PATIENT BLOOD MANAGEMENT IN THE CRITICAL PATIENT.

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IRCCS Policlinico S.Donato

DISCLOSURES

Marco Ranucci received honoraria, consultancy fees, and reaserch grants from the following companies:

Medtronic
Grifols
CSL Behring
Sorin
The Medicines Company
Talecris
Novo Nordisk

TWO ISSUES

1. PREOPERATIVE ANEMIA
2. LIBERAL vs RESTRICTIVE TRANSFUSIONS

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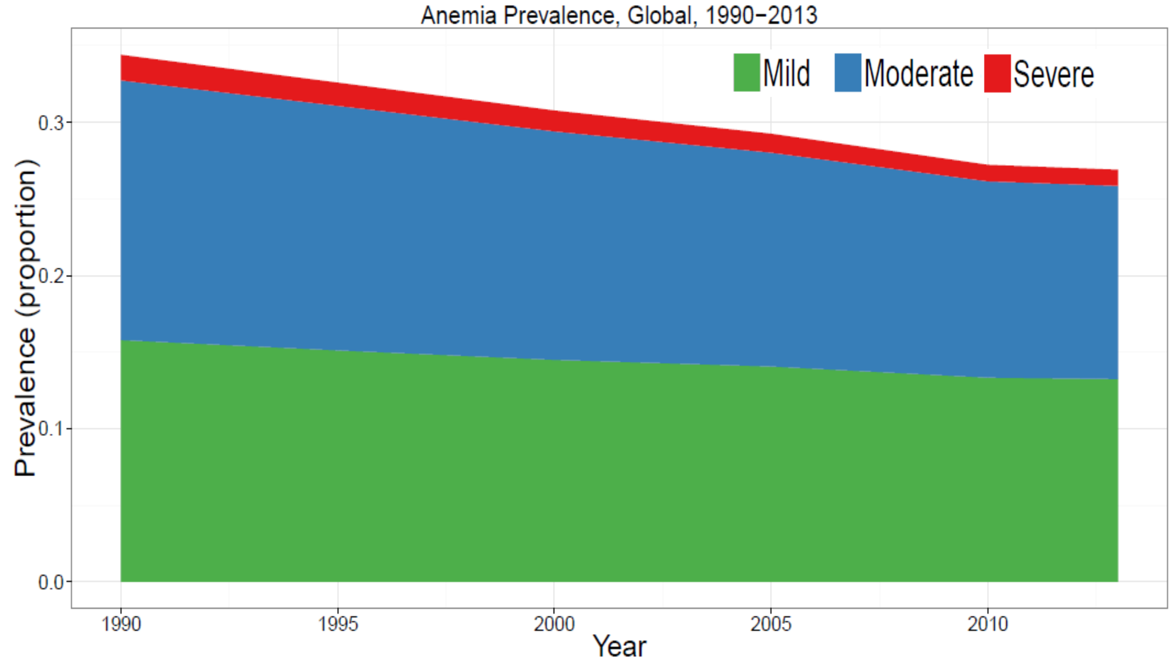
World Health Organization



Population coverage (%) by anaemia prevalence surveys (national or subnational) conducted between 1993 and 2005

WHO region	PreSAC[a]	PW	NPW	SAC	Men	Elderly	All
Africa (46)[b]	74.6 (26)[c]	65.8 (22)	61.4 (23)	13.2 (8)	21.9 (11)	0.0 (0)	40.7
Americas (35)	76.7 (16)	53.8 (15)	56.2 (13)	47.1 (9)	34.3 (2)	47.6 (1)	58.0
South-East Asia (11)	85.1 (9)	85.6 (8)	85.4 (10)	13.6 (3)	4.1 (2)	5.2 (1)	14.9
Europe (52)	26.5 (12)	8.3 (4)	28.0 (12)	9.3 (3)	14.1 (3)	8.0 (2)	22.9
Eastern Mediterranean (21)	67.4 (11)	58.7 (7)	73.5 (11)	15.5 (6)	27.5 (6)	3.2 (3)	84.3
Western Pacific (27)	90.4 (10)	90.2 (8)	96.9 (13)	83.1 (7)	96.2 (10)	93.3 (6)	13.8
Global (192)	**76.1 (84)**	**69.0 (64)**	**73.5 (82)**	**33.0 (36)**	**40.2 (34)**	**39.1 (13)**	**48.8**

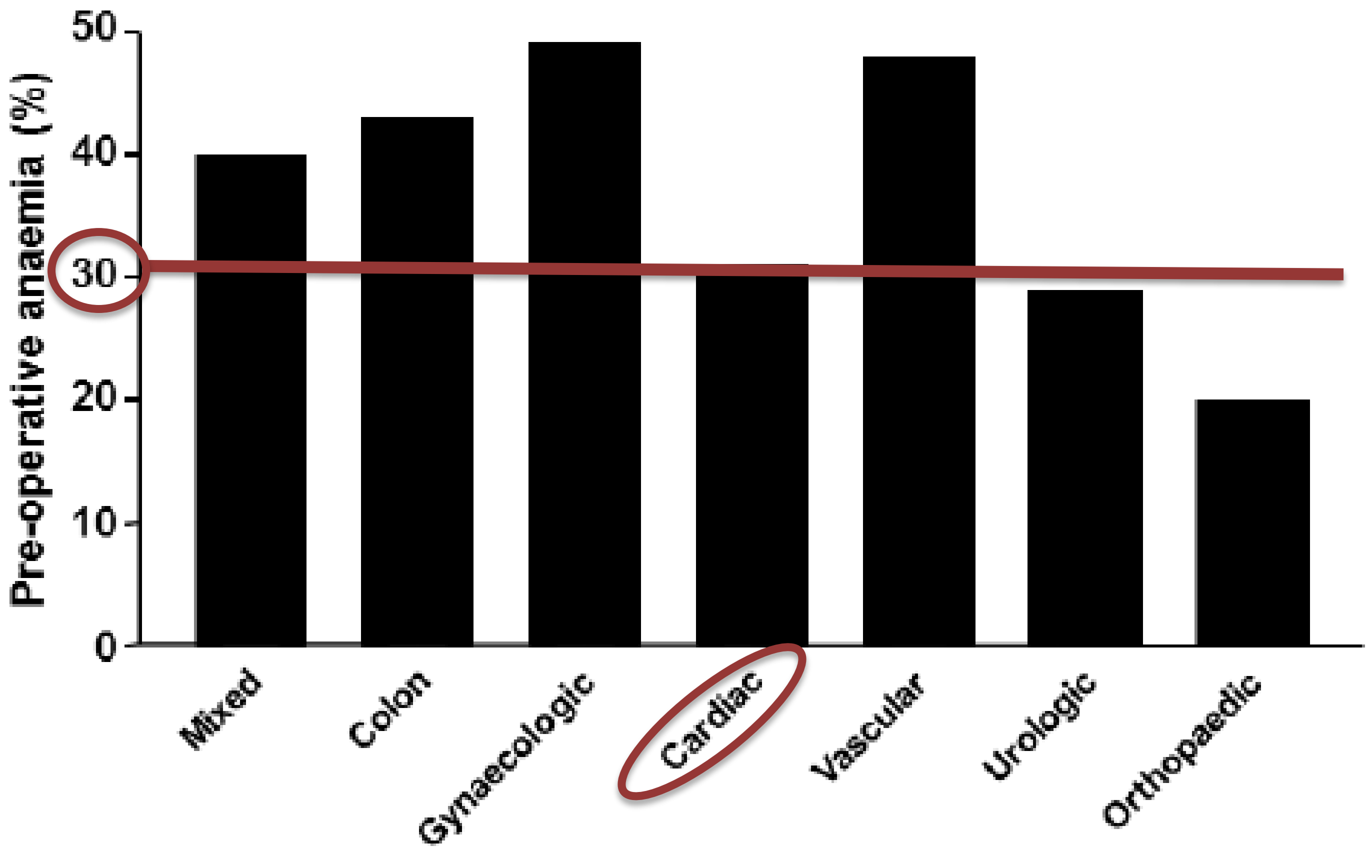
[a] Population groups: PreSAC, preschool-age children (0.00–4.99 yrs); PW, pregnant women (no age range defined); NPW, non-pregnant women (15.00–49.99 yrs), SAC, school-age children (5.00–14.99 yrs), Men (15.00–59.99 yrs), Elderly (≥60.00 yrs).

[b] Number of countries in each grouping.

[c] Total number of countries with data, no figure is provided for All since each country may be partially covered by some population groups, but few countries have data on all 6 population groups and no countries have data for women 50–59 yrs of age.

Prevalence of pre-operative anaemia in patients scheduled for major surgery, according to most frequent procedures (estimated from references[7-24]).

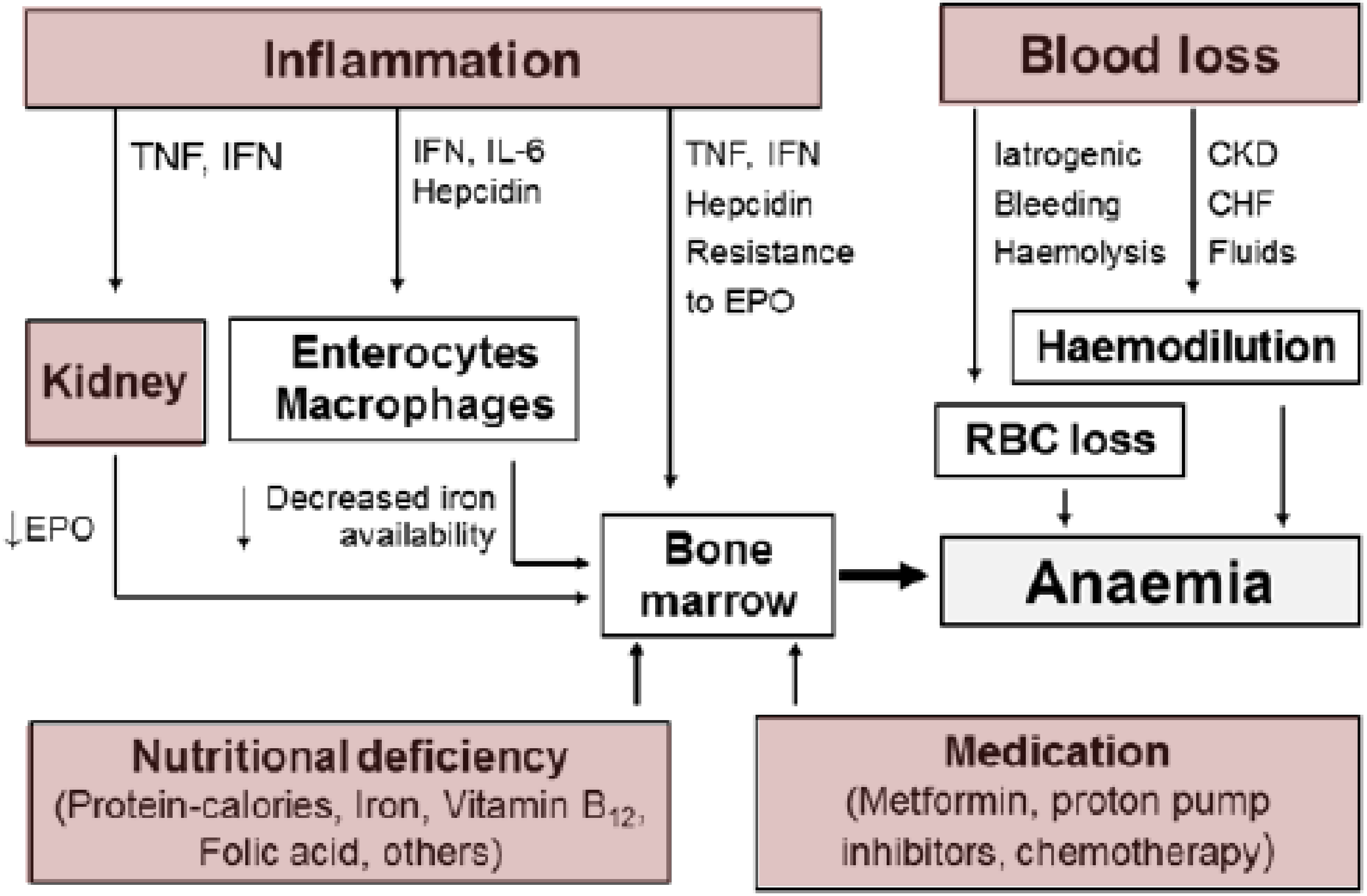
Blood Transfus 2015; 13; 370-9



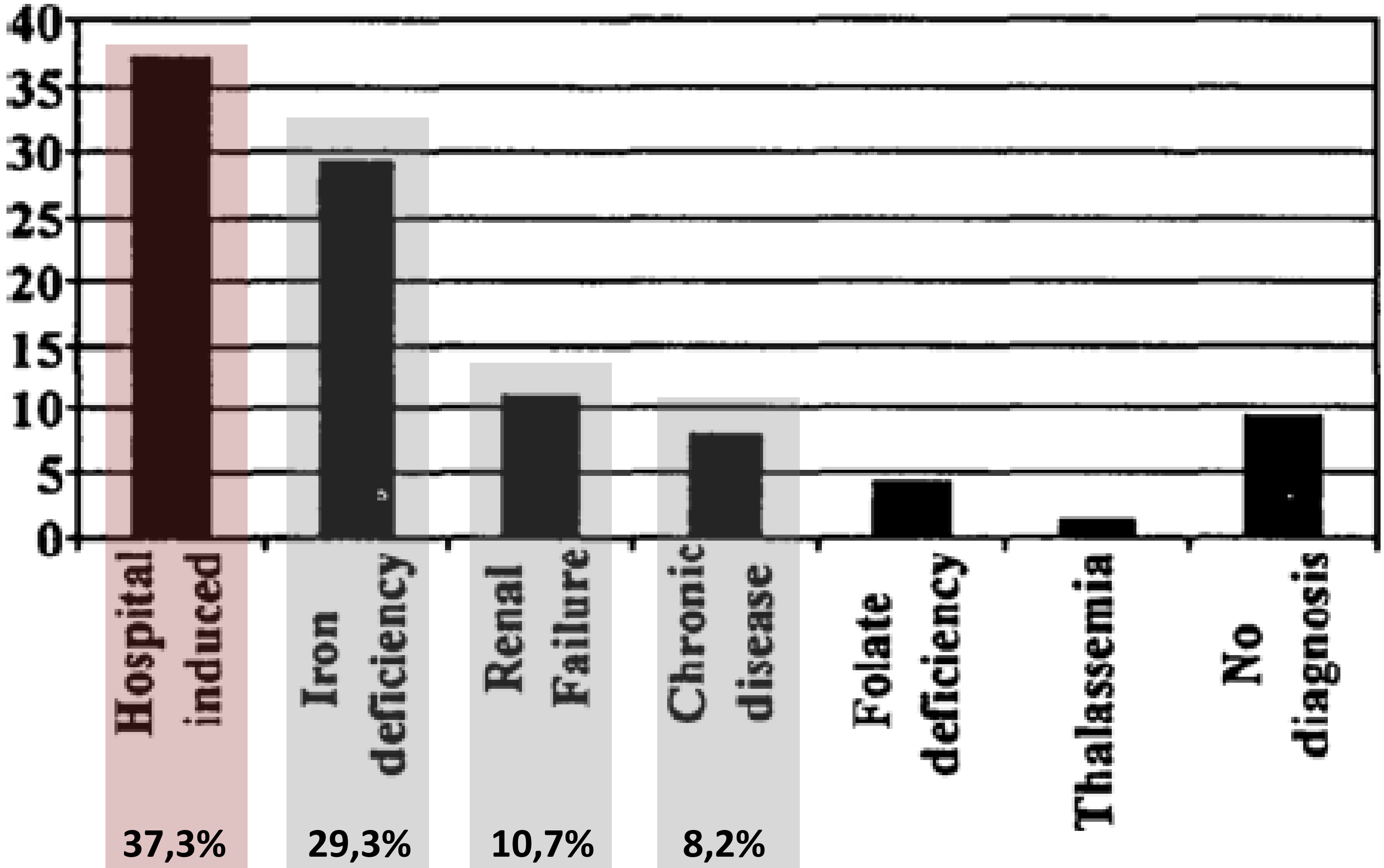
WHO region	PreSAC[a]	PW	NPW	SAC	Men	Elderly	All
Europe (52)	26.5 (12)	8.3 (4)	28.0 (12)	9.3 (3)	14.1 (8)	8.0 (2)	22.9

Multifactorial aetiology of preoperative anaemia

Blood Transfus 2015; 13; 370-9



CAN J ANESTH 1999 / 46: 10 / pp 979–982



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

Summary

Background Preoperative anaemia is associated with adverse outcomes after cardiac surgery but outcomes after non-cardiac surgery are not well established. We aimed to assess the effect of preoperative anaemia on 30-day postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.

Methods We analysed data for patients undergoing major non-cardiac surgery in 2008 from The American College of Surgeons' National Surgical Quality Improvement Program database (a prospective validated outcomes registry from 211 hospitals worldwide in 2008). We obtained anonymised data for 30-day mortality and morbidity (cardiac, respiratory, CNS, urinary tract, wound, sepsis, and venous thromboembolism outcomes), demographics, and preoperative and perioperative risk factors. We used multivariate logistic regression to assess the adjusted and modified (nine predefined risk factor subgroups) effect of anaemia, which was defined as mild (haematocrit concentration >29–<39% in men and >29–<36% in women) or moderate-to-severe (≤29% in men and women) on postoperative outcomes.

Findings We obtained data for 227 425 patients, of whom 69 229 (30·44%) had preoperative anaemia. After adjustment, postoperative mortality at 30 days was higher in patients with anaemia than in those without anaemia (odds ratio [OR] 1·42, 95% CI 1·31–1·54); this difference was consistent in mild anaemia (1·41, 1·30–1·53) and moderate-to-severe anaemia (1·44, 1·29–1·60). Composite postoperative morbidity at 30 days was also higher in patients with anaemia than in those without anaemia (adjusted OR 1·35, 1·30–1·40), again consistent in patients with mild anaemia (1·31, 1·26–1·36) and moderate-to-severe anaemia (1·56, 1·47–1·66). When compared with patients without anaemia or a defined risk factor, patients with anaemia and most risk factors had a higher adjusted OR for 30-day mortality and morbidity than did patients with either anaemia or the risk factor alone.

Interpretation Preoperative anaemia, even to a mild degree, is independently associated with an increased risk of 30-day morbidity and mortality in patients undergoing major non-cardiac surgery.

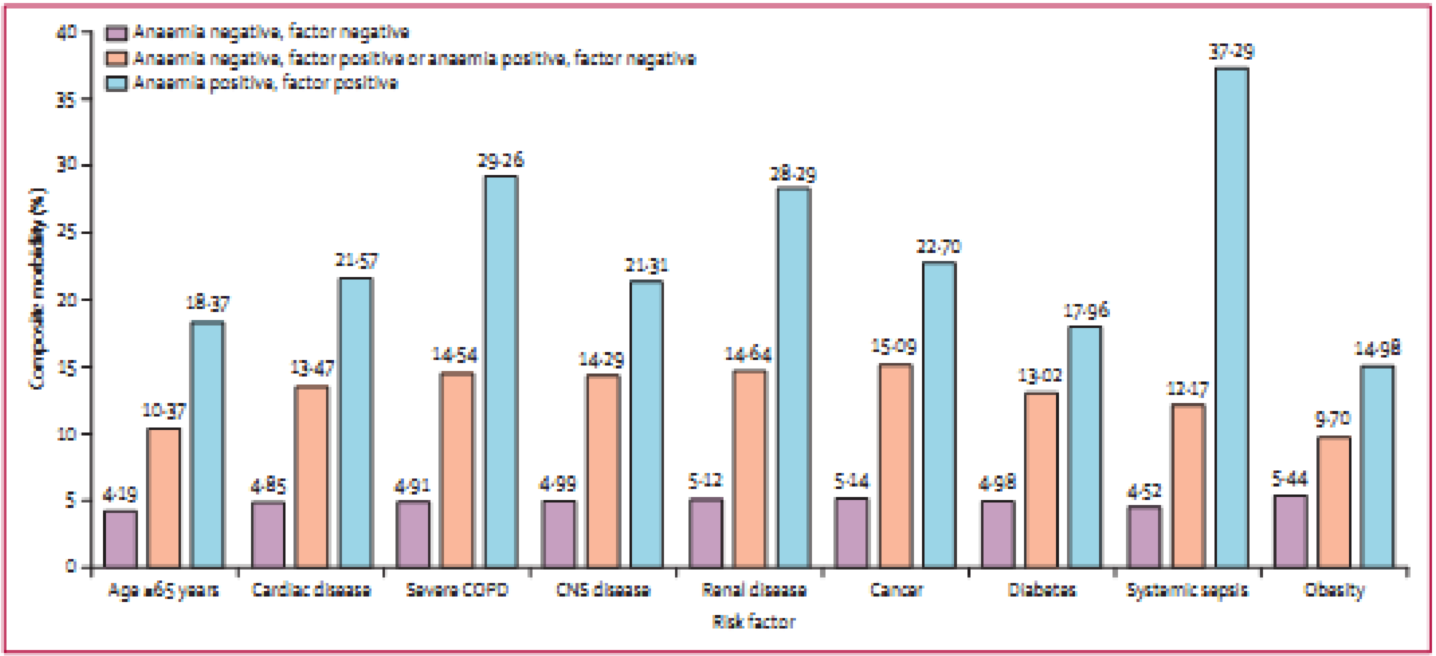


Figure 2: 30-day composite morbidity, by anaemia and risk factor status
COPD=chronic obstructive pulmonary disease.

Systematic review

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

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

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Background: Numerous published studies have explored associations between anaemia and adverse outcomes after surgery. However, there are no evidence syntheses describing the impact of preoperative anaemia on postoperative outcomes.

