bbts brighton 3-5 oct '18

Kenneth Goldsmith Lecture

Blood, Sweat, and Tears: are we ready for personalised transfusion practice?

Tim Walsh

Professor of Critical Care, Edinburgh University

NHS Lothian

British Blood Transfusion Society | #BBTS2018

Blood transfusion during acute illness: a logic model

Patient	Condition	Complication	Intervention	Outcomes
Age Gender Co-Morbidities CVD Respiratory Neurological Haemato-Logical Marrow failure Oncology Other anaemias	Trauma Sepsis Cancer Surgery Radiotherapy chemotherapy Obstetrics Liver disease Illness severity Physiological disturbance Organ failure	Major Bleeding Trauma GI bleeding Surgery Anaemia Bleeding Acute marrow impairment Blood sampling Haemodilution Anaemia severity	Blood transfusion Volume No. units Target Hb RBC product Leucodepletion Storage age Storage conditions Whole blood	Mortality Timing Illness severity Organ failures Quality of Life QALYS Patient symptoms Fatigue Breathlessness Resource Length of stay Costs

EDINBURGH CRITICAL CARE RESEARCH GROUP

Critical and acute illness: the ideal model for studying transfusion practice?

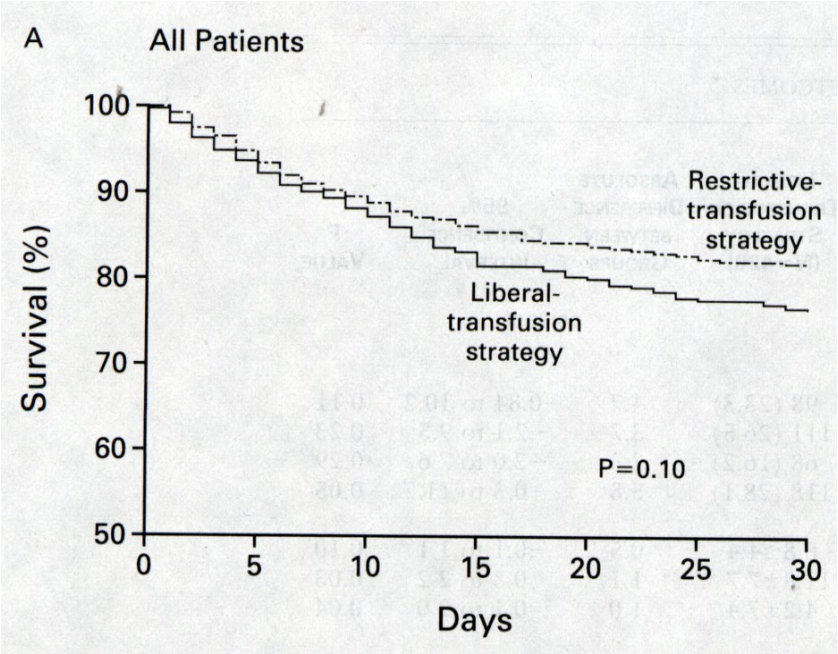
- High prevalence of anaemia
- High transfusion requirement
- Strong biological plausibility that keeping oxygen delivery high decreases organ failures and other complications
- High ‘event rates’ relevant to transfusion
  - Mortality ≈20%
  - High illness costs ≈£1500 per day
  - High burden of symptoms relevant to anaemia

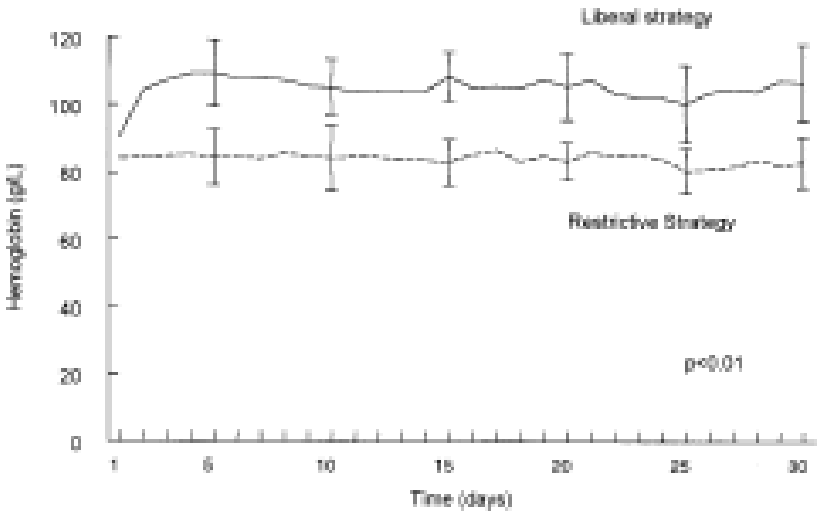
A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

PAUL C. HÉBERT, M.D., GEORGE WELLS, PH.D., MORRIS A. BLAJCHMAN, M.D., JOHN MARSHALL, M.D., CLAUDIO MARTIN, M.D., GIUSEPPE PAGLIARELLO, M.D., MARTIN TWEEDDALE, M.D., PH.D., IRWIN SCHWEITZER, M.SC., ELIZABETH YETISIR, M.SC., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*

"TRICC" NEJM 1999

70g/L vs 100g/L

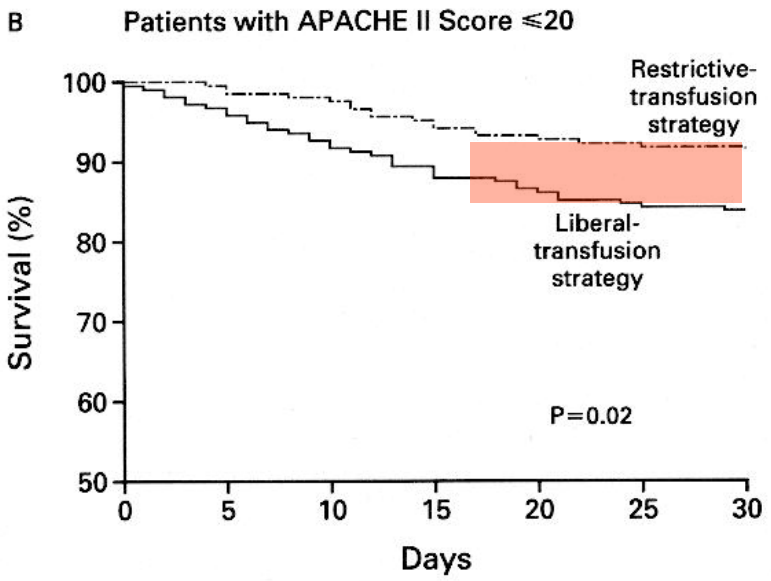


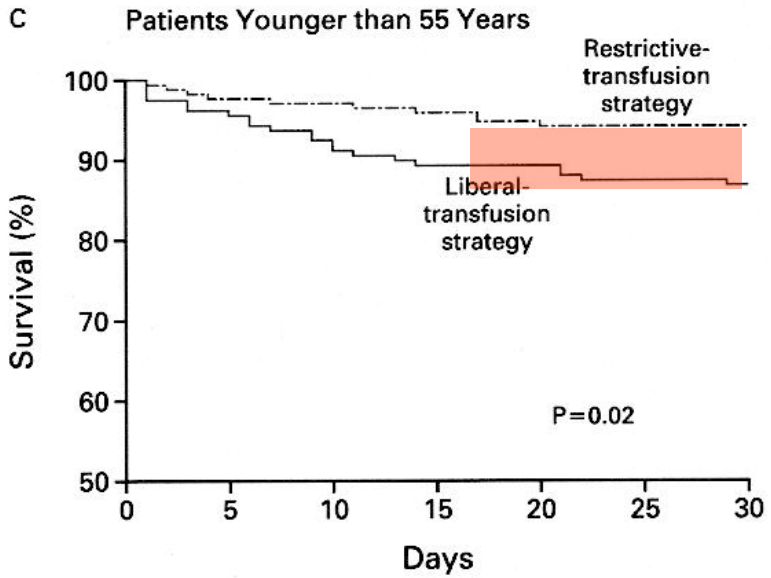


Aggregate mortality at 60 days 25%
Difference in mortality at 60 days 3-8% overall

Main differences:
[1] Degree of anaemia
[2] Exposure to stored non-leucodepleted red cells

Mean time in study 11 days
Difference in RBC exposure 2.7 units
Difference in proportion exposed 33%





Outcome Measure	Restrictive-Transfusion Strategy (N=418)	Liberal-Transfusion Strategy (N=420)	Absolute Difference between Groups	95% Confidence Interval	P Value
			percent		
Death — no. (%)					
30-day	78 (18.7)	98 (23.3)	4.7	−0.84 to 10.2	0.11
60-day†	95 (22.7)	111 (26.5)	3.7	−2.1 to 9.5	0.23
ICU	56 (13.4)	68 (16.2)	2.3	−2.0 to 7.6	0.29
Hospital	93 (22.2)	118 (28.1)	5.8	−0.3 to 11.7	0.05
Multiple-organ-dysfunction score					
Unadjusted score	8.3±4.6	8.8±4.4	0.5	0.1 to 1.1	0.10
Adjusted score‡	10.7±7.5	11.8±7.7	1.1	0.8 to 2.2	0.03
Change from base-line score§	3.2±7.0	4.2±7.4	1.0	0.1 to 2.0	0.04
No. of organs failing — no. (%)					
0	100 (23.9)	82 (19.5)			
1	136 (32.5)	149 (35.5)			
2	109 (26.1)	108 (26.0)			
3	51 (12.2)	63 (15.0)			
>3	22 (5.3)	18 (4.3)	1.8¶	−3.4 to 7.1¶	0.53¶
Length of stay — days					
ICU	11.0±10.7	11.5±11.3	0.5	−1.0 to 2.1	0.53
Hospital	34.8±19.5	35.5±19.4	0.7	−1.9 to 3.4	0.58

