: CAS, condition assessment survey; DVT, deep vein thrombosis; ICU, intensive care unit; LOS, length of stay; MD, mean difference; MI, myocardial infarction; NR, not reported; NS, not significant; OR, odds ratio; PE, pulmonary embolism; RR, relative risk; SD, standard deviation

Mortality

The study examining cardiovascular surgery found that the use of a restrictive transfusion strategy did not result in an increase in mortality rate[141]. Among patients undergoing orthopaedic or vascular surgery, three studies found that a restrictive transfusion strategy had no significant effect on mortality[142–144]; however, mortality rate was found to be significantly higher with the use of a restrictive transfusion strategy in another study[145].

Morbidity

In patients undergoing cardiovascular surgery, the use of a restrictive transfusion strategy did not increase the rate of any morbidity outcome, including cardiovascular morbidity, respiratory morbidity, renal morbidity and infection rate[141]. In patients undergoing orthopaedic or vascular surgery, all studies showed that a restrictive transfusion strategy did not increase morbidity outcomes, including infection rate and cardiovascular morbidities[142–145]; although Foss et al[145] reported that a restrictive transfusion strategy resulted in an increase in overall cardiovascular morbidity just reaching statistical significance.

Transfusion requirements

In patients undergoing cardiac or noncardiac surgery, use of a restrictive transfusion strategy resulted in a significant decrease in both the amount of RBC transfused per patient as well as the number of patients receiving a blood transfusion[141–145].

Resource use

In patients undergoing cardiac or noncardiac surgery, use of a restrictive transfusion strategy did not result in an increase in hospital length of stay[141–145]. Additionally, in patients undergoing vascular, noncardiac surgery, a restrictive transfusion strategy did not increase ICU length of stay[142].

Evidence statements

Box 3.5.8 outlines the evidence statement (GN2.6) for the effect of a restrictive transfusion strategy on mortality, morbidity or hospital length of stay in a cardiac surgery population.

Box 3.5.8 GN2.6 Evidence statement for the effect of a restrictive transfusion strategy on mortality, morbidity or hospital length of stay in a cardiac surgery population

Evidence base	Satisfactory (C) One fair quality Level II study[141]
Consistency	Not applicable (NA): Only one study
Clinical impact	Satisfactory (C): There was a moderate clinical impact
Generalisability	Excellent (A): The results of the study are directly generalisable to a perioperative cardiac surgery population
Applicability	Satisfactory (C): Reduced applicability—the study was conducted in the USA

Evidence statement GN2.6

In patients undergoing cardiac surgery, use of a restrictive transfusion strategy is not associated with increased mortality, morbidity or hospital length of stay (Grade C)[141].

Box 3.5.9 presents the evidence statement (GN2.7a) for the effect of a restrictive transfusion strategy on mortality, morbidity and hospital length of stay in patients undergoing noncardiac surgery, including orthopaedic and vascular surgery.

Box 3.5.9 GN2.7a Evidence statement for the effect of a restrictive transfusion strategy on mortality and morbidity in a noncardiac surgery population

Evidence base	Good (B): Two good quality[142,145] and two fair quality[143,144] Level II studies
Consistency	Satisfactory (C): One study presented conflicting results. Foss et al (2009) showed an increase in mortality; however, there was an imbalance between study groups in severity of illness at baseline and mortality was not a primary outcome.
Clinical impact	Satisfactory (C): There was moderate clinical impact
Generalisability	Poor (D): The studies included patients undergoing orthopaedic[143–145] or vascular[142] surgery. The population undergoing orthopaedic surgery typically includes a large proportion of elderly patients, making it difficult to determine whether these results are generalisable to the wider noncardiac surgical perioperative patient population. Intervention not considered to be sufficiently restrictive.
Applicability	Satisfactory (C): The studies were conducted in the USA, Denmark and the UK

Box 3.5.10 presents the evidence statement (GN2.7b) for the effect of a restrictive transfusion strategy on hospital LOS in a noncardiac surgery population.

Box 3.5.10 GN2.7b Evidence statement for the effect of a restrictive transfusion strategy on hospital length of stay in a noncardiac surgery population

Evidence base	Good (B): Two good quality[142,145] and two fair quality[143,144] Level II studies
Consistency	Excellent (A): The results of the studies are consistent in showing no effect on hospital LOS
Clinical impact	Satisfactory (C): There is moderate clinical impact
Generalisability	Satisfactory (C): All studies included patients undergoing orthopaedic[143–145] or vascular[142] noncardiac surgery
Applicability	Satisfactory (C): The studies were conducted in the USA (two studies), Denmark and the UK

Evidence statement GN2.7

In patients undergoing noncardiac surgery, the effect of a restrictive transfusion strategy on mortality and morbidity is uncertain (Grade C)[142–145]. In orthopaedic or vascular surgery, the use of a restrictive transfusion strategy is not associated with an increased hospital length of stay (Grade B)[142–145].

3.6 Question 6

In patients undergoing surgery, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion? (Referred to as GN3)

Results of the systematic review for this research question are presented by intervention:

- oral iron
- intravenous iron
- intravenous versus oral iron
- erythropoietin.

3.6.1 Effect of oral iron: Summary of evidence

Methods

A total of seven Level II studies[146–152] and two Level III studies[153,154] investigating the effect of oral iron on morbidity, mortality and need for RBC transfusion in a perioperative population were identified through the systematic review process (see **Appendix C,** Volume 2). One level study [149] was a late exclusion as it presented only level IV evidence for oral iron. (see **Appendix B 10**, Volume 2).The evidence statements are presented below.

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for this research question.

No published cost-effectiveness analyses on the effect of interventions to increase haemoglobin concentration were identified in the literature search for this research question.

Level I evidence

No existing systematic reviews examining the effect of oral iron on patient outcomes in a perioperative patient population were identified by the literature search.

Level II evidence

Seven randomised controlled trials (RCTs)[146–152] were initially identified by the systematic literature review. One was a late exclusion due to reporting only level IV evidence for the intervention in question[149] . Of the six included RCTs, three investigated the effect of oral iron in patients undergoing cardiac surgery[146–148].; The main characteristics of these studies are summarised in **Table 3.6.1**. The remaining three studies investigated the effect of oral iron in noncardiac surgery patients[150-152]. The main characteristics of these studies are summarised in **Table 3.6.2**.

Table 3.6.1 Summary of Level II evidence for the effect of oral iron: Cardiac surgery

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Postoperative iron administration					
Aufricht et al (1994)[146]	RCT *Fair*	Children undergoing CPB N=17	Postoperative treatment with oral iron (5 mg/kg) N=8	No treatment N=9	Hb concentration
Crosby et al (1994)[147]	RCT *Fair*	Males and postmenopausal females aged >50 years undergoing CABG surgery N=128	Postoperative treatment with oral iron (50 mg/day) N=28 Postoperative treatment with oral iron (200 mg/day) N=34	No treatment N=33 Placebo treatment N=26	Hb concentration
Del Campo et al (1982)[148]	RCT *Poor*	Adult patients undergoing elective CABG N=37	Patients receiving oral iron (325 mg tid) N=18	No treatment N=16	Hb concentration

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; Hb, haemoglobin; RCT, randomised controlled trial; tid, three times daily

Table 3.6.2 Summary of Level II evidence for the effect of oral iron: Noncardiac surgery

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Preoperative iron administration					
Lidder et al (2007)[150]	RCT *Good*	Patients undergoing surgery for colorectal cancer. It is unclear whether all patients had preoperative anaemia N=45	Preoperative treatment with oral iron (200 mg tid) N=23	No treatment (standard care) N=22	Hb concentration, need for blood transfusion
Postoperative iron administration					
Mundy et al (2005)[151]	RCT *Good*	Patients undergoing elective primary total hip or knee arthroplasty N=99	Postoperative treatment with oral iron (200 mg tid) N=50	Postoperative treatment with placebo (tid) N=49	Hb level

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Weatherall et al (2004)[152]	RCT *Fair*	Patients undergoing elective hip or knee replacement surgery N=72	Postoperative treatment with oral iron (325 mg/day) N=36	Postoperative treatment with control medication (folic acid, 5 mg/day) N=36	HB level, QoL assessed via VAS

Abbreviations: bid, twice daily; Hb, haemoglobin; QoL, quality of life; RCT, randomised controlled trial; tid, three time daily; THR, total hip replacement; TKR, total knee replacement; VAS, visual analogue scale

Of the six included Level II studies, one investigated the effects of preoperative oral iron therapy[150] and five investigated the effects of postoperative oral iron therapy[146–148,151,152]. Three studies used no treatment or standard of care as control[146,148,150]; one study used placebo tablets in the control group149[151]; one study[147] used two control groups—a placebo group and a no treatment group; and one study used a control medication of folic acid[152]. Results from the Level II studies are presented in **Table 3.6.3** for cardiac surgery and **Table 3.6.4** for noncardiac surgery.

Table 3.6.3 Results of Level II evidence for the effect of oral iron: Cardiac surgery

Study	Outcome	Oral Iron	Control	OR (95% CI)	Statistical significance
Postoperative iron administration					
Aufricht et al (1994)[146]	Haemoglobin[a] (g/dL)	12.1 ± 1.0	11.8 ± 1.0	NR	NS
	Reticulocyte count[a] (%)	11.5 ± 4.3	11.3 ± 4.2	NR	NS
	Transferrin saturation[a] (%)	33.5 ± 15.3	18.0 ± 11.9	NR	p<0.05
	Free erythrocyte protoporphyrin[a] (ng/mL)	0.57 ± 0.23	0.63 ± 0.69	NR	NS
	Ferritin[a] (ng/mL)	22.4 ± 9.5	13.0 ± 6.3	NR	p<0.05
	Ferritin ≤12 ng/mL[a] (n/N(%))	0/8 (0%)	5/9 (55%)	NR	p<0.05
Crosby et al (1994)[147]	Haemoglobin[b] (g/dL) 6 days	NR	NR	NR	NS
	Haemoglobin[b] (g/dL) 59 days	NR	NR	NR	NS
	Ferritin[b] (ng/mL) 59 days	NR	NR	NR	NS
Del Campo et al (1982)[148]	Haemoglobin (g/dL) 10 days	11.3 ± 1.2	11.7 ± 1.0	NR	p>0.1
	Haemoglobin (g/dL) 6 weeks	14.4 ± 1.2	14.8 ± 1.0	NR	p>0.1

Abbreviations: Hb, haemoglobin; NR, not reported; NS, not significant
[a] Measurement taken at 56 days post surgery
[b] The results for this study were reported graphically

Table 3.6.4 Results of Level II evidence for the effect of oral iron: Noncardiac surgery

Study	Outcome	Oral Iron	Control	OR (95% CI)	Statistical significance
Preoperative iron administration					
Lidder et al (2007)[150]	Number of patients transfused (n/N (%))	6/23 (26%)	13/22 (59%)	0.24 (0.06, 1.01)	p=0.047
	Total units transfused	15	47	Absolute difference: 32 units	NR
	Median units transfused (range)	0 (0–4)	2 (0–11)	NR	P=0.031
Postoperative iron administration					

Study	Outcome	Oral Iron	Control	OR (95% CI)	Statistical significance
Mundy et al (2005)[151]	Percentage recovery in Hb 3 weeks after surgery (men)	85.1%	86.6%	NR	p=0.45
	Percentage recovery in Hb 3 weeks after surgery (women)	86.7%	88.5%	NR	p=0.35
	Further percentage recovery in Hb 6 weeks after surgery (men)	6%	3%	NR	p<0.01
	Further percentage recovery in Hb 6 weeks after surgery (women)	5%	1.5%	NR	p<0.05
Weatherall et al (2004)[152]	Hb level[a] (g/L)	132.8 ± 13.4	128.0 ± 10.6	Difference: 4.8 (–1.2, 6.8)	p=0.15
	QoL[a] (mm, 100 mm VAS)	78.6 ± 18.2	77.4 ± 17.0		p=0.78

Abbreviations: Hb, haemoglobin; NR, not reported; NS, not significant; QoL, quality of life; VAS, visual analog scale

[a] Measurement taken at 10 weeks after surgery

Three included studies investigated the effect of oral iron in patients undergoing cardiac surgery[146–148]. These studies showed that postoperative iron has no effect on haemoglobin levels in children or adults following cardiac surgery. However in the study of a small number of children by Aufricht, post operative treatment with oral iron was associated with a significant increase in iron stores[146]

Three studies investigated the effect of oral iron therapy in patients undergoing noncardiac surgery[150-152]. The effects of preoperative[,150] and postoperative[151,152] iron administration were investigated. Preoperative treatment with oral iron among patients undergoing colorectal surgery was reported to decrease transfusion requirements significantly compared with patients in a control group[150]. Postoperative oral iron therapy was found to be only slightly more effective than standard care in accelerating recovery of haemoglobin iron level after orthopaedic surgery[151]. Postoperative iron therapy was not found to result in a faster rate of increase in haemoglobin iron levels compared with a control (folate) treatment, nor was it associated with a difference, or increase in quality of life[152].

Level III evidence

There were two Level III studies identified by the systematic literature review that investigated the effect of oral iron therapy on patient outcomes[153,154]. Both studies were performed in groups of patients who were undergoing noncardiac surgery. The main characteristics of these studies are summarised in **Table 3.6.5**.

The Level III evidence consisted of one historical control cohort study[153] and one retrospective cohort study[154]. Both Level III studies were performed in patients undergoing noncardiac surgery and investigated the effect of preoperative oral iron therapy. The results for these studies are presented in **Table 3.6.6**.

Both Level III studies showed that preoperative oral iron treatment in patients undergoing noncardiac surgery was associated with resulted in a decrease in the proportion of patients undergoing intraoperative blood transfusions[153,154], and a decrease in the amount of blood transfused per patient[153]. Preoperative iron treatment had no effect on length of hospital stay in this patient population[153].

Level IV evidence

One Level IV study [149]was identified by the systematic literature review investigating the effect of oral iron therapy in a perioperative patient population. Data were not presented because higher level evidence exists.

Table 3.6.5 Summary of Level III evidence for the effect of oral iron: Noncardiac surgery

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Preoperative iron administration					
Cuenca et al (2007)[153]	Historical control Level III *Fair*	Unilateral TKR patients N=312	Preoperative treatment with iron (256 mg/day), Vitamin C (1000 mg/day) and folic acid (5 mg/day) N=156	No treatment N=156	Hb concentration, number of patients transfused, transfusion index, hospital LOS
Okuyama et al (2005)[154]	Retrospective cohort study Level III-2 *Fair*	Anaemic colorectal cancer surgery patients (<10 g/dL)	Preoperative oral iron therapy (200 mg/day) N=32	No treatment N=84	Hb concentration, number of patients transfused

Abbreviations: Hb, haemoglobin; LOS, length of stay; TKR, total knee replacement

Table 3.6.6 Results of Level III evidence for the effect of oral iron: Noncardiac surgery

Study	Outcome	Oral Iron	Control	OR (95% CI)	Statistical significance
Preoperative iron administration					
Cuenca et al (2007)[153]	Postoperative haemoglobin (mg/dL)	10.8 ± 1.4	10.5 ± 1.2	NR	p<0.05[a]
	Rate of blood transfusion (n/N [%]) Preoperative Hb <130 g/L Preoperative Hb >130 g/L	9/156 (5.8%) 19.3% 2.4%	50/156 (32.0%) 61.5% 26.1%	OR=0.13 [0.05, 0.28]	p<0.01 χ^2=10.6, p<0.01 χ^2=28.9, p<0.001
	Transfusion index (units/transfused patient)	1.78 ± 0.44	2.22 ± 0.65	NR	p<0.05
	Length of hospital stay (days)	11 ± 5	12 ± 4	NR	NS
Okuyama et al (2005)[154]	Preoperative haemoglobin (mg/dL)[b]	10.1 ± 1.3	8.9 ± 1.3	NR	p<0.0001
	Postoperative haemoglobin (mg/dL)	9.5 ± 1.0	9.5 ± 1.5	NR	p=0.82
	Rate of intraoperative blood transfusion (n/N [%])	3/32 (9.4%)	23/84 (27.4%)	OR= 0.27 (0.05, 1.03)[c]	p<0.05

Abbreviations: CI, confidence interval; NR, not reported; NS, not significant

[a] This result is statistically significant, but not clinically significant; [b] Measurement taken immediately before surgery; the result is statistically significant but clinically unimportant;

[c] Although the point estimate is clinically significant, the CI included clinically non-significant effects

3.6.2 Effect of intravenous iron: Summary of evidence

Methods

Three Level III studies[155–157] and one Level IV study were identified that investigated the effect of intravenous iron on morbidity, mortality and need for RBC transfusion in a perioperative population (see **Appendix C** in Volume 2). The evidence statements are presented below.

Level I evidence

No existing systematic reviews examining the effect of intravenous iron on patient outcomes in a perioperative patient population were identified by the literature search.

Level II evidence

No existing randomised controlled trials examining the effect of intravenous iron on patient outcomes in a perioperative patient population were identified by the literature search.

Level III evidence

There were three Level III studies identified by the systematic literature review that investigated the effect of intravenous iron therapy on patient outcomes.[155–157] All these studies were performed among patients undergoing noncardiac surgery. The main characteristics of these studies are summarised in **Table 3.6.7**.

Table 3.6.7 Summary of Level III evidence for the effect of intravenous iron: Noncardiac surgery

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Preoperative iron administration					
Cuenca et al (2004)[155]	Historical control *Fair*	Patients undergoing hip fracture repair surgery N=157	Preoperative iron (100 mg); 2–3 doses before surgery N=55	No preoperative iron therapy N=102	Hb concentration, number of patients transfused, transfusion rate, infection rate, 30-day mortality, hospital LOS
Cuenca et al (2005)[156]	Historical control *Fair*	Patients undergoing hip fracture repair surgery N=77	Preoperative IV iron (100 mg); 2–3 doses before surgery N=20	No preoperative iron therapy N=57	Hb concentration, number of patients transfused, transfusion rate, infection rate, 30-day mortality, hospital LOS
Postoperative iron administration					
Munoz et al (2006)[157]	Historical control *Fair*	Patients undergoing THR surgery N=46	Postoperative IV iron (100 mg/day) for 3 days starting after surgery N=24	No postoperative iron therapy N=22	Number of patients transfused, transfusion rate, infection rate, hospital LOS

Abbreviations: Hb, haemoglobin; IV, intravenous; LOS, length of stay; THR, total hip replacement

The Level III evidence consisted of three historical control studies—two investigated the effects of preoperative intravenous iron therapy[155,156] and one looked at the effects of postoperative intravenous iron therapy[157]. All three studies involved patients undergoing noncardiac orthopaedic surgery. The results of these studies are summarised in **Table 3.6.8**.

