Haematology Issues in Orthopaedics

Pre-operative management of the emergency orthopaedic patient

B.S.O.A Spring Meeting 2016

Dr Ben Clevenger FRCA

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

PREVENTT

Preoperative intravenous iron to treat anaemia in major surgery

Haematology Issues in Orthopaedics

- Anaemia and transfusion
- Recent guidance
- Patient blood management
  - Diagnosis and treatment of anaemia
  - Reducing blood loss
  - Managing anaemia / transfusion decisions
- Anticoagulation and antiplatelet agents

Anaemia

- Insufficient circulating red cell mass or haemoglobin concentration
  - Hb <130 g/L men
  - Hb <120 g/L women

Prevalence of anaemia

Data from third National Health and Examination Survey 1988 -1994 (USA)

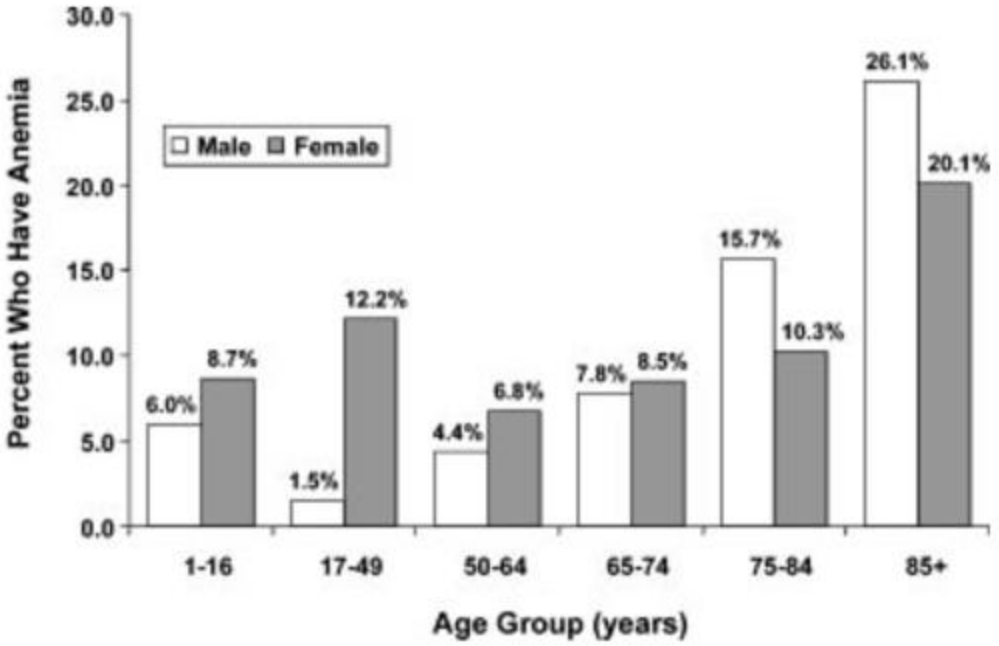


Figure 1. Percentage of persons considered anemic according to age and sex.
NHANES III, phases 1 and 2, 1988 to 1994.

Guralnik et al, Blood 2004

Aetiology

- Iron deficiency most common
  - Absolute iron deficiency
  - Anaemia of chronic disease is a state of functional iron deficiency
  - Hepcidin regulates iron metabolism

Multimorbidity and increasing age

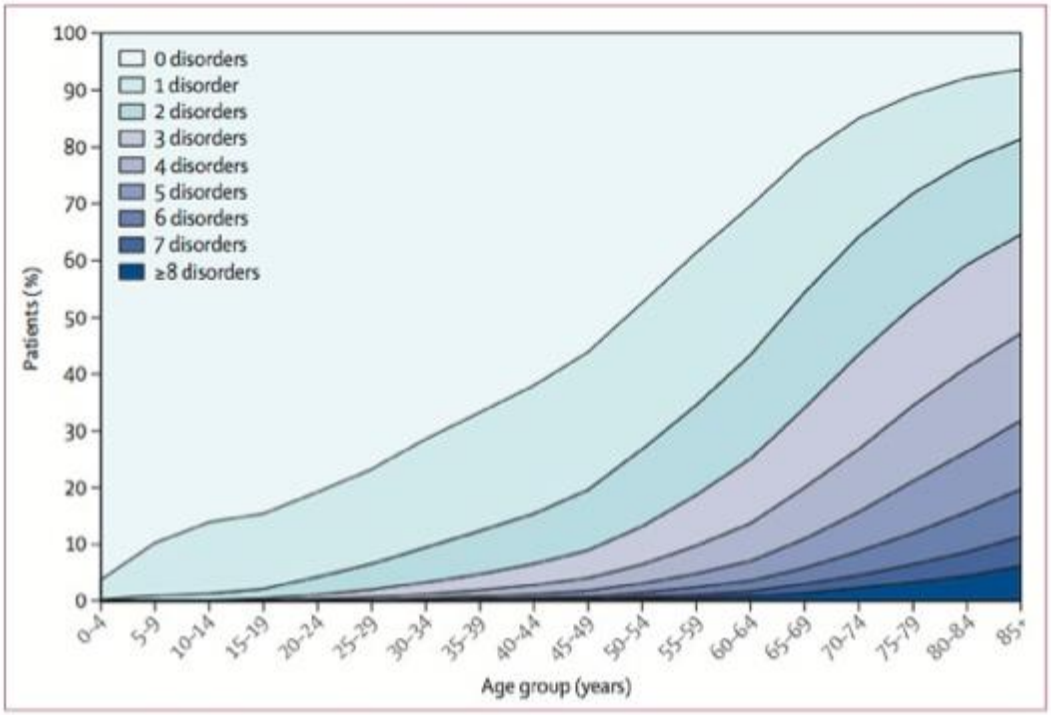


Figure **1:** Number of chronic disorders by age-group

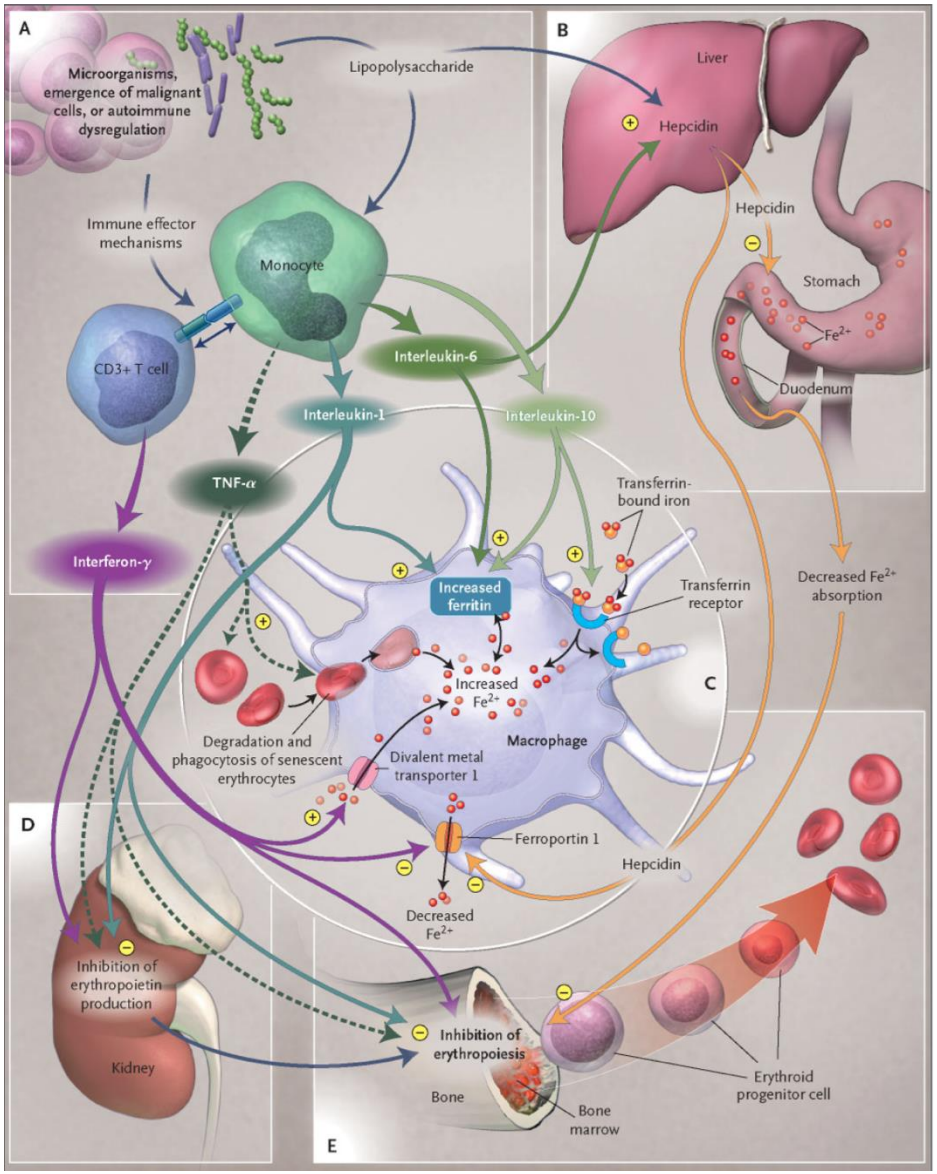
Barnett et al, The Lancet, 2012;380:37-43

Iron and inflammation

Inflammation

Reduced free iron

Reduced EPO

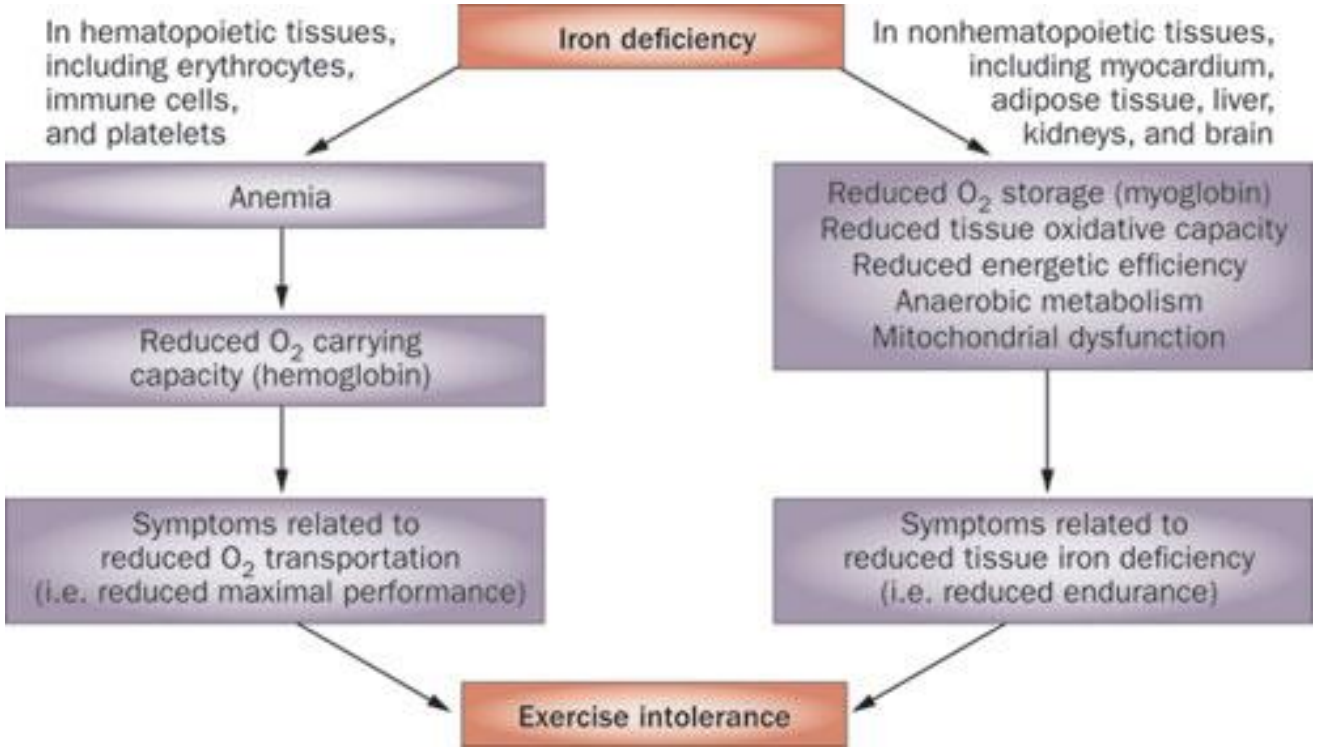


Failure of Absorption

Reduced Erythropoiesis

Weiss, G. & Goodnough, L.T., 2005. NEJM, 352(10), pp.1011–1023.

