

Has TRISS changed the guidelines?

Bodil Steen Rasmussen

Professor, consultant, PhD

Department of Cardiothoracic Anaesthesia and Intensive
Care

Aalborg University Hospital

Denmark

President-elect EACTA

Conflicts of interest - none



October 2014

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.,
Sari Karlsson, M.D., Ph.D., Pär I. Johansson, M.D., Ph.D.,
Anders Åneman, M.D., Ph.D., Marianne L. Vang, M.D., Robert Winding, M.D.,
Lars Nebrich, M.D., Helle L. Nibro, M.D., Ph.D., Bodil S. Rasmussen, M.D., Ph.D.,
Johnny R.M. Lauridsen, M.D., Jane S. Nielsen, M.D., Anders Oldner, M.D., Ph.D.,
Ville Pettilä, M.D., Ph.D., Maria B. Cronhjort, M.D., Lasse H. Andersen, M.D.,
Ulf G. Pedersen M.D., Nanna Reiter, M.D., Jørgen Wiis, M.D.,
Jonathan O. White, M.D., Lene Russell, M.D., Klaus J. Thornberg, M.D.,
Peter B. Hjortrup, M.D., Rasmus G. Müller, M.D., Morten H. Møller, M.D., Ph.D.,
Morten Steensen, M.D., Inga Tjäder, M.D., Ph.D., Kristina Kilsand, R.N.,
Suzanne Odeberg-Wernerman, M.D., Ph.D., Brit Sjøbø, R.N.,
Helle Bundgaard, M.D., Ph.D., Maria A. Thyø, M.D., David Lodahl, M.D.,
Rikke Mærkedahl, M.D., Carsten Albeck, M.D., Dorte Illum, M.D., Mary Kruse, M.D.,
Per Winkel, M.D., D.M.Sci., and Anders Perner, M.D., Ph.D.,
for the TRISS Trial Group* and the Scandinavian Critical Care Trials Group

Sepsis versus cardiac surgery

- HAEMODILUTION due to fluid resuscitation
 - Crystalloids
 - Colloids
- Systemic inflammatory response
 - C-Reactive Protein ↑
 - Leucocytes ↑
 - Capillary leakage ↑



Transfusion Requirements In Septic Shock

- The Capital Hospital in Denmark
- Scandinavian Critical Care Trials Group



- Funded by the Danish Research Council

Transfusion and septic shock

- 50% of patients with septic shock receive red blood cells (RBCs)

Perner et al. N Engl J Med 2012

- Median 3-5 units of RBCs

Rosland et al. Scand J Trauma Resusc Emerg Med. 2014

Brandstrup et al. LIVES 2014

Is a lower threshold safe?



Risks of anaemia

- Low DO_2
- Ischemia
- Organ dysfunction

Risks of transfusion

- Infectious
- Non-infectious
 - Storage-lesion
 - Immunomodulation

Aims



To assess the **effects and safety** of a lower versus a higher haemoglobin threshold for red blood cell transfusion on **mortality and morbidity** in patients with **septic shock** in the ICU

Design

TRISS
TRIAL

Multicentre, randomised, partly blinded trial

Patients with septic shock

+

Hgb \leq 9 g/dl

RBC transfusion

at

Hb \leq **7 g/dl**



RBC transfusion

at

Hb \leq **9 g/dl**

Primary outcome

Death by 90 days

Secondary outcomes

Use of life support

Ischemic events in the ICU

Serious adverse reactions

Days alive and out of hospital

Primary outcome

Death by 90 days

Secondary outcomes

Use of life support

Ischemic events in the ICU

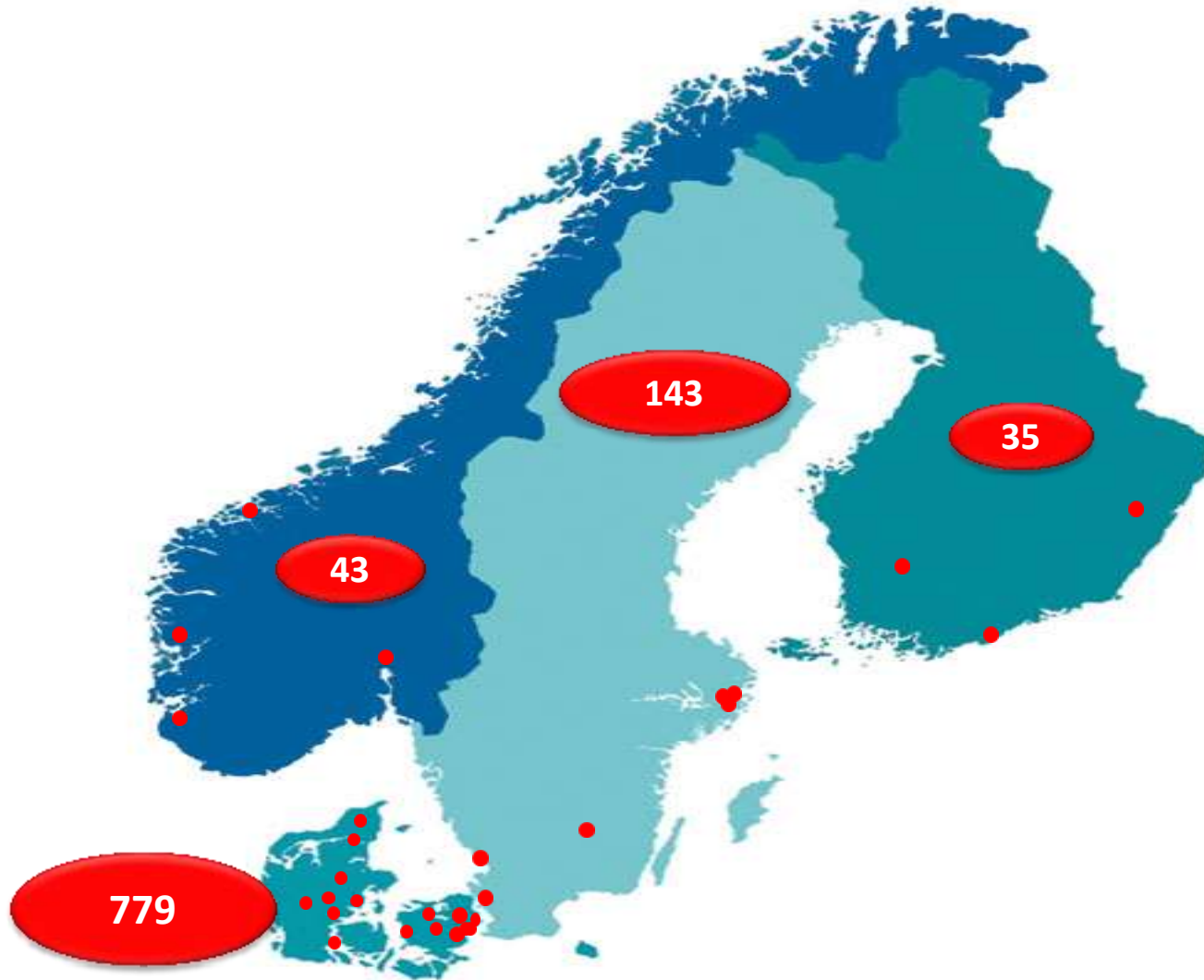
Sample size

2 x 500 patients to show a 9%* absolute difference in death at day 90 from expected 45%, an alpha of 0.05 and a power of 80%