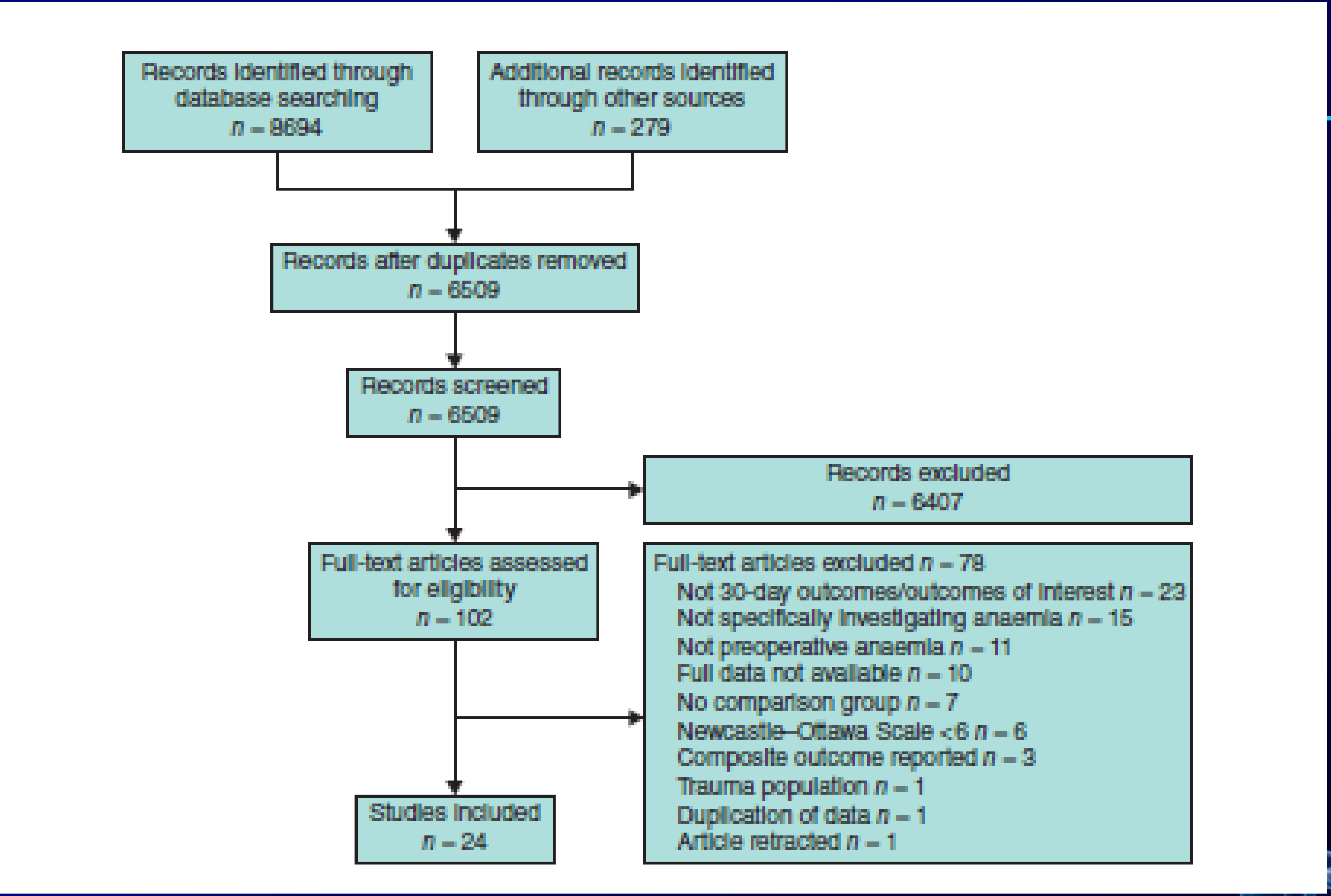
Methods: A systematic review and meta-analysis of observational studies exploring associations between preoperative anaemia and postoperative outcomes was performed. Studies investigating trauma, burns, transplant, paediatric and obstetric populations were excluded. The primary outcome was 30-day or in-hospital mortality. Secondary outcomes were acute kidney injury, stroke and myocardial infarction. Predefined analyses were performed for the cardiac and non-cardiac surgery subgroups. A *post hoc* analysis was undertaken to evaluate the relationship between anaemia and infection. Data are presented as odds ratios (ORs) with 95 per cent c.i.

Results: From 8973 records, 24 eligible studies including 949 445 patients were identified. Some 371 594 patients (39·1 per cent) were anaemic. Anaemia was associated with increased mortality (OR 2·90, 2·30 to 3·68; $I^2 = 97$ per cent; $P < 0.001$), acute kidney injury (OR 3·75, 2·95 to 4·76; $I^2 = 60$ per cent; $P < 0.001$) and infection (OR 1·93, 1·17 to 3·18; $I^2 = 99$ per cent; $P = 0.01$). Among cardiac surgical patients, anaemia was associated with stroke (OR 1·28, 1·06 to 1·55; $I^2 = 0$ per cent; $P = 0.009$) but not myocardial infarction (OR 1·11, 0·68 to 1·82; $I^2 = 13$ per cent; $P = 0.67$). Anaemia was associated with an increased incidence of red cell transfusion (OR 5·04, 4·12 to 6·17; $I^2 = 96$ per cent; $P < 0.001$). Similar findings were observed in the cardiac and non-cardiac subgroups.

Conclusion: Preoperative anaemia is associated with poor outcomes after surgery, although heterogeneity between studies was significant. It remains unclear whether anaemia is an independent risk factor for poor outcome or simply a marker of underlying chronic disease. However, red cell transfusion is much more frequent amongst anaemic patients.

PODCAST AVAILABLE ONLINE

Paper accepted 20 April 2015
Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9861


Records identified through database searching n = 8694
Additional records identified through other sources n = 279
Records after duplicates removed n = 6509
Records screened n = 6509
Records excluded n = 6407
Full-text articles assessed for eligibility n = 102
Full-text articles excluded n = 78
Not 30-day outcomes/outcomes of interest n = 23
Not specifically investigating anaemia n = 15
Not preoperative anaemia n = 11
Full data not available n = 10
No comparison group n = 7
Newcastle–Ottawa Scale <6 n = 6
Composite outcome reported n = 3
Trauma population n = 1
Duplication of data n = 1
Article retracted n = 1
Studies included n = 24

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

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

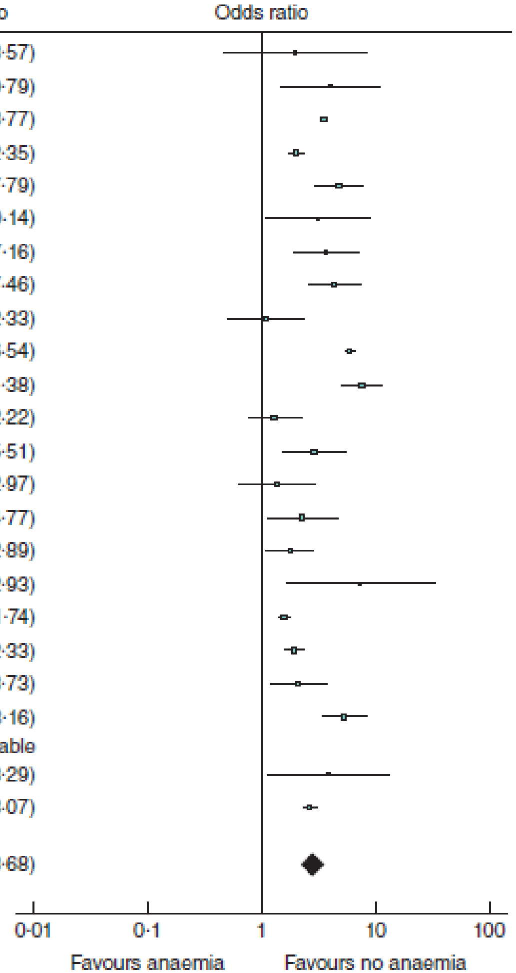
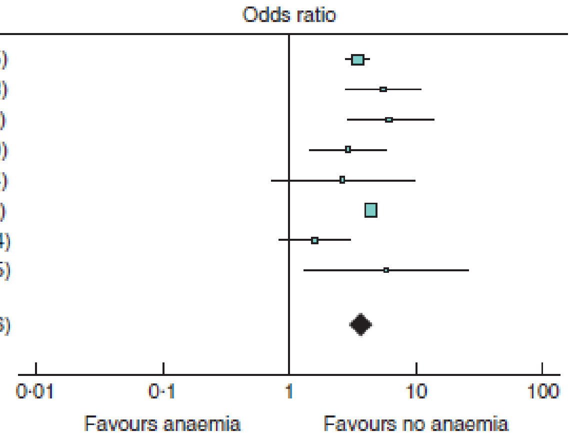


Fig. 2 Forest plot showing composite outcome of 30-day or in-hospital mortality after surgery, according to author-defined anaemia. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95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

Reference	Acute kidney injury: Anaemia	Acute kidney injury: No anaemia	Weight (%)	Odds ratio
Bell *et al.*[20]	183 of 6143	262 of 30196	26·9	3·51 (2·90, 4·25)
Boening *et al.*[21]	12 of 185	38 of 3126	9·3	5·64 (2·89, 10·98)
Cladellas *et al.*[22]	20 of 42	20 of 159	7·5	6·32 (2·94, 13·59)
De Santo *et al.*[23]	20 of 320	16 of 727	9·2	2·96 (1·51, 5·80)
Munoz *et al.*[31]	6 of 210	4 of 366	3·2	2·66 (0·74, 9·54)
Musallam *et al.*[32]	1285 of 69229	675 of 158196	30·9	4·41 (4·02, 4·85)
Ranucci *et al.*[34]	28 of 401	18 of 401	10·5	1·60 (0·87, 2·94)
Zhang *et al.*[41]	22 of 432	2 of 223	2·5	5·93 (1·38, 25·45)
Total	1576 of 76962	1035 of 193394	100·0	3·75 (2·95, 4·76)



Heterogeneity: $\tau^2 = 0·05$; $\chi^2 = 17·72$, 7 d.f., $P = 0·01$; $I^2 = 60\%$
Test for overall effect: $Z = 10·79$, $P < 0·001$

Fig. 3 Forest plot of acute kidney injury, according to author-defined anaemia. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i.

Reference	Stroke: Anaemia	Stroke: No anaemia	Weight (%)	Odds ratio
Bell *et al.*[20]	124 of 6143	481 of 30 196	87·9	1·27 (1·04, 1·55)
Boening *et al.*[21]	5 of 185	82 of 3126	4·9	1·03 (0·41, 2·58)
Cladellas *et al.*[22]	2 of 42	5 of 159	1·1	1·54 (0·29, 8·23)
De Santo *et al.*[23]	9 of 320	11 of 727	3·6	1·88 (0·77, 4·59)
Munoz *et al.*[31]	0 of 210	5 of 366	2·2	0·16 (0·01, 2·84)
Ranucci *et al.*[34]	4 of 401	0 of 401	0·3	9·09 (0·49, 169·40)
Total	144 of 7301	584 of 34 975	100·0	1·28 (1·06, 1·55)

Heterogeneity: $\chi^2 = 4{\cdot}73$, 5 d.f., $P = 0{\cdot}45$; $I^2 = 0\%$
Test for overall effect: $Z = 2{\cdot}61$, $P = 0{\cdot}009$

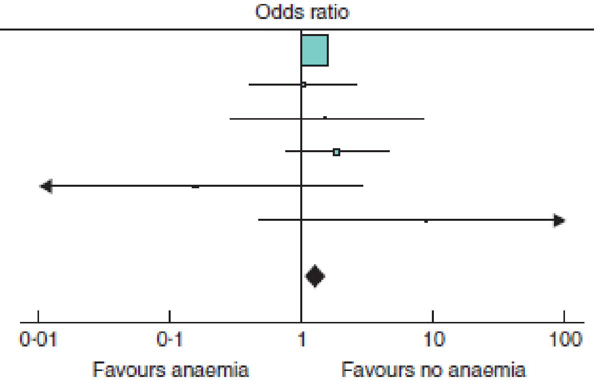


Fig. 4 Forest plot of stroke, according to author-defined anaemia. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i.

Reference	Myocardial infarction: Anaemia	Myocardial infarction: No anaemia	Weight (%)	Odds ratio
Boening *et al.*[21]	1 of 185	24 of 3126	8·9	0·70 (0·09, 5·22)
Cladellas *et al.*[22]	2 of 42	4 of 159	5·3	1·94 (0·34, 10·96)
Munoz *et al.*[31]	16 of 210	17 of 366	38·0	1·69 (0·84, 3·43)
Ranucci *et al.*[34]	6 of 401	12 of 401	39·2	0·49 (0·18, 1·33)
Zhang *et al.*[41]	5 of 432	2 of 223	8·7	1·29 (0·25, 6·72)
Total	30 of 1270	59 of 4275	100·0	1·11 (0·68, 1·82)

Heterogeneity: $\chi^2 = 4{\cdot}60$, 4 d.f., $P = 0{\cdot}33$; $I^2 = 13\%$
Test for overall effect: $Z = 0{\cdot}43$, $P = 0{\cdot}67$

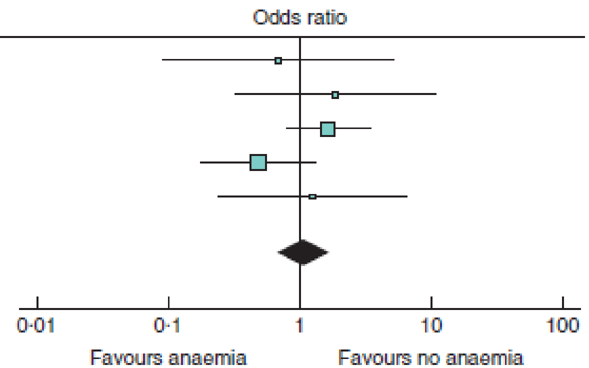
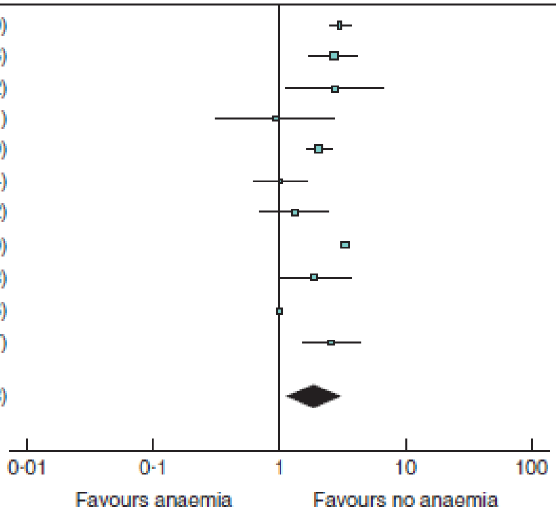


Fig. 5 Forest plot of myocardial infarction, according to author-defined anaemia. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i.

Reference	Infection: Anaemia	Infection: No anaemia	Weight (%)	Odds ratio	Odds ratio
Bell *et al.*[20]	208 of 6143	338 of 30 196	10·0	3·10 (2·60, 3·69)	
Boening *et al.*[21]	30 of 185	206 of 3126	9·4	2·74 (1·81, 4·16)	
Cladellas *et al.*[22]	10 of 42	16 of 159	7·7	2·79 (1·16, 6·72)	
De Santo *et al.*[23]	5 of 320	12 of 727	7·0	0·95 (0·33, 2·71)	
Greenky *et al.*[25]	130 of 2991	259 of 12 231	9·9	2·10 (1·69, 2·60)	
Melis *et al.*[30]	46 of 197	49 of 216	9·3	1·04 (0·66, 1·64)	
Munoz *et al.*[31]	20 of 210	27 of 366	8·8	1·32 (0·72, 2·42)	
Musallam *et al.*[32]	4592 of 69 229	3214 of 158 196	10·1	3·43 (3·27, 3·59)	
Ranucci *et al.*[34]	26 of 401	14 of 401	8·6	1·92 (0·99, 3·73)	
Saager *et al.*[35]	7337 of 119 298	7194 of 119 298	10·1	1·02 (0·99, 1·06)	
Shirzad *et al.*[37]	21 of 650	47 of 3782	9·1	2·65 (1·58, 4·47)	
Total	12 425 of 199 666	11 376 of 328 698	100·0	1·93 (1·17, 3·18)	



Heterogeneity: $\tau^2 = 0{\cdot}64$; $\chi^2 = 1819{\cdot}28$, 10 d.f., $P < 0{\cdot}001$; $I^2 = 99\%$
Test for overall effect: $Z = 2{\cdot}57$, $P = 0{\cdot}01$

Fig. 6 Forest plot of risk of infection in anaemic *versus* non-anaemic patients. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i.

BJA

British Journal of Anaesthesia, 123 (2): 161–169 (2019)

doi: 10.1016/j.bja.2019.04.058
Advance Access Publication Date: 19 June 2019
Clinical Practice

Association of preoperative anaemia with cardiopulmonary exercise capacity and postoperative outcomes in noncardiac surgery: a substudy of the Measurement of Exercise Tolerance before Surgery (METS) Study

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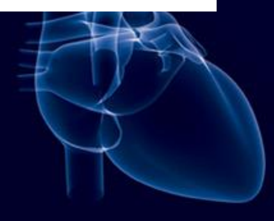


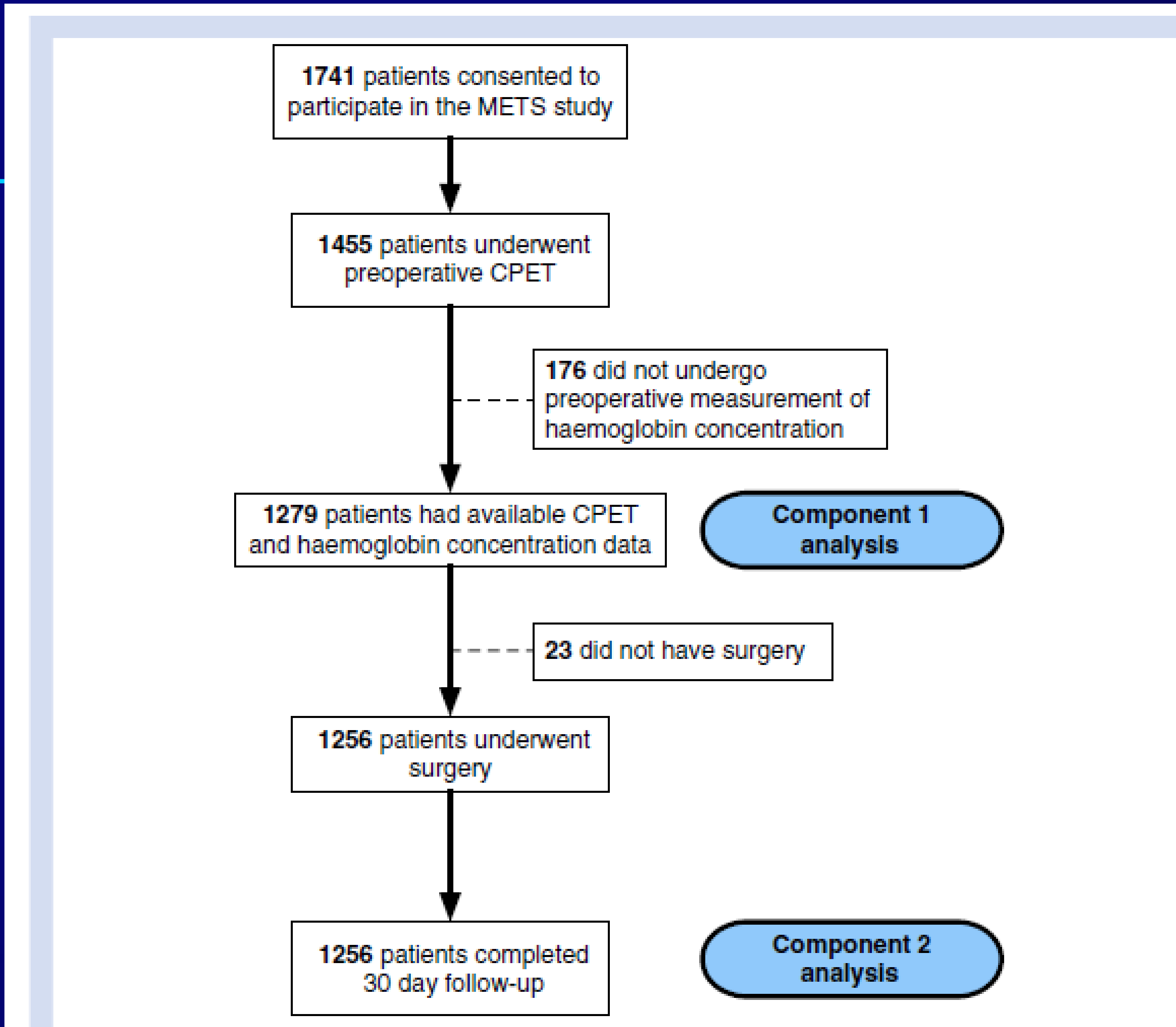

1741 patients consented to participate in the METS study
1455 patients underwent preoperative CPET
176 did not undergo preoperative measurement of haemoglobin concentration
1279 patients had available CPET and haemoglobin concentration data
Component 1 analysis
23 did not have surgery
1256 patients underwent surgery
1256 patients completed 30 day follow-up
Component 2 analysis

Table 1 Characteristics of study cohort, stratified by WHO anaemia class. Means and standard deviations (SD) or medians and inter-quartile ranges (IQR) shown for continuous data. Counts and proportions are shown for categorical data. Continuous data were compared between strata using either analysis of variance (ANOVA) or the Wilcoxon rank-sum test. Categorical data were compared using Fisher's exact test. AT, anaerobic threshold; eGFR, estimated glomerular filtration rate calculated using the CKD-Epi formula.[16,27]

Variables	Non-anaemic (n=1045)	Mild anaemia (n=177)	Moderate or severe anaemia (n=57)	P-value
Haemoglobin concentration (g L^{-1}), mean (SD)	143.0 (11.4)	119.9 (5.7)	100.2 (9.0)	<0.001
Age (yr), mean (range)	64.1 (40–92)	65.7 (40–88)	64.3 (40–86)	0.18
BMI (kg m^{-2}), median (IQR)	28.0 (25.0, 31.8)	27.5 (23.5, 31.4)	25.5 (22.1 29.6)	0.0002
VO_2 peak (ml kg^{-1} min^{-1}), median (IQR)	19.0 (15.0, 23.0)	16.1 (13.6, 20.0)	14.7 (12.0, 18.9)	<0.001
AT (ml kg^{-1} min^{-1}), median (IQR)	12.0 (10.0, 15.0)	11.1 (9.2, 14.0)	10.6 (8.8, 12.0)	<0.001
eGFR (ml min^{-1} 1.73 m^{-2})				
≥60	876 (83.8%)	138 (79.0%)	36 (63.2%)	<0.001
30–59	146 (14.0%)	27 (15.3%)	8 (14.0%)	
<30 or dialysis	23 (2.2%)	12 (6.8%)	13 (22.8%)	
Comorbidities				
Coronary artery disease	72 (6.9%)	30 (17.0%)	10 (17.5%)	<0.001
Heart failure	83 (7.9%)	33 (18.6%)	11 (19.3%)	<0.001
Diabetes mellitus	193 (18.5%)	36 (20.3%)	10 (17.5%)	0.82
Obstructive lung disease	119 (11.4%)	25 (14.1%)	9 (15.8%)	0.39
Preoperative chemotherapy	62 (5.9%)	34 (19.2%)	11 (19.3%)	<0.001
Arthritis	381 (36.5%)	57 (32.2%)	14 (24.6%)	0.21

Table 2 Adjusted multivariate modelling (prediction of VO_2 peak and AT simultaneously). AT, anaerobic threshold; VO_2 peak, peak oxygen consumption; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate (calculated using CKD-Epi formula[16]); CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration.