Anaemia and Exercise Capacity



van Veldhuisen, D. J. et al. Nat. Rev. Cardiol. 2011

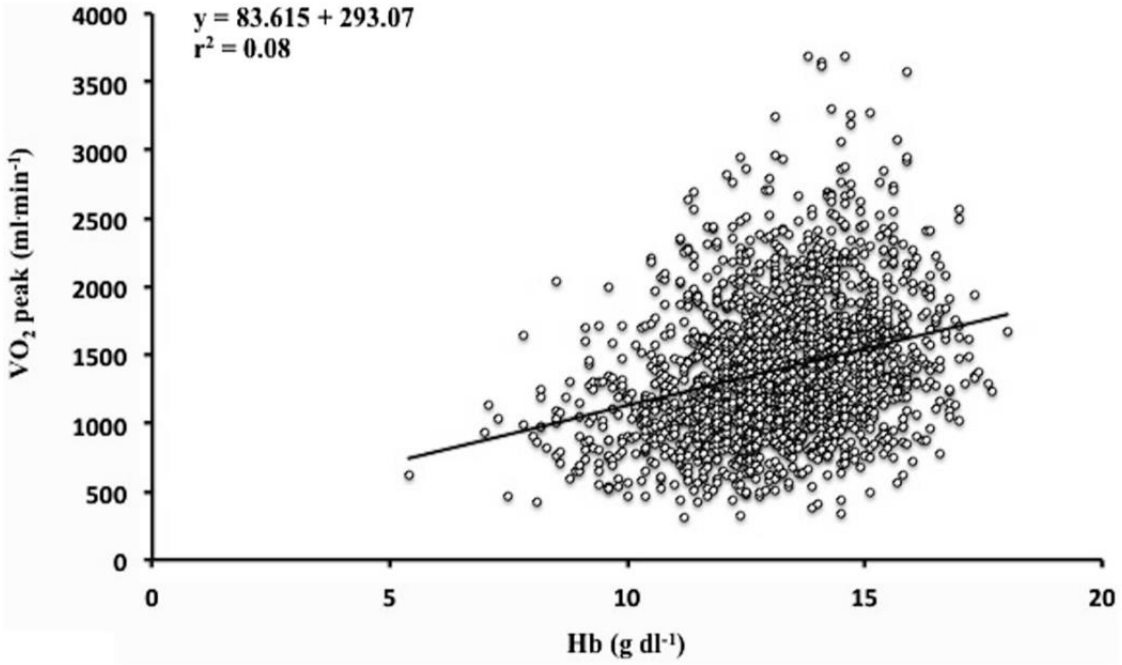


Figure 1 Linear regression between unadjusted $\dot{V}O_2$ peak (ml min^{-1}) and haemoglobin concentration ([Hb]), n = 1,774.

- Reduced VO2 and AT known to be associated with adverse outcomes
- Anaemia associated with reduced VO2 peak and exercise performance

1774 preoperative patients

Otto et al. Perioperative Medicine 2013, 2:18

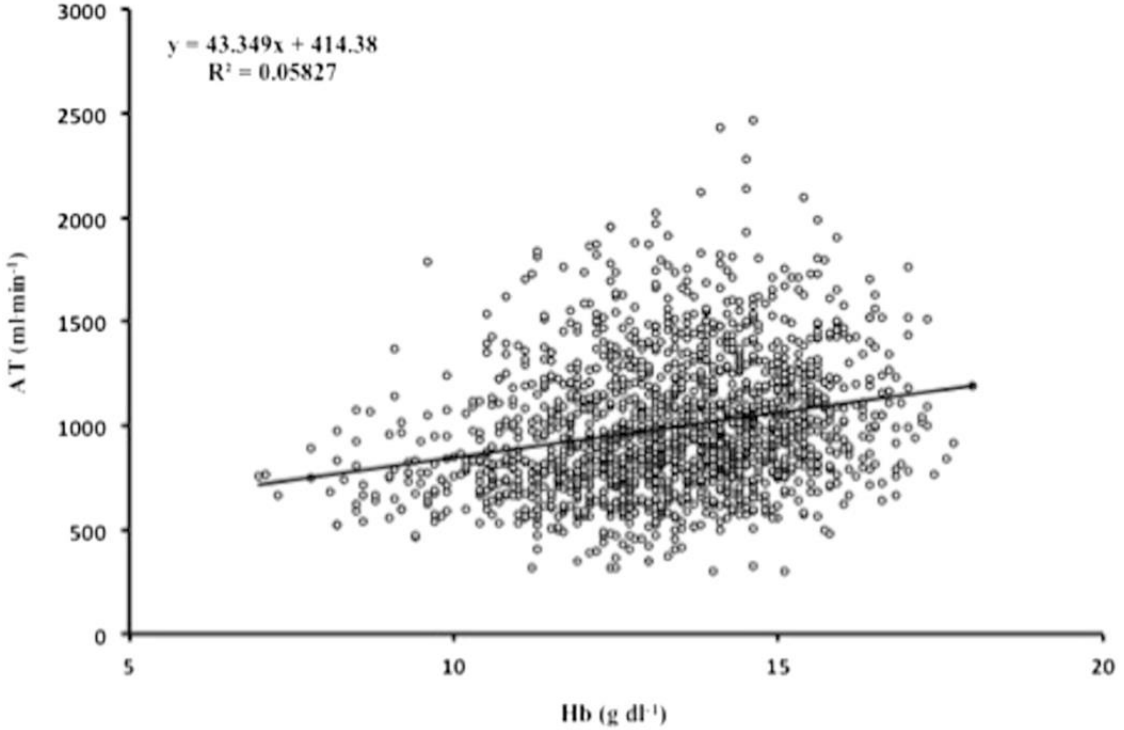


Figure 2 Linear regression between unadjusted oxygen uptake at anaerobic threshold (AT) (ml min^{-1}) and haemoglobin concentration ([Hb]), n = 1,631.

- Anaemia associated with reduced AT

Otto et al. Perioperative Medicine 2013, 2:18

Systematic review

Meta-analysis of the association between preoperative anaemia and mortality after surgery

A. J. Fowler[1], T. Ahmad[1], M. K. Phull[2], S. Allard[3], M. A. Gillies[4] and R. M. Pearse[1]

Reference	Year	Mortality: Anaemia	Mortality: No anaemia	Weight (%)	Odds ratio
Gruson *et al.*[26]	2002	5 of 180	3 of 215	1·8	2·02 (0·48, 8·57)
Cladellas *et al.*[22]	2006	9 of 42	10 of 159	2·9	4·06 (1·53, 10·79)
Wu *et al.*[40]	2007	8660 of 132 970	3351 of 177 341	5·9	3·62 (3·47, 3·77)
Bell *et al.*[20]	2008	325 of 6143	798 of 30 196	5·8	2·06 (1·80, 2·35)
Beattie *et al.*[19]	2009	76 of 3047	24 of 4632	4·8	4·91 (3·10, 7·79)
Melis *et al.*[30]	2009	14 of 197	5 of 216	2·8	3·23 (1·14, 9·14)
De Santo *et al.*[23]	2009	25 of 320	16 of 727	4·1	3·77 (1·98, 7·16)
Shirzad *et al.*[37]	2010	26 of 650	35 of 3782	4·6	4·46 (2·67, 7·46)
Munoz *et al.*[31]	2010	12 of 210	19 of 366	3·7	1·11 (0·53, 2·33)
Musallam *et al.*[32]	2011	3192 of 69 229	1240 of 158 196	5·9	6·12 (5·73, 6·54)
Boening *et al.*[21]	2011	44 of 185	121 of 3126	5·1	7·75 (5·28, 11·38)
Vochteloo *et al.*[39]	2011	30 of 536	31 of 726	4·6	1·33 (0·79, 2·22)
Hung *et al.*[28]	2011	45 of 1463	13 of 1225	4·2	2·96 (1·59, 5·51)
Dubljanin-Raspopovic *et al.*[24]	2011	19 of 185	12 of 158	3·7	1·39 (0·65, 2·97)
Greenky *et al.*[25]	2012	12 of 2991	21 of 12 231	3·9	2·34 (1·15, 4·77)
Ranucci *et al.*[34]	2012	51 of 401	30 of 401	4·8	1·80 (1·12, 2·89)
Oshin and Torella[33]	2013	16 of 193	2 of 167	1·8	7·46 (1·69, 32·93)
Saager *et al.*[35]	2013	1288 of 119 298	811 of 119 296	5·9	1·59 (1·46, 1·74)
Gupta *et al.*[27]	2013	368 of 15 272	206 of 16 585	5·8	1·96 (1·65, 2·33)
van Straten *et al.*[38]	2013	20 of 351	38 of 1385	4·5	2·14 (1·23, 3·73)
Seicean *et al.*[36]	2013	63 of 5879	37 of 18 594	5·1	5·43 (3·62, 8·16)
Jung *et al.*[29]	2013	0 of 125	0 of 463		Not estimable
Zhang *et al.*[41]	2013	22 of 432	3 of 223	2·3	3·93 (1·16, 13·29)
Baron *et al.*[5]	2014	656 of 11 295	604 of 27 439	5·9	2·74 (2·45, 3·07)
Total		14 978 of 371 594	7430 of 577 851	100·0	2·90 (2·30, 3·68)

Heterogeneity: $\tau^2 = 0{\cdot}24$; $\chi^2 = 768{\cdot}79$, 22 d.f., $P < 0{\cdot}001$; $I^2 = 97\%$
Test for overall effect: $Z = 8{\cdot}88$, $P < 0{\cdot}001$

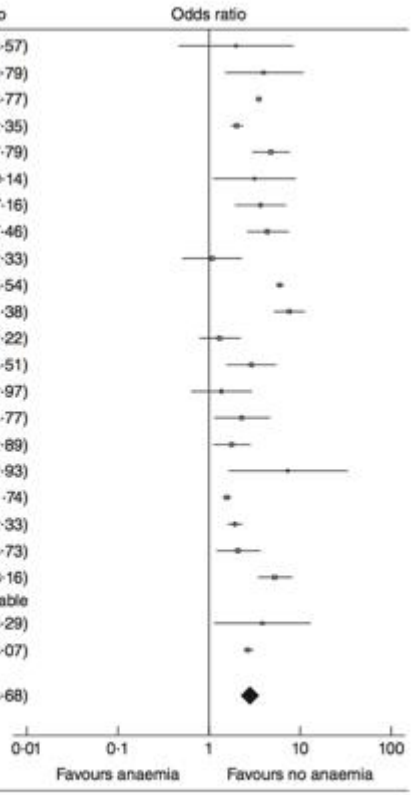


Fig. 2 Forest plot showing composite outcome of 30-day or in-hospital mortality after surgery, according to author-defined anaemia. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i.

949445 patients

371594 patients (39.1%) anaemic

Increased mortality Odds Ratio 2·90

Fowler, A.J. et al., 2015. British Journal of Surgery, 102(11), pp.1314–1324.