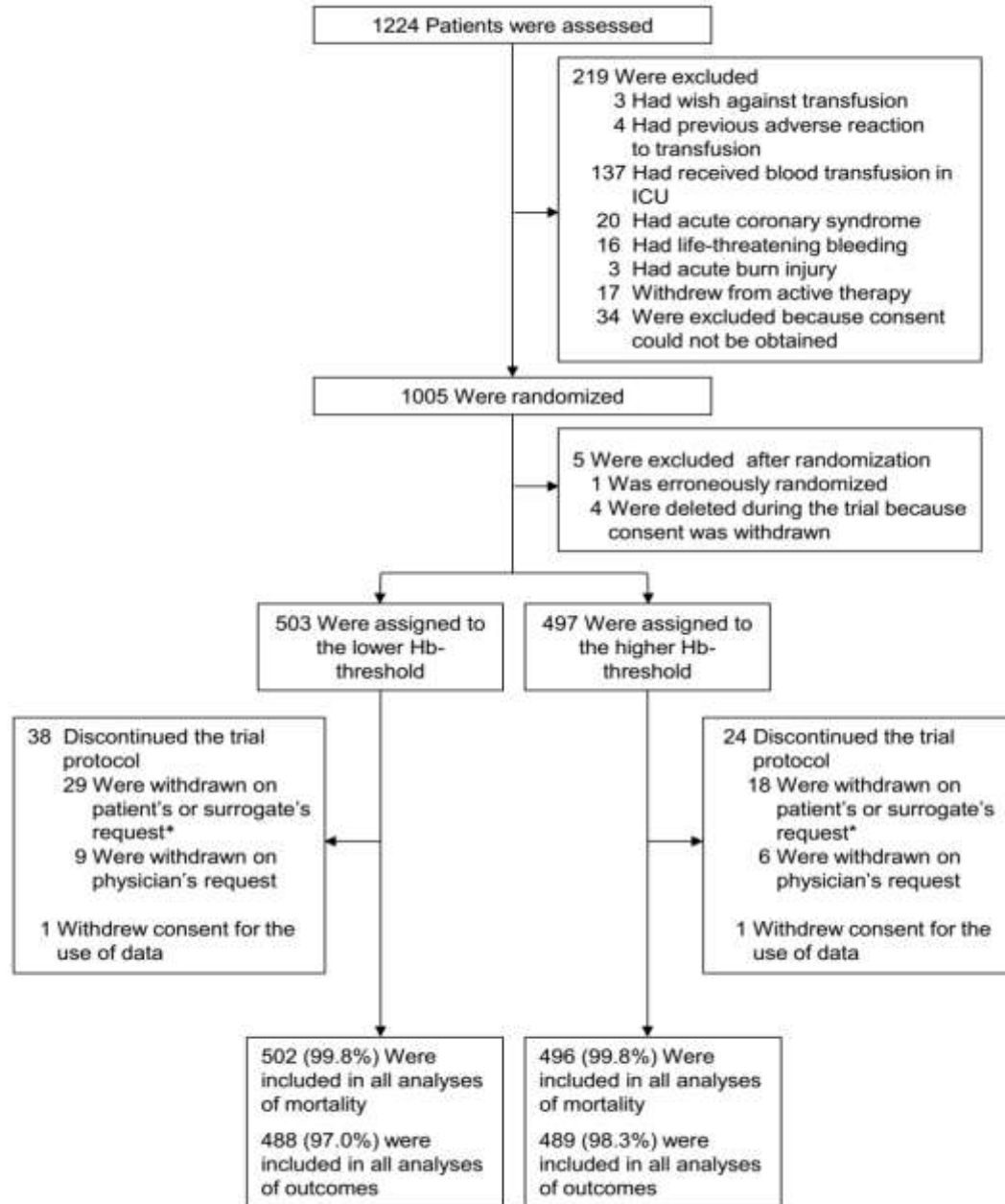
*derived from the 20% RRR in the subgroup of patients with severe infection in TRICC, NEJM 1999

32 Scandinavian ICUs

**TRISS
TRIAL**



Trial flow



Exclusions

219 Were excluded

3 Had wish against transfusion

4 Had previous adverse reaction
to transfusion

137 Had received blood transfusion in
ICU

20 Had acute coronary syndrome

16 Had life-threatening bleeding

3 Had acute burn injury

17 Withdrew from active therapy

34 Were excluded because consent
could not be obtained

Baseline characteristics

Lower
n = 503

Higher
n=497

	Lower n = 503	Higher n=497
Age	67 (57-73)	67 (58-75)
Emergency surgery	38%	44%
Chronic cardiovascular disease	15%	13%
Haematological malignancy	8%	7%
SAPS II score	51 (42-62)	52 (44-64)
SOFA score	10 (8-12)	10 (8-12)

Values are medians (IQR) or %

Number of units transfused



4633 units of RBCs

Lower Threshold : 1545

(P <0.001)

Higher Threshold : 3088

Number of patients transfused



Lower Threshold :

