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PERIOPERATIVE ANEMIA

2019

Dr. Ion Chesov, MD, PhD, Associate Prof.

Conflicts of interests



Objectives

- Patient blood Management (PBM)
- Anemia – definition and risks
- Causes
- Pathophysiology
- Anemia assessment
- Clinical Management
- Transfusion thresholds
- Point of care testing
- Take home messages

Patient Blood Management



- Patient blood management is the timely application of evidence-based medical and surgical concepts design to maintain hemoglobin concentration, optimize homeostasis and minimize blood loss in an effort to improve patient outcome.

<https://www.sabm.org/>, accessed on 30.11.19

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<https://www.sabm.org/>, accessed on 30.11.19

PBM – Blood transfusion

- ◆ Severe malaria induced anemia in children
- ◆ Major trauma with exsanguination
- ◆ Major surgery in severely anemic patients without possibility of preoperative anemia correction
- ◆ Very severe intra- / postoperative anemia with signs of cardiovascular insufficiency

Lackritz, E. M. et al. Lancet (1992) 340: 524

English M. et al. Lancet (2002) 359: 494

Meremikwu M. et al. Cochrane Database Syst Rev 2000:CD001475

Spahn D. R. et al. Crit Care (2013) 17:R76

Spahn D. R. et al. Lancet (2013) 381: 1855

Wu W. C. et al. Ann Surg (2010) 252: 11

PBM – Blood transfusion

- ◆ Mortality ↑
- ◆ Length of hospital stay ↑
- ◆ Organ dysfunction ↑
 - ⇒ Lung injury (TRALI, TACO)
 - ⇒ Renal impairment
 - ⇒ Stroke
 - ⇒ Myocardial infarction
- ◆ Infection ↑
- ◆ Transfusion reactions
- ◆ Tumor growth promotion ↑
- ◆ Costs ↑
- ◆ Non-Hodgkin lymphoma ↑

PBM key points

Patient Blood Management

A clinical maxim to increase patient safety

Early detection and
treatment of
preoperative anaemia
in patients undergoing
surgery with a high
transfusion probability

Minimizing blood loss
and intensified use of
blood conserving
measures

Rational and
guideline-appropriate
use of allogenic blood
products



Anemia -WHO

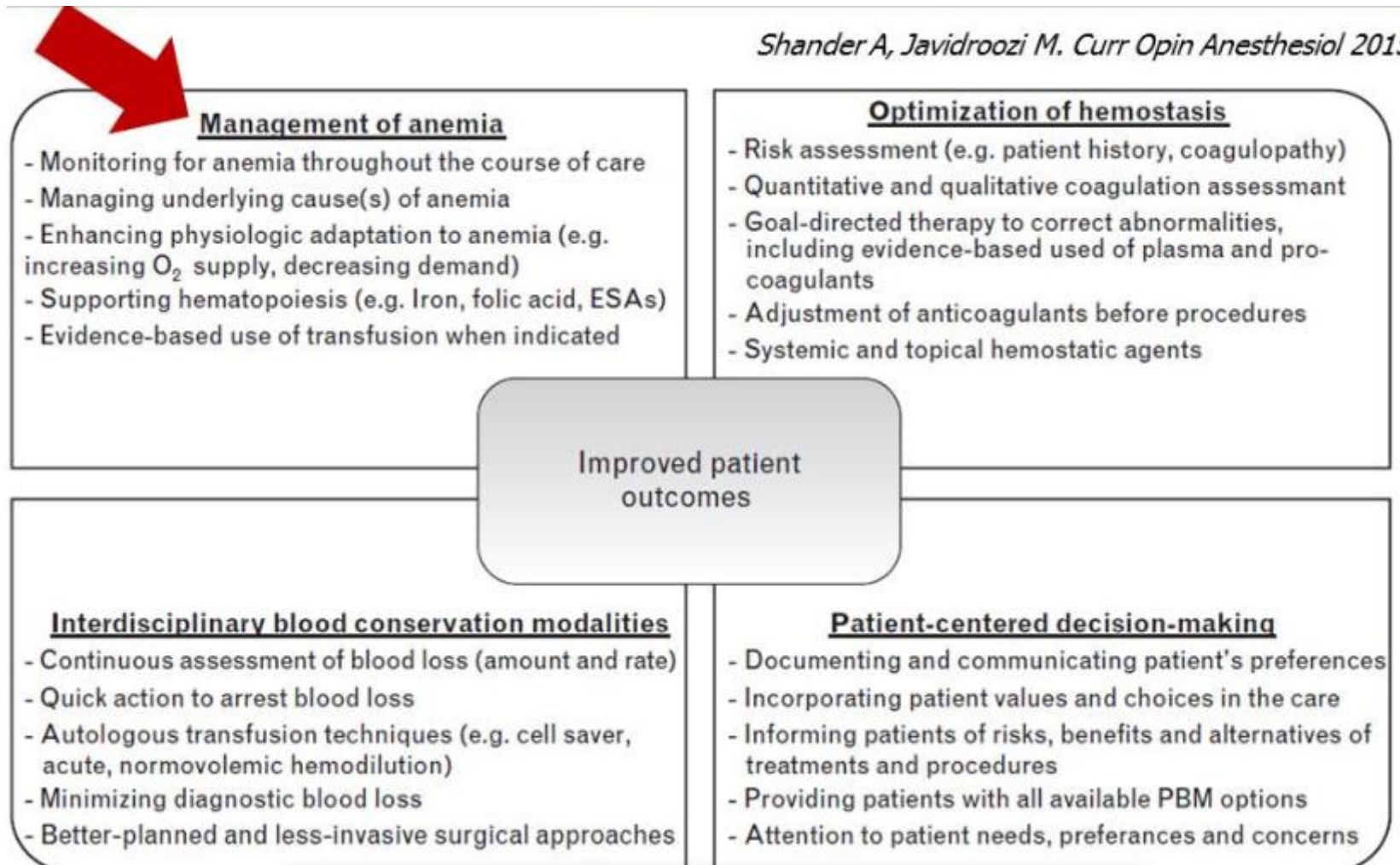
- Haemoglobin concentration of less than
 - 130 g dl¹ for men
 - 120 g dl¹ for non-pregnant women.

Table I Definitions of anaemia according to the WHO and the NCI schemes.
WHO, World Health Organization; NCI, National Cancer Institute

	WHO	NCI
Male	Hb <13 g dl ⁻¹	Hb <12 g dl ⁻¹
Female	Hb <12 g dl ⁻¹	Hb <11 g dl ⁻¹

Anemia & PBM

Shander A, Javidroozi M. Curr Opin Anesthesiol 2015



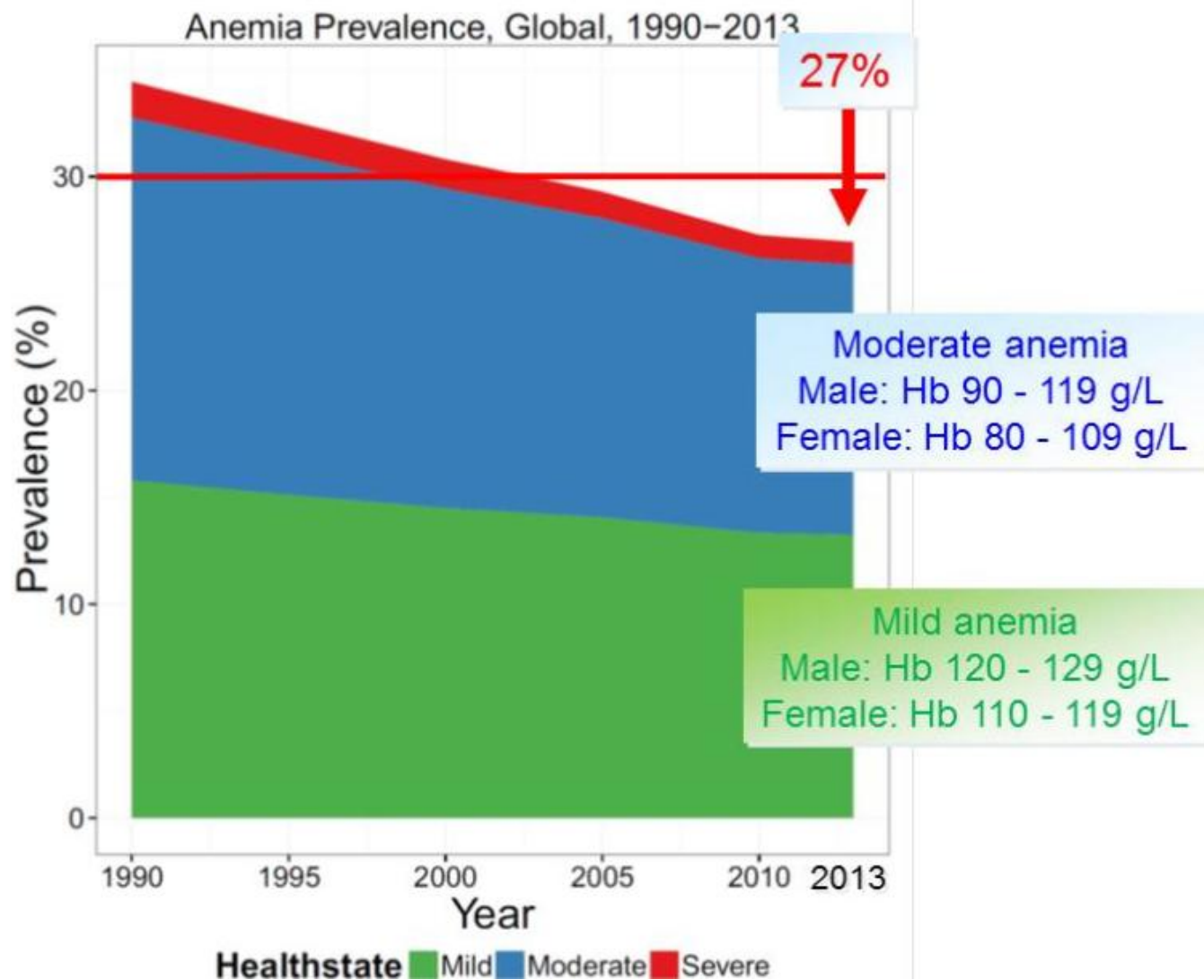
Anemia prevalence



- Up to 60% of surgical population
- 5–78% of patients requiring a surgical intervention

Shander A, AmJMed 2004; 116: 58S–69S

GA Hans, Continuing Education in Anaesthesia, Critical Care & Pain, 2013



Anemia - outcome

Anaesthesia

Peri-operative medicine, critical care and pain



Association
of Anaesthetists

Original Article | [Free Access](#)

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✉, T. J. Collier, M. S. Brar, C. Evans, G. Hallward, S. N. Fletcher, T. Richards, on behalf of the Association of Cardiothoracic Anaesthetists (ACTA)

First published: 18 March 2016 | <https://doi.org/10.1111/anae.13423> | Cited by: 25

Anemia - outcome

- Higher mortality -**2 times more likely to die**
- Higher transfusion requirements for small haemoglobin changes (10g/dL)
- Longer hospital stays (median 2 days)
- Death linked to severity of anaemia and to gender

Anemia - outcome

- Increase risk of AKI .
- Poorer surgical outcomes.
- Increase perioperative blood transfusion
- Haematocrit less 39% was associated with an increased risk of 30 day postoperative mortality and cardiac events.