Table 3.6.8 Results of Level III evidence for the effect of intravenous iron: Noncardiac surgery

Study	Outcome	Intravenous iron	Control	Statistical significance
Preoperative intravenous iron administration				
Cuenca et al (2004)[155]	Postoperative haemoglobin level[a] (g/dL)	9.5 ± 1.7	9.6 ± 1.6	NS
	Number of patients transfused (n/N (%))	24/55 (43.6%)	57/102 (55.9%)	NS
	Transfusion rate (units per patient)	0.89 ± 1.22	1.27 ± 1.34	NS
	Number of infections (n/N (%))	9/55 (16.4%)	34/102 (33.3)	p<0.001
	30-day mortality (n/N (%))	5/55 (8.9%)	17/102 (16.7%)	p=0.22
	Length of hospital stay (days)	12.6 ± 4.4	14.3 ± 3.6	NS
Cuenca et al (2005)[156]	Postoperative haemoglobin level[a] (g/dL)	9.6 ± 1.3	10.1 ± 1.4	p=0.178
	Number of patients transfused (n/N (%))	3/20 (15.0%)	21/57 (36.8%)	p=0.059
	Transfusion rate (units per patient)	0.26 ± 0.65	0.77 ± 1.09	p=0.18
	Number of infections (n/N (%))	3/20 (15.0%)	19/57 (33.3%)	p=0.099
	30-day mortality (n/N (%))	0/20 (0.0%)	11/57 (19.3%)	p=0.034
	Length of hospital stay (days)	11.9 ± 2.1	14.1 ± 3.1	p=0.004
Postoperative intravenous iron administration				
Munoz et al (2006)[157]	Number of patients transfused (n/N (%))	11/24 (46%)	16/22 (73%)	p=0.07
	Transfusion rate (units per patient)[b]	0.96 ± 1.12	1.68 ± 1.17	p=0.04
	Transfusion rate (units per patient)[c]	1.12 ± 1.17	2.18 ± 0.98	p=0.019
	Number of infections (n/N (%))	2/24 (8%)	5/22 (23%)	p=0.23
	In-hospital mortality (n/N (%))	0/22 (0%)	1/24 (4%)	p=0.49
	Length of hospital stay (days)	10.1 ± 4.4	11.4 ± 3.4	p=0.29

Abbreviation: NS, not significant

[a] Measurement taken 48 hours after surgery; [b] Includes all patients; [c] Includes patients with a preoperative haemoglobin level of <13 g/dL

Intravenous preoperative iron therapy resulted in a trend for a decrease in the number of patients transfused as well as the amount of blood transfused per patient[155,156]. This finding was similar for postoperative intravenous iron administration, where there was also a trend for a decrease in the number of patients transfused, with a significant reduction in the units of blood transfused postoperatively per patient[157]. Both preoperative and postoperative intravenous iron therapy resulted in a reduction in the number of postoperative infections; however, this was only significant in one study for preoperative intravenous iron therapy[155].

Both preoperative and postoperative intravenous iron therapy resulted in a decrease in mortality rate; but this result was significant in only one study[156].

Hospital length of stay was also reduced with both preoperative and postoperative intravenous iron therapy with this result being significant in one study[156].

Level IV evidence

One Level IV study that investigated intravenous iron therapy in perioperative patients was identified in the literature search. As higher level evidence was available, no data were extracted (see **Appendix B**, Volume 2). No quality of life data were reported in this study.

3.6.3 Effect of intravenous iron versus oral iron: Summary of Evidence

Methods

Three Level II studies[158–160] that compared the effect of intravenous iron with oral iron on morbidity, mortality and need for RBC transfusion in a perioperative population were identified through the systematic review process (see **Appendix C** in Volume 2). The evidence statements are presented below.

Level I evidence

No existing systematic reviews comparing the effects of intravenous iron with oral iron on patient outcomes in a perioperative patient population were identified by the literature search.

Level II evidence

Two Level II studies were identified that compared the effect of intravenous iron therapy with oral iron therapy on patient outcomes. Of these, one study was performed in patients undergoing cardiac or noncardiac surgery[159], and the other in patients undergoing noncardiac surgery[160]. Because the study that involved patients undergoing either cardiac or noncardiac surgery did not report these results separately, its characteristics are presented together with those of the cardiac surgery studies. The main characteristics of the studies are summarised in **Table 3.6.9** for cardiac surgery and **Table 3.6.10** for noncardiac surgery.

Table 3.6.9 Summary of Level II evidence comparing the effect of intravenous iron with oral iron: Cardiac surgery

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Postoperative iron administration					
Karkouti et al (2006a)[159]	RCT *Fair*	Adult patients who underwent open heart surgery, total hip arthroplasty or spinal fusion with Hb range 7–9 g/dL N=38	A postoperative single dose of EPO (300 U/kg) and IV iron (200 mg/day) for 3 days plus oral iron (150 mg/day) N=12 IV iron alone (200 mg/day) plus oral iron (150 mg/day) N=13	Control group received oral iron (150 mg/day) N=13	Hb levels

Abbreviations: CPB, cardiopulmonary bypass; EPO, erythropoietin; Hb, haemoglobin; IV, intravenous; RCT, randomised controlled trial

Table 3.6.10 Summary of Level II evidence comparing the effect of intravenous iron with oral iron: Noncardiac surgery

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Preoperative iron administration					
Kim et al (2009)[160]	Open label RCT *Poor*	Menorrhagic patients with established iron deficiency anaemia scheduled to undergo surgical treatment N=76	Preoperative IV iron therapy: weight x [target Hb – actual Hb] x 2.4 ÷ 500 mg 3 times weekly for 3 weeks N=39	Oral iron (80 mg/day) for 3 weeks before surgery N=37	Hb concentration, ferritin concentration

Abbreviations: Hb, haemoglobin; IV, intravenous; RCT, randomised controlled trial

The Level II cardiac surgery evidence consisted of one blinded RCT, comparing postoperatively administered intravenous and oral iron with oral iron alone[159]. The studies involved patients with postoperative anaemia who underwent postoperative iron therapy. The study[159] involved patients who had undergone cardiac surgery, but one also included patients who had undergone noncardiac surgeries such as hip and spinal surgery[159]. Because this study did not report results from the surgical populations separately, they were combined and are reported together under cardiac surgery.

The Level II evidence for noncardiac surgery consisted of one open label randomised controlled trial that compared preoperatively administered intravenous iron with oral iron[160]. The study was performed in patients undergoing surgery for menorrhagia who had iron deficiency anaemia. The results of these studies are summarised in **Table 3.6.11** for cardiac surgery and **Table 3.6.12** for noncardiac surgery.

Table 3.6.11 Results of Level II evidence for comparison of intravenous iron with oral iron: Cardiac surgery

Study	Outcome	Intravenous iron	Oral Iron	Statistical significance
Postoperative iron administration				
Karkouti et al (2006a)[159]	Need for transfusion (n/N (%))	2/13 (15.4%)	4/13 (30.1%)	NS
	Hb Day 42 (g/dL)	12.7 ± 0.6	12.0 ± 1.3	NS
	Ferritin Day 7 (ng/mL)	513 ± 221	311 ± 286	NS

Abbreviations: Hb, haemoglobin; NS, not significant

Table 3.6.12 Results of Level II evidence for comparison of intravenous iron with oral iron: Noncardiac surgery

Study	Outcome	Intravenous iron	Oral Iron	Statistical significance
Preoperative Iron Administration				
Kim et al (2009)[160]	Postoperative Hb level (g/dL)	10.5 ± 1.4	8.6 ± 1.4	p<0.0001
	Postoperative ferritin level (μg/L)	231.4 ± 561.7	9.7 ± 10.3	p<0.0001

Abbreviations: Hb, haemoglobin; NS, not significant

The Level II studies showed that, among patients who had undergone cardiac surgery or noncardiac surgery, intravenously administered iron is not associated with reduced incidence of transfusion. IV iron was reported to be no better than oral iron at decreasing the need for transfusion[159]; decreasing transfusion rate[159]; or increasing postoperative haemoglobin levels[159] when compared with patients treated with oral iron. However, postoperative intravenous iron was significantly more effective than oral iron at increasing postoperative ferritin levels[159].

Results from the study investigating preoperative iron therapy in patients undergoing surgery for menorrhagia noncardiac surgery showed that in a perioperative population with iron

deficiency anaemia, intravenous iron therapy is significantly more effective than oral iron therapy in increasing haemoglobin and ferritin levels[160].

Level III evidence

No Level III studies comparing the effect of intravenous iron with oral iron in a perioperative patient population were identified by the literature search.

Level IV evidence

No Level IV studies comparing the effect of intravenous iron with oral iron in a perioperative patient population were identified by the literature search.

3.6.4 Effect of erythropoietin (with or without iron): Summary of evidence

Methods

There were 31 studies identified that investigated the effect of erythropoietin on morbidity, mortality and need for RBC transfusion in a perioperative population (see **Appendix C**, Volume 2). Of these, two were classified as providing Level I evidence, 13 as Level II, six as Level III and ten as Level IV. Because iron therapy, administered either orally or intravenously, has become part of standard care, studies involving therapy with erythropoietin and iron were included in this review. Evidence statements are presented. The evidence statements not include evidence from seven studies[163,164,165,168,170,177,178] that were late exclusions found during internal quality peer review to have been conducted in patients who were not anaemic at baseline (see **Appendix B 10**, Volume 2).

Level I evidence

The literature search identified two systematic reviews[161,162] of RCTs that examined the efficacy of erythropoietin among perioperative patients. Both present Level I evidence[161,162]. The main characteristics of these studies are summarised in **Table 3.6.13**.

The efficacy of erythropoietin was investigated in noncardiac surgery[161] and in both cardiac and noncardiac surgery[162]. Results from the Level I systematic reviews are presented in **Table 3.6.14**.

Table 3.6.13 Summary of Level I evidence for the effect of erythropoietin: Cardiac and noncardiac surgery

Level I Evidence					
Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Devon et al (2009)[161]	Systematic review of RCTs (4)	Anaemic patients undergoing colorectal cancer surgery. Anaemia was defined	Pre- and/or perioperative administration of EPO	Placebo, other haematinic treatment, or no treatment	Proportion of transfused patients, transfusion rate,

Level I Evidence					
Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
	Good	as Hb <14 g/dL in males and <12.5 g/dL in females		(standard of care)	Hb levels, 30-day and/or hospital mortality, thrombotic events
Laupacis et al (1998)[162]	Systematic review of RCTs (5) *Fair*	Patients undergoing cardiovascular (2 RCTs) or orthopaedic (3 RCTs) surgeries	Perioperative administration of EPO	Placebo, other haematinic treatment, or no treatment (standard of care)	Proportion of transfused patients

Abbreviations: EPO, erythropoietin; Hb, haemoglobin; RCT, randomised controlled trial

Table 3.6.14 Results of Level I evidence for the efficacy of erythropoietin: Cardiac and noncardiac surgery

Level I evidence		
Study	Number of included studies	Results and conclusions
Devon et al (2009)[161]	4 RCTs in colorectal surgery	Mortality Two studies reported evaluable mortality data. There was no difference in postoperative mortality rate between the EPO and control groups (RR: 2.12; 95% CI: [0.59, 7.65]) Thrombotic Complications This outcome was included in all 4 studies and data were combined. There was no difference in the proportion of patients who had a thrombotic complication between the EPO-treated and control groups (RR: 1.71; 95% CI: [0.41, 7.08]) Risk of Transfusion Three studies included this outcome. There was no difference in the proportion of patients who received blood transfusions between EPO and placebo (RR: 0.92; 95% CI: [0.65, 1.31]) Transfusion Rate Three studies reported this outcome; however, high heterogeneity among studies meant that results were not combined for this outcome. Of the 3 studies, 2 reported no significant difference in transfusion rates between EPO and control groups. The remaining study found that the control group received significantly more transfusions per patient compared with the EPO group (MD: –1.3; 95% CI: [–1.85, –0.75]) Haemoglobin Concentration No study measured the change in Hb between the start of the study and 3–4 weeks later

		The authors concluded that there is no sufficient evidence to date to recommend pre and perioperative erythropoietin use in colorectal cancer surgery
Laupacis et al (1998)[162]	5 RCTs in cardiovascular surgery (2) and orthopaedic surgery (3)	Risk of Transfusion There were 3 RCTs of EPO in orthopaedic surgery (N=684 patients) and 2 studies in cardiac surgery (N=245 patients). There was no significant heterogeneity between the studies. OR for the need for blood transfusion in orthopaedic patients was OR: 0.36 (95% CI: [0.24, 0.56]) and the OR in cardiovascular patients was OR: 0.25 (95% CI: [0.06, 1.04])
		The authors concluded that erythropoietin decreases exposure to allogeneic blood transfusion in patients undergoing orthopaedic and cardiac surgeries

Abbreviations: RCT, randomised controlled trial; EPO, erythropoietin; Hb, haemoglobin; CI, confidence interval; OR, odds ratio; MD, mean difference; RR relative risk

The Level I evidence showed that erythropoietin therapy has no significant effect on mortality or thrombotic outcomes among patients undergoing colorectal cancer surgery[161]. Erythropoietin was shown to be associated with a reduced incidence of RBC transfusion decrease the likelihood of need for RBC transfusion among patients undergoing orthopaedic and cardiovascular surgeries[162]; however, this was not the case for patients undergoing colorectal surgery[161]. Furthermore, there were conflicting results regarding transfusion rate in colorectal surgery; only one of the three studies that reported on this found that patients treated with erythropoietin received fewer transfusions per patient compared with the control group[162].

Level II evidence

Twenty RCTs were initially identified that investigated the efficacy of erythropoietin in a perioperative patient population. These 20 RCTs included four trials that were considered in the review by Devon et al[161]; and five studies considered in the review by Laupacis et al[162]. One of the five reviewed by Laupacis et al was cited by them as an abstract (DeAndrade, 1996[168]), and a complete report could not be located during the current systematic literature review. Its results are taken from the Laupacis review and yielded limited data, which could not be verified against the original. Of these 7 studies, including DeAndrade 1996 were late exclusions as they were in a non-anaemic population (see Volume 2 Appendix B.10).

The main characteristics of the thirteen Level II studies for cardiac and noncardiac surgery are summarised in **Table 3.6.15** and **Table 3.6.16** respectively.

Table 3.6.15 Summary of Level II evidence on the effects of erythropoietin: Cardiac surgery

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Preoperative EPO administration					
Postoperative EPO administration					
Madi-Jebara et al (2004)[158]	RCT *Good*	Patients who underwent cardiopulmonary bypass surgery and had a post-pump Hb range 7–10 g/dL N=120	A postoperative single dose of EPO (300 U/kg) and intravenous iron (200 mg/day) N=40 IV iron alone (200 mg/day) N=40	Control group N=40	Hb and ferritin levels
Karkouti et al (2006a)[159]	RCT *Fair*	Adult patients who underwent open-heart surgery, total hip arthroplasty or spinal fusion with Hb range 7–9 g/dL N=38	A postoperative single dose of EPO (300 U/kg) and intravenous iron (200 mg/day) for 3 days plus oral iron (150 mg/day) N=12 IV iron alone (200 mg/day) plus oral iron (150 mg/day) N=13	Control group receiving oral iron (150 mg/day) N=13	Hb levels, postoperative quality of life via the SF-36 and the FIS

Abbreviations: CABG, coronary artery bypass graft; FIS, Fatigue Inventory Scale; Hb, haemoglobin. RCT, randomised controlled trial; EPO, erythropoietin; IV, intravenous, SC, subcutaneous; tid, three times daily

[a] Included in the review by Laupacis et al[162]

Table 3.6.16 Summary of Level II evidence on the effects of erythropoietin: Noncardiac surgery

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Preoperative EPO administration					
COPES[a] (1993)[166]	RCT *Good*	Anaemic patients scheduled for elective unilateral hip replacement aged <84 years N=208	EPO (300 U/kg) 14 days before surgery and oral iron (300 mg tid) 21 days before surgery N=77 EPO (300 U/kg) 5 days before and 3 days after surgery and oral iron (325 mg tid) 21 days before surgery N=53	Placebo 14 days before surgery and oral iron (300 mg tid) 21 days before surgery N=78	Need for blood transfusion, mean change in Hb levels, thrombotic events
Christodoulakis[b] et al (2005)[167]	Open label RCT *Fair*	Colorectal cancer patients who were anaemic and scheduled for surgery N=223	EPO (EPO-α,300 IU/kg/day) and oral iron (200 mg/day) 10 days before and 1 day after surgery N=67 EPO (EPO-α,150 IU/kg/day) and oral iron (200 mg/day) 10 days before and 1 day after surgery N=69	Control group receiving oral iron (200 mg/day) N=68	Need for blood transfusion, and units of blood transfused per patient
Faris[a] et al (1996)[169]	RCT *Good*	Patients scheduled for major orthopaedic surgery N=200 N=81 (anaemic subgroup)	EPO (300 IU/kg/day) 10 days before surgery and oral iron (325 mg tid) throughout the study N=25 EPO (100 IU/kg/day) 10 days before surgery and oral iron (325 mg tid) throughout the study N=28	Placebo and oral iron (325 mg tid) N=28	Need for blood transfusion, units of blood transfused, morbidity

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Goldberg et al (1996)[171]	Open-label RCT *Fair*	Mild to moderate anaemic patients scheduled for major elective hip or knee surgery N=145	EPO (600 IU/kg) as a weekly injection 3 weeks before surgery and oral iron (200 mg/day) throughout the study N=73	EPO (300 IU/kg) as a daily injection 10 days before surgery until 4 days after surgery and oral iron (200 mg/day) throughout the study N=72	Hb concentration, need for transfusion, units of blood transfused
Heiss[b] et al (1996)[172]	RCT *Fair*	Patients with moderate anaemia undergoing colorectal cancer surgery N=30	EPO (150 IU/kg) SC injection every 2 days starting 10 days before surgery until 2 days after surgery and oral iron (200 mg/day) and folate (5 mg/day) throughout the study N=20	Placebo as SC injection every 2 days starting 10 days before surgery until 2 days after surgery and oral iron (200 mg/day) and folate (5 mg/day) throughout the study N=10	Need for blood transfusion, units of blood transfused, Hb concentration, morbidity and mortality
Kettelhack[b] et al (1998)[173]	RCT *Fair*	Anaemic patients with colon cancer 35 years or older undergoing colorectal surgery N=109	EPO (as epoetin β 20 000 U) as SC injection every day starting 5–10 days before surgery until 4 days after surgery and oral iron throughout the study as well as IV iron 1 day after surgery N=48	Placebo as SC injection every day starting 5–10 days before surgery until 4 days after surgery and oral iron throughout the study as well as IV iron 1 day after surgery N=54	Need for blood transfusion, morbidity and mortality
Kosmadakis et al (2003)[174]	RCT *Good*	Moderately anaemic patients aged 40–90 years undergoing surgery for non-metastatic gastrointestinal tract malignancies N=63	EPO (300 IU/kg) as SC injection every day starting 7 days before surgery until 6 days after surgery and intravenous iron (100 mg) throughout the study N=31	Placebo as SC injection every day starting 7 days before surgery until 6 days after surgery and intravenous iron (100 mg) throughout the study N=32	Need for blood transfusion, Hb concentration, hospital LOS
Larson et al (2001)[175]	Open-label RCT *Fair*	Anaemic women with uterine myoma undergoing hysterectomy N=31	EPO (as epoetin β 5 000 U) as SC injection twice a week and oral iron (100 mg bid) 4 weeks before surgery N=15	Control group receiving oral iron (100 mg bid) 4 weeks before surgery N=16	Infection, hospital LOS, Hb concentrations

Study	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Qvist[b] et al (1999)[176]	RCT *Good*	Anaemic patients with colorectal cancer undergoing colorectal surgery N=100	EPO (300 IU/kg/day) as SC injection for 4 days before surgery then erythropoietin (150 IU/kg/day) until 6 days after surgery and oral iron (200 mg/day) for the 4 days before surgery N=38	Placebo as SC injection 4 days before until 6 days after surgery and oral iron (200 mg/day) for the 4 days before surgery N=43	Need for blood transfusion, morbidities
Weber et al (2005b)[179]	RCT *Fair*	Mild to moderate anaemic patients undergoing elective major orthopaedic surgery N=704	EPO (as epoetin α 40 000 IU) as SC injection once weekly and oral daily iron for 3 weeks before surgery N=467	Controls receiving oral daily iron for 3 weeks before surgery N=237	Need for blood transfusion, number of units transfused, infection rate, Hb levels, hospital LOS
Postoperative EPO administration					
Green et al (1996)[180]	RCT *Good*	Patients rehabilitating after orthopaedic surgery at least 2 weeks previously with Hb <10 g/dL N=27	EPO (100 IU/kg) as a subcutaneous injection 3 times a week for 8 weeks and oral iron (325 mg tid) throughout the study N=10	Placebo as a subcutaneous injection 3 times a week for 8 weeks and oral iron (325 mg tid) throughout the study N=13	Hb levels

Abbreviations: Hb, haemoglobin; EPO, erythropoietin; LOS, length of stay; SC, subcutaneous; IV, intravenous; RCT, randomised controlled trial; tid, three times daily

[a] Included in the review by Laupacis et al[162]; [b] Included in the review by Devon et al[161]; [c] This study could not be evaluated as the results have been taken from Laupacis et al (1996)[162]

Of the 13 identified RCTs investigating the efficacy of erythropoiesis stimulating agents (ESAs) in an anaemic perioperative patient population, two were performed in cardiac surgery settings and both were postoperative therapy[158,159]). The remaining 11 studies were performed in noncardiac surgery settings[166,167,169,171,172,173,174,175,176,,179180]. ESAs administered preoperatively in all noncardiac studies except Green et al [180]. ESAs administered pre and post operatively in six studies [166, 167, 172,173, 174, 176] . All studies involved co-administration of iron with ESAs. Although iron was administered orally as part of standard care in most studies, three studies included intravenous iron therapy[158,159,174,] , and one study considered administration of oral iron with 1 day of intravenous iron as part of standard care[173]. Administration of oral folate in addition to oral iron was included as a component of standard care by one study[172].