312 patients (64%) received RBC

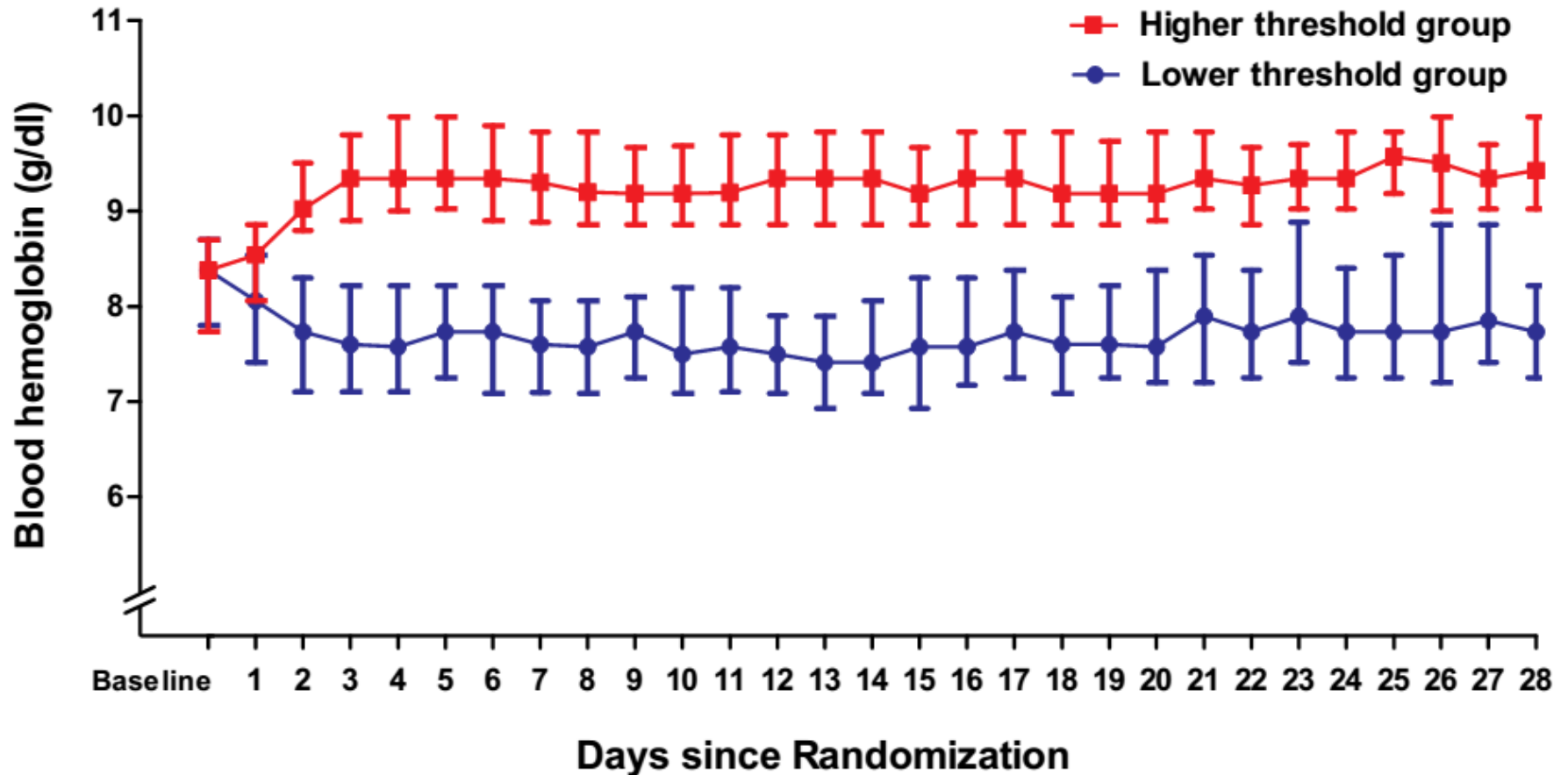
(P <0.001)

Higher Threshold :

490 patients (99%) received RBC

Lowest median Hb

**TRISS
TRIAL**



Death by 90 days

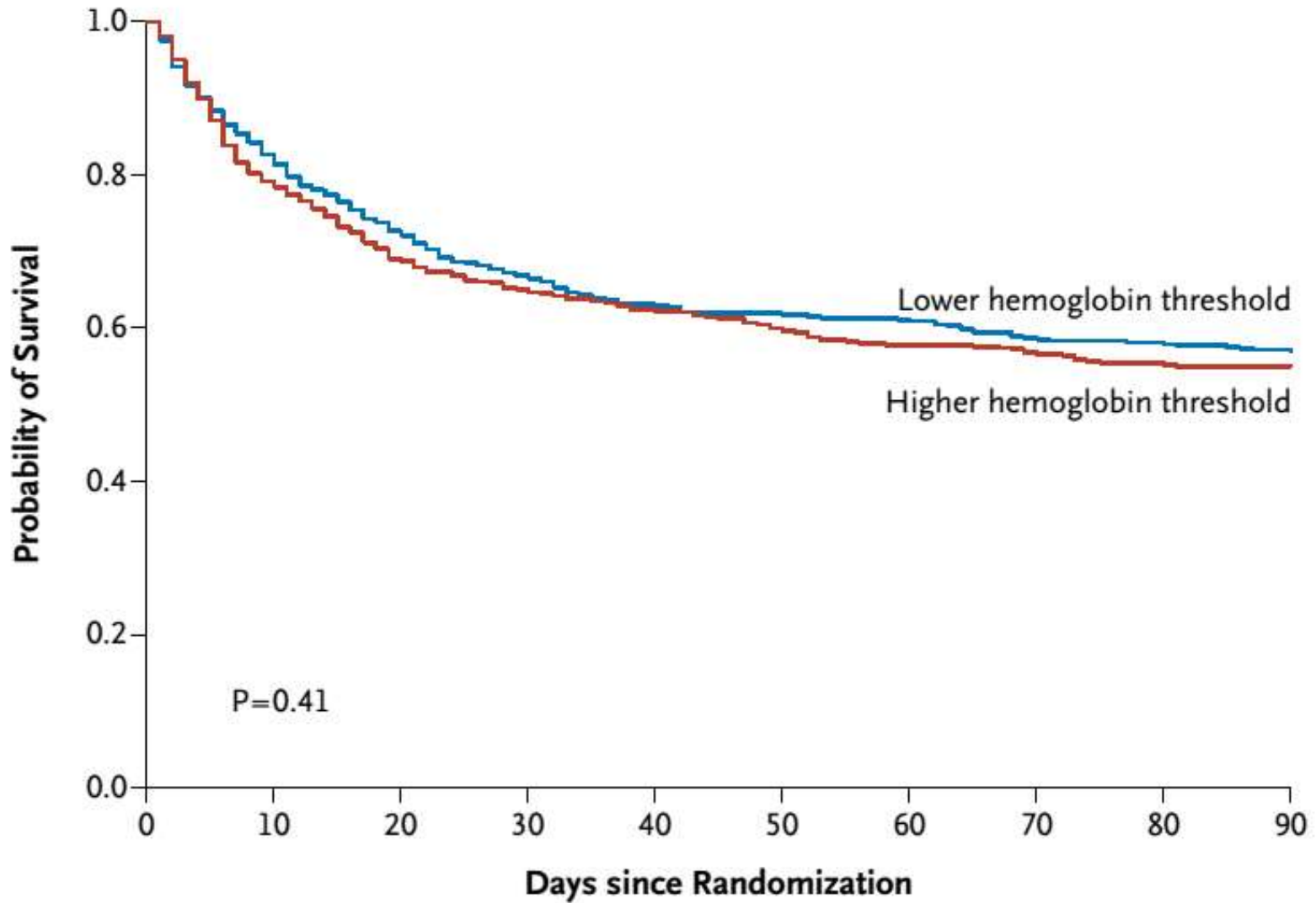


Lower		Higher	P-value
216 / 502 (43.0)	vs	223 / 496 (45.0)	0.44

Relative Risk 0.94 (95% CI 0.78 – 1.09)