Arora P et, al, J Cardiothorac Vasc Anesth 2012

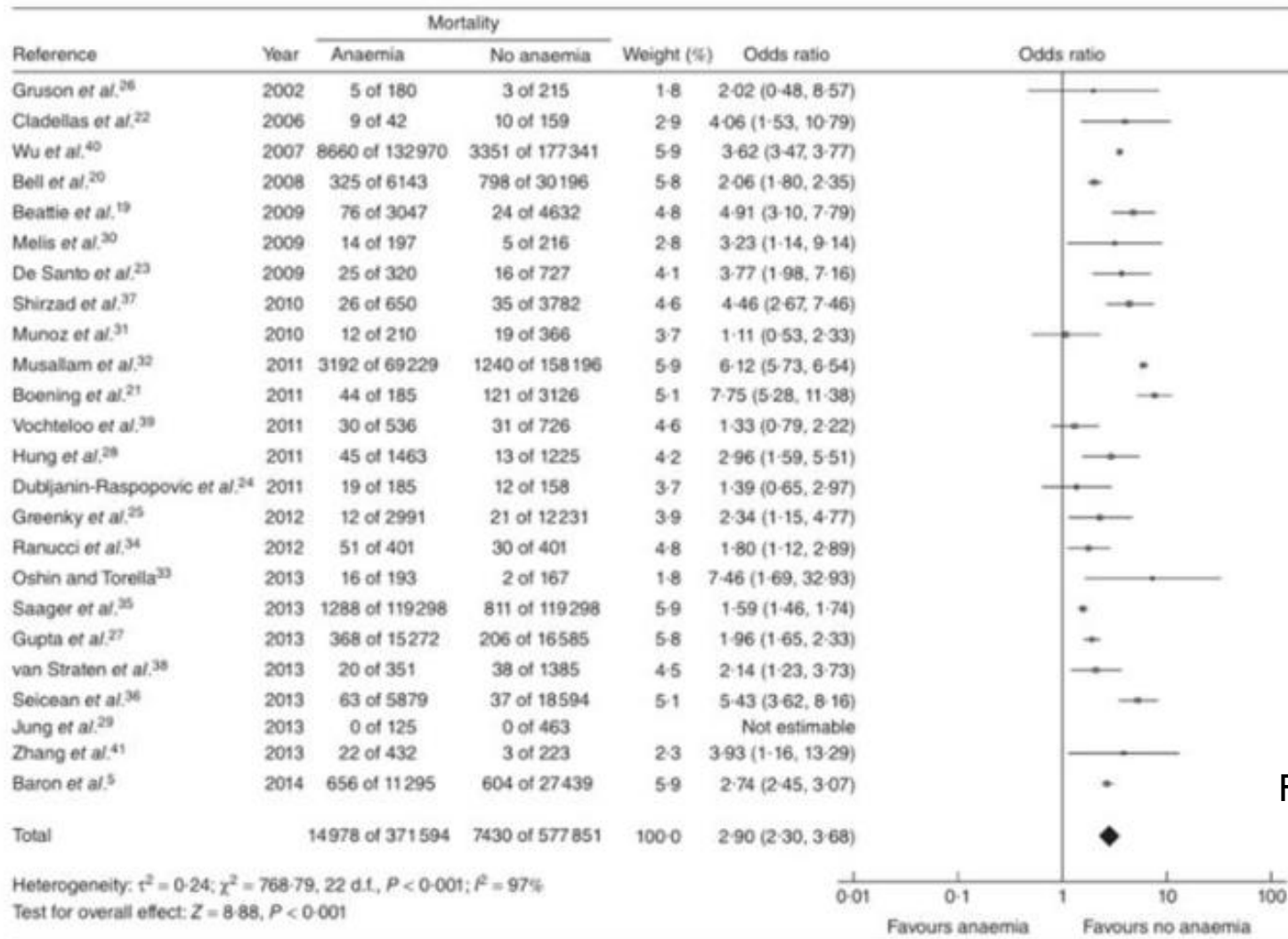
Browning RM et al, Aust N Z J Obstet Gynaecol 2012

David O et al Anaesth Intensive Care 2013

Klein et al. Anaesthesia June 2016

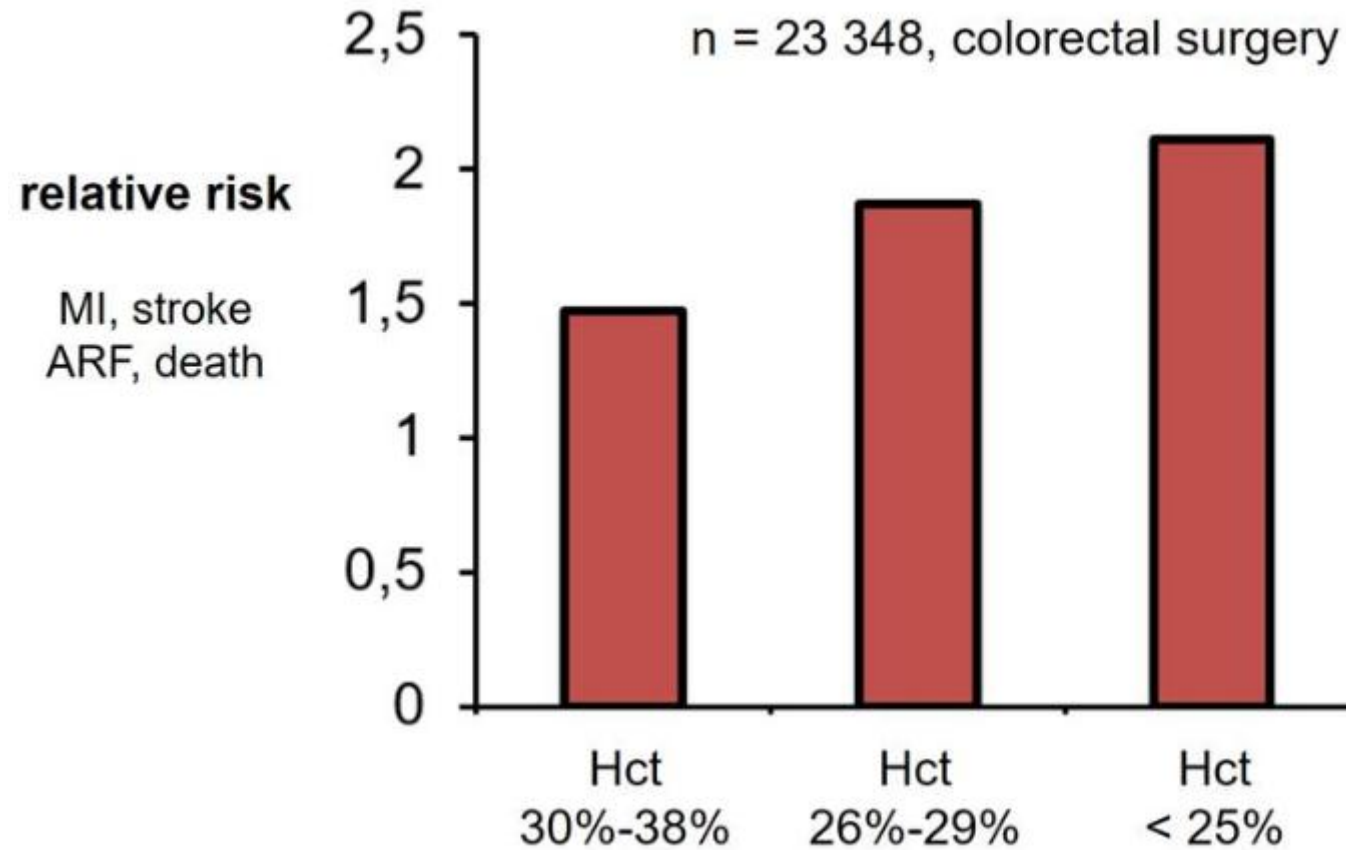
Wu W et al, J Am Med Assoc 2007; 22: 2481–8