Variable	Proportion of variance explained	P-value
Age	0.034	<0.001
Female sex	0.093	<0.001
Haemoglobin concentration (g L^{-1})	0.038	<0.001
Coronary artery disease	0.004	0.11
Heart failure	0.003	0.14
Diabetes mellitus	0.023	<0.001
eGFR (ml min^{-1} 1.73 m^{-2})	0.002	0.29
Obstructive lung disease	0.004	0.11
Preoperative chemotherapy	0.006	0.03
Arthritis	0.003	0.18

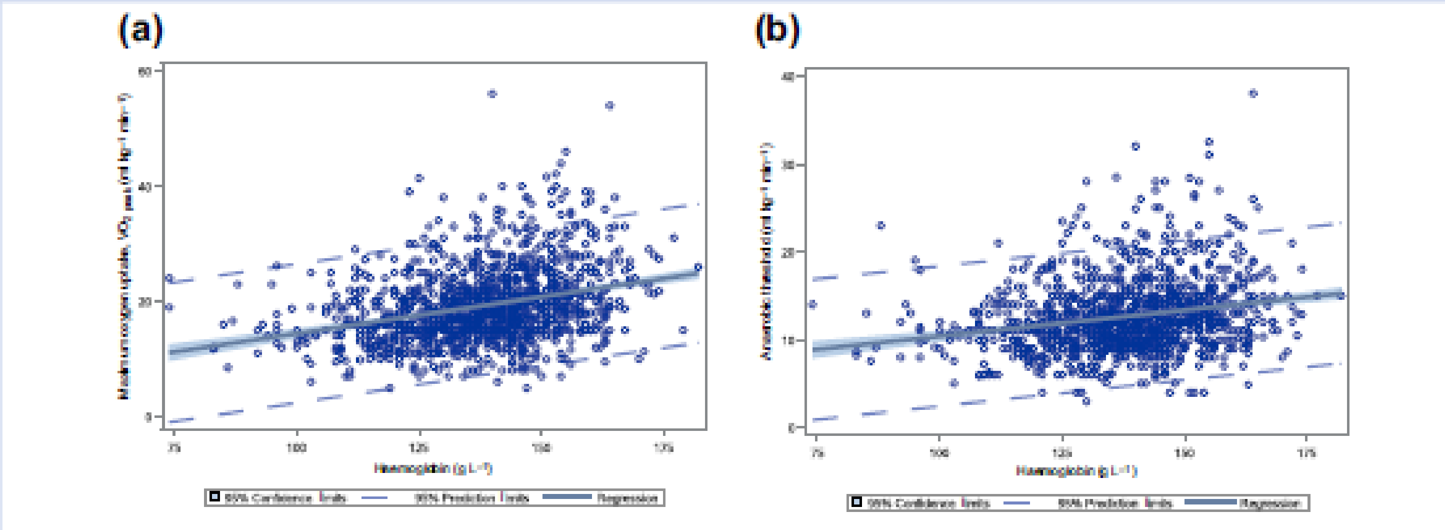


Fig 2. Fit plots for unadjusted linear regression modelling of haemoglobin concentration with VO_2 peak and anaerobic threshold (AT). (a) Association between haemoglobin concentration and VO_2 peak. (b) Association between haemoglobin concentration and anaerobic threshold.

Table 4 Multivariable logistic regression models predicting moderate and severe complications, with separate model results for VO_2 peak and anaerobic threshold; CI, confidence interval; VO_2 peak, peak oxygen consumption.

Independent variable	Odds ratio	95% CI	P-value
Adjusted association between haemoglobin concentration and moderate or severe complications—with adjustment for VO_2 peak			
Age (per 10 yr)	1.04	0.88–1.24	0.62
Female sex	0.53	0.35–0.79	0.002
Haemoglobin concentration (per 10 g L^{-1})	0.86	0.77–0.96	0.007
VO_2 peak (ml kg^{-1} min^{-1})	0.96	0.93–0.99	0.01
Surgical procedure type			
Intra- or retroperitoneal or intrathoracic or vascular	Reference		
Urology or gynaecology	0.33	0.22–0.49	<0.001
Orthopaedic	0.12	0.06–0.22	
Others	0.35	0.16–0.68	
Adjusted association between haemoglobin concentration and moderate or severe complications—with adjustment for anaerobic threshold			
Age (per 10 yr)	1.11	0.93–1.32	0.26
Female sex	0.58	0.38–0.87	0.009
Haemoglobin concentration (per 10 g L^{-1})	0.86	0.77–0.97	0.01
Anaerobic threshold (ml kg^{-1} min^{-1})	0.98	0.93–1.02	0.35
Surgical procedure type			
Intra- or retroperitoneal or intrathoracic or vascular	Reference		
Urology or gynaecology	0.31	0.20–0.47	<0.001
Orthopaedic	0.12	0.05–0.23	
Others	0.32	0.14–0.64	

c-Statistic=0.74; Hosmer–Lemeshow goodness-of-fit test, P=0.21; interaction term between haemoglobin concentration and VO_2 peak was not statistically significant (P=0.12).

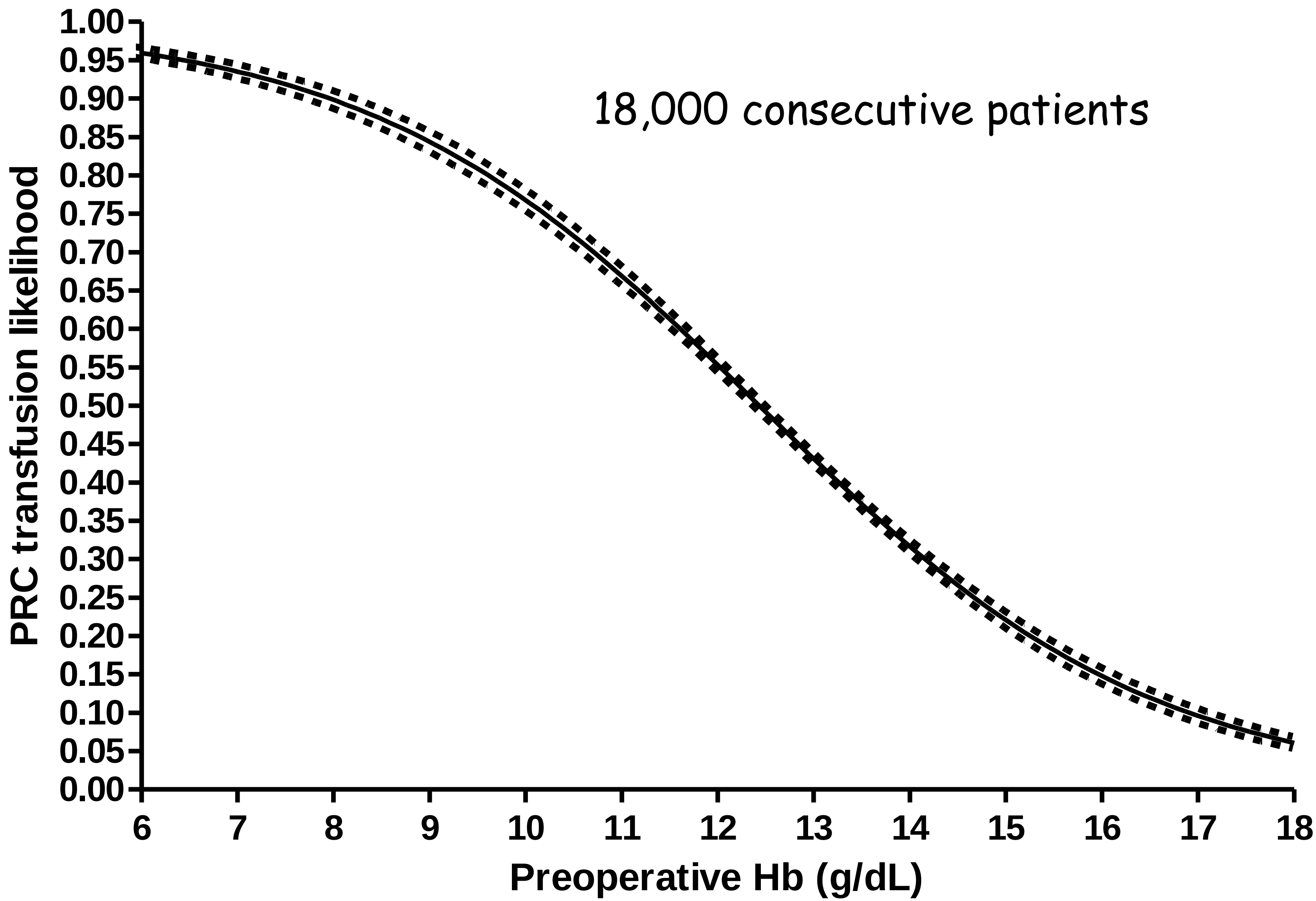
c-Statistic=0.73; Hosmer–Lemeshow goodness-of-fit test, P=0.95; interaction term between haemoglobin concentration and AT was not statistically significant (P=0.09).

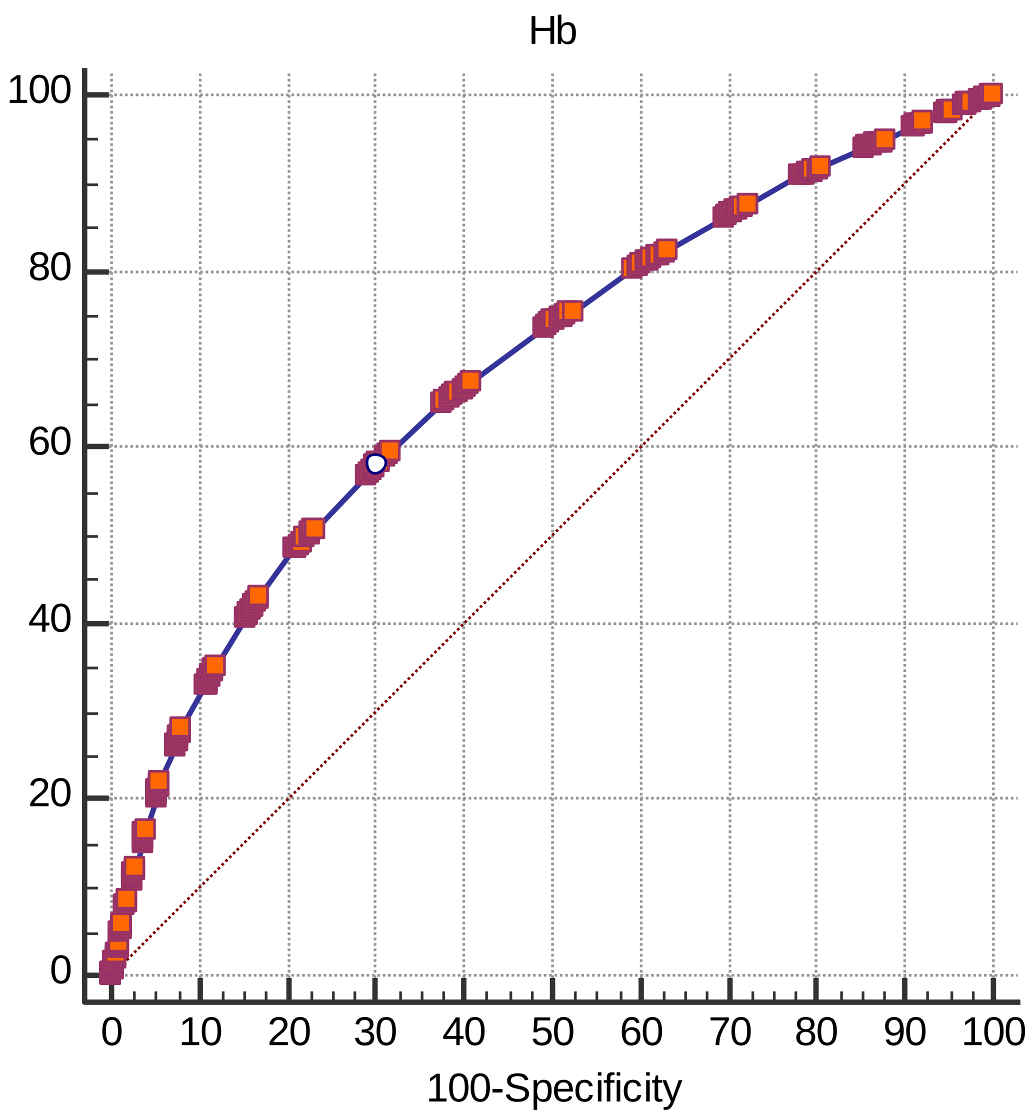
PBM PROJECT AT IRCCS Policlinico San Donato
PREOPERATIVE IRON DEFICIENCY CORRECTION

Table 4 Five-variable risk model for transfusions and TRACK score development

Factor	Coefficient β	*P* value	Odds ratio	TRACK score points (range for total: 0–32)
Age > 67 years	0·643	0·001	1·903	6
Weight < 60 kg (female) or < 85 kg (male)	0·240	0·001	1·272	2
Gender – female	0·359	0·001	1·418	4
Complex surgery	0·724	0·001	2·063	7
Haematocrit (continuous)	−0·109	0·001	0·895	1 point per each value (%)
Constant	3·484	0·001	32·600	Below 40% (max 13 points)

TRACK, Transfusion Risk And Clinical Knowledge.


18,000 consecutive patients
PRC transfusion likelihood
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
6
7
8
9
10
11
12
13
14
15
16
17
18
Preoperative Hb (g/dL)



Hb
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
100-Specificity

ROC curve

Variable	Hb
Classification variable	Tras

Sample size	17861
Positive group [a]	7850 (43,95%)
Negative group [b]	10011 (56,05%)

[a] Tras = 1
[b] Tras = 0

Disease prevalence (%)	44,0

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0,686
Standard Error [a]	0,00401
95% Confidence interval [b]	0,679 to 0,692
z statistic	46,298
Significance level P (Area=0.5)	<0,0001

[a] DeLong et al., 1988
[b] Binomial exact

Youden index

Youden index J	0,2785
Associated criterion	≤12,77
Sensitivity	57,73
Specificity	70,11

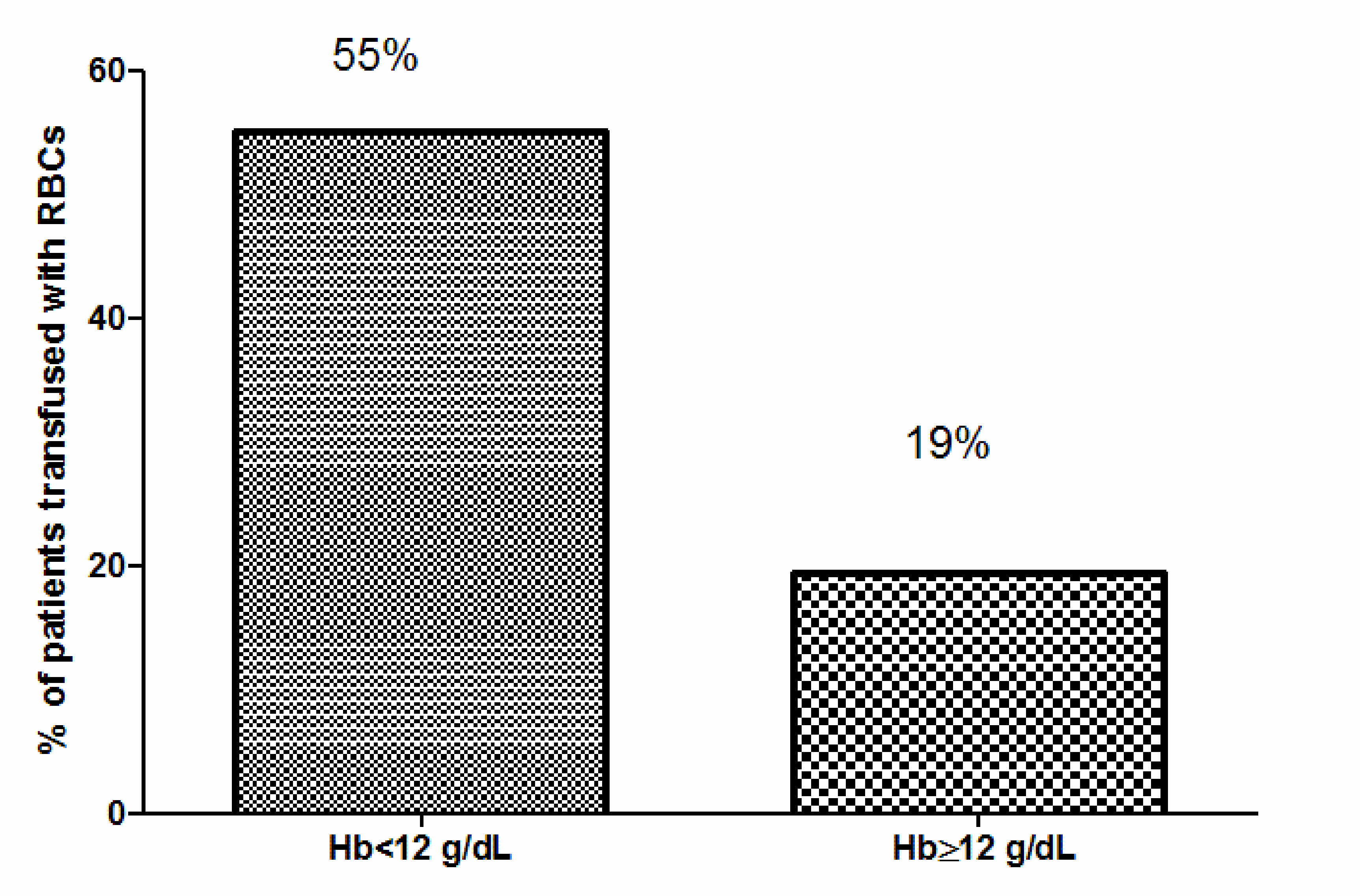
Optimal criterion

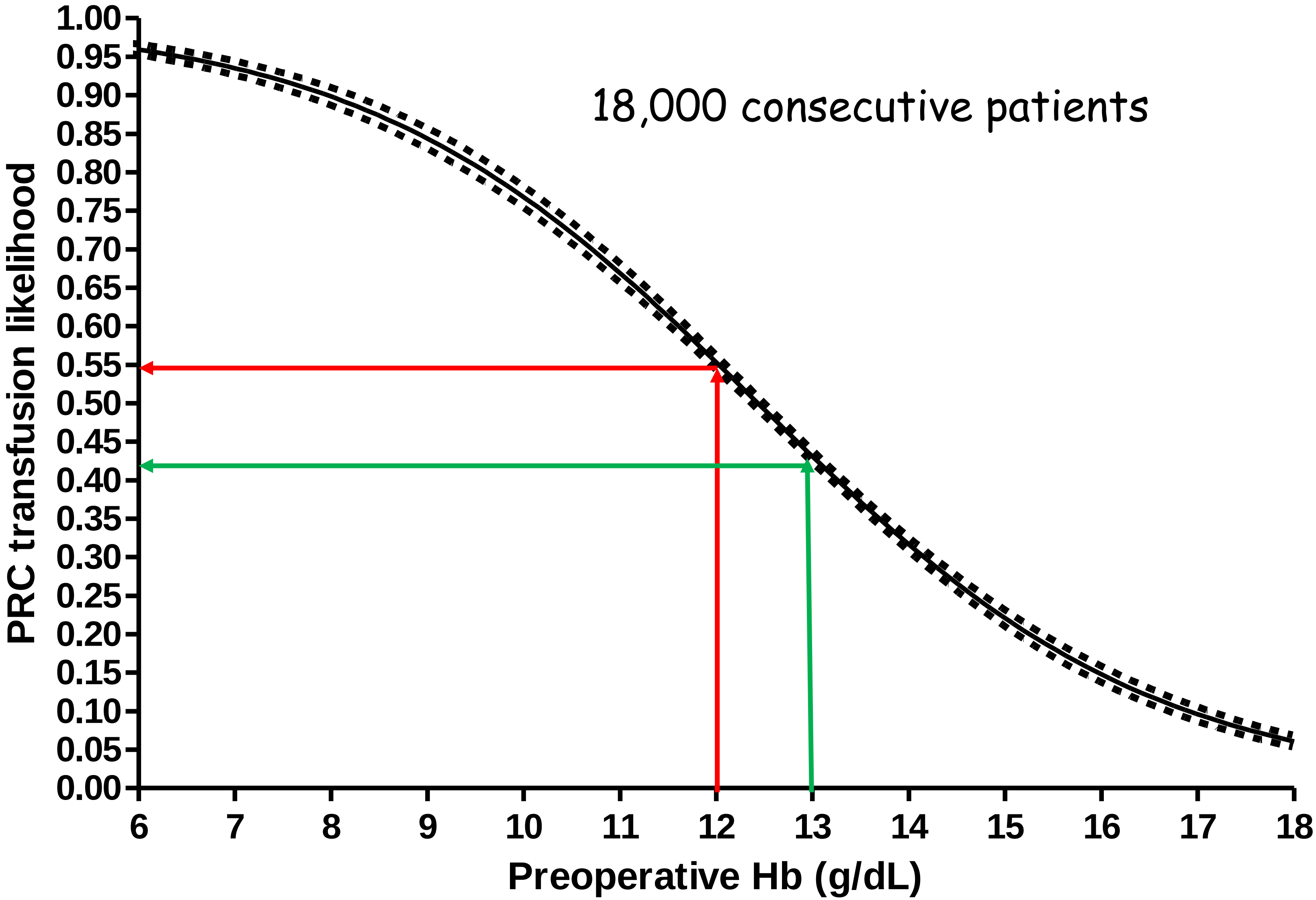
Optimal criterion [a]	≤12,33
Sensitivity	48,50
Specificity	79,01