Values are No.(%) and CI denotes confidence interval

Time to death



Use of any life support

**TRISS
TRIAL**

	Lower	Higher	Relative Risk (95% CI)	P-value
Day 5	64%	62%	1.04 (0.93 - 1.14)	0.47
Day 14	37%	37%	0.99 (0.81 - 1.19)	0.95
Day 28	16%	20%	0.77 (0.54 - 1.09)	0.14

Ischemic events in the ICU

**TRISS
TRIAL**

	Lower		Higher	Relative Risk (95% CI)	P-value
Any event*	7%	vs	8%	0.90 (0.58-1.39)	0.64

*Cerebral, myocardial, intestinal or limb

Clinical implications

Safe using a lower Hb-threshold (7g/dl) to guide RBC transfusion in patients with septic shock resulting in

- **Fewer transfusions**
- **Fewer patients transfused**

Danish Ministry of Health



Guidelines 2007

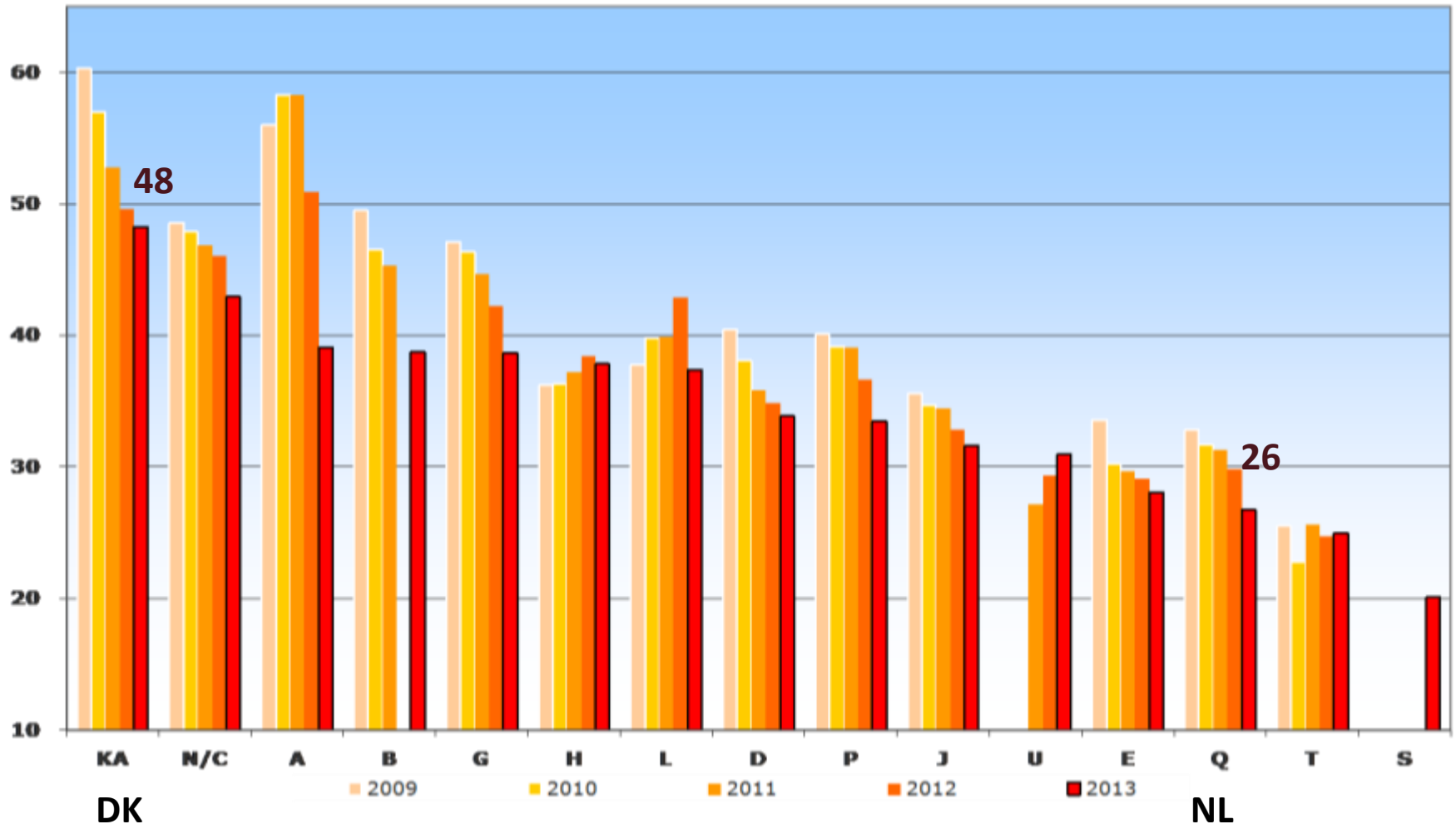
Hb < 9.8 g/dl

- * Severe ischemic heart disease
- * Early phase of septic shock
- * Acute and severe bleeding

