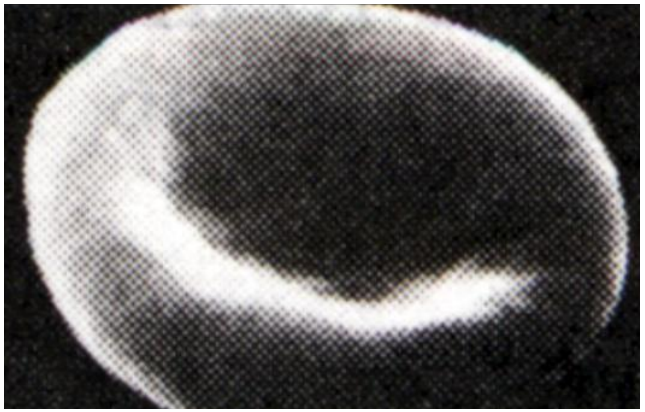
Anaemia in Critical Care

Tim Walsh

Professor of Critical Care, Edinburgh University



World Health Organisation grading of the severity of anaemia

Grade of anaemia	**Haemoglobin range ($g.dL^{-1}$)**
0 (none)	>11
1 (mild)	9.5-10.9
2 (moderate)	8.0-9.4
3 (severe)	6.5-7.9
4 (life threatening)	<6.5

Questions answered?

- Why are so many critically ill patients anaemic?
- Should I give all patients iron?
- Should I use erythropoietin?
- What is my “default” haemoglobin transfusion trigger?
- What should I do in sepsis?
- What should I do for patients with cardiovascular disease?
- Should I ask for “fresh” blood?

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Causes of anaemia during critical illness

Pre-existing anaemia

Acquired anaemia

Haemodilution

Blood loss

- Blood sampling
- Haemorrhage

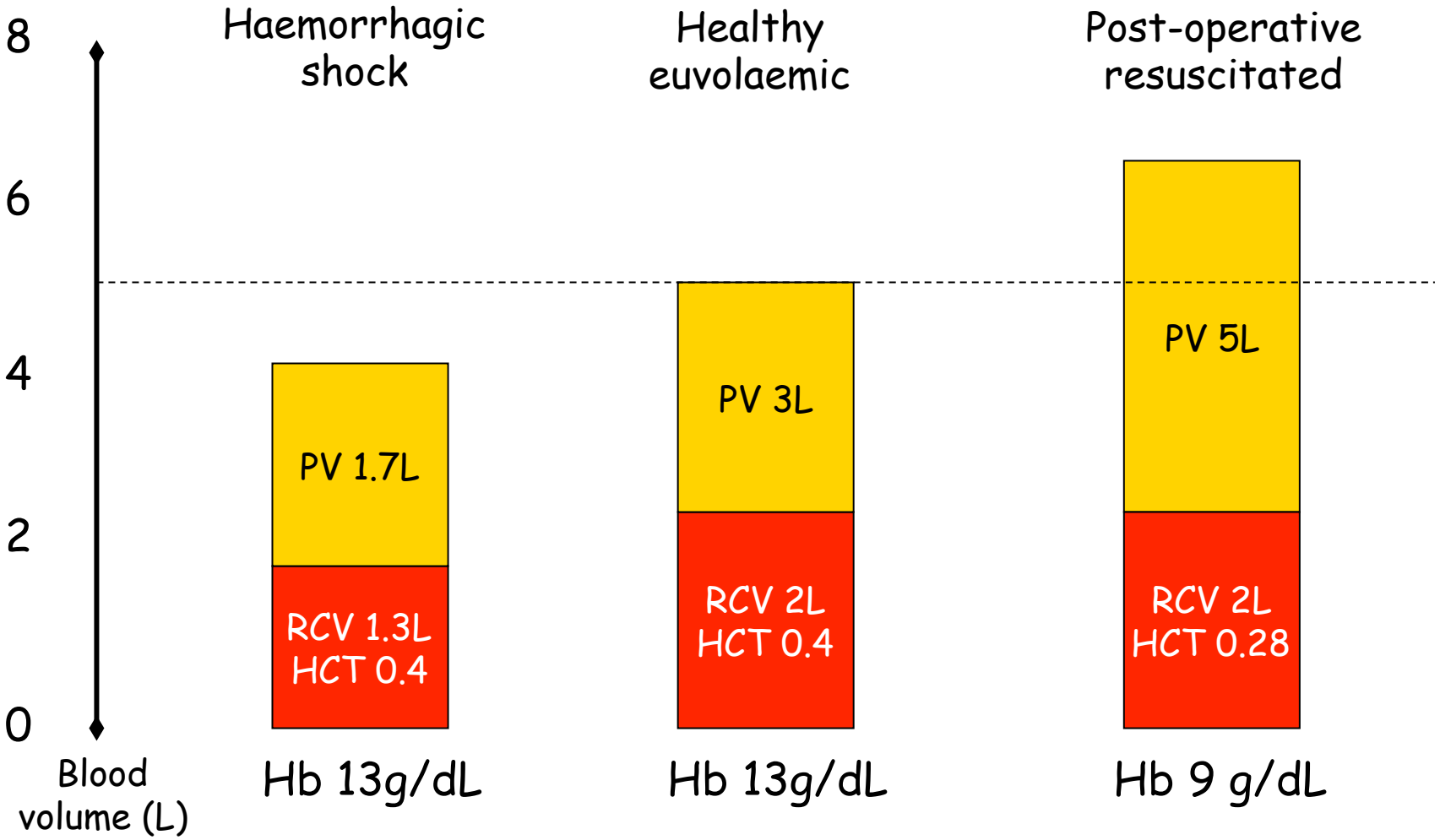
Reduced red cell survival

Reduced red cell production

- Abnormal iron metabolism
- Nutritional deficiencies
- Inappropriate erythropoietin production

Abnormal red cell production

What does haemoglobin concentration or HCT mean?



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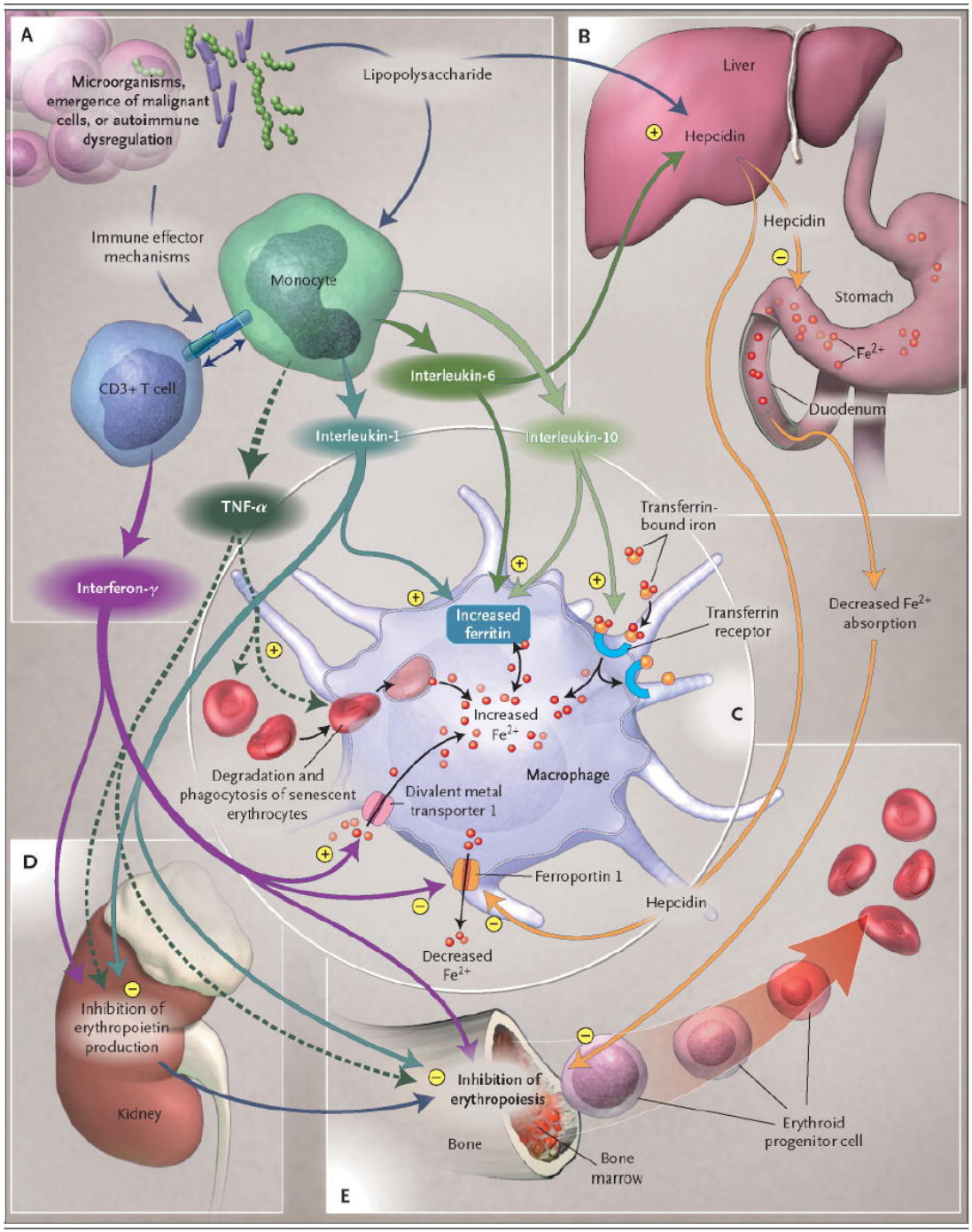
Abnormal red cell production

Erythroid indices during critical Illness

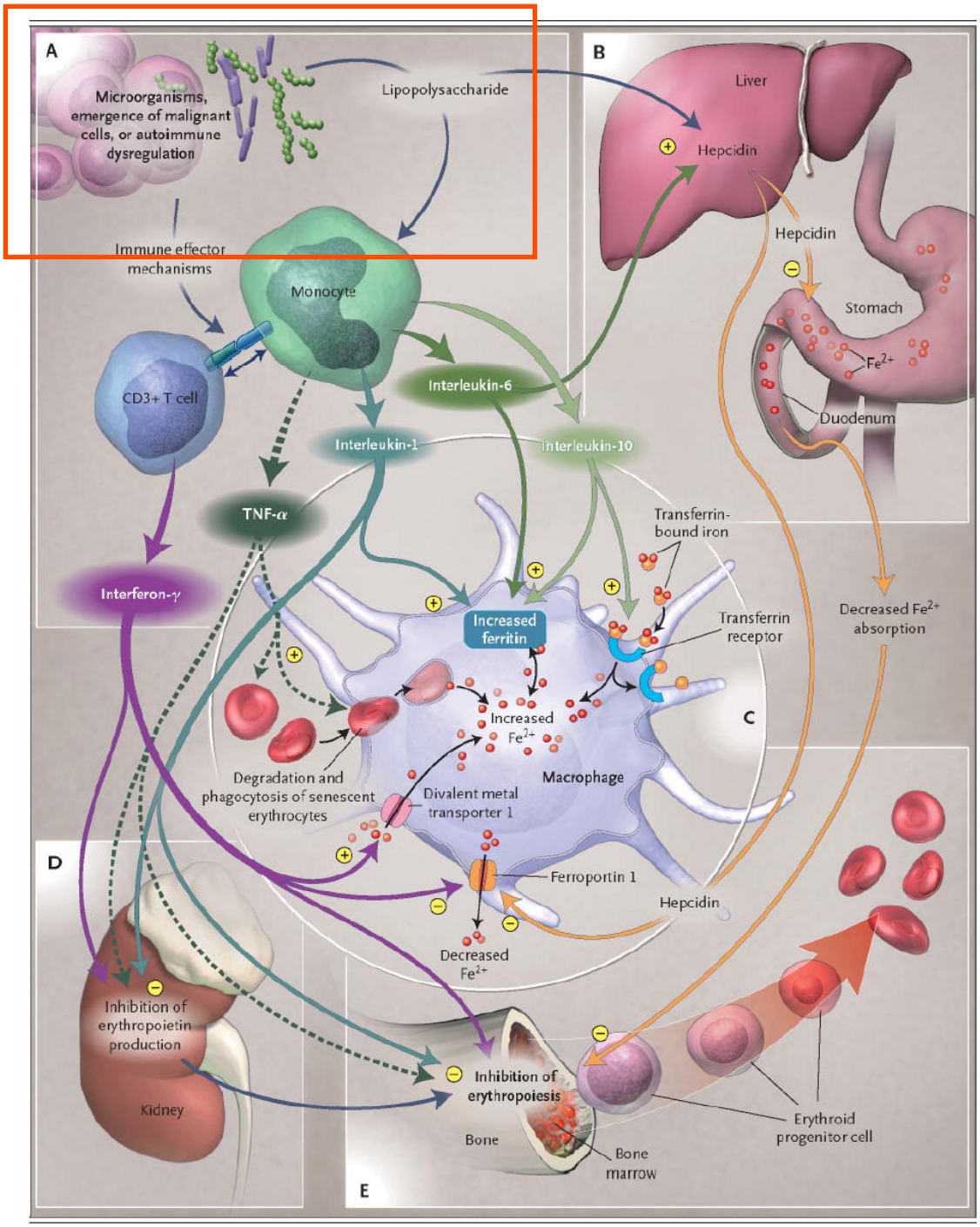
	Change
Serum iron	↓
Total iron binding capacity	↓
Serum iron/total iron binding capacity ratio	↓
Ferritin	↑
Transferrin	↓
Transferrin saturation	↓
Vitamin B12 and folate	N
Erythropoietin concentration	N/slight increase
Reticulocytes	Non-anaemic levels
Serum transferrin receptors	Normal



The anaemia of chronic disease

Weiss, G. and Goodnough, L. T.