There were no studies identified that examined the effect of erythropoietin without iron against iron alone, or a control. However, erythropoietin with intravenous iron compared with intravenous iron alone, or a control without iron or erythropoietin, was investigated[158]. The effect of erythropoietin plus iron administered both orally and intravenously was compared with results for a group who received intravenous and oral iron, and another group who underwent only oral iron therapy in a further study[159]. One study was identified that investigated the effect of two different dosing regimens of erythropoietin, but the design of this study did not include a control group[171].

Studies included patients who were mildly to moderately anaemic.One study could not be evaluated because haemoglobin levels were not reported[162].

The results of these studies are summarised in **Table 3.6.17** and **Table 3.6.18** for cardiac and noncardiac surgery respectively.

Table 3.6.17 Results of Level II evidence on the effects of erythropoietin: Cardiac surgery

Study	Outcome	EPO Dose	EPO	Control	OR (95% CI)	Statistical significance
Preoperative EPO administration – NO STUDIES						
Postoperative EPO administration						
Madi-Jebara et al (2004)[158]	Need for transfusions (n/N (%)	EPO + IV Fe	7/40 (17%)	9/40 (22%)	NR	p=0.709
	Transfusion rate (units/person)		2.4	2.3	NA	NR
	Hb Day 30 (g/dL)		12.42 ± 1.2	11.87 ± 1.21	NA	NS
	Ferritin Day 15 (ng/mL)		464.60 ± 331.89	253.72 ± 154.27	NA	p<0.001
Karkouti et al (2006a)[159]	Need for transfusion (n/N (%))	EPO + IV Fe + Fe	2/12 (16.7%)	4/13 (30.1%)	NR	NS
	Hb Day 42 (g/dL)		12.8 ± 1.1	12.0 ± 1.3	NA	NS
	Ferritin Day 7 (ng/mL)		435 ± 289	311 ± 286	NA	NS

Abbreviations: Fe, iron; IV, intravenous; EPO, erythropoietin; HCT, haematocrit; NA, not applicable; NR, not reported; NS, not significant; sc, subcutaneous.
[a] Result indicates a lack of power in the study to assess this outcome; [b] There was a higher all cause mortality in the EPO group but the study was not powered to detect a difference in this outcome

Table 3.6.18 Results of Level II evidence on the effects of erythropoietin: Noncardiac surgery

Study	Outcome	EPO Dose	EPO	Control	OR (95% CI)	Statistical significance
Preoperative EPO administration						
COPES[a] (1993)[166]	Need for blood transfusion (n/N %))	300 IU/kg 14d before surgery	13/50 (26%)	29/49 (59%)	NR	NR
		300 IU/kg 9d before surgery	15/35 (43%)		NR	
Christodoulakis[c] et al (2005)[167]	Need for perioperative transfusion (n/N (%))	150 IU/kg	34/69 (49.3%)	36/68 (52.2%)	NR	NR
		300 IU/kg	25/67 (37.3%)		NR	NR
	Need for postoperative transfusion (n/N (%))	150 IU/kg	33/69 (47.8%)	36/68 (52.2%)	NR	NR
		300 IU/kg	27/67 (40.3%)		NR	NR

Study	Outcome	EPO Dose	EPO	Control	OR (95% CI)	Statistical significance
	Transfusion rate perioperatively (U/person)	150 IU/kg	1.19 ± 1.46	1.34 ± 1.59	NA	NS
		300 IU/kg	0.81 ± 1.22		NA	p=0.016
	Transfusion rate postoperatively (U/person)	150 IU/kg	1.10 ± 1.42	1.35 ± 1.58	NA	NS
		300 IU/kg	0.87 ± 1.21		NA	p=0.023
	Mortality	150 IU/kg	2/69 (2.9%)	0/68 (0%)	NR	NR
		300 IU/kg	3/67 (4.5%)		NR	NR
Faris[a] et al (1996)[169]	Need for transfusion (n/N (%))	300 IU/kg/day	5/25 (20%)	22/28 (79%)	NR	p<0.001
		100 IU/kg/day	12/28 (43%)		NR	p<0.001
Goldberg et al (1996)[171]	Preoperative increase in Hb (g/dL)	600 IU/week	1.44 ± 1.03	No control	NA	NS[d]
		300 IU/day	0.73 ± 0.87		NA	
	Peri-surgical decrease in Hb (g/dL)[e]	600 IU/week	–2.94 ± 1.45		NA	NS[d]
		300 IU/day	–2.3 ± 1.3		NA	
	Need for transfusion	600 IU/week	11/69 (16%)		NR	NS[d]
		300 IU/day	14/71 (20%)		NR	
	Transfusion rate (U/person)	600 IU/week	0.33 ± 0.87		NA	NS[d]
		300 IU/day	0.30 ± 0.64			
Heiss[c] et al (1996)[172]	Need for transfusion (n/N (%))	150 IU/kg	9/17 (53%)	4/10 (40%)	NR	NR
	Transfusion rate (U/person)	150 IU/kg	1.82 ± 0.8	1.80 ± 0.97	NA	NR
	Preoperative increase in Hb (g/dL)	150 IU/kg	0.4	0.1	NA	p=0.065
Kettelhack[c] et al (1998)[173]	Need for transfusion (n/N (%))	20 000 IU	16/48 (33%)	15/54 (28%)	NR	p=0.27

Study	Outcome	EPO Dose	EPO	Control	OR (95% CI)	Statistical significance
Kosmadakis et al (2003)[174]	Need for intra-surgical transfusion (n/N (%))	300 IU/day	9/31 (29%)	19/32 (59.3%)	NR	S[f]
	Need for postoperative transfusion (n/N (%))		1/31 (3.2%)	9/32 (28%)	NR	p=0.001
	Hb level at discharge (g/dL)		12.1 ± 0.12	11.1 ± 0.15	NA	p=0.0001
	Hospital LOS (days)		10 ± 0.5	13 ± 0.9	NA	p=0.022
Larson et al (2001)[175]	Pre-surgery Hb concentration (g/dL)	5 000 IU twice per week	12.6 ± 1.3	12.0 ± 1.4	NA	p=0.007
	Postoperative Hb concentration[g] (g/dL)		11.6 ± 1.4	11.7 ± 0.6	NA	NS
	Infection rate (n/N (%))		1/15 (6.66%)	2/16 (12.5%)	NA	NR
	Hospital LOS (days)		6.4 ± 2.4	8.1 ± 7.1	NA	NS
Qvist[c] et al (1999)[176]	Need for transfusion (n/N (%))	150 IU/kg	13/38 (35%)	23/43 (53%)	NR	NS[h]
	Transfusion rate (U/person)		0.3	1.6	NA	p<0.05
	Post-surgery Hb concentration (median (range), mmol/L)		7.8 (5.5, 9.2)	7.2 (4.6, 8.5)	NA	p<0.05
	Discharge Hb concentration (median (range), mmol/L)		7.8 (5.9, 8.8)	7.2 (5.4, 8.6)	NA	p<0.002
	Hospital LOS (days)		10.5	10.9	NR	NS[h]
Weber et al (2005b)[179]	Need for transfusion (n/N (%))[j]	40 000 IU/wk	55/460 (12%)	108/235 (46%)	NR	p<0.05
	Transfusion rate (U/person)		2.36 ± 1.95	2.41 ± 1.24	NA	NS
	Preoperative increase in Hb (g/dL)		2.1	0	NA	p<0.05
	Postoperative Hb (g/dL)		11.4 ± 1.4	9.7 ± 1.2	NA	p<0.05
	Postoperative Hb (4–6 weeks) (g/dL)		12.3 ± 1.0	11.9 ± 0.9	NA	p<0.05
	Hospital LOS (days)		10.8 ± 5.5	10.8 ± 5.5	NA	NS
Postoperative EPO administration						

Study	Outcome	EPO Dose	EPO	Control	OR (95% CI)	Statistical significance
Green et al (1996)[180]	Postoperative Hb (Week 4)	100 IU/kg, 3 times a week	12.6 ± 1.5	11.0 ± 1.5	NA	p=0.02
	Postoperative Hb (Week 8)	100 IU/kg, 3 times a week	13.5 ± 1.4	11.7 ± 1.7	NA	p=0.01
	FIM (mobility)	100 IU/kg, 3 times a week	6.10 ± 0.31	5.69 ± 0.63	NA	NS

Abbreviations: DVT, deep vein thrombosis; EPO, erythropoietin; Hb, haemoglobin; IV, intravenous; LOS, length of stay; NA, not applicable; NR, not reported; NS, not significant

[a] Included in the review by Laupacis et al[162]

[b] The result indicates a lack of power in the study to assess this outcome

[c] Included in the review by Devon et al[161]

[d] This was based on the 95% confidence intervals for the difference between the two groups reported in the study

[e] Defined as immediately pre-surgery to perioperative Day 1

[f] The authors report in the text that this result is significant but do not report a p-value

[g] Measure taken 2 weeks after surgery

[h] The authors did not report a p-value, they did however, report in the text that this result did not reach statistical significance

[i] Measurement taken at postoperative Day 10

[j] This included allogeneic and autologous transfusions; however, most transfusions were allogeneic

Mortality

The review identified no studies that involved anaemic patients who underwent cardiac or noncardiac surgery and received ESAs preoperatively and for which mortality was reported.

Morbidity

The review identified no studies that involved anaemic patients who received ESAs preoperatively and underwent cardiac surgery that reported morbidity outcomesConsequently, no conclusions could be drawn concerning the safety of preoperative ESAs in combination with iron therapy for anaemic patients undergoing cardiac surgery.

In patients undergoing noncardiac surgery, three studies investigated the incidence of morbidity outcomes in patients receiving ESAs preoperatively[166,169, 175]. All studies reported no difference in the incidence of morbidity outcomes between ESA-treated patients and control patients, including the incidence of thrombotic vascular events[166,169,], or the incidence of infections[175]. Again, the studies investigating thrombotic vascular events were underpowered to detect a difference in this outcome. In patients undergoing noncardiac surgery, no conclusions can be drawn regarding the safety of preoperative ESA therapy.

Transfusion requirements

Postoperative treatment with ESAs for patients undergoing cardiac surgery did not decrease the need for transfusion or number of units of blood transfused per patient[158,159].

Studies that considered noncardiac surgery patients included five that related to orthopaedic surgical procedures[166,169,171,179,180] and six to cancer surgeries[167,172–,176,] (four colorectal[167,172,173,176], one gynaecological[175] and one gastrointestinal[174,178]).

Among patients who underwent orthopaedic surgical procedures, preoperative ESAs were found to be effective in reducing need for blood transfusion compared with those who received standard care[166, 169,179]. Transfusion rate was reported by two studies[169,179]; one showed that preoperative ESA therapy can reduce transfusion rates[169].

Results varied among studies investigating cancer surgeries. After preoperative administration of ESAs, use of blood transfusion was reported to decrease[167,174,176], although only one study[174] showed this to be significant. No difference in blood transfusion requirements was found between patients treated with standard care and those who received preoperative ESA therapy[172,173].

Transfusion rate was investigated and reported in three studies [167,172,176]. Reduction in the amount of blood transfused per patient afterESA administration was reported in two studies [167,176], but not in another[172].

The effect of different preoperative erythropoietin treatment regimens was investigated[171]. It was found that a weekly 600 IU/kg regimen was similar to a daily 300 IU/kg regimen with respect to avoiding blood transfusion and transfusion rates[171].

Haematological parameters

No studies were identified that reported haematological parameters amount cardiac surgery patients receiving preoperative ESA therapy. Among cardiac patients treated postoperatively with ESAs, no difference was found in postoperative haemoglobin levels between patients treated with ESAs plus intravenous iron and those treated with intravenous iron alone, or those who received standard care[158,159].

In noncardiac surgery patients, preoperative ESA therapy was found to result in higher haemoglobin levels preoperatively[170,172,175,179], post-surgically[176,178] and postoperatively[174,175,176,178,179]. A study that compared weekly and daily treatment regimens found no difference in haemoglobin levels pre- or postoperatively[171].The effect of postoperative administration of ESAs plus oral iron for patients undergoing orthopaedic noncardiac surgery who were anaemic post operatively was also investigated and it was found to result in higher levels of haemoglobin at four and eight weekspostoperatively[180].

Quality of life

Although no studies reported quality of life, data from application of the Functional Independence Measurement (FIM) was reported[180]. Postoperative administration of erythropoietin for orthopaedic surgery patients who were anaemic post operatively was reported to be no more effective than standard care in improving functional ability[180].

Resource use

The effect of ESA therapy on hospital length of stay was investigated among patients undergoing noncardiac surgery who were treated with erythropoietin preoperatively[174,175,176,179]. Although it was found that hospital length of stay was shorter in patients treated preoperatively with ESAs compared with patients who underwent standard care[174], the balance of evidence found that preoperative ESA therapy had no significant effect on hospital length of stay[175,176,179].

Level III and IV evidence

The literature review identified six Level III and ten Level IV studies that investigated the effect of ESAs on patient outcomes in a perioperative population. Given the quantity of higher level evidence on this treatment, data were not extracted from these studies. They are listed in **Appendix B**, Volume 2: No quality of life data were reported in these Level III and Level IV studies.

Evidence statements

Box 3.6.1 outlines the evidence statement (GN3.1) for the effect of postoperative oral iron on haematological parameters in an anaemic cardiac surgical patient population.

Box 3.6.1 GN3.1 Evidence statement for whether postoperatively administered oral iron increases haematological parameters in cardiac surgical patients

Evidence base	Satisfactory (C): The evidence consists of two fair quality Level II studies[146,147] and one poor quality Level II study[148]
Consistency	Excellent (A): All studies consistent
Clinical impact	Poor (D): Slight or restricted—no impact on haemoglobin, although iron stores improved
Generalisability	Satisfactory (C): One study was performed in paediatric patients undergoing cardiac surgery while the other two studies were performed in adult patients undergoing cardiac surgery
Applicability	Satisfactory (C): One study was conducted in Austria, one in Canada and the other in the USA

Evidence statement GN3.1

In paediatric and adult cardiac surgery patients with postoperative anaemia, postoperative oral iron had no effect on haemoglobin (Grade C)[146–148].

Box 3.6.2 presents the evidence statement for the effect of preoperative oral iron on haemoglobin levels in a noncardiac surgical population.

Box 3.6.2 GN3.2a Evidence statement for whether preoperative oral iron increases haemoglobin levels in a noncardiac surgical population with preoperative anaemia

Evidence base	Good (B): The evidence consists of one good quality Level II study[150], and one fair quality Level III studies[,154]
Consistency	Good (B): Most studies consistent, and inconsistency can be explained by the patient population
Clinical impact	Satisfactory (C): There is moderate clinical impact—approximately 1.0 g/dL haemoglobin increase as a consequence of preoperative iron supplementation
Generalisability	Good (B): The studies included patients undergoing orthopaedic or cancer surgery and the results are probably generalisable to a wider perioperative noncardiac surgical population
Applicability	Good(B): The studies were conducted in Japan and the UK

Evidence statement GN3.2a

In patients with preoperative anaemia undergoing noncardiac surgery, preoperative oral iron increases haemoglobin levels (Grade B)[150,154].

Box 3.6.3 presents the evidence statement (GN3.2b) for the effect of preoperative oral iron on transfusion requirements in a noncardiac surgical population with preoperative anaemia.

Box 3.6.3 GN3.2b Evidence statement for whether preoperative oral iron reduces transfusion requirements in a noncardiac surgical population with preoperative anaemia

Evidence base	Good (B): The evidence consists of one good quality Level II study[150], and two fair quality Level III studies[153,154]
Consistency	Excellent (A): All studies reported similar results, despite slightly different dosing, the good quality Level II study and one of the fair quality studies [153] likely including patients who were non-anaemia.
Clinical impact	Good (B): There is substantial clinical impact
Generalisability	Good (B): Studies include patients from orthopaedics and colorectal surgery suggesting that the results should be generalisable to the wider noncardiac perioperative population
Applicability	Satisfactory (C): The studies were conducted in Japan, Spain and the UK respectively

Evidence statement GN3.2b

In patients with preoperative anaemia undergoing noncardiac surgery, preoperative oral iron reduces the incidence of transfusion requirements[150,153,154] (Grade B).

Overall evidence statement GN3.2

In patients with preoperative anaemia undergoing noncardiac surgery, preoperative oral iron increases haemoglobin levels (Grade B)'[150,,154] and reduces the incidence of transfusion requirements[150153,154] ((Grade B).

Box 3.6.4 presents the evidence statement (GN3.3) for the effect of preoperative oral iron on transfusion incidence requirements in a noncardiac surgical population without preoperative anaemia.

Box 3.6.4 GN3.3 Evidence statement for whether preoperative oral iron reduces transfusion incidence requirements in a noncardiac surgical population without preoperative anaemia

Evidence base	Satisfactory (C): The evidence consists of one fair quality Level III study[153]
Consistency	Not Applicable(NA): Only one study
Clinical impact	Satisfactory (C): There is moderate clinical impact
Generalisability	Satisfactory (C): Study was performed in patients undergoing orthopaedic surgery and may not be generalisable to a wider perioperative noncardiac surgical patient population
Applicability	Satisfactory (C): The studies were conducted in Spain

Evidence statement GN3.3

In noncardiac surgery patients without preoperative anaemia, there is insufficient evidence to determine whether oral iron treatment before surgery affects the incidence of transfusion. (Grade D) [153].

Box 3.6.5 presents the evidence statement (GN3.4) for the effect of postoperative oral iron on haemoglobin levels in a noncardiac surgical population.

Box 3.6.5 GN3.4 Evidence statement for whether postoperative oral iron increases haemoglobin levels in a noncardiac surgical population

Evidence base	Good (B): The evidence consists of one good quality Level II study[151] and one fair quality Level II study[152]
Consistency	Good (B): Both studies report minimal effect
Clinical impact	Poor (D): There is slight or restricted clinical impact
Generalisability	Satisfactory (C): Both studies were performed in orthopaedic patients and may not be generalisable to a wider perioperative noncardiac surgical patient population
Applicability	Good (B): The studies were performed in the UK and New Zealand and therefore has good applicability to the Australian healthcare context

Evidence statement GN3.4

In noncardiac surgery patients with postoperative anaemia, postoperative oral iron is not clinically effective (Grade C)[151].

Box 3.6.6 presents the evidence statement (GN3.5) for the effect of preoperative or postoperative intravenous iron on mortality, hospital length of stay, risk of infection and incidence of transfusion in a noncardiac surgical population transfusion requirements in a noncardiac surgical population.

Box 3.6.6 GN3.5 Evidence statement for whether preoperative or postoperative intravenous iron reduces mortality, hospital length of stay, risk of infection and incidence of transfusion in a noncardiac surgical population

Evidence base	Poor (D): The evidence consists of three fair quality Level III studies[155–157]
Consistency	Satisfactory (C): All studies trended in the same direction; however, not all the results reached statistical significance. This could be due to the fact that some of the studies were small
Clinical impact	Poor (D): There is slight or restricted clinical impact
Generalisability	Satisfactory (C): All the studies were performed in an orthopaedic population and may not be directly generalisable to a wider perioperative noncardiac surgical patient population
Applicability	Satisfactory (C): The studies were performed in Spain

Evidence statement GN3.5

In noncardiac surgery patients, preoperative and postoperative intravenous iron may reduce mortality and hospital length of stay, risk of infection and incidence of transfusion (Grade D)[155–157].

Box 3.6.7 presents the evidence statement (GN3.6) for the effect of postoperative intravenous iron plus oral iron compared with postoperative oral iron alone on the incidence of transfusion, postoperative haemoglobin levels and ferritin levels in a cardiac and noncardiac surgical population.