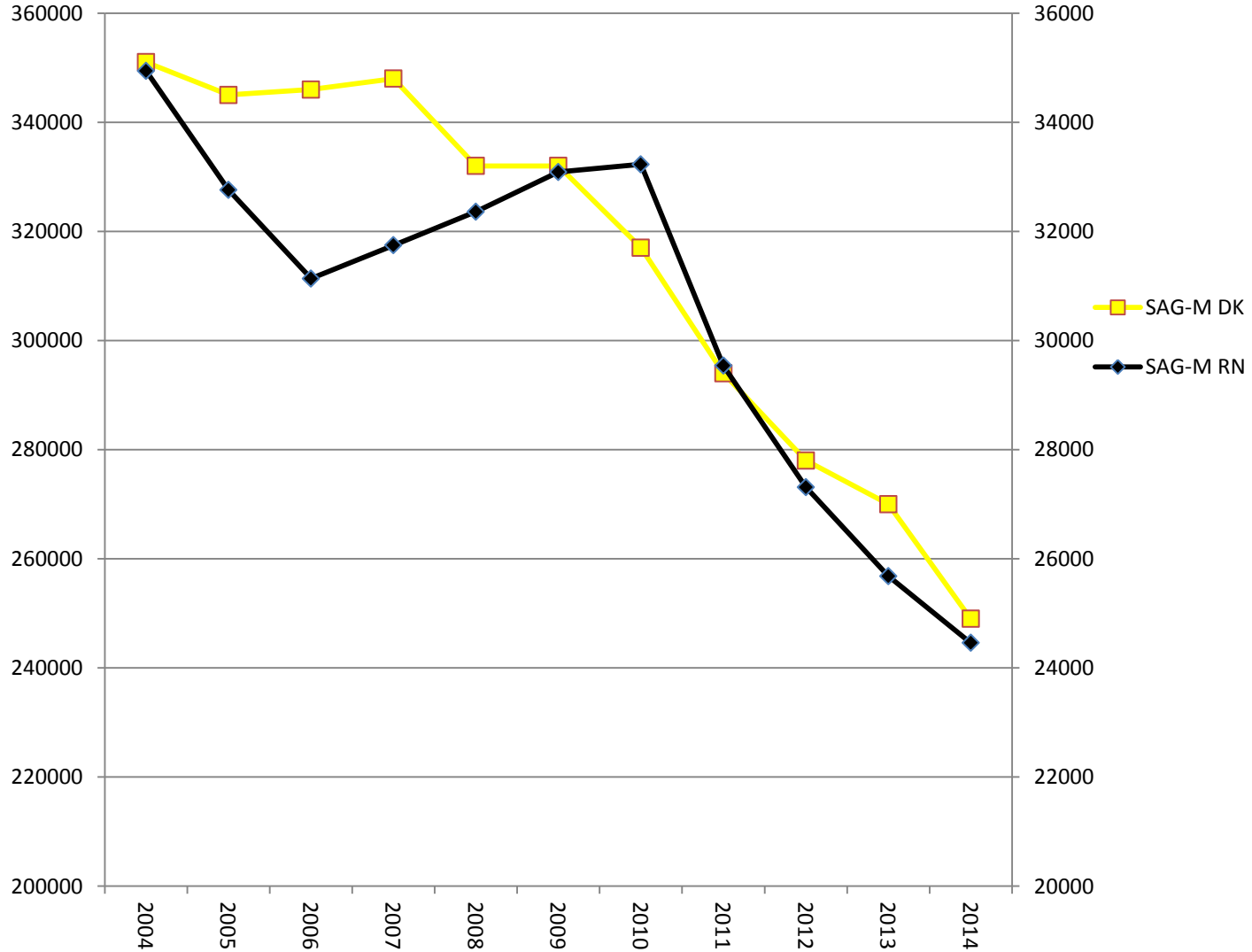
Hb < 7.4 g/dl

- * All other patients

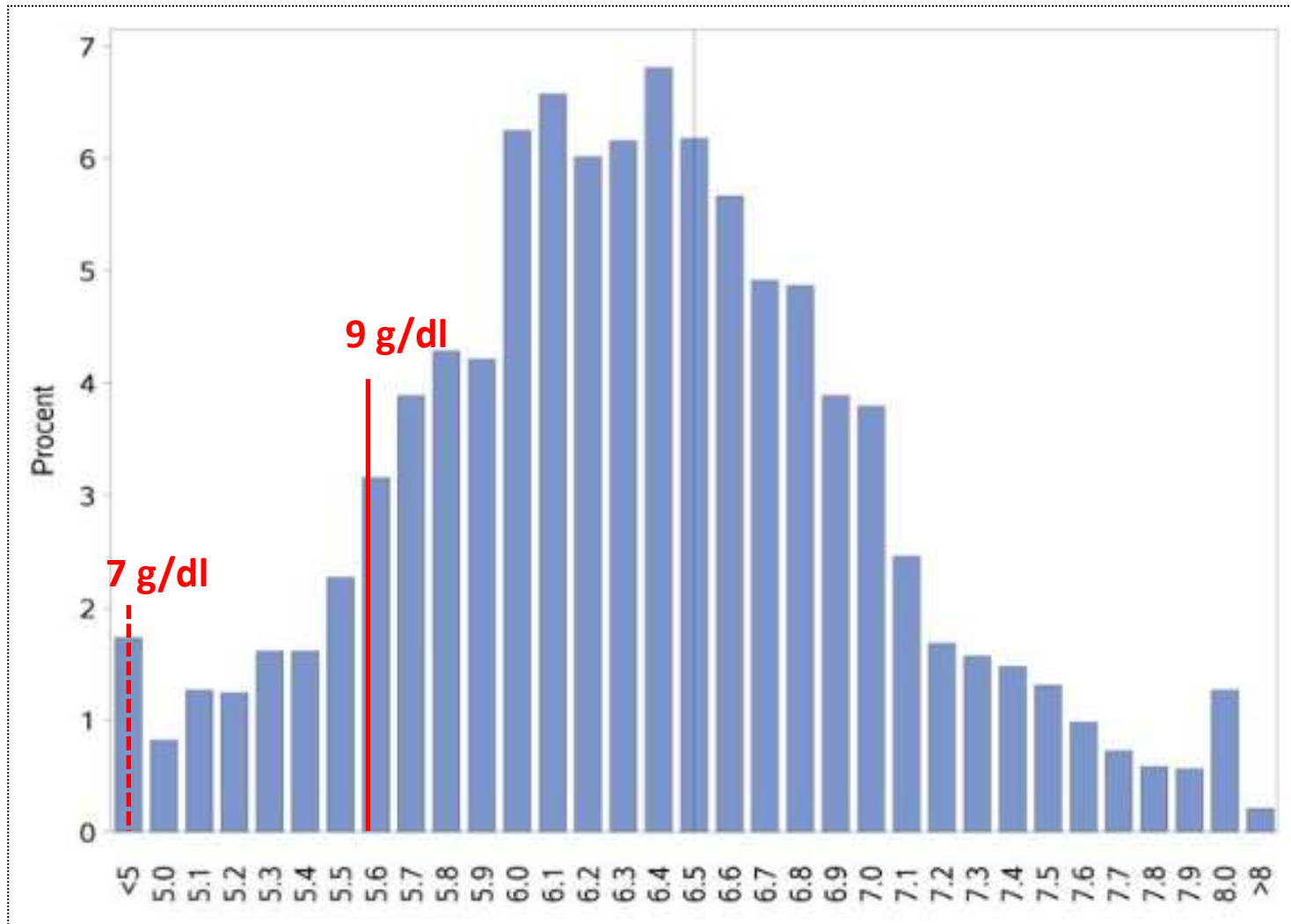
RBC per 1000 population



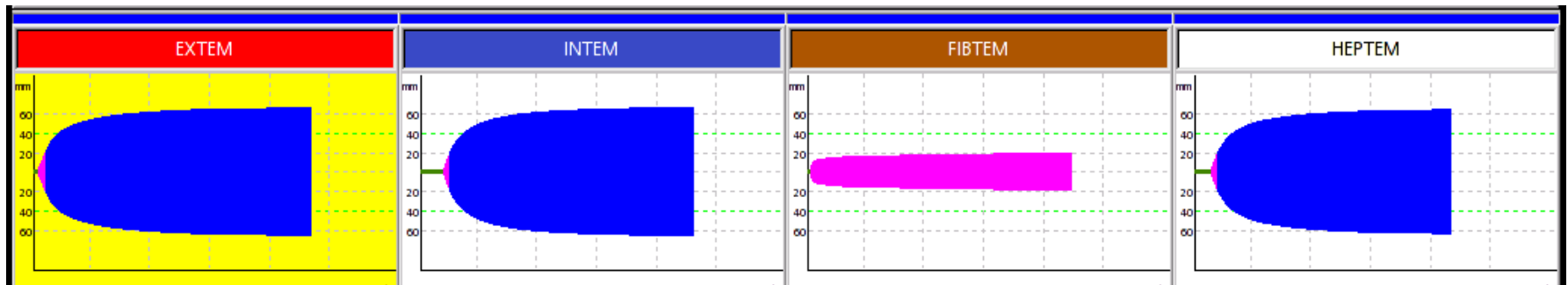
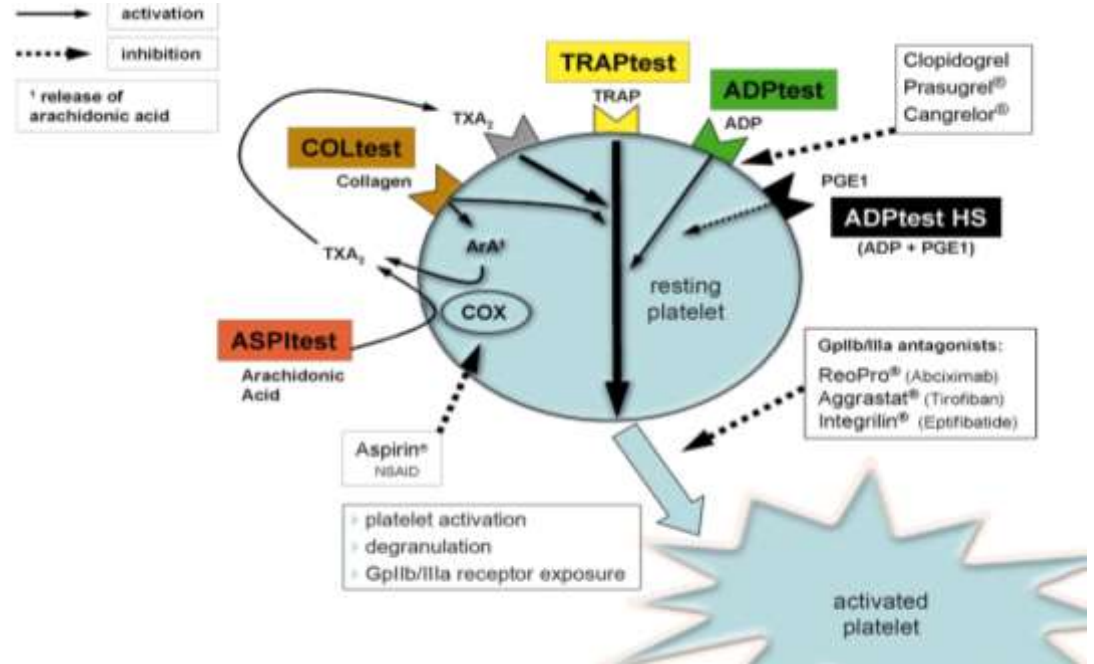
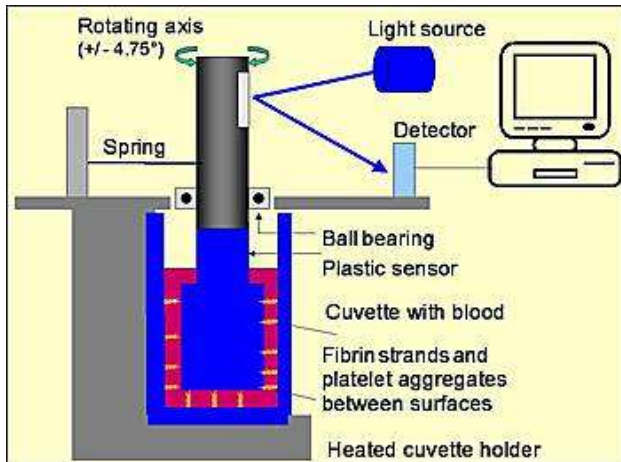
26% reduction RBCs



Posttransfusion Hb 2014



ROTEM & MULTIPLE



Cardiac surgery

Table 1. The Unadjusted and Adjusted Relative Risk With 95% Confidence Intervals for Allogeneic Blood Transfusion According to the Year of Surgery Among Patients Undergoing Elective First-Time CABG Surgery

