Transfusion thresholds and beyond

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To transfuse or not to transfuse: that is the question! And this is a longstanding issue that has to be faced if we want to consider allogeneic blood transfusion to be a life-saving procedure. It does, however, involve several risks, including infectious (viral and bacterial) complications, transfusion-related acute lung injury, ABO- and non-ABO-associated haemolytic transfusion reactions, transfusion-associated Graft-versus-Host disease, and transfusion-associated circulatory overload[1]. These complications represent the principal causes of allogeneic blood transfusion-related morbidity and mortality. Over the last thirty years, this has led to a number of randomised controlled trials (RCTs) being carried out aimed at comparing the effect on patients of restrictive (haemoglobin concentration 7-8 g/dL) with more liberal (haemoglobin concentration approximately 10 g/dL) blood transfusion strategies in a variety of clinical settings[2]. In parallel, a number of systematic reviews and meta-analyses[3-10] have been conducted with the aim of performing a pooled analysis of the data from these RCTs (see Table I for a summary of results).

A systematic review of papers published up to 2000 identified 10 trials, and the investigators concluded that the evidence supported the use of restrictive transfusion triggers in patients without serious cardiac disease[3]. A 2012 Cochrane systematic review, including 19 trials with 6,264 patients, showed that patients receiving liberal transfusion had higher in-hospital mortality compared with those transfused with a restrictive strategy[4]. A 2014 meta-analysis and systematic review by Salpeter *et al.* focused on the question as to whether the lower 7 g/dL threshold is superior to the higher threshold of 8 g/dL. Their study showed that, in patients with critical illness or bleeding, restricting blood transfusions by using a haemoglobin trigger lower than 7 g/dL significantly reduces negative outcomes, as well as in-hospital and total mortality[6].

A more recent systematic review and meta-analysis of 31 RCTs by Holst *et al*. revealed a reduction in the number of units and of patients transfused in the restrictive group compared with the liberal group, but there was no difference in mortality and morbidity[7]. From the overall analysis of these systematic reviews (Table I), it is clear that, in terms of morbidity and mortality, a restrictive red blood cell (RBC) transfusion approach is superior[3,4,6] or equivalent[5,7-9] to a liberal strategy.

Recently, Fominskiy *et al.*[10] performed yet another meta-analysis, justifying their efforts on the basis of the inclusion of three additional RCTs published in 2015 that had not been included in the previous systematic reviews[11-13]. The authors claimed that their meta-analysis, which included 27 RCTs with 11,021 patients, demonstrated unequivocally the superiority in terms of overall survival of the liberal transfusion strategy over the conservative approach in peri-operative adult patients (but not in critically ill patients). Besides a number of criticisms that could be raised on the selection criteria and data analysis, such as the inclusion of studies with a wide clinical heterogeneity, the overlaps between restrictive and non-restrictive blood transfusion thresholds, and the choice of the 90-day all-cause mortality as primary outcome (instead of the more reasonable 30-days cut-off chosen by the majority of trials), the main weakness of their work lies in the statistical analysis performed. Indeed, in their meta-analysis the authors should have calculated the risk ratio (RR) rather than the odds ratio (OR). The pooled effect size measured by the RR is a more appropriate tool for a meta-analysis aimed at evaluating the efficacy of a treatment protocol (liberal *vs*. restrictive transfusion approach) in preventing an adverse event (90-day all-cause mortality). This is corroborated by the fact that all previous meta-analyses published on this topic used an RR-based meta-analytical approach. If we re-analyse the 17 peri-operative studies from the meta-analysis conducted by Fominskiy *et al.* using the RR[10], the already border-line statistical significance regarding a lower all-cause mortality with liberal *vs* restrictive transfusion strategy observed using the OR (0.81, 95% CI: 0.66-1; p=0.050) disappears (RR 0.83, 95% CI: 0.689-1.001; p=0.051) (Figure 1). Notably, when the same authors performed a sub-analysis of all included trials (i.e. peri-operative and critically ill patients) considering only the high-quality studies with

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Table I - Main results of the systematic reviews and meta-analyses of trials on blood transfusion strategies in various clinical settings.

First author, year [reference]	Selection criteria	Studies/patients included	Main findings
Carson, 2002 [3]	RCTs 1970-2001	10/1,780	The literature analysis supported the use of restrictive transfusion triggers in patients without serious cardiac disease.
Carson, 2012 [4]	RCTs 1970-2011	19/6,264	Restrictive *vs* liberal transfusion strategy was associated with a statistically significant reduction in hospital mortality (RR 0.77, 95% CI: 0.62-0.95).
Curley, 2014 [5]	RCTs 1950-2013	7/1,262	Restrictive vs liberal transfusion strategy was associated with a decreased transfusion of RBCs (mean difference −0.71, 95% CI: −0.31 to −1.09) without an associated change in adverse events in patients undergoing cardiovascular surgery.
Salpeter, 2014 [6]	RCTs 1966-2013	3/23,641	Restrictive vs liberal transfusion strategy significantly reduced cardiac events (RR 0.44; 95% CI: 0.22-0.89), re-bleeding (RR 0.64, 95% CI: 0.45-0.90), bacterial infections (RR 0.86; 95% CI: 0.73-1.00), in-hospital mortality (RR 0.74, 95% CI: 0.60-0.92), and total mortality (RR 0.80; 95% CI: 0.65-0.98).
Holst, 2015 [7]	RCTs 1950-2014	31/9,813	Restrictive *vs* liberal transfusion strategy was associated with a decreased transfusion of RBCs (mean difference −1.43, 95% CI: −2.01 to −0.86) with no effect on overall morbidity and mortality risks.
Brunskill, 2015 [8]	RCTs 1946-2014	6/2,272	No difference in mortality, functional recovery or post-operative morbidity between restrictive and liberal thresholds was observed.
Ripollés Melchor, 2015 [9]	RCTs 1950-2014	6/2,156	No differences in mortality between the restrictive and liberal groups (RR 0.86, 95% CI: 0.70-1.05; p=0.14) were observed.
Fominskiy, 2015 [10]	RCTs 1986-2015	27/11,021	Liberal transfusion strategy compared with restrictive strategy improved survival in perioperative patients (OR 0.81, 95% CI: 0.66-1; p=0.050)