Box 3.6.7 GN3.6 Evidence statement for whether postoperative intravenous iron and oral iron is more effective than oral iron alone in reducing the incidence of transfusion and increasing postoperative haemoglobin and ferritin levels in a cardiac or noncardiac surgical population

Evidence base	Satisfactory (C): The evidence consists of one fair quality Level II study[159]
Consistency	Not applicable (NA): Only one study
Clinical impact	Poor (D): There is slight or restricted clinical impact
Generalisability	Satisfactory (C): The study was in patients undergoing cardiac surgery or orthopaedic surgery. The results may be generalisable to a wider perioperative patient population
Applicability	Good (B): The study was conducted in Canada

Evidence statement GN3.6

In cardiac and orthopaedic surgery patients, the effectiveness of postoperative intravenous iron plus oral iron compared with postoperative oral iron alone on the incidence of transfusion and postoperative haemoglobin levels and ferritin levels is uncertain (Grade D)[159].

Box 3.6.8 presents the evidence statement (GN3.7) for the effect of preoperative intravenous iron compared with oral iron at increasing haemoglobin and ferritin levels in a noncardiac surgical population.

Box 3.6.8 GN3.7 Evidence statement for whether preoperative intravenous iron is more effective than oral iron in increasing haemoglobin and ferritin levels in a noncardiac surgical population

Evidence base	Poor (D): The evidence consists of one poor quality Level II study[160]
Consistency	Not applicable (NA): Only one study
Clinical impact	Satisfactory (D): There is slight or restricted clinical impact
Generalisability	Satisfactory (C): The study was performed in women with anaemia due to menorrhagia undergoing surgery for this condition and therefore may not be directly generalisable to a wider perioperative noncardiac surgical patient population
Applicability	Satisfactory (C): The study was performed in Korea and may not be directly applicable to the Australian healthcare context

Evidence statement GN3.7

In gynaecological surgical patients with iron deficiency anaemia, preoperative intravenous iron is more effective than preoperative oral iron at increasing postoperative haemoglobin and ferritin levels (Grade D)[160].

Box 3.6.9 presents the evidence statement (GN3.8) for the effect of preoperative erythropoiesis stimulating agents (ESAs) in addition to iron on morbidity in a noncardiac surgical population.

Box 3.6.9 GN3.8 Evidence statement for the effect of preoperative ESAs in addition to iron on morbidity in a noncardiac surgical population

Evidence base	Excellent (A): The evidence consists of two good quality Level II studies[166,169,] and one fair quality Level II study[175]
Consistency	Satisfactory (C): Studies were underpowered to detect a difference in this outcome
Clinical impact	Satisfactory (C): There is moderate clinical impact

Generalisability	Good (B): Two studies were performed in orthopaedic surgery and one in patients undergoing hysterectomy. The results are probably generalisable to a wider perioperative noncardiac surgical population
Applicability	Good (B): One of the studies was conducted in Canada, and one each in Sweden and the USA

Evidence statement GN3.8

In noncardiac surgery patients, there is insufficient evidence about the effect on morbidity of preoperative treatment with an erythropoiesis-stimulating agent in combination with oral iron (Grade C)[166,169,175].

Box 3.6.10 presents the evidence statement (GN3.9) for the effect of preoperative erythropoietin in addition to iron on transfusion requirements in an orthopaedic surgical population.

Box 3.6.10 GN3.9 Evidence statement for the effect of preoperative ESAs in addition to iron on transfusion requirements in an orthopaedic surgical population

Evidence base	Excellent (A): The evidence consists of one good quality Level II studies[169,], one fair quality Level II[179]
Consistency	Excellent (A): Both studies reported consistent results
Clinical impact	Good (B): There is substantial clinical impact
Generalisability	Good (A): Both studies were performed in patients undergoing orthopaedic surgery and are therefore directly generalisable to an orthopaedic surgical population. The results may not be generalisable to a wider perioperative population
Applicability	Good (B): One study was conducted in the USA; one was a multicentre trial (Netherlands, France, Germany, Sweden, Belgium, Australia); and one was conducted in an unknown location

Evidence statement GN3.9

In orthopaedic surgical patients, preoperative treatment of anaemia with an erythropoiesis-stimulating agent in combination with oral iron reduces the incidence of transfusion (Grade A)[168–,179].

Box 3.6.11 presents the evidence statement (GN3.10) for the effect of preoperative ESAs in addition to iron on incidence of transfusion in a colorectal surgical population.

Box 3.6.11 GN3.10 Evidence statement for the effect of preoperative ESAs in addition to iron on incidence of transfusion in a colorectal surgical population

Evidence base	Good (B): The evidence consists of one good quality Level II study[176] and three fair quality Level II studies[167,172,173]
Consistency	Satisfactory (C): Only one study demonstrates an effect of erythropoietin on the transfusion ? outcome
Clinical impact	Satisfactory (C): There is moderate clinical impact
Generalisability	Excellent (A): Because all studies were performed in patients undergoing surgery for colorectal cancer, the results are directly transferable to this patient population. Results may not be generalisable to a wider perioperative population
Applicability	Satisfactory (C): Two studies were conducted in Germany and one each in Denmark and Greece

Evidence statement GN3.10

In colorectal surgical patients, preoperative treatment of anaemia with an erythropoiesis-stimulating agent in combination with oral iron starting less than 10 days before surgery has an inconsistent effect on incidence of transfusion (Grade C)[167,172,173,176].

Box 3.6.12 presents the evidence statement (GN3.11) for the effect of preoperative ESAs in addition to iron on haemoglobin levels in a noncardiac surgical population.

Box 3.6.12 GN3.11 Evidence statement for the effect of preoperative ESAs in addition to iron on haemoglobin levels in a noncardiac surgical population

Evidence base	Excellent (A): The evidence consists of two good quality Level II studies[174,176] and three fair quality [172,175,179]and one poor quality[178,] Level II studies
Consistency	Excellent (A): All studies gave consistent results
Clinical impact	Good (B): There is substantial clinical impact
Generalisability	Good (B): Studies were performed in a range of noncardiac surgeries, although the majority were performed in orthopaedic and cancer surgeries. The results are probably generalisable to a wider perioperative noncardiac surgical population
Applicability	Good (B): The studies were conducted in Germany, Sweden, Denmark, Greece and Japan; one was a multicentre study conducted in the Netherlands, France, Germany, Sweden, Belgium and Australia

Evidence statement GN3.11

In noncardiac surgery patients, preoperative treatment of anaemia with an erythropoiesis-stimulating agent in combination with oral iron increases preoperative haemoglobin levels (Grade A) [172,174, 175,176,178,179].

Box 3.6.13 presents the evidence statement (GN3.12) for the effect of preoperative ESAs in addition to iron on hospital length of stay in a noncardiac surgical population.

Box 3.6.13 GN3.12 Evidence statement for the effect of preoperative ESAs in addition to iron on hospital length of stay in a noncardiac surgical population

Evidence base	Good (B): The evidence consists of one good quality Level II study[176] and two fair quality Level II studies[175,179]
Consistency	Good (B): Only one study showed an effect on this outcome
Clinical impact	Satisfactory (C): There is moderate clinical impact
Generalisability	Good (B): Studies were performed in a range of noncardiac surgeries, and the results are probably generalisable to a wider perioperative noncardiac surgical population
Applicability	Good (B): Studies were conducted in Denmark and Greece; and one was a multicentre study conducted in the Netherlands, France, Germany, Sweden, Belgium and Australia

Evidence statement GN3.12

In noncardiac surgery patients, preoperative treatment of anaemia with an erythropoiesis-stimulating agent in combination with oral iron does not affect hospital length of stay (Grade B)[175,176,179].

Box 3.6.14 presents the evidence statement (GN3.13) for the effect of weekly preoperative ESAs in addition to iron compared with preoperative daily erythropoietin in addition to iron on increasing haemoglobin levels in an orthopaedic surgical population.

Box 3.6.14 GN 3.13 Evidence statement for the effect of preoperative weekly ESAs in addition to iron compared with preoperative daily ESAs in addition to iron on haemoglobin levels in an orthopaedic surgical population

Evidence base	Satisfactory (C): The evidence consists of one fair quality Level II study[171]
Consistency	Not applicable (NA): Only one study
Clinical impact	Satisfactory (C): There is moderate clinical impact
Generalisability	Good (B): The study was performed in patients undergoing orthopaedic surgery and may be generalisable to a wider perioperative noncardiac surgical population
Applicability	Satisfactory (C): Study was performed in the USA

Evidence statement GN3.13

In orthopaedic surgery patients with anaemia, preoperative administration of an erythropoiesis-stimulating agent (epoetin alfa) weekly is no different to daily administration in combination with oral iron at increasing preoperative haemoglobin levels (Grade C)[171].

Box 3.6.15 presents the evidence statement (GN3. 14) for the effect of postoperative ESAs in addition to intravenous iron on the incidence of transfusion in a cardiac and orthopaedic surgical population.

Box 3.6.15 GN3.14 Evidence statement for the effect of postoperative ESAs in addition to intravenous iron on the incidence of transfusion in a cardiac and orthopaedic surgical population

Evidence base	Satisfactory (C): The evidence consists of one fair quality Level II study[159]
Consistency	Not applicable (NA): Only one study
Clinical impact	Poor (D): There is slight or restricted clinical impact
Generalisability	Good (B): The study was performed in patients undergoing cardiac surgery or orthopaedic surgery. The results are probably generalisable to a wider perioperative patient population
Applicability	Good (B): The study was conducted in Canada

Evidence statement GN3.14

In cardiac and orthopaedic surgical patients, treatment of postoperative anaemia with an erythropoiesis-stimulating agent in combination with intravenous iron may not decrease the incidence of transfusion compared with intravenous iron plus oral iron or oral iron alone (Grade D)[159].

Box 3.6.16 presents the evidence statement (GN3.15) for the effect of postoperative erythropoietin in addition to oral iron on haemoglobin levels in an orthopaedic surgical population.

Box 3.6.16 GN3.15 Evidence statement for the effect of postoperative erythropoietin in addition to oral iron on haemoglobin levels in an orthopaedic surgical population

Evidence base	Good (B): The evidence consists of one good quality Level II study[180]
Consistency	Not applicable (NA): Only one study
Clinical impact	Poor (D): There is slight or restricted clinical impact
Generalisability	Satisfactory (C): The study was performed in patients undergoing orthopaedic surgery. The results may be generalisable to a wider perioperative patient population
Applicability	Satisfactory (C): The study was conducted in the USA

Evidence statement GN3.15

In orthopaedic surgical patients with postoperative anaemia, treatment with an erythropoiesis-stimulating agent in combination with oral iron increases haemoglobin levels (Grade D)[180].

3.7 Question 7

In patients undergoing surgery, what is the effect of recombinant activated factor VII (rFVIIa) (prophylaxis or treatment) on morbidity, mortality and transfusion rate? (Referred to as GN4)

3.7.1 Summary of evidence

Methods

There were 11 studies identified through the systematic review process (see **Appendix C** in Volume 2). Another six systematic reviews were identified but were excluded because they included data from non-perioperative studies. Another eight Level II studies were identified but were excluded as duplicates because they were reported in the included systematic reviews. Because Level I and Level II evidence is presented, Level III and Level IV evidence was not included. One study was a late exclusion[189] as it was a wrong population. Details of excluded studies are provided in **Appendix B**, Volume 2.

Study characteristics and results are summarised below for each included study and evidence statements are presented for outcomes where evidence was identified.

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for this research question.

Level I evidence

Three Level I systematic reviews were identified that investigated the clinical effectiveness of rFVIIa as either prophylaxis or treatment to manage bleeding in the perioperative setting[181–183]. The main characteristics of identified systematic reviews are summarised in **Table 3.7.1**.

Of the three included systematic reviews, two presented evidence pertaining only to cardiac surgery[181,182] and one presented evidence from studies on a range of surgery types[183], including prostatectomy, liver transplant, orthopaedic surgery and cardiac surgery.

Table 3.7.1 Summary of systematic reviews on the effects of rFVIIa in surgery

Level I evidence					
Author	Study type (number of included studies) Study quality	Population	Intervention (number of studies)	Comparator	Outcomes
Cardiac surgery					

Level I evidence					
Author	Study type (number of included studies) Study quality	Population	Intervention (number of studies)	Comparator	Outcomes
Warren et al (2007)[181]	Systematic review of Level II (2 primary studies) and Level III-2 (4 primary studies) *Poor*	Cardiac surgery patients (complex non-coronary cardiac surgery, various procedures, aortic dissection)	rFVIIa dose ranged from 40 μg/kg to 90 μg/kg)	Placebo	Blood loss, transfusion requirements, morbidity (thromboembolic effects)
Zangrillo et al (2009)[182]	Systematic review of Level II (1 primary study) and III-2 studies (4 primary studies) *Fair*	Cardiac surgery patients (CABG, various procedures)	rFVIIa dose ranged from 18 to 90 μg/kg	Placebo	Mortality, surgical re-exploration, and morbidity (stroke, MI, AKI)
General surgery					
Ranucci et al (2008b)[183]	Systematic review of Level II studies (7 primary studies) *Good*	Surgical patients (pelvic trauma, cardiovascular, prostatectomy, liver resection, liver transplantation)	rFVIIa dose ranged from 20 to 120 μg/kg	Placebo	Mortality, transfusion requirements, thromboembolic events

Abbreviations: AKI, acute kidney injury; CABG, coronary artery bypass graft; RBC, red blood cells; MI, myocardial infarction; rFVIIa, recombinant factor VIIa

Results from the systematic reviews are presented in **Table 3.7.2** (cardiac surgery) and **Table 3.7.3** (noncardiac surgery).

Table 3.7.2 Results of systematic reviews on the effects of rFVIIa in cardiac surgery

Level I evidence		
Study	Number of included studies	Results and conclusion
Warren et al (2007)[181]	Level II (2 primary studies), and Level III-2 (4 primary studies) *Poor*	Morbidity (Level II and III-2) Treatment with rFVIIa—Aggregated adverse event rate for thromboembolic events was 5.3% in adult patients. Rate NR for control patients (inter study heterogeneity not assessed) Blood loss/transfusion requirements (Level II) In one study of infants aged <1 year (n=82), prophylactic rFVIIa had no effect on volumes of transfusion products required In one small (underpowered) study of adult patients (n=19), 13 units of allogeneic blood were transfused among patients in the group who received prophylactic rFVIIa, vs. 105 units transfused to patients in the placebo group (RR, any transfusion=0.26, p=0.037) Time to chest closure (Level II) In one study of infants aged <1 year (n=82), prophylactic rFVIIa significantly increased the time to chest closure (p=0.02) Conclusion Findings suggest that prophylactic rFVIIa has potential to reduce transfusion requirements among adult patients. However, this small study is inadequately powered to detect the effects of rFVIIa
Zangrillo et al (2009)[182]	Level II (1 primary study) and Level III-2 (4 primary studies) *Fair*	Mortality (Level II and III-2) rFVIIa=15% vs. control=15%; OR_p=0.96[a] (95% CI: [0.50, 1.86]), p=0.90 (NS) (I^2=0% with 298 patients included in 5 studies) Morbidity (Level II and III-2) Rate of thromboembolic events (MI, stroke and DVT): rFVIIa=9% vs. control=6%; OR_p=1.62[a] (95% CI: [0.68, 3.86]), p=0.28 (NS) (I^2=0% with 298 patients included in 5 studies) Rate of perioperative stroke: rFVIIa=5% vs. control=1.4%; OR_p=3.17[a] (95% CI: [0.83, 12.10]), p=0.09 (NS) (I^2=0% with 298 patients included in 5 studies) Rate of MI: rFVIIa=4.5% vs. control=6.5%; OR_p=0.70[a] (95% CI: [0.21, 2.29]), p=0.55 (I^2=0% with 218 patients included in 4 studies) Rate of acute kidney injury: rFVIIa=15% vs. control=9%; OR_p=1.86[a] (95% CI: [0.81, 4.31]), p=0.15 (NS) (I^2=39% with 228 patients included in 3 studies) Surgical re-exploration (Level II and III-2) Rate of re-exploration: rFVIIa=13% vs. control=57%; OR_p=0.25[a] (95% CI: [0.01, 7.01]), p=0.42 (NS) (I^2=90% with 150 patients included in 3 studies) Conclusion Results suggest that rFVIIa may reduce the rate of surgical re-exploration after cardiac surgery, although this difference was not statistically significant. There was also significant heterogeneity among the three studies that reported this outcome. Furthermore, this potential benefit should be considered with awareness of a possible increase in the risk of thromboembolic events. The use of rFVIIa appears to have no effect on mortality, but this result was not statistically significant. For all reported OR_p values, the CIs were broad and captured the value of no effect (i.e. 1.00). No definitive conclusions can be drawn from this systematic review because of the absence of statistical significance. Studies included in this systematic review were not adequately powered to measure the effects of rFVIIa

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; MI, myocardial infarction; NR, not reported; NS, not significant; OR, odds ratio; OR_p, pooled odds ratio; rFVIIa, recombinant factor VIIa; RR, relative risk
[a] Pooled result for therapeutic and prophylactic rFVIIa

Table 3.7.3 Results of a systematic review on the effects of rFVIIa in noncardiac surgery

Level I evidence		
Study	Number of included studies	Results and conclusions
Ranucci et al (2008b)[183]	Level II studies (7 primary studies) *Good*	Mortality (Level II evidence) Mortality rates were not different between prophylactic rFVIIa and placebo-treated patients (OR_p=0.99, 95% CI: [0.37, 2.68], p=0.99; I^2=0%, p=0.94) Morbidity (Level II evidence) Thromboembolic complication rates were not different between prophylactic rFVIIa and placebo-treated patients (OR_p=1.32, 95% CI: [0.69, 2.52], p=0.40; I^2=0%, p=0.99) Transfusion requirements (Level II evidence) Prophylaxis with rFVIIa reduced the likelihood of receiving allogeneic RBCs (OR_p=0.29, 95% CI: [0.10, 0.80], p=0.02; I^2=60%, p=NR) Subgroup analysis found that only patients receiving at least 50 µg/kg rFVIIa had a significant benefit in terms of reduction in transfusion requirements (OR_p=0.43, 95% CI: [0.23, 0.78], p=0.006) Conclusion Findings from this systematic review suggest that prophylactic rFVIIa is beneficial in terms of reducing need for allogeneic RBC transfusion. However, no definitive conclusions can be made regarding the effect of prophylactic rFVIIa on mortality or morbidity—the wide CI for the OR_p shows that included studies are not sufficiently powered for these outcomes

Abbreviations: CI, confidence interval; MI, myocardial infarction; NR, not reported; OR_p, pooled odds ratio; rFVIIa, recombinant factor VIIa; RBC, red blood cells; TE, thromboembolic event

Mortality

The use of rFVIIa in cardiac surgery was reported by one systematic review to have no effect on mortality risk[182]. Results were not stratified by the therapeutic and prophylactic use of rFVIIa[182]. Similar results were reported[183] that the prophylactic use of rFVIIa in a range of surgical procedures did not affect mortality. However, the absence of statistical significance (wide confidence interval) shows that studies included in this analysis were inadequately powered. Analysis of heterogeneity for this outcome in both systematic reviews[182,183] indicates that there was no variation in the effect of rFVIIa (I^2=0%) among included studies. However, no definitive conclusions could be drawn from the results of these systematic reviews because of the absence of statistical significance, with pooled odds ratio ($OR_{p)}$ confidence intervals capturing values representing no effect (**Table 3.7.2** and **Table 3.7.3**).

