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EDITORIAL

Restrictive transfusion practice in cardiac surgery patients is safe, but what transfusion threshold is safe for my patient?

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This editorial refers to 'Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis'†, by N. Shehata *et al.*, on page 1081.

Cardiac surgery patients remain major consumers of allogeneic red blood cells. In the UK, >5% of all red cells are utilized by cardiac surgical patients.[1] Until recently, transfusion decisions were not informed by high-quality evidence.[2] This was reflected by wide variation in red cell transfusion rates across cardiac surgical units throughout the world.[3] The study by Shehata and colleagues[4] published in this issue of the *European Heart Journal* addresses this knowledge gap. The authors conducted a systematic review and meta-analysis of all randomized controlled trials that compared liberal with restrictive transfusion thresholds in both adult and paediatric patients undergoing cardiac surgery. The meta-analysis, which included >9000 patients, found restrictive transfusion thresholds to be as safe as liberal transfusion thresholds for 30-day mortality, myocardial infarction, stroke, renal failure, and infection. There was little between-study variability, and subgroup analyses of adult and paediatric trials showed no significant interaction. Prudently, the authors conducted a trial sequential analyses; although this did not achieve the required information size (>12 000 patients), the current sample size of 9019 patients was adequate to demonstrate the non-inferiority of restrictive transfusion practice and the futility of further testing. The authors conducted a comprehensive systematic review, assessed risk of bias in all trials, and used appropriate meta-analytical methods. The results provide the best available evidence to date that restrictive red cell transfusion practice is as safe as liberal transfusion strategies in patients undergoing cardiac surgery.

The review also highlights several unanswered questions. First, are the effects on outcomes observed at 30 days still evident at longer term follow-up? The Transfusion Indication Threshold Reduction (TITRe 2) trial demonstrated no difference in mortality or adverse events at 28 days, but did demonstrate a small but statistically significant increase in mortality in the restrictive group at 90 days.[5] A longer term follow-up of the larger Transfusion Requirements in Cardiac Surgery (TRICS) III trial is planned and will address this question. Secondly, how do we apply this evidence of non-inferiority to clinical care? Protocolized transfusion thresholds are the norm, and this review indicates that there are no benefits to transfusing adult cardiac surgery patients with haemoglobin concentrations >8 g/dL. However, there is some heterogeneity across patient populations. The recent TRICS III trial, for example, suggested that patients over 75 years of age may benefit from a restrictive transfusion strategy compared with a liberal transfusion strategy.[6] This points towards the need for personalized transfusion triggers that are stratified by age or co-morbidity. Individual patient data meta-analyses of the trials identified by Shehata *et al.* may address this unknown. However, given that oxygen supply and demand change during the course of the cardiac surgical patient's journey for individual patients, a single personalized transfusion threshold may not be identifiable. This brings us to the third unanswered question raised by the current systematic review: are we testing the correct hypothesis? For example, to use a simple analogy, if trials of antihypertensive agents in >9000 patients consistently demonstrated reductions in blood pressure but no effect on clinically important outcomes, it would be reasonable to conclude that blood pressure is not a determinant of outcome. The trial sequential analysis reported by Shehata *et al.* addresses this pretty conclusively. The counter to this statement is to ask how low can you go. Should we be evaluating transfusion thresholds well below 8 g/dL in a predominantly elderly cohort with advanced cardiovascular disease? Alternatively, one might argue that a biomarker of tissue hypoxia will provide the most effective personalized indicator for transfusion, with the caveat that it is unclear whether tissue hypoxia is the basis of post-cardiac surgery organ failure and morbidity. A recent trial evaluating the role of cerebral oximetry as part of a personalized transfusion trigger detected cerebral desaturation in <2% of patients and yet

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>40% developed organ dysfunction affecting the heart, brain, or kidneys.[7] A final response may be that reducing transfusion is in itself of clinical benefit. Red cells are a precious resource that should not be wasted. Counter to this, however, is a recent health economic analysis of the TITRe2 trial which demonstrated that the restrictive strategy was not cost-effective.[8] A new research question might be to ask what factors confounded the early observational analyses that showed strong associations between transfusion and adverse outcomes. Both anaemia and haemorrhage, the two indications for transfusion in cardiac surgery, are more common in frail patients and those with multiple co-morbid conditions. Attempting to identify personalized indicators for transfusion might start with better phenotyping of those conditions.

In summary, red cell transfusion is essential for successful cardiac surgery. This systematic review by Shehata *et al.*[4] definitively demonstrates that restrictive transfusion practice is as safe as a liberal transfusion strategy. The next phase of research should identify patient subgroups that benefit from either strategy, at what stage in their clinical journey, and provide greater clarity on transfusion thresholds and investigate new, more meaningful transfusion triggers.

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References

1. Wells AW, Llewelyn CA, Casbard A, Johnson AJ, Amin M, Ballard S, Buck J, Malfroy M, Murphy MF, Williamson LM. The EASTR Study: indications for transfusion and estimates of transfusion recipient numbers in hospitals supplied by the National Blood Service. *Transfus Med* 2009;**19**:315–328.
2. Authors/Task Force Members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–2619.
3. Bennett-Guerrero E, Zhao Y, O'Brien SM, Ferguson TB Jr, Peterson ED, Gammie JS, Song HK. Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA* 2010;**304**:1568–1575.
4. Shehata N, Mistry N, da Costa BR, Pereira TV, Whitlock R, Curley GF, Scott DA, Hare GMT, Jüni P, Mazer CD. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis. *Eur Heart J* 2019;**40**:1081–1088.
5. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, Reeves BC, Investigators TI. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med* 2015;**372**:997–1008.
6. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, Khanykin B, Gregory AJ, de Medicis E, McGuinness S, Royse A, Carrier FM, Young PJ, Villar JC, Grocott HP, Seeberger MD, Fremes S, Lellouche F, Syed S, Byrne K, Bagshaw SM, Hwang NC, Mehta C, Painter TW, Royse C, Verma S, Hare GMT, Cohen A, Thorpe KE, Juni P, Shehata N, TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Perioperative Anesthesia Clinical Trials Group. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med* 2017;**377**:2133–2144.
7. Rogers CA, Stoica S, Ellis L, Stokes EA, Wordsworth S, Dabner L, Clayton G, Downes R, Nicholson E, Bennett S, Angelini GD, Reeves BC, Murphy GJ. Randomized trial of near-infrared spectroscopy for personalized optimization of cerebral tissue oxygenation during cardiac surgery. *Br J Anaesth* 2017;**119**:384–393.
8. Stokes EA, Wordsworth S, Bargo D, Pike K, Rogers CA, Brierley RC, Angelini GD, Murphy GJ, Reeves BC, TITRe2 Investigators. Are lower levels of red blood cell transfusion more cost-effective than liberal levels after cardiac surgery? Findings from the TITRe2 randomised controlled trial. *BMJ Open* 2016;**6**:e011311.