Blood transfusion during acute illness: a logic model

Patient	Condition	Complication	Intervention	Outcomes
Age Gender Co-Morbidities CVD Respiratory Neurological Haemato-Logical Marrow failure Oncology Other anaemias	Trauma Sepsis Cancer Surgery Radiotherapy chemotherapy Obstetrics Liver disease Illness severity Physiological disturbance Organ failure	Major Bleeding Trauma GI bleeding Surgery Anaemia Bleeding Acute marrow impairment Blood sampling Haemodilution Anaemia Severity <100g/L	Blood transfusion Volume Single units RBC product Leucodepletion Storage age Storage conditions Whole blood	Mortality Timing Illness severity Organ failures Quality of Life QALYS Patient symptoms Fatigue Breathlessness Resource Length of stay Costs

EDINBURGH CRITICAL CARE RESEARCH GROUP

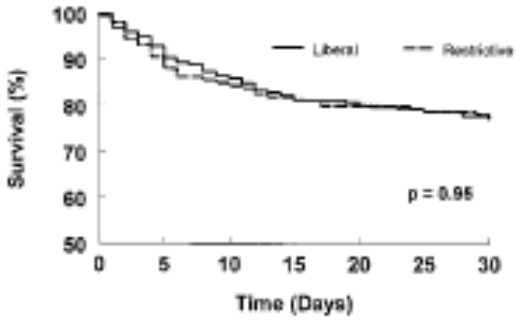
Possible explanations

- Transfusion is harmful
  - White cells
  - Storage lesion
- Anaemia is beneficial
  - Blood rheology/flow
  - Oxygen supply to tissues is not limited at Hb values >70g/L despite critical illness

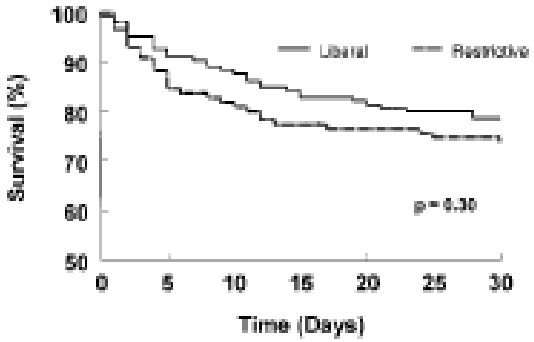
- Do these effects apply to the entire ‘logic model’?

Is low transfusion threshold safe in critically ill patients with cardiovascular disease?

Hebert PC et al. Crit Care Med 2001; 29: 227



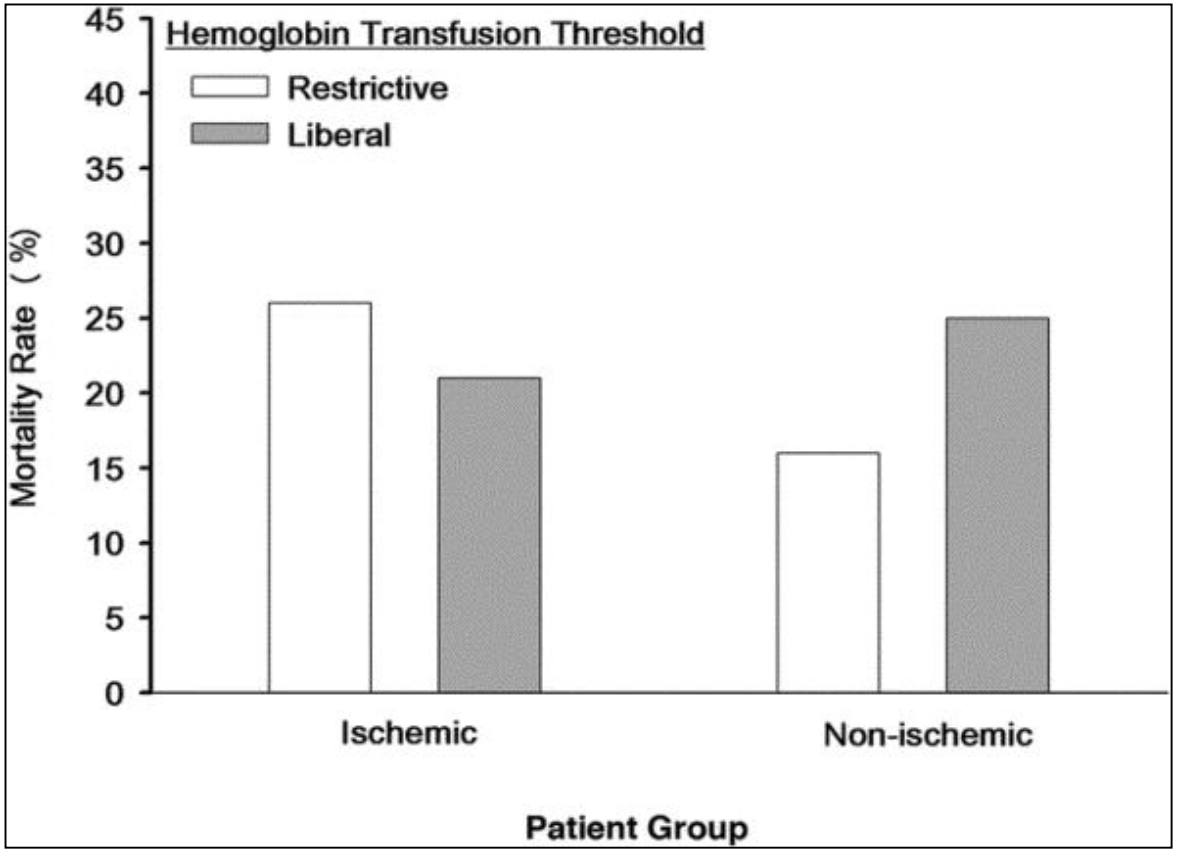
Subgroup of 357 patients with cardiovascular disease



Subgroup of 257 patients with ischaemic heart disease 30 day mortality

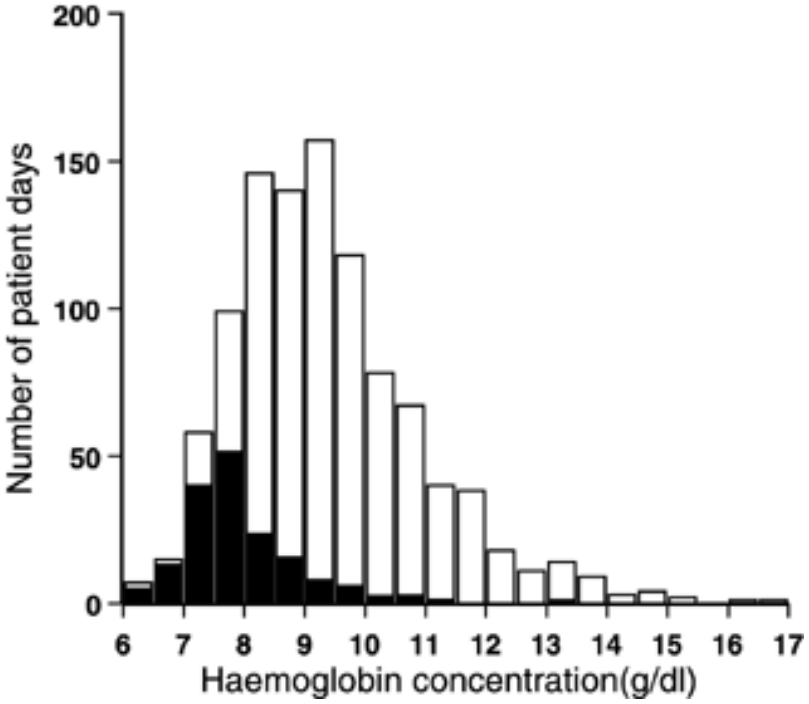
Difference –4.9% (-15.3% to 5.6%)

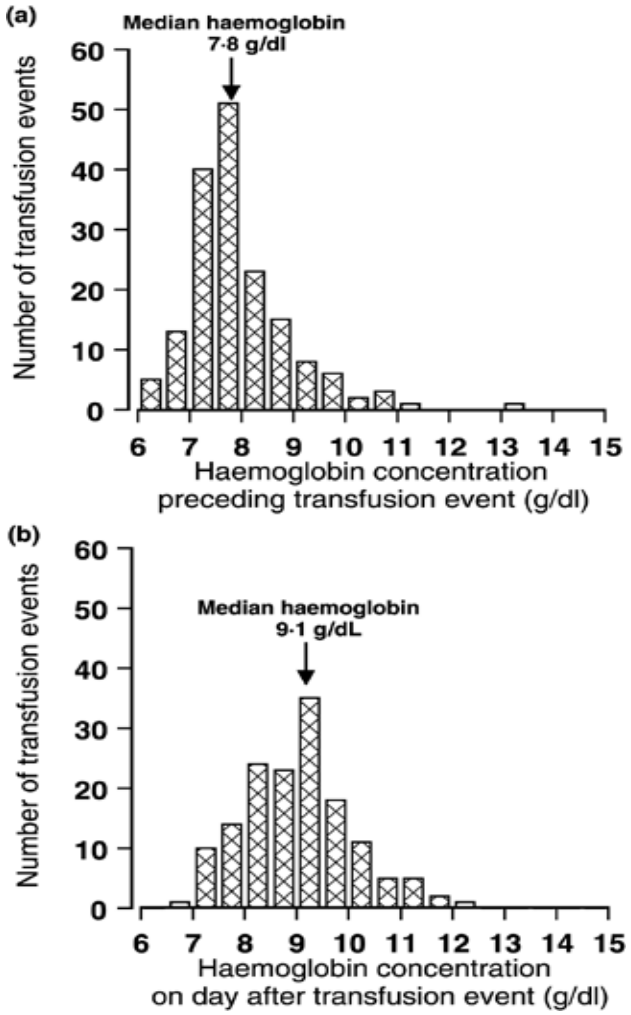
Randomization in clinical trials of titrated therapies: Unintended consequences of using fixed treatment protocols *.
Deans, Katherine et al. Critical Care Medicine. 35(6):1509-1516, June 2007.
DOI: 10.1097/01.CCM.0000266584.40715.A6