N Engl J Med 2005;**352**:1011



The inflammatory "hit"

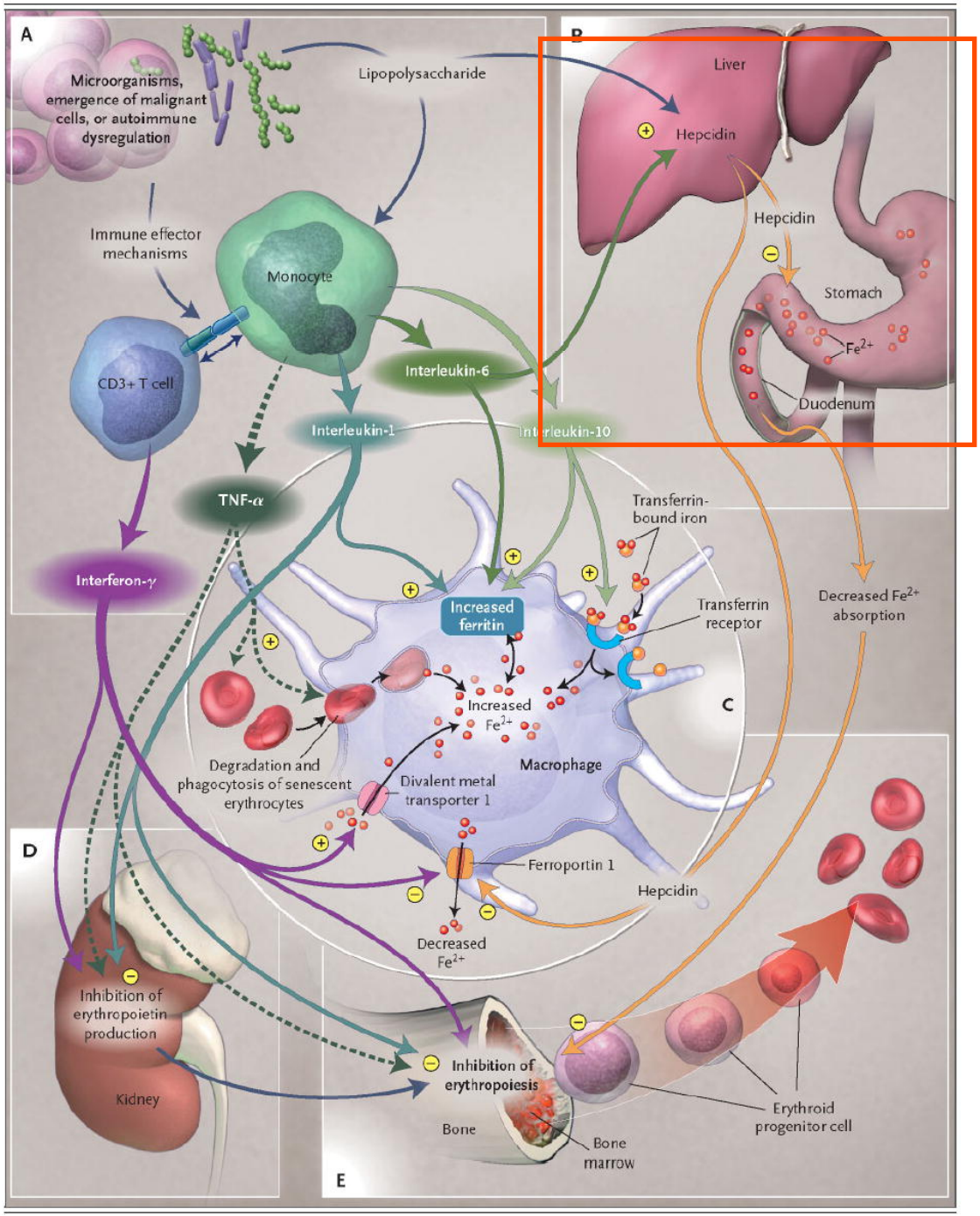
The anaemia of chronic disease

Weiss, G. and Goodnough, L. T.

N Engl J Med 2005;**352**:1011

Effects of inflammation

- Inhibition of renal erythropoietin production
  - Blunted “inappropriate” response to anaemia
- Direct effects on erythropoiesis in bone marrow
- Effects on acute phase proteins



"Acute phase" effects on the liver

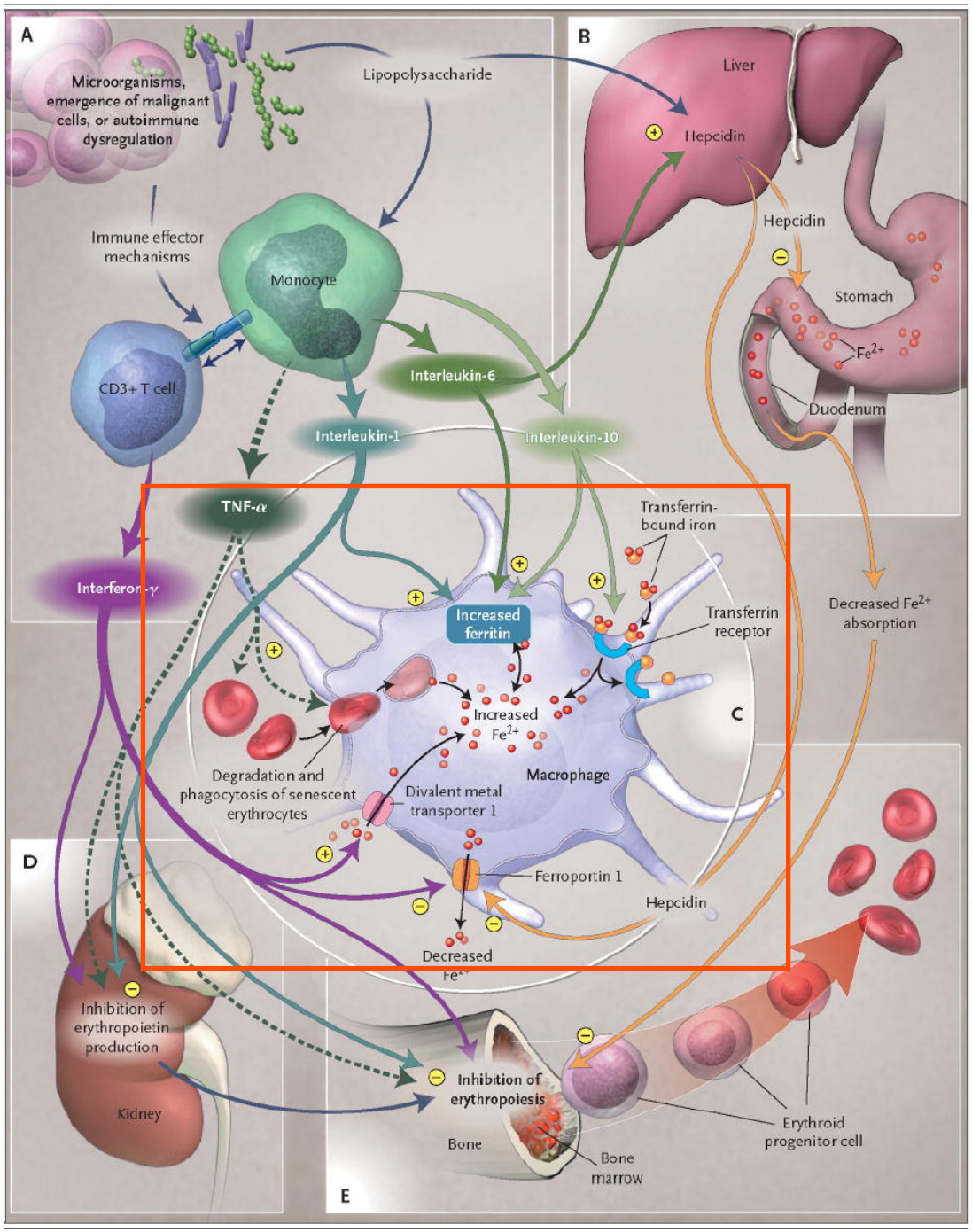
The anaemia of chronic disease

Weiss, G. and Goodnough, L. T.

N Engl J Med 2005;**352**:1011

Acute phase effects on the liver

- Up-regulation of ferritin production
  - Increased storage iron
- Down-regulation of transferrin production
  - Decreased iron availability for erythropoiesis
- Up-regulation of hepcidin production
  - Decreased duodenal iron absorption



Altered iron handling by macrophages and RES

The anaemia of chronic disease

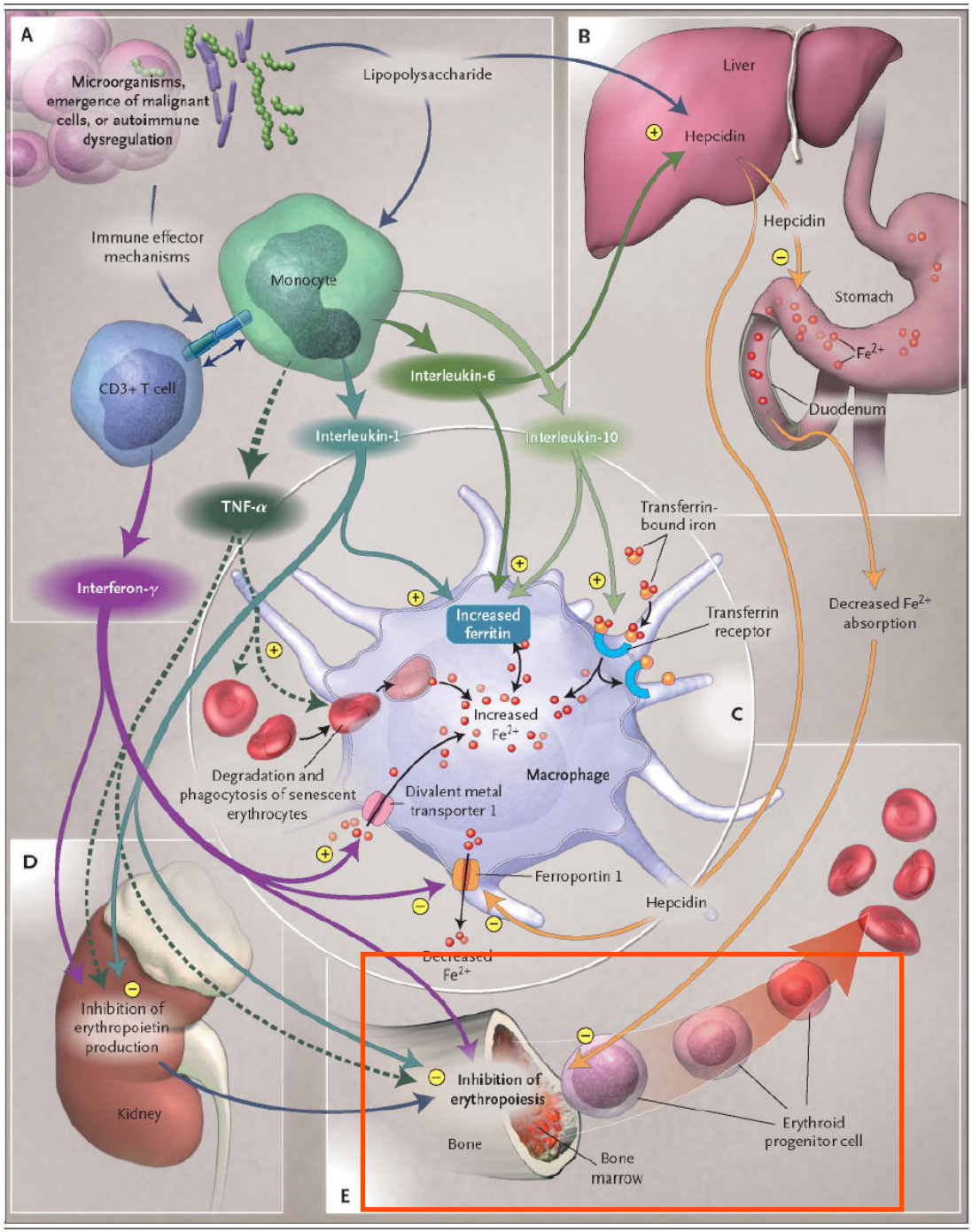
Weiss, G. and Goodnough, L. T.

