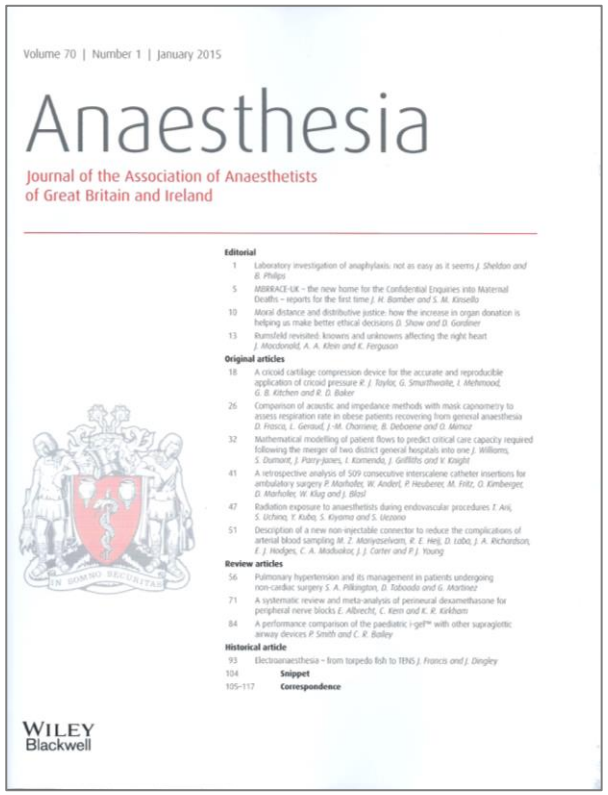
Management of iron deficiency with or without anaemia in surgical patients

Dr Andrew A Klein

Papworth Hospital

Cambridge UK

- Conflicts of interest:
  - Unrestricted educational grants/honoraria from CSL Behring, Brightwake Ltd, Vifor Pharma, Fisher and Paykel and Pharmacosmos
  - Editor-in-Chief of *Anaesthesia*



- Impact Factor ~~3.4~~ 3.8
- Turnaround on decisions:
  - < 2 weeks for 90% of submissions
  - < 1 week for 50% of submissions
- Friendly editors who correspond directly with you
- Online Early e-publication for rapid publication

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland
WILEY

- *Anaesthesia* iPad®/iPhone® app available from App Store
- Android version also available
- Dynamic figures, tables & references
- Instant access to breaking research
- Personalised experience
- Free for AAGBI members, using your membership login details to access

Learning Objectives

- Definition of anaemia
- Scale of the problem
- Causes of anaemia
- Consequences
- Pre-operative treatment

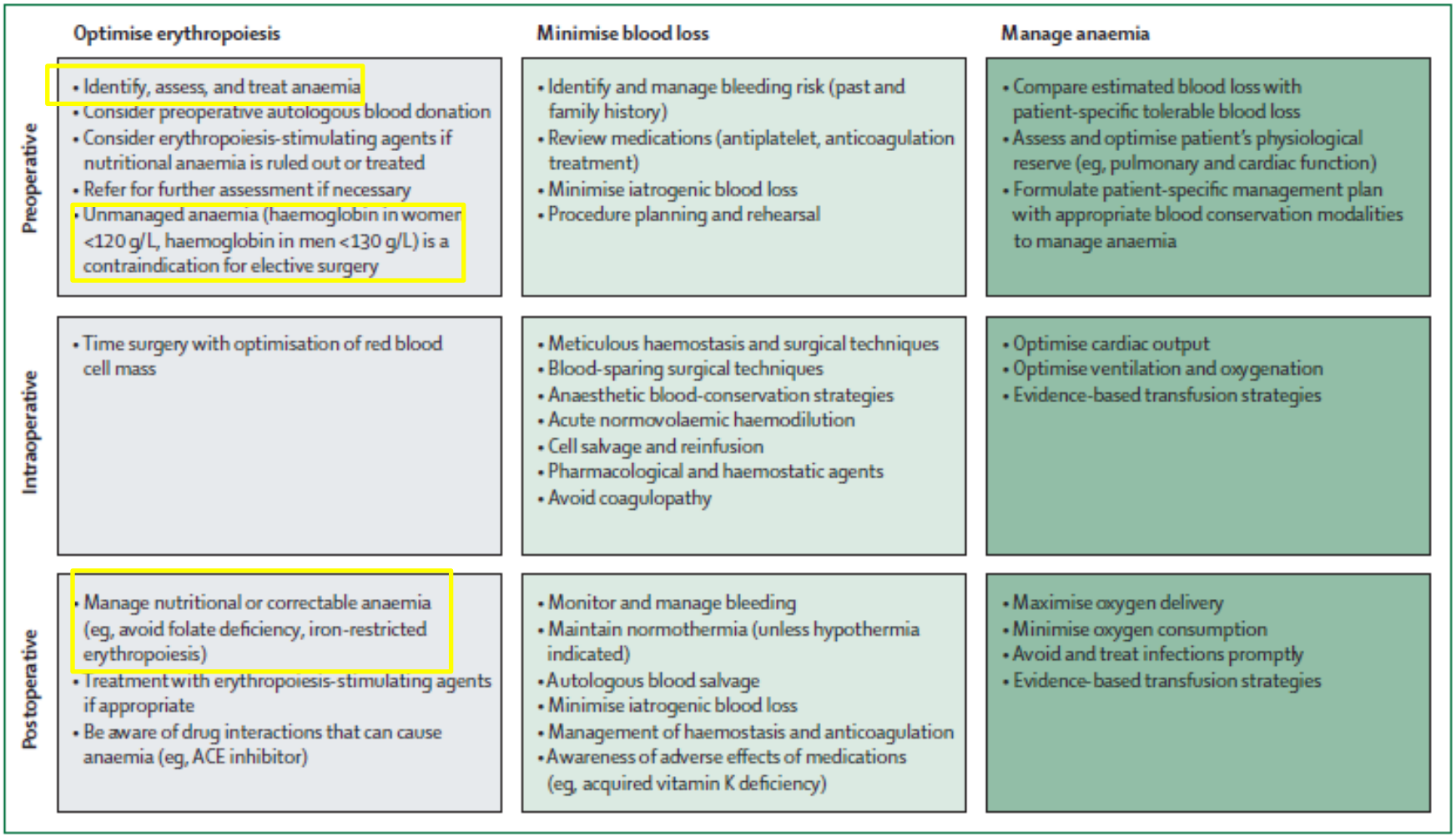


Figure 1: **Patient blood management**

These recommendations apply in the perisurgical period enable treating physicians to have the time and methods to provide patient-centred and evidence-based patient blood management to minimise allogeneic blood transfusions. Modified from Goodnough and Shander,[19] by permission of the American Society of Anesthesiologists.

Pillar One

- Identify, assess and treat anaemia
- Consider postponing elective non-urgent surgery if anaemic
- Time surgery with optimization of red blood cell mass

Definition

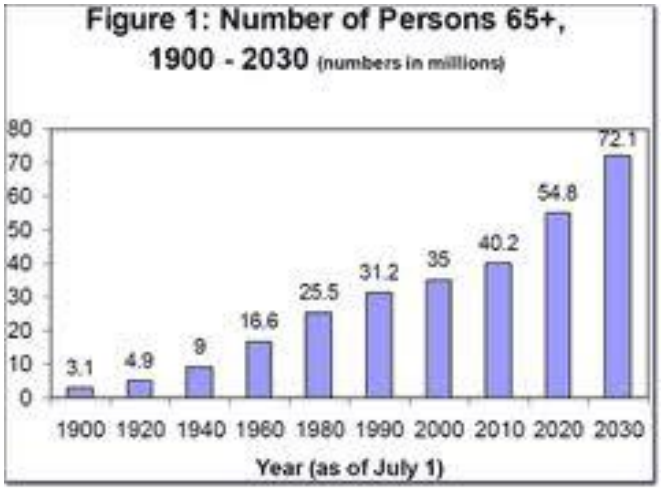
- WHO: 13 g/dL men, 12 women (1968)

Gender bias

- Should be we aiming for an Hb > 130 g/L in men and women?
- Women are smaller than men
- Women have smaller body surface area and less blood
- Women bleed just as much as men!