Morbidity

Warren and colleagues[181] reported the rate of thromboembolic events for adult patients who had used rFVIIa. The absence of a comparison with control data meant that conclusions could not be drawn from this finding. Zangrillo et al[182] reported that the rate of thromboembolic events (combined MI, stroke and deep vein thrombosis [DVT]) and risk of

perioperative stroke and acute kidney injury increased among cardiac surgery patients who received rFVIIa, whereas the risk of MI was slightly reduced[182]. In contrast, Ranucci et al[183] found that thromboembolic complication rates were not different between prophylactic rFVIIa and placebo-treated patients: rFVIIa vs. placebo group comparison: OR_p=1.32 (95% CI: [0.69, 2.52], p=0.40)[183]. Analysis of heterogeneity for this outcome[182,183] indicated that there was no variation in the effect of rFVIIa (I^2=0%) among included studies. However, no definitive conclusions could be made from the results of these systematic reviews because of the absence of statistical significance; OR_p confidence intervals captured values representing 'no effect' (**Table 3.7.2** and **Table 3.7.3**).

Transfusion requirements

Warren et al[181] reported two studies in cardiac surgery patients that assessed rFVIIa impact on transfusion requirements. Of these, a study that involved infants (aged less than one year) found that prophylactic rFVIIa had no effect on transfusion requirements. In contrast, a small study (n=19) involving adults found that prophylactic rFVIIa significantly reduced need for transfusion (**Table 3.7.2**). However, both studies were small and inadequately powered to accurately demonstrate the effect of rFVIIa. In addition, Ranucci et al[183] found that the prophylactic use of rFVIIa among patients undergoing a variety of surgical procedures resulted in a statistically significant reduction in the requirement for RBC transfusion, irrespective of its prophylactic or therapeutic use (rFVIIa vs. placebo group comparison: OR_p=0.29, 95% CI: [0.10, 0.80], p=0.02) (**Table 3.7.3**). The I^2 test for heterogeneity among included studies for this outcome suggested that there was a moderate degree of variability in the effect of rFVIIa on transfusion requirements[183] (**Table 3.7.3**). Furthermore, Ranucci et al[183] also reported a subgroup analysis indicating that patients who received at least 50 µg/kg rFVIIa experienced significant benefit in reduced need for transfusion (OR_p=0.43, 95% CI: [0.23, 0.78], p=0.006).

Re-operation

In a meta-analysis of three studies[182] it was reported that the use of rFVIIa reduced the need for re-operation among cardiac surgery patients. This result was not statistically significant and the I^2 test for heterogeneity showed considerable variation in the effect of rFVIIa on re-operation[182] (**Table 3.7.2**).

Findings from the systematic reviews discussed should be interpreted with caution because of heterogeneity among studies in terms of variations in included patients (types of surgery) and rFVIIa regimen (dosage and therapeutic or prophylactic use). Most included studies had small patient populations and were inadequately powered to measure the clinical impact of rFVIIa. Nevertheless, the presented systematic reviews indicate that the therapeutic or prophylactic use of rFVIIa in the perioperative setting may provide some benefits, including reducing transfusion requirements[182,183] and decreasing the likelihood of re-operation[182]. These potential benefits, however, need to be balanced against the potential for an increased risk of thromboembolic events[182].

Level II evidence

In addition to the studies reported in the included systematic reviews, another seven Level II studies were identified that investigated the clinical effectiveness of rFVIIa either as prophylaxis or treatment to manage bleeding in the perioperative setting[184,195,186,187, 188, 190,191]. The main characteristics of these additional Level II studies are presented in **Table 3.7.4**. Of these, three studies presented evidence pertaining to cardiac surgery[184–186] and the remaining four presented evidence on a range of surgical procedures[187, 199, 190,191].

Table 3.7.4 Summary of Level II studies on the effects of rFVIIa

Level II evidence					
Author	Study type Study quality	Population	Intervention (N)	Comparator (N)	Outcomes
Cardiac surgery					
Essam (2007)[184]	RCT, blinding NR, placebo-controlled *Fair*	Elective cardiac revascularisation patients who underwent CPB N=30	Prophylactic rFVIIa, dose=90 μg/kg following weaning from CPB (15)	Placebo (15)	Transfusion requirements, chest tube drainage, Hb level
Gill et al (2009)[185]	RCT, dose-escalation, double-blind, placebo-controlled *Fair*	Postoperative cardiac surgery patients who underwent CPB N=174	Postoperative treatment with rFVIIa, dose=40 μg/kg (35) or 80 μg/kg (69)	Placebo (68)	Mortality, morbidity, re-operation, transfusion requirements
Ma et al (2006)[186]	Single-centre, randomised, double-blind, placebo-controlled trial N/A[a]	Cardiac valve replacement under CPB Full details unknown: study reported in foreign language article N=22	Prophylactic rFVIIa, 40 μg/kg (11)	Placebo (11)	Morbidity, transfusion requirements; blood loss; ICU LOS, hospitalisation costs
Thoracic surgery					
Alavi et al (2008)[187]	RCT N/A[b]	Elective thoracic surgery patients N=40	Prophylactic rFVIIa, dose=90 μg/kg (20)	Placebo (20)	Blood loss, transfusion requirements
Burn grafting					
Johansson et al (2007)[188]	Single-centre, randomised, double-blind, placebo-controlled trial *Fair*	Patients with thermal burns aged ≥18 years, scheduled to have full thickness burn wound excision of >10% of total BSA and skin grafting N=18	rFVIIa, prophylactically, 40 μg/kg as IV bolus injection immediately before surgery, and second dose (40 μg/kg) 90 minutes later	No rFVIIa—same placebo regimen before and after surgery as intervention group (9)	Mortality (survival rate on Day 30); adverse events; ICU and hospital LOS

Level II evidence					
Author	Study type Study quality	Population	Intervention (N)	Comparator (N)	Outcomes
			(9)		
Orthotopic liver transplantation					
Pugliese et al (2007)[190]	Single-centre, randomised, double-blind, placebo-controlled trial *Poor*	Patients scheduled for orthotopic liver transplant, with Hb >8 mg/dL, INR >1.5, fibrinogen >100 mg/dL N=20	Prophylactic rFVIIa 40 µg/kg administered as a single bolus before anaesthesia induction (10)	Placebo (10)	Mortality, morbidity, transfusion requirements, blood loss, ICU LOS
Spinal surgery					
Sachs et al (2007)[191]	Multicentre, randomised, double-blind, placebo-controlled trial *Fair*	Patients 15 to 70 years of age, scheduled to undergo elective spinal fusion surgery of 3 or more motion segments by posterior approach N=49	rFVIIa: three different dosing regimens: Cohort 1=3 x 30 µg/kg (12) Cohort 2=3 x 60 µg/kg (12) Cohort 3=3 x 120 µg/kg (12) rFVIIa given at 2 hourly intervals	Placebo Cohort 1 (4) Cohort 2 (4) Cohort 3 (5)	Mortality; morbidity, transfusion requirements, blood loss

Abbreviations: BSA, body surface area; CPB, cardiopulmonary bypass; Hb, haemoglobin; ICU, intensive care unit; INR, international normalised ratio; IV, intravenous; LOS, length of stay; NR, not reported; RCT, randomised controlled trial, rFVIIa, recombinant factor VIIa.

[a] N/A, not assessable: cannot assess quality level—limited information reported in English in the publication

[b] N/A, not assessable: cannot assess quality level because of non-reporting of RCT design

Results from the Level II studies are presented in **Table 3.7.5** (cardiac surgery) and **Table 3.7.6** (a range of noncardiac surgical procedures).

Table 3.7.5 Results of Level II studies on the effects of rFVIIa in cardiac surgery

Level II studies				
Study	Outcome	rFVIIa	Placebo	Statistical significance
Prophylactic rFVIIa				
Essam (2007)[184]	Transfusion requirements (24 h) (mean ± SD)	RBC: 316.6 ± 333.6 FFP: 60 ± 94.8 PLT: 40 ± 69.6	RBC: 516.66 ± 175.93 FFP: 270 ± 181.06 PLT: 106.6 ± 67.78	p=0.047 p=0.004 p=0.021
	Chest tube drainage (24 h) (mean ± SD)	435 mL ± 93.86	620.33 mL ±108.33	p=0.001

Level II studies				
	Hb levels (g/dL) (mean ± SD)	Baseline Hb=12.56 ± 0.79 T1 Hb (off CPB)=8.66 ± 0.47 T2 Hb (CICU admission)=9.26 ± 0.68 T3 Hb (12 h CICU)=9.71 ± 0.61 T4 Hb (24 h CICU)=9.9 ± 0.74	Baseline Hb=12.56 ± 1.22 T1 Hb (off CPB)=8.53 ± 0.72 T2 Hb (CICU admission)=9.27 ± 0.82 T3 Hb (12 h CICU)=9.51 ± 0.63 T4 Hb (24 h CICU)=9.03 ± 2.26	p=0.985 p=0.34 p=0.959 p=0.098 p=0.159
Therapeutic rFVIIa				
Gill et al (2009)[185]	Mortality	40 µg/kg=11% 80 µg/kg=9%	6%	p=NR
	Morbidity (critical SAEs)	40 µg/kg=14% 80 µg/kg=12%	7%	p=0.25 p= 0.43
	Re-operation	40 µg/kg=14% 80 µg/kg=12%	25%	p=0.21 p=0.04
	Allogeneic transfusion (mL, 25–75% IQR)	40 µg/kg=640 (0–1920) 80 µg/kg=500 (0–1750)	825 (326.5–1893)	p=0.047 p=0.042

Abbreviations: CICU, coronary intensive care unit; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; Hb, haemoglobin; IQR, interquartile range; rFVIIa, recombinant factor VIIa; NA, not applicable; NR, not reported; PLT, platelets; RBC, red blood cells; SAE, serious adverse event; SD, standard deviation

A small RCT, with no reported blinding, investigated the prophylactic effect of rFVIIa among patients undergoing coronary revascularisation surgical procedures with cardiopulmonary bypass (CPB)[184]. Prophylactic rFVIIa (90 µg/kg dose) administered following weaning from CPB reduced transfusion requirements (RBC, fresh frozen plasma [FFP], platelets) in the 24 hour period following surgery (**Table 3.7.5**). It also reduced chest tube drainage during this period[184]. However, the wide range of standard deviation values reported for these outcomes indicate that the data set is skewed. Therefore, definitive conclusions could not be made about the effect of rFVIIa owing to the absence of statistical analysis appropriate for skewed data. There was no difference in haemoglobin levels between the prophylactic rFVIIa and placebo groups[184]. Results from this study suggest that prophylactic rFVIIa administered following weaning from CPB has benefits in terms of reducing blood loss (chest tube drainage) and transfusion requirements. These findings should be interpreted with caution because of the inappropriate statistical analysis used to assess the variation in results. These results were not included in the body of evidence for development of evidence statements and associated recommendation.

A dose-escalation study investigated the therapeutic use of rFVIIa among patients who experienced bleeding after cardiac surgery[185]. It was reported that in the rFVIIa treatment groups, significantly fewer patients underwent re-operation for bleeding and the need for transfusion was decreased (**Table 3.7.5**). More critical serious adverse events occurred among patients in the rFVIIa groups, but these differences were not statistically significant. There were also more deaths in the rFVIIa groups, but statistical significance was not

reported. Findings from this investigation indicate that rFVIIa treatment for postoperative cardiac surgery patients may be beneficial in reducing transfusion and re-operation rates[185]. Nevertheless, these benefits should be considered in the light of the increased frequency of critical serious adverse events (including stroke and MI) in rFVIIa-treated patients reported in this study. Furthermore, the small sample size meant that this study was inadequately powered to assess the genuine effect of rFVIIa.

Ma et al[186] studied the effects of prophylactic rFVIIa (40 µg/kg) among patients undergoing cardiac valve replacement with CPB (**Table 3.7.4**). This study was published in Chinese language, with some results presented in English (see **Appendix F**, Volume 2). No quality appraisal was possible, but results are discussed to disclose additional information on the effects of prophylactic rFVIIa. This study was small (N=22) and therefore underpowered. Nevertheless, it was found that prophylactic rFVIIa reduced transfusion requirements (RBC and platelets) and ICU length of stay[186] (**Appendix F**, Volume 2). There were no deaths and no patients had thromboembolic complications (**Appendix F**, Volume 2). Because a quality appraisal could not be performed, findings from this study are not considered in the body of evidence for recommendation development.

Table 3.7.6 Results of Level II studies on the effects of rFVIIa in noncardiac surgery

Level II studies				
Study	Outcome	rFVIIa	Placebo	Statistical significance
Prophylactic				
Johansson et al (2007)[188]	Mortality (proportion with survival at Day 30)	100%	66.7%	p=0.20
	Morbidity (postoperative complications)	Wound infection n=2 Sepsis (days): 20 Pneumonia n=6 Acute lung injury n=2 MOF n=3 TE n=0	Wound infection n=2 Sepsis (days): 62 Pneumonia n=5 Acute lung injury n=1 MOF n=7 TE n=0	 p=0.71 p=0.44 p=0.50 p=0.50 p=0.08
	ICU LOS (days; median, range)	4 (0–63)	8 (0–37)	p=0.59
	Hospital LOS (days; median, range)	49 (33–110)	36 (28–72)	p=0.22
Pugliese et al (2007)[190]	Mortality	No deaths	No deaths	NA
	Morbidity	No TE	No TE	NA
	Transfusion requirements (mL):			
	RBC during hepatectomy	120	240	p<0.049
	RBC during anahepatic phase	180	330	p<0.17
	FFP 1 h after bolus	0	240	p<0.001

Level II studies						
Study	Outcome	rFVIIa		Placebo		Statistical significance
	FFP during hepatectomy	280		600		p<0.001
	FFP during anahepatic phase	320		560		p<0.16
	Blood loss (mL):					
	During hepatectomy	160		280		p<0.049
	During anahepatic phase	310		470		p<0.001
	After vascular unclamping	270		390		p<0.049
	ICU LOS (days, mean ± SD)	4.8±1.3		5.2±1.2		p=NS
Therapeutic						
Sachs et al (2007)[191]	Mortality (30-day follow-up) [n (%)]	3x30 µg/kg n=1 (8%)	3x60 µg/kg n=0	3x120 µg/kg n=0	n=0	NR
	Morbidity (%) Stroke MI Troponin 1 increased Visual acuity reduction Bradycardia PE Seroma Postoperative infection	3x30 µg/kg 1 (8%) 0 0 0 0 0 1 (8%) 1 (8%)	3x60 µg/kg 0 1 (8%) 1 (8%) 0 0 1 (8%) 0 0	3x120 µg/kg 0 0 0 0 0 0 0 0	 0 0 0 1 (8%) 1 (8%) 0 0 0	NR for any morbidity outcomes
	Total transfusion volume (mL, combined RBC, FFP, cryoprecipitate, PLT; adjusted mean[b], 95% CI)	3x30 µg/kg 258 (67, 991) p=0.002	3x60 µg/kg 89 (16, 496) p<0.001	3x120 µg/kg 287 (112, 736) p<0.001	1488 (971, 2279)	Note: p values based on ratio of rFVIIa results to placebo result
Sachs et al (2007) continued	Units of blood products (combined RBC, FFP, cryoprecipitate, PLT; adjusted mean[b])	3x30 µg/kg 1.1 p=0.03	3x60 µg/kg 1.3 p=0.03	3x120 µg/kg 0.8 p=0.03	5	
	RBC units	3x30 µg/kg 0.9 p=0.002	3x60 µg/kg 1.2 p=0.012	3x120 µg/kg 0.8 p=0.033	1.6	

Level II studies						
Study	Outcome	rFVIIa		Placebo		Statistical significance
	Blood loss (mL, adjusted mean[b], 95% CI)	3x30 µg/kg 1120 (647, 1938) p=0.001	3x60 µg/kg 400 (151, 1059) p<0.001	3x120 µg/kg 824 (435, 1558) p<0.001	2536 (1869, 3441)	

Abbreviations: FFP, fresh frozen plasma; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; MOF, multiple organ failure; NA, not applicable; NR, not reported; NS, not significant; PE, pleural effusion; PLT, platelets; RBC, red blood cells; SAE, serious adverse event; SD, standard deviation; TE, thromboembolic events

[a] Serious adverse events described by study authors: death, threat to life of patient, in-patient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity; important medical events that may not result in death, be life threatening, or require hospitalisation may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the outcomes

[b] Mean adjusted for number of spinal segments fused, duration of surgery and initial blood volume

Results from Level II studies assessing the impact of rFVIIa on patients undergoing a range of surgical procedures are presented. Because of the heterogeneity in surgical procedures and patient populations, no pooling (meta-analysis) of study results has been performed. The prophylactic[188,190] and therapeutic[190,191] uses of rFVIIa were assessed (**Table 3.7.6**).

Results from an RCT that investigated rFVIIa prophylaxis in patients undergoing elective thoracic surgery were reported in a letter by Alavi and colleagues[187]. A full report of the trial could not be found in the current systematic literature review and quality appraisal was not possible. Alavi et al reported that prophylactic rFVIIa (90 µg/kg) produced significant differences in both perioperative bleeding (intraoperatively and 2 days postoperatively) and the use of blood products ($p<0.05$)[187]. No complications were observed, but no data were presented to support these positive findings[187]. Therefore, definitive conclusions cannot be drawn about the use of prophylactic rFVIIa in elective thoracic surgery. Because a quality appraisal could not be performed, findings from this study were not considered in the body of evidence for recommendation development.

Mortality

In a study of patients receiving skin grafts for burn wounds, no deaths were reported among patients who received prophylactic rFVIIa (40 µg/kg)[188] (**Table 3.7.6**); in comparison, survival at Day 30 was 66.7% among patients in the placebo group. This result was not statistically significant; the study was small (N=18), and therefore underpowered.

Results from a small study that investigated prophylactic use of rFVIIa for patients undergoing orthotopic liver transplantation indicated that there were no deaths in either the rFVIIa or placebo groups[190] (**Table 3.7.6**). The duration of follow-up after rFVIIa administration in this study was, however, only 6 hours.

An investigation into the therapeutic use of rFVIIa for patients undergoing spinal surgery reported one death (1/12) in the low rFVIIa dose (30 µg/kg) group[191]. No deaths were reported in either the placebo patient group or those who received either 60 µg/kg or 120 µg/kg rFVIIa (**Table 3.7.6**).

Results from two studies suggest that the prophylactic use of rFVIIa does not affect mortality[188,190]. Where rFVIIa was used therapeutically[191], dosing at 40, 60, 80 and 120 µg/kg did not affect mortality. However, the small sample sizes of these three studies[188, 190,191], and the variety of surgical procedures/patient populations investigated, mean that generalisations cannot be made about the prophylactic or therapeutic effect of rFVIIa on mortality.

Morbidity

Several postoperative complications were reported in both the prophylactic rFVIIa and placebo groups in the study of burn graft patients by Johansson et al[188] with no significant differences between the groups (**Table 3.7.6**). In liver transplant patients, there was no significant difference in the frequency of complications between the prophylactic rFVIIa and placebo groups, and no thromboembolic events were reported in either group[190].

In spinal surgery patients who were treated with rFVIIa[191], stroke occurred in one patient (1/12) in the group treated with 30 µg/kg rFVIIa and MI occurred in one patient (1/12) in the group who received 60 µg/kg rFVIIa (**Table 3.7.6**).

The prophylactic use of rFVIIa does not appear to be associated with an increased risk of adverse events, whereas thromboembolic complications occurred in some patients who received rFVIIa therapeutically. However, the small sample sizes of these studies and the variety of surgical procedures/patient populations investigated mean that generalisations cannot be made about the prophylactic or therapeutic effect of rFVIIa on morbidity.

Transfusion requirements

The prophylactic use of rFVIIa for patients undergoing liver transplant was reported to reduce requirements for both RBC and FFP[190]. These reductions were significant in relation to hepatectomy. FFP requirements were also significantly reduced when assessed 1 hour after rFVIIa administration (before anaesthesia)[190] (**Table 3.7.6**).

Therapeutic rFVIIa use was reported to reduce the total volume and number of units of blood products required for patients undergoing spinal surgery[191]. The number of units of RBC required was also reduced[191]. A regimen of 3 x 60 µg/kg rFVIIa appears to be the most effective in reducing the total volume of transfusion requirements for these patients[191] (**Table 3.7.6**).

In liver transplant[190] and spinal surgery[191] patients, the use of rFVIIa appears to reduce transfusion requirements. Further studies in these and other surgical patient populations are required to determine whether these findings are consistent and generalisable.