N Engl J Med 2005;**352**:1011

Effects on macrophage and RES

- Increased iron uptake
  - Increased ferritin
  - Opening of divalent metal transported protein
  - Closure of ferroportin 1
- Increased phagocytosis of senescent red cells by activated macrophages
- Increased uptake of transferrin bound iron

- Functional iron deficiency

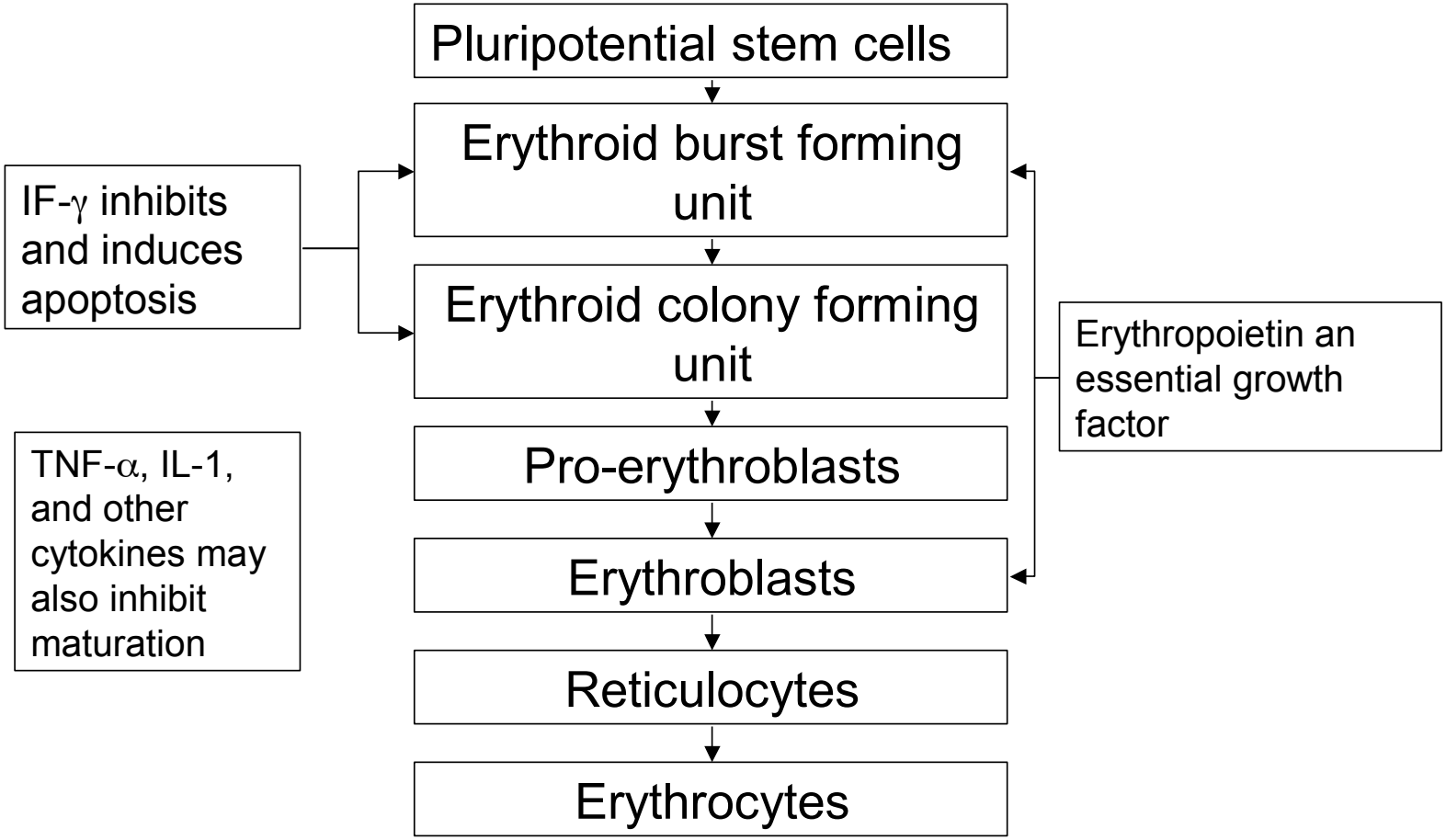


Impaired erythrogenesis

The anaemia of chronic disease

Weiss, G. and Goodnough, L. T.

N Engl J Med 2005;**352**:1011



Lack of reticulocyte response

Last Hb prior to ICU discharge among ICU survivors

	Males	Females
Last Hb value in ICU Median (IQR) g/dL	10.0 (9.0 – 11.7)	9.8 (8.8 – 11.0)
Last Hb in ICU < ref range [M <13; F <11.5 g/L] %	87.0	79.6
Last Hb in ICU <9 g/dL %	24.1	27.9

Walsh et al. Intensive Care Medicine 2006; 32: 100-109

Prevalence of anaemia at hospital discharge.

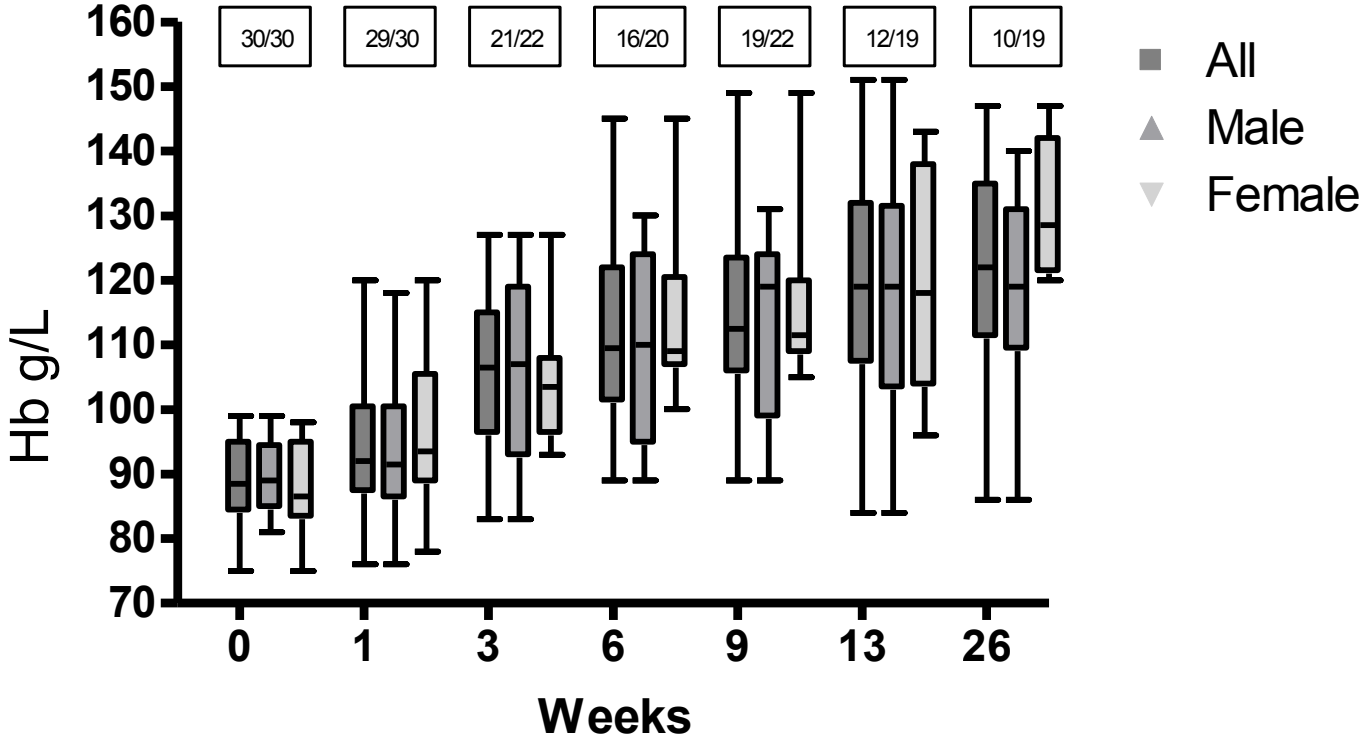
Hb level	Males (n=161) N (%)	Females (n=122) N (%)	All patients (n=283) N (%)
Hb < 90 g/L	14 (8.7)	18 (14.8)	32 (11.3)
Hb < 100g/L	48 (29.8)	44 (36.1)	92 (32.5)
Hb < reference range.	137 (85.1)	82 (67.2)	219 (77.4)

Walsh et al. Intensive Care Medicine 2006; 32: 1206

	Males n (%) n = 97	Females n (%) n = 65
Normochromic normocytic	76 (78)	56 (86)
Normocytic hyperchromic	10 (10)	4 (6)
Normo/microcytic hypochromic	5 (5)	3 (5)
Other	6 (6)	2 (3)

Walsh et al. Intensive Care Medicine 2006; 32: 1206

Recovery from anaemia over 6 months post-ICU discharge



At 13 weeks: 32% Hb <11 g/dL
At 26 weeks: 16% Hb <11 g/dL

Bateman AP, McArdle FI, Walsh TS.
Critical Care Medicine; 37(6):1906-12, 2009

Factors associated with slow or failure to recover

- Higher circulating inflammatory markers following discharge (IL-6 and CRP)
- Lack of reticulocyte response

- Erythropoietin concentrations inappropriately low in all patients
- No evidence of nutritional deficiency
- “Inflammatory” anaemia

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Iron

- Functional not absolute iron deficiency
  - Trends in Pharmacological Sciences 2014; 35:155-61
- Iron therapy associated with increased infections
- No benefit in trauma critical care
  - Crit Care Med 2014; 42:2048–2057
- No RCT evidence in other populations
- Await larger pragmatic trial
  - IRONMAN trial (ACTRN12612001249842)

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Erythropoietin

- Pharmacologic doses required in combination with iron
- Sequential trials showed lower blood-sparing effects as transfusion triggers more restrictive
- Not clinically or cost-effective effective in trials with restrictive transfusion triggers
- Excess of thrombotic events

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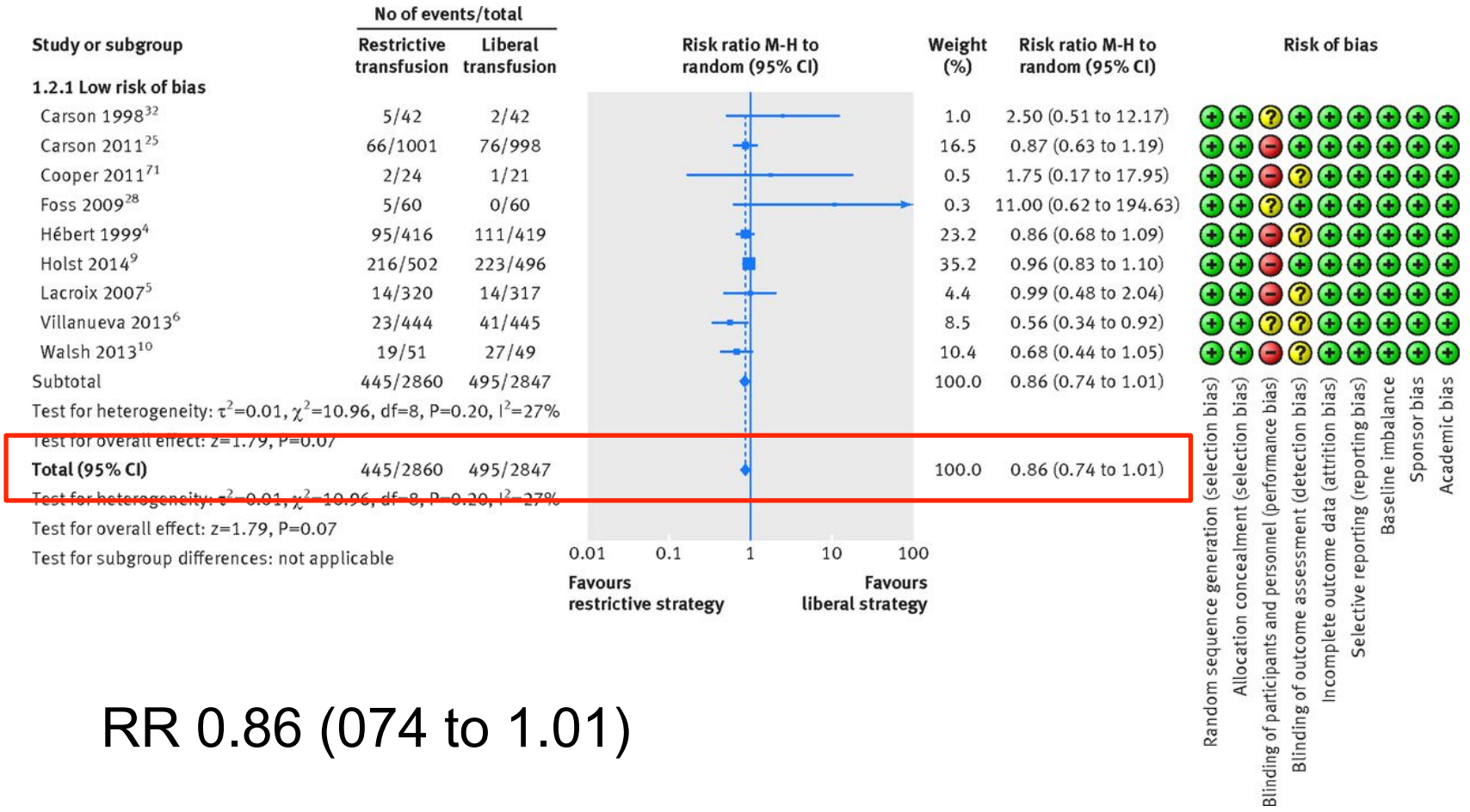
Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis

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



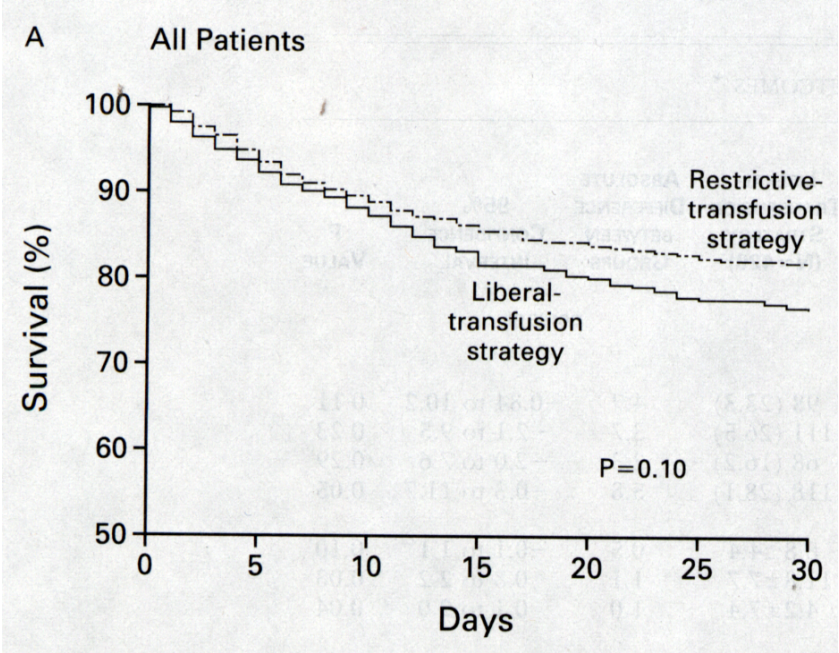
RR 0.86 (074 to 1.01)