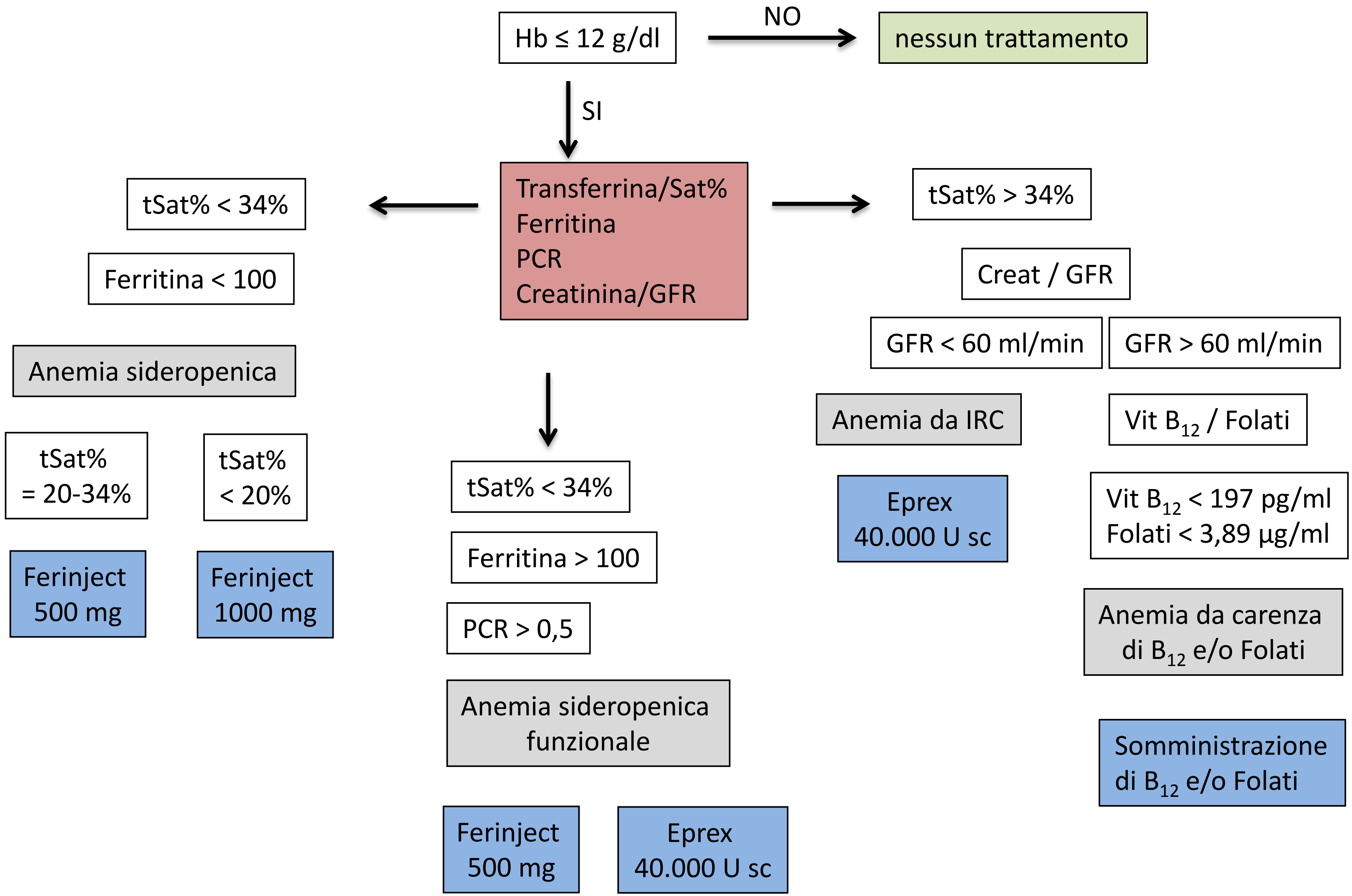
[a] Taking into account disease prevalence (44,0%) and estimated costs:
cost False Positive: 1; cost False Negative: 1
cost True Positive: 0; cost True Negative: 0

<12 g/dL = 22% patient population

220 patients/year


55%
19%
60
40
20
0
% of patients transfused with RBCs
Hb<12 g/dL
Hb≥12 g/dL


18,000 consecutive patients
PRC transfusion likelihood
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
6
7
8
9
10
11
12
13
14
15
16
17
18
Preoperative Hb (g/dL)



Al ricovero verranno eseguiti esami di controllo per verificare l’efficacia del trattamento

HYPOTHESIS

If we can increase the preoperative Hb value by 1 mg/dL, the expected transfusion rate will decrease by 13%

This accounts for 130 pts/year.
Given a mean RBC transfusion of 2 units,
a blood saving of 260 Units

Total saving accounts to 65,000 Euros/yr
Much more considering the additional costs of transfusions (about 100,000 Euros/year)

Anemia correction

- Ferrocarboxymalthose 700 mg ± 302 (in 57 pts)

- Erithropoyetin 40.000 U (in 27 pts)

ONGOING STUDY

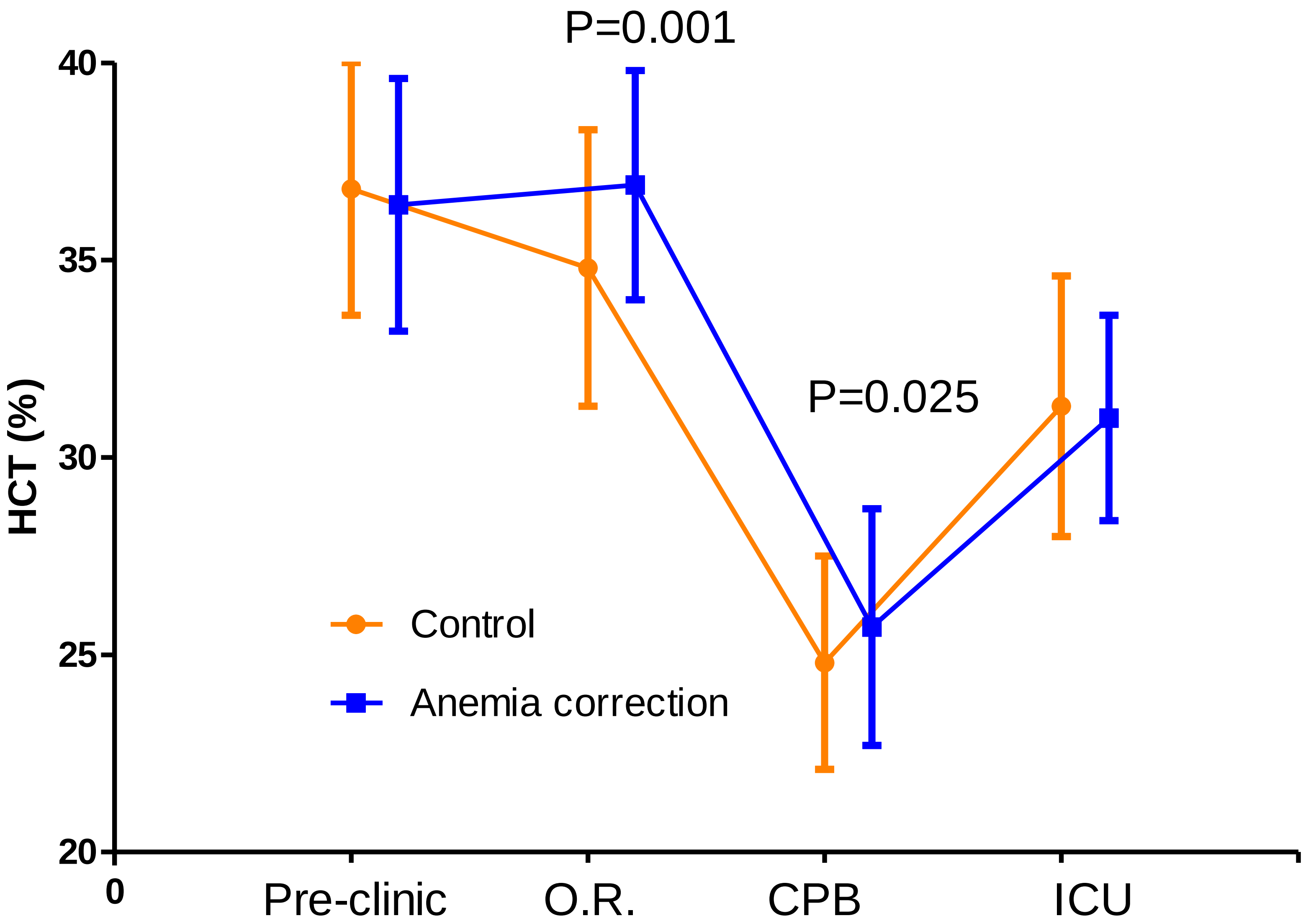
Sixty-one patients received anemia correction

Control patients were 520 (rough data)

After propensity matching, a control group of 174 was selected

61 174

VARIABLE	Anemia correction	Control	P value
Age	72.1±11.4	73.6±5.0	0.314
Gender male	31.1%	26.4%	0.479
Weight	64.5±14.2	66.0±11.8	0.420
Ejection fraction	58.4±7.8	57.0±8.4	0.283
Serum creatinine	1.2±1.8	1.2±1.3	0.845
Combined surgery	41%	39%	0.793
EuroSCORE II	1.7%	1.6%	0.999
Diabetes	21.3%	21.8%	0.931
COPD	1.7%	1.6%	0.985


P=0.001
P=0.025
HCT (%)
40
35
30
25
20
0
Pre-clinic
O.R.
CPB
ICU
Control
Anemia correction

OUTCOME

VARIABLE	Anemia correction	Control	P value
Transfusion RBC	55.7%	70.7%	0.033
Transfusion PLT	8.2%	10.3%	0.627
Bleeding	302±286	430±324	0.007
LOS	8.2%	17.2%	0.088
Stroke	1.6%	1.7%	0.99
F.A.	26.6%	28.7%	0.533
SEPSI	1.6%	2.3%	0.789
Mechanical Ventilation	16.5±13.6	33.8±87	0.01
Days in ICU	2.60±3.82	3.91±8.7	0.065
Hospitalization	9.4±4.8	11.2±9.0	0.034
Peak Creatinina	1.10±1.0	1.27±1.30	0.372
Mortality	1.6%	3.0%	0.415

TOO LITTLE PATIENT POPULATION AT PRESENT

HOWEVER, A POSITIVE TREND ON OUTCOMES AND SIGNIFICANT REDUCTION IN RBC TRANSFUSIONS

A LARGE MULTICENTER TRIAL IN UK IS ONGOING

Can J Anesth/J Can Anesth (2019) 66:716–731
https://doi.org/10.1007/s12630-019-01351-6

Check for updates

REVIEW ARTICLE/BRIEF REVIEW

Efficacy and safety of erythropoietin and iron therapy to reduce red blood cell transfusion in surgical patients: a systematic review and meta-analysis

Efficacité et innocuité d'un traitement d'érythropoïétine et de fer pour réduire la transfusion de culots sanguins chez les patients chirurgicaux: une revue systématique et méta-analyse

Tiffanie Kei, MHSc · Nikhil Mistry, MSc · Gerard Curley, MB, MSc, PhD · Katerina Pavenski, MD · Nadine Shehata, MD · Rosa Maria Tanzini, BSc (Pharm) · Marie-France Gauthier, PharmD, ACPR · Kevin Thorpe, MMath · Tom A. Schweizer, PhD · Sarah Ward, MD · C. David Mazer, MD · Gregory M. T. Hare, MD, PhD

Received: 24 July 2018 / Revised: 19 December 2018 / Accepted: 29 December 2018 / Published online: 28 March 2019

Study or Subgroup	ESA + Iron Events	ESA + Iron Total	Iron Events	Iron Total	Weight	Risk Ratio IV, Random, 95% CI	Year
4.2.1 ESA + Oral Iron vs. Oral Iron							
COPES 1993	53	130	44	78	6.3%	0.72 [0.54, 0.96]	1993
Faris 1996	25	118	36	69	5.6%	0.41 [0.27, 0.61]	1996
de Andrade 1996	23	213	24	101	5.0%	0.45 [0.27, 0.76]	1996
Heiss 1996	9	17	4	10	3.3%	1.32 [0.55, 3.20]	1996
D'Ambra 1997	36	119	25	56	5.7%	0.68 [0.45, 1.01]	1997
Sowade 1997	4	36	19	36	2.9%	0.21 [0.08, 0.56]	1997
Qvist 1999	13	38	23	43	5.0%	0.64 [0.38, 1.08]	1999
Feagan 2000	23	123	35	78	5.5%	0.42 [0.27, 0.65]	2000
Podesta 2000	1	30	26	30	1.1%	0.04 [0.01, 0.27]	2000
Larson 2001	0	15	1	16	0.4%	0.35 [0.02, 8.08]	2001
Wurnig 2001	41	124	28	51	6.0%	0.60 [0.42, 0.86]	2001
Scott 2002	19	29	24	29	6.2%	0.79 [0.58, 1.08]	2002
Dousias 2003	0	23	5	27	0.5%	0.11 [0.01, 1.82]	2003
Christodoulakis 2005	59	136	36	68	6.3%	0.82 [0.61, 1.10]	2005
Weber 2005	56	458	107	235	6.3%	0.27 [0.20, 0.36]	2005
Weltert 2015	51	300	117	300	6.3%	0.44 [0.33, 0.58]	2015
Wu 2016	2	30	6	32	1.6%	0.36 [0.08, 1.63]	2016
Subtotal (95% CI)		**1939**		**1259**	**74.1%**	**0.51 [0.40, 0.65]**	
Total events	415		560				
Heterogeneity: Tau² = 0.15; Chi² = 65.02, df = 16 (P < 0.00001); I² = 75%							
Test for overall effect: Z = 5.50 (P < 0.00001)							
4.2.2 ESA + IV Iron vs. IV Iron							
Kyo 1992	20	40	12	16	5.6%	0.67 [0.44, 1.01]	1992
Kettelhack 1998	16	48	15	54	4.7%	1.20 [0.67, 2.16]	1998
Kosmadakis 2003	10	31	28	32	5.0%	0.37 [0.22, 0.62]	2003
Bernabeu-Wittel 2016	52	100	53	103	6.4%	1.01 [0.77, 1.32]	2016
Urena 2017	13	48	13	52	4.3%	1.08 [0.56, 2.10]	2017
Subtotal (95% CI)		**267**		**257**	**25.9%**	**0.79 [0.54, 1.18]**	
Total events	111		121				
Heterogeneity: Tau² = 0.14; Chi² = 14.40, df = 4 (P = 0.006); I² = 72%							
Test for overall effect: Z = 1.15 (P = 0.25)							
Total (95% CI)		**2206**		**1516**	**100.0%**	**0.57 [0.46, 0.71]**	
Total events	526		681				
Heterogeneity: Tau² = 0.17; Chi² = 96.33, df = 21 (P < 0.00001); I² = 78%							
Test for overall effect: Z = 5.07 (P < 0.00001)							
Test for subgroup differences: Chi² = 3.51, df = 1 (P = 0.06), I² = 71.5%							

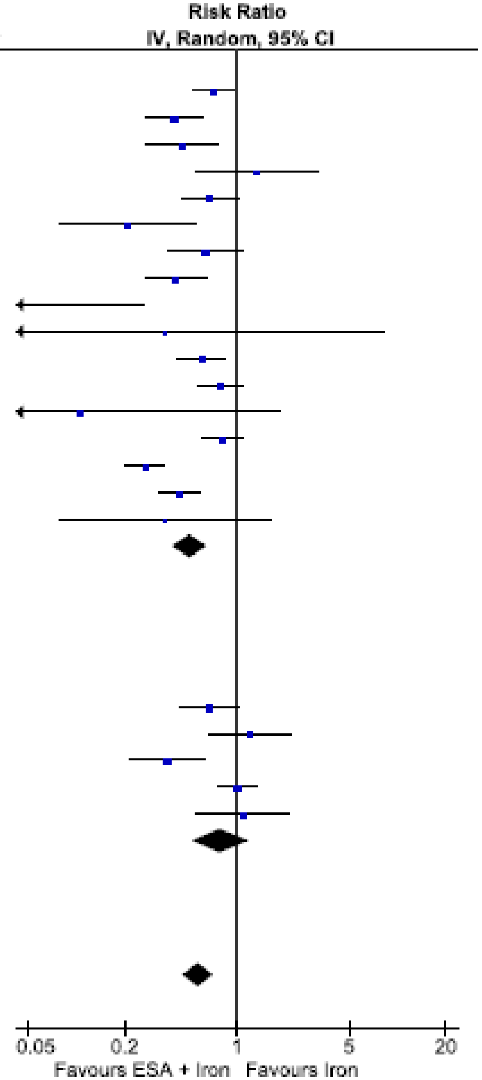


Fig. 2 Forest plot showing the effect of erythropoiesis stimulating agents (ESA) and iron *vs* iron on number of patients transfused with red blood cells (RBCs) (primary outcome), stratified into subgroups by study interventions

Study or Subgroup	ESA + Iron Events	ESA + Iron Total	Iron Events	Iron Total	Weight	Risk Ratio IV, Random, 95% CI	Year
5.3.1 Low Dose ESA + Iron vs. Iron							
Kyo 1992	20	40	12	16	5.5%	0.67 [0.44, 1.01]	1992
Qvist 1999	13	38	23	43	4.9%	0.64 [0.38, 1.08]	1999
Feagan 2000	18	79	18	39	4.9%	0.49 [0.29, 0.84]	2000
Podesta 2000	1	30	26	30	1.0%	0.04 [0.01, 0.27]	2000
Larson 2001	0	15	1	16	0.4%	0.35 [0.02, 8.08]	2001
Wurnig 2001	41	124	28	51	5.8%	0.60 [0.42, 0.86]	2001
Weltert 2015	51	300	117	300	6.1%	0.44 [0.33, 0.58]	2015
Bernabeu-Wittel 2016	52	100	53	103	6.2%	1.01 [0.77, 1.32]	2016
Wu 2016	2	30	6	32	1.5%	0.36 [0.08, 1.63]	2016
Urena 2017	13	48	13	52	4.2%	1.08 [0.56, 2.10]	2017
Subtotal (95% CI)		**804**		**682**	**40.6%**	**0.60 [0.44, 0.82]**	
Total events	211		297				
Heterogeneity: Tau² = 0.14; Chi² = 30.52, df = 9 (P = 0.0004); I² = 71%							
Test for overall effect: Z = 3.20 (P = 0.001)							
5.3.2 High Dose ESA + Iron vs. Iron							
COPES 1993	53	130	44	78	6.1%	0.72 [0.54, 0.96]	1993
Faris 1996	25	118	36	69	5.5%	0.41 [0.27, 0.61]	1996
Heiss 1996	9	17	4	10	3.2%	1.32 [0.55, 3.20]	1996
de Andrade 1996	23	213	24	101	4.9%	0.45 [0.27, 0.76]	1996
D'Ambra 1997	36	119	25	56	5.6%	0.68 [0.45, 1.01]	1997
Sowade 1997	4	36	19	36	2.8%	0.21 [0.08, 0.56]	1997
Kettelhack 1998	16	48	15	54	4.5%	1.20 [0.67, 2.16]	1998
Feagan 2000	5	44	17	39	3.1%	0.26 [0.11, 0.64]	2000
Scott 2002	19	29	24	29	6.0%	0.79 [0.58, 1.08]	2002
Dousias 2003	0	23	5	27	0.5%	0.11 [0.01, 1.82]	2003
Kosmadakis 2003	10	31	28	32	4.9%	0.37 [0.22, 0.62]	2003
Weber 2005	56	458	107	235	6.2%	0.27 [0.20, 0.36]	2005
Christodoulakis 2005	59	136	36	68	6.1%	0.82 [0.61, 1.10]	2005
Subtotal (95% CI)		**1402**		**834**	**59.4%**	**0.54 [0.40, 0.73]**	
Total events	315		384				
Heterogeneity: Tau² = 0.22; Chi² = 64.54, df = 12 (P < 0.00001); I² = 81%							
Test for overall effect: Z = 4.03 (P < 0.0001)							
Total (95% CI)		**2206**		**1516**	**100.0%**	**0.56 [0.45, 0.70]**	
Total events	526		681				
Heterogeneity: Tau² = 0.17; Chi² = 97.56, df = 22 (P < 0.00001); I² = 77%							
Test for overall effect: Z = 5.27 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.59), I² = 0%							

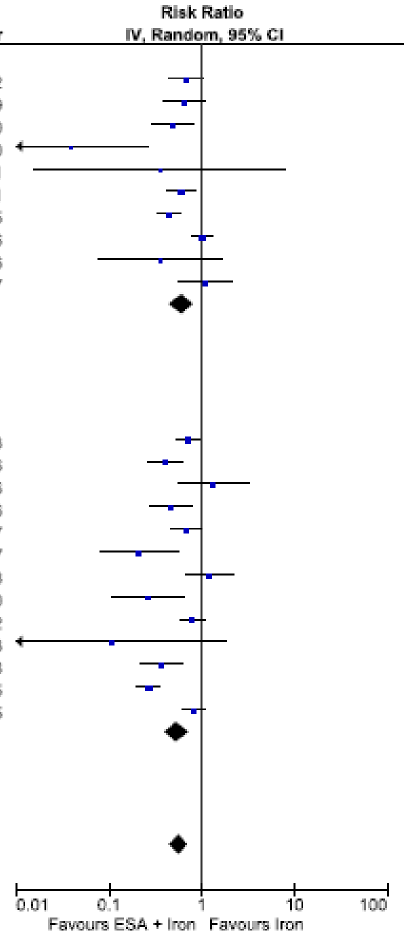


Fig. 3 Forest plot showing the effect of erythropoiesis stimulating agents (ESA) and iron *vs* iron on number of patients transfused with red blood cells (RBCs) (primary outcome), stratified by low dose (≤ 80,000 IU) *vs* high dose ESA (> 80,000 IU)