Pre-op anemia

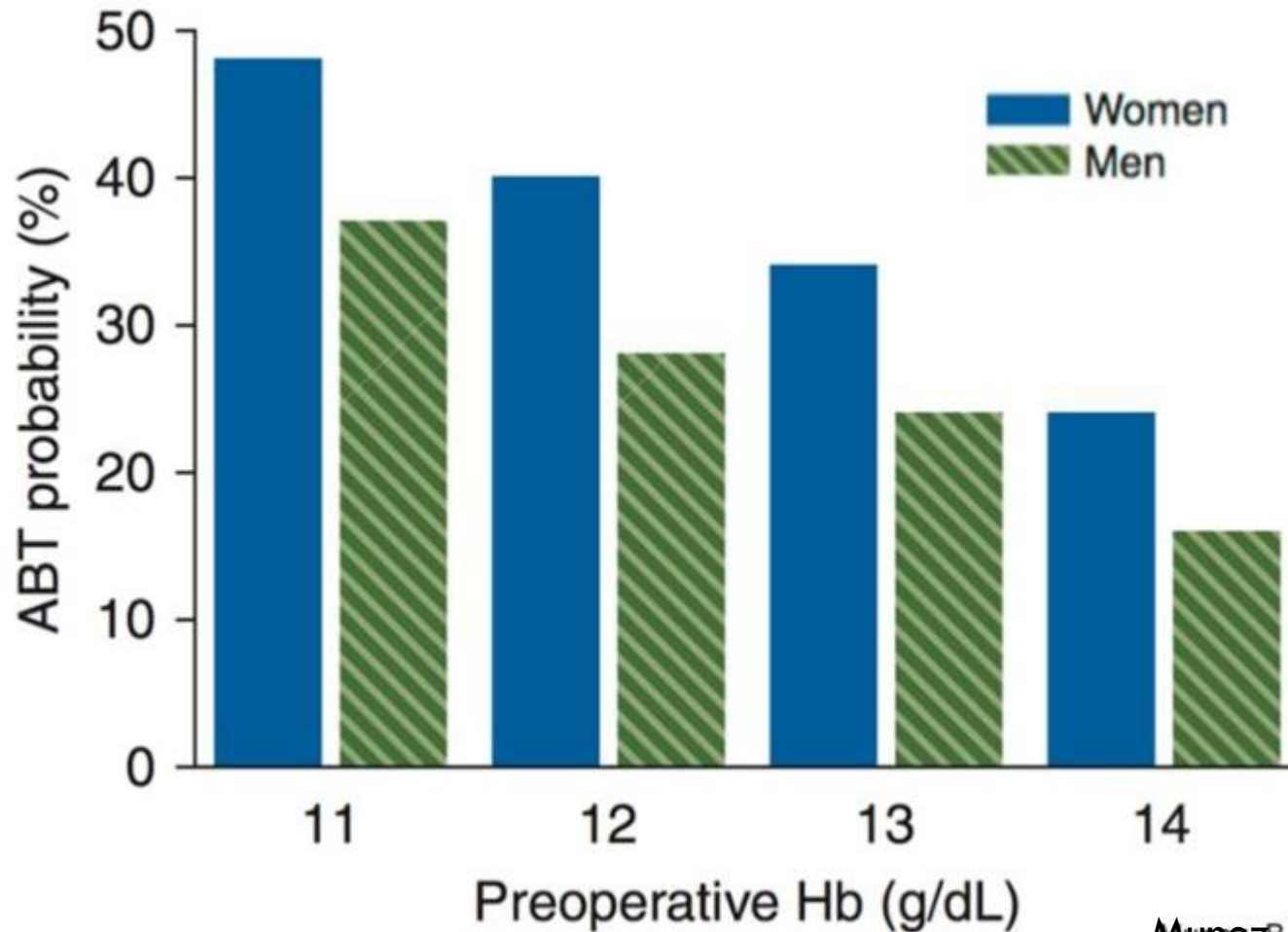


Fowler, BJS, 2015

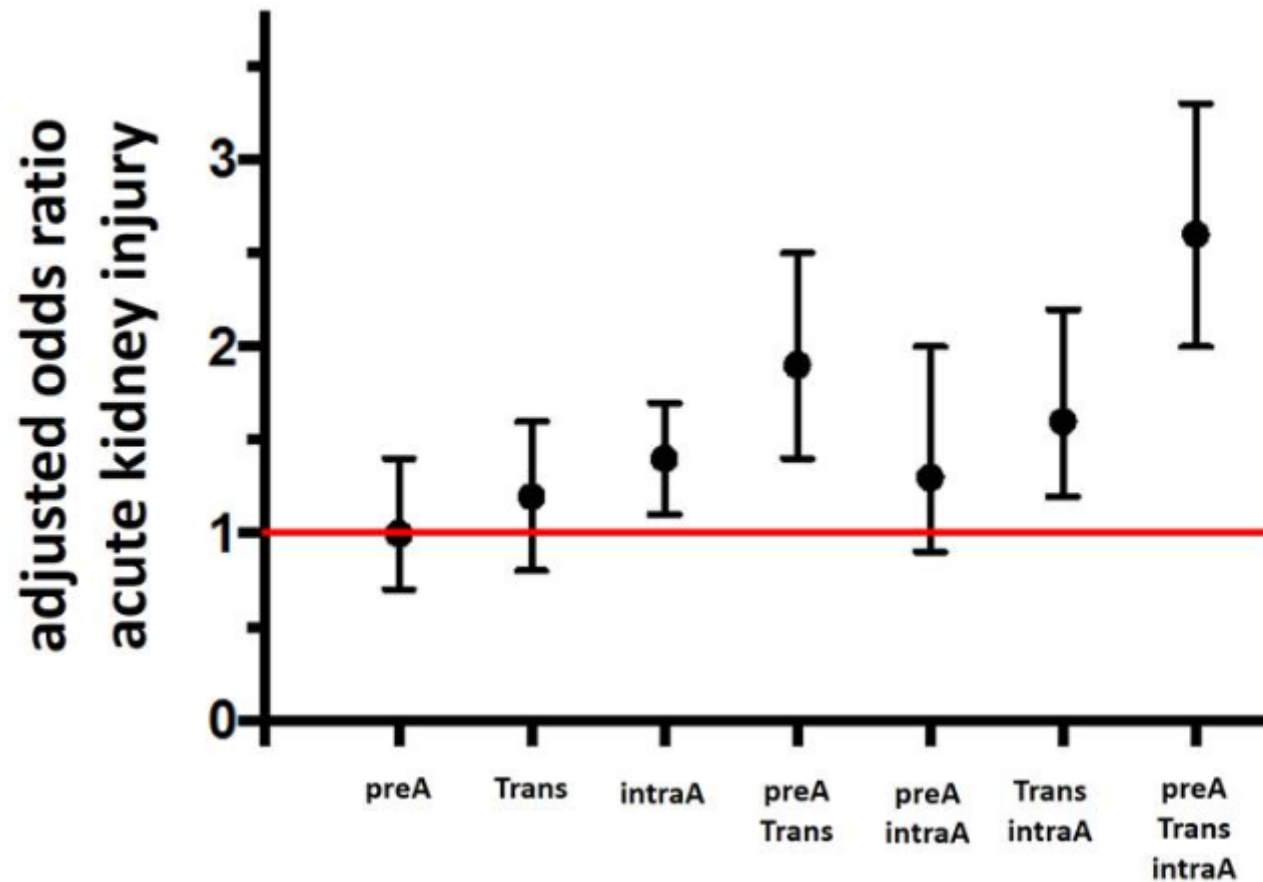
Pre-op anemia



Anemia -Transfusion



Anemia and Transfusion



Anemia and Transfusion

Anaemia Blood loss Transfusion



Ranucci M et al. Ann Thorac Surg 2013;96:478-85

Pathophysiology

□ DO_2 CO SpO_2 Hb SaO_2 PO_2 PaO_2 PO

The diagram shows the equation for oxygen delivery (DO_2) inside a rounded rectangular box. Five labels with arrows point to the variables in the equation:

- Oxygen delivery**: Points to DO_2 on the left side of the equation.
- Cardiac output**: Points to \dot{Q} (represented as \dot{Q} in the image) in the middle of the equation.
- Hemoglobin**: Points to Hb on the right side of the equation.
- Arterial O_2 saturation**: Points to SaO_2 on the right side of the equation.
- Amount of dissolved O_2 in the blood**: Points to PaO_2 on the right side of the equation.

$$\text{DO}_2 = \dot{Q} \times (\text{Hb} \times \text{SaO}_2 \times 1.34 + (\text{PaO}_2 \times 0.003))$$

Fig. 1. Equation for oxygen delivery.

Pathophysiology

Table 2 Impact of anaemia on oxygen delivery. Hb, haemoglobin; CaO₂, arterial blood oxygen content; DO₂, oxygen delivery to tissue; CO, cardiac output

Parameter	Hb 15 g dl ⁻¹	Hb 7.5 g dl ⁻¹
Inspired oxygen (%)	21	21
PaO ₂ (kPa)	12	12
Sats (%)	98	98
Dissolved oxygen (ml litre ⁻¹)	3	3
Hb-bound oxygen (ml litre ⁻¹)	197	98
Total CaO ₂ (ml litre ⁻¹)	200	101
DO ₂ if CO 5 litre min ⁻¹ (ml min ⁻¹)	1000	505

Pathophysiology

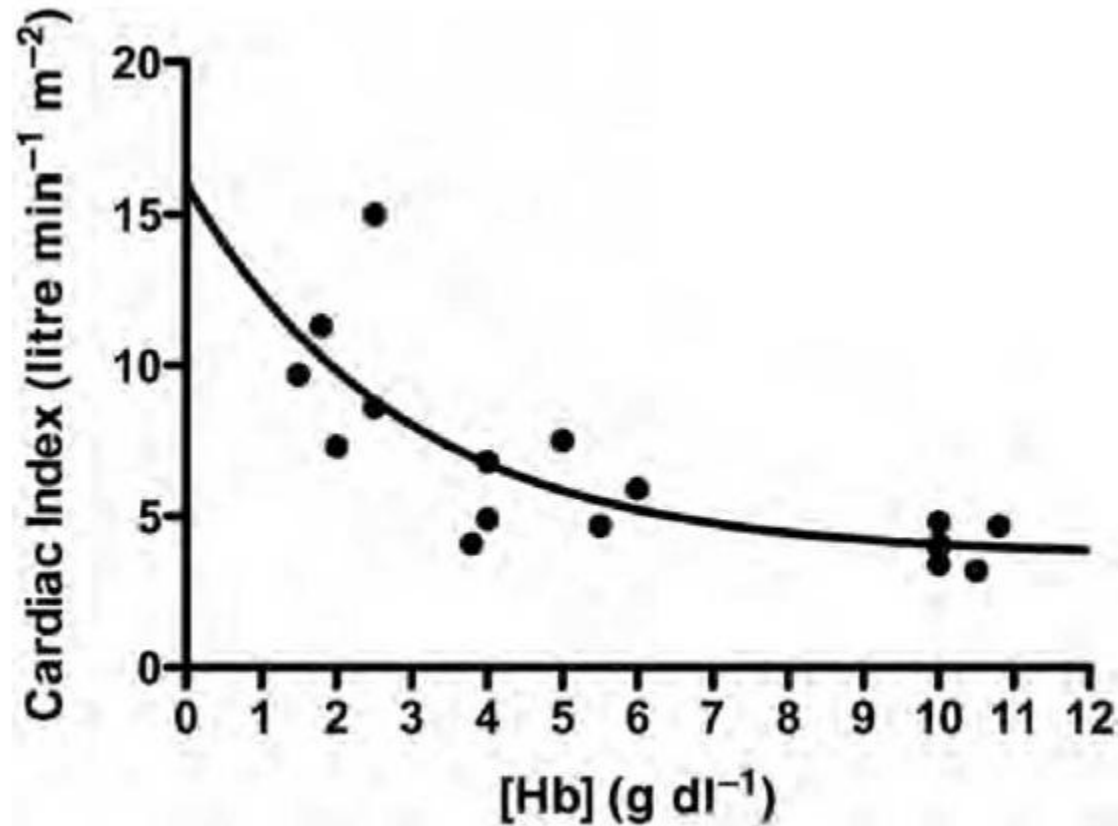


Fig 1 Effect of anaemia on cardiac index. Derived from data from Roy and colleagues.

Pathophysiology

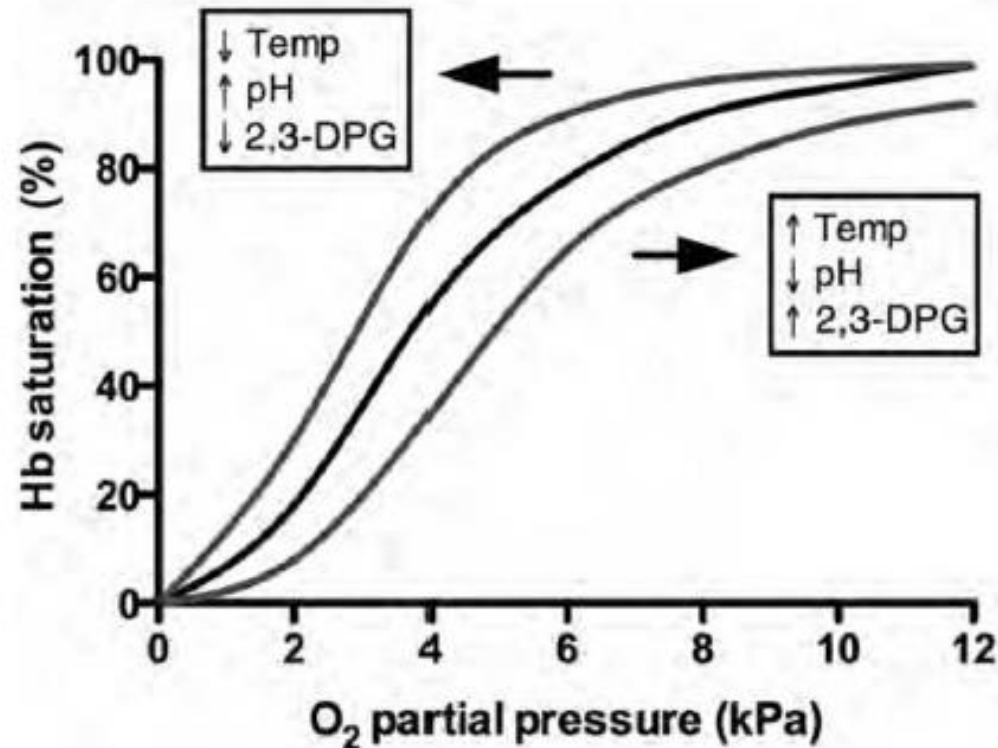


Fig 2 Haemoglobin–O₂C. Temp, temperature; 2,3-DPG, 2,3-diphosphoglycerate.

Pathophysiology

Table 3 Causes of imbalance between oxygen supply and demand in the perioperative period

Reduced oxygen delivery

- Reduction in CO due to hypovolaemia or cardiac depression by drugs, e.g. anaesthetic agents
- Decrease in oxygen saturation due to atelectasis, postoperative pneumonia, thromboembolic event
- Further reduction in haemoglobin as a consequence of surgical blood loss or inhibition of erythropoiesis by the altered cytokine milieu
- Increased affinity of haemoglobin for oxygen due to the leftward shift in the ODC by hypothermia

Increased oxygen requirements

- Pain
 - Fever
 - Shivering
 - The stress response
-

Causes

- Microcytic anaemia:
 - iron deficiency
 - congenital haemoglobinopathies
 - sideroblastic anaemia
 - Vitamin B6 deficiency

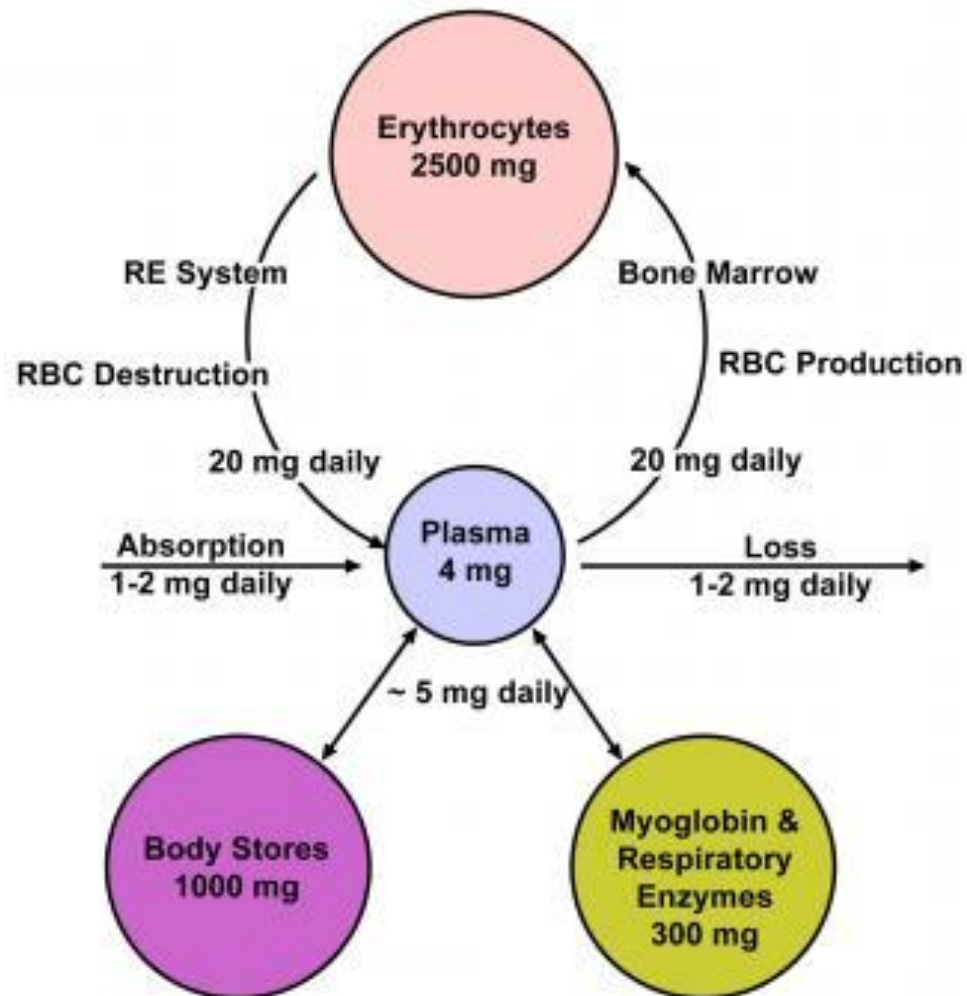
The most common cause in the surgical population is **iron deficiency** *,**