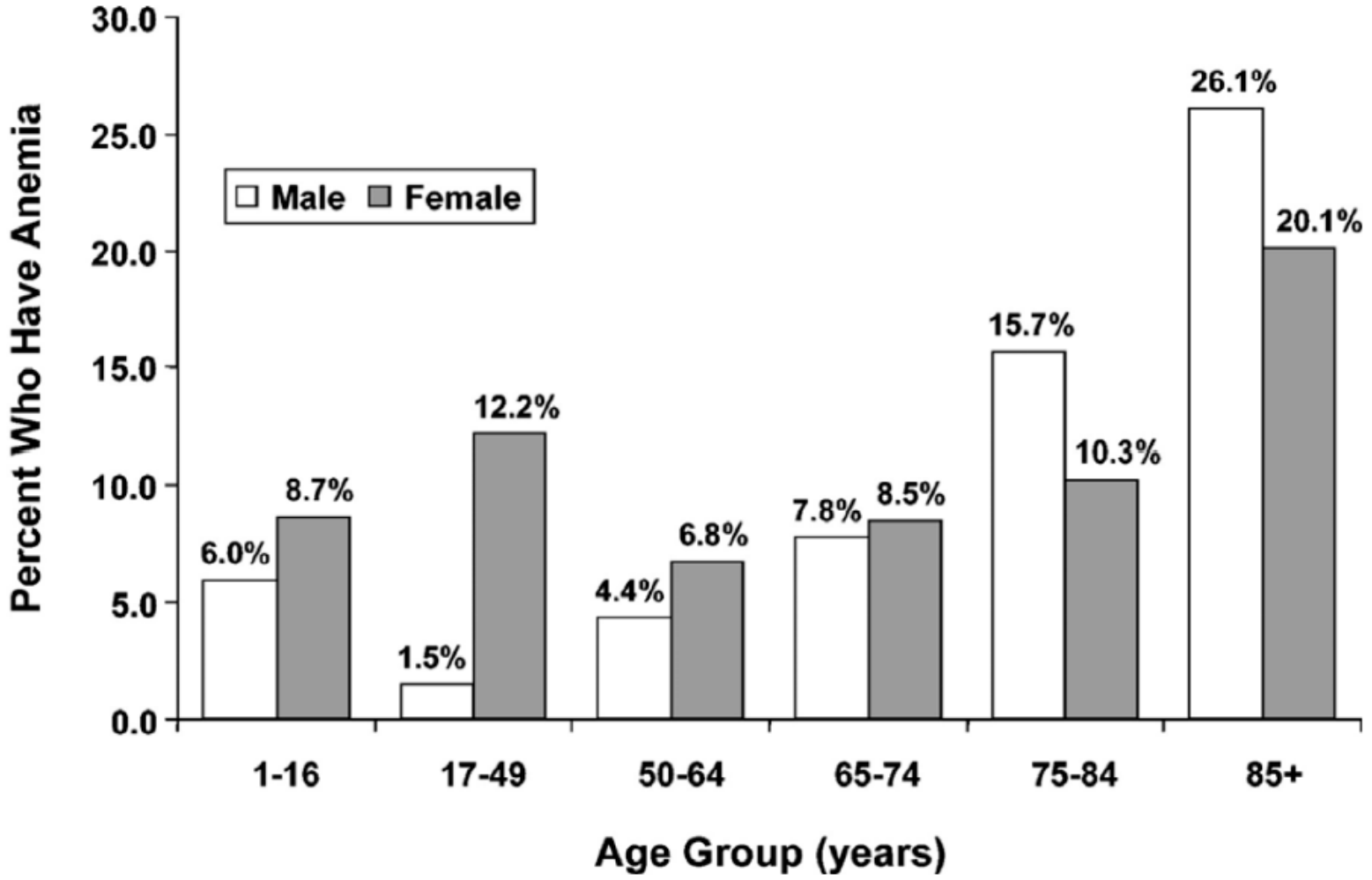
Population Demographics

- Increasing age
- More comorbidities
- More healthcare
- Epidemic of anaemia?



Data from 1995 - 2005

Patel KV et al. *Semin Hematol* 2008; **45**: 210-7.



Incidence of anemia

- Increases with age

Gaskell H et al. *BMC Geriatrics* 2008; **8**: 1.