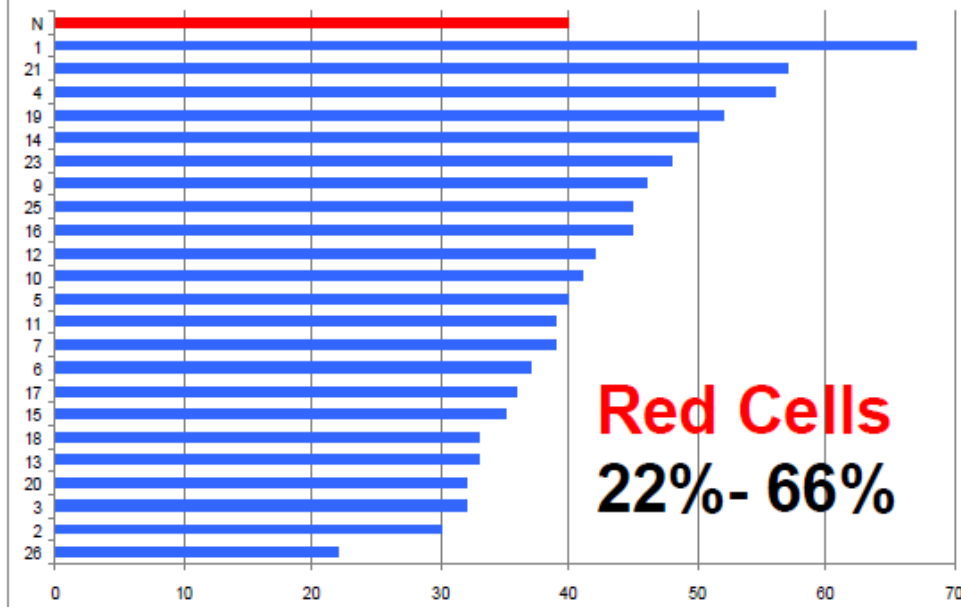
Year	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
2004	1.0 (reference)	1.0 (reference)
2008	0.9 (0.7-1.0)	0.7 (0.5-0.9)
2010	0.7 (0.6-0.9)	0.6 (0.5-0.8)
2014	0.4 (0.3-0.6)	0.3 (0.2-0.5)

Abbreviation: CI, confidence interval.

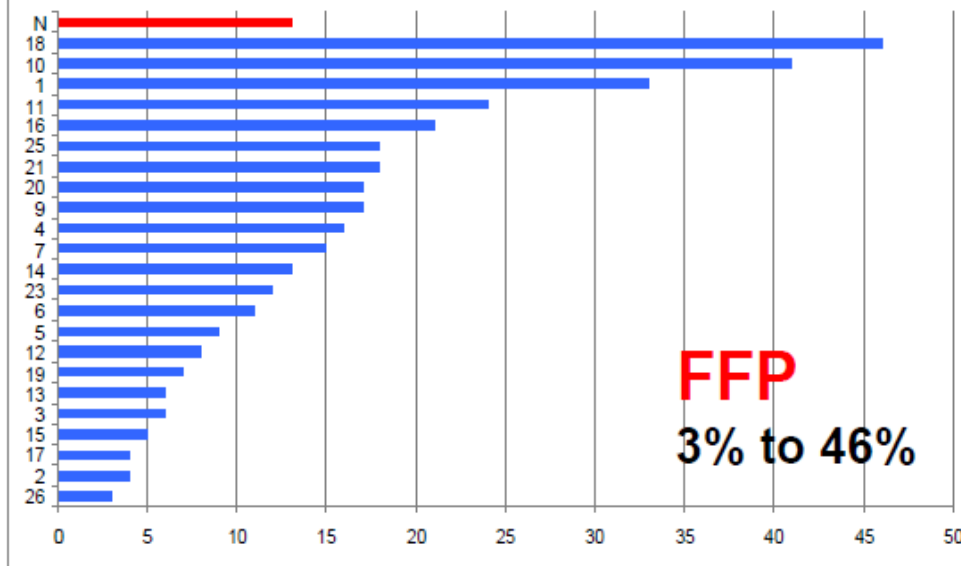
2011 NCA of Cardiac Surgery

Each line represents the transfusion rate for each component at one hospital

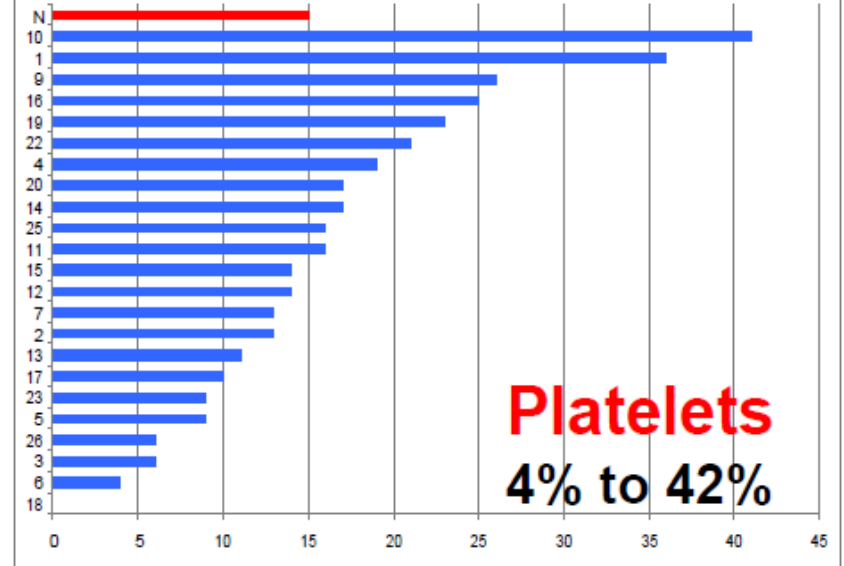
% CABG patients receiving Red Blood Cells