*. World Health Organisation 2014

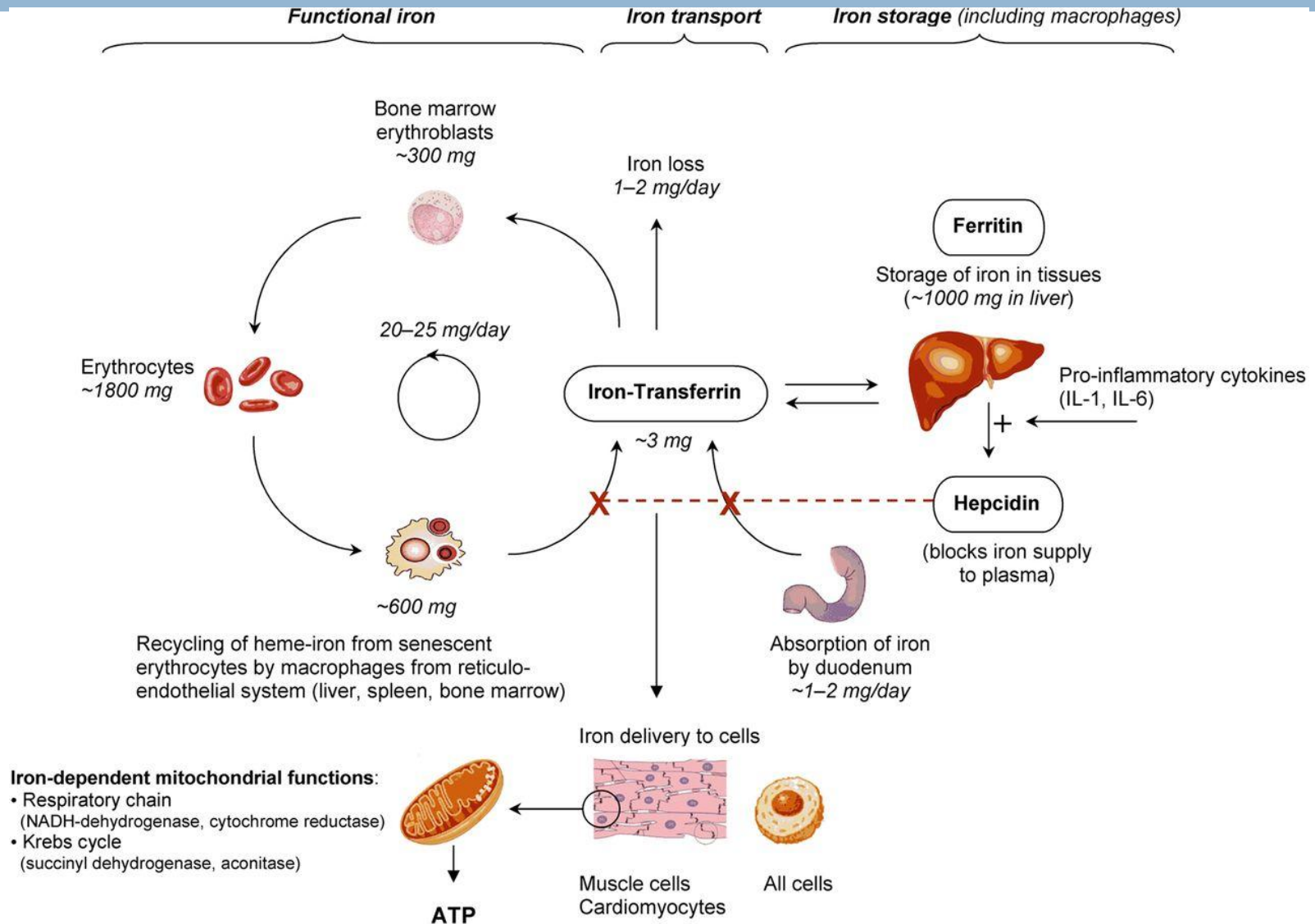
** . Preoperative anaemia Clevenger et al Anaesthesia 2015

- Normocytic anaemia
 - chronic disease, aplastic and sickle cell anaemia,
 - haemolysis,
 - pregnancy,
 - riboflavin, and pyridoxine deficiency.