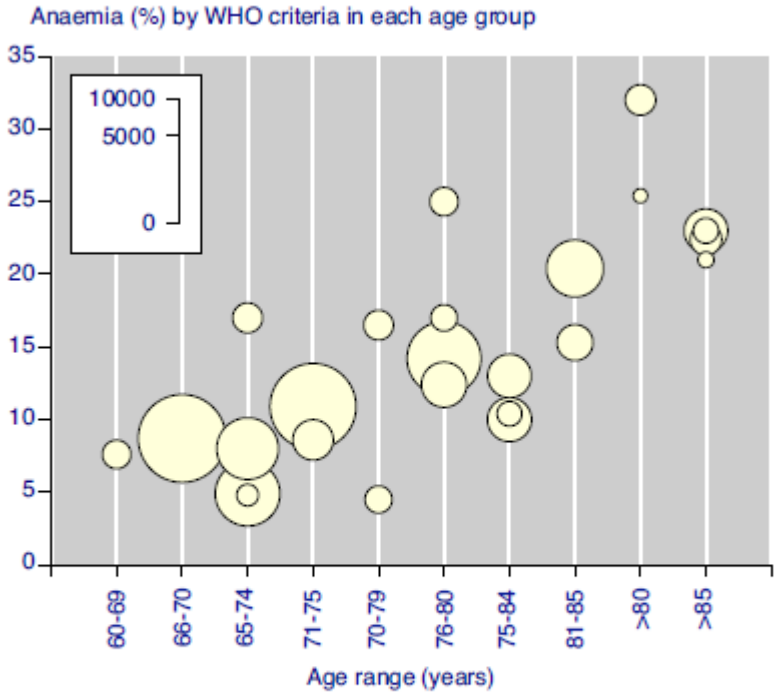
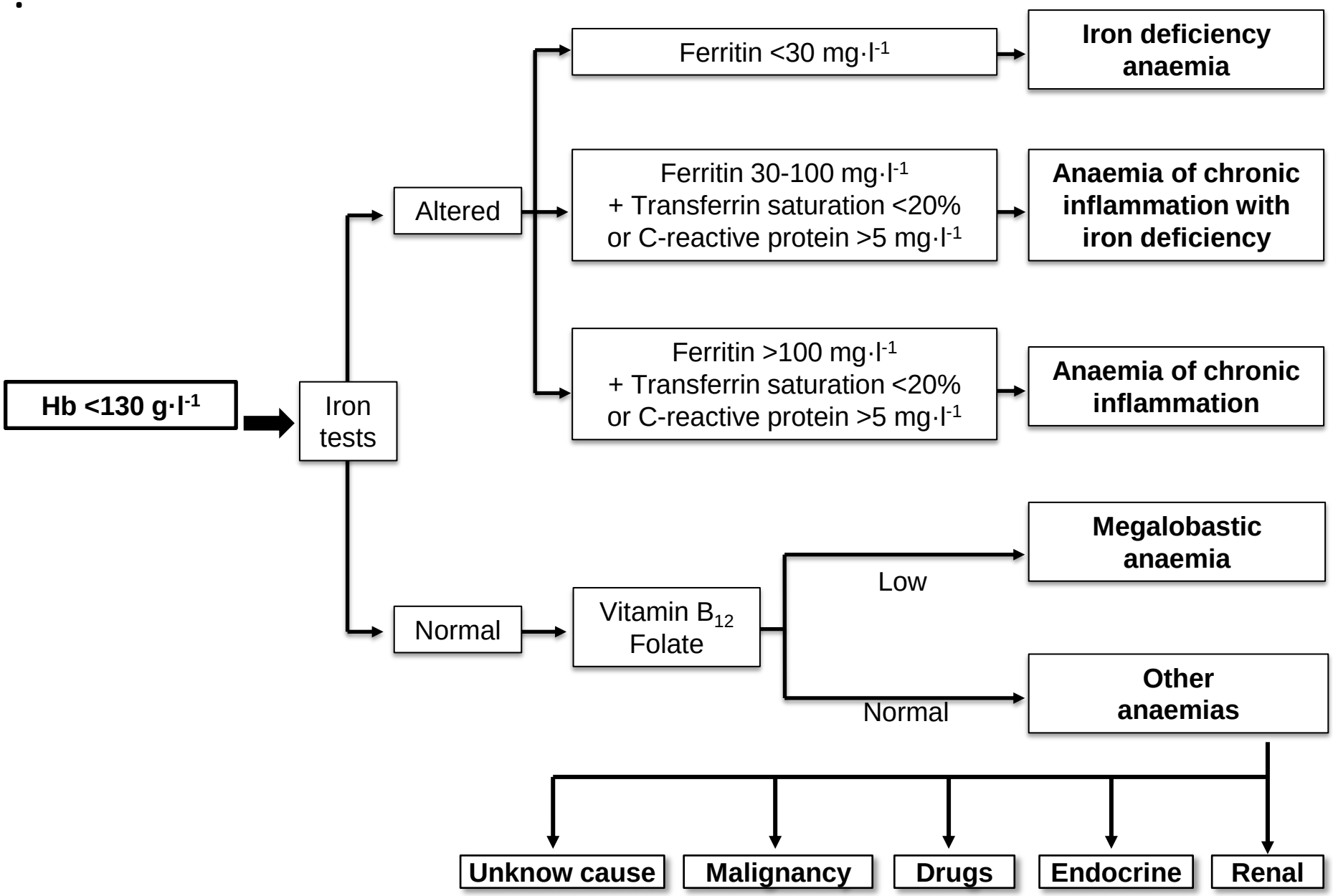
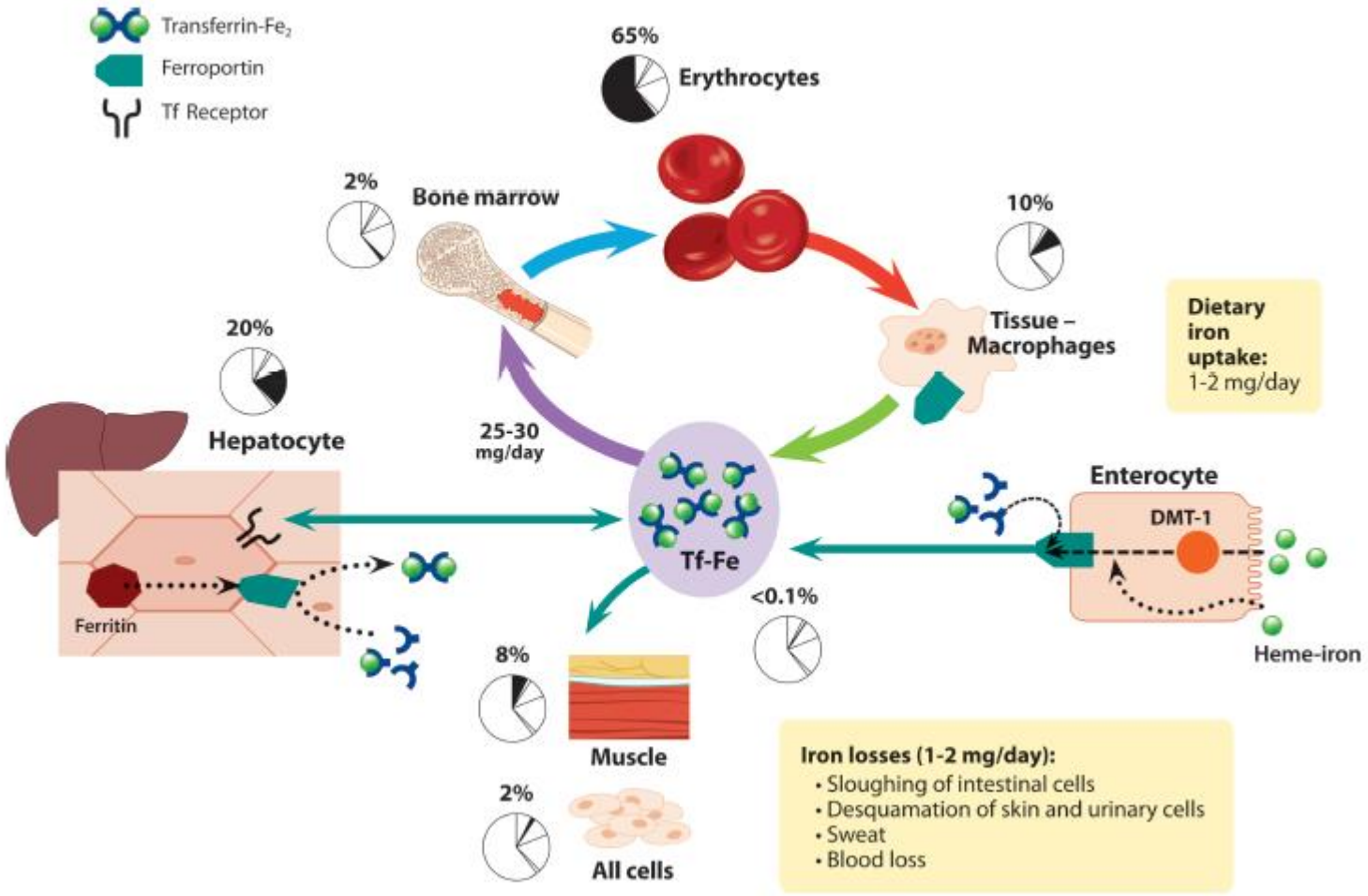


Figure 2
Anaemia prevalence by age range. Size of the symbol is proportional to the size of the cohort (inset scale)

Causes of anaemia

- Nutrient deficiency
  - Iron
  - Folate
  - B12
- Renal failure
- **Chronic disease**


Hb <130 g·l-1
Iron tests
Altered
Ferritin <30 mg·l-1
Iron deficiency anaemia
Ferritin 30-100 mg·l-1
+ Transferrin saturation <20%
or C-reactive protein >5 mg·l-1
Anaemia of chronic inflammation with iron deficiency
Ferritin >100 mg·l-1
+ Transferrin saturation <20%
or C-reactive protein >5 mg·l-1
Anaemia of chronic inflammation
Normal
Vitamin B12
Folate
Low
Megalobastic anaemia
Normal
Other anaemias
Unknow cause
Malignancy
Drugs
Endocrine
Renal



- 55-45 mg/kg (3-4g) iron in the body
- Iron turnover less than 1-2mg/day:

Lasocki et al. Anesthesiology 2011; 114: 688-94

- Iron losses:
  - Desquamation of skin and urinary cells
  - Sloughing of intestinal cells
  - Sweat
  - Blood loss