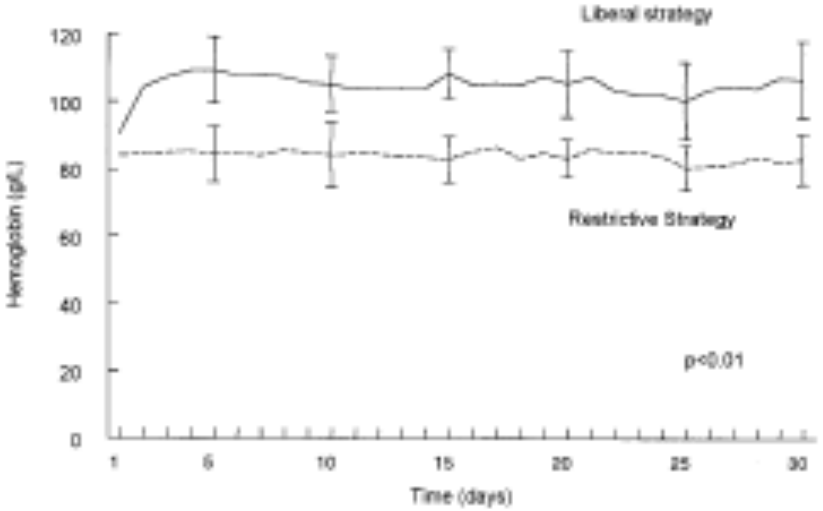
A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

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 YETIS'R, 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

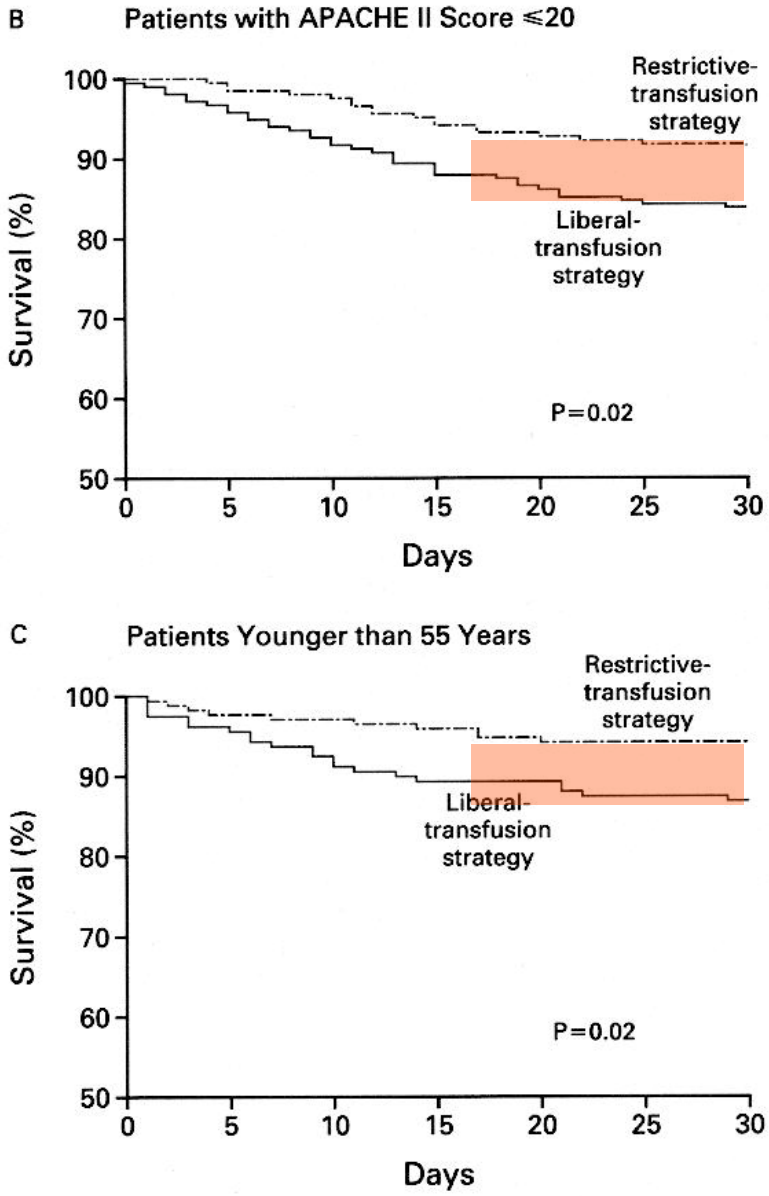




Aggregate mortality at 60 days 25%
Difference in mortality at 60 days 3-8% overall

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

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 29, 2011 VOL. 365 NO. 26

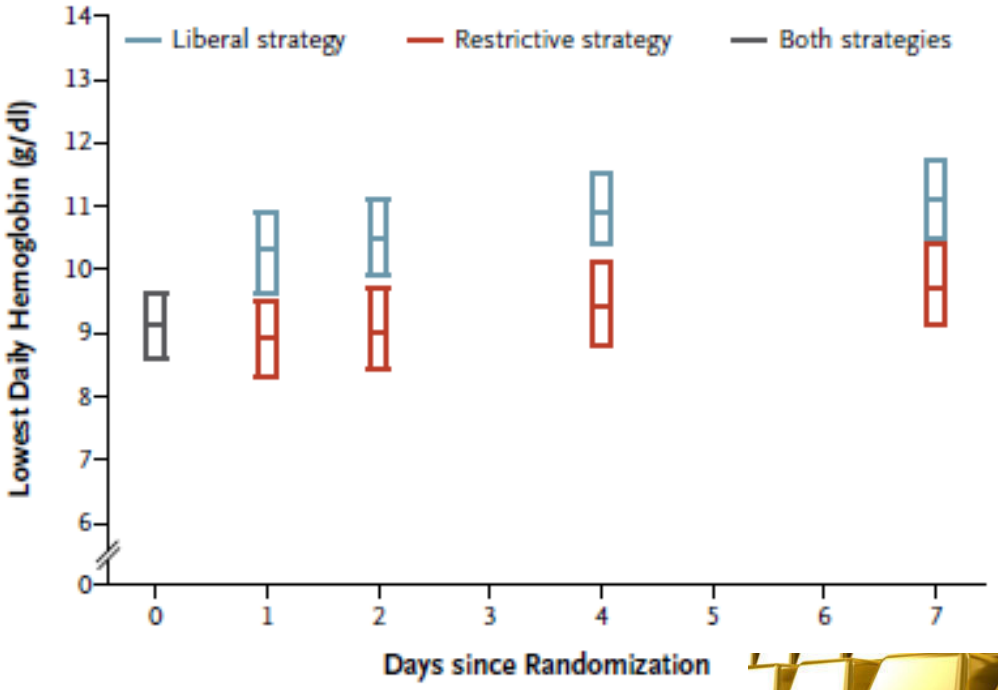
Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery

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*

Hb "symptomatic" or minimum 80 g/L versus 100 g/L

- Patients aged >50 years with cardiovascular disease or risk factors
- Mean age 82 years; cardiovascular disease 63%
- Protocolised liberal versus "clinician judgement" restrictive
- RBC use median 0 versus 2 units

- No difference in death, ability to walk unaided, or cardiovascular complications



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

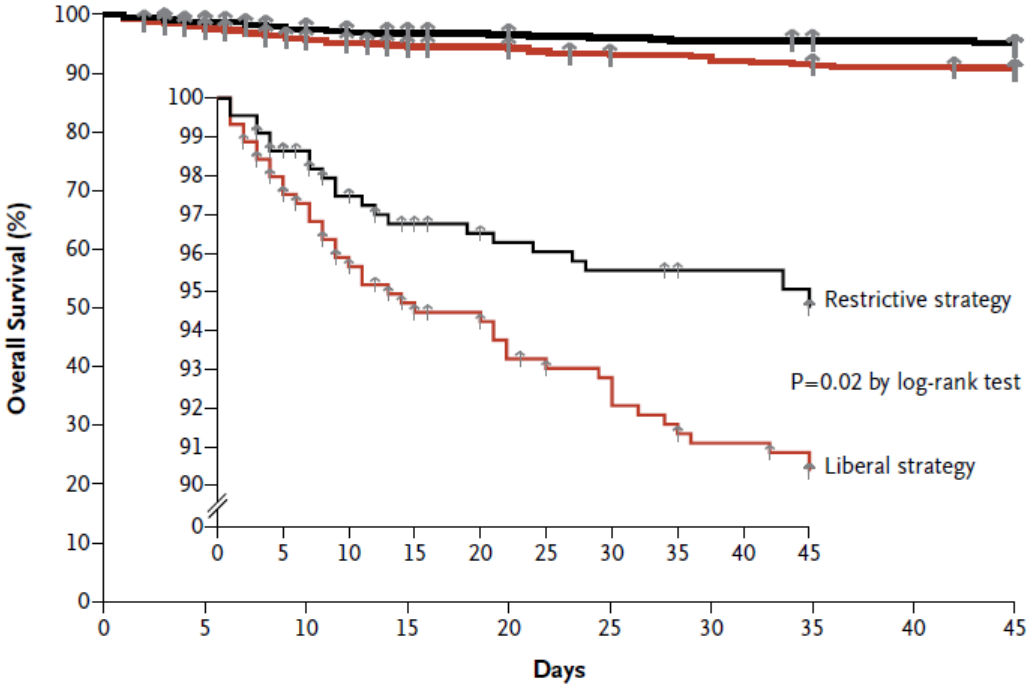
Exclusions

- Massive exsanguinating bleeding
- *Cardiovascular disease*

Stratified for presence of cirrhosis

- Single unit transfusions
- 8 hourly Hb during first 48 hours; daily thereafter
- All endoscoped within 6 hours (banding, sclerotherapy
- Portal hypertension: somatostatin infusion; prophylactic antibiotics
- Portal pressure measures within 48 hours and repeated after 2-3 days
- 31% cirrhosis; 49% peptic ulcer bleeding

A Survival, According to Transfusion Strategy

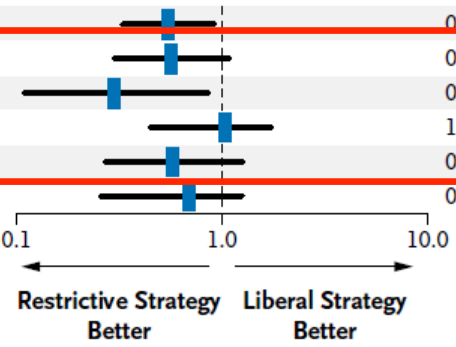


No. at Risk

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



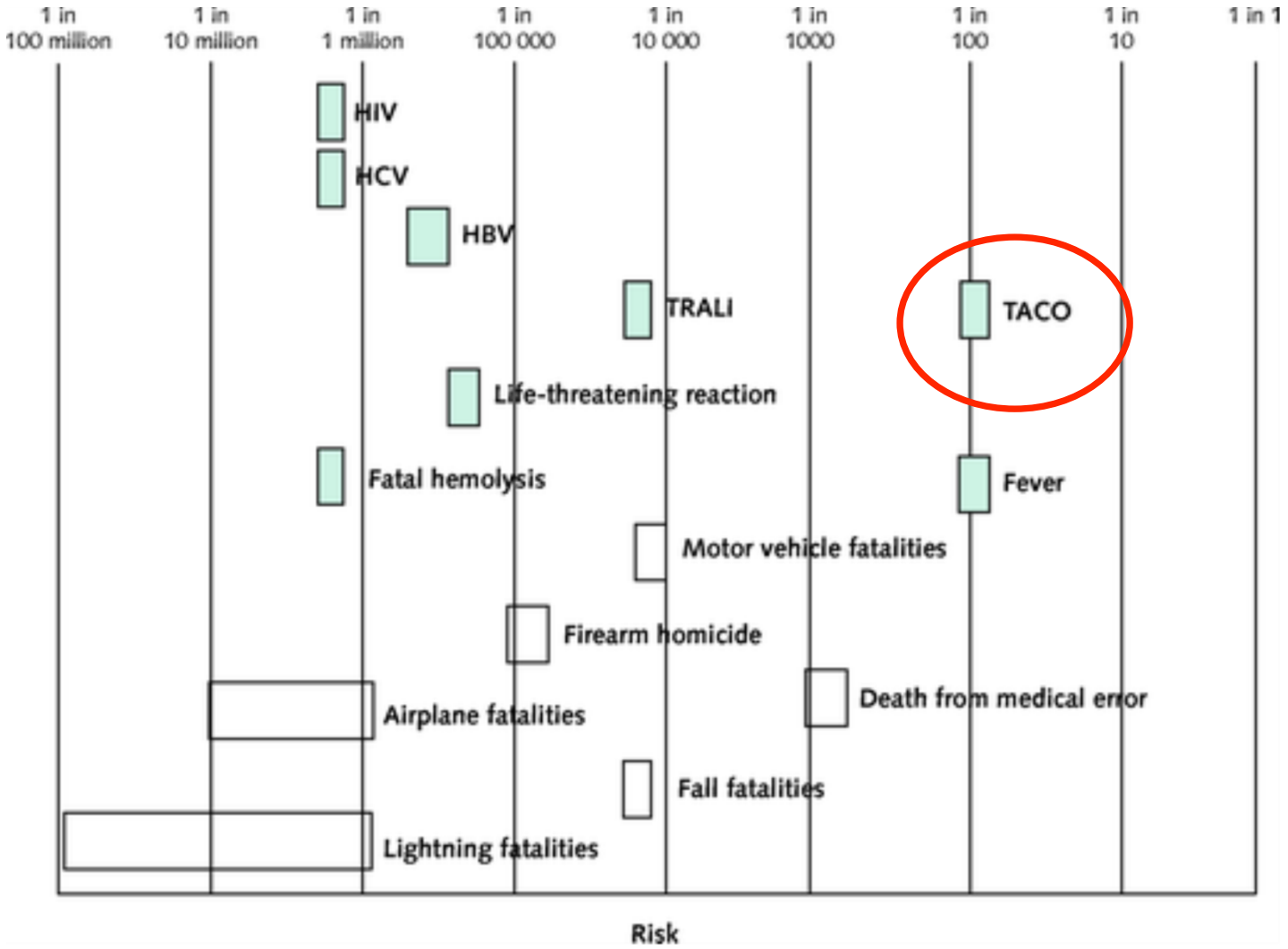
Outcomes

- Absolute risk difference for mortality in cirrhotic group 11 vs 18% (NNT 14)
- 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

- Fluid overload/hypervolaemia may have mediated adverse effects

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



The “default” haemoglobin trigger

- In “all comer” populations there is no benefit from transfusion at haemoglobin >70 g/L
- Strongest evidence for younger patients with lower illness severity
- Adverse effects may result from:
  - Hypervolaemia
  - The blood product

- When does this not apply?