Blood loss

Significant reductions in blood loss during the perioperative period were reported[190,191] (**Table 3.7.6**).

In liver transplant[190] and spinal surgery[191] patients, the use of rFVIIa appears to reduce blood loss.

Hospital and ICU LOS

In burns patients receiving skin grafts, there was a trend with prophylactic use of rFVIIa toward a reduction in ICU LOS and an increase in hospital LOS[188]. These findings were not statistically significant; a wide range of LOS values were recorded (**Table 3.7.6**).

Prophylactic rFVIIa did not affect ICU LOS among liver transplant patients[190] (**Table 3.7.6**).

Based on the results of these two small studies[188,190], it appears that rFVIIa has no effect on either hospital or ICU LOS. However, the limited evidence base means that definitive conclusions cannot be drawn about the effect of rFVIIa on either hospital or ICU LOS.

Level III evidence

Because Level I and Level II evidence is presented, Level III evidence is not discussed. Details of excluded Level III studies are provided in **Appendix B**, Volume 2. No quality of life outcome data were reported in any of the Level III studies.

Level IV evidence

Because Level I and Level II evidence is presented, Level IV evidence is not discussed. Details of excluded Level IV studies are provided in **Appendix B**, Volume 2. No quality of life outcome data were reported in any of the Level IV studies.

Evidence statements

Evidence statements are provided for the key outcomes reported in included studies.

Box 3.7.1 outlines the evidence statement (GN4.1) for the effect of prophylactic or therapeutic use of rFVIIa on mortality in surgery.

Box 3.7.1 GN4.1 Evidence statement for the effect of rFVIIa on mortality in surgery

Evidence base	Good (B): Six studies: two Level I studies, one with a low risk of bias[183] and one with a moderate risk of bias[182]; four Level II studies, three with a moderate risk of bias[185,188,,191] and one with a high risk of bias[190]. Included studies were small and underpowered
Consistency	Satisfactory (C): Generally similar direction of effect among included studies. Inconsistent results between studies of cardiac surgery[182,185], with mortality increased by rFVIIa use in one small primary study[185], but unaffected when results were pooled in a systematic review[182]. Some uncertainty about consistency because of the small sample size of included studies and variety of surgical procedures investigated
Clinical impact	Poor (D): May be some benefit in the use of rFVIIa for some surgical procedures, but there is uncertainty because of the limited evidence base, which comprises small studies
Generalisability	Excellent (A): Study populations are the same as the target population
Applicability	Good (B): Most included studies were from Europe. There are some differences in the healthcare system between Australia/New Zealand and included studies

Evidence statement GN4.1

In surgical patients, there is insufficient evidence to determine the effect of prophylactic or therapeutic use of rFVIIa on mortality (Grade C)[182,183,185,188, 190,191].

Box 3.7.2 outlines the evidence statement (GN4.2) for the effect of rFVIIa on adverse events in surgery.

Box 3.7.2 GN4.2 Evidence statement for the effect of rFVIIa on adverse events in surgery

Evidence base	Good (B): Six studies: two Level I studies, one with a low risk of bias[183] and one with a moderate risk of bias[182]; four Level II studies, four with a moderate risk of bias[185,188,,191], and one with a high risk of bias[190]. Included studies were small and underpowered
Consistency	Satisfactory (C): Some inconsistency, with rFVIIa use responsible for a trend towards reduced MI in cardiac surgery patients who received rFVIIa[182], but an increased risk of stroke in the same patients[182]. The prophylactic use of rFVIIa does not appear to increase adverse events during some surgical procedures[183,188,190], whereas thromboembolic complications occurred in some patients who received rFVIIa therapeutically[191] Although the difference in direction of effects may be explained by the different application of rFVIIa (i.e. prophylactic vs. therapeutic), there is uncertainty about consistency because of the small sample size of included studies and variety of surgical procedures investigated
Clinical impact	Poor (D): Impact of rFVIIa on adverse effects is uncertain—effect of rFVIIa on thromboembolic events in included studies was not statistically significant, with confidence intervals capturing values representing "no effect" and an absence of appropriate study powering because of the small sample sizes
Generalisability	Excellent (A): Study populations are the same as the target population
Applicability	Good (B): Most included studies were from Europe. There are some differences in the healthcare system between Australia/New Zealand and included studies

Evidence statement GN4.2

In surgical patients, there is insufficient evidence to determine the effect of prophylactic or therapeutic use of rFVIIa on the risk of thrombotic adverse events (Grade C)[182,183,185,188,191].

Box 3.7.3 outlines the evidence statement (GN4.3a) for the effect of rFVIIa on transfusion requirements in surgery.

Box 3.7.3 GN4.3a Evidence statement for the effect of rFVIIa on transfusion requirements in surgery

Evidence base	Good (B): Six studies: two Level I studies, one with a high risk of bias[181] and one with a low risk of bias[183]; four Level II studies, three with a moderate risk of bias[184,185,191] and one with a high risk of bias[190]. Included studies were small and underpowered
Consistency	Good (B): Most studies consistent—in general use of rFVIIa decreased transfusion requirements. However, prophylactic use of rFVIIa reduced transfusion requirements in adults[181] but had no effect in infants aged less than 1 year[181]. These studies were small and therefore underpowered for this outcome. Although the reduction in transfusion requirements was statistically significant in one Level I study with a low risk of bias[183], the effect of rFVIIa appears to vary between different surgical populations—I^2 results suggest moderate heterogeneity for this outcome across studies included in this Level I study[183]
Clinical impact	Satisfactory (C): Reduction in transfusion requirements was statistically significant in one Level I study with a low risk of bias[183], with a clinically important benefit for the range of plausible effect estimates (95% CI values). However, there was variation in the effect of rFVIIa on transfusion requirements across different surgical populations[183], and any reduction in transfusion in cardiac surgery was not statistically significant[181,184,185]. Reductions in transfusion requirements were statistically significant when rFVIIa was used in liver transplant[190] and spinal surgery[191]. Overall there is uncertainty about the potential benefit of rFVIIa to reduce transfusion
Generalisability	Excellent (A): Study populations are the same as the target population
Applicability	Satisfactory (C): Most included studies were from Europe. There are some differences in the healthcare system between Australia/New Zealand and included studies

Box 3.7.4 outlines the evidence statement (GN4.3b) for effect of rFVIIa on re-operation in cardiac surgery.

Box 3.7.4 GN4.3b Evidence statement for the effect of rFVIIa on re-operation in cardiac surgery

Evidence base	Satisfactory (C): One Level I study[182] and one Level II study[185], both with a moderate risk of bias. Included studies were small and underpowered
Consistency	Good (B): The two studies provided consistent results (same direction of effect). However, analysis of heterogeneity in the Level I study showed a high degree of variability for the effect of rFVIIa on re-operation rate across studies included in the meta-analysis[182]
Clinical impact	Satisfactory (C): Re-operation rate was reduced, but results were statistically significant only for one rFVIIa (low dose) treatment group in one small, underpowered study[185]. Analysis of heterogeneity indicates a variable effect of rFVIIa on re-operation rates in different types of cardiac surgery. Therefore, it is unclear whether rFVIIa use reduces the re-operation rate in all types of cardiac surgery
Generalisability	Excellent (A): Study populations are the same as the target population
Applicability	Satisfactory (C): Most included studies were from Europe. There are some differences in the healthcare system between Australia/New Zealand and included studies

Box 3.7.5 outlines the evidence statement (GN4.3c) for effect of rFVIIa on blood loss in surgery.

Box 3.7.5 GN4.3c Evidence statement for the effect of rFVIIa on blood loss in surgery

Evidence base	Satisfactory (C): Two Level II studies, one with a moderate risk of bias[191] and one with a high risk of bias[190]. Included studies were small and underpowered
Consistency	Good (B): Similar direction of effect in two studies, one on liver transplant patients[190] (prophylactic rFVIIa) and the other on spinal surgery patients[191] (therapeutic rFVIIa).
Clinical impact	Satisfactory (C): Evidence from three small studies employing rFVIIa in different surgical procedures suggests that blood loss is reduced. Reductions in blood loss in two studies were statistically significant[190,191], with a clinically important benefit observed for the estimated range of effects (95% CI) in one study[191]. Further evidence is required to establish whether this benefit is observed when rFVIIa is used in other surgical procedures
Generalisability	Excellent (A): Study populations are the same as the target population
Applicability	Satisfactory (C): One study from Europe, one from the USA.

Overall evidence statement GN4.3

In surgical patients, the prophylactic or therapeutic use of rFVIIa reduces blood loss (Grade C)[191] and may reduce the incidence of transfusion (Grade C)[181,183,185,190,191]. In cardiac surgery patients, the prophylactic or therapeutic use of rFVIIa may also reduce the likelihood of re-operation (Grade C)[182,185].

Box 3.7.6 outlines the evidence statement (GN4.4) for the effect of rFVIIa on hospital and ICU length of stay in surgery.

Box 3.7.6 GN4.4 Evidence statement for the effect of rFVIIa on hospital and ICU length of stay in surgery

Evidence base	Satisfactory (C): Two Level II studies, one with a moderate risk of bias[188] and one with a high risk of bias[190]
Consistency	Good (B): Consistent results between studies—prophylactic rFVIIa use had no statistically significant effect on ICU or hospital LOS
Clinical impact	Poor (D): Based on the findings of two small studies, prophylactic rFVIIa appears to have no benefit for this outcome. This evidence base is too small to make definitive conclusions regarding the effect of rFVIIa on ICU or hospital LOS
Generalisability	Excellent (A): Study populations are the same as the target population
Applicability	Satisfactory (C): One study conducted in the USA[190], the other in Denmark[188]. There are some differences in the healthcare system between Australia/New Zealand and included studies

Evidence statement GN4.4

In surgical patients, there is insufficient evidence to determine the impact of prophylactic or therapeutic use of rFVIIa on hospital or ICU LOS (Grade D)[188,190].

3.8 Question 8

In patients undergoing surgery, what is the effect of fresh frozen plasma (FFP), cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? (Referred to as GN5)

Results of the systematic review for this research question are presented by intervention:

- fresh frozen plasma
- cryoprecipitate
- fibrinogen concentrate
- platelets.

3.8.1 Effect of fresh frozen plasma: Summary of evidence

Methods

Two studies were identified by the systematic review process (see **Appendix C** in Volume 2). The evidence statements are presented below.

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for this research question.

Level I evidence

One systematic review investigating the effect of fresh frozen plasma (FFP) on patient outcomes in a perioperative patient population was identified by the literature search[192]. The main characteristics of this study are summarised in **Table 3.8.1**. See **Appendix F** in Volume 2 for further details.

Table 3.8.1 Summary of Level I evidence on the effects of fresh frozen plasma

Level I evidence					
Study	Study type (number of included studies) Study quality	Population	Intervention	Comparator	Outcomes
Casbard et al (2004)[192]	Systematic review of RCTs (6 primary Level II studies) *Good*	Cardiac surgery	Prophylactic administration of FFP	Placebo or no FFP	Blood loss at 24 hours, platelet count, fibrinogen, Hb, PT, APTT

Abbreviations: APTT, activated partial thromboplastin time; Hb, haemoglobin; FFP, fresh frozen plasma; PT, prothrombin time; RCT, randomised controlled trial

The results of the existing Level I study are summarised in **Table 3.8.2**. A total of six small trials were identified by the review, including 363 participants with six different dose regimens of FFP. The overall quality of the studies was poor owing to small patient numbers and lack of allocation concealment. Overall, there was no evidence that the prophylactic use of FFP affected perioperative blood loss in cardiac surgery. There was some evidence to suggest that FFP may improve fibrinogen concentration in this patient population. This is not unexpected, given the fibrinogen content of FFP.

Table 3.8.2 Results of Level I evidence on the effects of fresh frozen plasma

Level I evidence		
Study	Number of included studies	Results and conclusion
Casbard et al (2004)[192]	6 Level II studies	Blood loss at 24 hours: Including data from all 6 studies, no overall difference in the volume of blood loss was found, with a combined standardised mean difference of –0.01 (95% CI: [–0.22, 0.20]) Platelet count: The mean platelet count was reported by 4 studies. Including data from all 4 studies, the pooled standardised mean difference was 0.24 (95% CI: [–0.01, 0.48]). The confidence interval excluded the possibility that the control was better Fibrinogen: Fibrinogen concentration was reported by 2 studies. Pooled results gave a standardised mean difference of 0.47 (95% CI: [0.06, 0.87]), indicating that the concentration was significantly lower among those in the control arms, although still within the normal range Haemoglobin: Haemoglobin was adequately reported by 2 studies. When data from these two studies were combined, there was no evidence to indicate a difference in haemoglobin concentration, with a pooled standardised mean difference of –0.06 (95% CI: [–0.38, 0.27]) Activated partial thromboplastin time: Four studies recorded this information in seconds. When data from these studies were combined, the overall pooled standardised mean difference just reached significance at –0.27 (95% CI: [–0.51,–0.02]), with patients given FFP having a shorter activated partial thromboplastin time The authors conclude that none of the studies found any benefit of administering prophylactic intraoperative FFP during coronary artery bypass surgery. The size and design, and the small numbers of subjects in the included studies mean that this review is inconclusive, and will be unlikely to affect current practice until further evidence is obtained

Abbreviations: CI, confidence interval; FFP, fresh frozen plasma

Level II evidence

The literature search identified no Level II evidence published since the systematic review by Casbard et al[192] and no Level II evidence in other perioperative patient populations.

Level III evidence

One Level III study investigating the effect of FFP in a perioperative population was identified[193]. The main characteristics of this study are summarised in **Table 3.8.3**. See **Appendix F** in Volume 2 for further details.

Table 3.8.3 Summary of Level III evidence on the effects of fresh frozen plasma

Level III evidence					
Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Sarani et al (2008)[193]	Retrospective cohort study *Fair*	Non-trauma patients admitted to the surgical intensive care unit N=2438	FFP N=380	No FFP N=2058	Infections

Abbreviations: FFP, fresh frozen plasma; ICU, intensive care unit; LOS, length of stay

The results of this Level III study are presented in **Table 3.8.4**. The study included a mixture of perioperative patients admitted to an intensive care unit. The only outcome in this study was the rate of infection. The study found that treatment with FFP was significantly associated with an increased risk of infection.

Table 3.8.4 Results of Level III evidence on the effects of fresh frozen plasma

Level III evidence					
Author	Outcome	FFP	No FFP	OR (95% CI)	Statistical significance
Sarani et al (2008)[193]	Infection	69/380 (18.2%)	125/2058 (6.1%)	1.04 (1.01, 1.07)	p<0.01

3.8.2 Effect of cryoprecipitate: Summary of evidence

No studies investigating the effect of cryoprecipitate on patient outcomes in a perioperative population were identified by the literature search.

3.8.3 Effect of fibrinogen concentrate: Summary of evidence

No studies investigating the effect of fibrinogen concentrate on patient outcomes in a perioperative population were identified by the literature search.

3.8.4 Effect of platelets: Summary of evidence

Methods

Three studies investigating the effect of platelets on patient outcomes in a perioperative population were identified by the literature search (see **Appendix C** in Volume 2). The evidence statements are presented below.

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for this research question.

Level I evidence

No Level I studies investigating the effect of platelets on patient outcomes in a perioperative population were identified.

Level II evidence

No Level II studies investigating the effect of platelets on patient outcomes in a perioperative population were identified.

Level III evidence

Three Level III studies investigating the effect of platelet administration in a perioperative population were identified[194–196]. The main characteristics of these studies are summarised in **Table 3.8.5**. See **Appendix F** in Volume 2 for further details.

Table 3.8.5 Summary of Level III evidence on the effects of platelets

Level III evidence					
Author	Study type Study quality	Population N	Intervention N	Comparator N	Outcomes
Karkouti et al (2006b)[194]	Retrospective cohort study *Fair*	Patients who underwent cardiac surgery at a single institution over a 5 year period N=11,459	Platelets N=2174	No platelets N=9285	Low output syndrome, stroke, acute renal failure, MI, sepsis, in-hospital death
McGrath et al (2008)[195]	Retrospective cohort study *Fair*	Patients who underwent isolated CABG, an isolated valve procedure, or a combined CABG and valve procedure requiring CPB N=29,487	Platelets N=3599	No platelets N=25,888	In-hospital mortality, cardiac, pulmonary, renal, and neurologic morbidities, serious infection, and re-exploration for bleeding. A composite outcome of adverse events consisted of in-hospital mortality, cardiac morbidity, respiratory insufficiency, renal morbidity, serious infection and neurologic morbidity
Spiess et al (2004)[196]	Retrospective cohort study *Fair*	Patients undergoing CABG surgery N=1720	Platelets N=284	No platelets N=1436	MI, stroke, 30-day mortality, pulmonary dysfunction, low cardiac output syndrome (congestive cardiac failure), infection

Abbreviations: CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction

The results of these three studies[194–196] are presented in **Table 3.8.6**. All were carried out in a perioperative cardiac surgical population.

Table 3.8.6 Results of Level III evidence on the effects of platelets

Level III evidence					
Study	Outcome	Platelets	No Platelets	OR (95% CI)	Statistical significance
Karkouti et al (2006b)[194]	Low output syndrome[b]	53/924 (5.7%)	57/924 (6.2%)	NR	p=0.7
	Myocardial infarction[b]	37/924 (4.0%)	29/924 (3.1%)	NR	p=0.3
	Stroke[b]	13/924 (1.4%)	17/924 (1.8%)	NR	p=0.5
	Renal failure[b]	12/924 (1.3%)	19/924 (2.1%)	NR	p=0.2
	Sepsis[b]	20/924 (2.2%)	21/924 (2.3%)	NR	p=0.9
	Death[b]	20/924 (2.2%)	23/924 (2.5%)	NR	p=0.6
McGrath et al (2008)[195]	Hospital mortality[a]	121/3599 (3.4%)	207/25,888 (0.8%)	0.74 (0.58, 0.95)	p=0.017
	Composite outcome[b]	416/2774 (15.0%)	478/2774 (17.2%)	NR	p=0.024
	Hospital death[b]	57/2774 (2.1%)	85/2774 (3.1%)	NR	p=0.017
	Cardiac morbidity[b]	67/2774 (2.4%)	49/2774 (1.8%)	NR	p=0.09
	Pulmonary morbidity[b]	248/2774 (9.0%)	274/2774 (9.9%)	NR	p=0.23
	Renal morbidity[b]	37/2774 (1.3%)	41/2774 (1.5%)	NR	p=0.65
	Neurologic morbidity[b]	63/2774 (2.3%)	89/2774 (3.2%)	NR	p=0.033
	Serious infection[b]	115/2774 (4.2%)	148/2774 (5.3%)	NR	p=0.037
	Return to OT for bleeding[b]	195/2774 (7.0%)	69/2774 (2.5%)	NR	p<0.001
Spiess et al (2004)[196]	30-day mortality	NR	NR	4.76 (1.65, 13.73)	p=0.009
	Stroke	NR	NR	2.56 (0.99, 6.67)	p=0.054

Abbreviations: NR, not reported; OR, odds ratio; OT, operating theatre.
[a] This outcome was determined by logistic regression.
[b] Outcome was determined by propensity matching

Mortality

All three identified studies investigated the effect of platelet administration on mortality in patients undergoing cardiac surgery[194–196]. Of the three studies, two found that platelet administration was significantly associated with in-hospital mortality[195, 196]. In contrast, Karkouti and colleagues found no such association[194].

Morbidity

All three studies investigated the effect of platelet administration on a range of morbidity outcomes[194–196]. Results from the studies showed that administration of platelets to patients undergoing cardiac surgery was not associated with an increase in morbidity risk, excluding risk of re-operation. Morbidity outcomes investigated in the studies included cardiac morbidity as well as pulmonary, renal and neurologic morbidity and infections.

McGrath and colleagues showed that patients treated with platelets were significantly more likely to undergo re-operation to control bleeding[195].

Quality of life

No studies were identified that investigated quality of life outcomes.

Resource use

No studies were identified that investigated resource use.

Level IV evidence

One Level IV study was identified that examined the impact of platelet administration on patient outcomes. As higher level evidence was available, it was not included in the body of evidence for recommendation development (see **Appendix B**, Volume 2 for further details). No quality of life data were reported in this study.