- Iron absorbed from the diet into intestinal cells and exported into blood via ferroportin.
- Transferrin transports iron from stores (macrophages, hepatocytes) to utilisation sites (bone marrow, muscles)

Causes of Iron Deficiency

A. Increased demand

- Growth during infancy and childhood
- Treatment with erythropoiesis-stimulating agents

B. Limited supply

- Poor intake
- Inappropriate diet with deficit in bioavailable iron and/or ascorbic acid
- Malabsorption
  - Gastric resection
  - Helicobacter pylori infection (even without significant bleeding)
  - Malabsorption syndromes (Crohn's disease and celiac disease)
- Drug interference (gastric anti-acid agents and anti-secretory drugs)

C. Increased losses

- Phlebotomy
  - Blood donation
  - Dialysis (particularly haemodialysis)
- Haemorrhage
  - Surgery
  - Trauma
  - Gastrointestinal bleeding
  - Genitourinary bleeding
  - Respiratory tract bleeding

Anaemia of chronic disease

- Inflammation
- Iron deficiency – relative or absolute
- Impaired erythroid cell proliferation
- Dysregulation of iron metabolism
- Blunted erythropeitin synthesis

Hepcidin

- Central regulator of iron homeostasis
- Small 25-amino acid peptide produced mainly in the liver.
- Acts by binding to Ferroportin.
- Blocks Ferroportin in intestinal cells leading to iron deficiency.
- Blocks Ferroportin in macrophages leading to inhibition of iron release and iron-restricted erythropoiesis.

Hepcidin synthesis

- Induced by iron overload and INFLAMMATION via interleukin-6
- Repressed by iron deficiency, hypoxia and erythroid expansion.
- Cleared by the kidney.
- Ageing is a pro-inflammatory state in which iron absorption is impaired via Hepcidin.

Hepcidin

- Increased due to inflammation
- Also elevated in chronic kidney disease due to reduced renal clearance.
- Leads to iron-restricted erythropoiesis
- “Anaemia of chronic disease”

All the same!

- Anaemia of chronic disease
- Functional iron deficiency
- Iron restriction anaemia

Incidence

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2011, **66**, pages 812–818 doi:10.1111/j.1365-2044.2011.06819.x

ORIGINAL ARTICLE

The prevalence and association with transfusion, intensive care unit stay and mortality of pre-operative anaemia in a cohort of cardiac surgery patients*

M. Hung,[1] M. Besser,[2] L. D. Sharples,[3] S. K. Nair[4] and A. A. Klein[5]

1 Fellow, 5 Consultant, Department of Anaesthesia and Intensive Care, 4 Consultant, Department of Cardiothoracic Surgery, Papworth Hospital, Cambridge, UK
2 Consultant, Department of Haematology, Addenbrookes Hospital, Cambridge, UK
3 MRC Biostatistics Unit, Cambridge, UK

1463 out of 2688 patients (54.4%) anaemic from 2008-2009

Table 2 Outcome data of patients undergoing cardiac surgery. Anaemia defined as haemoglobin concentration $< 12\ g.dl^{-1}$ in women or $< 13\ g.dl^{-1}$ in men. Values are number (proportion), median (IQR [range]) or mean (SD).

	Non-anaemic (n = 1225)	Anaemic (n = 1463)	p value*
Transfusion	275 (22.4%)	791 (54.1%)	< 0.0001
Total units of RBC transfused	0 (0–1 [0–20])	0 (0–2 [0–34])	< 0.0001
Units of RBC if transfused	2 (1–3 [1–20])	2 (1–3 [1–24])	< 0.0001
Transfusion > 6 units RBC	25 (2%)	102 (7%)	0.098
Postoperative haemoglobin	10.5 (3.1)	9.2 (3.4)	< 0.001
In-hospital deaths	13 (1.1%)	45 (3.1%)	0.0005
ICU stay; days	1 (0–2 [0–81])	1 (0–2) [0–69]	< 0.0001
ICU stay > 2 days	168 (13.7%)	287 (19.6%)	< 0.0001
Transfusion cost per patient; £	133 (0–410 [0–4205]	362 (0–795 [0–4205]	< 0.0001

RBC, red blood cells. *p value refers to the Wilcoxon signed-rank test or Pearson's chi-squared test for contingency tables.

- Anaemic patients more likely to be transfused, higher mortality and stay longer in ICU and hospital.
- INCREASED COST

Anaesthesia 2016, 71, 627–635 doi:10.1111/anae.13423

Original Article

The incidence and importance of anaemia in patients undergoing cardiac surgery in the UK – the first Association of Cardiothoracic Anaesthetists national audit*

A. A. Klein,[1] T. J. Collier,[2] M. S. Brar,[3] C. Evans,[4] G. Hallward,[5] S. N. Fletcher[6] and T. Richards,[7] on behalf of the Association of Cardiothoracic Anaesthetists (ACTA)[#]

- All adult patients undergoing cardiac surgery at 12 ACTA-accredited UK centres, 2010-2012

Centre	Location	Sample size
Essex Cardiothoracic Centre	Essex, England	2,559
Bristol Heart Institute	Bristol, England	1,510
University Hospital of Wales	Cardiff, Wales	732
Castle Hill Hospital	Hull, England	2,058
Freeman Hospital	Newcastle, England	2,384
Liverpool Heart and Chest Centre	Liverpool, England	5,371
Manchester Royal Infirmary	Manchester, England	500
Royal Victoria Hospital	Belfast, Northern Ireland	960
Royal Brompton Hospital	London, England	2,241
St. Thomas' Hospital	London, England	1,986
Royal Infirmary of Edinburgh	Edinburgh, Scotland	1,099
King's College Hospital	London, England	2,400

Table 1 Patients' characteristics, pre-operative investigations and operative characteristics for all patients and stratified by anaemia status. Values are mean (SD), number (proportion) or median (IQR [range]).

	All patients (n = 19,033)	**Anaemic (n = 5895) 31.0%**	**Not anaemic (n = 13,138) 69.0%**
Age; years	67.0 (12.0)	69.5 (12.0)	65.9 (11.9)
Sex; men	13,669 (71.8%)	4157 (70.5%)	9512 (72.4%)
Body mass index; $kg.m^{-2}$	28.3 (5.1)	27.7 (5.1)	28.5 (5.0)
Pre-operative haemoglobin; $g.l^{-1}$	13.4 (12.1–14.4 [3.8–22.0])	11.5 (10.6–12.2 [3.8–12.9])	14.0 (13.3–14.9 [12.0–22.0])