Study or Subgroup	ESA + Iron Events	ESA + Iron Total	Iron Events	Iron Total	Weight	Risk Ratio IV, Random, 95% CI	Year
4.1.1 Orthopedic Surgery							
COPES 1993	53	130	44	78	7.5%	0.72 [0.54, 0.96]	1993
Faris 1996	25	118	36	69	6.8%	0.41 [0.27, 0.61]	1996
de Andrade 1996	23	213	24	101	6.2%	0.45 [0.27, 0.76]	1996
Feagan 2000	23	123	35	78	6.7%	0.42 [0.27, 0.65]	2000
Weber 2005	56	458	107	235	7.6%	0.27 [0.20, 0.36]	2005
Wu 2016	2	30	6	32	2.1%	0.36 [0.08, 1.63]	2016
Bernabeu-Wittel 2016	52	100	53	103	7.6%	1.01 [0.77, 1.32]	2016
Subtotal (95% CI)		**1172**		**696**	**44.5%**	**0.49 [0.32, 0.76]**	
Total events	234		305				
Heterogeneity: Tau² = 0.28; Chi² = 52.73, df = 6 (P < 0.00001); I² = 89%							
Test for overall effect: Z = 3.18 (P = 0.001)							
4.1.2 Cardiac Surgery							
Kyo 1992	20	40	12	16	6.8%	0.67 [0.44, 1.01]	1992
Sowade 1997	4	36	19	36	3.8%	0.21 [0.08, 0.56]	1997
D'Ambra 1997	36	119	25	56	6.9%	0.68 [0.45, 1.01]	1997
Podesta 2000	1	30	26	30	1.5%	0.04 [0.01, 0.27]	2000
Weltert 2015	51	300	117	300	7.5%	0.44 [0.33, 0.58]	2015
Urena 2017	13	48	13	52	5.4%	1.08 [0.56, 2.10]	2017
Subtotal (95% CI)		**573**		**490**	**31.8%**	**0.51 [0.32, 0.79]**	
Total events	125		212				
Heterogeneity: Tau² = 0.19; Chi² = 19.38, df = 5 (P = 0.002); I² = 74%							
Test for overall effect: Z = 3.02 (P = 0.003)							
4.1.3 Colorectal Cancer Surgery							
Heiss 1996	9	17	4	10	4.2%	1.32 [0.55, 3.20]	1996
Kettelhack 1998	16	48	15	54	5.8%	1.20 [0.67, 2.16]	1998
Qvist 1999	13	38	23	43	6.2%	0.64 [0.38, 1.08]	1999
Christodoulakis 2005	59	136	36	68	7.5%	0.82 [0.61, 1.10]	2005
Subtotal (95% CI)		**239**		**175**	**23.7%**	**0.86 [0.67, 1.12]**	
Total events	97		78				
Heterogeneity: Tau² = 0.01; Chi² = 3.49, df = 3 (P = 0.32); I² = 14%							
Test for overall effect: Z = 1.09 (P = 0.27)							
Total (95% CI)		**1984**		**1361**	**100.0%**	**0.58 [0.45, 0.74]**	
Total events	456		595				
Heterogeneity: Tau² = 0.21; Chi² = 88.37, df = 16 (P < 0.00001); I² = 82%							
Test for overall effect: Z = 4.23 (P < 0.0001)							
Test for subgroup differences: Chi² = 7.04, df = 2 (P = 0.03), I² = 71.6%							

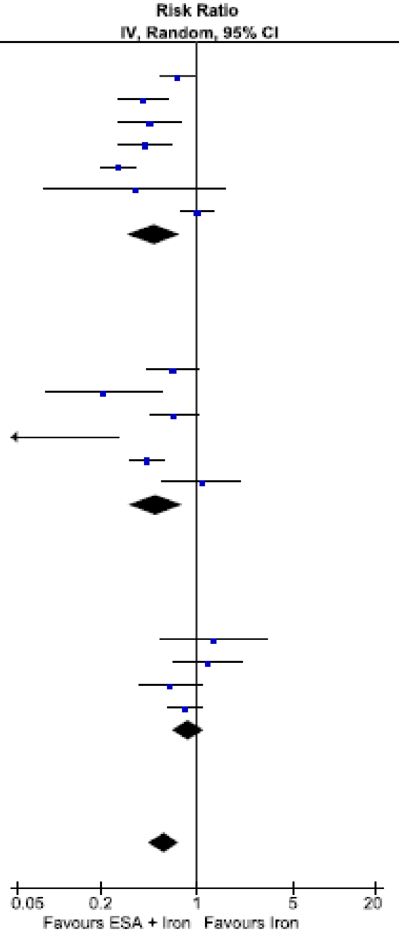


Fig. 4 Forest plot showing the effect of erythropoiesis stimulating agents (ESA) and iron *vs* iron on number of patients transfused with red blood cells (RBCs) (primary outcome), stratified by type of surgery

TWO ISSUES

1. PREOPERATIVE ANEMIA
2. LIBERAL vs RESTRICTIVE TRANSFUSIONS

TWO ISSUES

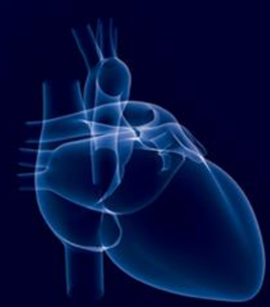
1. PREOPERATIVE ANEMIA

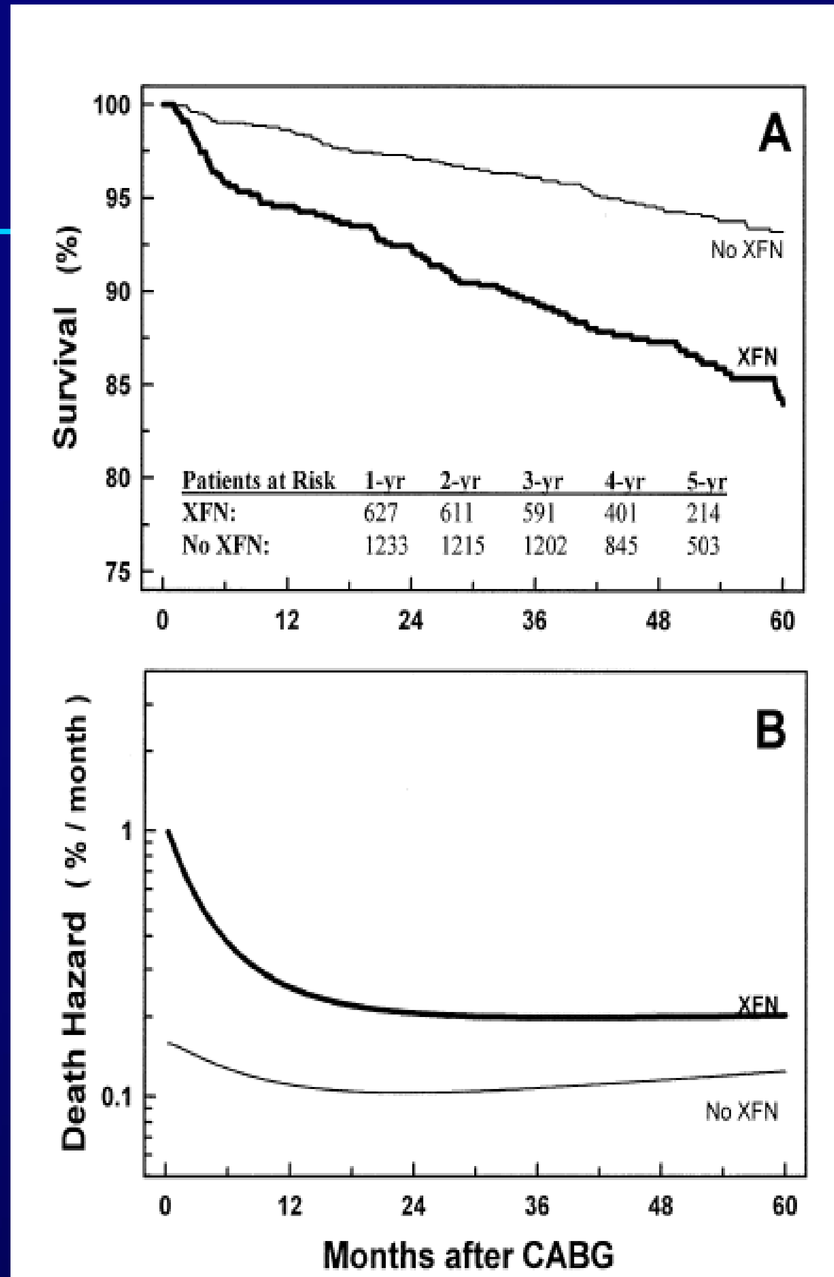
2. LIBERAL vs RESTRICTIVE TRANSFUSIONS

Effect of Blood Transfusion on Long-Term Survival After Cardiac Operation

Milo C. Engoren, MD, Robert H. Habib, PhD, Anoar Zacharias, MD,
Thomas A. Schwann, MD, Christopher J. Riordan, MD, and Samuel J. Durham, MD

Departments of Anesthesiology and Cardiovascular Surgery, St. Vincent Mercy Medical Center, and Medical College of Ohio, Toledo, Ohio




A
Survival (%)
100
95
90
85
80
75
No XFN
XFN
Patients at Risk 1-yr 2-yr 3-yr 4-yr 5-yr
XFN: 627 611 591 401 214
No XFN: 1233 1215 1202 845 503
0 12 24 36 48 60
B
Death Hazard (% / month)
1
0.1
XFN
No XFN
0 12 24 36 48 60
Months after CABG

Transfusion of Blood Components and Postoperative Infection in Patients Undergoing Cardiac Surgery*

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Table 2—*Significant Factors for the Acquisition of SPI***

Variables	Patients, % SPI (n = 70)	Patients, % Non-SPI (n = 668)	RR	p Value
Reintubation	42.9	3.4	9.7	0.001
MV ≥ 48 h	40	4.6	7.7	0.001
Sternal dehiscence	8.6	0.7	6.2	0.001
Reintervention	25.7	4.8	4.7	0.001
Neurologic dysfunction	28.6	5.7	4.7	0.001
Transfusion ≥ 4 U RBC concentrates	71.4	37.3	3.7	0.001
Total transfusion ≥ 4 U	72.9	40.6	3.5	0.001
Arterial hypotension	67.1	36.5	3.1	0.001
APACHE II score ≥ 12	61.4	33.5	2.8	0.001
Platelet transfusion ≥ 1 U	25.7	10.6	2.5	0.001
Mediastinal bleeding ≥ 800 mL	61.4	36.4	2.5	0.001
Postoperative cardiac failure	22.9	10.3	2.3	0.003
Transfusion ≥ 2 U plasma	35.7	18.9	2.2	0.002
Necessity of catecholamines	84.2	70	2.2	0.017
Perioperative AMI	15.7	7.6	2	0.036
Time of CPB ≥ 110 min	57.1	39.4	1.9	0.006
Left atrial catheter	37.1	25.1	1.6	0.043

*RR = relative risk; AMI = acute myocardial infarction. See Table 1 for abbreviations not used in text.

Cardiovascular Surgery

Increased Mortality, Postoperative Morbidity, and Cost After Red Blood Cell Transfusion in Patients Having Cardiac Surgery

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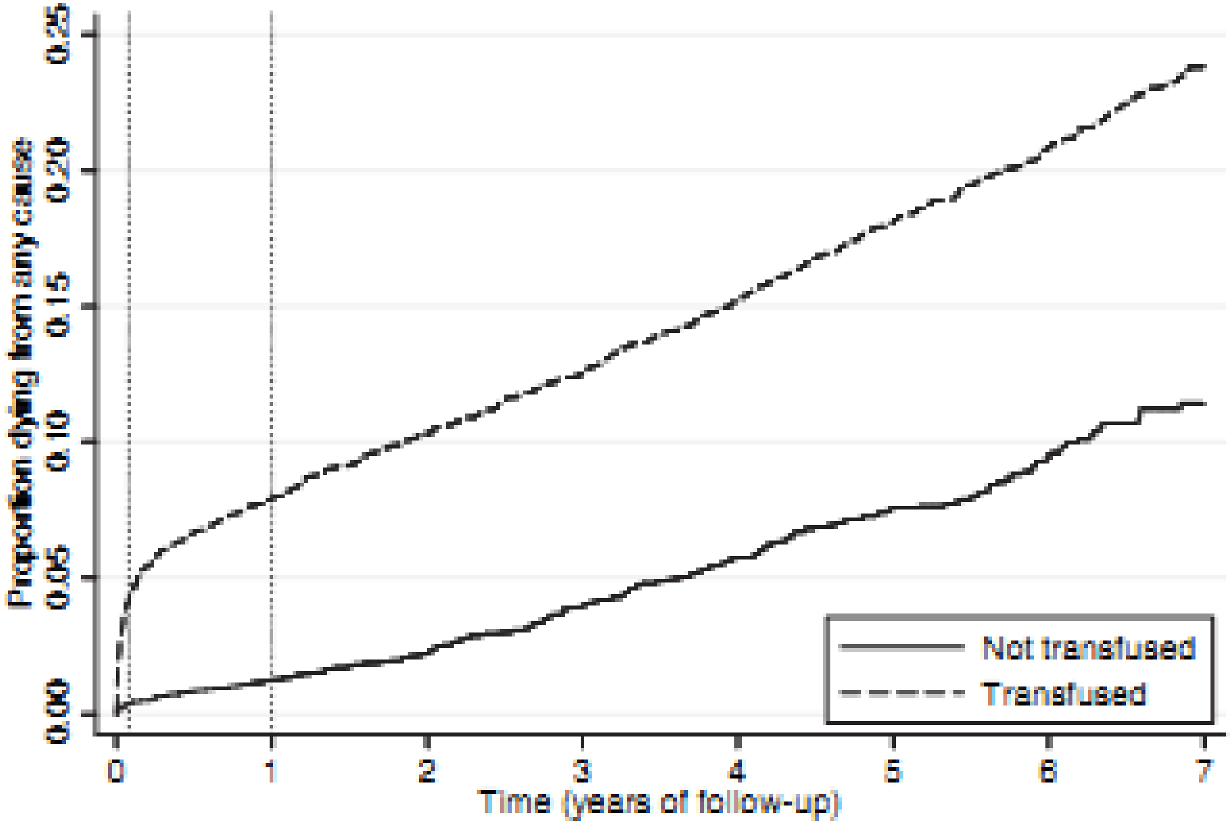
Background—Red blood cell transfusion can both benefit and harm. To inform decisions about transfusion, we aimed to quantify associations of transfusion with clinical outcomes and cost in patients having cardiac surgery.

Methods and Results—Clinical, hematology, and blood transfusion databases were linked with the UK population register. Additional hematocrit information was obtained from intensive care unit charts. Composite infection (respiratory or wound infection or septicemia) and ischemic outcomes (myocardial infarction, stroke, renal impairment, or failure) were prespecified as coprimary end points. Secondary outcomes were resource use, cost, and survival. Associations were estimated by regression modeling with adjustment for potential confounding. All adult patients having cardiac surgery between April 1, 1996, and December 31, 2003, with key exposure and outcome data were included (98%). Adjusted odds ratios for composite infection (737 of 8516) and ischemic outcomes (832 of 8518) for transfused versus nontransfused patients were 3.38 (95% confidence interval [CI], 2.60 to 4.40) and 3.35 (95% CI, 2.68 to 4.35), respectively. Transfusion was associated with increased relative cost of admission (any transfusion, 1.42 times [95% CI, 1.37 to 1.46], varying from 1.11 for 1 U to 3.35 for >9 U). At any time after their operations, transfused patients were less likely to have been discharged from hospital (hazard ratio [HR], 0.63; 95% CI, 0.60 to 0.67) and were more likely to have died (0 to 30 days: HR, 6.69; 95% CI, 3.66 to 15.1; 31 days to 1 year: HR, 2.59; 95% CI, 1.68 to 4.17; >1 year: HR, 1.32; 95% CI, 1.08 to 1.64).

Conclusions—Red blood cell transfusion in patients having cardiac surgery is strongly associated with both infection and ischemic postoperative morbidity, hospital stay, increased early and late mortality, and hospital costs. (***Circulation*. 2007;116:2544-2552.**)

Key Words: infection ■ myocardial infarction ■ stroke ■ surgery ■ blood transfusions



Number at risk:

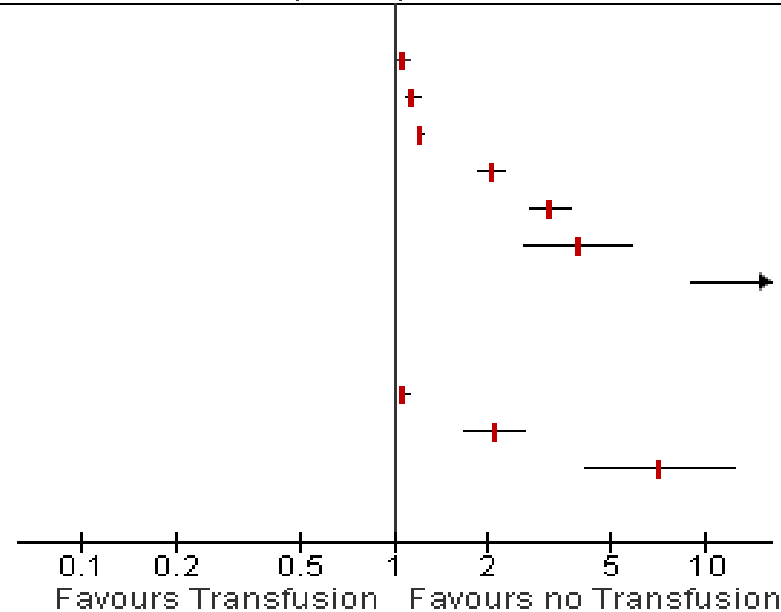
Not transfused:	3689	3529	2925	2383	1842	1291	772	391
Transfused:	4909	4449	3913	3340	2773	2213	1713	1073

Transfusion and Organ Injury

Acute Kidney Injury

Study or Subgroup	Odds Ratio IV, Fixed, 95% CI
1.3.1 Renal Replacement Therapy/ ARF	
Karkouti 2009	1.08 [1.03, 1.13]
Yap 2008	1.15 [1.09, 1.21]
Furnary 2007	1.22 [1.19, 1.26]
Koch 2006 (a)	2.06 [1.87, 2.27]
Bucerius 2004	3.15 [2.71, 3.66]
Habib 2005	3.87 [2.62, 5.72]
Bove 2004	28.70 [8.89, 92.67]
1.3.2 Acute Kidney Injury	
Karkouti 2009	1.08 [1.05, 1.12]
Habib 2005	2.09 [1.67, 2.62]
Bove 2004	7.10 [4.13, 12.20]

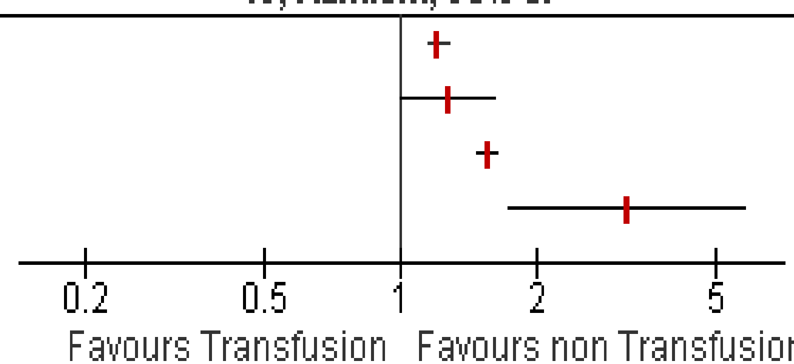
Odds Ratio
IV, Fixed, 95% CI



Low Cardiac Output

Study or Subgroup	Odds Ratio IV, Random, 95% CI
Kulier 2007	1.21 [1.15, 1.27]
Surgenor 2006	1.27 [1.00, 1.61]
Koch 2006 (a)	1.55 [1.47, 1.63]
de Santo 2009	3.16 [1.73, 5.79]

Odds Ratio
IV, Random, 95% CI



Ranucci et al. JTCVS 2011

Major Bleeding, Transfusions, and Anemia: The Deadly Triad of Cardiac Surgery

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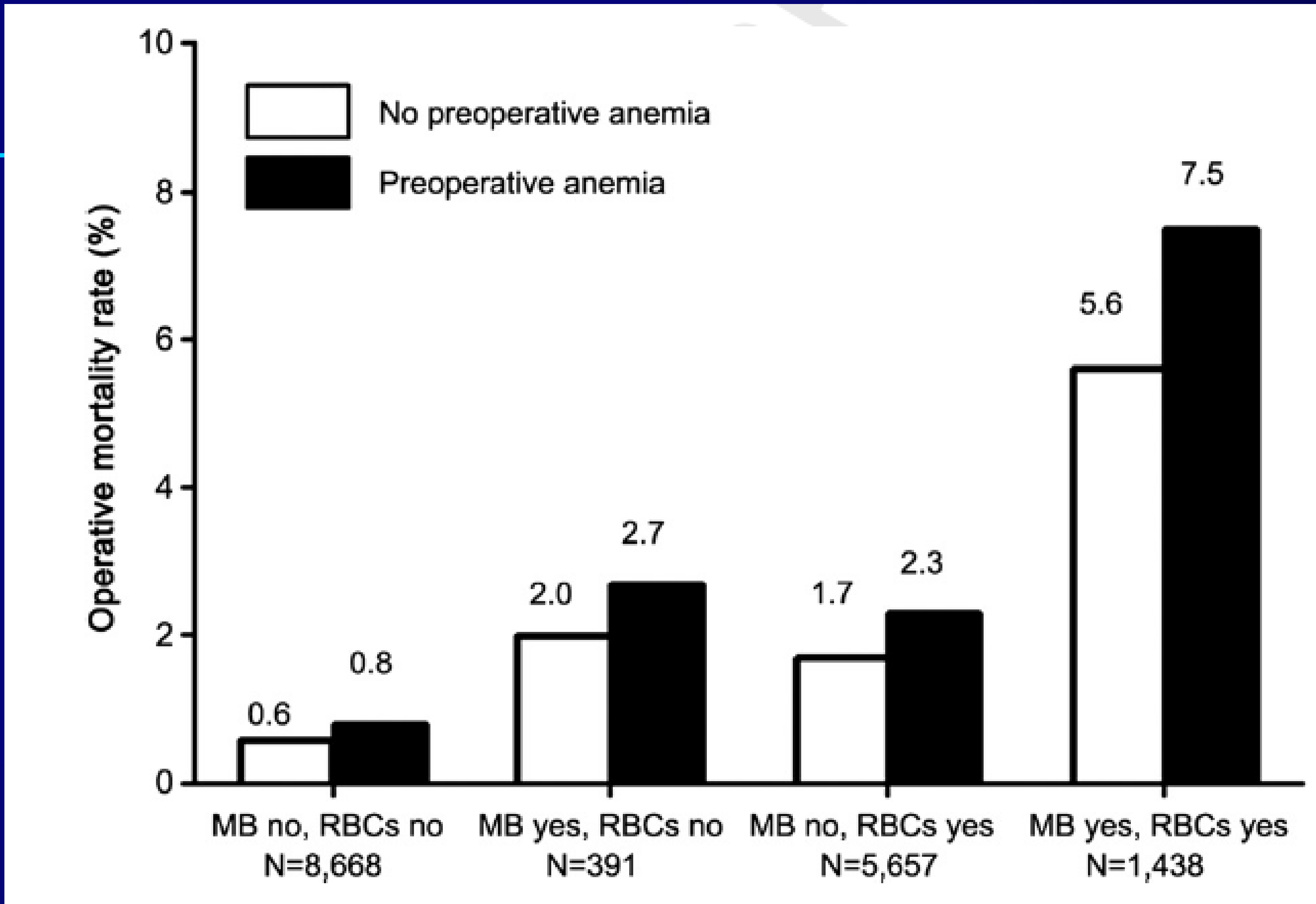
Background. Postoperative bleeding is common after cardiac surgery. Major bleeding (MB) is a determinant of red blood cell (RBC) transfusion, especially in patients with preoperative anemia. Preoperative anemia and RBC transfusions are recognized risk factors for operative mortality. The present study investigates the role of MB as an independent determinant of operative mortality in cardiac surgery.