Anaemia and Fractured neck of femur

- Approximately 40% of #NOF patients are anaemic on admission
  - Chronic anaemia
  - Malnutrition
  - Haemorrhage from #
  - Iatrogenic haemodilution
- 25 g/L drop in Hb during perioperative period
- Majority of patients may be anaemic post-op

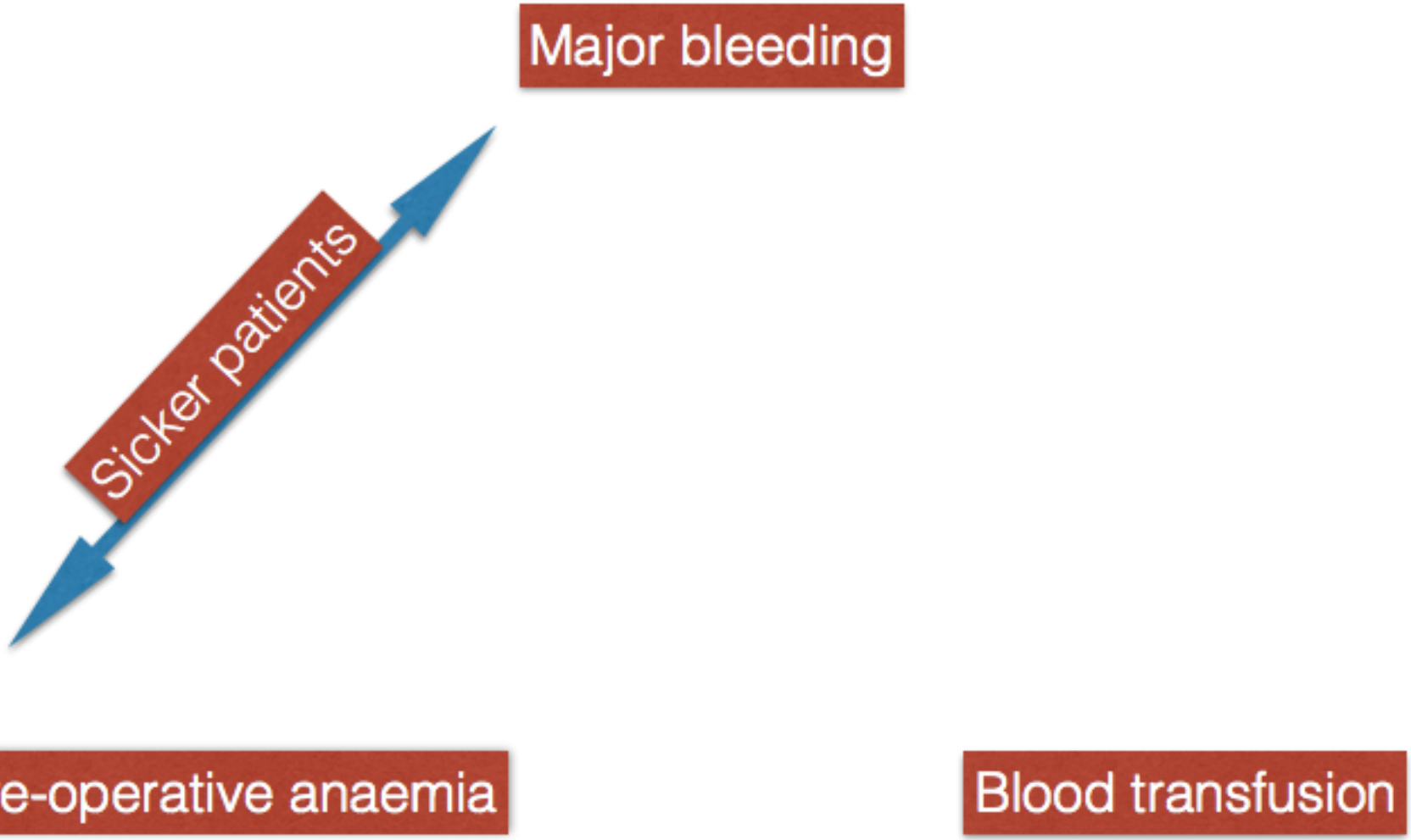
Triad of risk

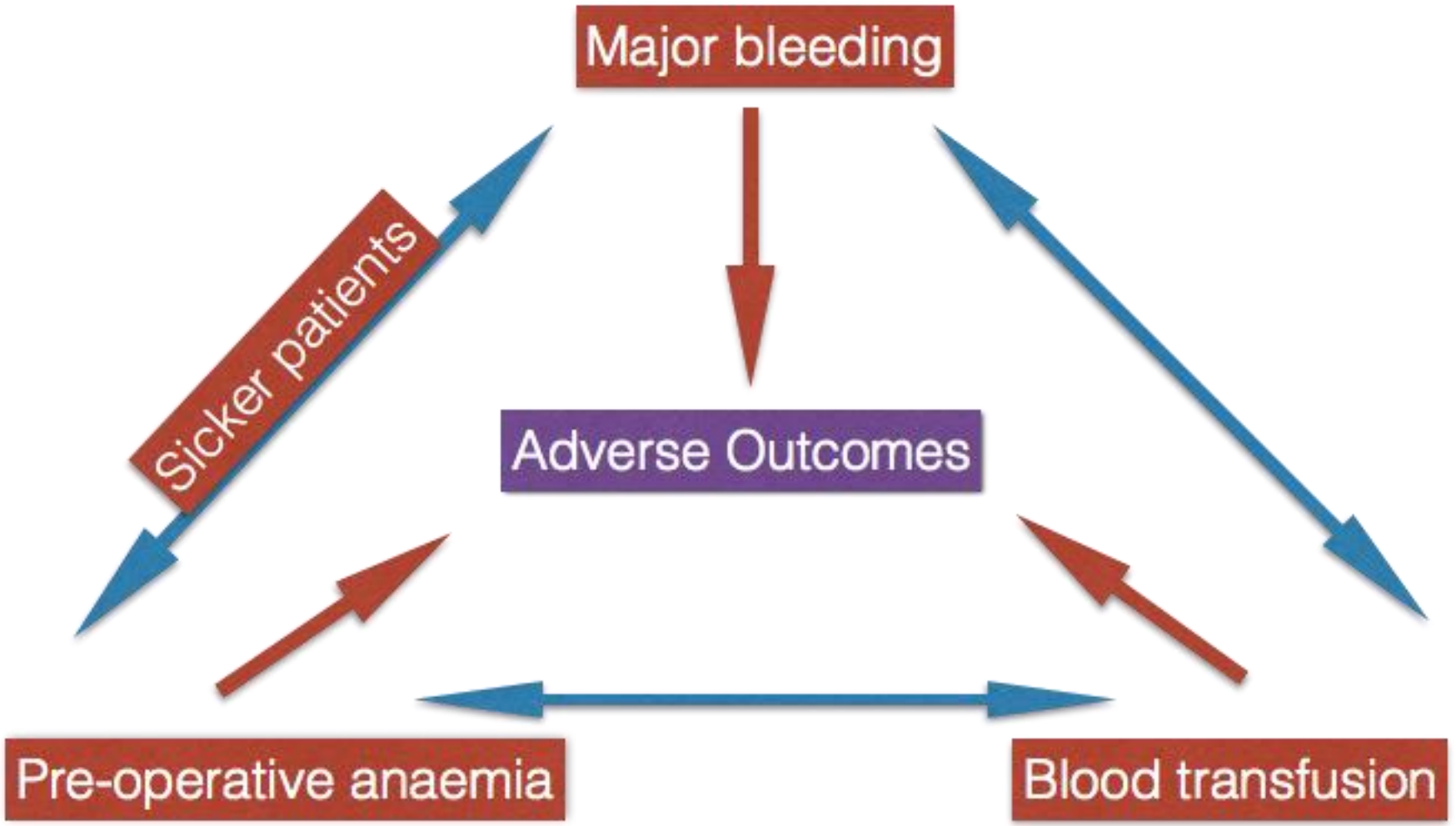
Major bleeding

Pre-operative anaemia

Blood transfusion

Triad of risk




Major bleeding
Sicker patients
Adverse Outcomes
Pre-operative anaemia
Blood transfusion

Anaemia and Transfusion

- Pre-operative anaemia is a significant risk factor for perioperative blood transfusion.

ORIGINAL ARTICLE

Surgical Outcomes and Transfusion of Minimal Amounts of Blood in the Operating Room

Victor A. Ferraris, MD, PhD; Daniel L. Davenport, PhD; Sibu P. Saha, MD, MBA; Peter C. Austin, PhD; Joseph B. Zwischenberger, MD

Arch Surg. 2012;147(1):49-55

- 941,406 patients
  - 173 Hospitals
  - 2005-2009
- 48,291 transfused

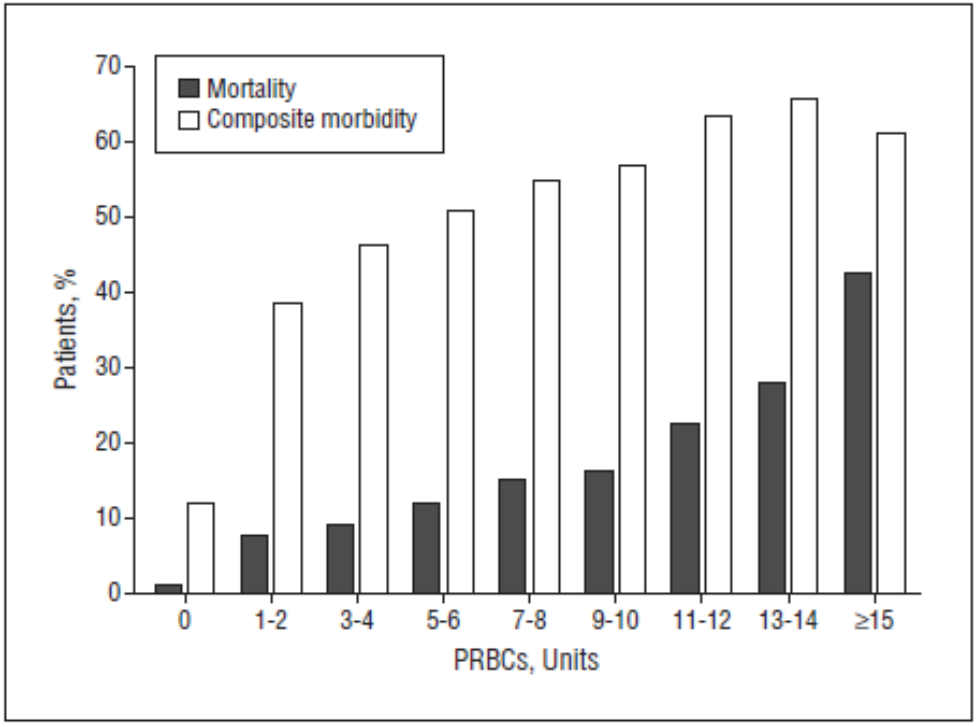


Figure. Unadjusted mortality and composite morbidity rates by number of units of packed red blood cells (PRBCs) received in intraoperative blood transfusion.