National variation in prevalence of anaemia

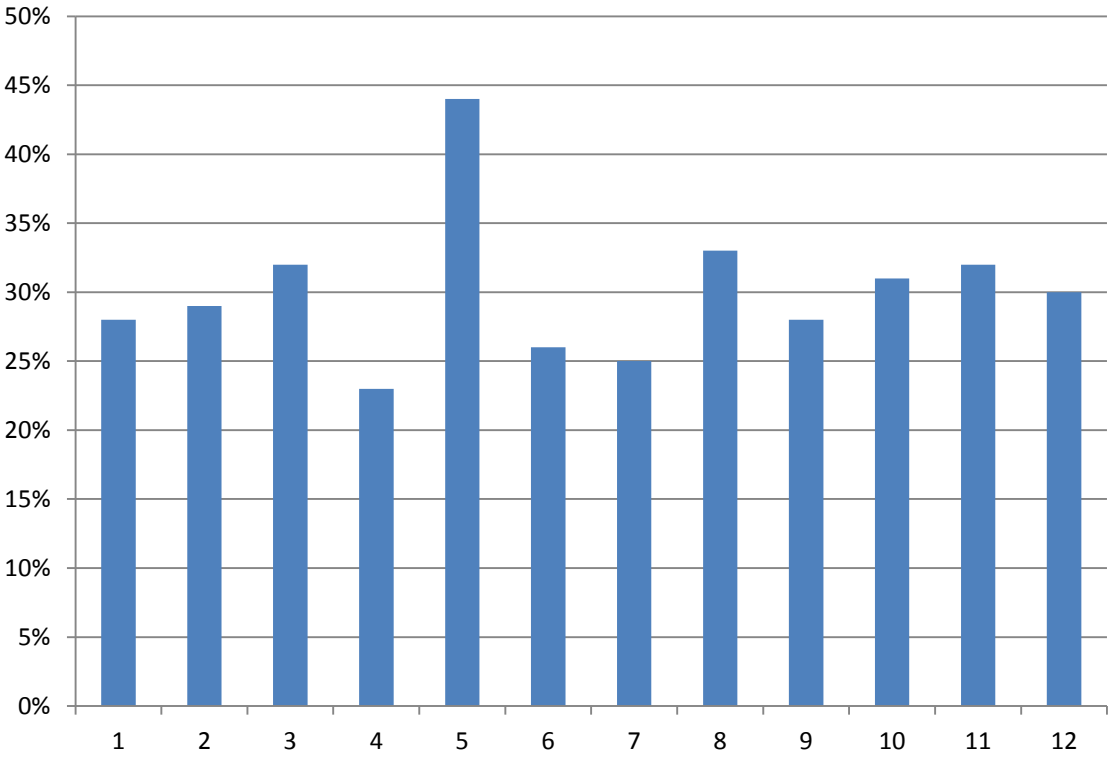


Table 3 Patient outcomes stratified by anaemia status. Values are number (proportion) or median (IQR [range]).

	All patients (n = 19,033)	Anaemic (n = 5895) 31.0%	Not anaemic (n = 13,138) 69.0%	p value
Transfused red blood cells	8579 (45.1%)	3764 (63.9%)	4815 (36.6%)	< 0.001
Units of red blood cells transfused*	2 (2–4 [1–78])	3 (2–5 [1–77])	2 (1–4 [1–78])	< 0.001
Massive transfusion (five or more units)	1933 (10.2%)	1025 (17.4%)	908 (6.9%)	< 0.001
ICU length of stay; days	2 (1–3 [0–373])	2 (1–4 [0–373])	2 (0–4 [0–368])	< 0.001
Hospital length of stay; days	7 (5–10 [0–370])	8 (6–14 [0–190])	6 (5–9 [0–370)	< 0.001
In-hospital mortality	628 (3.3%)	327 (5.6%)	301 (2.3%)	< 0.001

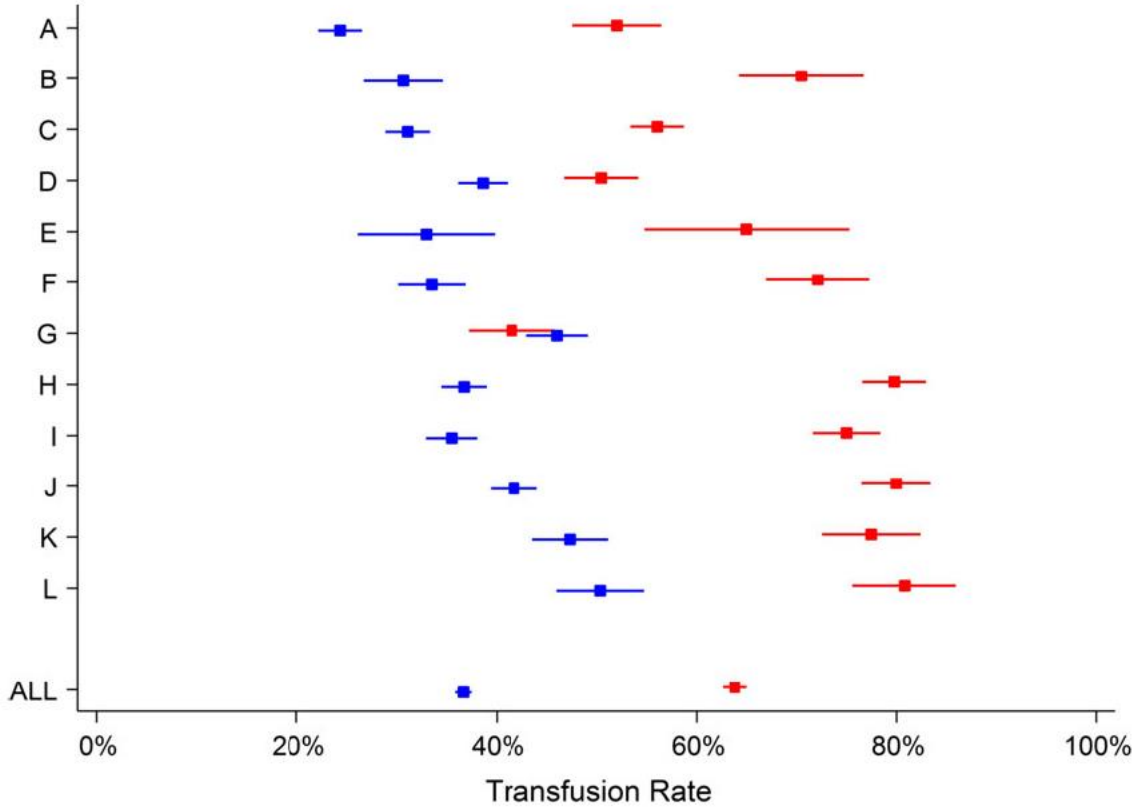


Figure 1 Transfusion rates in anaemic (red) and non-anaemic (blue) patients at the 12 centres (anonymised A-L) audited between 2010 and 2012. Transusion rates are mean (squares) and 95% CI (horizontal bars).