[1] Only RCTs using a restrictive transfusion trigger <7 g/dL were included. RCTs: randomised controlled trials; RR: risk ratio; CI: confidence interval; RBCs: red blood cells; OR: odds ratio.

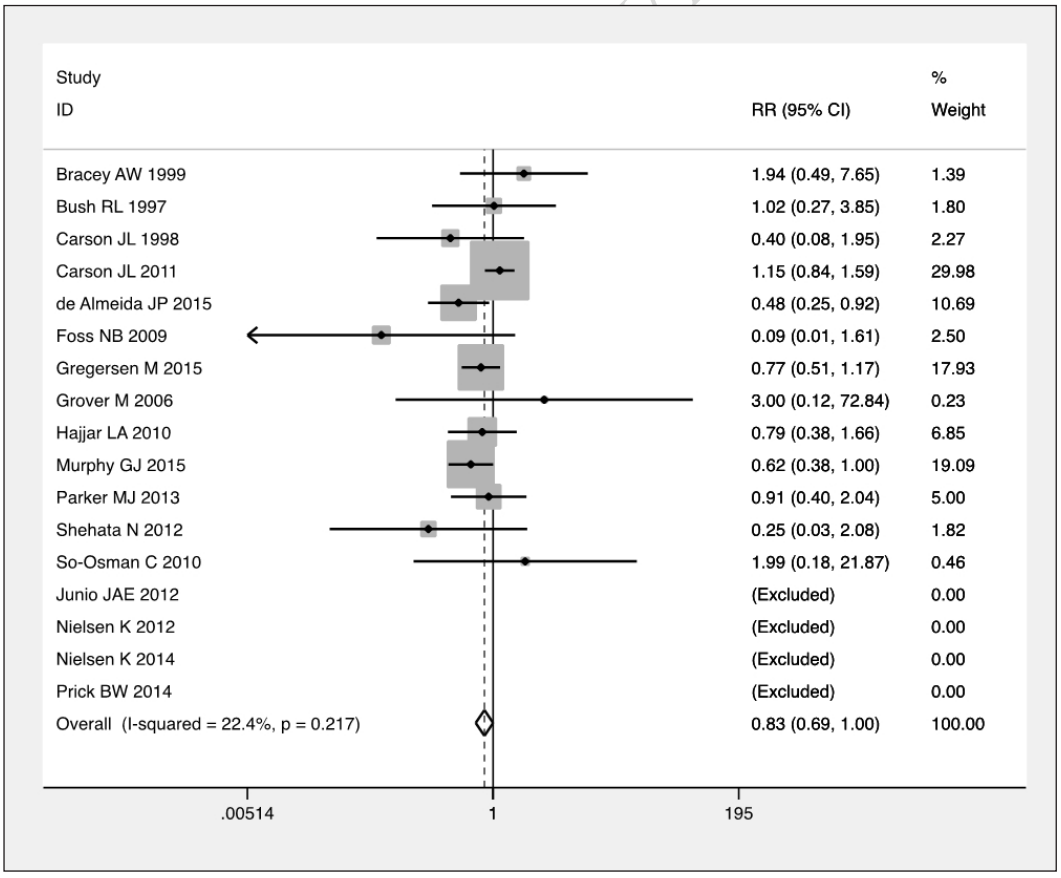

Figure 1 - Forest-plot of all-cause mortality in peri-operative patients: risk ratio calculation (data extracted from the meta-analysis by Fominskiy *et al.*[10]).
Four studies did not record events and were excluded from analysis. Statistical analysis performed using Stata 14.1 (StataCorp, College Station, TX, USA). RR: relative risk; CI: confidence interval.

a low risk of bias (Online Supplementary Table II of the meta-analysis[10]), the OR was not statistically significant (0.88, 95% CI: 0.75-1.04, p=0.13), thus aligning their results with those of previous meta-analyses. Therefore, we believe that the authors should have highlighted the limited evidence provided by their statistical analysis and suggested that an interpretation of their data should be approached with greater caution. In conclusion, it is our view that the meta-analysis by Fominskiy *et al.*[10] adds very little to the existing knowledge in this clinical setting. In addition, as specialists in transfusion medicine, we are well aware that RBC transfusion is a life-saving therapy not without risks[14,15] and, consequently, we recommend, in accordance with recent international transfusion medicine and multidisciplinary guidelines, that decisions on transfusion therapy with RBCs be based on both the patient's haemoglobin values as well as symptoms of anaemia, and a restrictive transfusion approach be adopted with the possible exception of patients with severe ischaemic heart disease[16-19].

The Authors declare no conflicts of interest.

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