Questions answered?

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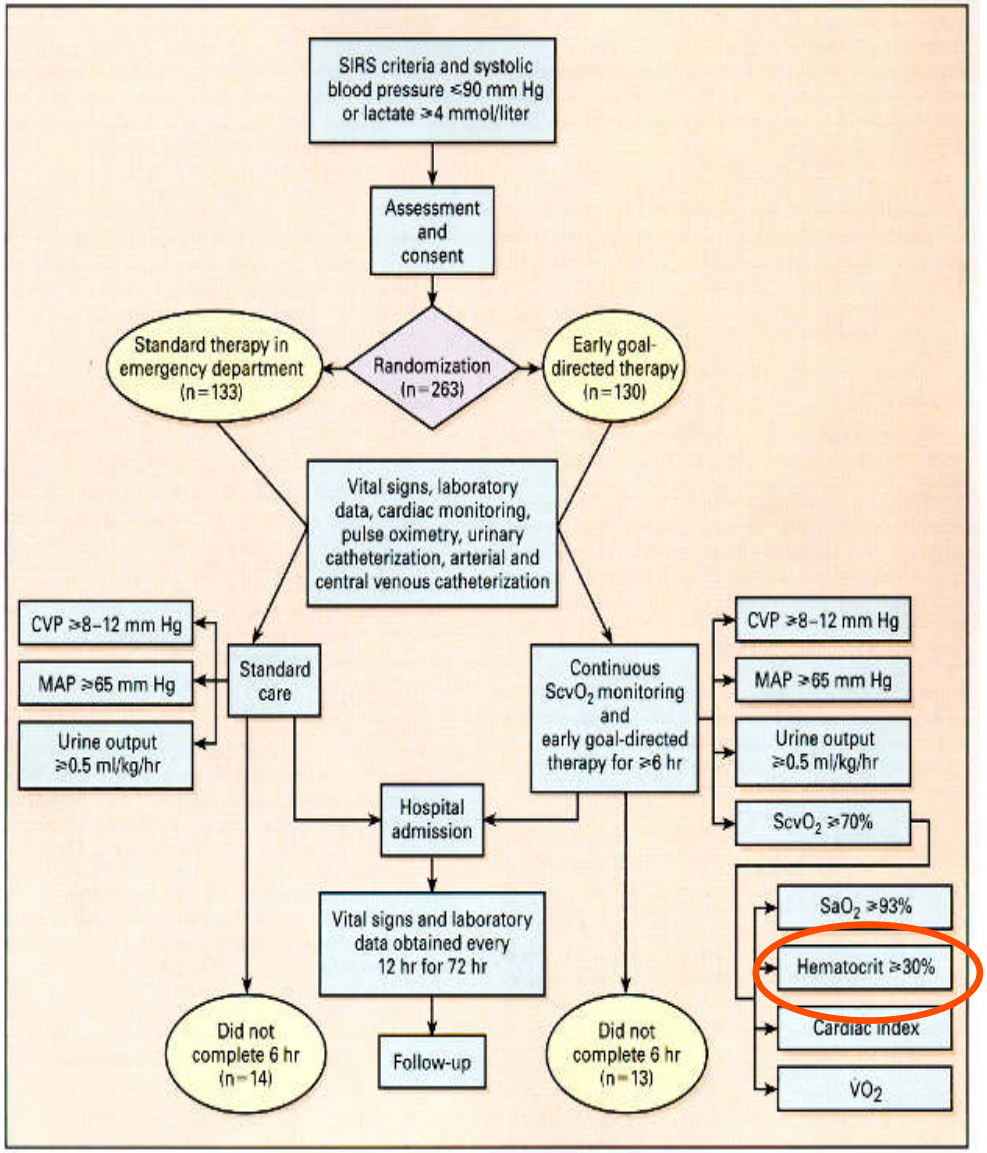
Early sepsis:
the first “golden 6 hours”?

Goal directed therapy
works if applied early
(Rivers E. NEJM
2001;345:1368-77)

Transfusing red cells to
achieve a HCT >0.3
(Hb >10 g/dL) was part
of the protocol

Only introduced if $ScvO_2$
<70%



Further down the River(s)

Propensity-matched studies:

•Association between early transfusion and improved outcome in sepsis

Trials of EGDT

•ProMISE (UK) "negative"

•PROCESS (USA) "negative"

•ARISE (Australasia) "negative"

TRISS trial (NEJM 2014;371:1381-91)

•Not an early sepsis intervention trial

•Not guided by algorithm based on correction of inadequate oxygen delivery

Comparing the “Rivers” and ARISE trials

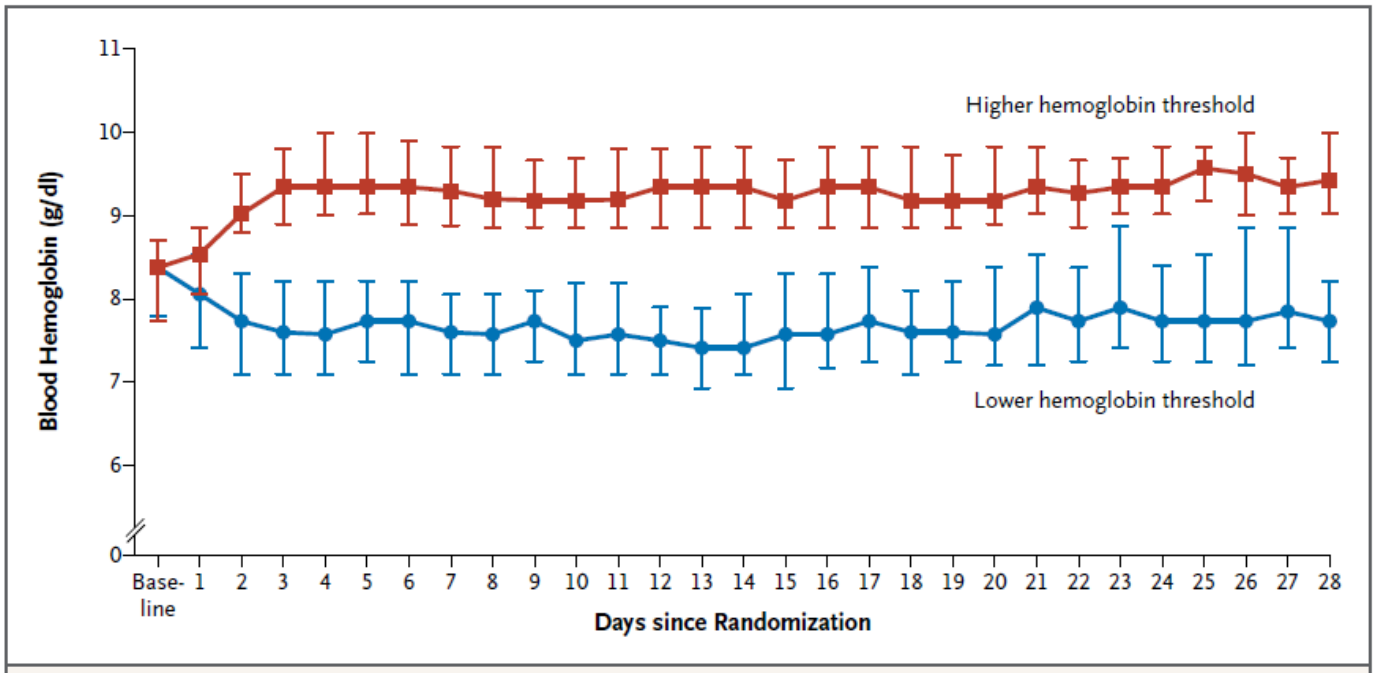
	Rivers		**ARISE**	
ED admission to randomisation	1.5 hours		2.8 hours	
APACHE II score	21		16	
Process	**Usual**	**EGDT**	**Usual**	**EGDT**
$ScVO_2$	49%	49%	-	73%
Antibiotics	89% in first 6 hours		100% (median time 70 minutes)	
Fluids 0-6 hours	3500	4900	1700 (2600)	2000 (2500)
RBCs (% transfused)	19	65	7	14
Vasopressors	30	27	58 (22)	67 (22)
Dobutamine	1	14	3	15
6 hour parameters				
Lactate	4.9	4.3	2.9	2.8

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



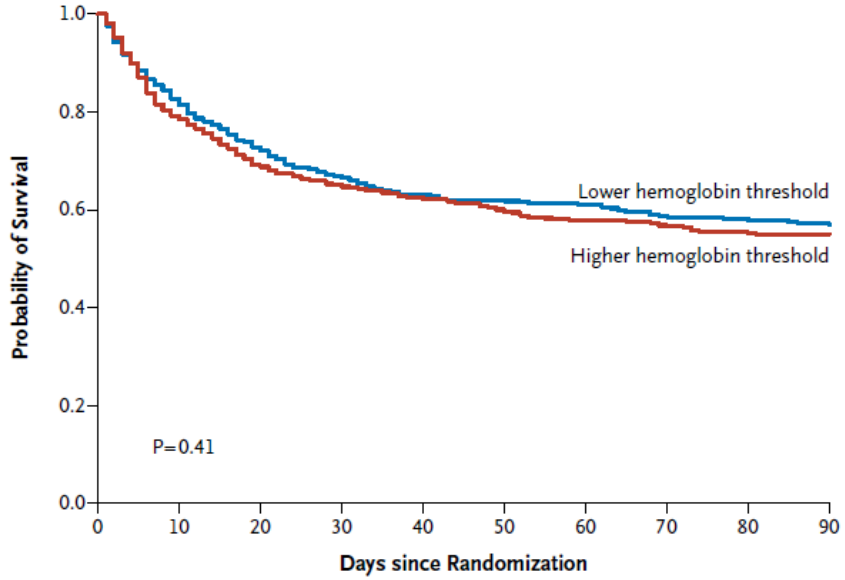
Transfusion exposure: restrictive 64% (median 1 unit)
liberal 99% (median 3 units)

Table 1. Characteristics of the Trial Patients at Baseline.*

Characteristic	Lower Hemoglobin Threshold (N = 502)	Higher Hemoglobin Threshold (N = 496)
Age — yr		
Median	67	67
Interquartile range	57–73	58–75
Male sex — no. (%)	272 (54.2)	259 (52.2)
Chronic cardiovascular disease — no. (%)†	75 (14.9)	66 (13.3)
Chronic lung disease — no. (%)‡	111 (22.1)	102 (20.6)
Hematologic cancer — no. (%)	39 (7.8)	36 (7.3)
Admission to a university hospital — no. (%)	323 (64.3)	324 (65.3)
Surgery during index hospitalization — no. (%)		
Emergency	191 (38.0)	217 (43.8)
Elective	59 (11.8)	53 (10.7)
Source of ICU admittance — no. (%)		
Emergency department	90 (17.9)	79 (15.9)
General ward	268 (53.4)	257 (51.8)
Operating or recovery room	113 (22.5)	121 (24.4)
Other ICU	31 (6.2)	39 (7.9)
Source of sepsis — no. (%)§		
Lungs	267 (53.2)	259 (52.2)
Abdomen	206 (41.0)	198 (39.9)
Urinary tract	58 (11.6)	61 (12.3)
Soft tissue	59 (11.8)	59 (11.9)
Other	50 (10.0)	47 (9.5)
Positive culture from blood or sterile site	188 (37.5)	160 (32.3)
Interval from ICU admission to randomization — hr		
Median	23	20
Interquartile range	7–50	7–43
SAPS II¶		
Median	51	52
Interquartile range	42–62	44–64