Methods. A single-center retrospective study based on the institutional database of cardiac surgery in the period 2000–2012 was conducted. Sixteen thousand one hundred fifty-four (16,154) consecutive adult patients undergoing cardiac surgery were analyzed. The impact of postoperative bleeding and MB on operative (30 days) mortality was analyzed univariately and after correction for preoperative anemia, RBC transfusions, and other confounders.

Results. Postoperative bleeding was significantly ($p < 0.001$) associated with operative mortality, both in univariate and multivariable models. The main complications associated with MB were thromboembolic complications, infections, and surgical reexploration. In a multivariable model, MB remained an independent predictor of operative mortality (odds ratio, 3.45; 95% confidence interval, 2.78 to 4.28). Preoperative anemia and RBC transfusions coexist in the model, acting with a multiplying effect when associated with MB.

Conclusions. Major bleeding is per se a risk factor for operative mortality. However, its deleterious effects are strongly enhanced by RBC transfusions and, to a lesser extent, preoperative anemia. Major bleeding is a partially modifiable risk factor, and adequate preemptive and treatment strategies should be applied to limit this event.

(Ann Thorac Surg 2013;■:■–■)



No preoperative anemia
Preoperative anemia
Operative mortality rate (%)
10
8
6
4
2
0
0.6
0.8
2.0
2.7
1.7
2.3
5.6
7.5
MB no, RBCs no
N=8,668
MB yes, RBCs no
N=391
MB no, RBCs yes
N=5,657
MB yes, RBCs yes
N=1,438

THE TRIAD

1. ANEMIA: A DISEASE
2. BLEEDING: A SYMPTOM OF A DISEASE
3. TRANSFUSION: A THERAPY OF A SYMPTOM / DISEASE

THE TRIAD

TRANSFUSION: A THERAPY OF A SYMPTOM / DISEASE

1. Transfusion is decided by the doctors

2. They can be used or avoided on clinical judgement

3. TRANSFUSION IS NOT AN OUTCOME

Can J Anesth/J Can Anesth (2016) 63:169–175
DOI 10.1007/s12630-015-0515-8

CrossMark

REVIEW ARTICLE/BRIEF REVIEW

Outcome measures and quality markers for perioperative blood loss and transfusion in cardiac surgery

Critères d'évaluation et marqueurs de qualité pour les pertes sanguines et les transfusions périopératoires en chirurgie cardiaque

Marco Ranucci, MD

Transfusion rates and volumes may be used as primary endpoints as a surrogate for bleeding in studies exploring the effects of hemostatic drugs/products, but such studies must strictly adhere to the transfusion protocols and measures to avoid the confounding effects of anemia. Transfusion-related endpoints may be good markers of quality of care and are appropriate to assess the success of PBM programs.

QUESTIONS

1. ARE TRANSFUSIONS HARMFUL IN SURGERY
2. WHAT IS THE LEVEL OF THE EVIDENCE?
3. WHAT IS «liberal» and WHAT IS «restrictive»?

TRANSFUSIONS LEAD
TO BAD OUTCOMES
IN CARDIAC SURGERY

WHERE IS THE EVIDENCE
COMING FROM?

Hundreds of studies found an association between RBC transfusions and bad outcomes in cardiac surgery

They all share one factor:
RETROSPECTIVE STUDIES

RETROSPECTIVE STUDIES

- ADJUSTED FOR CONFOUNDERS
- PROPENSITY MATCHED
- NEVER CONSIDERING THE CLINICAL JUDGEMENT
- TRANSFUSIONS ARE MORE OFTEN USED IF THE CLINICIANS FEEL THAT THE PATIENT IS LESS ABLE TO TOLERATE ANEMIA

RETROSPECTIVE STUDIES

EVERY TIME WE RETROSPECTIVELY INVESTIGATE THE ASSOCIATION BETWEEN A THERAPY AIMED TO CORRECT AN ACUTE CONDITION, WE WILL INVARIABLY FIND AN ASSOCIATION WITH BAD OUTCOMES

NEED EXAMPLES

WHENEVER WE DECIDE TO USE:

1. An inotropic support
2. An IABP
3. An ECMO
4. A ventilatory support
5. PEEP

….and dozen of other therapies…

NEED EXAMPLES

THOSE WHO ARE IN NEED FOR A THERAPY WILL HAVE, WHEN RETROSPECTIVELY ANALYZED, WORSE OUTCOMES THAN THOSE WHO DID NOT REQUIRE IT

Should we stop using inotropes, High PEEP, ECMO, because of this?

RETROSPECTIVE STUDIES

RETROSPECTIVE STUDIES MAY ONLY FIND **ASSOCIATION**, NOT **CAUSATION**.

THEY ARE VERY USEFUL TO RAISE A **HYPOTHESIS**

IF YOU WANT TO CONFIRM THE HYPOTHESIS, YOU NEED AN **RCT**

THE RANDOMIZED CONTROLLED TRIALS

Transfusion Requirements After Cardiac Surgery

The TRACS Randomized Controlled Trial

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Context Perioperative red blood cell transfusion is commonly used to address anemia, an independent risk factor for morbidity and mortality after cardiac operations; however, evidence regarding optimal blood transfusion practice in patients undergoing cardiac surgery is lacking.

Objective To define whether a restrictive perioperative red blood cell transfusion strategy is as safe as a liberal strategy in patients undergoing elective cardiac surgery.

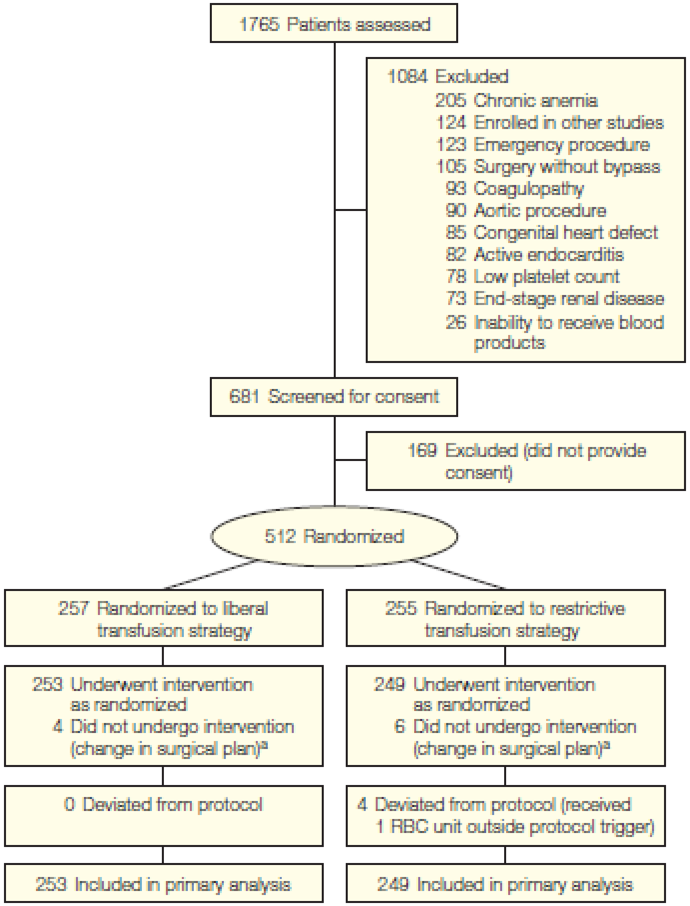
Design, Setting, and Patients The Transfusion Requirements After Cardiac Surgery (TRACS) study, a prospective, randomized, controlled clinical noninferiority trial conducted between February 2009 and February 2010 in an intensive care unit at a university hospital cardiac surgery referral center in Brazil. Consecutive adult patients (n=502) who underwent cardiac surgery with cardiopulmonary bypass were eligible; analysis was by intention-to-treat.

Intervention Patients were randomly assigned to a liberal strategy of blood transfusion (to maintain a hematocrit ≥30%) or to a restrictive strategy (hematocrit ≥24%).

Main Outcome Measure Composite end point of 30-day all-cause mortality and severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or hemofiltration) occurring during the hospital stay. The noninferiority margin was predefined at −8% (ie, 8% minimal clinically important increase in occurrence of the composite end point).

Results Hemoglobin concentrations were maintained at a mean of 10.5 g/dL (95% confidence interval [CI], 10.4-10.6) in the liberal-strategy group and 9.1 g/dL (95% CI, 9.0-9.2) in the restrictive-strategy group ($P<.001$). A total of 198 of 253 patients (78%) in the liberal-strategy group and 118 of 249 (47%) in the restrictive-strategy group received a blood transfusion ($P<.001$). Occurrence of the primary end point was similar between groups (10% liberal vs 11% restrictive; between-group difference, 1% [95% CI, −6% to 4%]; $P=.85$). Independent of transfusion strategy, the number of transfused red blood

Figure 1. Study Flow



30%

24%

RBC indicates red blood cell.

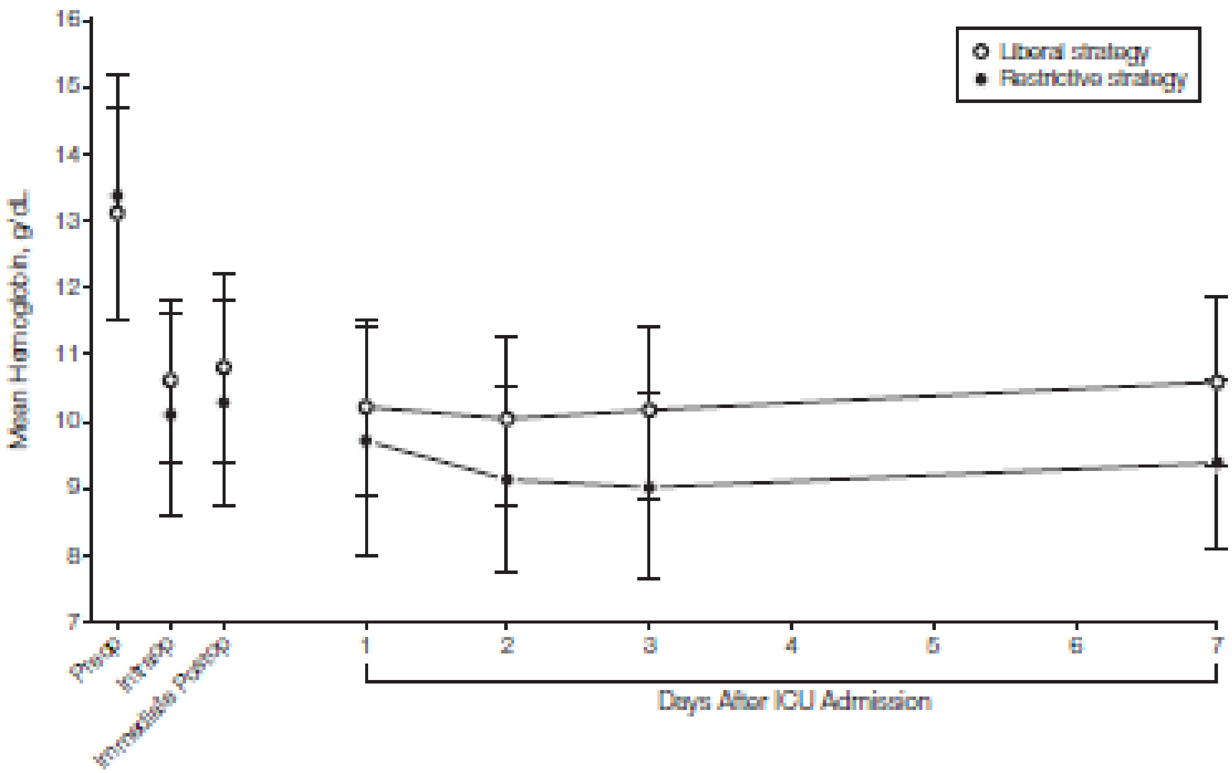
[a]Patients excluded after consent because of a change in surgical plan such that surgery was performed without cardiopulmonary bypass.

Table. Baseline Characteristics of Study Patients

Variable	Liberal Strategy (n = 253), No. (%)	Restrictive Strategy (n = 249), No. (%)	*P* Value
Age, mean (SD), y	60.7 (12.5)	58.6 (12.5)	.06
Men	161 (64)	149 (60)	.38
Body mass index, mean (SD)[a]	26.1 (4.3)	26.3 (4.4)	.65
Comorbid conditions			
Hypertension	201 (79)	192 (77)	.53
Diabetes	79 (31)	86 (35)	.45
Dyslipidemia	139 (55)	147 (60)	.33
Renal disease	26 (11)	26 (11)	.50
Smoking	34 (14)	38 (16)	.74
COPD	6 (2)	8 (3)	.55
Unstable angina	79 (31)	76 (31)	.87
Previous myocardial infarction	86 (34)	89 (36)	.61
Heart failure, NYHA classification			
I	8 (6)	8 (7)	.50
II	42 (34)	48 (41)	
III	65 (52)	49 (42)	
IV	10 (8)	11 (10)	
LVEF, %			
30-39	32 (13)	37 (15)	.75
40-59	76 (30)	75 (30)	
≥60	145 (57)	137 (55)	
Reoperation	11 (4)	13 (5)	.65
EuroSCORE, median (IQR)	5 (3-6)	4 (3-7)	.07
Preoperative laboratory values, mean (SD)			
Hemoglobin, g/dL	13.1 (1.6)	13.4 (1.8)	.18
Hematocrit, %	39.5 (4.3)	39.9 (5.2)	.65
Prothrombin time, s	11.3 (1.1)	11.3 (2.2)	.54
Platelet count, $\times 10^3/\mu L$	222 (67)	225 (66)	.83
Creatinine level, mg/dL	1.12 (0.4)	1.12 (0.3)	.99
Leukocyte count/μL	7600 (2100)	7700 (2000)	.56
Preoperative drug exposure			
Aspirin	103 (41)	94 (38)	.52
Heparin	3 (1)	2 (1)	>.99

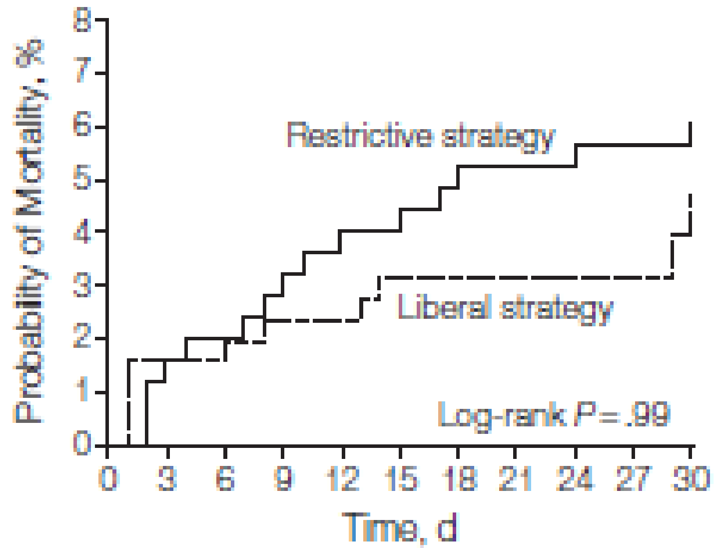
Abbreviations: COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
SI conversion factor: To convert creatinine values to μmol/L, multiply by 88.4.
[a]Calculated as weight in kilograms divided by height in meters squared.

Figure 2. Mean Hemoglobin Levels During the Study According to Transfusion Strategy



P < .05 between the groups at all points following preop. Error bars indicate 95% confidence intervals. ICU indicates intensive care unit.

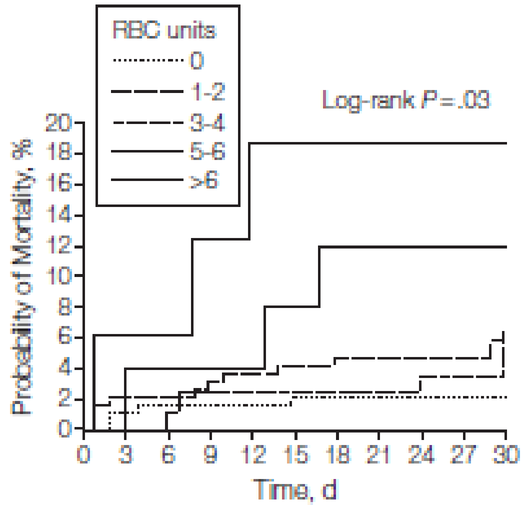
Figure 3. Kaplan-Meier Estimates of 30-Day Survival by Transfusion Strategy



No. at risk						
Restrictive	249	244	238	236	235	234
Liberal	253	248	247	245	245	242

Time zero was just after randomization (12 hours before surgery). Hazard ratio, 1.28 (95% confidence interval, 0.60-2.73) (P=.99) for restrictive strategy vs liberal strategy.

Figure 4. Kaplan-Meier Estimates of 30-Day Survival Based on Number of Red Blood Cell (RBC) Units Transfused



No. at risk

RBC units						
0	186	184	183	182	182	181
1-2	191	187	184	182	182	179
3-4	84	83	82	82	81	80
5-6	25	24	24	22	22	21
>6	16	15	13	13	13	12

Time zero was just after randomization (12 hours before surgery). With 0 RBC units as the reference category, the hazard ratio was 2.97 (95% confidence interval [CI], 0.96-9.21) (*P*=.06) for 1 to 2 RBC units; 2.78 (95% CI, 0.75-10.35) (*P*=.13) for 3 to 4 units; 5.82 (95% CI, 1.30-26.02) (*P*=.02) for 5 to 6 units; and 9.70 (95% CI, 2.17-43.34) (*P*=.003) for more than 6 units.

TRACS: Outcomes

Outcome	Liberal	Restrictive	Difference	P Value
Death, Major Morbidity	10%	11%	1.5 (-6% to 4%)	0.87
30 Day mortality	5%	6%		0.42
ARDS	1%	2%		0.99
RRT	5%	4%		0.99
Cardiac Morbidity	21%	24%		0.27
Infection	10%	12%		0.58
Transfusion	78%	47% !!!		<0.001

A liberal strategy of red blood cell transfusion reduces cardiogenic shock in elderly patients undergoing cardiac surgery

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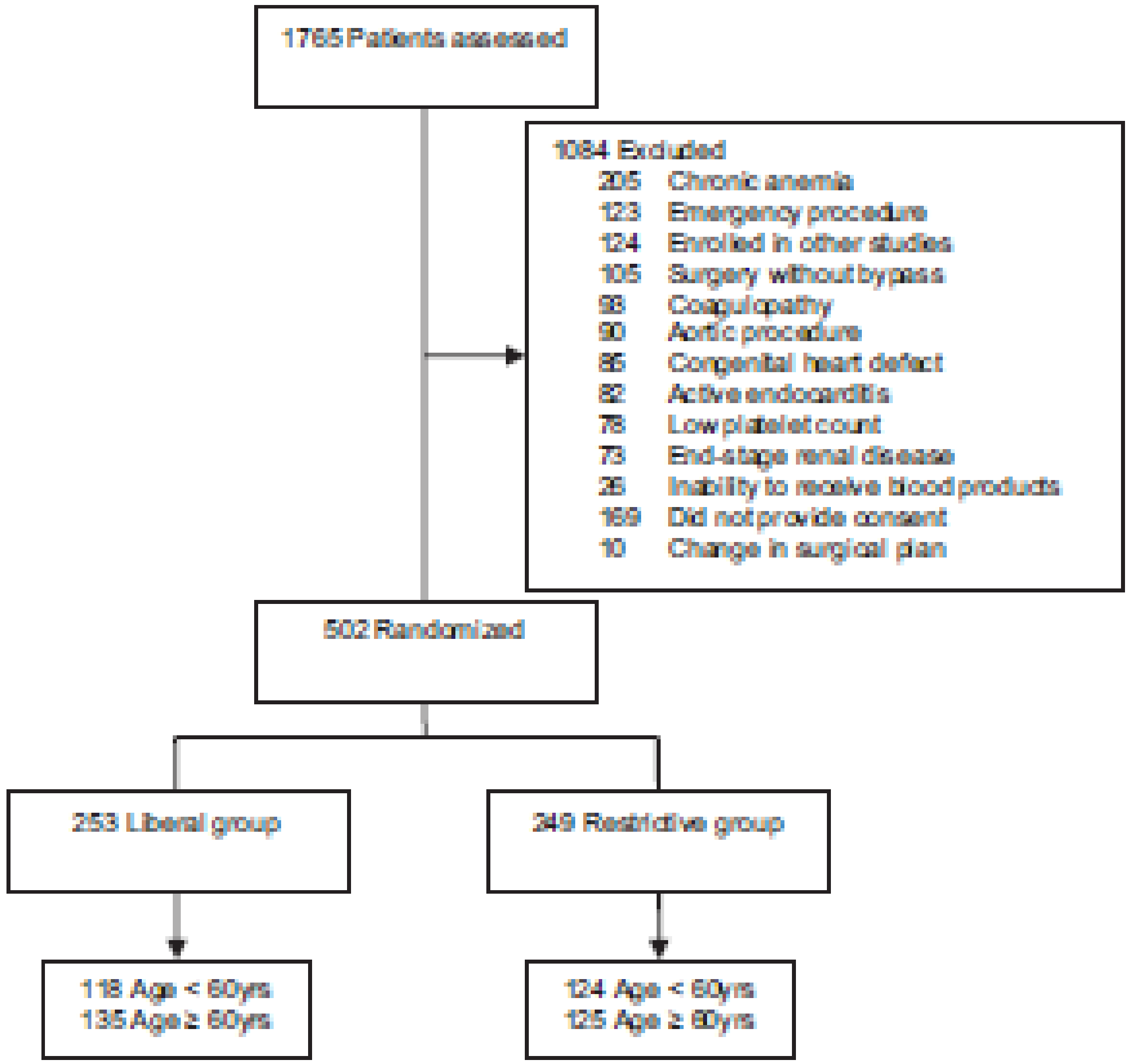

FIGURE 1. Flowchart of the study.