Practice misalignment in “fixed” intervention trials

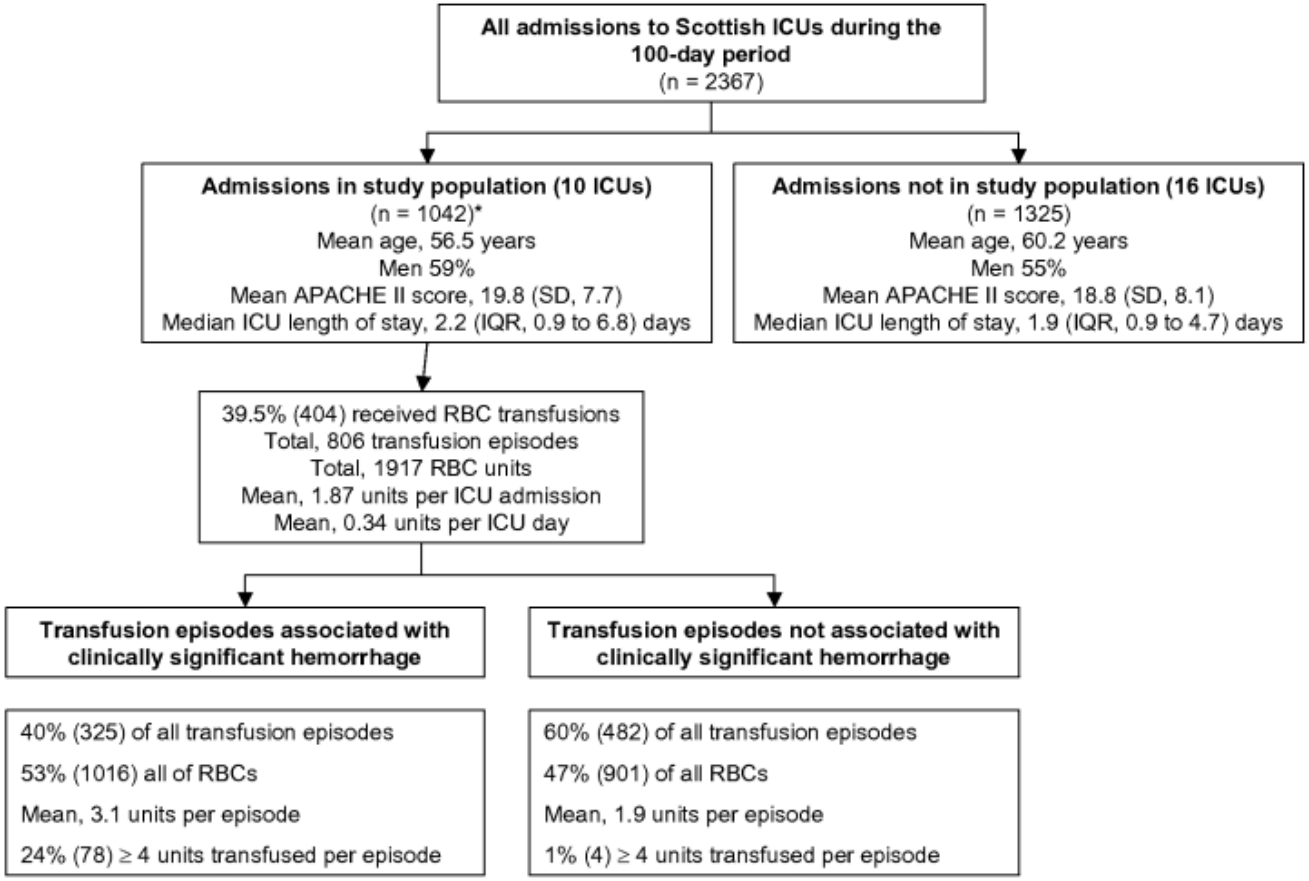
Red cell transfusion practice following the transfusion requirements in critical care (TRICC) study: prospective observational cohort study in a large UK intensive care unit





Vox Sanguinis Vol 84: pages 211-218, 2 APR 2003 DOI: 10.1046/j.1423-0410.2003.00284.x

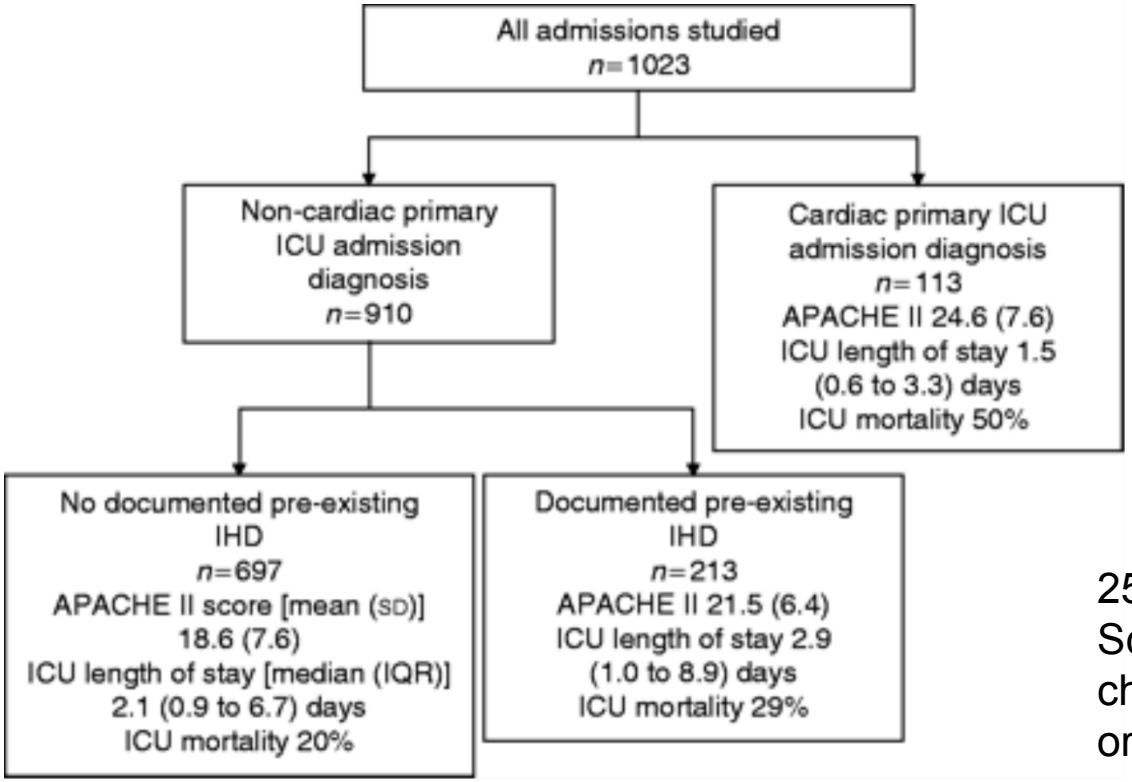
Red cell requirements for intensive care units adhering to evidence-based transfusion guidelines



Transfusion Vol 44: pages 1405-1411, 22 SEP 2004 DOI: 10.1111/j.1537-2995.2004.04085.x

Prevalence of ischaemic heart disease at admission to intensive care and its influence on red cell transfusion thresholds: multicentre Scottish Study

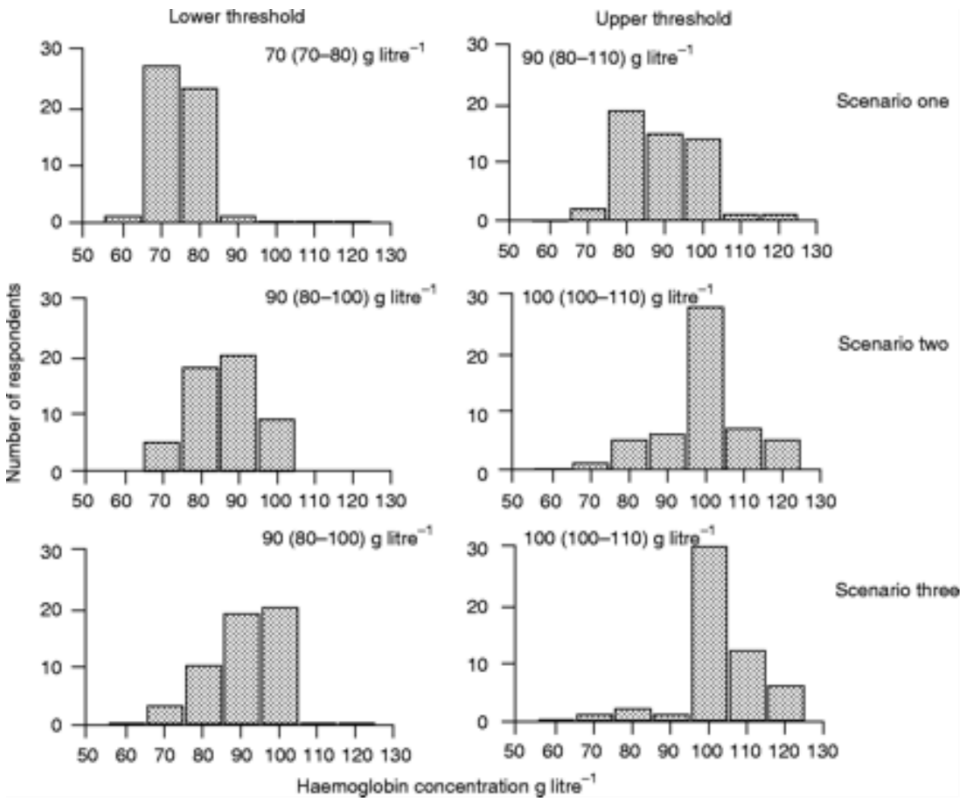
Br J Anaesth. 2005;94(4):445-452. doi:10.1093/bja/aei073



25% of patients admitted to Scottish ICUs had a history of chronic ischaemic heart disease or cardiac failure

Clinicians modified transfusion trigger according to chronic or acute cardiac diagnoses

	Group 1: non-cardiac ICU admission diagnosis, no documented IHD (n=697)	Group 2: non-cardiac ICU admission diagnosis, with documented IHD (n=213)	Group 3: cardiac ICU admission diagnosis (n=113)
Adjusted mean (SE) pre-transfusion haemoglobin concentration	74 (2.2)	77 (2.3)	79 (3.1)*



Clinician survey responses indicated cardiac diagnoses associated with major uncertainty and practice variation

No ischaemic heart disease

Co-existing ischaemic heart disease

Evidence of myocardial ischaemia

Br J Anaesth. 2005;94(4):445-452. doi:10.1093/bja/aei073

Restrictive Versus Liberal Transfusion Strategies for Older Mechanically Ventilated Critically Ill Patients: A Randomized Pilot Trial*.