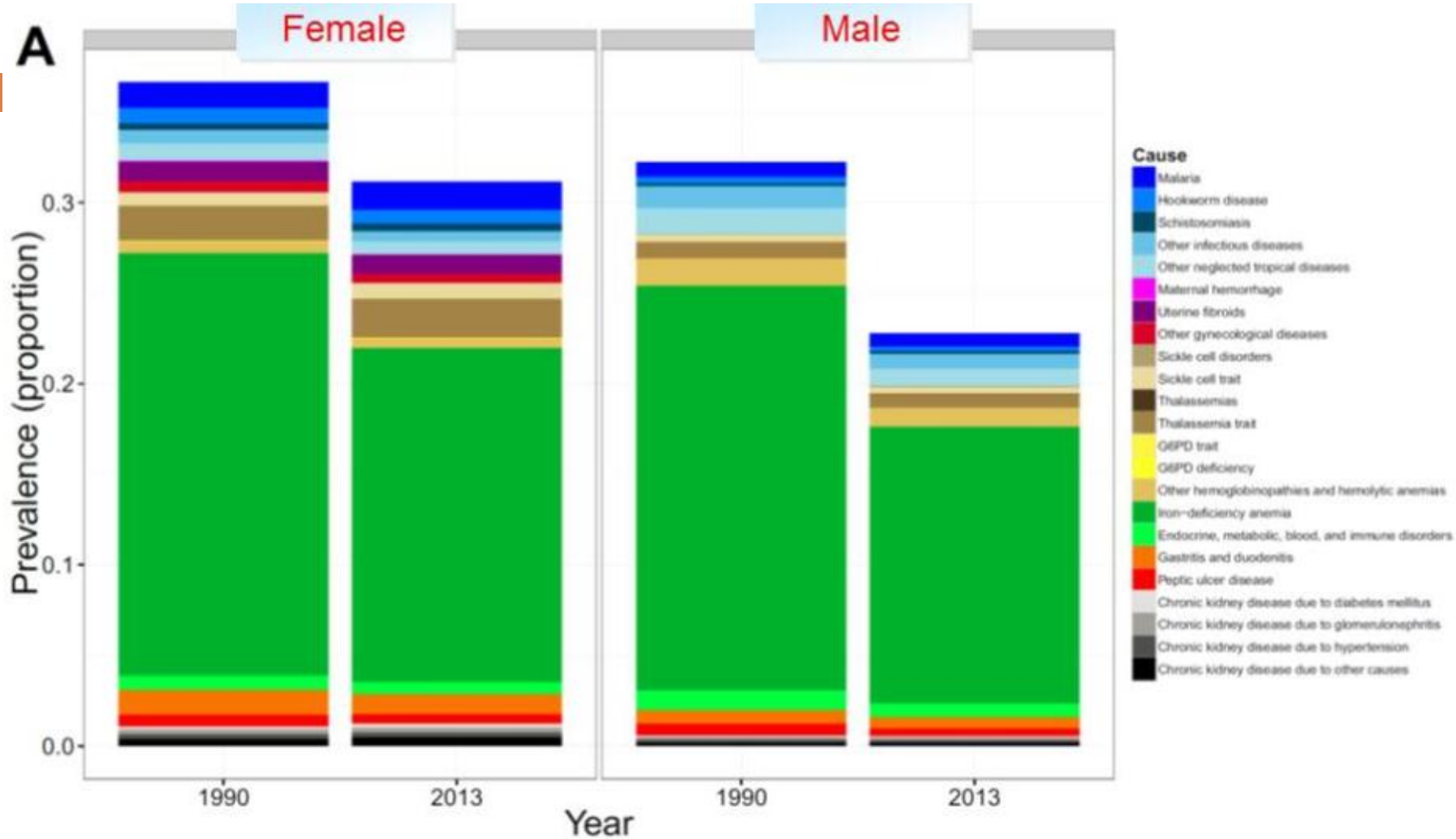
Iron deficiency

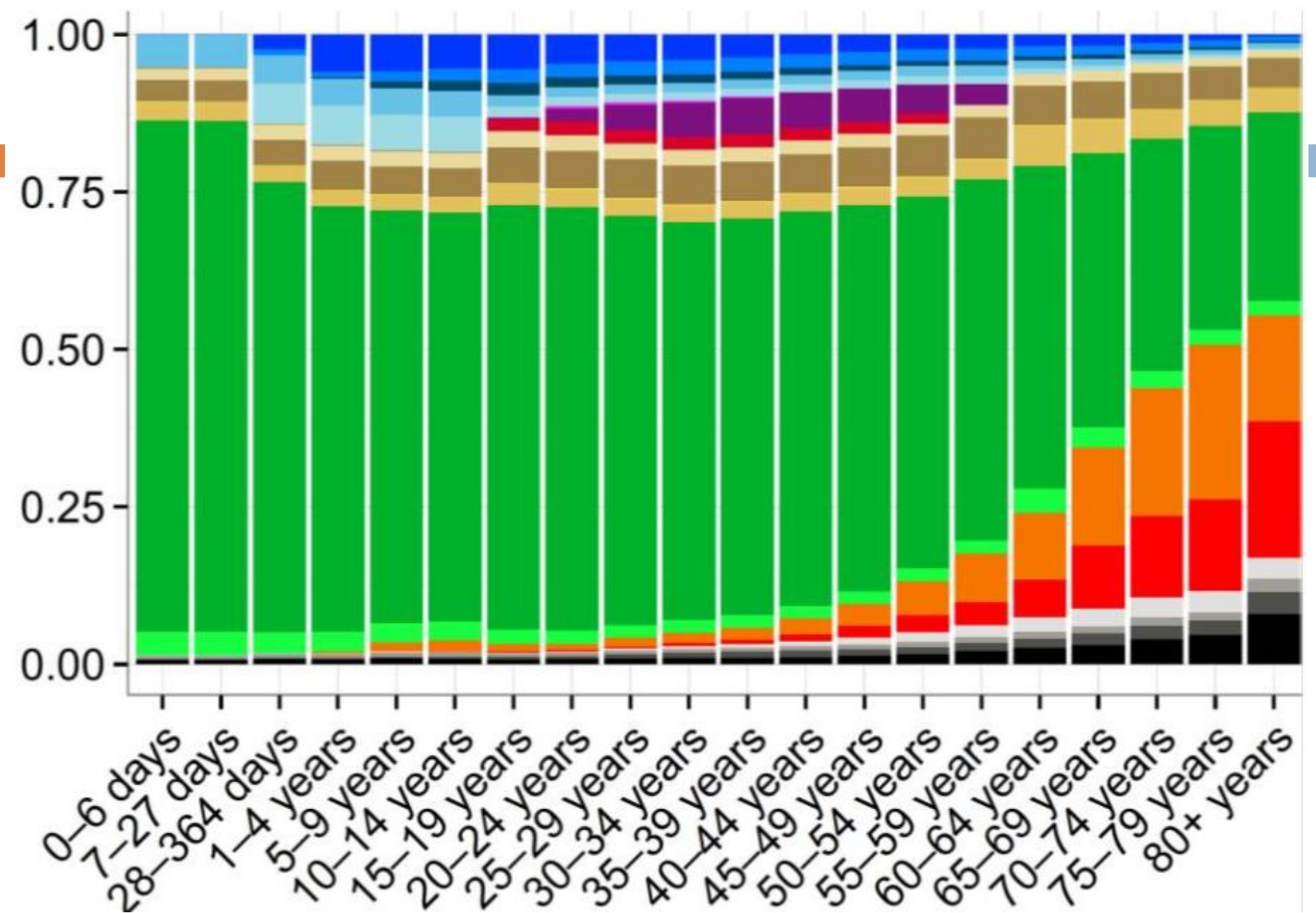


Inflammatory diseases

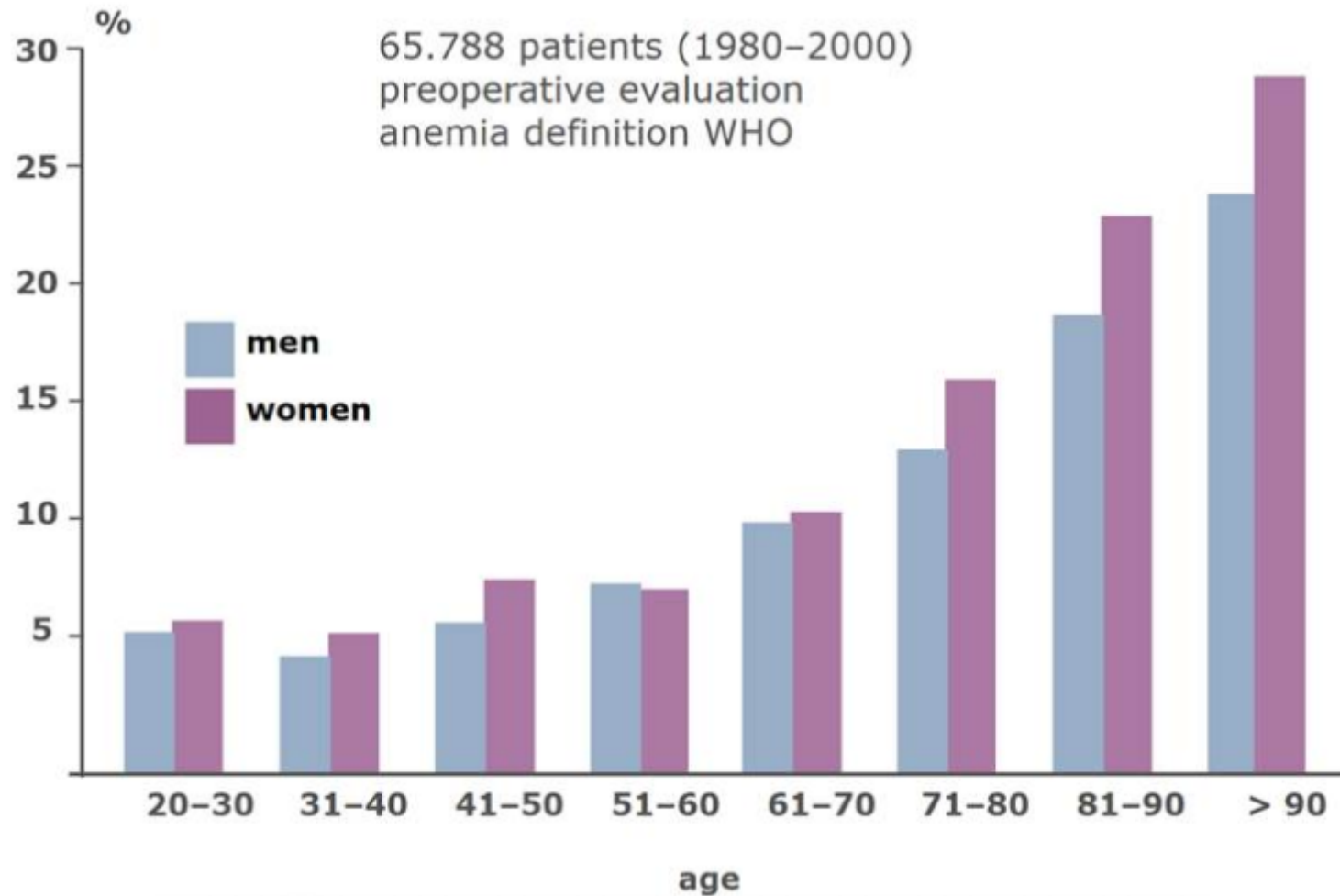


Causes



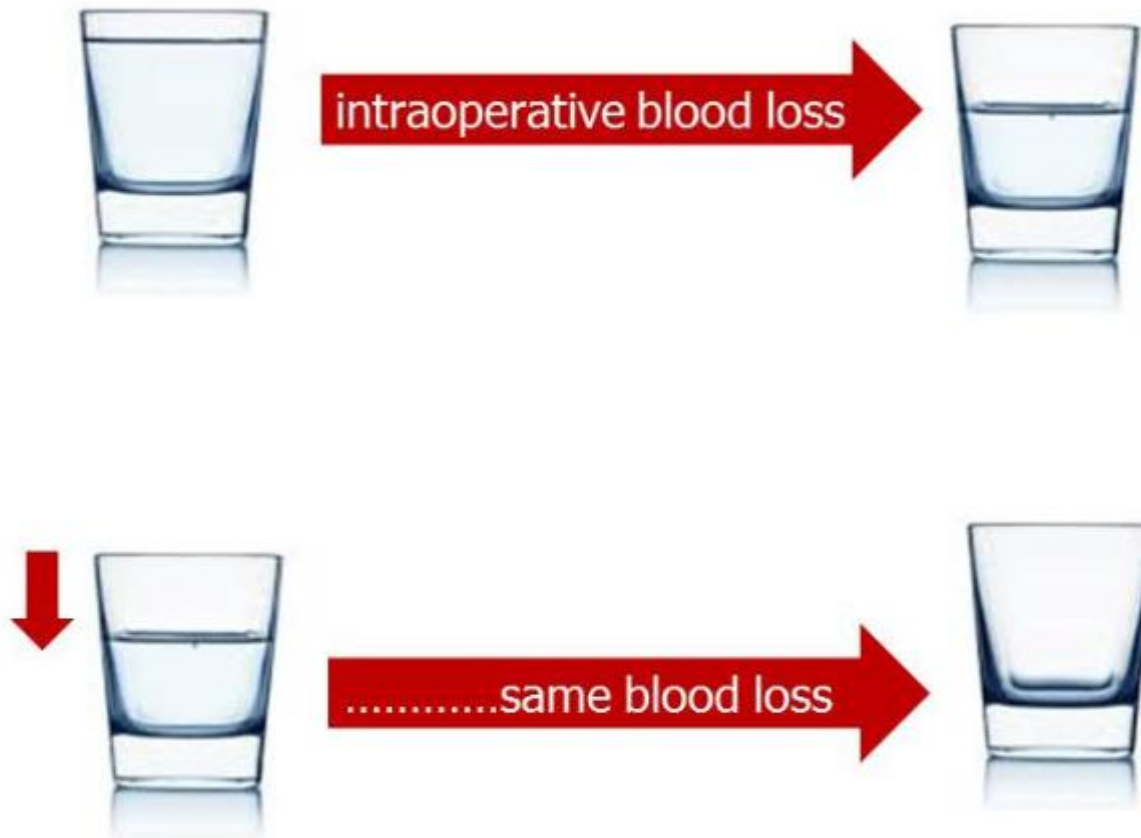


Age



Kuller, Anästhesist, 2001

Full glass



Clinical approach

EJA

Eur J Anaesthesiol 2017; **34**:332–395

GUIDELINES

Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology

First update 2016

Sibylle A. Kozek-Langenecker, Aamer B. Ahmed, Arash Afshari, Pierre Albaladejo, Cesar Aldecoa, Guidrius Barauskas, Edoardo De Robertis, David Faraoni, Daniela C. Filipescu, Dietmar Fries, Thorsten Haas, Matthias Jacob, Marcus D. Lancé, Juan V.L. Pitarch, Susan Mallett, Jens Meier, Zsolt L. Molnar, Niels Rahe-Meyer, Charles M. Samama, Jakob Stensballe, Philippe J.F. Van der Linden, Anne J. Wikkelsø, Patrick Wouters, Piet Wyffels and Kai Zacharowski

Anemia management



monitoring for anaemia throughout the course of care
correction of underlying causes(s) of anaemia
supporting haematopoiesis (e.g. iron, folic acid, ESAs)

Have a plan

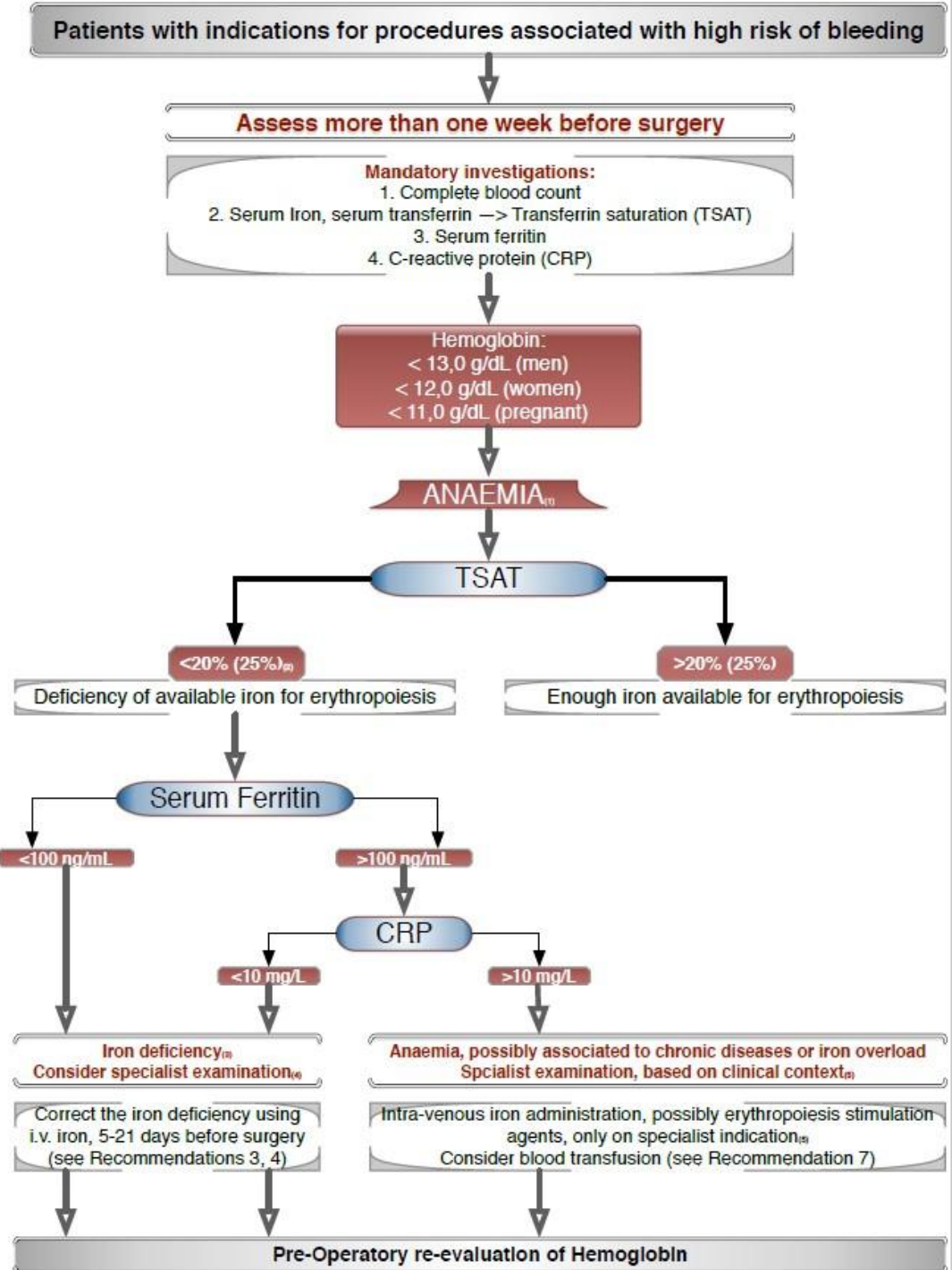


We recommend the application of intervention algorithms incorporating predefined triggers and targets based on monitoring to guide individualized ... intervention

(1C)