RESEARCH

Harms associated with single unit perioperative transfusion: retrospective population based analysis

Elizabeth L Whitlock,[1] Helen Kim,[1] Andrew D Auerbach[2]

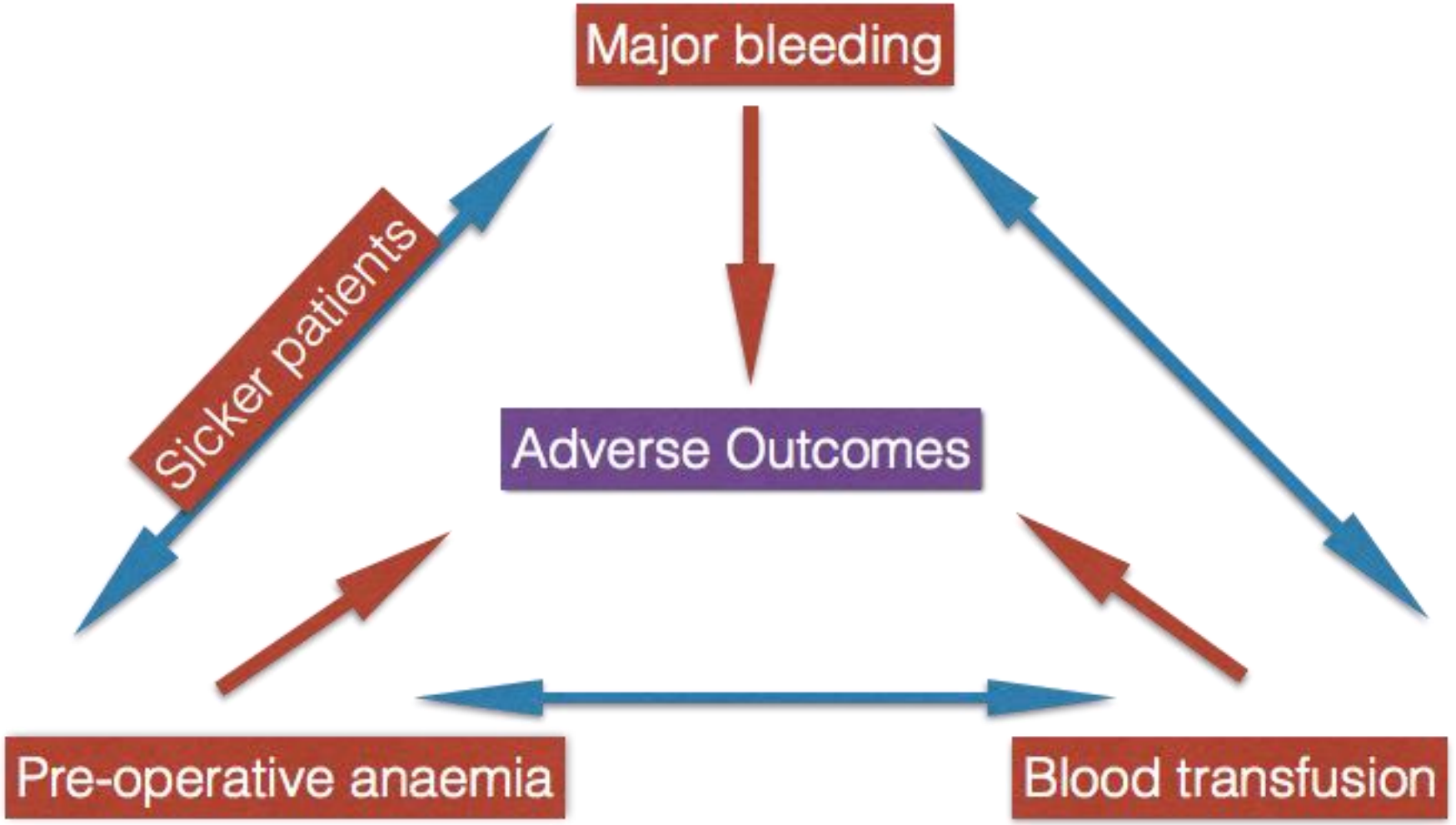
the bmj | BMJ 2015;350:h3037 | doi: 10.1136/bmj.h3037

N =1,583,819 Elective surgery in USA

41,421 transfused within 48 hours of surgery

Variable	No (%) without stroke/ MI (n=1 575 775)	No (%) with stroke/ MI (n=8044)	Multivariate OR
0	1 524 850 (97.4)	7 548 (93.8)	(reference)
1	12 715 (0.81)	132 (1.6)	2.33 (1.90 to 2.86)
2	21 420 (1.4)	222 (2.8)	2.37 (2.00 to 2.81)
3	2 881 (0.18)	45 (0.56)	3.13 (2.23 to 4.31)
≥4	3 909 (0.25)	97 (1.2)	4.87 (3.86 to 6.14)

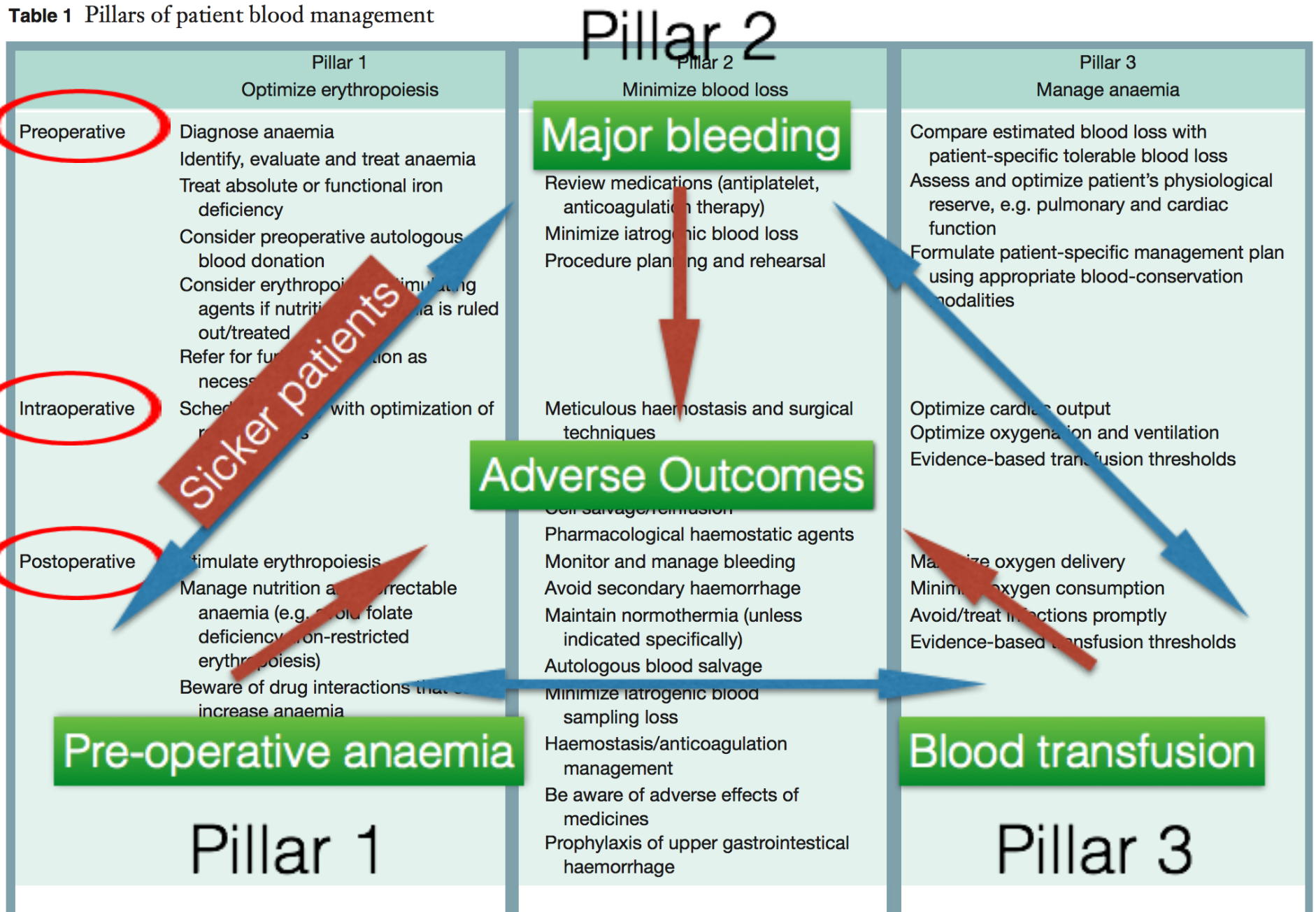
How do we modify these risks?



Patient Blood Management

- An evidence based approach to reduce the risk from anaemia and blood transfusion
- Three pillars of care in surgical patients:
  - the detection and treatment of preoperative anaemia
  - reduction of perioperative blood loss
  - Managing anaemia (including restrictive haemoglobin transfusion thresholds)

Table 1 Pillars of patient blood management



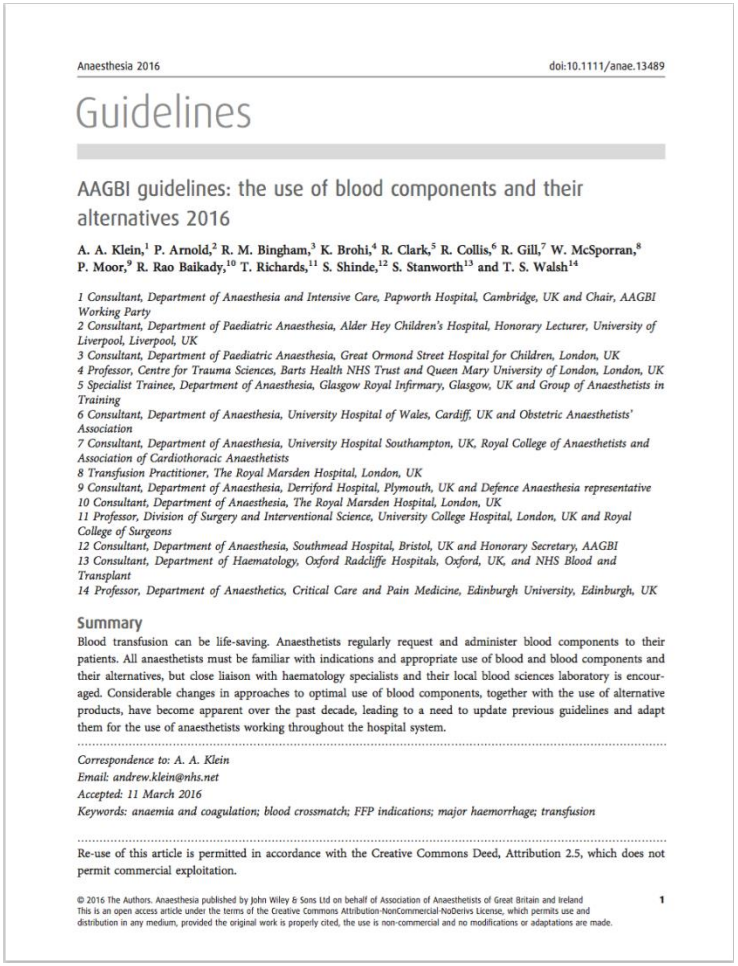
NICE Transfusion 2015

https://www.nice.org.uk/guidance/ng24

Summary of NICE Guidelines: Blood Transfusion

Alternatives to blood transfusion for patients having surgery	Offer oral iron in iron deficiency before and after surgery. Offer tranexamic acid in surgery expected to have>500ml blood loss. Consider cell salvage with tranexamic acid if high volume blood loss expected
Red blood cells	Consider a threshold of 70g/L and a target of 70-90g/L after transfusion when using restrictive red blood cell transfusions. Consider single-unit red blood cell transfusions for adults who do not have active bleeding.
Platelets	In patients not bleeding or not having an invasive procedure or surgery: Offer prophylactic platelets with platelet count below $10x10^9$/L and who do not have - Chronic bone marrow failure - Autoimmune thrombocytopenia - Heparin-induced thrombocytopenia - Thrombotic thrombocytopenic purpura Do not routinely transfuse more than a single dose of platelets.
Fresh Frozen Plasma (FFP)	Only consider FFP with clinically significant bleeding if coagulation tests are abnormal e.g.. Prothrombin time ratio, Activated partial thromboplastin time ratio >1.5 Do not offer FFP to correct abnormalities in coagulation in patients who: - are not bleeding (unless having a procedure with a risk of significant bleeding) - Require reversal of vitamin K antagonist
Prothrombin Complex Concentrate (PCC)	Offer immediate PCC for the emergency reversal of warfarin anticoagulation in: - severe bleeding or - head injury with suspected intracerebral haemorrhage
Cryoprecipitate	Consider cryoprecipitate for patients with clinically significant bleeding and fibrinogen <1.5g/L Consider prophylactic cryoprecipitate for patients with fibrinogen level <1.0g/L who are having invasive procedures or surgery with a risk of bleeding. Use 2 pools of cryoprecipitate and reassess the clinical condition
Patient Safety	Monitor for acute blood transfusion reactions Consider using electronic identification systems to improve safety and efficiency during the blood transfusion process
Patient information	Provide verbal and written information to patients who may have a transfusion explaining: - the reason for transfusion - the risks and benefits