TABLE 3. **Incidence of the primary end point—composite of 30-day all-cause mortality and severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or hemofiltration)—and its individual components according to transfusion strategy in the 2 age groups**

	Age <60 y			Age ≥60 y		
End point	**Liberal n (%)**	**Restrictive n (%)**	***P***	**Liberal n (%)**	**Restrictive n (%)**	***P***
Primary composite end point	8 (6.8)	7 (5.6)	.71	16 (11.9)	21 (16.8)	.25
30-d mortality	5 (4.2)	5 (4.0)	1.00	7 (5.2)	10 (8.0)	.35
Cardiogenic shock	5 (4.2)	6 (4.8)	.82	7 (5.2)	16 (12.8)	.03
ARDS	2 (1.7)	2 (1.6)	1.00	0 (0)	3 (2.4)	.11
Acute renal injury requiring RRT	3 (2.5)	4 (3.2)	1.00	10 (7.4)	6 (4.8)	.38

ARDS, Acute respiratory distress syndrome; *RRT*, renal replacement therapy.

TRANSFUSION MEDICINE
Official Journal of
the British Blood Transfusion Society
British Blood Transfusion Society
Transfusion Medicine | ORIGINAL ARTICLE

Risks of restrictive red blood cell transfusion strategies in patients with cardiovascular disease (CVD): a meta-analysis

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Received 20 October 2017; accepted for publication 4 April 2018

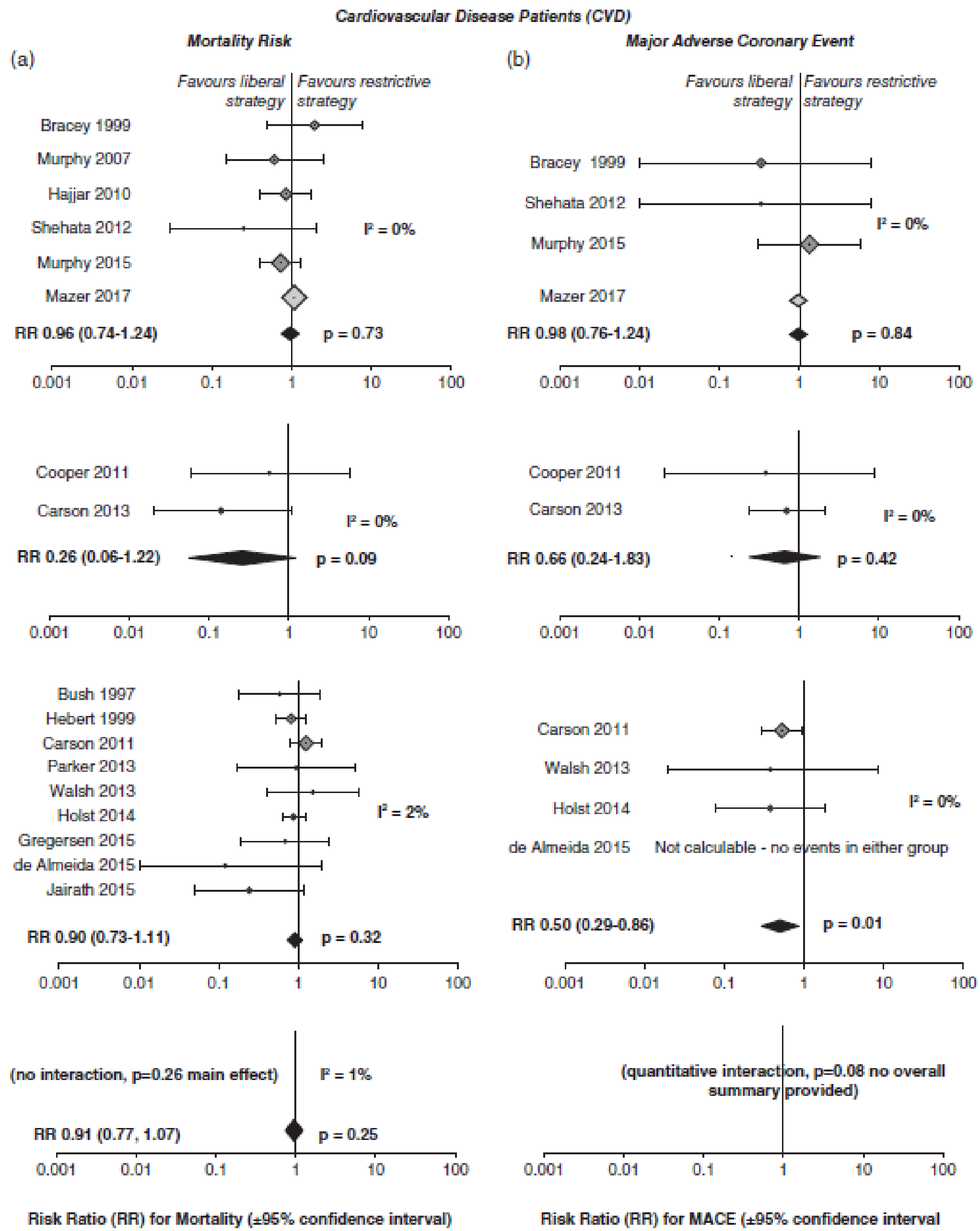

Fig. 5. Combined mortality and MACE rates for cardiovascular disease patients hospitalised for non-cardiac indications or percutaneous cardiac corrective procedures or cardiac surgery. The combined overall relative risk for mortality (a) and MACE (b) in patients with cardiovascular disease are plotted here for a liberal versus restrictive strategy for cardiovascular disease patients hospitalised for cardiac surgery (top panels) or percutaneous cardiac corrective procedures (middle panels) or non-cardiac indications (bottom panels).

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 12, 2015 VOL. 372 NO. 11

Liberal or Restrictive Transfusion after Cardiac Surgery

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ABSTRACT

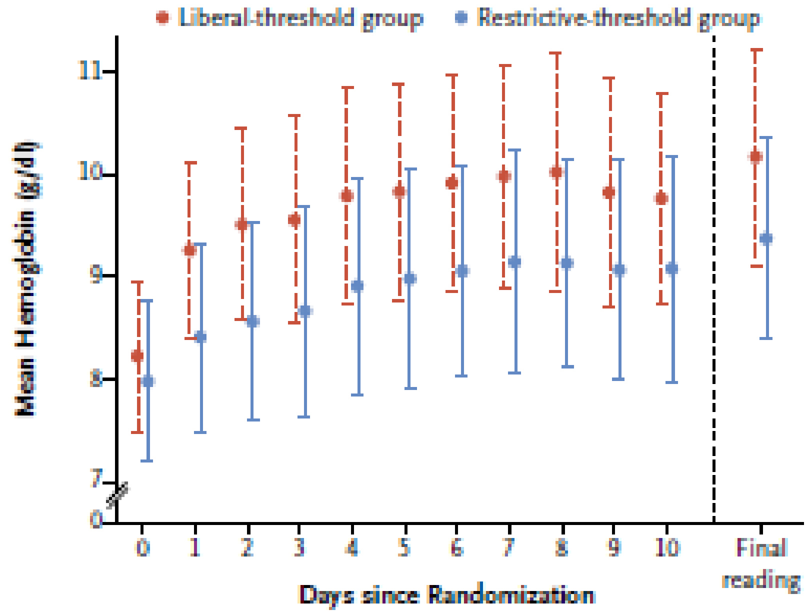
Table 1. Preoperative and Intraoperative Characteristics.*

Hb 7.5 g/dL Hb 9 g/dL

Characteristic	Restrictive Transfusion Threshold (N=1000)	Liberal Transfusion Threshold (N=1003)
Preoperative		
Age — yr		
Median	69.9	70.8
Interquartile range	63.1–76.0	64.1–76.7
Male sex — no. (%)	693 (69.3)	680 (67.8)
Body-mass index†	28.2±5.0	28.2±4.9
EuroSCORE‡		
Median	5.0	5.0
Interquartile range	3.0–7.0	3.0–7.0
NYHA class — no./total no. (%)§		
I	235/977 (24.1)	258/974 (26.5)
II	445/977 (45.5)	440/974 (45.2)
III	268/977 (27.4)	257/974 (26.4)
IV	29/977 (3.0)	19/974 (2.0)
CCS angina class — no./total no. (%)¶		
No angina	365/982 (37.2)	353/980 (36.0)
I	169/982 (17.2)	193/980 (19.7)
II	273/982 (27.8)	253/980 (25.8)
III	139/982 (14.2)	142/980 (14.5)
IV	36/982 (3.7)	39/980 (4.0)

Table 2. Transfusions.*

Type of Transfusion	Restrictive Transfusion Threshold (N=1000)	Liberal Transfusion Threshold (N=1003)	Odds Ratio (95% CI)	P Value
	number (percent)			
≥1 Units of red cells transfused before randomization — no. of patients (%)†	250 (25.0)	264 (26.3)		
Units of red cells transfused after randomization‡				
Total units transfused — no.	1494	2494		
Median — no.	1.0	2.0		
Interquartile range	0–2.0	1.0–3.0		
Distribution — no. of patients (%)			0.58 (0.54–0.62)§	<0.001
0 units	466 (46.6)	78 (7.8)		
1 unit	193 (19.3)	341 (34.0)		
2 units	152 (15.2)	262 (26.1)		
3 units	66 (6.6)	141 (14.1)		
4 units	50 (5.0)	62 (6.2)		
≥5 units	73 (7.3)	119 (11.9)		
Transfused red cells during entire index admission — no. of patients (%)¶	637 (63.7)	952 (94.9)		
Other transfusions — no. of patients (%)¶				
Fresh-frozen plasma	297 (29.7)	284 (28.3)	1.08 (0.88–1.33)	0.45
Platelets	376 (37.6)	362 (36.1)	1.08 (0.89–1.31)	0.42
Cryoprecipitate	99 (9.9)	102 (10.2)	0.99 (0.72–1.35)	0.95
Activated factor used — no. of patients (%)¶	7 (0.7)	5 (0.5)	1.41 (0.45–4.45)	0.56
Human blood coagulation factor IX used — no. of patients (%)¶	52 (5.2)	48 (4.8)	1.21 (0.73–2.03)	0.46
Severe nonadherence — no. of patients (%)‖	97 (9.7)	62 (6.2)		
Any nonadherence — no. of patients (%)**	300 (30.0)	453 (45.2)		



No. at Risk

	0	1	2	3	4	5	6	7	8	9	10	Final reading
Liberal-threshold group	994	967	894	773	732	501	405	338	245	204	170	998
Restrictive-threshold group	998	971	894	758	713	502	401	303	226	175	147	1003

Figure 1. Mean Daily Nadir in Hemoglobin Level.

I bars indicate standard deviations, which were calculated independently at each time point.

Table 3. Outcomes.

Outcome	Restrictive Transfusion Threshold (N=1000)	Liberal Transfusion Threshold (N=1003)	Estimated Treatment Effect	
			Odds Ratio or Hazard Ratio (95% CI)	P Value
Serious infection or ischemic event: primary outcome				
Overall	331/944 (35.1)	317/962 (33.0)	1.11 (0.91–1.34)*	0.30
Infectious event†	238/936 (25.4)	240/954 (25.2)	1.02 (0.83–1.26)*	0.83
Sepsis	210/982 (21.4)	214/983 (21.8)		
Wound infection	55/921 (6.0)	46/936 (4.9)		
Ischemic event	156/991 (15.7)	139/99 (114.0)	1.16 (0.90–1.49)*	0.26
Permanent stroke	15/989 (1.5)	17/985 (1.7)		
Myocardial infarction	3/987 (0.3)	4/981 (0.4)		
Gut infarction	6/987 (0.6)	1/982 (0.1)		
Acute kidney injury	140/989 (14.2)	122/989 (12.3)		
Stage 1	49/989 (5.0)	40/989 (4.0)		
Stage 2	39/989 (3.9)	35/989 (3.5)		
Stage 3	50/989 (5.1)	46/989 (4.7)		
Secondary outcomes				
No. of hours in ICU or high-dependency unit‡				
Median	49.5	45.9	0.97 (0.89–1.06)§	0.53
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.

Subgroup	No. of Patients	Restrictive	Liberal	Odds Ratio (95% CI)	P Value for Interaction
		no. of events/total no. (%)			
Surgery type					0.64
CABG	400	77/192 (40.1)	85/208 (40.9)	0.92 (0.61–1.40)	
Non-CABG	1487	251/743 (33.8)	229/744 (30.8)	1.17 (0.94–1.46)	
Age					0.45
<75 yr	604	108/296 (36.5)	94/308 (30.5)	1.30 (0.92–1.84)	
≥75 yr	1302	223/648 (34.4)	223/654 (34.1)	1.03 (0.81–1.30)	
Diabetes					0.76
Yes	567	114/275 (41.5)	118/292 (40.4)	1.04 (0.74–1.47)	
No	1337	217/669 (32.4)	199/668 (29.8)	1.14 (0.90–1.45)	
COPD or asthma					0.16
Yes	239	49/106 (46.2)	48/133 (36.1)	1.59 (0.93–2.71)	
No	1667	282/838 (33.7)	269/829 (32.4)	1.06 (0.86–1.30)	
Renal impairment					0.67
Estimated GFR ≤60	371	85/181 (47.0)	85/190 (44.7)	1.05 (0.69–1.59)	
Estimated GFR >60	1535	246/763 (32.2)	232/772 (30.1)	1.13 (0.90–1.41)	
Sex					0.27
Male	583	114/270 (42.2)	129/313 (41.2)	1.01 (0.72–1.42)	
Female	1323	217/674 (32.2)	188/649 (29.0)	1.19 (0.94–1.51)	
LV function					0.33
Good	1145	218/569 (38.3)	204/576 (35.4)	1.14 (0.89–1.46)	
Moderate or poor	761	113/375 (30.1)	113/386 (29.3)	1.04 (0.76–1.42)	

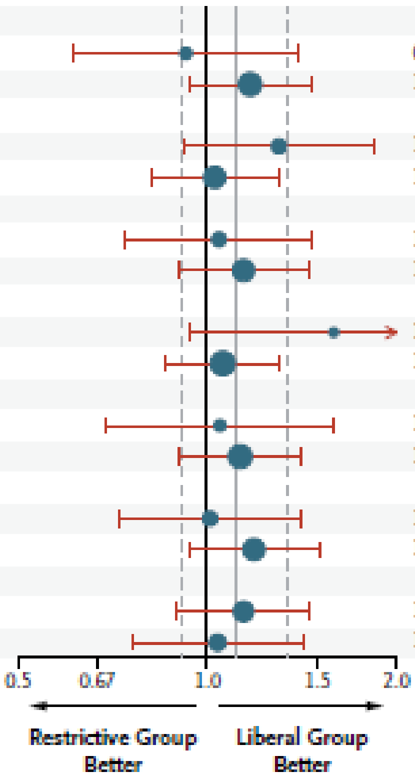


Figure 2. Subgroup Analyses.

The gray vertical lines represent the overall treatment estimate (solid line) and the 95% confidence interval (dashed lines) for the primary outcome as calculated for the entire analysis cohort. The sizes of the circles designating the point estimates reflect the sizes of the subgroups. The restrictive transfusion threshold for hemoglobin was less than 7.5 g per deciliter, and the liberal transfusion threshold was less than 9 g per deciliter. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, GFR glomerular filtration rate, and LV left ventricular.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery

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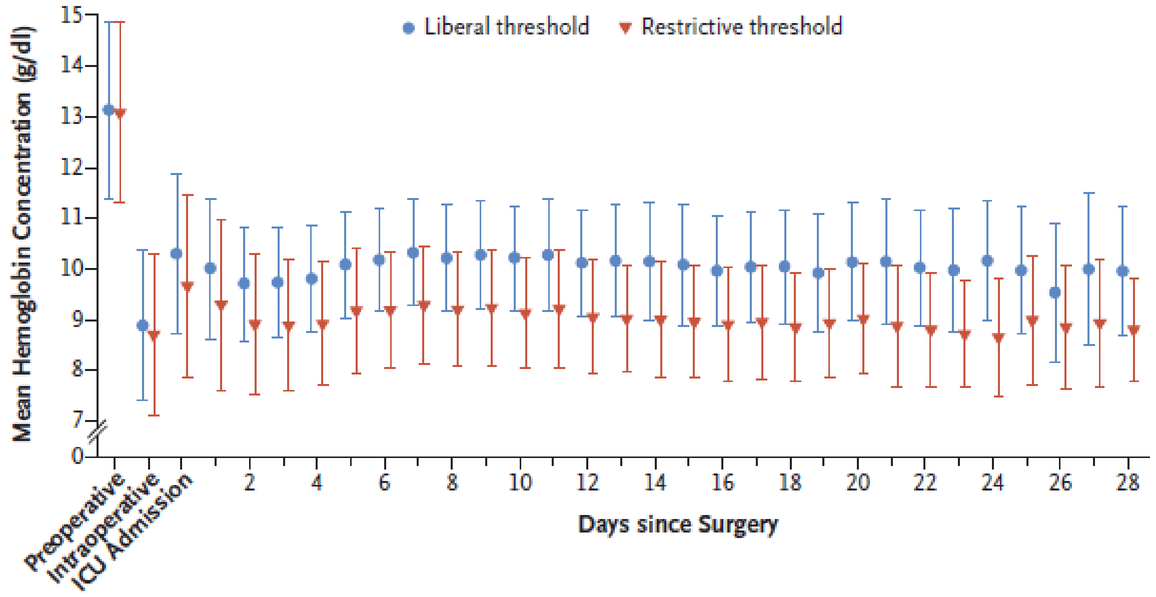
ABSTRACT

Table 1. Baseline and Operative Characteristics.*

Characteristic	Hb 7.5 Restrictive Threshold (N=2430)	Hb 9.5 Liberal Threshold (N=2430)
Preoperative characteristics		
Age — yr	72±10	72±10
Male sex — no. (%)	1553 (63.9)	1586 (65.3)
Body-mass index†	28.1±6.0	28.0±5.2
EuroSCORE I‡	7.9±1.8	7.8±1.9
Previous cardiac surgery — no. (%)	307 (12.6)	280 (11.5)
Myocardial infarction in previous 90 days — no. (%)	562 (23.1)	601 (24.7)
Left ventricular function — no./total no. (%)§		
Good	1485/2430 (61.1)	1523/2427 (62.8)
Moderately reduced	733/2430 (30.2)	710/2427 (29.3)
Poor	166/2430 (6.8)	156/2427 (6.4)
Very poor	46/2430 (1.9)	38/2427 (1.6)
Diabetes mellitus — no. (%)	646 (26.6)	686 (28.2)
Treated hypertension — no. (%)	1797 (74.0)	1803 (74.2)
Emergency surgery — no. (%)	37 (1.5)	34 (1.4)
Renal function — no./total no. (%)¶		
Normal	1090/2332 (46.7)	1071/2348 (45.6)
Moderately impaired	857/2332 (36.7)	866/2348 (36.9)
Severely impaired	355/2332 (15.2)	385/2348 (16.4)
Use of dialysis	30/2332 (1.3)	26/2348 (1.1)
Use of aspirin — no./total no. (%)	1274/2428 (52.5)	1293/2423 (53.4)
Hemoglobin — g/dl	13.1±1.8	13.1±1.7
Operative characteristics		
Type of surgery — no./total no. (%)		
CABG only	622/2429 (25.6)	645/2430 (26.5)
CABG and valve surgery	464/2429 (19.1)	472/2430 (19.4)
CABG and other, nonvalve surgery	205/2429 (8.4)	203/2430 (8.4)
Valve surgery only	703/2429 (28.9)	716/2430 (29.5)
Other, non-CABG surgery	433/2429 (17.8)	394/2430 (16.2)
Duration of cardiopulmonary bypass — min	120±59	121±57
Intraoperative tranexamic acid — no./total no. (%)	2219/2428 (91.4)	2235/2428 (92.1)



No. at Risk

Liberal threshold	2428	2435	2015	1354	731	443	327	233	153	122	112	76	69	57	51
Restrictive threshold	2429	2454	2007	1431	841	527	376	305	215	165	131	117	91	77	76

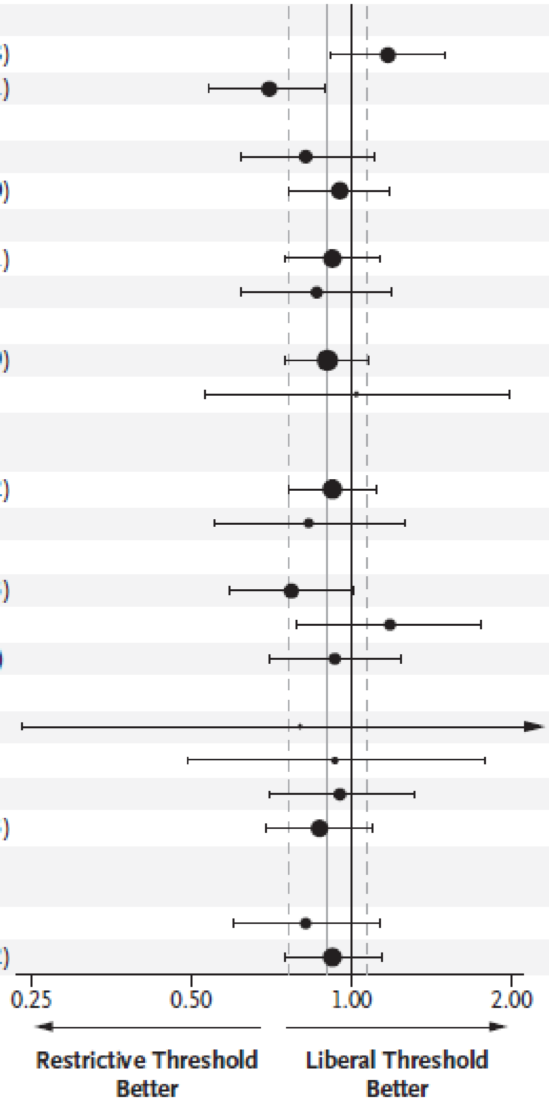
Figure 1. Hemoglobin Concentration during the Trial Period.