Assessment

- Medical history
- Full blood count



Alternative approach

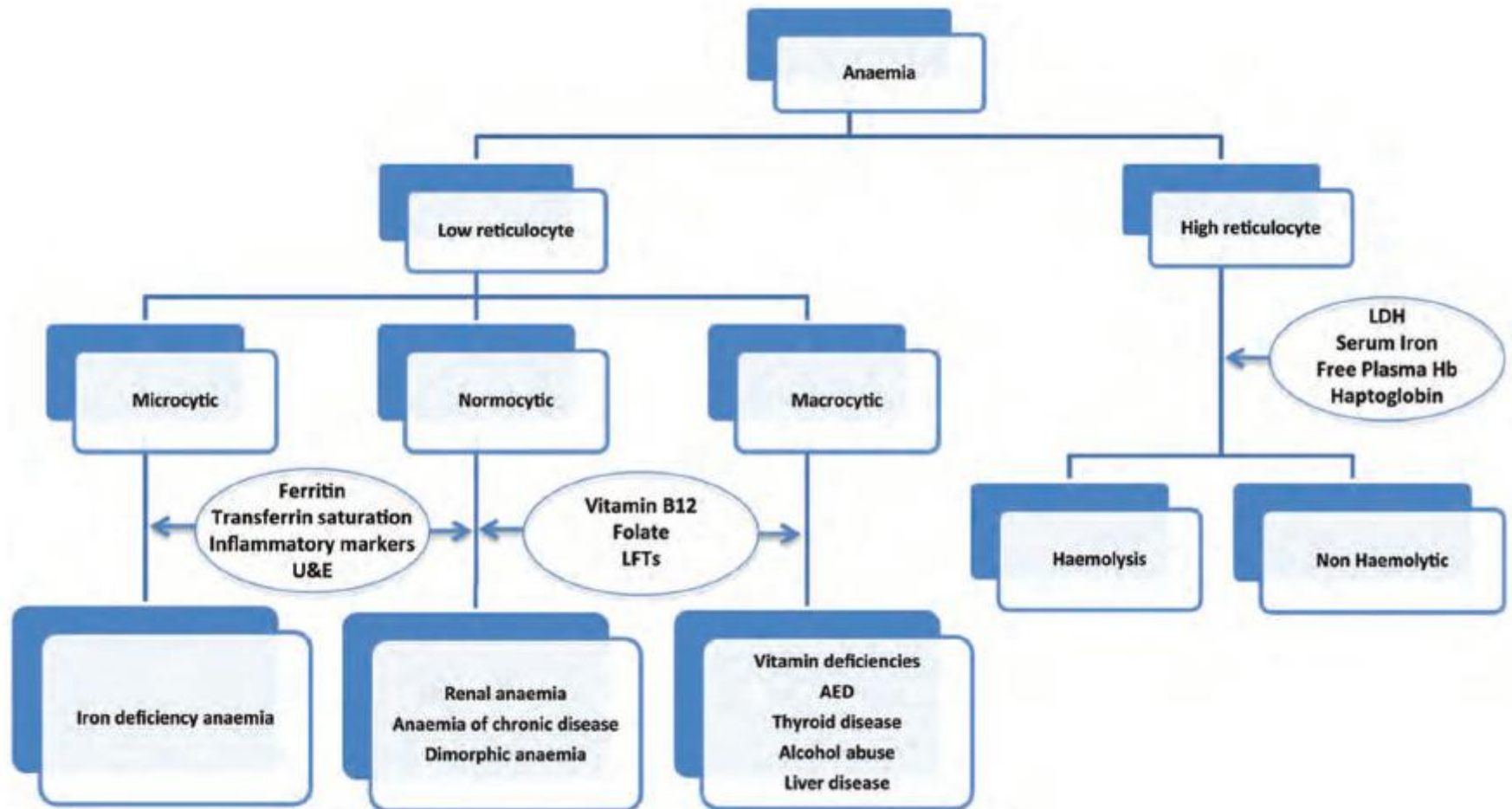


Fig 3 Suggested algorithm for the aetiological diagnosis of preoperative anaemia. U&E, urea and electrolytes; LFTs, liver function tests; LDH, lactate dehydrogenase; AED, anti-epileptic drugs.

Chronic disease vs. Iron deficiency

	Iron deficiency anemia (IDA)	Anemia of chronic disease (ACD)	Anemia of mixed origin (AMO)
Serum ferritin	↓	N or ↑	N
Serum iron	↓	↓	↓
Transferrin	↑	↓ or N	↓
Transferrin saturation	↓	↓	↓
Mean corpuscular volume	↓	↓ or N	↓ or N
Iron-binding capacity	↑	↓	↓ to low N
Serum transferrin receptor	↑	N	↑ or N
Serum transferrin receptor index	High (>2)	Low (<1)	High (>2)
C-reactive protein	N	↑	↑
Erythropoietin	↑	N or slightly ↑	↑ or N
Cytokine levels	N	↑	↑

ESA - guidelines

Preoperative anaemia in adults and children appears to be a strong predictor for perioperative transfusion across various types of conditions and surgeries and may be associated with adverse events.

B

We recommend that patients at risk of bleeding are assessed for anaemia 3 to 8 weeks before surgery.

1C

ESA - guidelines

We recommend that patients at risk of bleeding are assessed for anaemia 3 to 8 weeks before surgery. 1C

Theusinger OM et al. Blood Transfus 2014; 12:195–203.

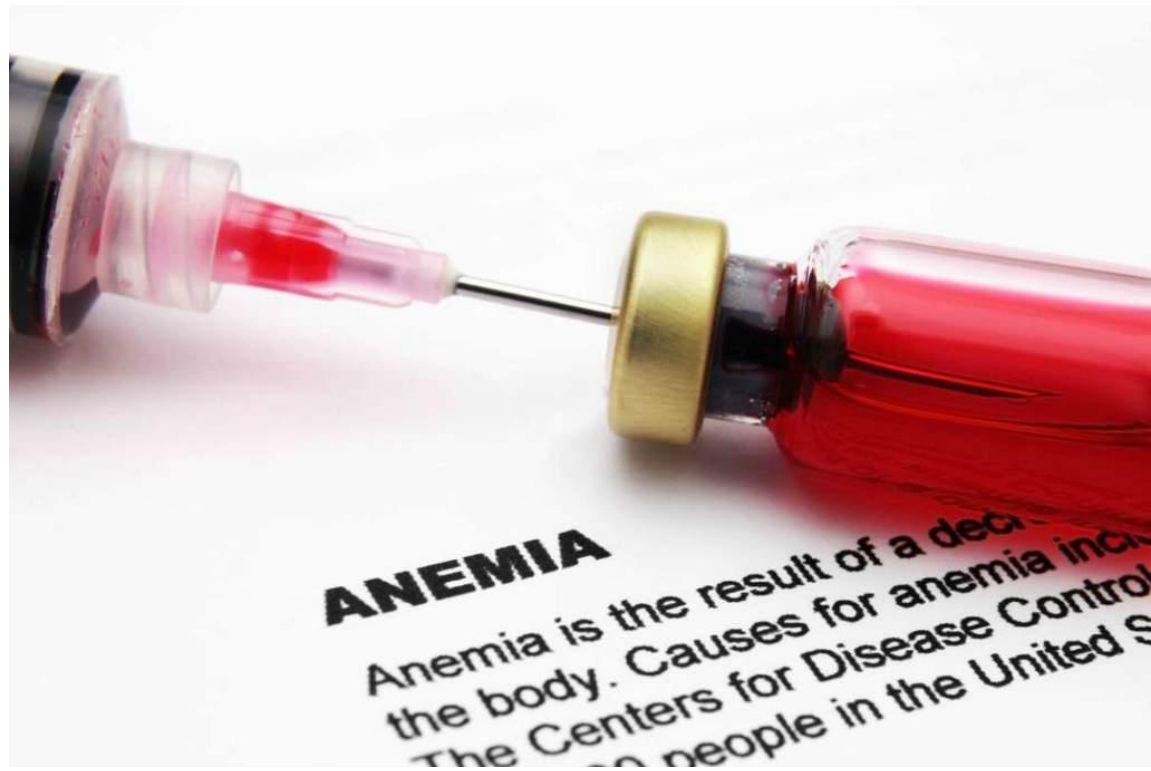
Enko D et al. Anemia 2013; 2013:641876.

Harwin SF et al. Hip Int 2014; 24:69–76.

Qureshi M et al. Transfusion 2012; 52:2063–2064.

ESA - guidelines

If anaemia is present, we recommend identifying the cause (iron deficiency, renal insufficiency or inflammation). 1C



ESA - guidelines

□ Treat iron deficiency

We recommend treating iron deficiency with iron supplementation. 1B

We recommend the use of intravenous iron in preference to oral iron. 1C



Iron supplementation

IV: earlier and more robust recovery of Hb

Lin DM, Lin ES, Tran MH.

Efficacy and safety of erythropoietin and intravenous iron in perioperative blood management: a systematic review.

Transfus Med Rev 2013; 27:221–234.

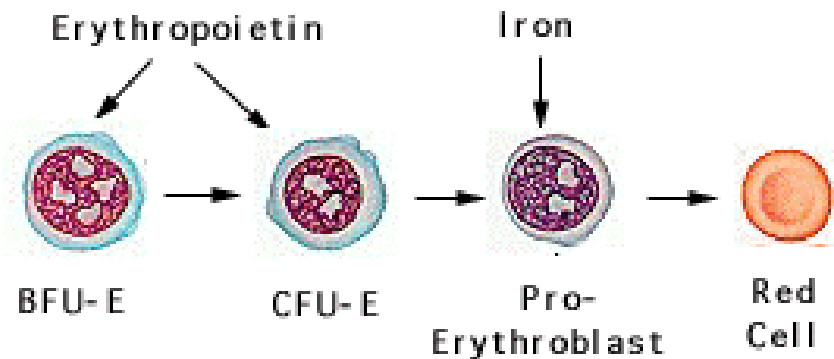
Leahy MF, Roberts H, Mukhtar SA, et al.

A pragmatic approach to embedding patient blood management in a tertiary hospital.

Transfusion 2014; 54:1133–1145.

ESA - guidelines

*If other causes of anaemia have been excluded or treated, we suggest erythropoietin-stimulating agents. **2B***



ESA's efficacy

increase in Hb + reduced RBC requirements

Alsaleh K, Alotaibi GS, Almodaimegh HS, et al.

The use of preoperative erythropoiesis-stimulating agents (ESAs) in patients who underwent knee or hip arthroplasty: a meta-analysis of randomized clinical trials.

J Arthroplasty 2013; 28:1463–1472.

Lin DM, Lin ES, Tran MH.

Efficacy and safety of erythropoietin and intravenous iron in perioperative blood management: a systematic review.

Transfus Med Rev 2013; 27:221–234.

ESA's efficacy

effective in knee and hip arthroplasty with preoperative Hb 10-13 g/dl without iron deficiency or after iron supplementation

Doodeman HJ, van Haelst IM, Egberts TC, et al.

The effect of a preoperative erythropoietin protocol as part of a multifaceted blood management program in daily clinical practice (CME).

Transfusion 2013;53:1930–1939.

van Haelst IM, Egberts AC, Doodeman HJ, et al. Occurrence and determinants of poor response to short-term preoperative erythropoietin treatment.

Acta Anaesthesiol Scand 2013; 57:350–357.

ESA-guidelines



If autologous blood donation is performed, we suggest treatment with iron and/or erythropoietin-stimulating agents to avoid preoperative anaemia and increased overall transfusion rates. 2C

Autologus blood donation

<http://www.oegari.at>

We recommend preoperative autologous blood donation in procedures involving special groups of patients **(e.g. rare blood types, special antibody constellation)** or at the express **wish of the patient** if there is a high transfusion probability.

ESA guidelines



*In patients with preoperative anaemia, we recommend the use of combined therapy with intravenous iron and erythropoietin along with a restrictive transfusion policy. **1C***

Iron + ESA's

effective in knee and hip arthroplasty with preoperative Hb 12 or 13 g/dl:

- ✓ fewer transfusions
- ✓ shorter LOS
- ✓ less readmission

Kotze A, Carter LA, Scally AJ.

Effect of a patient blood management programme on preoperative anaemia, transfusion rate, and outcome after primary hip or knee arthroplasty: a quality improvement cycle.

Br J Anaesth 2012; 108:943–952.

Iron +ESA's + Folate (3-4 weeks)

in anaemic patients
refusing allogeneic transfusions

Harwin SF, Pivec R, Naziri Q, et al.

Is total hip arthroplasty a successful and safe procedure in Jehovah's Witnesses?
Mean five-year results.

Hip Int 2014; 24:69–76.

Cladellas M, Farre N, Comin-Colet J, et al.

Effects of preoperative intravenous erythropoietin plus iron on outcome in anemic patients after cardiac valve replacement.

Am J Cardiol 2012; 110:1021–1026.

Iron +ESAs + Folate +B12



modifying the risk of anaemia on RBC transfusions

Theusinger OM, Kind SL, Seifert B, et al.

Patient blood management in orthopaedic surgery: a four-year follow-up of transfusion requirements and blood loss from 2008 to 2011 at the Balgrist University Hospital in Zurich, Switzerland. Blood Transfus 2014; 12:195–203.

ESA guidelines



In non-cancer patients with preoperative anaemia scheduled for elective major surgery, we recommend postponing surgery until anaemia has been corrected. 1C

ESA guidelines

In patients who are anaemic following surgery, we suggest the use of intravenous iron. 2C



Post-op Iron

effective in knee and hip arthroplasty,
especially in case of anaemia:

- ✓ fewer transfusions
- ✓ cost neutral

Bisbe E, Molto L, Arroyo R, et al. Randomized trial comparing ferric carboxymaltose vs oral ferrous glycine sulphate for postoperative anaemia after total knee arthroplasty. Br J Anaesth 2014; 113:402–409.