AAGBI Guidelines 2016



Anaesthesia 2016 doi:10.1111/anae.13489

Guidelines

AAGBI guidelines: the use of blood components and their alternatives 2016

A. A. Klein,[1] P. Arnold,[2] R. M. Bingham,[3] K. Brohi,[4] R. Clark,[5] R. Collis,[6] R. Gill,[7] W. McSporran,[8] P. Moor,[9] R. Rao Baikady,[10] T. Richards,[11] S. Shinde,[12] S. Stanworth[13] and T. S. Walsh[14]

1 Consultant, Department of Anaesthesia and Intensive Care, Papworth Hospital, Cambridge, UK and Chair, AAGBI Working Party
2 Consultant, Department of Paediatric Anaesthesia, Alder Hey Children's Hospital, Honorary Lecturer, University of Liverpool, Liverpool, UK
3 Consultant, Department of Paediatric Anaesthesia, Great Ormond Street Hospital for Children, London, UK
4 Professor, Centre for Trauma Sciences, Barts Health NHS Trust and Queen Mary University of London, London, UK
5 Specialist Trainee, Department of Anaesthesia, Glasgow Royal Infirmary, Glasgow, UK and Group of Anaesthetists in Training
6 Consultant, Department of Anaesthesia, University Hospital of Wales, Cardiff, UK and Obstetric Anaesthetists' Association
7 Consultant, Department of Anaesthesia, University Hospital Southampton, UK, Royal College of Anaesthetists and Association of Cardiothoracic Anaesthetists
8 Transfusion Practitioner, The Royal Marsden Hospital, London, UK
9 Consultant, Department of Anaesthesia, Derriford Hospital, Plymouth, UK and Defence Anaesthesia representative
10 Consultant, Department of Anaesthesia, The Royal Marsden Hospital, London, UK
11 Professor, Division of Surgery and Interventional Science, University College Hospital, London, UK and Royal College of Surgeons
12 Consultant, Department of Anaesthesia, Southmead Hospital, Bristol, UK and Honorary Secretary, AAGBI
13 Consultant, Department of Haematology, Oxford Radcliffe Hospitals, Oxford, UK, and NHS Blood and Transplant
14 Professor, Department of Anaesthetics, Critical Care and Pain Medicine, Edinburgh University, Edinburgh, UK

Summary

Blood transfusion can be life-saving. Anaesthetists regularly request and administer blood components to their patients. All anaesthetists must be familiar with indications and appropriate use of blood and blood components and their alternatives, but close liaison with haematology specialists and their local blood sciences laboratory is encouraged. Considerable changes in approaches to optimal use of blood components, together with the use of alternative products, have become apparent over the past decade, leading to a need to update previous guidelines and adapt them for the use of anaesthetists working throughout the hospital system.

Correspondence to: A. A. Klein
Email: andrew.klein@nhs.net
Accepted: 11 March 2016
Keywords: anaemia and coagulation; blood crossmatch; FFP indications; major haemorrhage; transfusion

http://onlinelibrary.wiley.com/doi/10.1111/anae.13489/abstract

Royal College of Physicians

National Comparative Audit of Blood Transfusion

NHS Blood and Transplant

National Comparative Audit of Blood Transfusion

2015 Audit of Patient Blood Management in Adults undergoing elective, scheduled surgery

National Comparative Audit of Blood Transfusion

PBM1	**Pre-operative anaemia management**
PBM2	Pre-operative transfusion allowed
PBM3	Pre-operative transfusion allowed only if preoperative anaemia optimisation has been attempted where appropriate
PBM4	Pre-operative transfusion - single unit transfusion policy
PBM5	Pre-operative anticoagulant and antiplatelet management
PBM6	Patients having intra operative transfusion in whom at least one PBM measure has been attempted (where appropriate)
PBM7	Patients having intra operative transfusion in whom all PBM measures have been attempted (where appropriate)
PBM8	Post operative transfusion allowed (whether or not PBM measures attempted) - FIRST EPISODE
PBM9	Post operative transfusion following the single unit policy – FIRST EPISODE
PBM10	Post operative in whom at least one PBM measure has been attempted (where appropriate)- FIRST EPISODE
PBM11	Post operative in whom all PBM measures have been attempted (where appropriate) FIRST EPISODE

National Comparative Audit of Blood Transfusion

	National
• Primary unilateral total hip replacement	16% (610)
• Primary bilateral total hip replacement	1% (30)
• Primary unilateral total knee replacement	9% (341)
• Primary bilateral total knee replacement	1% (27)
• Unilateral revision hip replacement	7% (258)
• Unilateral revision knee replacement	2% (67)
• Colorectal resection for any indication (open or laparoscopic)	8% (300)
• Open arterial surgery e.g. scheduled (non-ruptured) aortic aneurysm repair, infrainguinal femoropopliteal or distal bypass	4% (157)
• Primary coronary artery bypass graft	3% (116)
• Valve replacement +/- CABG	11% (423)
• Simple or complex hysterectomy	9% (342)
• Cystectomy	1% (37)
• Nephrectomy	3% (130)
• # neck of femur (arthroplasty)	27% (1044)
Not known	(15)

National Comparative Audit of Blood Transfusion

Table 6: *Was the patient on any of the following treatments before they had their operation?*

	National	Your site
Known for	3793	4
• **Oral iron**	11% (399)	0
• **IV iron**	0.8% (29)	0
• **Erythrocytosis-stimulating agent (ESA) therapy**	0.3% (12)	0
• **B_{12}**	2% (71)	0
• **Folic acid**	4% (151)	1
• **Red cell transfusion***	7% (279)	0
• **None**	79% (3009)	3

Iron in Major Surgery

- Very few high quality RCTs have been conducted in surgical patient populations.

Pre-operative IV Iron

Iron therapy for pre-operative anaemia (Review)

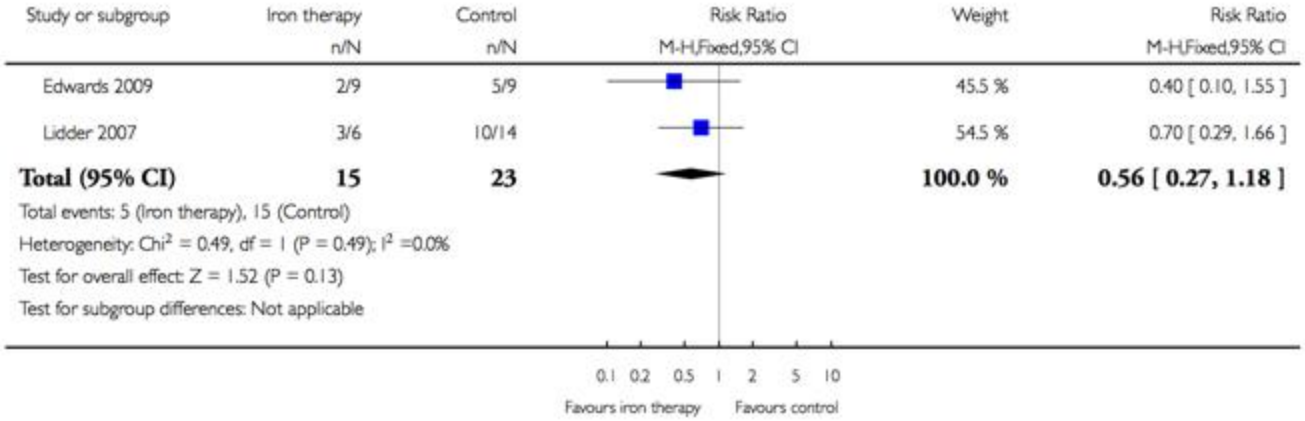
Ng O, Keeler BD, Mishra A, Simpson A, Neal K, Brookes MJ, Acheson AG

Analysis 1.1. Comparison 1 Iron therapy versus placebo or no iron therapy, Outcome 1 Proportion of patients who received a blood transfusion.

Review: Iron therapy for pre-operative anaemia

Comparison: 1 Iron therapy versus placebo or no iron therapy

Outcome: 1 Proportion of patients who received a blood transfusion



THE COCHRANE COLLABORATION®

Ng et al, Cochrane Database of systematic reviews, 2015

Pre or Peri-operative Iron for #NOF

TRANSFUSION PRACTICE

Role of perioperative intravenous iron therapy in elderly hip fracture patients: a single-center randomized controlled trial

José Antonio Serrano-Trenas, Pilar Font Ugalde, Laura Muñoz Cabello, Luis Castro Chofles, Pilar Serrano Lázaro, and Pedro Carpintero Benítez

- Standard treatment vs Iron Sucrose (200mg IV x3 doses from day of admission)
- Transfusion rates were primary outcome

TRANSFUSION *2011;51:97-104.*

Pre or Peri-operative Iron for #NOF

- Transfusion rates:
  - Standard care 41.3% vs IV Iron 33.3% of patients (not significant)
  - Only significant differences found in patients with higher pre-op Hb (>120 g/L) and intracapsular fractures

Anaemia and iron for hip fractures

Anaesthesia 2015, 70, 483–500 doi:10.1111/anae.12978

Review Article

CPD available at http://www.learnataagbi.org

A systematic review of pre-operative anaemia and blood transfusion in patients with fractured hips*

L. J. Potter,[1] B. Doleman[2] and I. K. Moppett[3]

1 Core Trainee, 2 Foundation Doctor, 3 Associate Professor and Honorary Consultant, Anaesthesia and Critical Care Research Group, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK