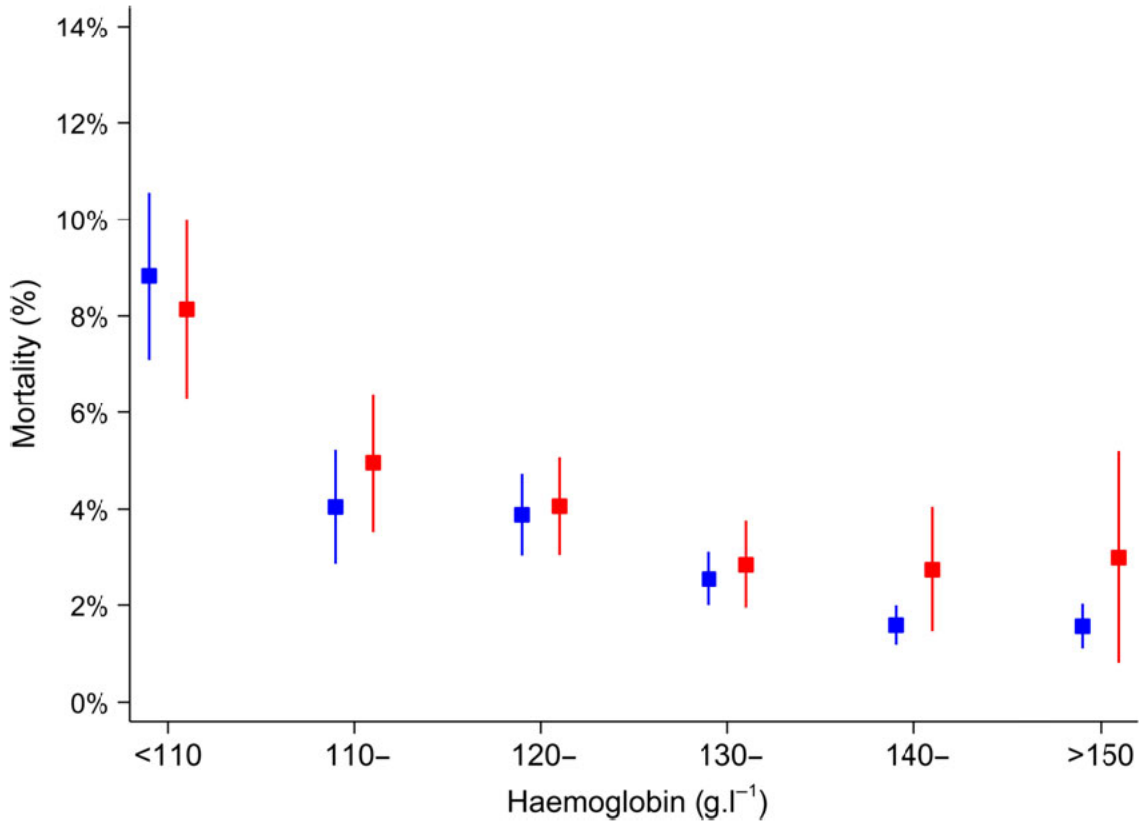


Figure 2 Mortality rates in patients with varying pre-operative haemoglobin concentrations in men (blue) and women (red). Mortality is mean (square) and 95% CI (horizontal bars).

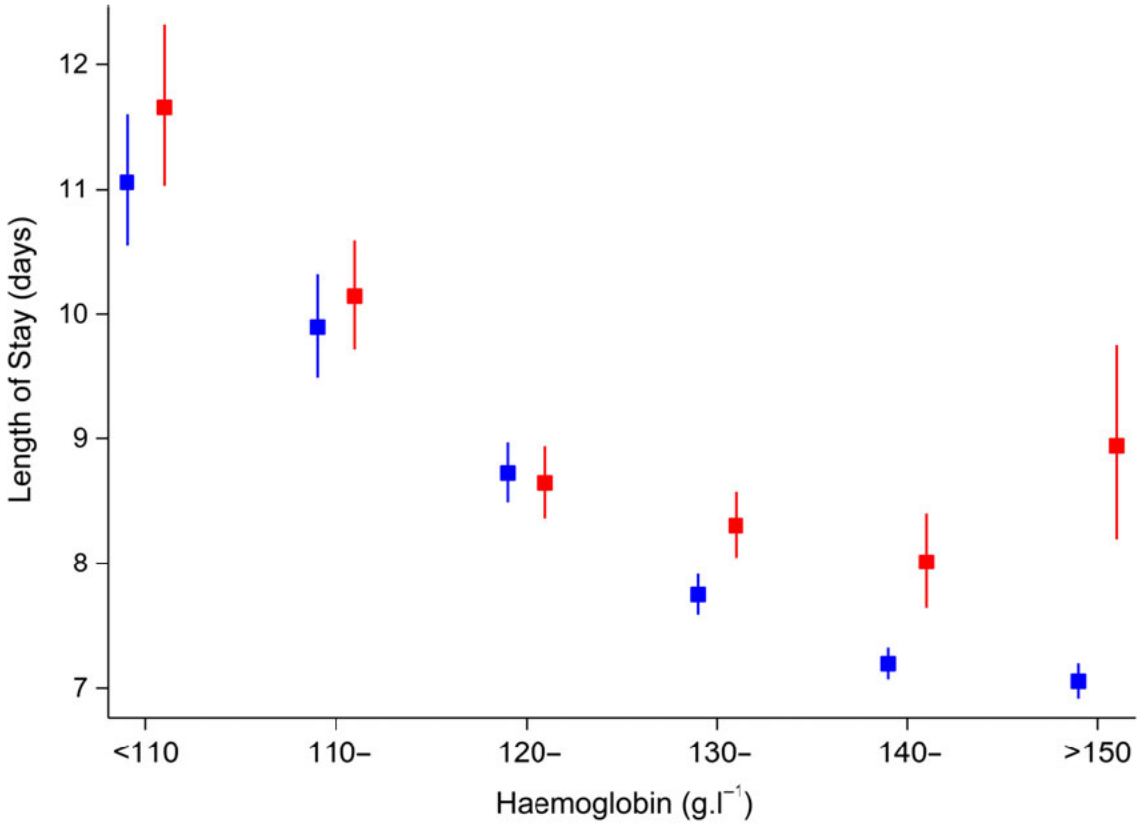


Figure 3 Length of stay in patients with varying heamoglobin concentrations in men (blue) and women (red). Length of stay is geometric mean (square) and 95% CI (horizontal bars).

Table 4 Association of anaemia and haemoglobin concentration (Hb) with outcome, adjusted for age, sex, logistic EuroSCORE, centre, operation type and body surface area; length of stay additionally adjusted for hypertension.

	Transfusion		Death		Length of stay	
	Adjusted OR [95% CI]	**p value**	**Adjusted OR [95% CI]**	**p value**	**Adjusted GMR [95% CI]**	**p value**
Anaemia	2.75 [2.55–2.95]	< 0.001	1.42 [1.18–1.71]	< 0.001	1.15 [1.13–1.17]	< 0.001
Hb (per 10 $g.l^{-1}$ decrease)	1.43 [1.40–1.46]	< 0.001	1.16 [1.10–1.22]	< 0.001	1.04 [1.04–1.05]	< 0.001
Hb; $g.l^{-1}$						
< 110	3.63 [3.18–4.15]	< 0.001	1.60 [1.21–2.11]	< 0.001	1.23 [1.19–1.27]	< 0.001
110–119	2.49 [2.20–2.82]		1.01 [0.74–1.38]		1.15 [1.11–1.18]	
120–129	1.70 [1.54–1.88]		1.07 [0.82–1.40]		1.05 [1.03–1.08]	
130–139	Ref		Ref		Ref	
140–149	0.80 [0.73–0.88]		0.64 [0.46–0.88]		0.97 [0.94–0.99]	
150+	0.51 [0.45–0.57]		0.76 [0.54–1.09]		0.97 [0.94–0.99]	

OR, odds ratio; GMR, geometric mean ratio.

THE LANCET

Articles

Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study

Khaled M Musallam, Hani M Tamim, Toby Richards, Donat R Spahn, Frits R Rosendaal, Aida Habbal, Mohammad Khreiss, Fadi S Dahdaleh, Kaivan Khavandi , Pierre M Sfeir, Assaad Soweid, Jamal J Hoballah, Ali T Taher, Faek R Jamali

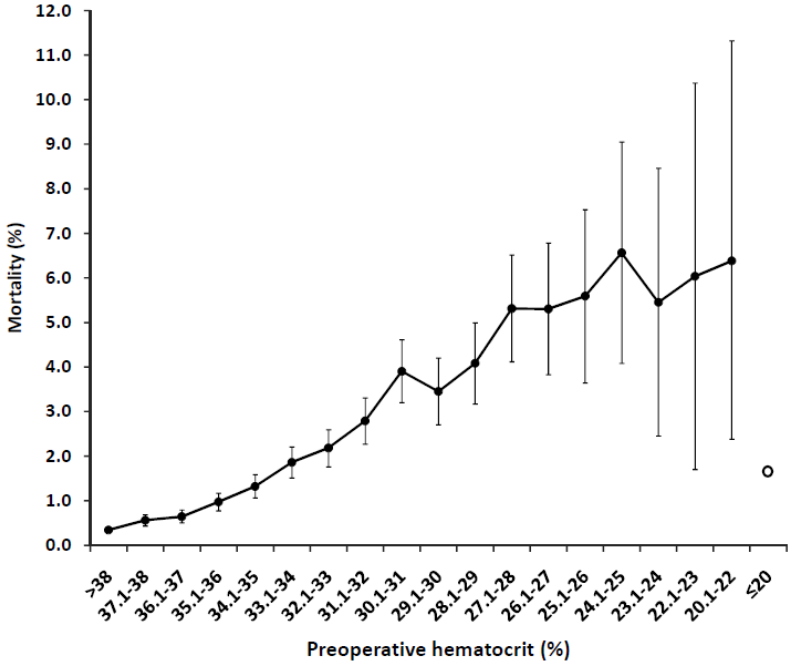
US Veterans Database (NSQIP) (n=227,425)