Munoz M, Gomez-Ramirez S, Martin-Montanez E, et al. Cost of postoperative intravenous iron therapy in total lower limb arthroplasty: a retrospective, matched cohort study. Blood Transfus 2014; 12:40–49.

IV iron

dose of isomaltoside [mg iron]=

body weight [kg] x (target – current Hb) [g/dl] x 2.4
+ iron for iron stores [mg iron]

short infusion in 100-250 ml NaCl 0.9% over 30 min (-10 mg/kg)
or 60 min (10-20 mg/kg)

Iron + ESA's + B12 + Folate

Pragmatic approach „global correction“

1 g isomaltosid IV

+ 40.000 U erythropoietin alpha s.c.

+ 1 mg/day vitamin B12 p.o.

+ 5 mg/day folate p.o.

ESA guidelines

We recommend a target haemoglobin concentration of 7 to 9 g dl^{-1} during active bleeding. 1C



Post-op transfusion trigger

Tab.: Vereinfachter Algorithmus zur Indikationsstellung einer Erythrozytenkonzentrat-(EK-)Transfusion postoperativ auf der Normalstation.

Hb level (g/dl)	Clinical criteria: • ability to compensate anaemia? signs of hypoxia? • risk factors: comorbidity? • relevant postOP bleeding?	Decision for pRBC transfusion
< 6		yes (1-2 pRBCs)
6 - 8	compensation adequate no risk factors no relevant postOP bleeding	no
	compensation recuded e.g. ST-segment dynamics, tachycardia > 80 bpm, hypotension, lactate acidosis risk factors present: e.g.. CHD, cardiac failure, stroke, renal dysfunction	yes
8 - 10	compensation adequate	no
	compensation reduced: e.g. ST-segment dynamics, tachycardia > 80 bpm, hypotension, lactate acidosis	yes
> 10		no

Post-op anemia

To be consider

- haemolysis due to, e.g. hypotonic solutions , sepsis, incompatible transfusion
- clinically apparent or occult blood loss from or into the gastro-intestinal tract
- inappropriately low erythropoietin synthesis and secretion due to stress-related inflammation
- diminished responsiveness of erythroid precursor cell to erythropoietin due to inflammation and/or decreased availability of iron (iron sequestration)
- nutritional deficiencies (e.g., vitamin B₁₂, folic acid) and pharmacological interactions
- haemodilution due to (excessive) fluid administration

Post-op

volume monitoring



Restrictive vs. Liberal

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MARCH 12, 2015

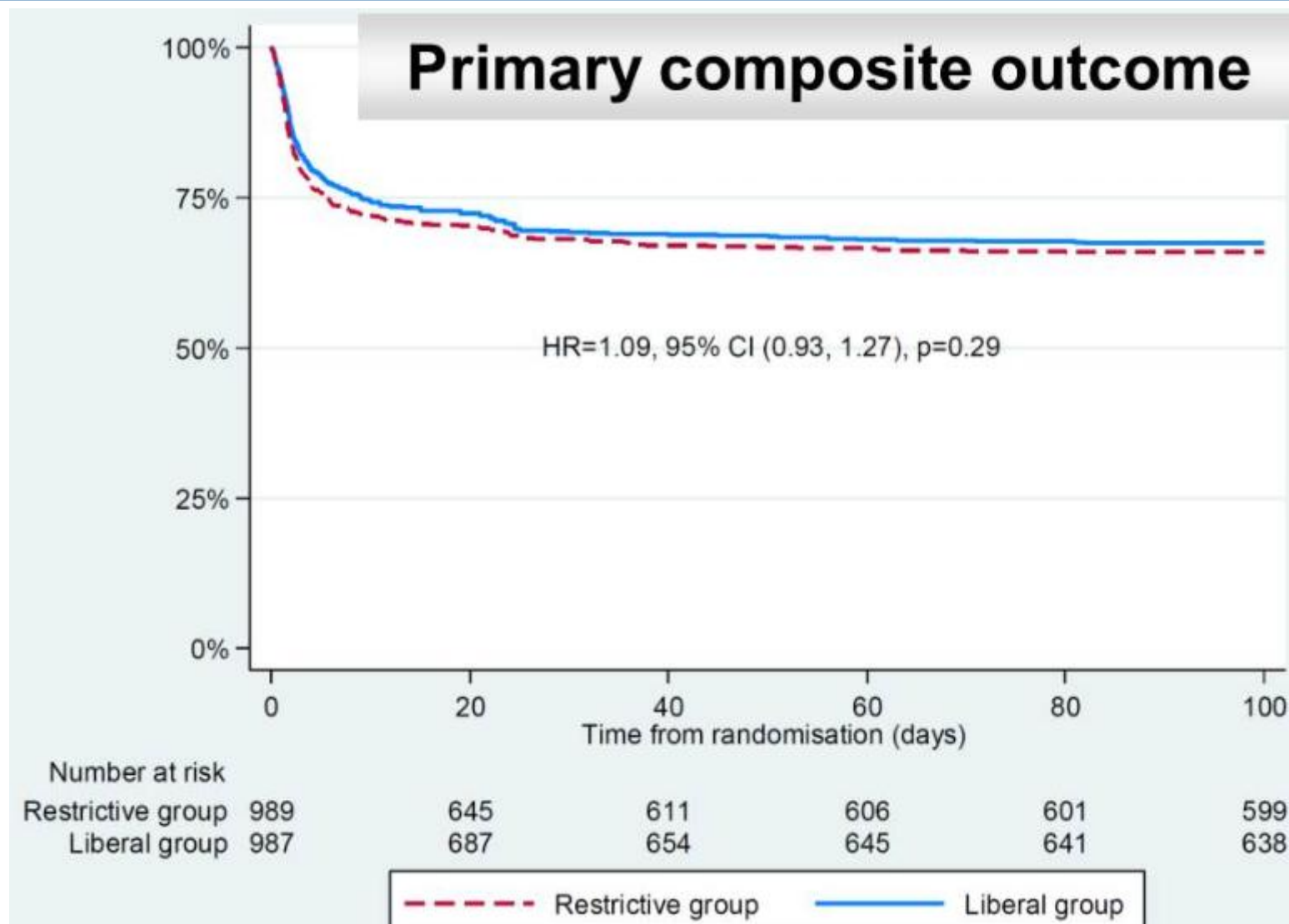
VOL. 372 NO. 11

Liberal or Restrictive Transfusion after Cardiac Surgery

Gavin J. Murphy, F.R.C.S., Katie Pike, M.Sc., Chris A. Rogers, Ph.D., Sarah Wordsworth, Ph.D., Elizabeth A. Stokes, M.Sc., Gianni D. Angelini, F.R.C.S., and Barnaby C. Reeves, D.Phil., for the TITRe2 Investigators*

- ◆ PRT in 2007 patients undergoing cardiac surgery and having a postop. Hb < 9.0 g/dL
- ◆ Hb transfusion trigger: 7.5 g/dL vs. 9.0 g/dL
- ◆ Primary outcome = 3 months composite of
 - ⇒ Serious infection / Ischemic event
 - ⇒ Myocardial infarction / AKI
 - ⇒ Infarction of the gut

Restrictive vs. Liberal



Restrictive vs. Liberal

ORIGINAL ARTICLE

Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery

- ◆ PRT in 5243 patients undergoing cardiac surgery on CPB having a EuroSCORE ≥ 6
- ◆ Hb transfusion trigger: <7.5 g/dL vs. <9.5 g/dL OR / ICU and <8.5 g/dL on the regular ward
- ◆ Primary outcome = 28 days composite of Death / MI / Stroke / new renal failure with dialysis
- ◆ Secondary outcomes
 - ⇒ RBC transfusions
 - ⇒ Clinical outcomes

This article was published on November 12, 2017, at NEJM.org.



Restrictive vs. Liberal

Table 3. Primary and Secondary Outcomes in the Per-Protocol Population.

Characteristic	Restrictive Threshold (N = 2430)	Liberal Threshold (N = 2430)	Odds Ratio or Hazard Ratio (95% CI)
Primary outcome			
Composite-outcome event — no./total no. (%)	276/2428 (11.4)	303/2429 (12.5)	0.90 (0.76–1.07)
Death — no./total no. (%)	74/2427 (3.0)	87/2429 (3.6)	0.85 (0.62–1.16)
Stroke — no./total no. (%)	45/2428 (1.9)	49/2429 (2.0)	0.92 (0.61–1.38)
Myocardial infarction — no./total no. (%)	144/2428 (5.9)	144/2429 (5.9)	1.00 (0.79–1.27)
New-onset renal failure with dialysis — no./total no. (%)	61/2428 (2.5)	72/2429 (3.0)	0.84 (0.60–1.19)

Table 2. Transfusion Outcomes in the Per-Protocol Population.

Characteristic	Restrictive Threshold (N = 2430)	Liberal Threshold (N = 2430)	Odds Ratio or Rate Ratio (95% CI)
Red-cell transfusions after randomization			
≥1 Unit of red cells — no. (%)	1271 (52.3)	1765 (72.6)	0.41 (0.37–0.47)
No. of units of red cells transfused			
Median	2	3	0.85 (0.82–0.88)*

Restrictive vs. Liberal

EDITORIAL



Transfusion Threshold of 7 g per Deciliter — The New Normal

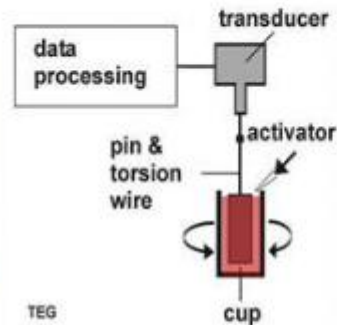
Paul C. Hébert, M.D., and Jeffrey L. Carson, M.D.

We believe it has become abundantly clear that a transfusion threshold of 7 g per deciliter should become the new normal, recommended in all critically ill patients, including those with severe sepsis and septic shock. To speed up adoption, we should ensure that clinical practice

Hébert P. C. et al. New Engl J Med (2014) 371: 1459

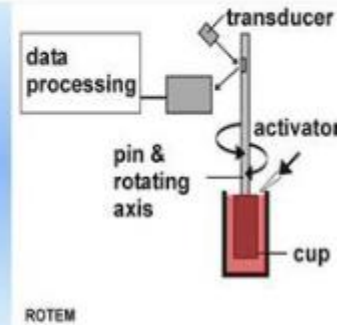
Point of care testing

TEG[®]