Effect of anaemia

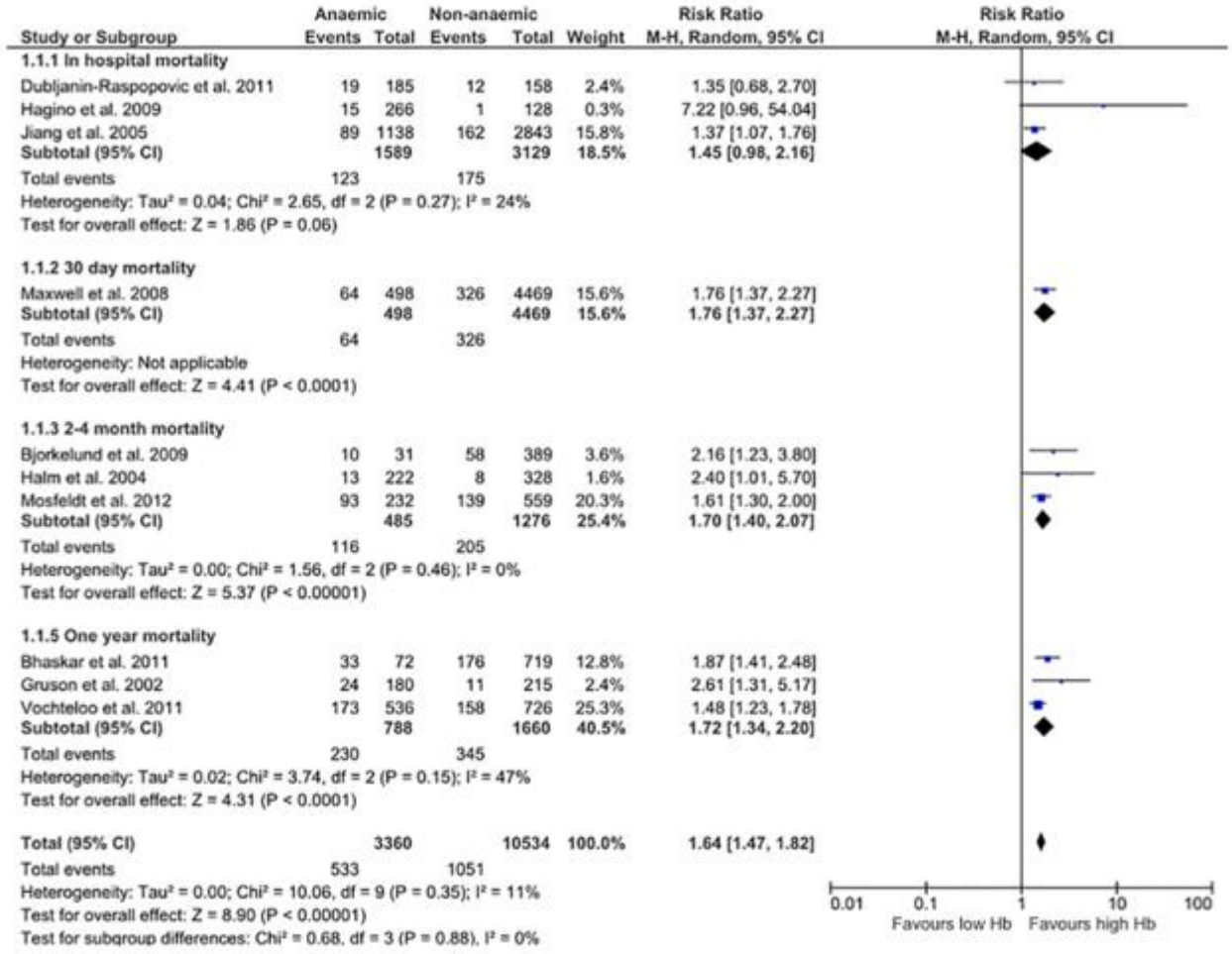
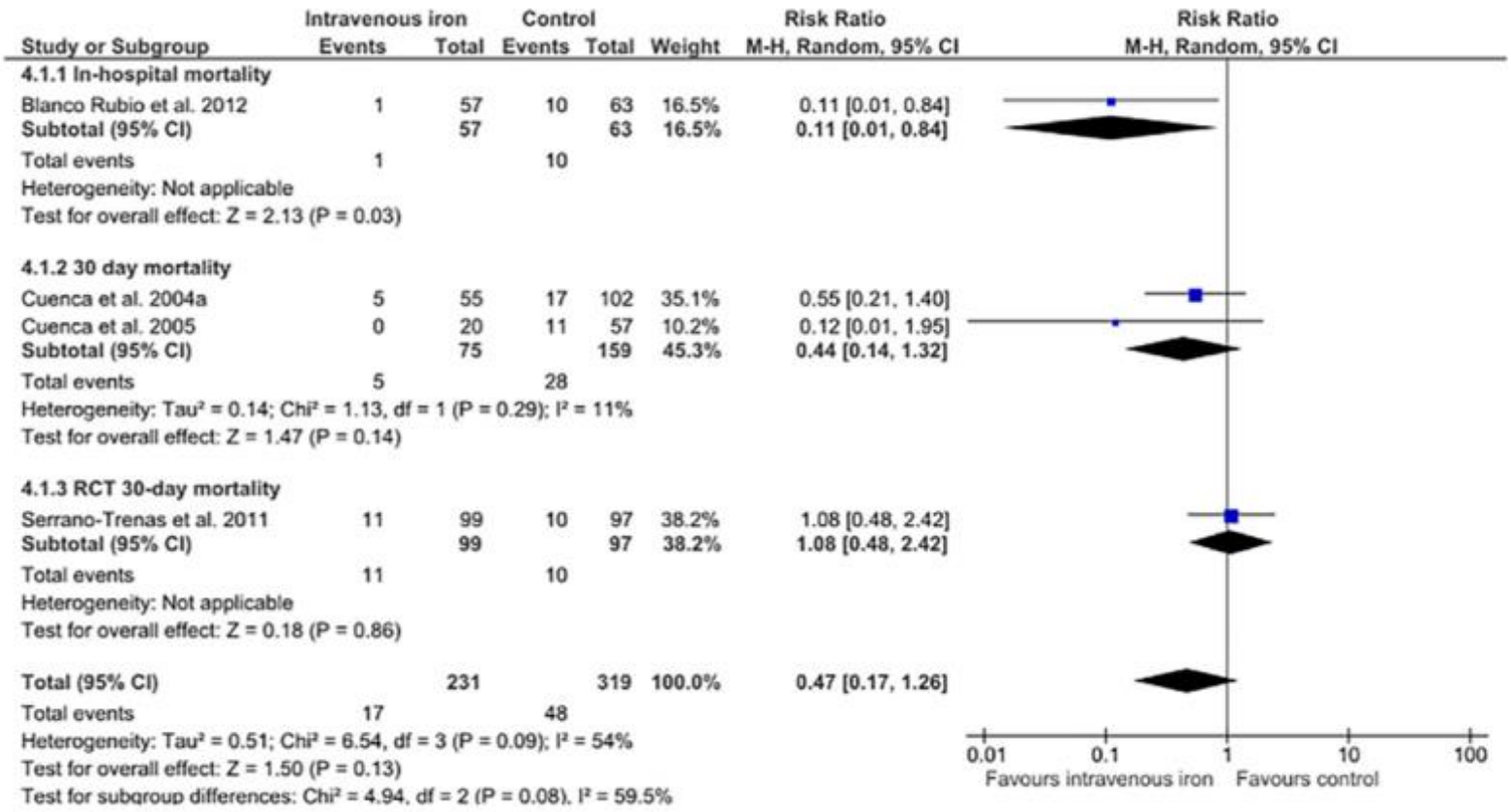


Figure 3 Forest plot for the association of anaemia on admission with mortality recorded to one postoperative year. Hb, haemoglobin concentration.

Anaesthesia 2015, 70, 483–500

Impact of intravenous iron on mortality



Anaesthesia 2015, 70, 483–500

Transfusion in hip fracture

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 29, 2011 VOL. 365 NO. 26

Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery

Jeffrey L. Carson, M.D., Michael L. Terrin, M.D., M.P.H., Helaine Noveck, M.P.H., David W. Sanders, M.D., Bernard R. Chaitman, M.D., George G. Rhoads, M.D., M.P.H., George Nemo, Ph.D., Karen Dragert, R.N., Lauren Beaupre, P.T., Ph.D., Kevin Hildebrand, M.D., William Macaulay, M.D., Courtland Lewis, M.D., Donald Richard Cook, B.M.Sc., M.D., Gwendolyn Dobbin, C.C.R.P., Khwaja J. Zakriya, M.D., Fred S. Apple, Ph.D., Rebecca A. Horney, B.A., and Jay Magaziner, Ph.D., M.S.Hyg., for the FOCUS Investigators*

N Engl J Med 2011;365:2453-62

Transfusion in hip fracture

- Liberal vs restrictive transfusion threshold after hip fracture surgery
- Cardiovascular disease
- No significant difference in rates of death or inability to walk independently at 60 days

Transfusion in hip fracture

Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial

Jeffrey L Carson, Frederick Sieber, Donald Richard Cook, Donald R Hoover, Helaine Noveck, Bernard R Chaitman, Lee Fleisher, Lauren Beaupre, William Macaulay, George G Rhoads, Barbara Paris, Aleksandra Zagorin, David W Sanders, Khwaja J Zakriya, Jay Magaziner

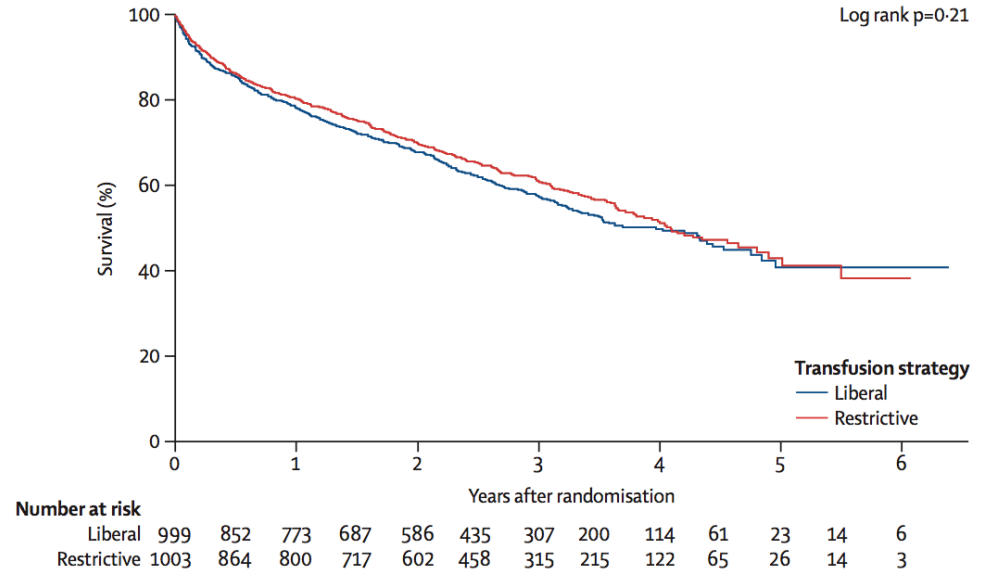


Figure 2: **Long-term survival with liberal versus restrictive transfusion strategies**

Lancet 2015; 385: 1183–89

Red blood cell transfusion for people undergoing hip fracture surgery (Review)

Brunskill SJ, Millette SL, Shokoohi A, Pulford EC, Doree C, Murphy MF, Stanworth S

- Six RCTs including 2722 participants undergoing surgery for hip fracture
- Liberal transfusion threshold (100 g/L) vs Restrictive transfusion threshold (<80 g/L)
- Liberal <113 g/L within 3 weeks of surgery vs Restrictive <97 g/L within 3 weeks of surgery

Cochrane Library
Cochrane Database of Systematic Reviews

Brunskill SJ, Millette SL, Shokoohi A, Pulford EC, Doree C, Murphy MF, Stanworth S. Red blood cell transfusion for people undergoing hip fracture surgery. *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD009699. DOI: 10.1002/14651858.CD009699.pub2.

www.cochranelibrary.com

Liberal versus restrictive threshold transfusion for people undergoing hip fracture surgery

Patient or population: people undergoing hip fracture surgery[1]
Settings: hospital
Intervention: liberal threshold red blood cell transfusion[2]
Comparison: restrictive threshold red blood cell transfusion[3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Restrictive threshold	Liberal threshold			
30-day mortality Follow-up: mean 30 days	**50 per 1000**[4]	**46 per 1000** (33 to 63)	**RR 0.92** (0.67 to 1.26)	2683 (5 studies)	⊕⊕◯◯ **low**[5,6]
Inability to walk 10 feet (3 m; or across a room) without human assistance Follow-up: mean 60 days	**283 per 1000**[4]	**283 per 1000** (246 to 326)	**RR 1.00** (0.87 to 1.15)	2083 (2 studies)	⊕⊕◯◯ **low**[7,8]
Thromboembolism (in hospital)	**20 per 1000**[4]	**23 per 1000** (11 to 47)	**RR 1.15** (0.56 to 2.37)	2416 (4 studies)	⊕⊕◯◯ **low**[6,9]
Stroke (in hospital)	**2 per 1000**[4]	**5 per 1000** (2 to 14)	**RR 2.4** (0.85 to 6.79)	2416 (4 studies)	⊕⊕◯◯ **low**[6,9]
Wound infection (in hospital)	**8 per 1000**[4]	**13 per 1000** (6 to 27)	**RR 1.61** (0.77 to 3.35)	2332 (3 studies)	⊕⊕◯◯ **low**[6,10]
Cardiovascular events - myocardial infarction	**24 per 1000**[4]	**14 per 1000** (9 to 23)	**RR 0.59** (0.36 to 0.96)	2217 (3 studies)	⊕◯◯◯ **very low**[6,11]