The restrictive transfusion threshold was less than 7.5 g per deciliter intraoperatively and postoperatively, and the liberal transfusion threshold was less than 9.5 g per deciliter intraoperatively or postoperatively in the intensive care unit (ICU) or less than 8.5 g per deciliter on the non-ICU ward. I bars indicate the standard deviation.

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)
Secondary outcomes			
Length of stay in ICU			
No. of patients with data	2422	2418	
Median — days	2.1	1.9	0.89 (0.84–0.94)*
Interquartile range — days	1.0–4.0	1.0–3.9	
Length of stay in hospital			
No. of patients with data	2419	2419	
Median — days	8.0	8.0	0.93 (0.88–0.99)*
Interquartile range — days	7.0–13.0	7.0–12.0	
Duration of mechanical ventilation			
No. of patients with data	2416	2421	
Median — days	0.38	0.36	0.94 (0.89–1.00)*
Interquartile range — days	0.22–0.75	0.22–0.71	
Prolonged low-output state — no./total no. (%)†	994/2429 (40.9)	987/2430 (40.6)	1.01 (0.90–1.14)
Infection — no./total no. (%)	121/2428 (5.0)	101/2429 (4.2)	1.21 (0.92–1.58)
Bowel infarction — no./total no. (%)	6/2428 (0.2)	5/2429 (0.2)	1.20 (0.37–3.94)
Acute kidney injury — no./total no. (%)	792/2332 (34.0)	797/2348 (33.9)	1.00 (0.89–1.13)
Seizure — no./total no. (%)	50/2428 (2.1)	42/2429 (1.7)	1.20 (0.79–1.81)
Delirium — no./total no. (%)	306/2428 (12.6)	264/2429 (10.9)	1.18 (0.99–1.41)
Encephalopathy — no./total no. (%)	26/2428 (1.1)	22/2429 (0.9)	1.18 (0.67–2.10)

Subgroup	No. of Patients	Restrictive Threshold	Liberal Threshold	Unadjusted Odds Ratio (95% CI)	P Value for Interaction
		no. of patients with event/total no. (%)			
Age					0.004
<75 yr	2426	152/1218 (12.5)	131/1208 (10.8)	1.17 (0.91–1.50)	
≥75 yr	2431	124/1210 (10.2)	172/1221 (14.1)	0.70 (0.54–0.89)	
Sex					0.45
Female	1719	99/876 (11.3)	113/843 (13.4)	0.82 (0.62–1.10)	
Male	3138	177/1552 (11.4)	190/1586 (12.0)	0.95 (0.76–1.18)	
Diabetes					0.75
No	3526	200/1783 (11.2)	211/1743 (12.1)	0.92 (0.75–1.13)	
Yes	1331	76/645 (11.8)	92/686 (13.4)	0.86 (0.62–1.19)	
Creatinine level					0.71
≤2.26 mg/dl	4685	253/2348 (10.8)	277/2337 (11.9)	0.90 (0.75–1.08)	
>2.26 mg/dl	172	23/80 (28.7)	26/92 (28.3)	1.02 (0.53–1.99)	
Chronic pulmonary disease					0.67
No	4057	229/2023 (11.3)	249/2034 (12.2)	0.92 (0.76–1.11)	
Yes	800	47/405 (11.6)	54/395 (13.7)	0.83 (0.55–1.26)	
Surgery category					0.22
Non-CABG	2247	111/1138 (9.8)	136/1109 (12.3)	0.77 (0.59–1.01)	
CABG only	1266	57/621 (9.2)	51/645 (7.9)	1.18 (0.79–1.75)	
CABG+ other	1344	108/669 (16.1)	116/675 (17.2)	0.93 (0.70–1.24)	
Left ventricular function					0.78
Very poor	84	6/46 (13.0)	6/38 (15.8)	0.80 (0.24–2.72)	
Poor	322	21/166 (12.7)	21/156 (13.5)	0.93 (0.49–1.78)	
Moderate	1441	88/731 (12.0)	89/710 (12.5)	0.95 (0.70–1.31)	
Good	3010	161/1485 (10.8)	187/1525 (12.3)	0.87 (0.69–1.09)	
Preoperative hemoglobin concentration					0.54
<12.0 g/dl	1149	84/593 (14.2)	93/556 (16.7)	0.82 (0.60–1.13)	
≥12.0 g/dl	3708	192/1835 (10.5)	210/1873 (11.2)	0.92 (0.75–1.14)	



RESULTS

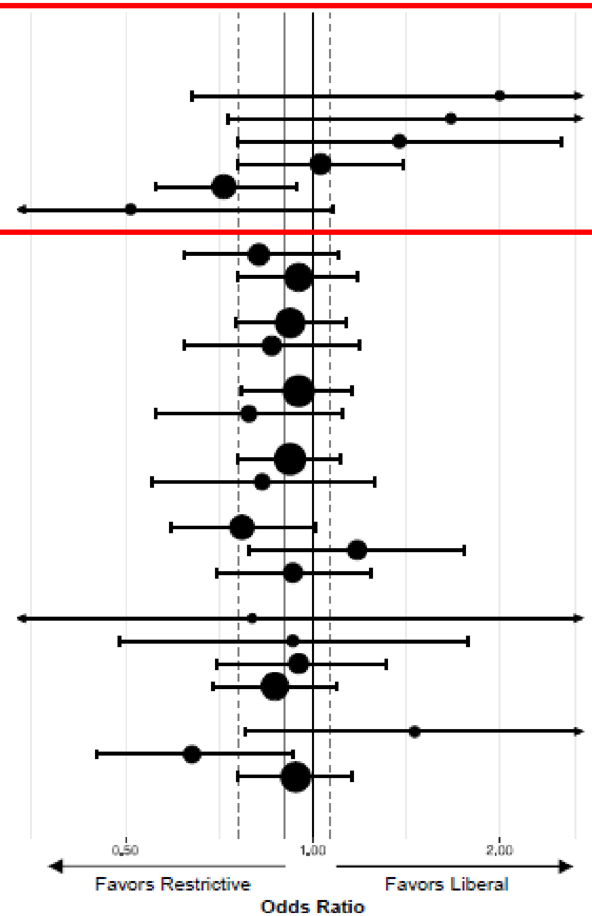
The primary outcome occurred in 11.4% of the patients in the restrictive-threshold group, as compared with 12.5% of those in the liberal-threshold group (absolute risk difference, −1.11 percentage points; 95% confidence interval [CI], −2.93 to 0.72; odds ratio, 0.90; 95% CI, 0.76 to 1.07; P<0.001 for noninferiority). Mortality was 3.0% in the restrictive-threshold group and 3.6% in the liberal-threshold group (odds ratio, 0.85; 95% CI, 0.62 to 1.16). Red-cell transfusion occurred in 52.3% of the patients in the restrictive-threshold group, as compared with 72.6% of those in the liberal-threshold group (odds ratio, 0.41; 95% CI, 0.37 to 0.47). There were no significant between-group differences with regard to the other secondary outcomes.

CONCLUSIONS

In patients undergoing cardiac surgery who were at moderate-to-high risk for death, a restrictive strategy regarding red-cell transfusion was noninferior to a liberal strategy with respect to the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis, with less blood transfused. (Funded by the Canadian Institutes of Health Research and others; TRICS III ClinicalTrials.gov number, NCT02042898.)

Supplementary Figure S2: Expanded Subgroup Analysis

	N	Restrictive	Liberal	Unadjusted OR (95% CI)	p–value for interaction
Age					
< 45 years	109	10/57 (17.5)	5/52 (9.6)	2.00 (0.64–6.30)	0.00044
45–54 years	184	17/92 (18.5)	11/92 (12)	1.67 (0.73–3.79)	
55–64 years	533	28/272 (10.3)	20/261 (7.7)	1.38 (0.76–2.52)	
65–74 years	1600	97/797 (12.2)	95/803 (11.8)	1.03 (0.76–1.40)	
75–84 years	2202	112/1094 (10.2)	151/1108 (13.6)	0.72 (0.56–0.94)	
85+ years	229	12/116 (10.3)	21/113 (18.6)	0.51 (0.24–1.08)	
Sex					
Female	1719	99/876 (11.3)	113/843 (13.4)	0.82 (0.62–1.10)	0.451
Male	3138	177/1552 (11.4)	190/1586 (12)	0.95 (0.76–1.18)	
Diabetes					
No	3526	200/1783 (11.2)	211/1743 (12.1)	0.92 (0.75–1.13)	0.753
Yes	1331	76/645 (11.8)	92/686 (13.4)	0.86 (0.62–1.19)	
Renal Function					
Moderate/Normal CrCl >=50 ml/min	4003	204/2016 (10.1)	210/1987 (10.6)	0.95 (0.77–1.16)	0.388
Severe/Dialysis CrCl <50 ml/min	854	72/412 (17.5)	93/442 (21)	0.79 (0.56–1.12)	
Preexisting Pulm Disease					
No	4057	229/2023 (11.3)	249/2034 (12.2)	0.92 (0.76–1.11)	0.674
Yes	800	47/405 (11.6)	54/395 (13.7)	0.83 (0.55–1.26)	
Surgery Category					
CABG–	2247	111/1138 (9.8)	136/1109 (12.3)	0.77 (0.59–1.01)	0.219
CABG Only	1266	57/621 (9.2)	51/645 (7.9)	1.18 (0.79–1.75)	
CABG+	1344	108/669 (16.1)	116/675 (17.2)	0.93 (0.70–1.24)	
LV Function					
Very Poor	84	6/46 (13)	6/38 (15.8)	0.80 (0.24–2.72)	0.778
Poor	322	21/166 (12.7)	21/156 (13.5)	0.93 (0.49–1.78)	
Moderate	1441	88/731 (12)	89/710 (12.5)	0.95 (0.70–1.31)	
Good	3010	161/1485 (10.8)	187/1525 (12.3)	0.87 (0.69–1.09)	
Preoperative Hemoglobin Concentration					
< 10.0g/dl	229	31/120 (25.8)	21/109 (19.3)	1.46 (0.78–2.73)	0.945
10.0 – 12.0g/dl	1006	57/517 (11)	79/489 (16.2)	0.64 (0.45–0.93)	
> 12.0g/dl	3622	188/1791 (10.5)	203/1831 (11.1)	0.94 (0.76–1.16)	



QUESTIONS

1. ARE TRANSFUSIONS HARMFUI IN SURGERY?

NO (unless massive?)

THERE IS NOT A SINGLE RANDOMIZED CONTROLLED TRIAL WHERE A LIBERAL STRATEGY ARM HAD A SIGNIFICANT GREATER RATE OF EVENTS, SAME FOR POOLED DATA

QUESTIONS

SO, IF IT IS TRUE THAT THERE ARE NO DANGEROUS RBC TRANSFUSIONS…

IT IS TRUE AS WELL THAT THERE ARE MANY INAPPROPRIATE TRANSFUSIONS


A RESTRICTIVE STRATEGY
IS NOT INFERIOR
TO A LIBERAL STRATEGY,
AND THEREFORE AVOIDS
UNNECESSARY TREATMENTS
A LIBERAL STRATEGY DOES NOT
INDUCE ANY COMPLICATION
HOWEVER, IN MANY CASES
MAY TRIGGER AVOIDABLE
TREATMENT

QUESTIONS

1. ARE TRANSFUSIONS HARMFUL IN SURGERY?
2. WHAT IS THE LEVEL OF THE EVIDENCE?
3. WHAT IS «liberal» and WHAT IS «restrictive»?

Table 1 Characteristics of included studies

Study	N	Age: Restrictive	Age: Control	Setting	Strategy of blood transfusion: Restrictive – Triggered Hb	Restrictive – Observed Hb	Control – Triggered Hb	Control – Observed Hb	Units of RBC transfusion or transfusion rate: Restrictive	Control
Bracey et al.1999 [12]	428	61 ± 11	62 ± 11	Elective CABG	Hb < 8 g/dl	9.1 g/dl	Hb < 9 g/dl	9.7 g/dl	0.9 ± 1.5	1.4 ± 1.8
Murphy et al. 2007 [16]	321	NS	NS	Elective or urgent cardiac surgery	Hb < 7 g/dl	NS	Hb < 8 g/dl	NS	NS	NS
Hajjar et al. 2010 [13]	502	58.6 ± 12.5	60.7 ± 12.5	Elective cardiac surgery	Hct < 24%	9.6 g/dl	Hct < 30%	10.7 g/dl	0 (0–2)	2 (1–3)
Shehata et al. 2012 [15]	50	67.2 ± 11.2	68.8 ± 9.2	Cardiac surgery with CARE score of 3 or 4	Hb < 7.5 g/dl	9.1 g/dl	Hb < 10 g/dl	10.7 g/dl	11 (44)	17 (68)
Murphy et al. 2015 [14]	2003	69.9(63.1 –76.0)	70.8(64.1–76.7)	Elective or urgent cardiac surgery	Hb < 7.5 g/dl	9.0 g/dl	Hb < 9 g/dl	9.8 g/dl	1 (0–2)	2 (1–3)
Koch et al. 2017 [10]	717	59 ± 15	60 ± 13	Elective CABG or HVR	Hct < 24%	28%	Hct < 28%	30%	195 (54)	265 (75)
Mazer et al. 2017 [9]	4860	72 ± 10	72 ± 10	Cardiac surgery with a EuroSCORE I of 6 or more	Hb < 7.5 g/dl	Hb < 8.5 g/dl	Hb < 9.5 g/dl	10.5 g/dl?	2 (1–4)	3 (2–5)

CABG coronary artery bypass grafting, *Hb* hemoglobin, *Hct* hemotocrit, *HVR* heart valve replacement, *NS* normal saline

TRANSFUSION RATE RE VE ARM:

Bracey
Shehata 4%
Hajjar (TRA 47%
Mazer (T) 53%
Koc 54%
Murp (TITRE 2) 64%

Restrictive????

International Journal of Cardiology xxx (xxxx) xxx

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Patient blood management in cardiac surgery: The "Granducato algorithm"☆,☆☆

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TRANSFUSION PROTOCOL

Hb (g/dL)	HCT (%)	RBC transfusion
≥ 10	≥30	NO
≥ 8, <10	≥24, <30	Only in case of clinical indication*
≥7, <8	≥21, <24	Could be considered
<7	<21	YES

*Clinical indications:

- Lactates > 4mMol/L
- SVO_2 < 65%
- O_2 ER > 40%
- Low C.O. (despite inotropic drugs / IABP)
- Active bleeding
- End organ ischemia
- Age

Table 2
Transfusion needs and general outcome of the two groups.

Variable	Before G-PBMa $N = 1955$, year 2014	After G-PBMa $N = 1884$, year 2016	Relative risk or mean difference (95% confidence interval)	*P*
Transfusion				
Any kind	753 (38.5)	600 (31.8)	0.75 (0.65–0.85)	0.001
Red blood cells	725 (37.1)	583 (30.9)	0.76 (0.66–0.87)	0.001
Fresh frozen plasma	251 (12.8)	102 (5.4)	0.39 (0.31–0.49)	0.001
Platelet concentrate	168 (8.6)	85 (4.5)	0.50 (0.38–0.66)	0.001
Transfused volume (units)				
Red blood cells	1.17 (2.25)	0.77 (1.57)	0.41 (0.28–0.53)	0.001
Fresh frozen plasma	0.63 (2.1)	0.15 (0.84)	0.48 (0.38–0.58)	0.001
Platelet concentrate	0.13 (0.57)	0.05 (0.27)	0.15 (0.05–0.10)	0.001
Chest drain blood loss (mL/12 h)	320 (220–480)	300 (200–500)	N/A	0.020
Surgical re-exploration	93 (4.8)	80 (4.3)	0.90 (0.66–1.21)	0.489
Intensive care unit stay (days)	1 (1–3)	1 (1–2)	N/A	0.168
Hospital stay (days)	7 (6–11)	7 (6–10)	N/A	0.001
Hospital mortality	73 (3.7)	68 (3.6)	0.96 (0.69–1.21)	0.837

THE GRANDUCATO PATIENT BLOOD MANAGEMENT ALGORITHM

PREOPERATIVE

- Correct preoperative absolute iron deficiency anemia with ferrocarboxymalthose; consider EPO for functional iron deficiency or CRD anemia
- Consider RBC transfusion in severe anemia (Hb < 10 g/dL)
- ASPIRIN: do not discontinuate
- $P2Y_{12}$ inhibitors: discontinue
  - TICAGRELOR 3 days
  - CLOPIDOGREL 5 days
  - PRASUGREL 7 days
  - TICOPLIDINE 7 days
- If Multiplate® available; admit to surgery regardless of withdrawal time if ADPtest ≥30 U
- Stop warfarin, bridge with LMWH and admit to surgery when the INR ≤ 1.5
- Discontinue DOACs at least 48 hours before surgery. Apply longer discontinuation times (up to 96 hours) based on creatinine clearance. Consider direct titration with diluted thrombin time (dabigatran) or calibrated anti FXa activity (rivaroxaban, apixaban, edoxaban)
- Stop LMWH at least 12 hours before surgery
- Stop fondaparinux at least 24 hours before surgery. Longer discontinuation time based on serum creatinine clearance. Consider direct titration with calibrated Anti FXa activity

INTRAOPERATIVE

- Always use tranexamic acid according to the institutional protocol, however not less than a total dose of 30 mg/kg
- Anticoagulation: to establish the heparin dose, use Heparin Monitoring Systems if available, and start CPB at an ACT > 450 seconds
- Reduce intraoperative hemodilution as much as possible, using retro-prime, vacuum assisted venous return, and an ideal CPB priming volume target at 1,000 mL. Avoid hydroxyethyl starches in the priming.
- Consider RBC transfusion during CPB if the HCT < 21% and the SvO_2 < 68%
- Always transfuse RBC if the HCT on CPB < 18%
- Establish the protamine dose using Heparin Monitoring Systems is available; otherwise start with a 1:1 ratio protamine:heparin loading dose.
- Use of cell saver and ultra-filtration according to the local policies.

POST-CARDIOPULMONARY BYPASS and ICU

- Apply the following VET-based bleeding management in actively bleeding patients

1. Protamine (25-50 mg) if CT Intem > 300 and CT Heptem < 80% CT Intem (ROTEM®) or R time at TEG® with heparinase is 3 minutes shorter than R time standard
2. Fibrinogen concentrate (2 grams) if Fibtem MCF < 8 mm or Functional Fibrinogen < 6 mm. Target value Fibtem MCF 14 mm or Clauss fibrinogen 2.5 g/L
3. Desmopressin 0.3 µg /Kg and/or Platelet concentrate transfusion (1 unit) when fibrinogen is normalized and one of the following: platelet count < 100,000 cells/ µL; $P2Y_{12}$ inhibitors not whitdawn; ADPtest < 12 U
4. Additional dose of tranexamic acid + 1 gram fibrinogen concentrate if signs of hyperfibrinolysis at VET
5. Prothrombin complex concentrate (better 4-factors) 20 IU/kg if CT Extem > 90 seconds or R time at TEG with heparinase > 15 minutes. Consider FFP as second option only.
6. Uncontrolled, life-threating bleeding: FFP 15 mL/kg; normalize platelet count, administer fibrinogen concentrate to a target Fibtem MCF of 22 mm or Clauss fibrinogen level 3.5 g/L
7. If ongoing bleeding with negative VET tests, consider surgical re-exploration

ANEMIA CORRECTION | BLOOD-SAVING MEASURES | BLEEDING CONTROL

PREOPERATORIO

Correzione anemia pre-operatoria (se valutata almeno 2 settimane prima della chirurgia)

Condizione	Intervento suggerito
Anemia da deficit di ferro (assoluto): Saturazione transferrina < 34% Ferritina < 100 ng/ml	Ferrocarbossimaltosio e.v. 500 mg (se Sat Transferrina 20-33%) 1000 mg (se Sat Transferrina < 20%)
Anemia da deficit di ferro (funzionale): Saturazione transferrina < 34% Ferritina ≥ 100 ng/ml Aumento indici infiammazione	Ferrocarbossimaltosio e.v. 500 mg (se Sat Transferrina 20-33%) 1000 mg (se Sat Transferrina < 20%) Eritropoietina 40.000 U s.c.
Anemia da insufficienza renale cronica Saturazione transferrina ≥ 34% Clearance creatinina > 60 ml/min/1.73m^2	Eritropoietina 40.000 U s.c.
Anemia grave (Hb < 10 g/dL)	Considerare trasfusione globuli rossi prima della CEC

INTRAOPERATORIO – Post protamina- sanguinamento microvascolare

Step	Se ROTEM o TEG	Trattamento
1) Eparina residua	CT INTEM >300'' e CT HEPTEM/CT INTEM <0.8	25-50 mg protamina
	R Hep < 3' *vs* R standard	
2) Fibrinogeno *(se CEC < 90' effettuare i test)*	FIBTEM MCF < 8 mm	Fibrinogeno Concentrato 2 g , ripetibile (target FIBTEM 14mm, Fibrinogenemia Clauss 250 mg/dL)
	FF < 8 mm	
3) Piastrine	Se Fibrinogeno nella norma e 1 dei seguenti: - PLT preoperatorie <100.000/µL - Inibitori P2Y$_{12}$ non sospesi nei tempi consigliati - ADP test Multiplate postoperatorio < 12 U	Desmopressina 0.3 µg /Kg Se permane sanguinamento microvascolare, 1 unità Piastrine concentrate
4) Iperfibrinolisi	Test viscoelastici significativi	Acido tranexamico + Fibrinogeno Concentrato
5) Generazione trombina (dopo eventuali correzioni punti 2-4)	CT EXTEM > 90''	1° scelta: PCC 20UI/kg (preferibile 4 Fattori) 2° scelta: FFP 15 mL/kg
	R Hep >15'0''	
6)	Se Fibrinogeno e PLT normali/corretti ed emorragia non controllata con pericolo di vita	Mantenimento volemia con FFP + ulteriore correzione con Fibrinogeno (target FIBTEM >22mm, Clauss >350 mg/dL) + eventuale rFVIIa
7)	Se parametri normali/corretti	Emostasi chirurgica

Algoritmo condiviso per la gestione dell'emorragia pz CCH

COMING SOON…

GRANDUCATO II

LIBERAL vs RESTRICTIVE BLEEDING CONTROL ALGORITHM

NON-INFERIORITY TRIAL

Restrictive targets (i.e. FIBTEM < 6 mm) vs Liberal targets (i.e. FIBTEM < 9 mm) for pro-coagulants administration