Mean time to recruitment 21 hours post-ICU admission

A Time to Death

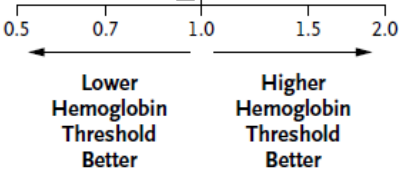


No. at Risk

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

B Relative Risk of the Primary Outcome

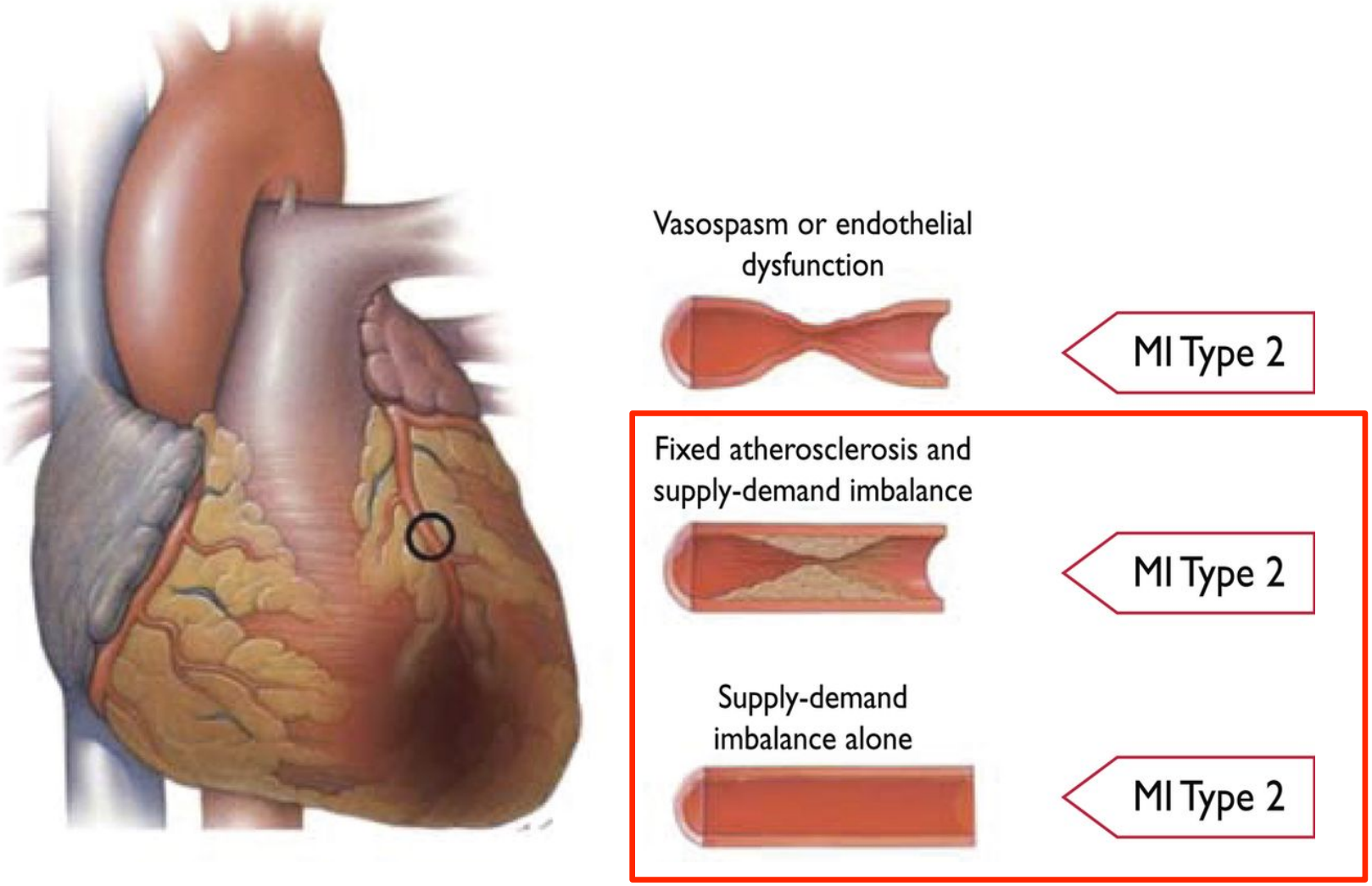
Subgroup	Lower Hemoglobin Threshold	Higher Hemoglobin Threshold	Relative Risk (95% CI)	P Value for Heterogeneity
	no. of events/no. of patients in subgroup			
Age				0.85
>70 yr	93/173	98/185	0.98 (0.79–1.18)	
≤70 yr	123/329	125/311	0.94 (0.75–1.14)	
Chronic cardiovascular disease				0.25
Yes	42/75	33/66	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)	



Questions answered?

- Why are so many critically ill patients anaemic?
- Should I give all patients iron?
- Should I use erythropoietin?
- What is my “default” haemoglobin transfusion trigger?
- What should I do in sepsis?
- What should I do for patients with cardiovascular disease?
- Should I ask for “fresh” blood?

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

Issues in relation to transfusion:
different patient types

- Cardiac surgery
- Stable chronic IHD or cardiovascular disease with concurrent disease
- Acute coronary syndrome

Liberal or restrictive transfusion after cardiac surgery.

Murphy GJ; Pike K; Rogers CA; Wordsworth S; Stokes EA; Angelini GD; Reeves BC; TITRe2 Investigators
New England Journal of Medicine. 372(11):997-1008, 2015 Mar 12.
DOI: 10.1056/NEJMoa1403612

Hb 75g/L versus 90g/L

- Randomisation post-surgery
- Transfusion exposure 53% versus 92%
- Median 1 unit versus 2 units

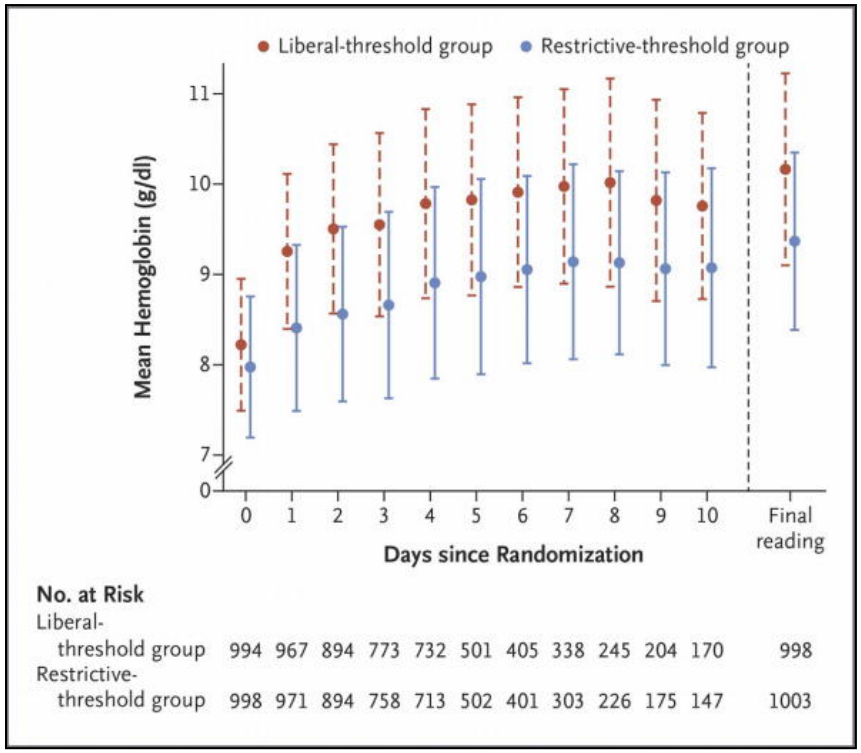
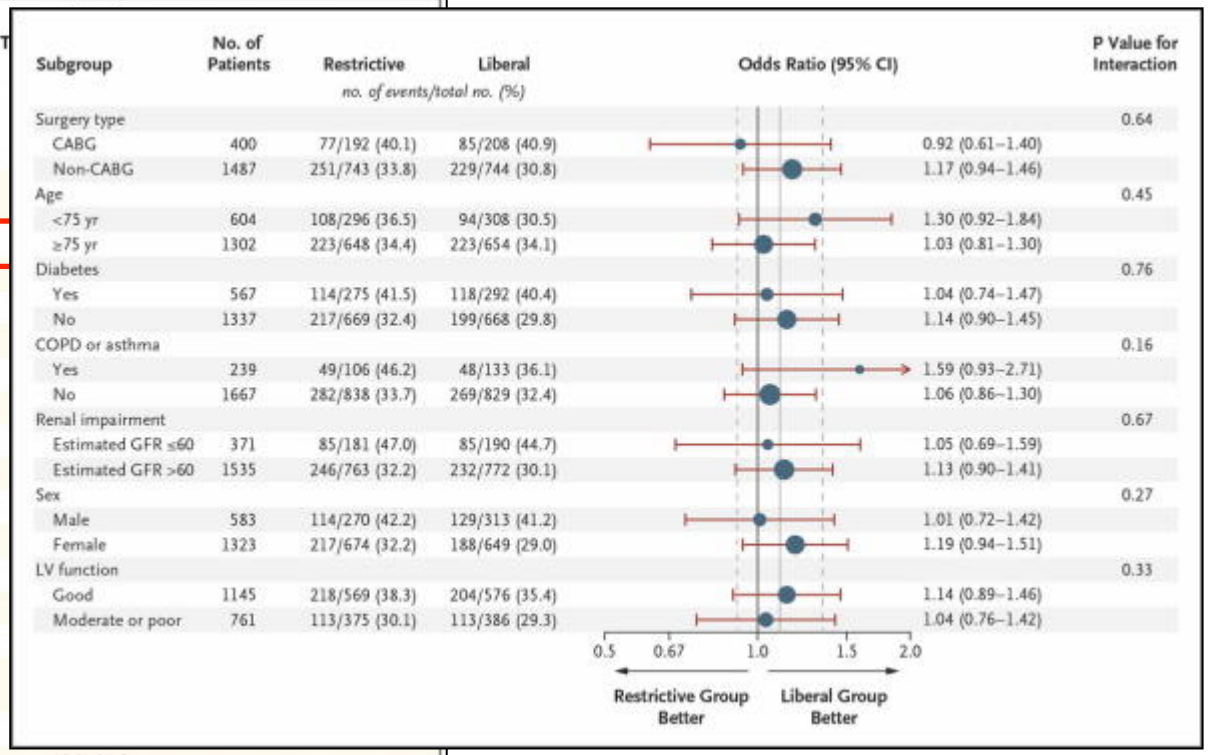


Table 3. Outcomes.

Outcome	Restrictive Transfusion Threshold (N=1000)	T		
Serious infection or ischemic event: primary outcome				
Overall	331/944 (35.1)			
Infectious event†	238/936 (25.4)			
Sepsis	210/982 (21.4)			
Wound infection	55/921 (6.0)			
Ischemic event	156/991 (15.7)			
Permanent stroke	15/989 (1.5)			
Myocardial infarction	3/987 (0.3)			
Gut infarction	6/987 (0.6)			
Acute kidney injury	140/989 (14.2)			
Stage 1	49/989 (5.0)			
Stage 2	39/989 (3.9)			
Stage 3	50/989 (5.1)			
Secondary outcomes				
No. of hours in ICU or high-dependency unit‡				
Median	49.5			
Interquartile range	21.9–99.7	20.1–94.8		
No. of days in hospital¶				
Median	7.0	7.0	1.00 (0.92–1.10)§	0.94
Interquartile range	5.0–10.0	5.0–10.0		
All-cause mortality at 90 days	42/1000 (4.2)	26/1003 (2.6)	1.64 (1.00–2.67)§	0.045
Clinically significant pulmonary complications	127/979 (13.0)	116/982 (11.8)	1.11 (0.85–1.45)*	0.45
All-cause mortality at 30 days	26/1000 (2.6)	19/1003 (1.9)		

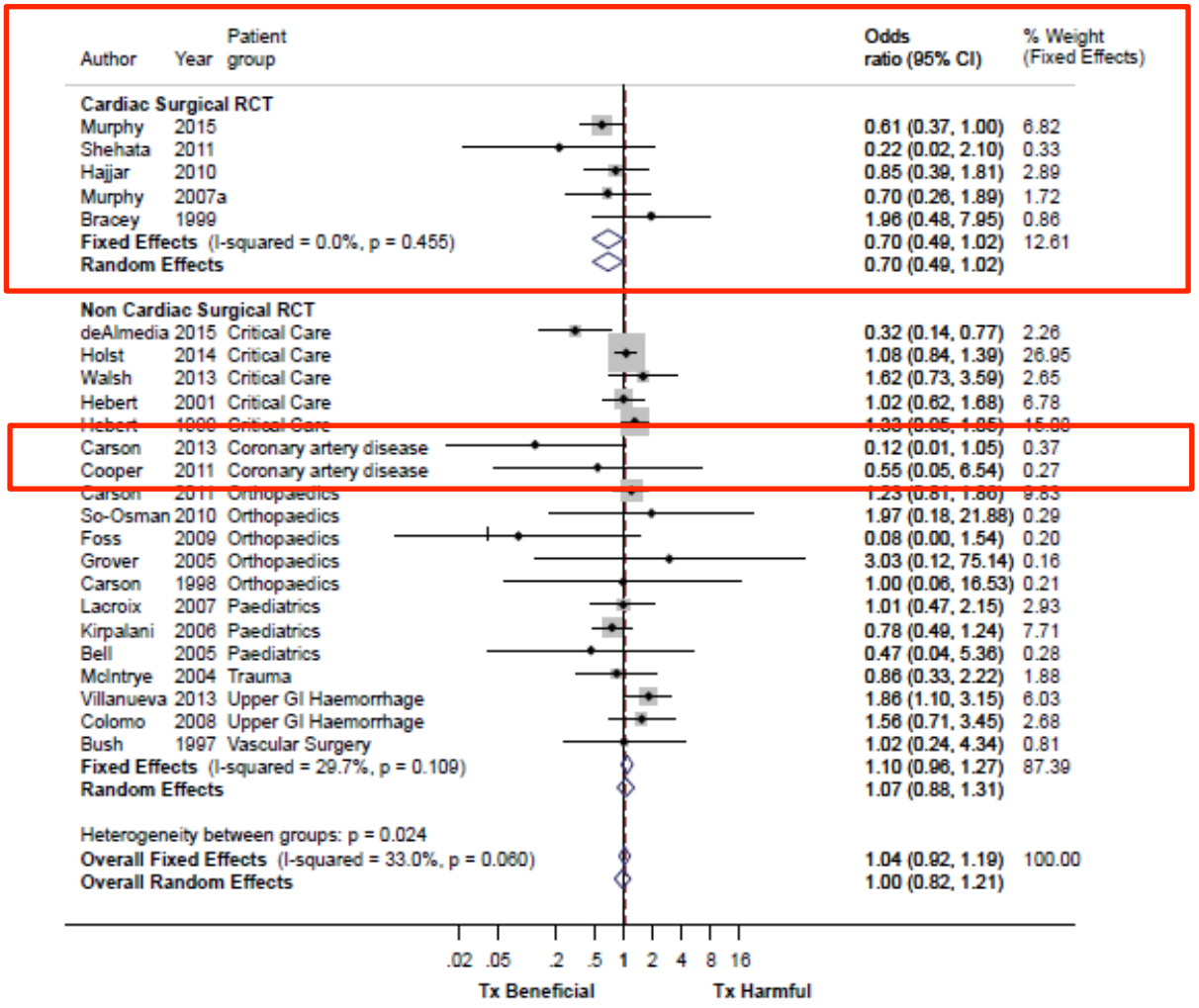


* This value is an odds ratio.
† Since the amount of missing data was greater than 5% (owing primarily to missing data on posthospital discharge), a separate treatment estimate was estimated for infections that occurred before hospital discharge (according to the rules regarding missing data outlined in the statistical analysis plan in the study protocol). For this treatment effect, we estimated an odds ratio of 1.07 (95% CI, 0.85 to 1.36; P=0.55).
‡ The duration of stay in the intensive care unit (ICU) or high-dependency unit after randomization was 0 days for 63 patients in the restrictive-threshold group and 61 patients in the liberal-threshold group; data were censored for 23 patients in the restrictive-threshold group and 15 patients in the liberal-threshold group. In addition, 37 patients in the restrictive-threshold group and 32 patients in the liberal-threshold group had more than one admission to the ICU or high-dependency unit.
§ This value is a hazard ratio.
¶ The duration of hospital stay after randomization was 0 days for 4 patients in the restrictive-threshold group and 2 patients in the liberal-threshold group; data were censored for 25 patients in the restrictive-threshold group and 17 patients in the liberal-threshold group.