Brunskill SJ, Millette SL, Shokoohi A, Pulford EC, Doree C, Murphy MF, Stanworth S. Red blood cell transfusion for people undergoing hip fracture surgery. *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD009699. DOI: 10.1002/14651858.CD009699.pub2.

www.cochranelibrary.com

Pre-operative assessment of bleeding risk

- Bleeding history
- Past medical history, drug history
- Must balance risk of bleeding with risk of thrombosis
- Vitamin K antagonists
  - Warfarin
- Novel oral anticoagulants
  - Direct factor Xa inhibitors: rivaroxaban, apixaban
  - Direct thrombin inhibitor: dabigatran
- Antiplatelet agents

Pre-operative Planning

- Assess need for anticoagulation to be interrupted for surgery
- Determine whether patient is standard risk or high risk of thrombosis
  - Recent VTE (3 months), recent stroke (6 months), recent coronary stent
  - Whether very high bleeding risk?
- Consideration of bridging anticoagulation

Non-vitamin K Oral Anticoagulants (NOACs)

- Increasing use as alternatives to warfarin
  - Especially patients with poor control
  - Laboratory monitoring not required
- Dabigatran – direct thrombin inhibitor
- Apixaban, Rivaroxaban – factor Xa inhibitors
- New challenges when managing patients for surgery

Non-vitamin K Oral Anticoagulants (NOACs)

- Lack of specific antidotes
- Coagulation monitoring non-specific
- Significantly lower rates of intracranial haemorrhage compared to warfarin

	Rivaroxaban	Apixaban	Dabigatran
Mechanism of action	Factor Xa inhibitor	Factor Xa inhibitor	Direct thrombin inhibitor
Dosing frequency	Once daily	Twice daily	Twice daily
Half-life (h)	5–13	12	8–15
Bioavailability (%)	80	66	6·5
Renal clearance (%)	66	25	80
Plasma protein binding (%)	> 90	87	35

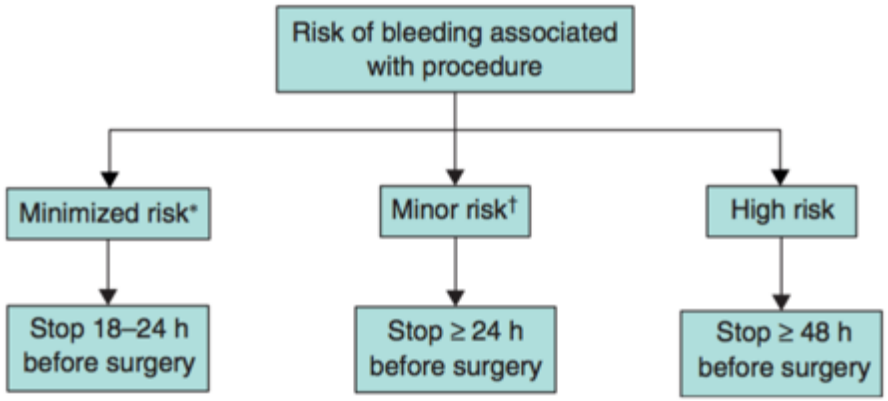
Key Management Points for NOACs

- Time of last dose of NOAC
- Current renal function
- Planned procedure

NOACs in Elective Surgery

- No need for bridging
- European Heart Rhythm Association (EHRA) guidelines 2013 for stopping pre-op:

Rivaroxaban/Apixaban
Factor Xa inhibitors



If CrCl > 30 mL/min

Direct thrombin inhibitor

	Dabigatran	
		No important
	Low risk (h)	
CrCl ≥80 mL/min	≥24	≥48
CrCl 50–80 mL/min	**≥36**	**≥72**
CrCl 30–50 mL/min[b]	**≥48**	**≥96**
CrCl 15–30 mL/min[b]	not indicated	not indicated
CrCl <15 mL/min		

Perioperative management of NOACs

- Stop NOAC
- Perform specific coagulation tests and interpret according to NOAC being taken
- Aim to defer surgery for 12 hours, ideally 24 hours
  - Activated charcoal if ingestion <2 hours
- Vitamin K / FFP have no effect
- If severe life threatening bleeding:
  - PCC 25-50 units/kg
  - Haemodialysis for dabigatran

Reversal of NOACs

The NEW ENGLAND JOURNAL of MEDICINE

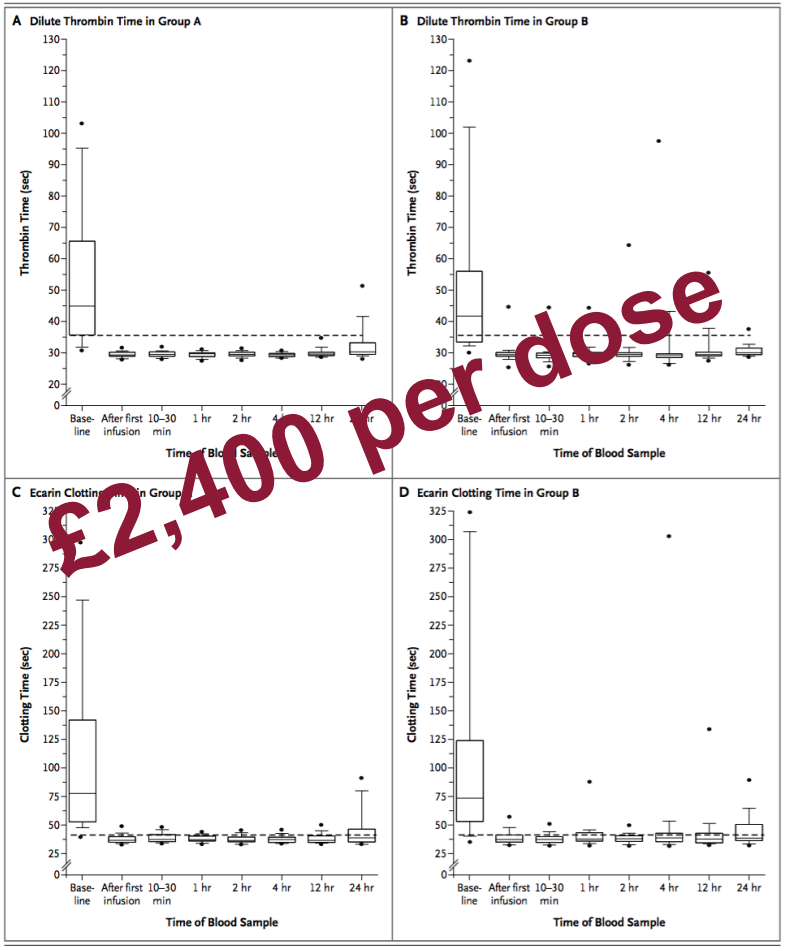
ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

N Engl J Med 2015;373:511-20.

Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial



£2,400 per dose

N Engl J Med 2015;373:511-20.

http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=6275

Reversal of NOACs

- Andexanet Alpha: PRT064445
  - Binds and inhibits FXa inhibitors
  - Healthy volunteer trial
  - rivaroxban = normalised PT
  - apixaban = thrombin generation restored

Siegal et al, N Engl J Med 2015;373:2413-24

- Perosphere: PER977
  - Edoxoban reversal

Ansell et al, N Engl J Med 2014; 371:2141-2142

Neuraxial Anaesthesia and Anticoagulants

Neuraxial anaesthesia and anticoagulants

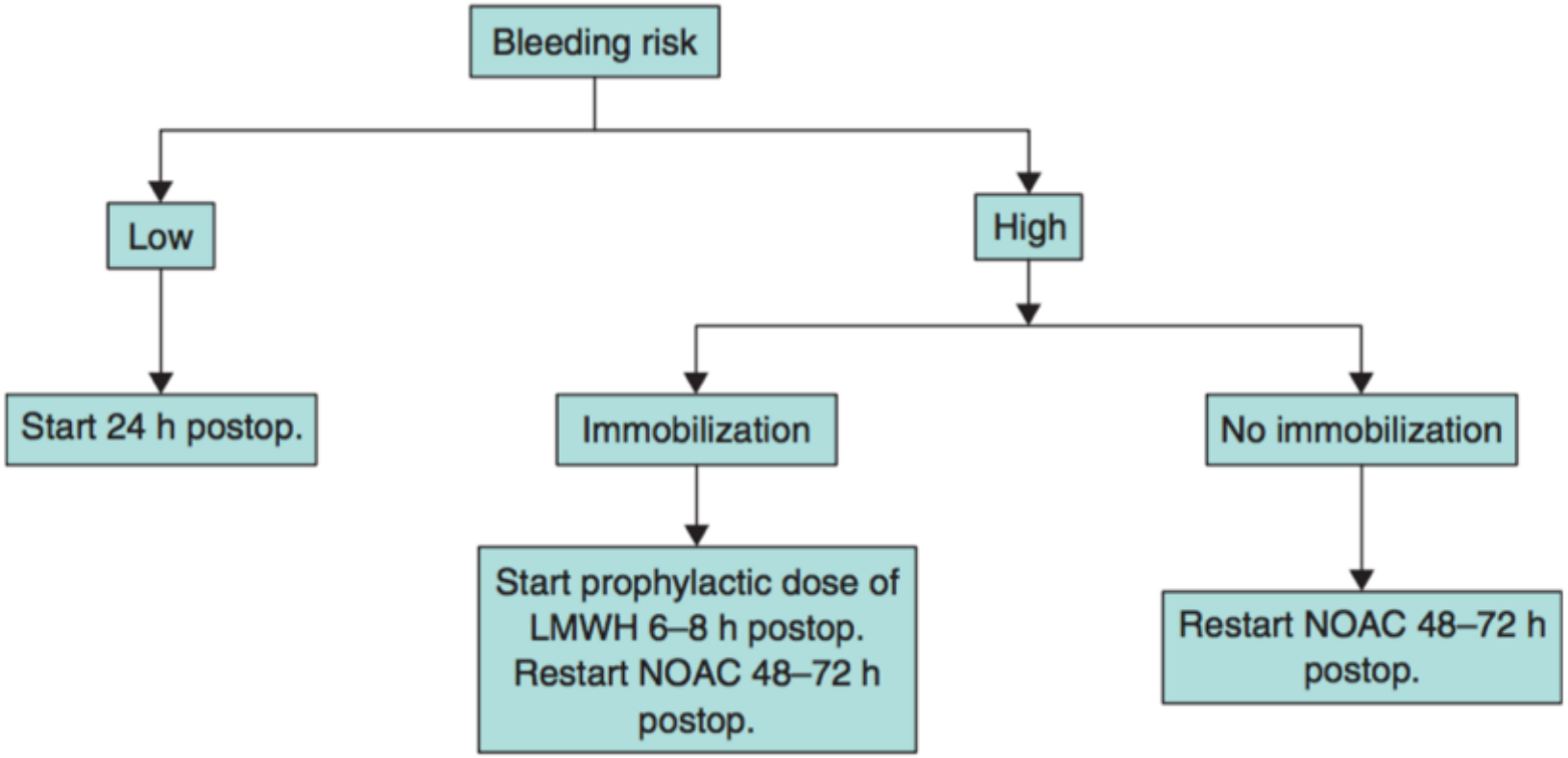
Table 1 Recommendations related to drugs used to modify coagulation. Recommended minimum times are based in most circumstances on time to peak drug effect + (elimination half-life × 2), after which time < ¼ of the peak drug level will be present. For those drugs whose actions are unrelated to plasma levels, this calculation is not relevant. Data used to populate this Table are derived from ASRA and ESRA guidelines [1, 2] and information provided by drug manufacturers. These recommendations relate primarily to neuraxial blocks and to patients with normal renal function except where indicated.