Walsh, Timothy; Boyd, Julia; Watson, Douglas; et al

Critical Care Medicine. 41(10):2354-2363, October 2013. DOI: 10.1097/CCM.0b013e318291cce4

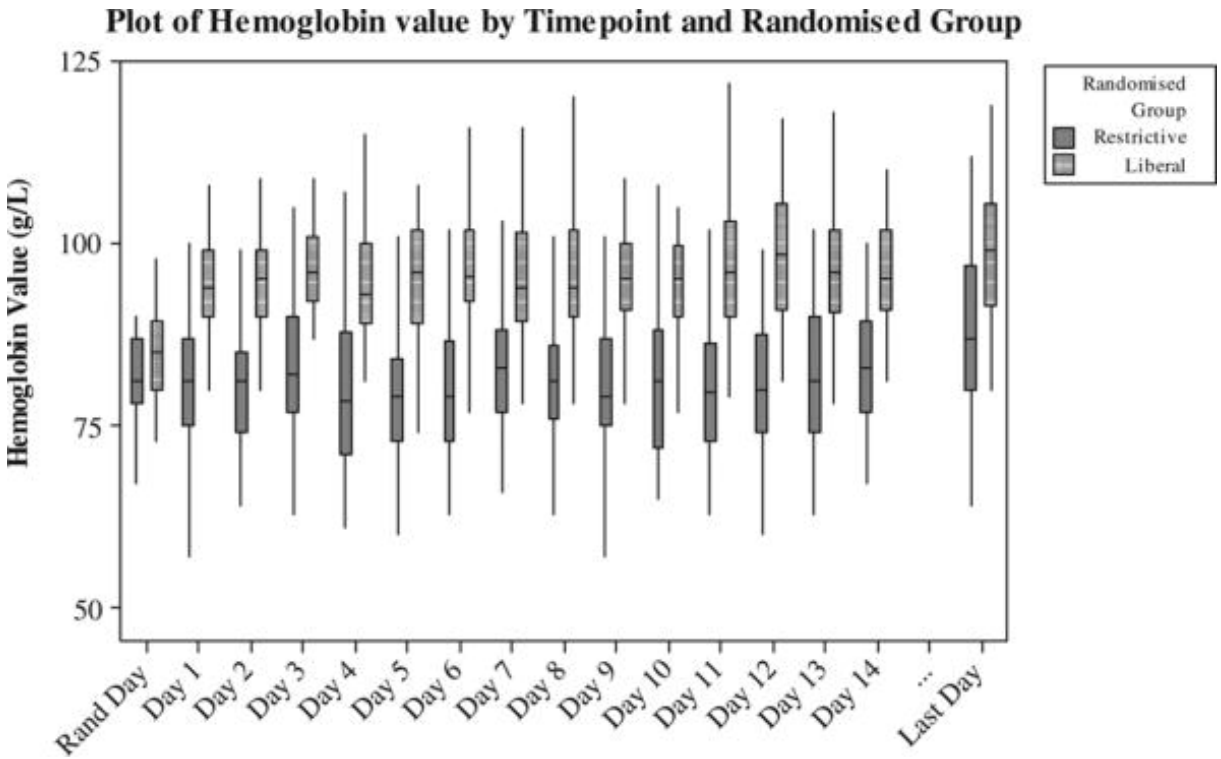
Patients

Aged >55 years

At least 4 days of MV

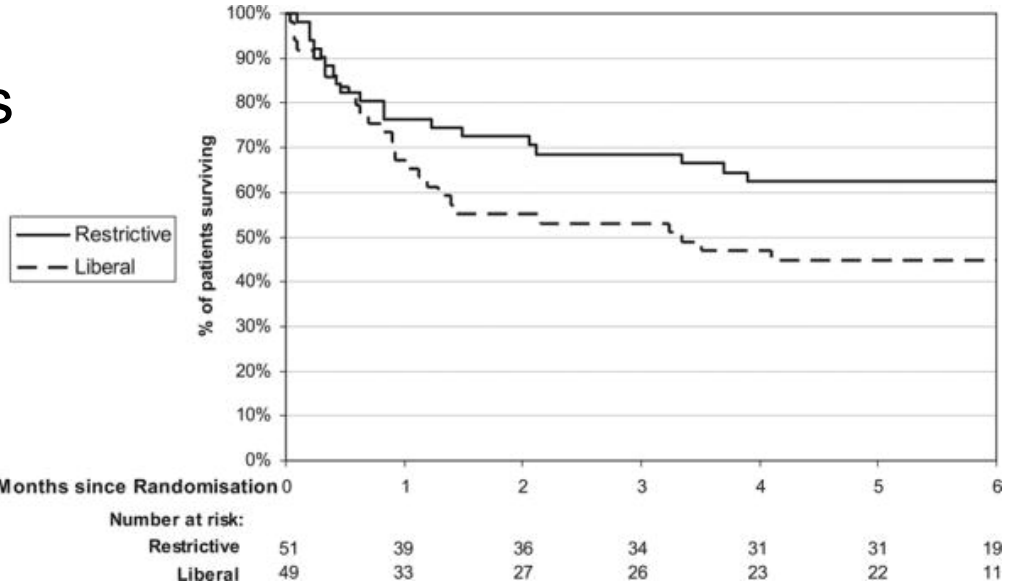
Hb 90g/L

All leucodepleted RCC



CHIEF SCIENTIST OFFICE

Major clinical outcomes



Outcome	Restrictive Transfusion Group ($n = 51$)	Liberal Transfusion Group ($n = 49$)	Mean Difference (95% CI)
ICU mortality	14 (27.5)	17 (34.7)	0.79 (0.44 to 1.43)
Hospital mortality	19 (37.3)	24 (49.0)	0.76 (0.48 to 1.2)
30 d mortality	12 (23.5)	16 (32.7)	0.72 (0.38 to 1.36)
60 d mortality	14 (27.5)	22 (44.9)	0.61 (0.36 to 1.05)
180 d mortality	19 (37.3)	27 (55.1)	0.68 (0.44 to 1.05)
Rivermead Mobility Index: median (first, third quartile; range)			Difference in median (95% CI)
60 d	5 (0, 12; 0–15)	6 (3, 9; 0–14)	–0.32 (–3.2 to 2.60)
180 d	13 (7, 15; 0–15)	10 (5, 12; 0–15)	1.9 (–1.0 to 4.9)
SF-12 Physical Function Score: median (first, third quartile; range)			
60 d	26 (20, 33; 13–43)	29 (25, 39; 20–46)	–2.5 (–11.2 to 6.2)
180 d	30 (24, 40; 12–54)	31 (24, 39; 20–44)	–1.2 (–8.9 to 6.5)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2013 VOL. 368 NO. 1

Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

Càndid Villanueva, M.D., Alan Colomo, M.D., Alba Bosch, M.D., Mar Concepción, M.D., Virginia Hernandez-Gea, M.D., Carles Aracil, M.D., Isabel Graupera, M.D., María Poca, M.D., Cristina Alvarez-Urturi, M.D., Jordi Gordillo, M.D., Carlos Guarner-Argente, M.D., Miquel Santaló, M.D., Eduardo Muñiz, M.D., and Carlos Guarner, M.D.

Hb 70g/L versus 90g/L

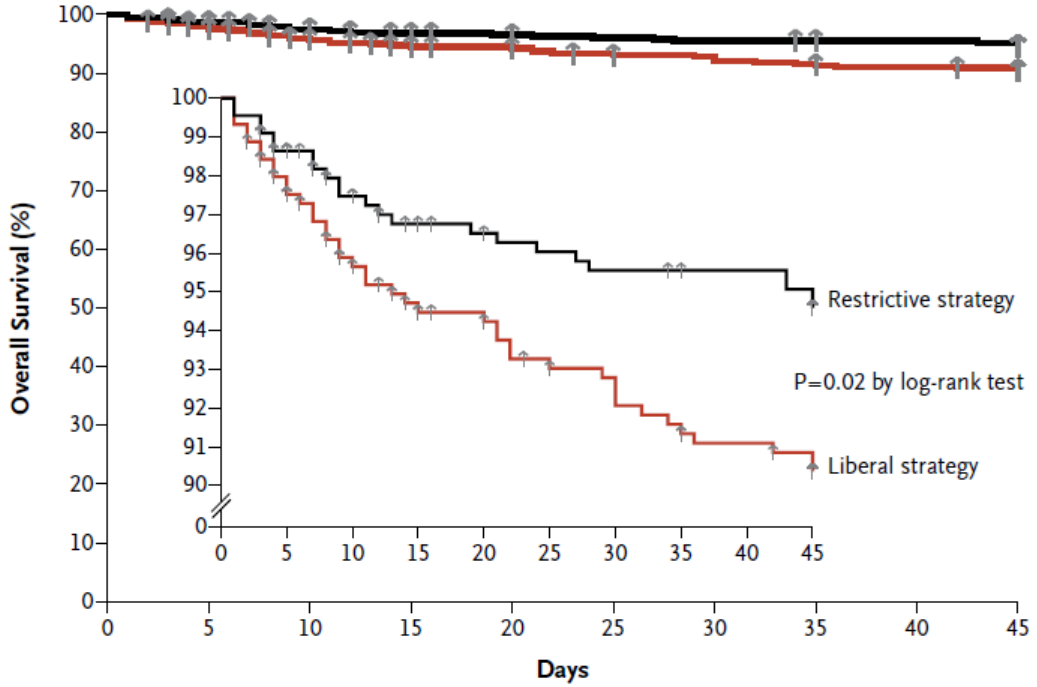
Exclusions

- Massive exsanguinating bleeding
- *Cardiovascular disease*

Stratified for presence of cirrhosis

- Single unit transfusions
- 31% cirrhosis; 49% peptic ulcer bleeding

A Survival, According to Transfusion Strategy

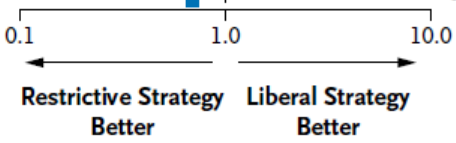


No. at Risk

Restrictive strategy	444	429	412	404	401	399	397	395	394	392
Liberal strategy	445	428	407	397	393	386	383	378	375	372