Sensitivity analyses suggested greater AKI

Indications for red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis

Patel et al. Lancet Haematology. Published online November 2015. http://dx.doi.org/10.1016/S2352-3026(15)00198-2

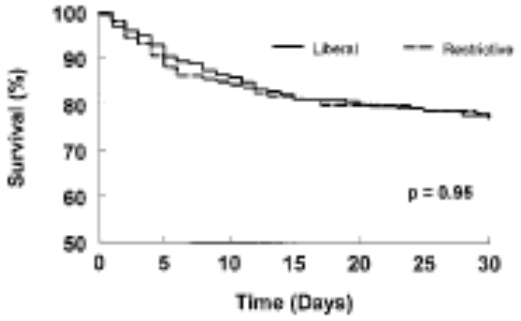


Cardiac surgery trials

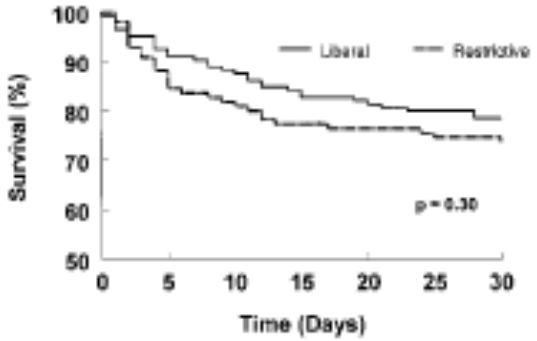
ACS feasibility trials

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

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

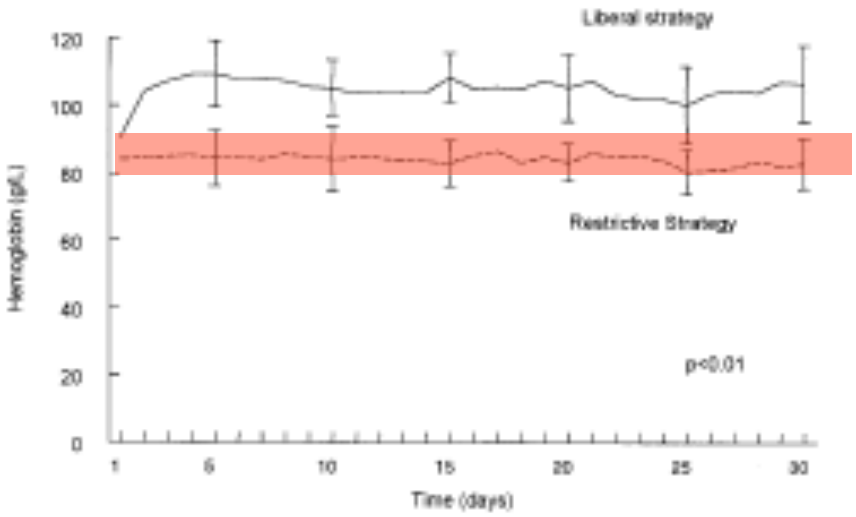


Subgroup of 357 patients with cardiovascular disease



Subgroup of 257 patients with ischaemic heart disease 30 day mortality

Difference –4.9% (-15.3% to 5.6%)

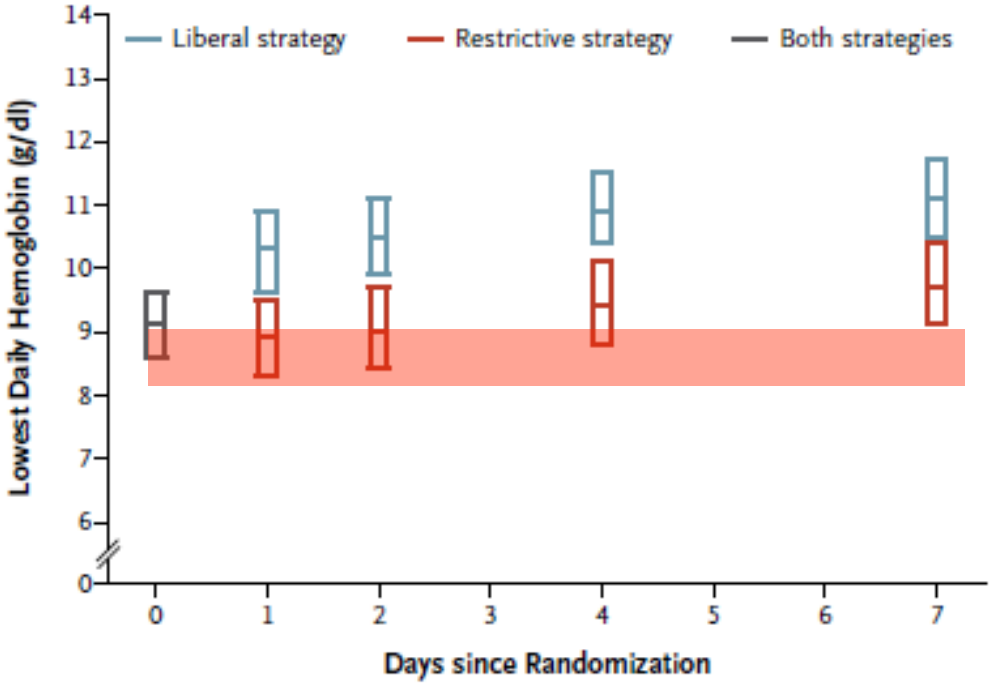


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 29, 2011 VOL. 365 NO. 26

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

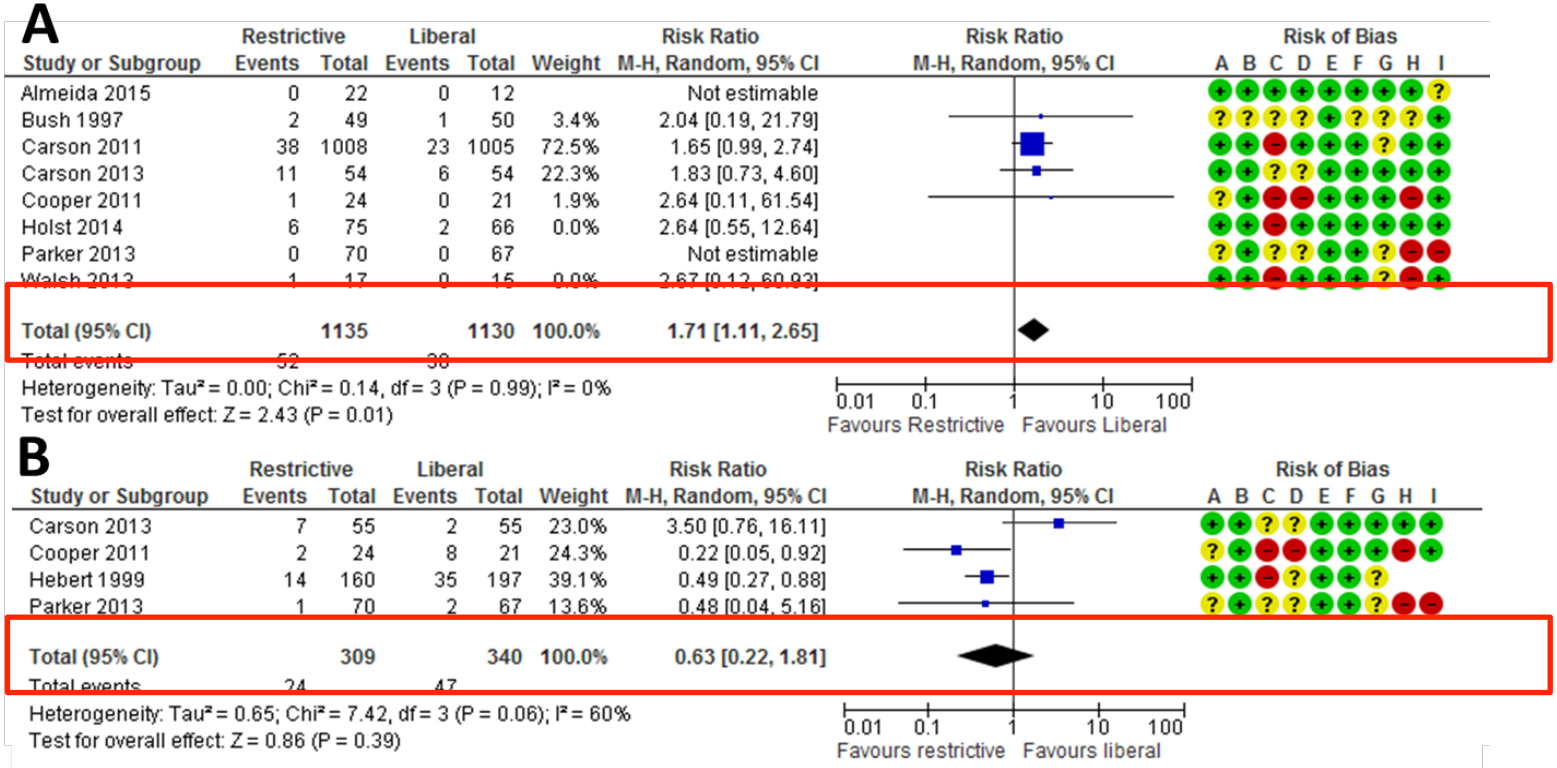
Jeffrey L. Carson, M.D., Michael L. Terrin, M.D., M.P.H., Helaine Noveck, M.P.H., David W. Sanders, M.D., Bernard R. Chaitman, M.D., George G. Rhoads, M.D., M.P.H., George Nemo, Ph.D., Karen Dragert, R.N., Lauren Beaupre, P.T., Ph.D., Kevin Hildebrand, M.D., William Macaulay, M.D., Courtland Lewis, M.D., 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*

- Patients aged >50 years with cardiovascular disease or risk factors
- Mean age 82 years; cardiovascular disease 63%
- Protocolised liberal versus "clinician judgement" restrictive
- No difference in death or physical ability
- No difference in cardiovascular complications
- Trend to higher rates of MI



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

Anne-Marie Docherty et al. BMJ; in press



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
(H) Assessment of Cardiovascular Event
(I) Definition of Cardiovascular Event

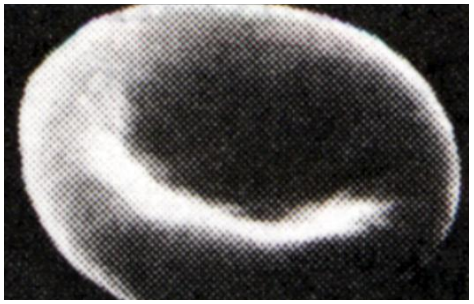
For ACS:

RR 1.71, 95% CI 1.11 to 2.65, P=0.01

NNH from restrictive 52

Questions answered?

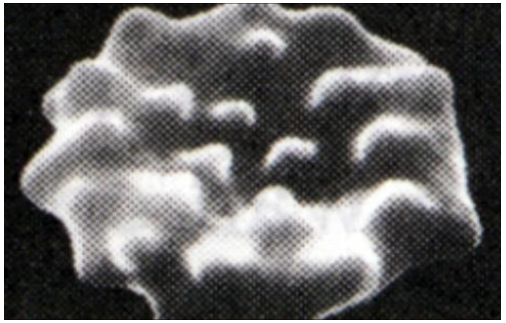
- Why are so many critically ill patients anaemic?
- Should I give all patients iron?
- Should I use erythropoietin?
- What is my “default” haemoglobin transfusion trigger?
- What should I do in sepsis?
- What should I do for patients with cardiovascular disease?
- Should I ask for “fresh” blood?



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

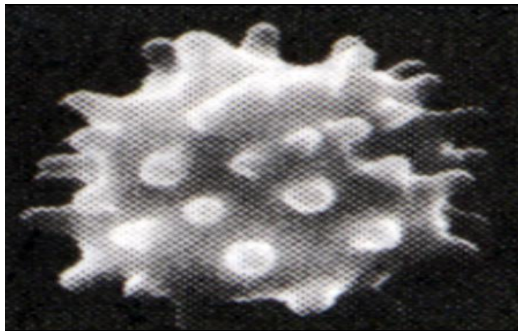
Damage and Loss of band 3 protein (increased susceptibility to oxidation)
Increased cellular permeability

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)



Age of transfused blood in critically ill adults.