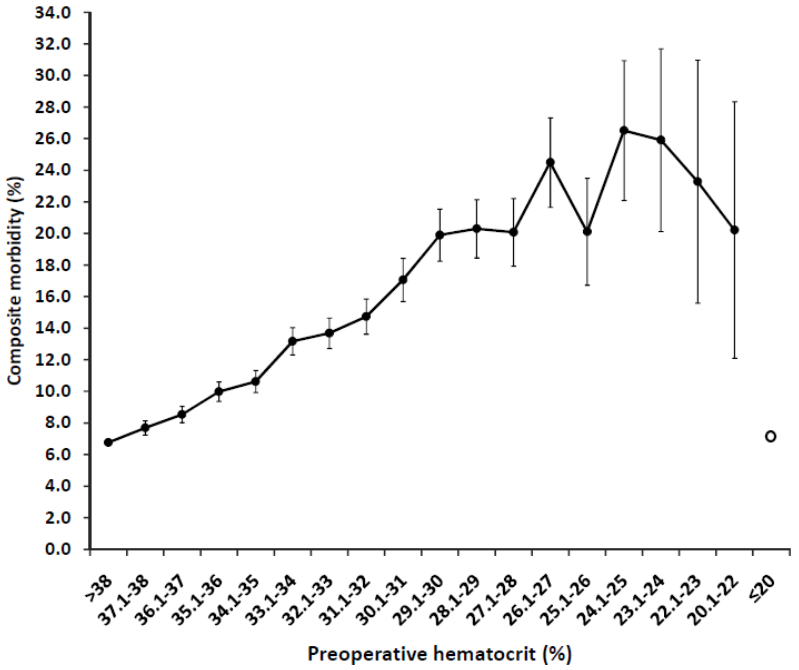
Anaemia (n=69,229; 30.4%)

30day mortality
30day composite morbidities (9 defined areas)

Multivariate regression
(9 defined subgroups)
(56 cofactors)

Effect of Anaemia on Outcome





Heart Online First, published on September 12, 2014 as 10.1136/heartjnl-2014-305856

Heart

ORIGINAL ARTICLE

A prospective observational cohort study to identify the causes of anaemia and association with outcome in cardiac surgical patients

Matthew Hung,[1] Erik Ortmann,[1] Martin Besser,[2] Pedro Martin-Cabrera,[2] Toby Richards,[3] Marcus Ghosh,[1] Fiona Bottrill,[4] Timothy Collier,[5] Andrew A Klein[1]

- January 2012 to 2013
- 200 anaemic cardiac surgical patients
- Blood and bone marrow analysis
- Primary outcome was days alive and out of hospital.

Causes of anaemia in cardiac surgical patients

- Folate/B12 deficiency 6%
- Renal failure 10%
- Iron deficiency 84%
  - Absolute iron deficiency 5%
  - Iron restriction (chronic disease) 79%

Treatment

- Oral Iron
  - Slow (2 – 3 months)
  - Poorly tolerated
  - absorption decreased by hepcidin therefore not effective in chronic disease
  - Effective in absolute iron deficiency

Treatment – oral iron

- At least 6-8 weeks before surgery
- Oral iron supplementation and nutritional advice may be appropriate.
- In iron deficient women, oral iron sulphate dose above 60 mg stimulates hepcidin release, which results in lower iron absorption from the next dose.
- Low-dose oral iron given on alternate days may maximise fractional iron absorption, increase dosage efficacy, reduce gastro-intestinal exposure to unabsorbed iron, and ultimately improve tolerance and adherence to treatment.
- Not effective in patients with inflammation or on-going blood loss

Treatment – oral iron

- Many patients will not respond to oral iron, especially those with functional iron deficiency and chronic illness or infection.
- Other patients will not tolerate oral iron due to gastro-intestinal side effects.
- Once oral iron has been commenced, the Hb should be measured, at least 4 weeks before surgery.
- In the absence of an increased Hb or if the patient is intolerant, iv iron is preferred.
- If < 6 weeks remains before surgery (not enough time for oral iron to work), intravenous iron may also be the most effective option.

Treatment

- Intravenous Iron
- Improves the anaemia-induced over-expression of hepcidin
- Effective in functional iron deficiency (anaemia of chronic disease)
- Excessive dose (exceeding transferrin iron-binding capacity) may promote free iron which can induce oxidant stress (?susceptibility to infection)
- Recent meta-analysis – effective at increasing Hb by 13 g/l, reduced risk for transfusion 0.74 (0.62 – 0.88) but increased risk of infection RR 1.3 (1.1-1.6)

Litton E et al. BMJ 2013; 347

Treatment – iv iron

- Intravenous iron is highly efficacious at replenishing iron stores and increasing Hb in anaemia due to iron deficiency with or without inflammation.
- A dose of 1000-1600 mg is sufficient in most surgical patients and can usually be given by slow infusion in one sitting or in two divided doses, depending on the preparation being used, over 15-30 minutes.
- Most patients feel better in three days, with a rapid Hb response (50% at 5 days, 75% at 10-14 days, maximal at 3 weeks).
- Data linking this to increased patient welfare, reduced peri-operative complications and length of hospital stay, and improved patient outcomes are incomplete.

Treatment

- Erythropoietin
- Recommended before orthopaedic surgery in Europe.
- Restricted by FDA to non-cardiac and non-vascular patients
- Concern about association with increased risk of postoperative thrombosis after spinal surgery
- Also some concern re. CVS and CVA (with higher Hb)
- Much more effective at lower dose if combined with iv iron

Inadequate Iron stores

- Inability to sustain erythropoiesis to recover from blood loss at operation.
- Indicated by the serum ferritin level; in a healthy adult, 1 $ng.l^{-1}$ ferritin reflects approximately 8 mg stored iron.
- As an example, a patient with a pre-operative ferritin <100 $ng.l^{-1}$ may not have enough iron reserves to recover from a 30-40 $g.l^{-1}$ Hb drop, while maintaining normal iron stores (ferritin >30 $ng.l^{-1}$).

Iron Deficiency

- True (absolute) iron deficiency without anaemia refers to a reduction in total body iron with normal Hb, as levels of erythroid iron are still sufficient for erythropoiesis.