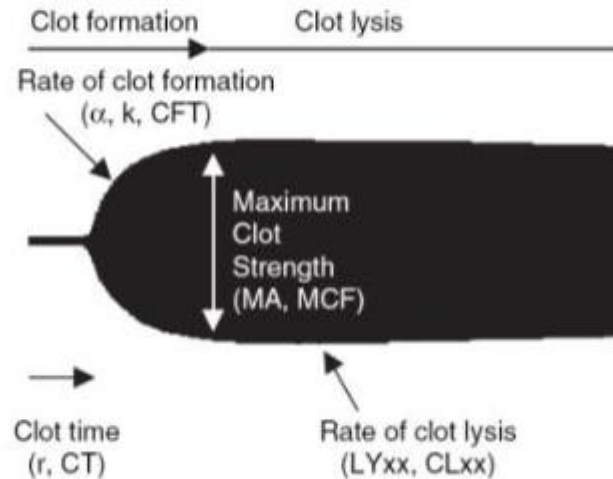


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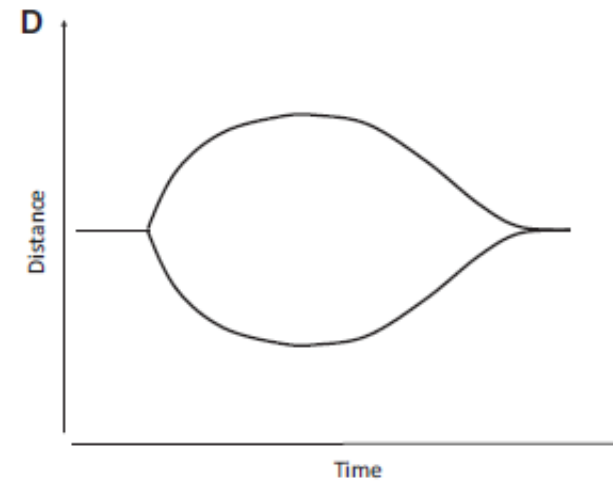
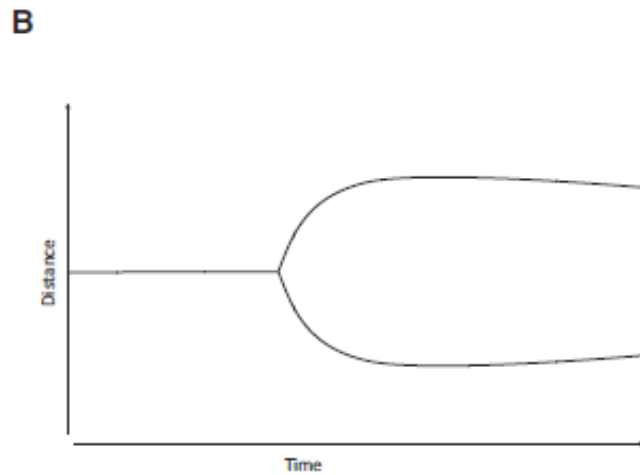
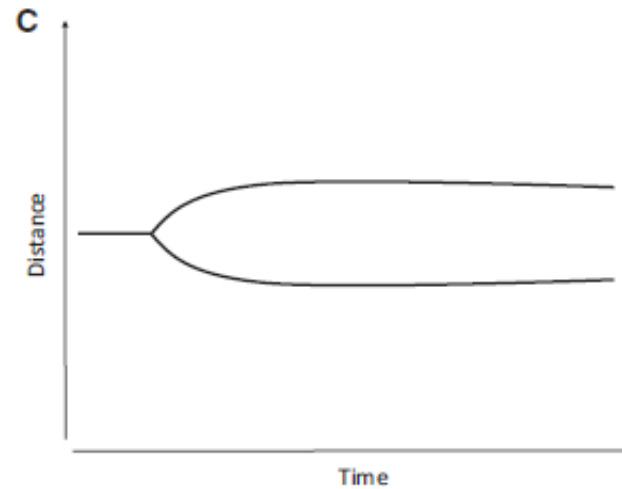
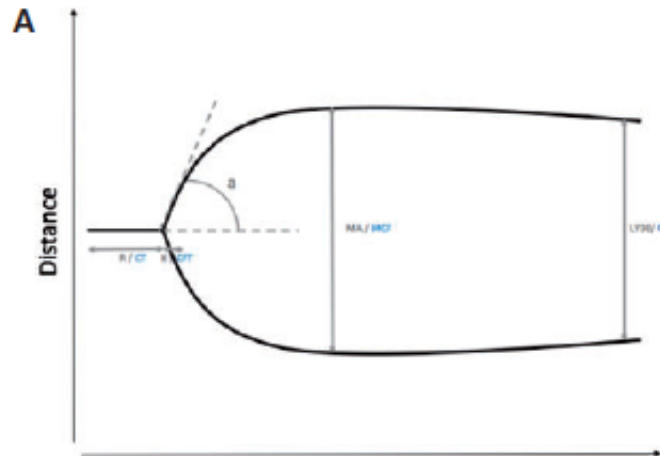
ROTEM[®]



ROTEM



Point of care testing



Rotem analysisi

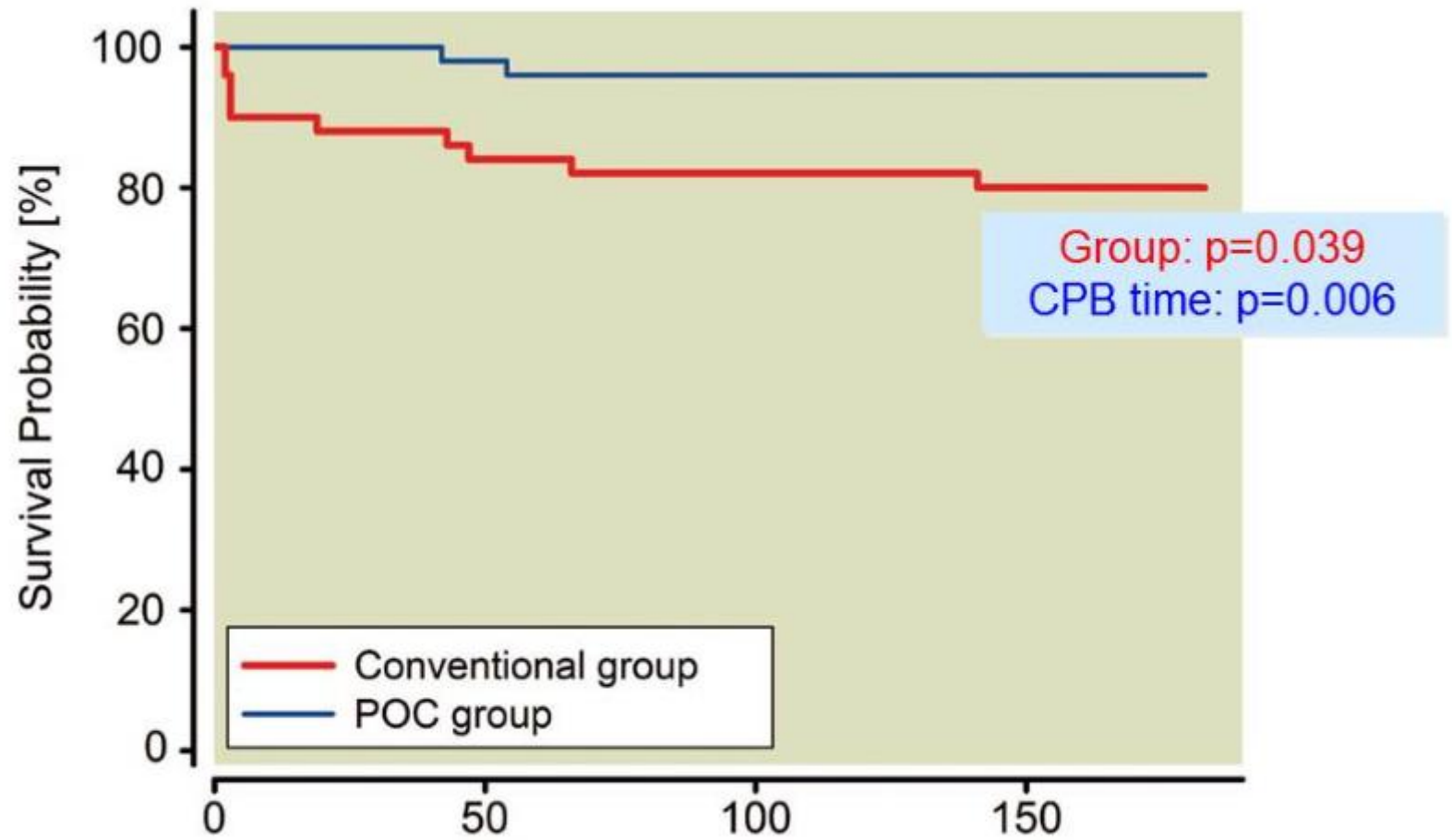
	CT (s)	CFT (s)	Amplitudinea după CT (mm)		MCF* (mm)	Indicele de liză a trombului (%)	
			10 min. A10	20 min. A20		30 min CLI30	60 min CLI60
INTEM	100-240	30-110	44-66	50-71	50-72	94-100	85-100
EXTEM	38-79	34-159	43-65	50-71	50-72	94-1000	85-100
HEPTEM	100- 240**	30-110			50-72		
FIBTEM			7-23	8-24	9-25***		
APTEM	38-79	34-159			50-72		

Conventional test vs. Rotem

	Conventional	ROTEM®	p value
RBC % transfused (%)	98	84	0.031
RBC units / patient	5	3	0.001
FFP % transfused (%)	80	40	0.001
FFP units / patient	5	0	0.001
PC % transfused (%)	66	56	0.412
PC units / patient	2	2	0.010
Fibrinogen % administered (%)	60	64	0.837
Fibrinogen units / patient	2	2	0.481
PCC % administered (%)	52	44	0.433
rFVIIa % administered (%)	24	2	0.002
Cost of hemotherapy (Euro)	3109	1658	0.001

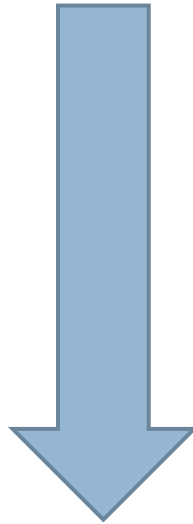
Weber C. F. et al. Anesthesiology (2012) 117: 531

Conventional test vs. Rotem



Active bleeding

Stop bleeding



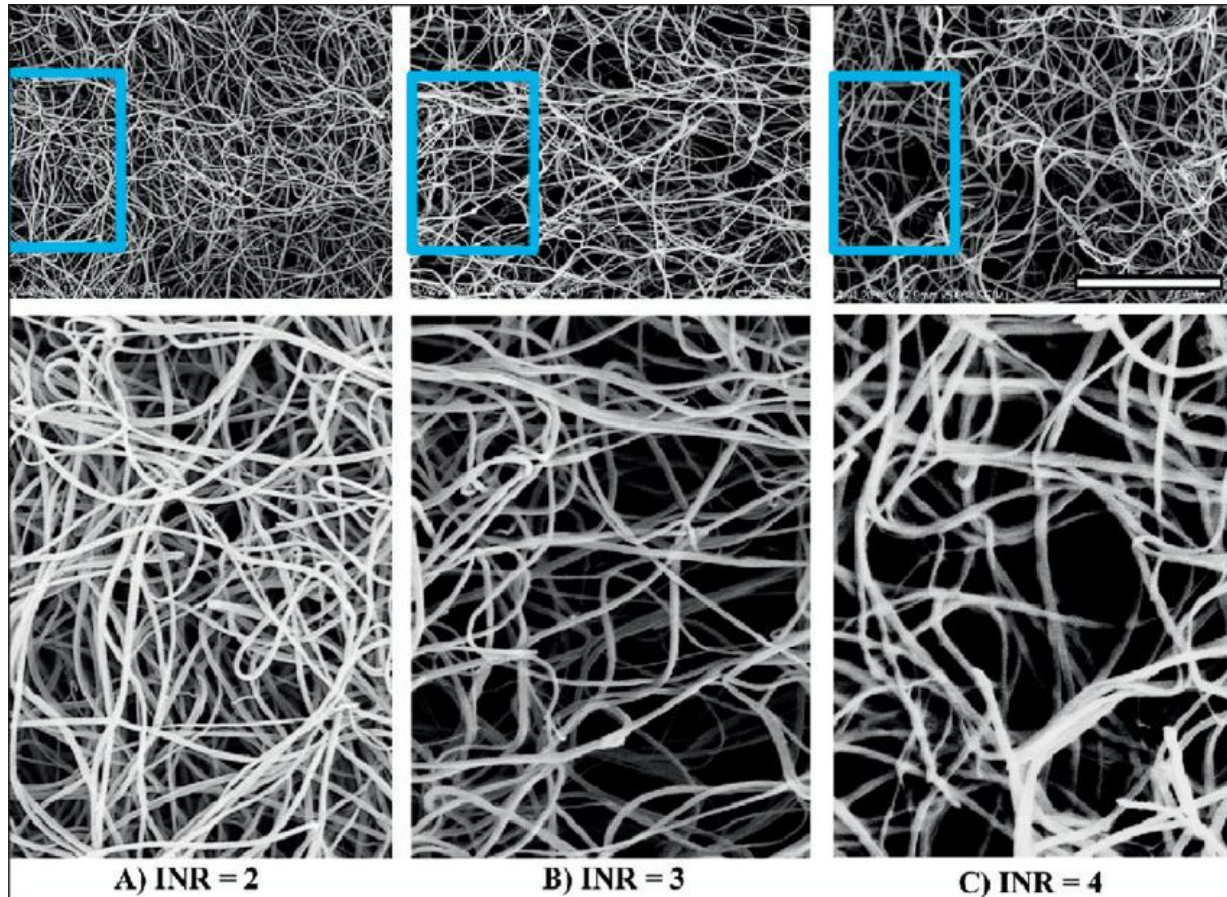
Perfusion

Stop hemorrhage



- Keep patient alive
 - permissive hypotension
 - limit fluid infusion (dilution)
- Stop hemorrhage
 - early surgery, damage control
- Maintain coagulation competence
 - target coagulopathy

Disease coagulopathy ?



FIBRINOLYSIS

Disease coagulopathy

- Antifibrinolytic: TxA
 - 1.0 gr. i.v. over 10 min.
 - if necessary after 30 min 1.0 gr. i.v./10 min
 - first 3 hours

- Co-factors: Ca^{++} , Ph, Temperature control

Take home messages



- Anaemia and allogenic blood transfusion are independent risk factors for poor postoperative outcomes: morbidity and mortality.
- One-third of patients are found to be anaemic on pre-assessment.
- PBM is a concept with the goal of avoiding unnecessary blood transfusions to improve patient outcomes and safety.
- Iron deficiency requires iron supplementation.