Drug	Time to peak effect	Elimination half-life	Acceptable time after drug for block performance	Administration of drug while spinal or epidural catheter in place[1]	Acceptable time after block performance or catheter removal for next drug dose
Heparins					
UFH sc prophylaxis	< 30 min	1–2 h	4 h or normal APTTR	Caution	1 h
UFH iv treatment	< 5 min	1–2 h	4 h or normal APTTR	Caution[2]	4 h
LMWH sc prophylaxis	3–4 h	3–7 h	12 h	Caution[3]	4 h[3]
LMWH sc treatment	3–4 h	3–7 h	24 h	Not recommended	4 h[4]
Heparin alternatives					
Danaparoid prophylaxis	4–5 h	24 h	Avoid (consider anti-Xa levels)	Not recommended	6 h
Danaparoid treatment	4–5 h	24 h	Avoid (consider anti-Xa levels)	Not recommended	6 h
Bivalirudin	5 min	25 min	10 h or normal APTTR	Not recommended	6 h
Argatroban	< 30 min	30–35 min	4 h or normal APTTR	Not recommended	6 h
Fondaparinux prophylaxis[5]	1–2 h	17–20 h	36–42 h (consider anti-Xa levels)	Not recommended	6–12 h
Fondaparinux treatment[5]	1–2 h	17–20 h	Avoid (consider anti-Xa levels)	Not recommended	12 h
Antiplatelet drugs					
NSAIDs	1–12 h	1–12 h	No additional precautions	No additional precautions	No additional precautions
Aspirin	12–24 h	Not relevant; irreversible effect	No additional precautions	No additional precautions	No additional precautions
Clopidogrel	12–24 h		7 days	Not recommended	6 h
Prasugrel	15–30 min		7 days	Not recommended	6 h
Ticagrelor	2 h	8–12 h	5 days	Not recommended	6 h
Tirofiban	< 5 min	4–8 h[6]	8 h	Not recommended	6 h
Eptifibatide	< 5 min	4–8 h[6]	8 h	Not recommended	6 h
Abciximab	< 5 min	24–48 h[6]	48 h	Not recommended	6 h
Dipyridamole	75 min	10 h	No additional precautions	No additional precautions	6 h
Oral anticoagulants					
Warfarin	3–5 days	4–5 days	INR ≤ 1.4	Not recommended	After catheter removal

Neuraxial anaesthesia and anticoagulants

Drug	Time to peak effect	Elimination half-life	Acceptable time after drug for block performance	Administration of drug while spinal or epidural catheter in place[1]	Acceptable time after block performance or catheter removal for next drug dose
Rivaroxaban prophylaxis[5] ($CrCl > 30$ ml.min^{-1})	3 h	7–9 h	18 h	Not recommended	6 h
Rivaroxaban treatment[5] ($CrCl > 30$ ml.min^{-1})	3 h	7–11 h	48 h	Not recommended	6 h
Dabigatran prophylaxis or treatment[7]					
($CrCl > 80$ ml.min^{-1})	0.5–2.0 h	12–17 h	48 h	Not recommended	6 h
($CrCl$ 50–80 ml.min^{-1})	0.5–2.0 h	15 h	72 h	Not recommended	6 h
($CrCl$ 30–50 ml.min^{-1})	0.5–2.0 h	18 h	96 h	Not recommended	6 h
Apixaban prophylaxis	3–4 h	12 h	24–48 h	Not recommended	6 h
Thrombolytic drugs					
Alteplase, anistreplase, reteplase, streptokinase	< 5 min	4–24 min	10 days	Not recommended	10 days

Restarting NOACs after surgery



Clopidogrel and #NOF

- Clopidogrel
  - ADP receptor blocker on platelet membrane
  - Irreversibly blocks platelet aggregation
  - 7 days until production of new platelets for reversal
  - Discontinuation recommended for 7 days before elective surgery and neuraxial anaesthesia
- Robust evidence for early intervention in these patients
  - Higher risk of operative morbidity and mortality contributed to by delaying surgery

Clopidogrel and #NOF

- Most recommendations are to avoid spinal for 7 days
- However, spinal anaesthesia is used
  - 40% of patients on clopidogrel in one series
  - Authors conclude:
  - In balance general anaesthesia is safe but spinal anaesthesia can be considered if all the risks are explained to the patient before the procedure.

D.R. Wordsworth et al. / Injury, Int. J. Care Injured 44 (2013) 743–746

Anaesthetic management

- Regional anaesthesia
  - Spinal and epidural anaesthesia significantly decrease estimated blood loss compared with GA or combined GA-epidural
- Maintain normothermia
  - 1ºc decrease in temperature = 16% increase in blood loss
- pH correction
- Maintain Calcium concentration >1mmol/l
- Fluid balance

Richman et al. Journal of Clinical Anaesthesia, 2006;18:427-435

Rajagopalan, Anesthesiology, 2008;108(1):71-77

Tranexamic acid

Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion (Review)

Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K

"effective in reducing blood loss during and after surgery, and appear to be free of serious adverse effects."

Henry, D.A. et al., 2011. The Cochrane database of systematic reviews, (3), p.CD001886.

- Lysine analogue
- Reversibly inhibits fibrinolysis
- Meta-analysis suggests reduction of surgical blood loss by about one-third.
- 1g (approx. 14 mg/kg) sufficient for most adults

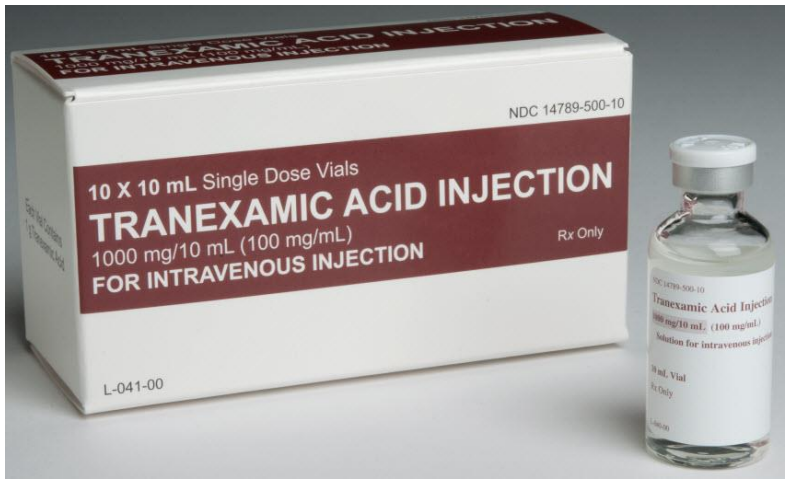
Ker et al.,Br J Surg 2013;100(10);1271-1279

Tranexamic Acid

Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

*CRASH-2 trial collaborators**

N = 20211



COST PER QALY

Tanzania	$48
India	$66
UK	$64

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value (two-sided)
Any cause of death	1463 (14·5%)	1613 (16·0%)	0·91 (0·85–0·97)	0·0035
Bleeding	489 (4·9%)	574 (5·7%)	0·85 (0·76–0·96)	0·0077
Vascular occlusion*	33 (0·3%)	48 (0·5%)	0·69 (0·44–1·07)	0·096
Multiorgan failure	209 (2·1%)	233 (2·3%)	0·90 (0·75–1·08)	0·25
Head injury	603 (6·0%)	621 (6·2%)	0·97 (0·87–1·08)	0·60
Other causes	129 (1·3%)	137 (1·4%)	0·94 (0·74–1·20)	0·63

Data are number (%), unless otherwise indicated. RR=relative risk. *Includes myocardial infarction, stroke, and pulmonary embolism.

Table 2: Death by cause

The Lancet, 2010; 376: 23-32

Cell salvage for minimising perioperative allogeneic blood transfusion (Review)

Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA

THE COCHRANE COLLABORATION®

Cell Salvage

- 75 trials (n=6025)
- Overall
  - Reduction in blood transfusion 0.62 (0.55-0.70)
    - ARR 21%
    - NNT 4.8
  - Allogenic Transfusion saving 0.68 units
    - Greatest in orthopaedics 54%
    - Cardiac 23%

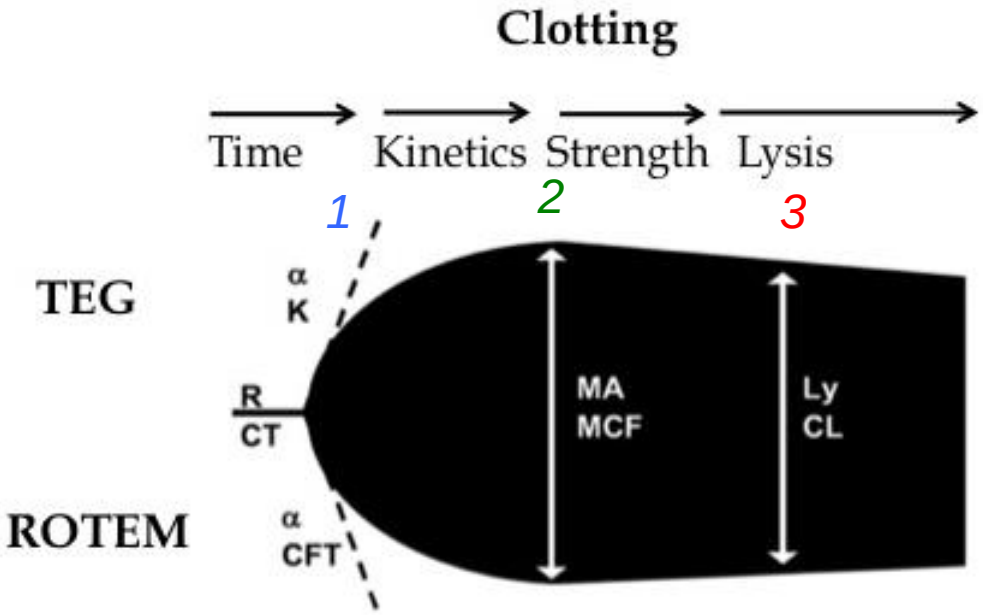
Carless et al, Cochrane Database Syst Rev, 2010;(4):CD001888

Point of Care Testing

- Laboratory coagulation tests
  - Turn around time
  - Delay in obtaining results
  - Empirical treatment

- Point of care tests
  - Rapid result reporting
  - Goal directed management of coagulopathy
  - Reduce empirical treatment

TEG / ROTEM



What do we need to know?

1. Is clot forming and how rapidly?
   - Clotting factor levels and anticoagulants
2. How strong is the clot?
   - Platelets and fibrinogen
3. Is it stable?
   - Fibrinolysis

TEG – Thromboelastography ROTEM – Rotational Thromboelastometry

Perioperative management

- Point of care based management algorithms
- Algorithms for perioperative bleeding
  - Predefined transfusion triggers to guide haemostatic interventions
- Restrictive transfusion triggers

- Single unit transfusions

Trauma and major bleeding

- NICE Trauma guidelines – February 2016
- British Society of Haematology major haemorrhage guidelines – July 2015

2016 GUIDELINES FOR THE PROVISION OF anaesthetic services

Chapter 5. Emergency anaesthetic services

- 2.27 Near-patient testing for haemoglobin, blood gases, lactate, blood sugar and ketones should be readily available for theatres.
- 2.28 Near-patient testing for coagulopathy should be considered, particularly in areas where major blood loss is likely…
- 2.34 Availability of a cell salvage system should be considered for procedures associated with blood loss exceeding 1.5 litres.

http://www.rcoa.ac.uk/gpas2016

Trauma and major bleeding

- Have a defined major haemorrhage protocol
- Damage control resuscitation for active bleeding
- Early haemorrhage control
- Permissive hypotension, use RBCs and FFP 1:1
- Early tranexamic acid
- Monitor by point-of-care and/or laboratory tests
- FFP if INR > 1.5
- Cryoprecipitate if fibrinogen < 1.5 $g.l^{1}$
- Platelets if platelet count < 75 x $10^{9}.l^{1}$

Conclusion

- Triad of risk: blood transfusion, major bleeding and anaemia significant in orthopaedics
- Patient blood management can improve outcomes in both elective and emergency surgery
- Requires organisational support and planning
- Increasingly robust guideline frameworks to aid implementation

Thank you

b.clevenger@nhs.net

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

PREVENTT

Preoperative intravenous iron to treat anaemia in major surgery