Evidence statements

Effect of fresh frozen plasma

Box 3.8.1 outlines the evidence statement (GN5.1) for the efficacy of prophylactic fresh frozen plasma on morbidity outcomes in patients undergoing cardiac surgery.

Box 3.8.1 GN5.1 Evidence statement for whether prophylactic fresh frozen plasma has a significant impact on patient outcomes: morbidity in cardiac surgery patients

Evidence base	Good (B): One Level I study with a low risk of bias[192] See table 1 in Casbard et al (2004).
Consistency	Good (B): Although only one study was included in the evidence, this was a systematic review of six studies. The included studies showed similar non-significant results
Clinical impact	Poor (D): The studies reported a small, not clinically relevant clinical impact.
Generalisability	Good (B): All studies were performed in a perioperative patient population involving cardiac surgery
Applicability	Satisfactory (C): Of the six studies included in the systematic review, three were conducted in Germany, and one each in the USA, Israel and the Netherlands

Evidence statement GN5.1

The prophylactic administration of fresh frozen plasma following cardiopulmonary bypass does not reduce perioperative blood loss (Grade B)[192].

Box 3.8.2 outlines the evidence statement (GN5.2) for the effect of fresh frozen plasma on infection rates in a post-surgical intensive care population.

Box 3.8.2 GN5.2 Evidence statement for whether fresh frozen plasma has a significant impact on patient outcomes: infection in surgery patients

Evidence base	Satisfactory (C): One Level III study with a moderate risk of bias[193]
Consistency	Not applicable (NA): Only one available study
Clinical impact	Satisfactory (C): The study reported a moderate clinical impact
Generalisability	Satisfactory (C): The single study was performed in any surgical patients (with the exception of trauma) who were admitted to the ICU. While this most likely covered a wide range of surgeries, it may bias towards a more severely ill ICU population
Applicability	Satisfactory (C): Study performed in the USA

Evidence statement GN5.2

Administration of fresh frozen plasma to a post-surgical population in intensive care is associated with an increase in the rate of infection (Grade C)[193].

Effect of platelet transfusion

Box 3.8.3 outlines the evidence statement (GN5.3a) for the effect of platelet transfusion on mortality in patients undergoing cardiac surgery.

Box 3.8.3 GN5.3a Evidence statement for whether platelet transfusion has a significant impact on patient outcomes: mortality in cardiac surgery patients

Evidence base	Good (B): Three Level III studies with a low risk of bias[194–196]
Consistency	Satisfactory (C): One of the three studies showed contrasting results[196]. This study was smaller than the other two, and a comparatively small number of patients received a transfusion of platelets
Clinical impact	Good (B): The studies showed a substantial clinical impact
Generalisability	Good (B): The studies were all performed in patients undergoing cardiac surgery
Applicability	Satisfactory (C): One study was conducted in Canada, one in the USA, and the other was a multicentre study performed in 37 institutions: one in Denmark, two in Israel, and 34 in the USA

Evidence statement GN5.3a

In patients undergoing cardiac surgery, platelet transfusion may be associated with an increase in mortality (Grade C) [194–196]

Box 3.8.4 presents the evidence statement (GN5.3b) for the effect of platelet transfusion on morbidity outcomes in patients undergoing cardiac surgery.

Box 3.8.4 GN5.3b Evidence statement for whether platelet transfusion has a significant impact on patient outcomes: morbidity in cardiac surgery patients

Evidence base	Good (B): Three Level III studies with a moderate risk of bias[194–196]
Consistency	Satisfactory (C): One study [194] reported no effect. One study reported a significant effect on return to OR for bleeding[195] and another study[196] reported a non-signficant effect on stroke
Clinical impact	Good (B): The studies showed a substantial clinical impact
Generalisability	Good (B): The studies were performed in patients undergoing cardiac surgery
Applicability	Satisfactory (C): One study was conducted in Canada, one in the USA, and the other was a multicentre study performed in 37 institutions: one in Denmark, two in Israel, and 34 in the USA

Evidence statement GN5.3b

In patients undergoing cardiac surgery, the effect of platelet transfusion on morbidity is uncertain (Grade C)[194–196].

Overall evidence statement GN5.3

In patients undergoing cardiac surgery, the effect of platelet transfusion on mortality and morbidity is uncertain (Grade C)[194–196].

3.9 Question 9

In patients undergoing surgery, at what international normalised ratio (INR (prothrombin time/activated partial thromboplastin time [PT/ APTT]) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelet concentrates should patients be transfused to avoid risks of significant adverse events? (Referred to as GN6)

3.9.1 Summary of evidence

Methods

A total of 16 studies were identified by the systematic review (see **Appendix C** in Volume 2). No studies investigating the INR (or PT/APTT), fibrinogen level or platelet count to determine the threshold for prophylactic transfusion of blood products in patients undergoing surgery were identified in the literature.

Further, the adverse events reported in the retrieved evidence below were considered by the Clinical/Consumer Reference Group to be not clinically significant.

Level I evidence

No existing systematic reviews of Level II evidence examining the effect of abnormal coagulation tests on patient outcomes in patients undergoing invasive procedures were identified by the literature search.

Level II evidence

Six Level II studies examining the effect of abnormal coagulation tests on patient outcomes in patients undergoing invasive procedures were identified by the literature search[197,200–202,210,211]. The details of these studies are presented in **Table 3.9.1**.

Level III evidence

Ten Level III studies examining the effect of abnormal coagulation tests on patient outcomes in patients undergoing invasive procedures were identified by the literature search[198,199,203–209,212]. The details of these studies are presented in **Table 3.9.1**.

Table 3.9.1 Summary of Level II and III evidence for invasive procedures

Author	Study type Study quality	Population N	Procedure	Coagulation Test	Outcomes
Dillon et al (1994)[197]	Prospective cohort *Fair*	Patients undergoing laparoscopic liver biopsy N=51 (60 procedures)	Laparoscopic liver biopsy	Platelet count: 55–100 x 10^9/L, n=7 LBs >100 x 10^9/L, n=53 LBs PTR <2.1 (lowest acceptable limit)	Liver bleeding time
McVay and Toy (1990)[198]	Retrospective cohort *Fair*	Adult patients undergoing percutaneous liver biopsy N=169 (177 procedures)	Liver biopsy	PT: Normal: ≤11.5 s, n=100 LBs Mildly prolonged: 11.6–13.5 s, n=65 LBs 13.6–15.7 s, n=11 LBs Platelet count: Normal: ≥100 x 10^9/L, n=157 LBs Mild thrombocytopenia: 50–99 x 10^9/L, n=18 LBs Moderate/marked thrombocytopenia: 16 and 48 x 10^9/L, n=2	Bleeding complications; average Hb difference
Misra et al (2008)[199]	Retrospective cohort *Fair*	Patients who underwent transjugular renal biopsy N=39 (39 procedures)	Renal biopsy	INR: ≤1.4, n=27 >1.4, n=11 Platelet count: ≤75 x 10^9/L, n=21 >75 x 10^9/L, n=17	Complication rate including bleeding and haematoma

Author	Study type Study quality	Population N	Procedure	Coagulation Test	Outcomes
Ray and Shenoy (1997)[200]	Prospective cohort *Fair*	Patients requiring radiologic placement of central venous access devices N=105 (112 procedures)	Central venous cannulation	Platelet count: <50 x 10^9/L, n=37 50–100 x 10^9/L, n=35 >100 x 10^9/L, n=33	Bleeding complications
Fisher and Mutimer (1999)[201]	Prospective cohort *Good*	Patients with acute or chronic liver diseases and patients undergoing liver transplantation or other hepatobiliary surgery N=283 (658 cannulations)	Central venous cannulation	INR: >5.0, n=137 cannulations <5.0, n=521 cannulations Platelet count: <50 x 10^9/L, n=146 cannulations ≥50 x 10^9/L, n=512 cannulations	Minor vascular complications including superficial haematoma and ooze
Weigand et al (2009)[202]	Prospective cohort *Fair*	Adult patients who were undergoing CVC insertion electively or in case of emergency N=196	Central venous cannulation	INR: ≥1.5, n=39 <1.5, n=157 Platelet count: ≤50 x 10^9/L, n=19 >50 x 10^9/L, n=177	Hb drop: a drop in haemoglobin of >1.5 g/dL was considered significant and was classified as a major bleeding event
Foster et al (1992)[203]	Retrospective cohort *Fair*	Liver allograft recipients N=40 (259 procedures)	Central venous cannulation	Abnormal platelet count: <80 x 10^9/L Abnormal PT: ≤40% of control Abnormal APTT: ≥77 s Categories of coagulopathy: I: 1 abnormal parameter, n=160 II: 2 abnormal parameters, n=40 III: 3 abnormal parameters, n=2 Normal, n=57	Bleeding complications

Author	Study type Study quality	Population N	Procedure	Coagulation Test	Outcomes
Doerfler et al (1996)[204]	Retrospective cohort *Good*	Patients with disorders of haemostasis who required central venous access for clinical management N=76 (104 procedures)	Central venous cannulation	Platelet count: <20 x 10^9/L, n=11 catheters 20–50 x 10^9/L, n=30 catheters 50–100 x 10^9/L, n=22 catheters >100 x 10^9/L, n=38 catheters PT: ≥1.5 x control, n=6 catheters 1.2–1.5 x control, n=12 catheters <1.2 x control, n=86 catheters	Haemorrhagic complications
Martin et al (2000)[205]	Retrospective cohort *Fair*	Patients who received a percutaneous nephrostomy N=160	Percutaneous nephrostomy	PT: >13.9 s, n=7 ≤13.9 s, n=153	Haemorrhagic complications
Mainwaring et al (1998)[206]	Retrospective cohort *Fair*	Patients with acute lymphoblastic leukaemia N=83	Lumbar puncture	Platelet count: <50 x 10^9/L, n=37 <20 x 10^9/L, n=5	Complication rate
Howard et al (2000)[207]	Retrospective cohort *Good*	Children with newly diagnosed acute lymphoblastic leukaemia N=958 (5442 procedures)	Lumbar puncture	Platelet count: 1–5 x 10^9/L, n=6 6–10 x 10^9/L, n=23 11–20 x 10^9/L, n=170 21–30 x 10^9/L, n=234 31–40 x 10^9/L, n=235 41–50 x 10^9/L, n=273 51–100 x 10^9/L, n=858 >100 x 10^9/L, n=3424	Complication rate: serious complications were defined as neurologic, infectious or haemorrhagic problems that resulted from LP. Traumatic LP was defined as the presence in CSF of ≥500 RBCs per high-powered microscopy field

Author	Study type Study quality	Population N	Procedure	Coagulation Test	Outcomes
Vavricka et al (2003)[208]	Retrospective cohort *Fair*	Adult patients with acute leukaemia N=66 (195 procedures)	Lumbar puncture	Platelet count: 20–30 x 10^9/L, n=35 LPs 30–50 x 10^9/L, n=40 LPs 50–100 x 10^9/L, n=43 LPs >100 x 10^9/L, n=77 LPs	Complication rate: traumatic LP was defined as >500 RBCs per high-powered field. Clinical events that were potentially attributable to LP and all neurologic, infectious or haemorrhagic events that occurred within 14 days after LP were recorded
Ruell et al (2007)[209]	Retrospective cohort *Fair*	Paediatric patients with haematological malignancy N=54 (738 procedures)	Lumbar puncture	Platelet count thresholds:[a] 31–50 x 10^9/L 51–70 x 10^9/L 71–90 x 10^9/L >90 x 10^9/L	Traumatic LP was defined as CSF containing at least 10 RBCs/μL. Bloody LP was defined as CSF containing at least 500 RBCs/μL
Darcy et al (1996)[210]	Prospective cohort *Good*	Patients who underwent femoral arterial puncture for a diagnostic or therapeutic vascular procedure N=1000	Femoral arteriography	Platelet count: <100 x 10^9/L, n=18 PT: >15 s, n=85	Post-angiographic haematoma formation
Weiss et al (1993)[211]	Prospective cohort *Fair*	Bone marrow transplant recipients undergoing fiberoptic bronchoscopy with bronchoalveolar lavage N=47 (66 procedures)	Fiberoptic bronchoscopy	Platelet count: <100 x 10^9/L, n=58 ≥100 x 10^9/L, n=8	Complication rate

Author	Study type Study quality	Population N	Procedure	Coagulation Test	Outcomes
Wolf et al (2007)[212]	Retrospective cohort *Fair*	Patients who received endoscopic therapy for non-variceal upper gastrointestinal haemorrhage N=233	Endoscopy	INR: ≥1.3, n=102 <1.3, n=131	Rebleeding

Abbreviations: CSF, cerebrospinal fluid; CVC, central venous catheter; Hb, haemoglobin; INR, international normalised ratio; LB, liver biopsy; LP, lumbar puncture; N, number; PT, prothrombin time; PTR, prothrombin time ratio; RBC, red blood cell

[a] Ruell et al[209] is a letter to the editor with limited data. Number of procedures in each category was not provided

Overall, the evidence base comprised one prospective cohort[197] and one retrospective cohort[198] study for liver biopsy; one retrospective cohort study for renal biopsy[199]; three prospective cohort[200–202] and two retrospective cohort[203,204] studies for central venous cannulation; one retrospective cohort study for percutaneous nephrostomy[205]; four retrospective cohort studies for lumbar puncture[206–209]; one prospective cohort study for femoral arteriography[210]; one prospective cohort study for fiberoptic bronchoscopy[211]; and one retrospective cohort study for endoscopy[212]. The CRG assessed the adverse events reported in these papers as not clinically significant, and/or that the reported adverse event rate differences between the treated and untreated groups were not statistically significant. The results of these studies are presented in **Table 3.9.2**.

Table 3.9.2 Results of Level II and III evidence for invasive procedures

Study	Outcome	Anticoagulation level	Rate of Outcome n/N (%; 95%CI)	Risk (95% CI)	Statistical significance	Threshold[a]
Liver biopsy						
Level II						
Dillon et al (1994)[197]	Bleeding	Platelet count	NR	NR	NS (correlation)	Platelets >55 x 10^9/L
		PTR	NR	NR	NS (correlation)	PTR <2.1
Level III						
McVay and Toy (1990)[198]	Bleeding	PT ≤11.5	4/100 (4.0%; 0.2, 7.8)	Reference group	–	PT <15.7
		PT 11.6–13.5	4/65 (6.2%; 0.3, 12.0)	OR: 1.57 (0.38, 6.52)	p=0.532	
		PT 13.6–15.7	0/11 (0.0%)	–	–	
		Platelets ≥100 x 10^9/L	5/157 (3.2%; 0.4, 5.9)	Reference group	–	Platelets ≥50 x 10^9/L
		Platelets 50–99 x 10^9/L	1/18 (5.6%; -5.0, 16.1)	OR: 1.79 (0.20,16.17)	p=0.605	
		Platelets 16, 48 x 10^9/L	2/2 (100.0%)	–	–	
Renal biopsy						
Level III						
Misra et al (2008)[199]	Haematoma	INR ≤1.4	9/27 (33.3%; 15.6, 51.1)	Reference group	-	None (INR range 0.9-2)
		INR >1.4	4/11 (36.4%; 7.9, 64.8)	OR: 1.14 (0.29, 4.50)	p=0.849	
		Platelets ≤75 x 10^9/L	7/21 (33.3%; 13.2, 53.5)	OR: 0.92 (0.26, 3.25)	p=0.893	None (platelet range 18–341 x 10^9/L)
		Platelets >75 x 10^9/L	6/17 (35.3%; 12.6, 58.0)	Reference group	–	

Study	Outcome	Anticoagulation level	Rate of Outcome n/N (%; 95%CI)	Risk (95% CI)	Statistical significance	Threshold[a]
Central venous cannulation						
Level II						
Ray and Shenoy (1997)[200]	Immediate complications	Platelets <50 x 10^9/L	2/37 (5.4%; -1.9, 12.7)	vs. >50 x 10^9/L OR: 1.87 (0.26, 13.94) vs. >100 x 10^9/L OR:1.83 (0.16, 21.10)	 p=0.534 p=0.629	None
		Platelets 50–100 x 10^9/L	1/35 (2.9%; -2.7, 8.4)	vs. >100 x 10^9/L OR: 0.94 (0.06, 15.67) <100 vs. >100 x 10^9/L OR: 1.39 (0.14, 13.88)	 p=0.966 p=0.778	
		Platelets >100 x 10^9/L	1/33 (3.0%; -2.8, 8.9)	Reference group	–	
	Delayed complications	Platelets <50 x 10^9/L	16/37 (43.2%; 27.3, 59.2)	vs. >50 x 10^9/L OR: 1.49 (0.70, 3.17) vs. >100 x 10^9/L OR:1.75 (0.70, 4.39)	 p=0.299 p=0.232	
		Platelets 50–100 x 10^9/L	13/35 (37.1%; 21.1, 53.2)	vs. >100 x 10^9/L OR: 1.36 (0.53, 3.52) <100 vs. >100 x 10^9/L OR: 1.55 (0.68, 3.55)	 p=0.573 p=0.299	
		Platelets >100 x 10^9/L	10/33 (30.3%)	Reference group	–	
Fisher and Mutimer (1999)[201]	Superficial haematoma	INR >5	17/137 (12.4%; 6.9, 17.9)	OR: 2.40 (1.28, 4.50)	p=0.006	None
		INR <5	29/521 (5.6%; 3.6, 7.5)			
		Platelets <50 x 10^9/L	12/146 (8.2%; 3.8, 12.7)	OR: 1.26 (0.64, 2.49)	p=0.509	
		Platelets ≥50 x 10^9/L	34/512 (6.6%; 4.5, 8.8)			

Study	Outcome	Anticoagulation level	Rate of Outcome n/N (%; 95%CI)	Risk (95% CI)	Statistical significance	Threshold[a]
Fisher and Mutimer (1999)[201] *continued*	Ooze	INR >5	3/137 (2.2%; -0.3, 4.6)	OR: 0.95 (0.26, 3.41)	p=0.937	
		INR <5	12/521 (2.3%; 1.0, 3.6)			
		Platelets <50 x 10^9/L	7/146 (4.8%; 1.3, 8.3)	OR: 3.17 (1.13, 8.90)	p=0.028	
		Platelets ≥50 x 10^9/L	8/512 (1.6%; 0.5, 2.6)			
Weigand et al (2009)[202]	Significant drop in haemoglobin	Platelets ≤50 x 10^9/L	1/19 (5.3%)	RR: 0.282	p=0.252	None
		INR ≥1.5	6/39 (15.4%)	RR: 0.863	p=0.9	
Level III						
Foster et al (1992)[203]	Serious complications	Coagulopathy by PT or platelet count	0/202	None	–	None
Doerfler et al (1996)[204]	Minor bleeding complications	Platelets <38 x 10^9/L	NR	NR	S	None
Percutaneous nephrostomy						
Level III						
Martin et al (2000)[205]	Haemorrhagic complication rate	PT ≤13.9 s	NR	NR	p=0.203	None
		PT >13.9 s	NR			
Lumbar puncture						
Level III						
Mainwaring et al (1998)[206]	Blood-stained tap or prolonged oozing	Platelets <50 x 10^9/L	8/37 (21.6%)	NR	NR	None
		Platelets ≥50 x 10^9/L	NR			