% CABG patients receiving FFP

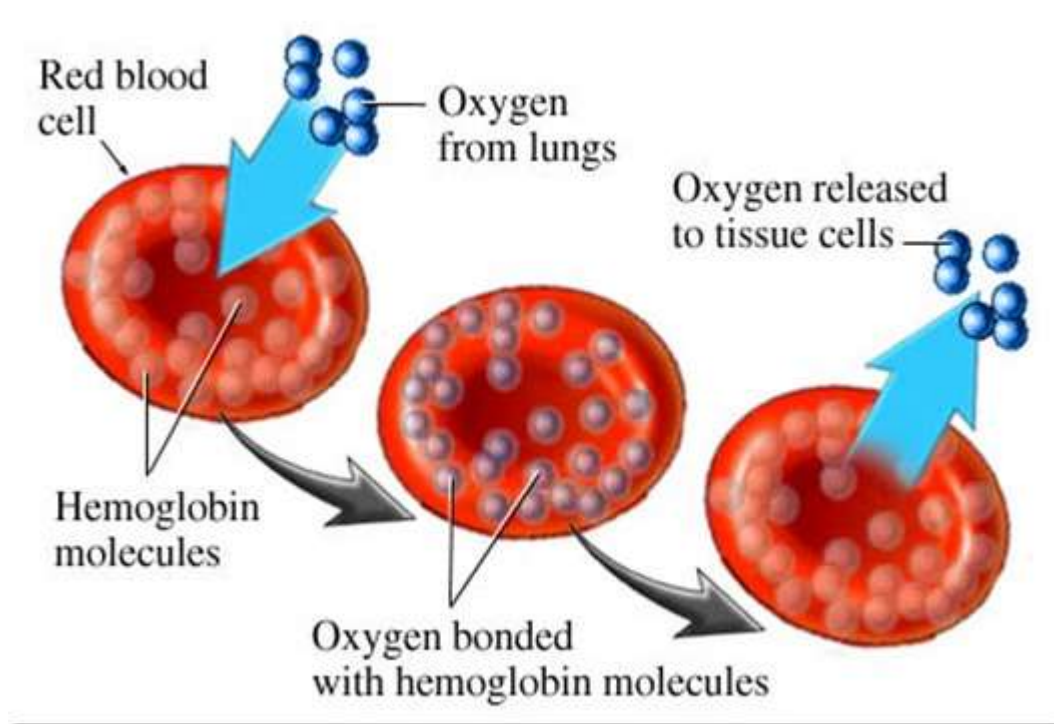


% CABG patients receiving Platelets



Haemodilution in cardiac surgery

- A low Hb is not the only trigger for RBC
 - Lactate, mixed venous saturation



UPDATE

Open Access

Transfusion Indication Threshold Reduction (TITRe2) randomized controlled trial in cardiac surgery: statistical analysis plan

Katie Pike¹, Rachel L Nash¹, Gavin J Murphy², Barnaby C Reeves¹ and Chris A Rogers^{1*}

Abstract

Background: The Transfusion Indication Threshold Reduction (TITRe2) trial is the largest randomized controlled trial to date to compare red blood cell transfusion strategies following cardiac surgery. This update presents the statistical analysis plan, detailing how the study will be analyzed and presented. The statistical analysis plan has been written following recommendations from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, prior to database lock and the final analysis of trial data. Outlined analyses are in line with the Consolidated Standards of Reporting Trials (CONSORT).

Methods and design: The study aims to randomize 2000 patients from 17 UK centres. Patients are randomized to either a restrictive (transfuse if haemoglobin concentration <7.5 g/dl) or liberal (transfuse if haemoglobin concentration <9 g/dl) transfusion strategy. The primary outcome is a binary composite outcome of any serious infectious or ischaemic event in the first 3 months following randomization.

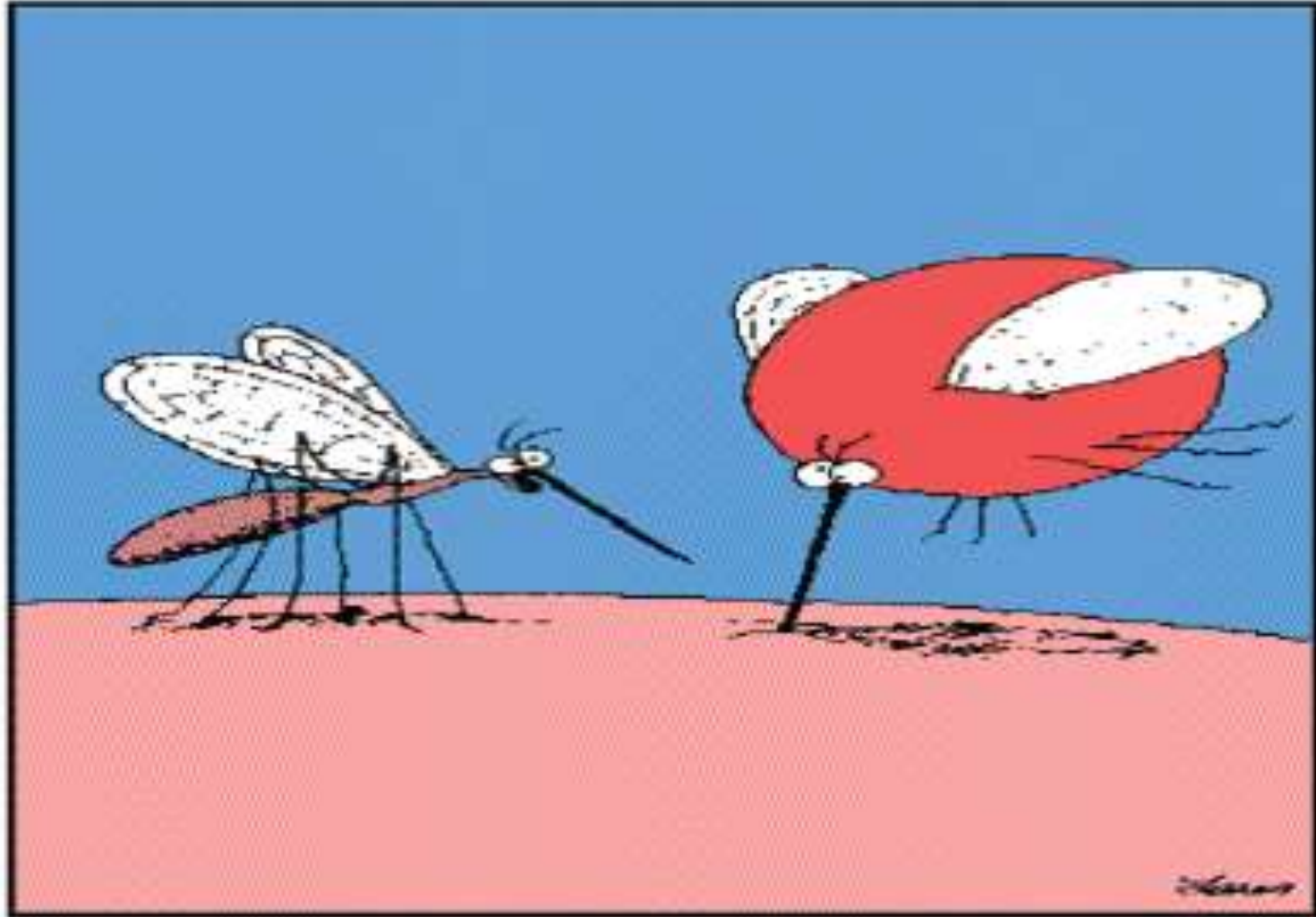
The statistical analysis plan details how non-adherence with the intervention, withdrawals from the study, and the study population will be derived and dealt with in the analysis. The planned analyses of the trial primary and secondary outcome measures are described in detail, including approaches taken to deal with multiple testing, model assumptions not being met and missing data. Details of planned subgroup and sensitivity analyses and pre-specified ancillary analyses are given, along with potential issues that have been identified with such analyses and possible approaches to overcome such issues.

Trial registration: ISRCTN70923932.

Keywords: Cardiac surgery, Red cell, Restrictive, Statistical analysis plan, Transfusion

THANK YOU

TRISS
TRIAL



"Pull out, Betty! Pull out! . . . You've hit an artery!"