B Death by 6 Weeks, According to Subgroup

Subgroup	Restrictive Strategy	Liberal Strategy	Hazard Ratio (95% CI)	P Value
	no. of patients/total no. (%)			
Overall	23/444 (5)	41/445 (9)	0.55 (0.33–0.92)	0.02
Patients with cirrhosis	15/139 (11)	25/138 (18)	0.57 (0.30–1.08)	0.08
Child–Pugh class A or B	5/113 (4)	13/109 (12)	0.30 (0.11–0.85)	0.02
Child–Pugh class C	10/26 (38)	12/29 (41)	1.04 (0.45–2.37)	0.91
Bleeding from varices	10/93 (11)	17/97 (18)	0.58 (0.27–1.27)	0.18
Bleeding from peptic ulcer	7/228 (3)	11/209 (5)	0.70 (0.26–1.25)	0.26



Outcomes

- Overall excess deaths in liberal group from uncontrolled bleeding (0.7 vs 3.1%)
- More re-bleeding and rescue therapy in liberal group
- Small (significant) increase in PPG in liberal group vs no change in restrictive group
- More pulmonary oedema and cardiac adverse events in liberal group

British Journal of Anaesthesia **109** (6): 919–27 (2012)
Advance Access publication 30 September 2012 · doi:10.1093/bja/aes337

BJA

Factors associated with prophylactic plasma transfusion before vascular catheterization in non-bleeding critically ill adults with prolonged prothrombin time: a case–control study

D. P. Hall[1], N. I. Lone[1,2], D. M. Watson[3], S. J. Stanworth[4] and T. S. Walsh[1*], for the Intensive Care Study of Coagulopathy (ISOC) Investigators

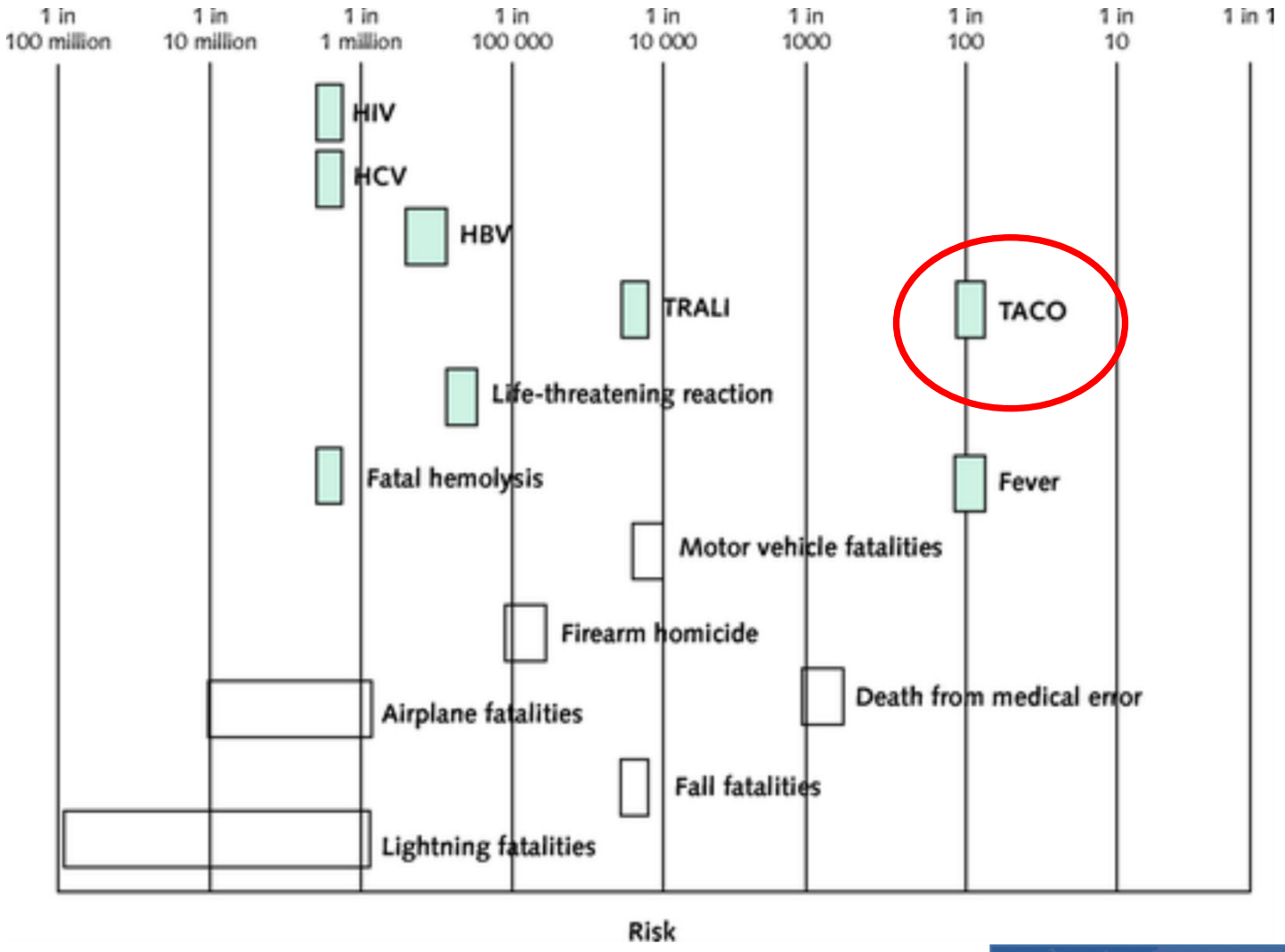
Factors associated with greater use of FFP

- Chronic liver disease; high bilirubin
- Concurrent RBC transfusion
- Worse coagulation tests (low platelets; higher APTT)

A national clinical scenario-based survey of clinicians' attitudes towards fresh frozen plasma transfusion for critically ill patients.
Transfusion Med 2011; 21: 124-129