Diagnosis

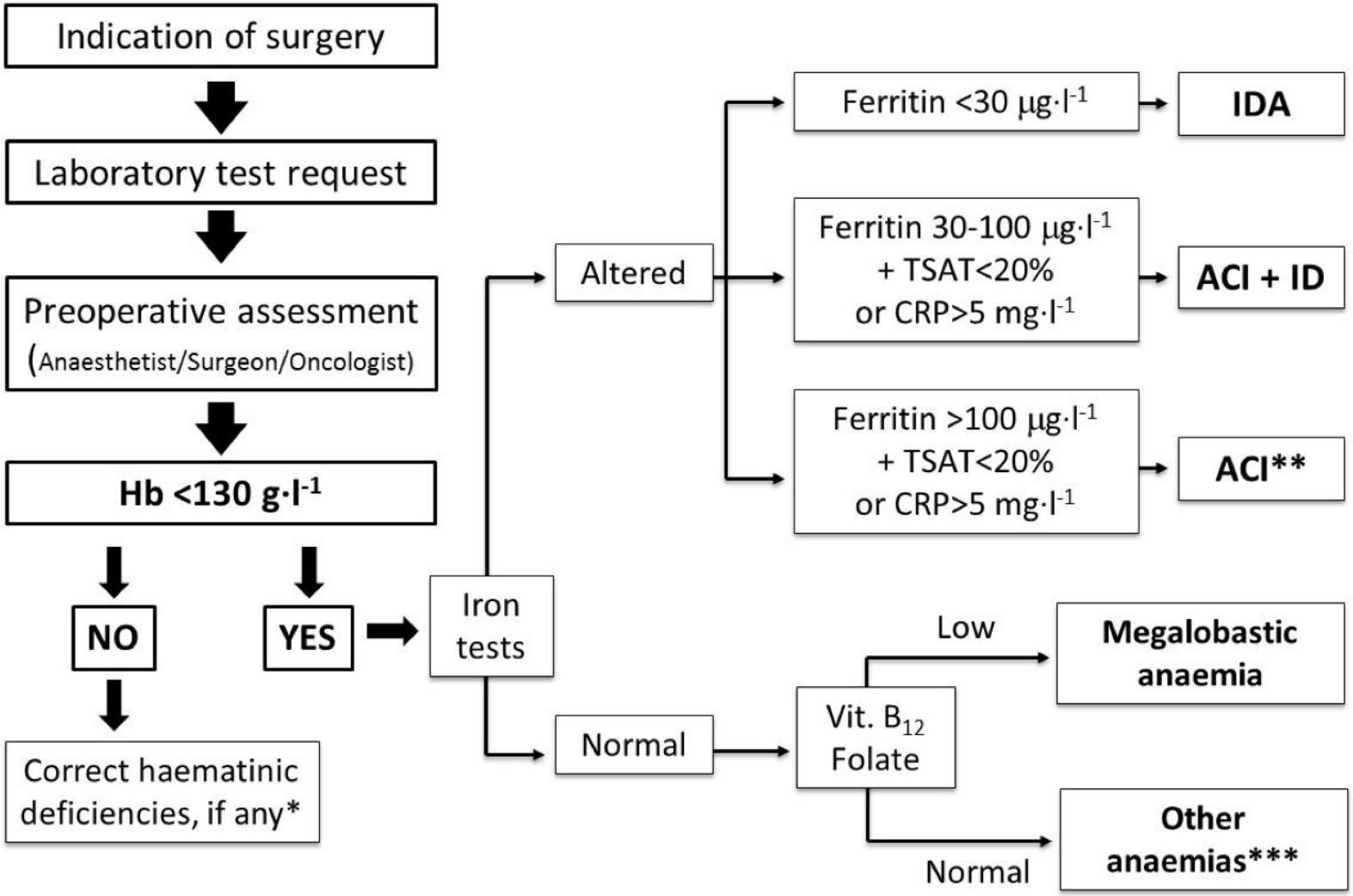
- A serum ferritin level <30 $\mu g \cdot l^{-1}$ is the most sensitive (92%) and specific (98%) cut-off level for the identification of **true iron deficiency** (with or without anaemia); no further laboratory work-up is needed.

Diagnosis

- In the presence of inflammation (CRP >5 mg.l-[1]) and/or TSAT < 20%
- Ferritin <100 µg.l^{-1} strongly suggests iron deficiency
- It also indicates inadequate iron stores for surgery during which moderate-to-high blood loss is expected.

Diagnosis

- Low reticulocyte Hb content (CHr <28 pg)
- Increase in hypochromic red cells (Hypo >5%, Low Density Hb),
- Ratio of serum transferrin receptor level to the log of ferritin (sTfr/log Ft), the so-called ferritin index. A ferritin index >2 indicates iron deficiency



ACI, anaemia of chronic inflammation (iron sequestration); ACI +ID, anaemia of chronic inflammation with true iron deficiency; CRP, C-reactive protein; IDA, iron deficiency anaemia; TSAT, transferrin saturation index

Delaying surgery

- Benign disease:
- In major surgery, blood loss > 500ml, patients should be informed about the relationship between anaemia, morbidity and mortality, and should be given the opportunity to postpone non-urgent surgery until their anaemia is investigated and treated.
- Several guidelines recommend postponing the operation for about four weeks to allow appropriate management of anaemia

Iron deficiency without anaemia

- Non-anaemic patients with iron deficiency or inadequate iron stores undergoing surgical procedures with expected moderate-to-high blood loss may benefit from pre-operative iron administration, to boost recovery from postoperative anaemia.
- Oral iron should be considered.
- Intravenous iron administration (e.g. 500 mg) if surgery is scheduled to take place < 4 wks or if the patient cannot tolerate oral iron

CAVIAR

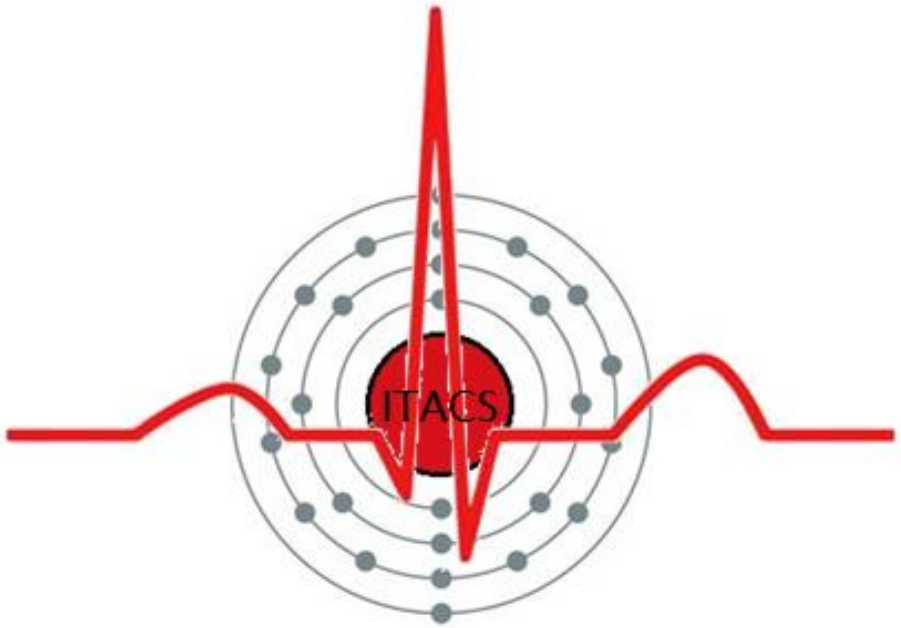
The CArdiac and Vascular surgery Interventional Anaemia Response study

Funded by ACTA, VASGBI and BJA via NIAA

12 centres recruiting patients

Functional outcomes before and after iv iron

Changes in Hepcidin due to surgery and iron administration



IV iron for Treatment of Anaemia before Cardiac Surgery

Funded by NHMRC

1000 patient RCT in Australia and UK (different formulations)

Staring to recruit in July (Australia) and December (UK)

Primary outcome – days alive and out of hospital

Clinic set-up

- Get FBC as soon as possible
- Hb<13 = clinic visit

- Full work up
- Intravenous iron on Day Ward
- 1 hour monitoring HR/SpO_2/BP

Conclusion

- Increasing incidence
- Many different causes
- Significant healthcare burden
- Large impact on outcomes
- Associated with increased mortality and morbidity
- Treatment is possible but will it improve outcome?
- ANAEMIA CLINICS