Study	Outcome	Anticoagulation level	Rate of Outcome n/N (%; 95%CI)	Risk (95% CI)	Statistical significance	Threshold[a]
Howard et al (2000)[207]	Serious complications	Platelets 1–5 x 10^9/L	0 (0%; 0, 40.19)	–	NS	Platelets 10 x 10^9/L
		Platelets 6–10 x 10^9/L	0 (0%; 0, 13.21)	–	NS	
		Platelets 11–20 x 10^9/L	0 (0%; 0, 2.05)	–	NS	
		Platelets 21–30 x 10^9/L	0 (0%; 0, 1.49)	–	NS	
		Platelets 31–40 x 10^9/L	0 (0%; 0, 1.48)	–	NS	
		Platelets 41–50 x 10^9/L	0 (0%; 0, 1.27)	–	NS	
		Platelets 51–100 x 10^9/L	0 (0%; 0, 0.40)	–	NS	
		Platelets >100 x 10^9/L	0 (0%; 0, 0.10)	–	NS	
Vavricka et al (2003)[208]	Traumatic LP	Decreasing platelet levels	NR	OR: 9.46	p<0.005	Platelets 20 x 10^9/L
	Serious complications	Platelets 20–30 x 10^9/L	0 (0%; 0, 10.0)	–	NS	
		Platelets 30–50 x 10^9/L	0 (0%; 0, 8.81)	–	NS	
		Platelets 50–100 x 10^9/L	0 (0%; 0, 8.22)	–	NS	
		Platelets >100 x 10^9/L	0 (0%; 0, 1.87)	–	NS	
Ruell et al (2007)[209]	Traumatic or bloody LP	Platelet count	NR	R^2: 0.004	NS	Platelets ≥30 x 10^9/L
Femoral arteriography						
Level II						
Darcy et al (1996)[210]	Medium or large haematoma formation	PT >15 s	1/85 (1.2%)	OR: NR	p=0.999	
		Platelets <100 x 10^9/L	3/18 (16.7%)	OR: 9.328	p=0.002	

Study	Outcome	Anticoagulation level	Rate of Outcome n/N (%; 95%CI)	Risk (95% CI)	Statistical significance	Threshold[a]
Fiberoptic bronchoscopy						
Level II						
Weiss et al (1993)[211]	Complication rate	Platelets <20 x 10^9/L	2/13 (15.4%; -4.2, 35.0)	vs. >100 x 10^9/L OR: 1.27 (0.10, 16.41)	p=0.8533	None
		Platelets 20–50 x 10^9/L	3/31 (9.7%; -0.7, 20.1)	vs. >100 x 10^9/L OR: 0.75 (0.07, 8.21) <50 vs. >50 x 10^9/L OR: 0.81 (0.18, 3.72)	p=0.8137 p=0.7883	
		Platelets 50–100 x 10^9/L	2/14 (14.3%; -4.0, 32.6)	vs. >100 x 10^9/L OR: 1.17 (0.09, 14.98) <100 vs. >100 x 10^9/L OR: 0.96 (0.10, 8.86)	p=0.9058 p=0.9718	
		Platelets >100 x 10^9/L	1/8 (12.5%; -10.4, 35.4)	Reference group	–	
Endoscopy						
Level III						
Wolf et al (2007)[212]	Rebleeding	INR 1.3–1.6	NR	vs. INR <1.3 OR: 1.21 (0.53, 2.75)	p=0.66	None
		INR 1.7–2.0	NR	OR: 0.55 (0.17, 1.85)	p=0.34	
		INR 2.1–2.5	NR	OR: <0.001 (<0.001, >999)	p=0.28	
		INR >2.5	NR	OR: 0.42 (0.67, 2.56)	p=0.35	

Abbreviations: CI, confidence interval; INR, international normalised ratio; NR, not reported; NS, not significant; OR, odds ratio; PT, prothrombin time; PTR prothrombin time ratio; R^2, coefficient of determination; RR, risk ratio; S, significant

[a] Threshold is the level beyond which transfusion is suggested as a result of the study.

Biopsy

The literature search identified one prospective[197] and one retrospective[198] cohort study investigating coagulopathy in liver biopsy and one retrospective cohort study[199] investigating coagulopathy in renal biopsy. In liver biopsy, the highest-level study found that in patients with a platelet count of >55 x 10^9/L, there was no significant correlation between decreasing platelets count or increasing prothrombin time ratio (PTR) and bleeding[197]. Although the study by McVay and Toy does not report on any statistical testing, the raw data suggest that the risk of bleeding increases with decreasing platelets count or increasing PT[198]. In the study by Misra and colleagues, platelet count and INR levels do not appear to affect the incidence of haematoma formation[199]. However, these studies were small studies and were most likely underpowered to detect a difference in outcomes between patients with different levels of platelets or INRs.

Central venous cannulation

Three prospective[200–202] and two retrospective[203,204] studies were identified that investigated coagulopathy in patients undergoing central venous cannulation. Although two of the five studies[201,204] found that a low platelets count or an increased INR were related to an increase in minor bleeding complications, all studies recommended that neither FFP nor platelets be transfused before the procedure, regardless of coagulopathy or platelet count.

Percutaneous nephrostomy

One retrospective cohort study was identified that investigated the effect of coagulopathy in patients undergoing percutaneous nephrostomy[205]. This study found no relationship between an elevated PT and haemorrhagic complication rate and the authors did not advocate the use of this test or FFP transfusion before the procedure.

Lumbar puncture

Four retrospective cohort studies were identified that investigated the effect of coagulopathy in patients undergoing lumbar puncture[206–209]. Three of these studies were performed in children[206,207,209] and one in adults[208]. The three studies in children found that low platelet counts were not related to an increase in minor bleeding[206], serious complications or traumatic or bloody lumbar punctures[207,209]. The study by Howard et al[207] concluded that there is no need to transfuse children with a platelet count of ≥10 x 10^9/L. The study by Ruell and colleagues[209] suggested a transfusion trigger of 30 x 10^9/L but did not include any patients with platelet counts below this level. The study by Vavricka et al[208] in adults found that the odds of a traumatic lumbar puncture were nine times greater in patients with the lowest platelet counts and the authors suggest that a trigger not lower than 20 x 10^9/L should be used for prophylactic transfusions in adults undergoing lumbar puncture.

Femoral arteriography

One prospective cohort study was identified that investigated coagulopathy in patients undergoing femoral arteriography[210]. This study found that although an increased PT was not related to the formation of a medium or large haematoma, patients with a platelet count

<100 x 10^9/L were nine times more likely to develop one of these haematomas than those with a platelet count ≥100 x 10^9/L.

Fiberoptic bronchoscopy

One prospective cohort study was identified that investigated coagulopathy in patients undergoing fiberoptic bronchoscopy[211]. This study found no increase in complication rates with decreasing platelet counts. The authors suggest that prophylactic transfusion in any patient before fiberoptic bronchoscopy may not be necessary.

Endoscopy

One retrospective cohort study was identified that investigated the effect of coagulopathy on rebleeding rates in patients with upper gastrointestinal haemorrhage undergoing endoscopy[212]. The study found that an increased INR did not increase the odds of rebleeding.

Evidence statement

Box 3.9.1 outlines the evidence statement (GN6.1) for the INR or platelet threshold in patients undergoing invasive procedures.

Box 3.9.1 GN6.1 Evidence statement for the INR or platelet threshold in patients undergoing invasive procedures

Evidence base	Good (B): The evidence base consists of two level II studies with a low risk of bias[201,210]; four level II studies with a moderate risk of bias[197,200,202,211]; two level III studies with a low risk of bias[204,207]; and eight level III studies with a moderate risk of bias[198,199,203,205,206,208,209,212].
Consistency	Excellent (A): All studies were consistent
Clinical impact	Poor (D): Slight clinical impact
Generalisability	Good (B): The evidence consisted of studies performed in patients undergoing various types of invasive procedures and is probably generalisable to a wider population undergoing invasive procedures
Applicability	Good (B): Ten studies were conducted in the USA, four in the UK, one in Germany and one in Switzerland

Evidence statement GN6.1

In patients undergoing invasive procedures, including biopsies (visceral, endoscopic and laparoscopic), central venous cannulation, lumbar puncture, nephrostomy and femoral arteriography, there is insufficient evidence to define a threshold platelet count, fibrinogen level or INR that is associated with significant adverse events (Grade B)[197–212]. Worsening thrombocytopenia may be associated with an increase in minor bleeding complications (Grade B)[198,201,204,208,210].

4 Appendixes

4.1 Appendix 1. Research question structure

The structure of the foreground research questions for perioperative patient blood management is presented in **Table 4.1.1** (questions specific to the perioperative patient blood management guidelines) and **Table 4.1.2**. (generic questions relevant to both the critical bleeding/massive transfusion module and the perioperative blood management module)**.** As the generic research questions were designed to identify evidence relevant to both modules, **Table 4.1.2** specifies subgroups relevant to both module's populations. Note that the morbidity outcome for all research questions included any adverse effects associated with the risk factor, intervention/comparator or predictor, such as infection and thromboembolism.

Table 4.1.1 Structure of foreground research questions specific to perioperative patient blood management

Foreground questions				
1. What is the effect of a multidisciplinary, multimodal, programmatic approach to perioperative patient blood management on patient outcomes? (Intervention foreground question)				
	Population	Intervention	Comparison	Outcome
Perioperative question	All patients scheduled for surgery—elective and emergency patients Subgroups • anaemic vs. non-anaemic	Multidisciplinary, multimodal approach (identification, stratification, cause and management of anaemic patients)	Non-multidisciplinary approach (i.e. usual care)	Primary Morbidity and mortality Quality of life Transfusion frequency and dose or type of transfusion Secondary Change in haemoglobin (preoperative, postoperative, discharge and 28-day Hb levels) Re-operation for bleeding Correction or prevention of DIC and coagulopathy Cost Hospital length of stay ICU admission and length of stay Hospital readmission

2. In patients before surgery or invasive procedures, what effect does the cessation and timing of cessation of medication that affect haemostasis have on morbidity, mortality, and RBC transfusion? (Intervention foreground question)				
	Population	Intervention	Comparison	Outcome
Perioperative question	All surgical and invasive procedures Subgroups • obstetrics patients • patients scheduled for neurosurgery and ophthalmic surgery • according to indication for intervention (prosthetic valve, VTE, AF, coronary stent)	Cessation and timing of cessation (including conversion to substitution therapy) of anticoagulants or antiplatelet therapy, including but not limited to • aspirin • clopidogrel • NSAIDs • warfarin • statins • complementary medicines • vitamins	Not ceasing anticoagulants, including • aspirin • clopidogrel • NSAIDs • warfarin • statins • complementary medicines • vitamins No substitution therapy	Primary Morbidity and mortality Quality of life Transfusion frequency and dose or type of transfusion Secondary Change in haemoglobin (preoperative, post-operative, discharge and 28-day Hb levels) Re-operation for bleeding Correction or prevention of DIC and coagulopathy Cost Hospital length of stay ICU admission and length of stay Hospital readmission

3. In patients undergoing surgery, what is the effect of perioperative strategies that minimise blood loss on morbidity, mortality, and blood transfusion? (Intervention foreground question)				
	Population	Intervention	Comparison	Outcome
Perioperative question	All surgical patients (elective, emergency, obstetrics and paediatric/neonates) Subgroups • stratified by surgical type (e.g. cardiothoracic, neurosurgery, trauma) • massive transfusion	1. Acute normovolaemic haemodilution (ANH) 2. Intraoperative cell salvage 3. Perioperative ANH + intraoperative cell salvage 4. Postoperative cell salvage 5. Deliberate induced hypotension 6. Prevention of hypothermia 7. Point-of-care testing for coagulation status and haemoglobin Restrictive sampling (minimal volume or microsampling, reduced number of tests) 8. Administration of antifibrinolytics (tranexemic acid, EACA, aprotinin) and DDAVP 9. Appropriate patient positioning 10. Preoperative autologous donation (PAD)	1. No perioperative ANH 2. No intraoperative cell salvage 3. No perioperative AHN + intraoperative cell salvage 4. No postoperative cell salvage 5. No deliberate induced hypotension 6. No prevention of hypothermia 7. No point-of-care testing for coagulation status and Hb 8. No administration of antifibrinolytics (tranexemic acid, EACA, aprotinin) and DDAVP 9. Usual patient positioning 10. No PAD	Primary Morbidity and mortality Quality of life Transfusion frequency and dose/type of transfusion Secondary Change in haemoglobin (preoperative, postoperative, discharge and 28-day Hb levels) Re-operation for bleeding Correction or prevention of DIC and coagulopathy Cost Hospital length of stay ICU admission and length of stay Hospital readmission

Table 4.1.2 Structure of generic research questions

1. Is anaemia an independent risk factor for adverse outcomes? (Aetiology foreground question)				
	Population	Risk factor	Comparison	Outcome
Generic question	All patients Subgroups • perioperative • trauma • shock • massive transfusion • cardiothoracic • surgical Stratify by • aetiology of anaemia if present (iron deficiency vs. other) • demographics (age/sex)	Anaemia by Hb level	No anaemia	Primary Morbidity and mortality Quality of life Transfusion frequency and dose or type of transfusion Secondary Cost Hospital length of stay ICU admission and length of stay Hospital readmission

2. What is the effect of red blood cell transfusion on patient outcomes? (Intervention foreground question) *Intervention vs. Comparator = (1) vs. (1), (2) vs. (2)*				
	Population	Intervention	Comparison	Outcome
Generic question	All patients, with or without defined anaemia (however defined) Subgroups • perioperative • trauma • shock • massive transfusion • cardiothoracic • surgical Stratify by • anaemia status according to Hb level	1. RBC transfusion 2. Restrictive transfusion (however defined)	1. No transfusion 2. Liberal transfusion (however defined)	Primary Morbidity and mortality Quality of life Transfusion frequency and dose or type of transfusion Secondary Change in Hb (preoperative, postoperative, discharge and 28-day Hb levels) Cost Hospital length of stay ICU admission and length of stay Re-operation for bleeding Hospital readmission Discharge Correction or prevention of DIC

3. What is the effect of interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion? (Intervention foreground question) **All interventions (1) to (5) compared with (1) to (5) in any combination: stratify results by type of iron therapy and preparation + Intervention vs. Comparator = (1) vs. (1 and 2), (2) vs. (2 and 3), and (3) vs. (1 and 2)*				
	Population	Intervention	Comparison	Outcome
Generic question	All patients with anaemia Subgroups • perioperative • trauma • shock • massive transfusion • cardiothoracic • surgical	ESAs including: 1. Erythropoietin 2. Oral or parenteral iron therapy 3. Other haematinics (folate, vitamin B_{12}, ascorbic acid) 4. Combination (1, 2, 3) 5. Preoperative RBC transfusion	No intervention or any combination of Interventions 1 to 5	Primary Morbidity and mortality Quality of life Transfusion frequency and dose or type of transfusion Secondary Change in Hb (preoperative, postoperative, discharge and 28-day Hb levels) Cost Hospital length of stay ICU admission and length of stay Hospital readmission

4. What is the effect of rFVIIa (prophylaxis or treatment) on morbidity, mortality and transfusion rate? (Intervention foreground question)				
	Population	Intervention	Comparison	Outcome
Generic question	All patients, with and without anaemia Subgroups • perioperative • trauma • shock • massive transfusion • cardiothoracic • surgical	rFVIIa as prophylaxis or treatment + usual care Stratify by dose	No rFVIIa + usual care	Primary Morbidity and mortality Quality of life Transfusion frequency and dose or type of transfusion Secondary Change in Hb (preoperative, postoperative, discharge and 28-day Hb levels) Re-operation for bleeding Correction or prevention of DIC and coagulopathy Cost Hospital length of stay ICU admission and length of stay Hospital readmission Note: Exclude patients who received rFVIIa for treatment of spontaneous intracranial haemorrhage, and for approved use (i.e. haemophilia, patients with inhibitors, Glanzmann thrombasthenia patients)

5. What is the effect of fresh frozen plasma, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcome? (Intervention foreground question)				
	Population	Intervention	Comparison	Outcome
Generic question	All patients, with and without anaemia Subgroups • perioperative • trauma • shock • massive transfusion • cardiothoracic • surgical	1. Fresh frozen plasma 2. Cryoprecipitate 3. Platelet transfusion 4. Fibrinogen concentrate	No administration or varying dose of: 1. Fresh frozen plasma 2. Cryoprecipitate 3. Platelet transfusion 4. Fibrinogen concentrate	Primary Morbidity and mortality Quality of life Transfusion frequency and dose or type of transfusion Secondary Change in Hb (preoperative, post-operative, discharge and 28-day Hb levels) Re-operation for bleeding Correction or prevention of DIC and coagulopathy Cost Hospital length of stay ICU admission and length of stay Hospital readmission

6. At what INR (or PT/APTT) for fresh frozen plasma, fibrinogen level for cryoprecipitate, platelet count for platelet concentrates should patients be transfused to avoid risks of significant adverse events? (Prognostic foreground question)				
	Population	Predictor	Comparison	Outcome
Generic question	All adult (medical, surgical or obstetric), neonatal and paediatric patients eligible for transfusion, with and without anaemia Subgroups • perioperative • trauma • shock • massive transfusion • cardiothoracic • surgical • non-surgical invasive procedures and minimally invasive surgical procedures Note: This subpopulation was considered in the generic question 6 literature search only for the perioperative module	1. INR threshold 2. Fibrinogen level 3. Platelets level	No comparator needed	Morbidity and mortality Quality of life Transfusion frequency and dose or type of transfusion

Abbreviations: APTT, activated partial thromboplastin time; AF, atrial fibrillation; DDAVP, desmopressin acetate; DIC, disseminated intravascular coagulation; EACA, epsilon-aminocaproic acid; ESA, erythropoiesis-stimulating agents; FFP, fresh frozen plasma; Hb, haemoglobin; INR, international normalised ratio; ICU, intensive care unit; LOS, length of stay; NSAIDs, non-steroidal anti-inflammatory drugs; PT, prothrombin time; RBC, red blood cells; rFVIIa, recombinant factor VII activated; VTE, venous thromboembolism

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

Citation	Article citation
☐	A. Was a clinical question clearly defined?
☐	B. Was an adequate search strategy used?
☐	C. Were the inclusion criteria appropriate and applied in an unbiased way?
☐	D. Was a quality assessment of included studies undertaken?
☐	E. Were the characteristics and results of the individual studies appropriately summarised?
☐	F. Were the methods for pooling the data appropriate?
☐	G. Were the sources of heterogeneity explored?
Comments	
Overall assessment	

Source of quality criteria: NHMRC (2000). How to use the evidence: assessment and application of scientific evidence. National Health and Medical Research Council, Canberra ACT5.

4.2.2 Randomised controlled trials

Citation	Article citation
☐	A. Was the allocation to treatment groups concealed from those responsible for recruiting subjects?
☐	B. Was the study double-blinded?
☐	C. Were patient characteristics and demographics similar between treatment arms at baseline?
☐	D. Were all randomised patients included in the analysis?
☐	E. Were the statistical methods appropriate?
☐	F. Were any subgroup analyses carried out?
Comments	
Overall assessment	

Source of quality criteria: NHMRC (2000). How to use the evidence: assessment and application of scientific evidence. National Health and Medical Research Council, Canberra ACT5.

4.2.3 Cohort studies

Citation	Article citation
☐	A. How were subjects selected for the 'new' intervention?
☐	B. How were subjects selected for the comparison or control group?
☐	C. Does the study adequately control for demographic characteristics, clinical features and other potential confounding variables in the study design or analysis?
☐	D. Was the measurement of outcomes unbiased (i.e. blinded to treatment group and comparable across groups?)
☐	E. Was follow-up long enough for outcomes to occur?
☐	F. Was follow-up complete and were there exclusions from analysis?
Comments	
Overall assessment	

Source of quality criteria: NHMRC (2000). How to use the evidence: assessment and application of scientific evidence. National Health and Medical Research Council, Canberra ACT5.

4.2.4 Case–control studies

Citation	Article citation
☐	A. How were the cases defined and selected?
☐	B. How were the controls defined and selected?
☐	C. Does the study adequately control for demographic characteristics, clinical features and other potential confounding variables in the study design or analysis?
☐	D. Was the measurement of exposure to the factor of interest (e.g. the new intervention) adequate and kept blinded to case/control status?
☐	E. Were all selected subjects included in the analysis?
Comments	
Overall assessment	

Source of quality criteria: NHMRC (2000). How to use the evidence: assessment and application of scientific evidence. National Health and Medical Research Council, Canberra ACT5.

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
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 GAR 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 GAR 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 following process was used to develop practice points through consensus.

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.

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.

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").

Stage 4 – First call for consensus

- When all concerns had been resolved, the Chair called for consensus.

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.

4.4.6 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.

4.4.7 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.

4.4.8 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 GAR expert (including members who were not present at the meeting), together with a consensus response template.

All CRG/NBA members and the GAR 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 IMS Health 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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