Lacroix J; Hebert PC; Fergusson DA; Tinmouth A; Cook DJ; Marshall JC; Clayton L; McIntyre L; Callum J; Turgeon AF; Blajchman MA; Walsh TS; Stanworth SJ; Campbell H; Capellier G; Tiberghien P; Bardiaux L; van de Watering L; van der Meer NJ; Sabri E; Vo D; ABLE Investigators; Canadian Critical Care Trials Group
New England Journal of Medicine. 372(15):1410-8, 2015 DOI: 10.1056/NEJMoa1500704

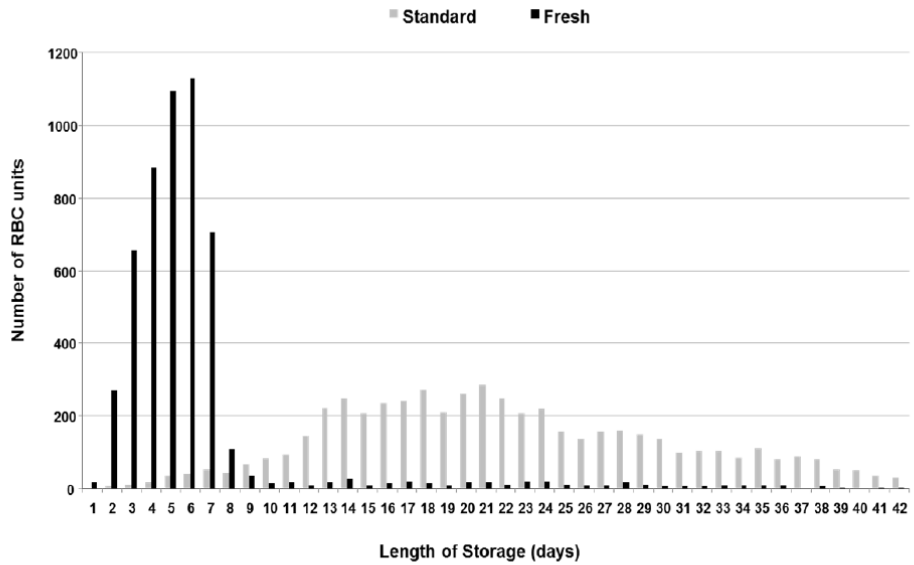
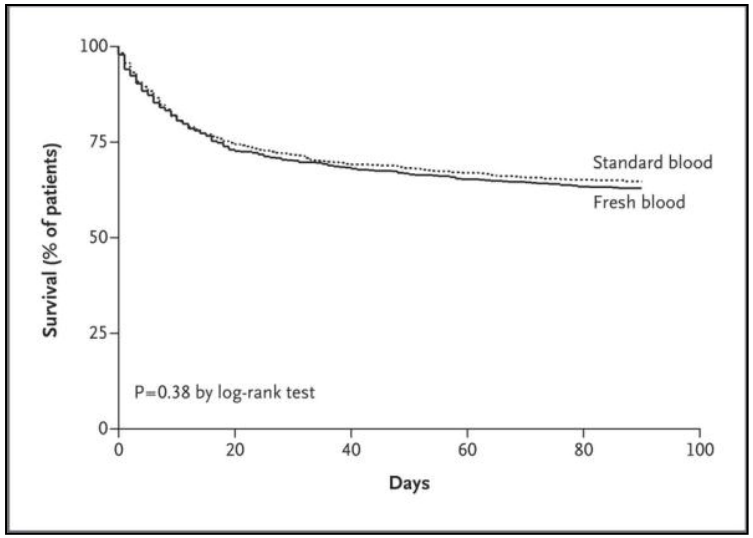


Figure S2. Distribution of red cell units per length of storage, as transfused to patients allocated to the fresh arm (black bars) and to the standard arm (white bars).

No control over transfusion practice

Mean transfusion trigger 75g/L
Mean 4.3 red cell units



No difference in any trial outcome

or for any pre-defined sub-group

A Primary Outcome and Secondary Outcomes Related to Death and Major Illnesses

Outcome	Fresh Blood	Standard Blood	Absolute Risk Difference (95% CI)
	no. of patients/total no. (%)		*percentage points*
Primary outcome: death by day 90	448/1211 (37.0)	430/1219 (35.3)	1.7 (−2.1 to 5.5)
Secondary outcomes			
Death			
In ICU	324/1214 (26.7)	295/1217 (24.2)	2.5 (−1.0 to 5.9)
In hospital	403/1212 (33.3)	386/1211 (31.9)	1.4 (−2.3 to 5.1)
By day 28	371/1214 (30.6)	353/1225 (28.8)	1.7 (−1.9 to 5.4)
Major Illnesses			
Multiple organ dysfunction syndrome	162/1206 (13.4)	157/1207 (13.0)	0.4 (−2.3 to 3.1)
Acute respiratory distress syndrome	69/1206 (5.7)	80/1207 (6.6)	−0.9 (−2.8 to 1.0)
Cardiovascular failure	61/1206 (5.1)	51/1207 (4.2)	0.8 (−0.8 to 2.5)
Cardiac ischemia or infarction	54/1206 (4.5)	44/1207 (3.6)	0.8 (−0.7 to 2.4)
Deep-vein thrombosis or pulmonary embolism	43/1206 (3.6)	43/1207 (3.6)	0.0 (−1.5 to 1.5)
Nosocomial infection	411/1206 (34.1)	378/1207 (31.3)	2.8 (−0.9 to 6.5)
Acute transfusion reaction	4/1206 (0.3)	6/1207 (0.5)	−0.2 (−0.7 to 0.3)

−10.0 −5.0 0.0 5.0 10.0

Fresh Blood Better — Standard Blood Better

B Other Secondary Outcomes

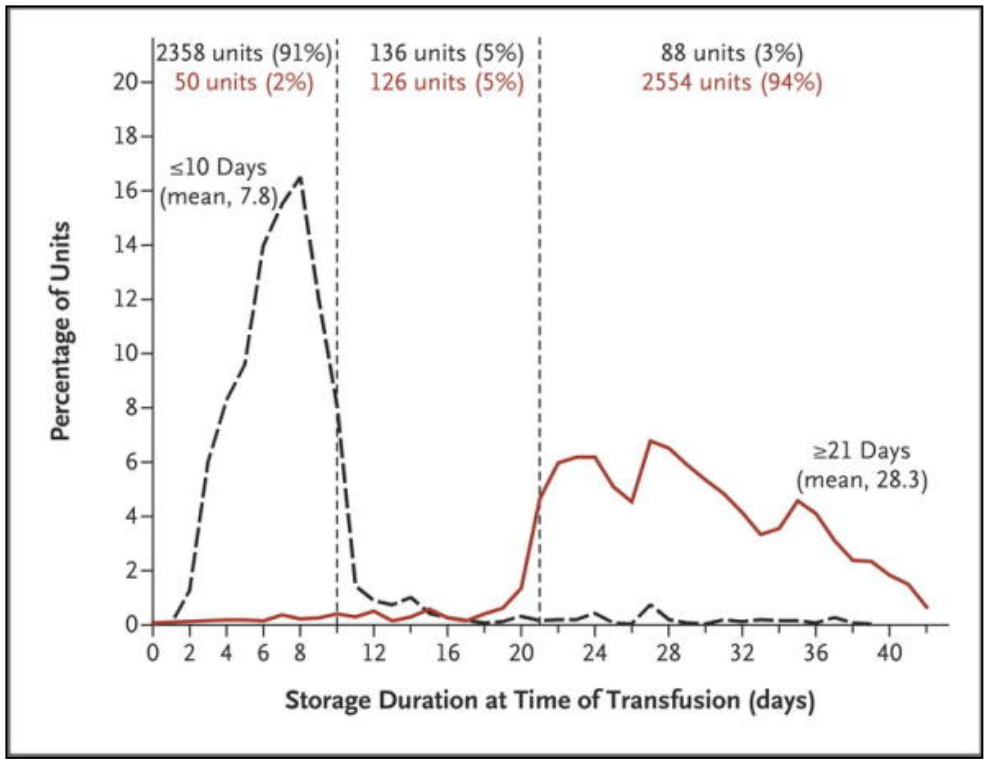
Outcome	Fresh Blood	Standard Blood	Mean Difference (95% CI)
	Mean (±SD)		*value*
MODS			
Highest score	6.4±3.2	6.2±3.2	0.2 (−0.1 to 0.4)
Delta score	1.4±1.8	1.4±1.9	−0.1 (−0.2 to 0.1)
Duration of supportive care (days)			
Mechanical ventilation	15.0±18.0	14.7±14.9	0.3 (−1.1 to 1.6)
Cardiac or vasoactive drugs	7.1±10.2	7.5±11.2	−0.4 (−1.2 to 0.5)
Extrarenal epuration	2.5±10.1	2.3±8.3	0.2 (−0.6 to 0.9)
Length of stay (days)			
In ICU	15.3±15.4	15.3±14.8	0.1 (−1.2 to 1.3)
In hospital	34.4±39.5	33.9±38.8	0.5 (−2.6 to 3.7)

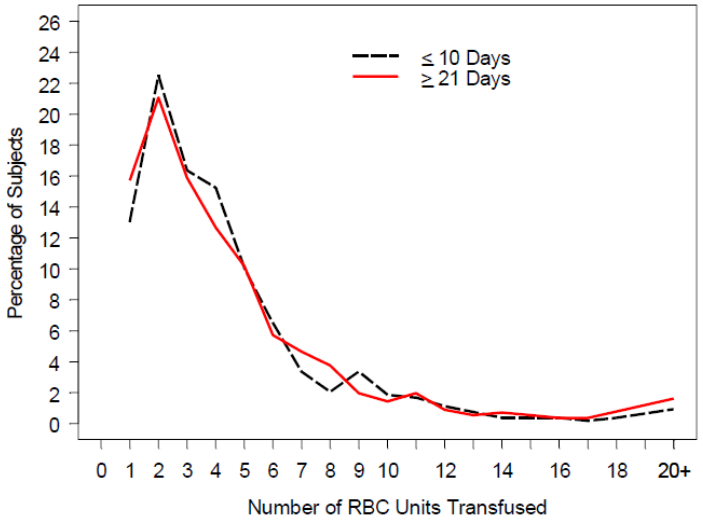
−10.0 −5.0 0.0 5.0 10.0

Fresh Blood Better — Standard Blood Better

Effects of red-cell storage duration on patients undergoing cardiac surgery.

Steiner ME; Ness PM; Assmann SF; et al
New England Journal of Medicine. 372(15):1419-29, 2015 Apr 9.
DOI: 10.1056/NEJMoa1414219





≈25% >8 RBC units

Outcome	Red-Cell Storage ≤10 Days (N=538)	Red-Cell Storage ≥21 Days (N=560)	Estimated Treatment Effect (95% CI)	P Value
Primary outcome: ΔMODS at 7 days†	8.5±3.6	8.7±3.6	−0.2 (−0.6 to 0.3)	0.44
Secondary outcomes‡				
ΔMODS at 28 days	8.7±4.0	9.1±4.2	−0.3 (−0.8 to 0.2)	0.20
All-cause mortality — no. (%)				
7 Days	15 (2.8)	11 (2.0)	0.8 (−1.0 to 2.7)	0.43
28 Days	23 (4.4)	29 (5.3)	−0.9 (−3.4 to 1.7)	0.57
Median stay in ICU — days§	3	3	1.07 (0.95 to 1.21)	0.27
Median stay in hospital — days§	8	8	0.99 (0.88 to 1.13)	0.92

* Plus–minus values are unadjusted means ±SD. Unless otherwise noted, all outcomes were assessed through postoperative day 7, hospital discharge, study withdrawal, or death, whichever occurred first. The group receiving red cells stored for 21 days or more is the reference group. Analysis of covariance was adjusted for baseline value.

† For the change in MODS at 7 days, data were unavailable for four participants in the group assigned to receive red cells stored for 10 days or less and for seven in the group assigned to receive red cells stored for 21 days or more.

‡ Data on the change in MODS at 28 days were unavailable for 7 participants in the group assigned to receive red cells stored for 10 days or less and for 5 in the group assigned to receive red cells stored for 21 days or more. Data on all-cause mortality through 7 days were unavailable for 7 participants in the group assigned to receive red cells stored for 10 days or less and for 4 in the group assigned to receive red cells stored for 21 days or more; data on all-cause mortality through 28 days were unavailable for 14 participants in the group assigned to receive red cells stored for 10 days or less and for 9 in the group assigned to receive red cells stored for 21 days or more.

§ Length of stay was measured from date of surgery through day 28±3, death, hospital discharge, or the end of the study, whichever occurred first. For these outcomes, the estimated treatment effect was calculated as a hazard ratio with the use of a Cox model.

No difference in organ dysfunction

No difference in other outcomes

Questions answered?

- Why are so many critically ill patients anaemic?
  Multifactorial; impaired erythropoiesis
- Should I give all patients iron?
- Should I use erythropoietin?
- What is my “default” haemoglobin transfusion trigger?
- What should I do in sepsis?
- What should I do for patients with cardiovascular disease?
- Should I ask for “fresh” blood?

Questions answered?

- Why are so many critically ill patients anaemic?
- Should I give all patients iron? No
- Should I use erythropoietin? No
- What is my “default” haemoglobin transfusion trigger?
- What should I do in sepsis?
- What should I do for patients with cardiovascular disease?
- Should I ask for “fresh” blood?

Questions answered?

- Why are so many critically ill patients anaemic?
- Should I give all patients iron?
- Should I use erythropoietin?
- What is my “default” haemoglobin transfusion trigger? 70g/L for the young, less severely ill, and those without cardiovascular disease
- What should I do in sepsis?
- What should I do for patients with cardiovascular disease?
- Should I ask for “fresh” blood?

Questions answered?

- Why are so many critically ill patients anaemic?
- Should I give all patients iron?
- Should I use erythropoietin?
- What is my “default” haemoglobin transfusion trigger?
- What should I do in sepsis? Not sure in early stage!
- What should I do for patients with cardiovascular disease?
- Should I ask for “fresh” blood?

Questions answered?

- Why are so many critically ill patients anaemic?
- Should I give all patients iron?
- Should I use erythropoietin?
- What is my “default” haemoglobin transfusion trigger?
- What should I do in sepsis?
- What should I do for patients with cardiovascular disease? Use a Hb trigger >80g/L
- Should I ask for “fresh” blood?

Questions answered?

- Why are so many critically ill patients anaemic?
- Should I give all patients iron?
- Should I use erythropoietin?
- What is my “default” haemoglobin transfusion trigger?
- What should I do in sepsis?
- What should I do for patients with cardiovascular disease?
- Should I ask for “fresh” blood? No

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THE UNIVERSITY OF EDINBURGH

NHS Lothian

EDINBURGH CRITICAL CARE RESEARCH GROUP