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

Ann Intern Med. 2012;157(1):49-58. doi:10.7326/0003-4819-157-1-201206190-00429

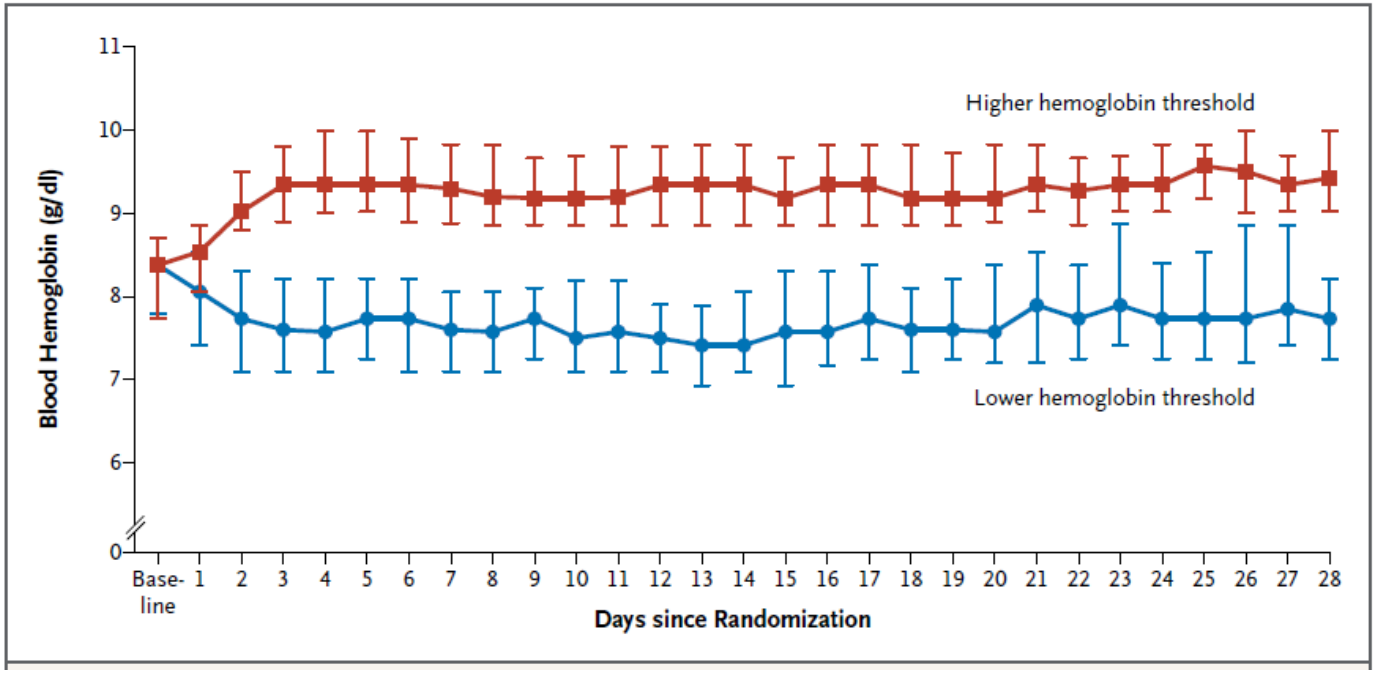


ORIGINAL ARTICLE

Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

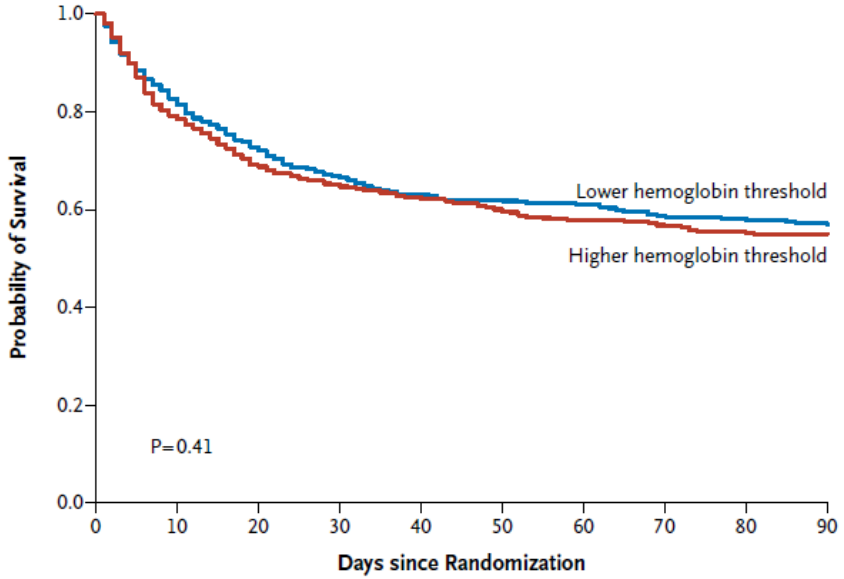
Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D.,
Jan Wernerman, M.D., Ph.D., Anne B. Guttormsen, M.D., Ph.D.

Hb 70g/L vs 90g/L



Transfusion exposure: restrictive 64% (median 1 unit)
liberal 99% (median 3 units)

A Time to Death

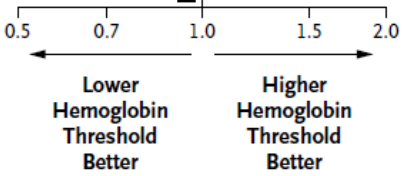


No. at Risk

Lower hemoglobin threshold	502	334	306	286
Higher hemoglobin threshold	496	321	287	273

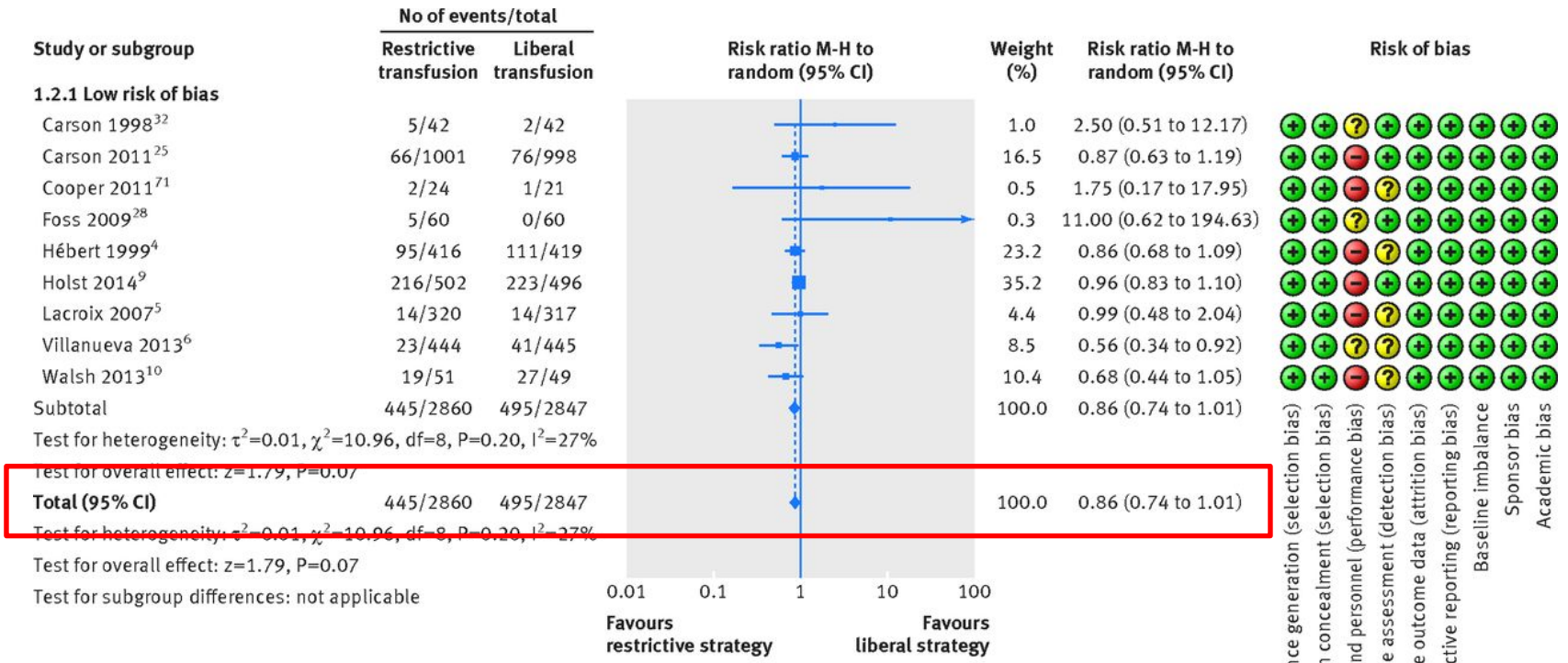
B Relative Risk of the Primary Outcome

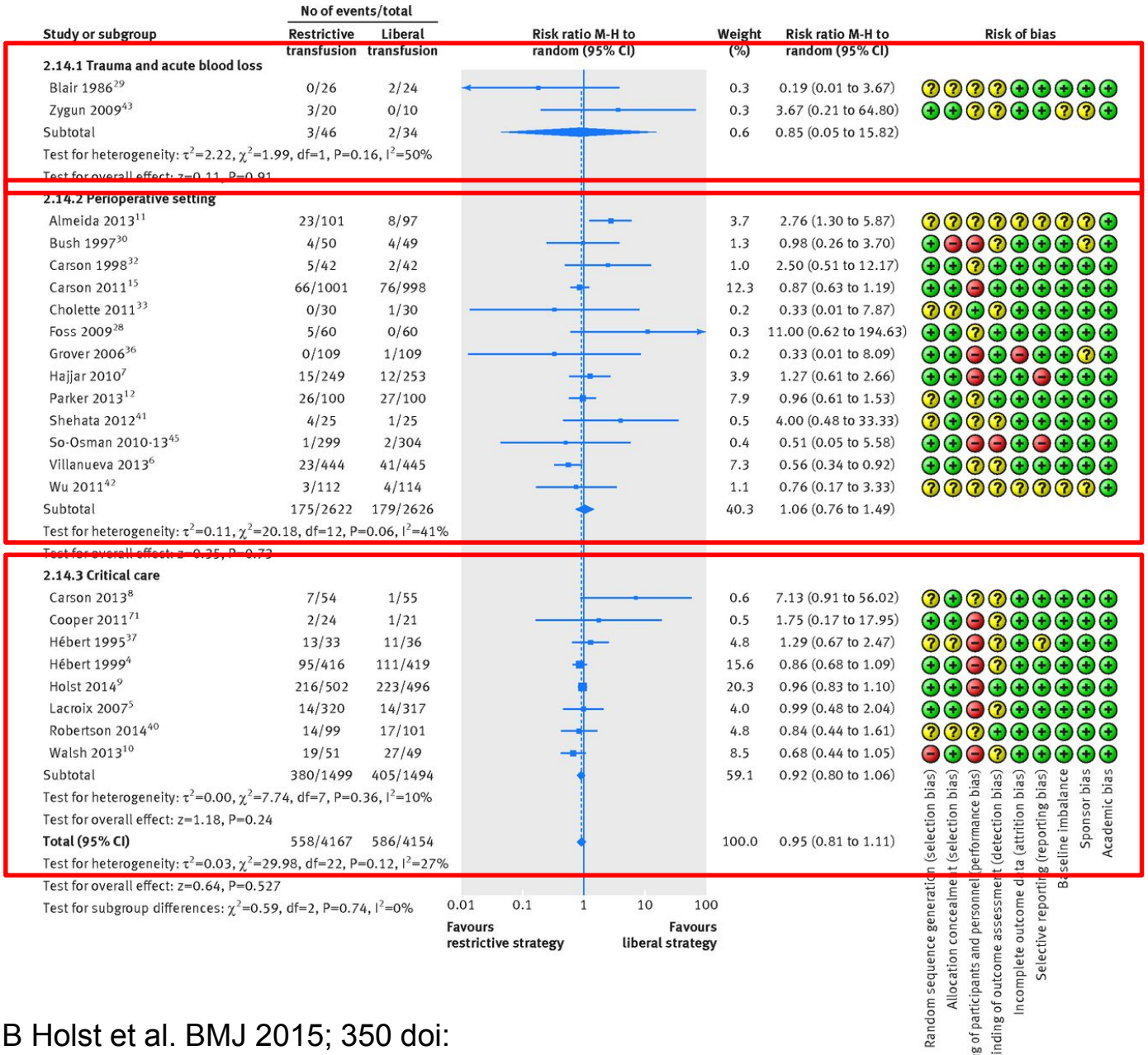
Subgroup	Lower Hemoglobin Threshold	Higher Hemoglobin Threshold	Relative Risk (95% CI)	P Value for Heterogeneity
	no. of events/no. of patients in subgroup			
Age				0.85
>70 yr	93/173	98/185	0.98 (0.79–1.18)	
≤70 yr	123/329	125/311	0.94 (0.75–1.14)	
Chronic cardiovascular disease				0.25
Yes	42/75	33/66	1.08 (0.75–1.40)	
No	174/427	190/430	0.90 (0.75–1.06)	
SAPS II at baseline				0.06
>53	112/207	139/226	0.83 (0.64–1.04)	
≤53	104/295	84/270	1.10 (0.91–1.30)	
All patients	216/502	223/496	0.94 (0.78–1.09)	



Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis

Lars B Holst et al. BMJ 2015; 350 doi: http://dx.doi.org/10.1136/bmj.h1354





Lars B Holst et al. BMJ 2015; 350 doi:
http://dx.doi.org/10.1136/bmj.h1354

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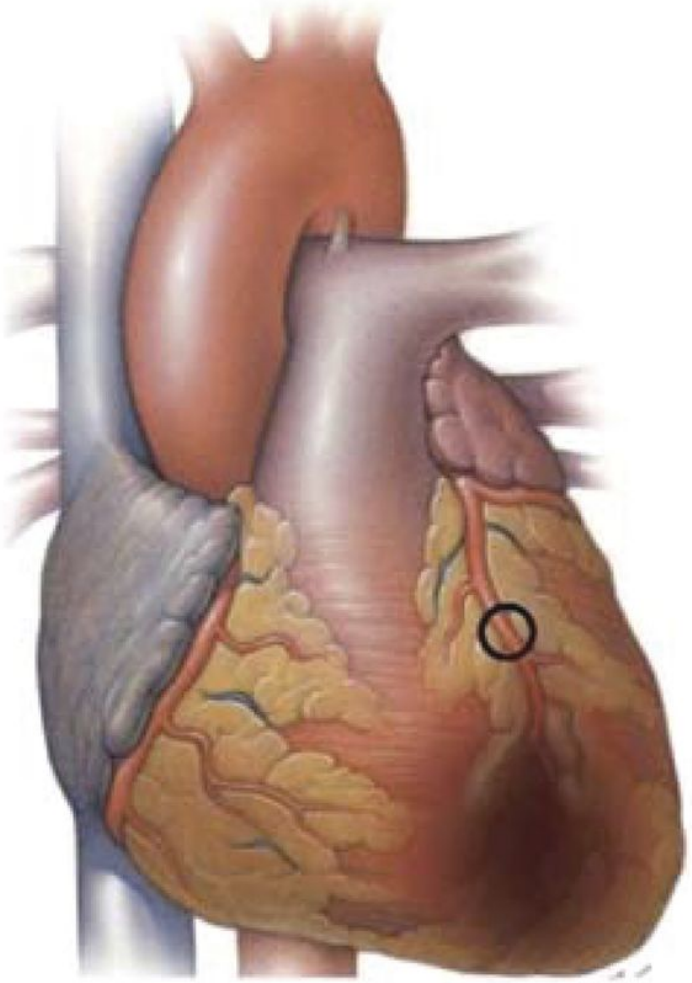
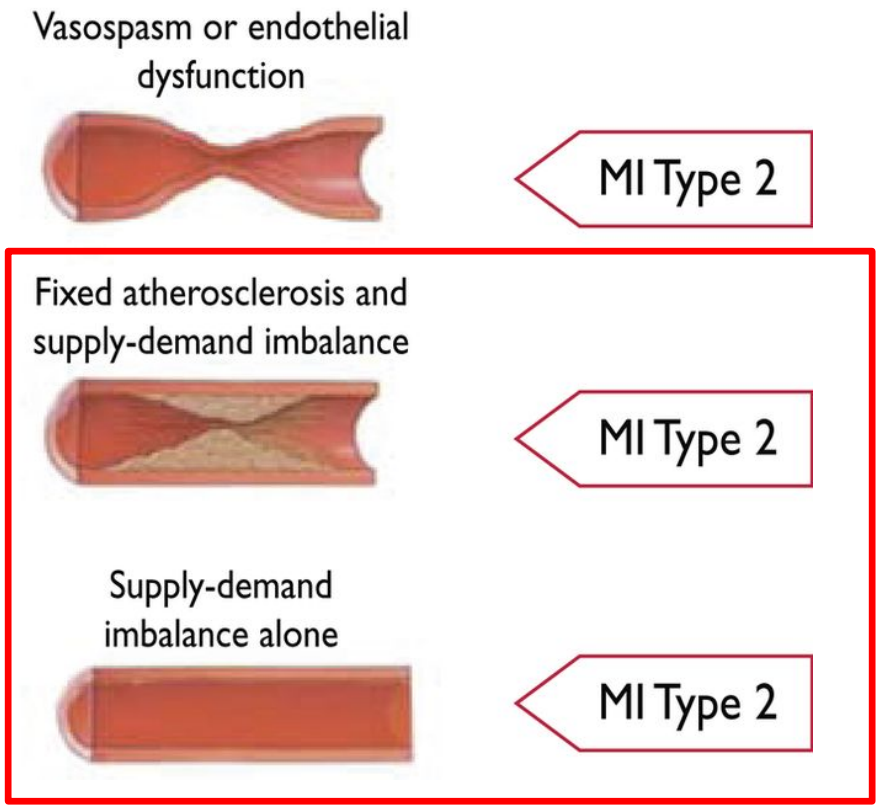
Differentiation between myocardial infarction (MI) types 1 and 2 according to the condition of the coronary arteries.

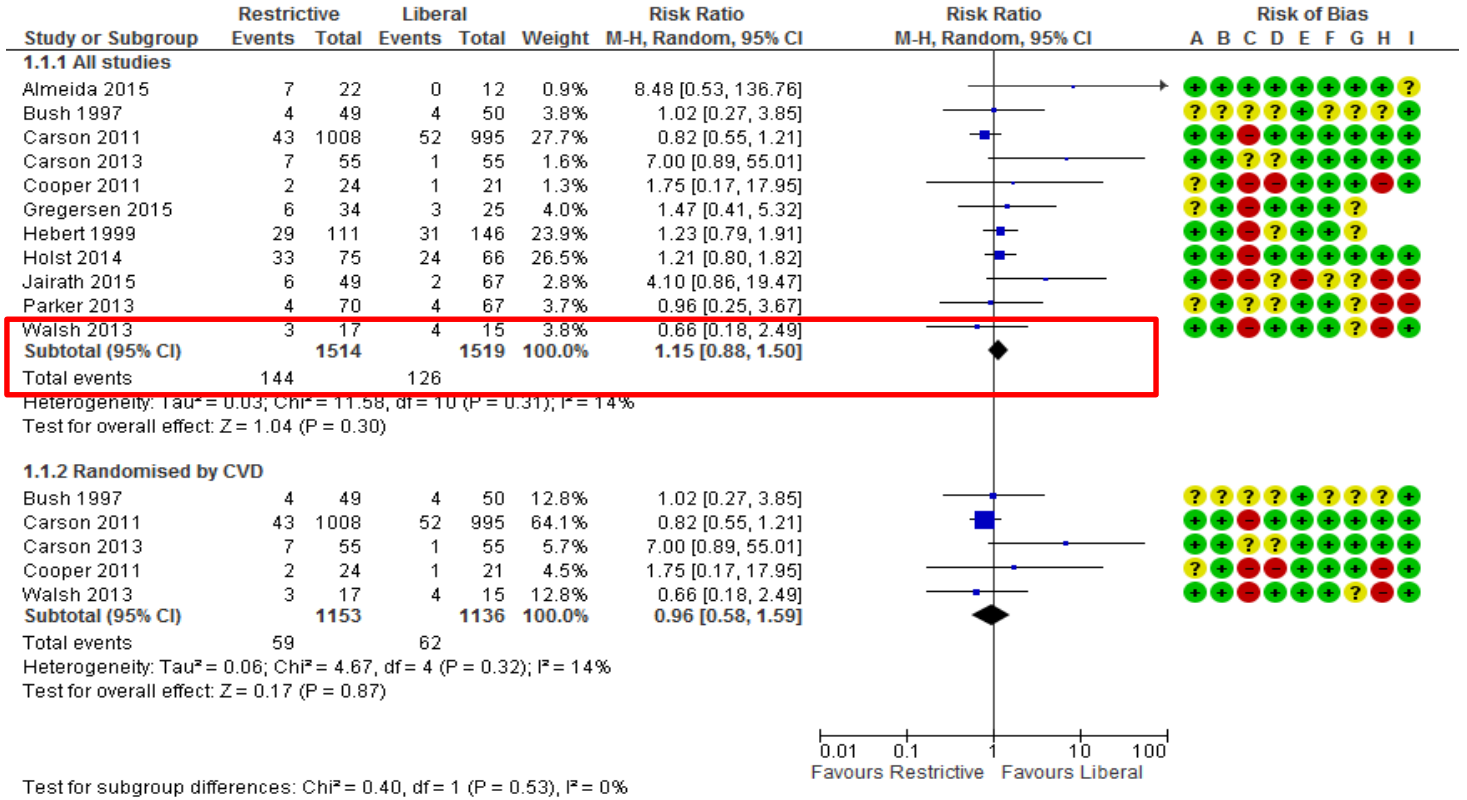




Thygesen K et al. Eur Heart J 2012;eurheartj.ehs184

Mortality in patients with chronic cardiovascular disease

Docherty AM, et al. BMJ. http://dx.doi.org/10.1136/bmj.i1351



Mortality at 30 days: **RR 1.15 (0.88 to 1.50)**

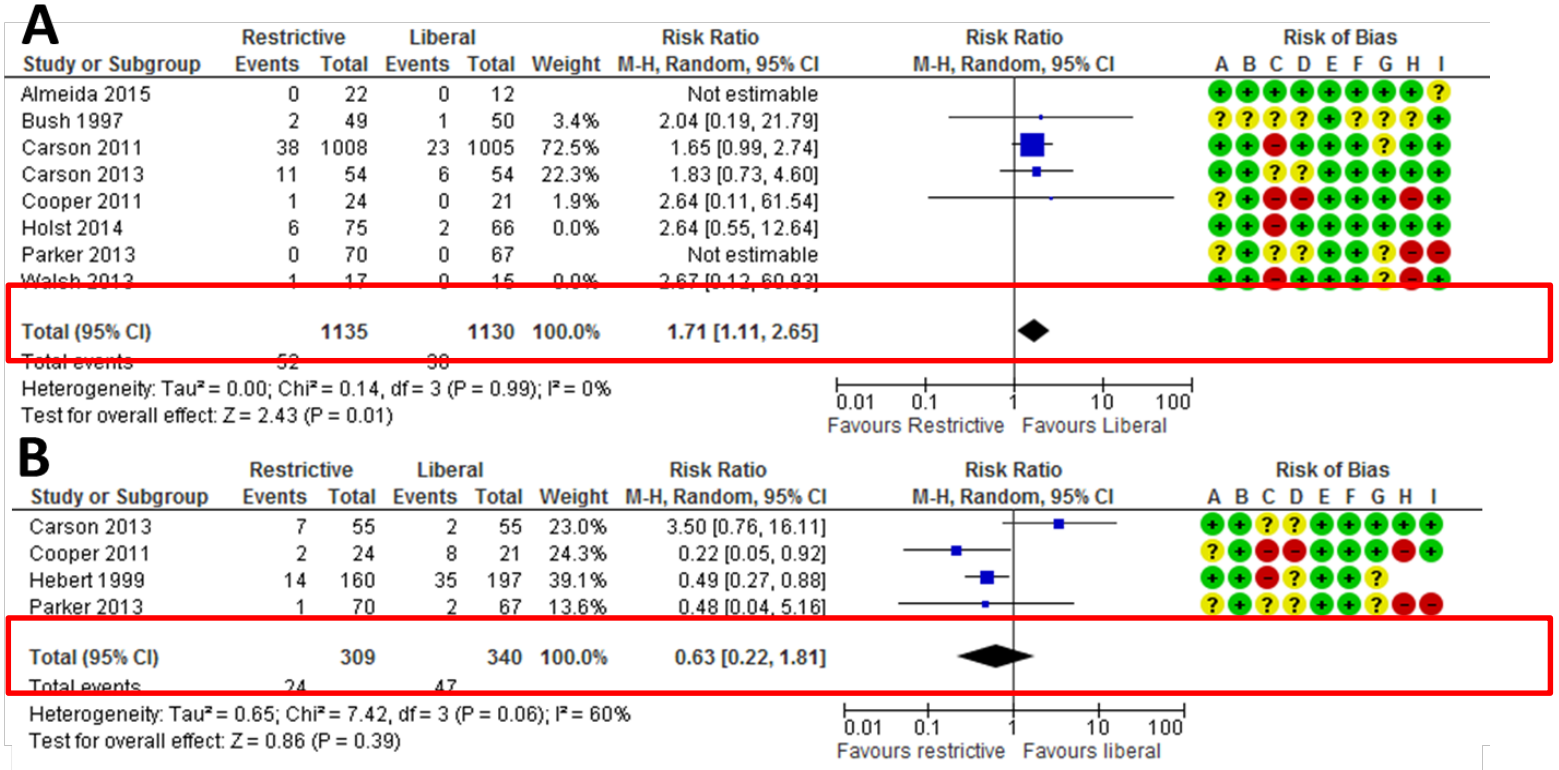
Holst et al Systematic Review

All comers (*including CVD*): **RR 0.86 (0.74 to 1.01)**

EDINBURGH CRITICAL CARE RESEARCH GROUP

Acute coronary syndrome and pulmonary oedema in patients with chronic cardiovascular disease

Docherty AM, et al. BMJ. http://dx.doi.org/10.1136/bmj.i1351



ACS: RR 1.71 (0.11 to 2.65); I^2 0%
Absolute risk difference ≈2%; NNT ≈50

bjh guideline

Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients

Andrew Retter,[1,2] Duncan Wyncoll,[1] Rupert Pearse,[3] Damien Carson,[4] Stuart McKechnie,[5] Simon Stanworth,[6] Shubha Allard,[7] Dafydd Thomas,[8] Tim Walsh[9] and British Committee for Standards in Haematology

British Journal of Haematology, 2013, **160**, 445–464

JAMA | Special Communication

Clinical Practice Guidelines From the AABB Red Blood Cell Transfusion Thresholds and Storage

Jeffrey L. Carson, MD; Gordon Guyatt, MD; Nancy M. Heddle, MSc; Brenda J. Grossman, MD, MPH; Claudia S. Cohn, MD, PhD; Mark K. Fung, MD, PhD; Terry Gernsheimer, MD; John B. Holcomb, MD; Lewis J. Kaplan, MD; Louis M. Katz, MD; Nikki Peterson, BA; Glenn Ramsey, MD; Sunil V. Rao, MD; John D. Roback, MD, PhD; Aryeh Shander, MD; Aaron A. R. Tobian, MD, PhD

JAMA. 2016;316(19):2025-2035. doi:10.1001/jama.2016.9185
Published online October 12, 2016.

Anaesthesia 2016, 71, 829–842 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]

Blood transfusion

NICE guidelines [NG24] Published date: November 2015

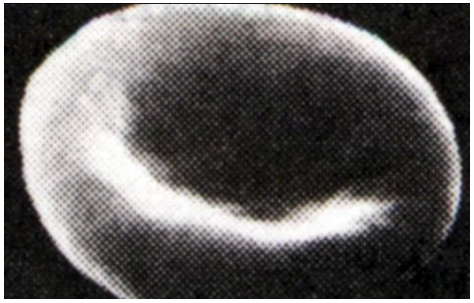
Guidance

This guideline covers the assessment for and management of blood transfusions in adults, young people and children over 1 year old. It covers the general principles of blood transfusion, but does not make recommendations relating to specific conditions.

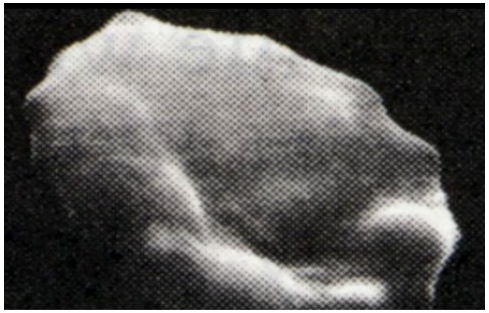
Recommendations

The guideline includes recommendations on:

- alternatives to transfusion for patients having surgery
- thresholds, targets and doses for red blood cells, platelets, fresh frozen plasma, cryoprecipitate, and prothrombin complex concentrate

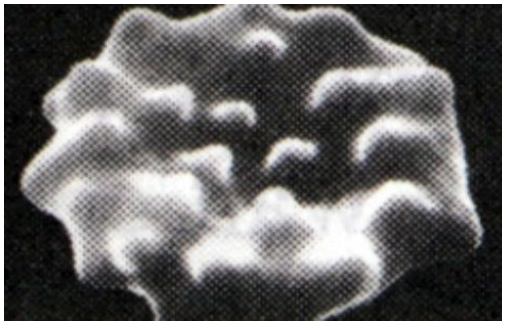


Membrane phospholipid vesiculation and blebbing
Cytoskeletal remodelling
Dissociation of membrane bi-layer from skeletal cytoskeleton
Loss of membrane (?pro-thrombotic)



Damage and Loss of band 3 protein (increased susceptibility to oxidation)
Increased cellular permeability

Depletion of cellular energy (ATP and total ATP/ADP/AMP stores)
(impaired oxygen release)
Lipid peroxidation
Proteolysis
Ca^{++} influx



Accumulation of bioreactive substances
(proinflammatory?)

Physical loss of membrane (contains lipids and cytoskeletal protein)
Altered volume to surface area
Micro-vesicle release
Loss of deformability (?↓ transit)
Increased interaction with endothelium
(?↑ adherence)

RBC storage age and outcomes

Four large trials comparing fresher RBCs versus older RBCs (stored around 20 days) in different patient groups

- ABLE trial (critical care) N Engl J Med 2015
  - DOI: 10.1056/NEJMoa1500704
- RECESS trial (cardiac surgery) N Engl J Med 2015
  - DOI: 10.1056/NEJMoa1414219
- INFORM trial (hospital wide) N Engl J Med 2016
  - DOI: 10.1056/NEJMoa160901
- TRANSFUSE trial (critical care) N Engl J Med 2017
  - DOI: 10.1056/NEJMoa170757

- No benefit from transfusing fresher over standard age (or older) RBCs in any clinical setting tested

Blood transfusion during acute illness: a logic model

Patient	Condition	Complication	Intervention	Outcomes
Age Gender Co-Morbidities CVD Respiratory Neurological Haemato-Logical Marrow failure Oncology Other anaemias	Trauma Sepsis Cancer Surgery Radiotherapy chemotherapy Obstetrics Liver disease Illness severity Physiological disturbance Organ failure	Major Bleeding Trauma GI bleeding Surgery Anaemia Bleeding Acute marrow impairment Blood sampling Haemodilution Anaemia severity	Blood transfusion Volume No. units Target Hb RBC product Leucodepletion Storage age Storage conditions Whole blood	Mortality Timing Illness severity Organ failures Quality of Life QALYS Patient symptoms Fatigue Breathlessness Resource Length of stay Costs

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Personalised transfusion medicine: the major uncertainties

- Chronic cardiovascular disease
- Acute myocardial infarction (MINT trial)
- Acute brain injury
  - Traumatic brain injury (Hemotion trial)
  - Sub-arachnoid haemorrhage (SAHaRA trial)

- Chronic anaemia
  - Marrow failure
  - Post acute/critical illness
  - RBC transfusion versus iron/EPO

‘Blut ist ein ganz besondrer Saft.’
(Blood is a very special juice.)

Faust. Goethe

‘The best transfusion is the one that was never given’

Anon.


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