Transfusion Triggers in Cardiac Surgery: Where do we go from here?

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Defining the appropriate indications for the transfusion of allogenic red cells is an area of intense study. Cardiac surgery utilizes a significant proportion (over 6%) of all red cells transfused in the United Kingdom (1) where demographic changes have reduced donor pools; it is also expensive. Indeed, the total societal cost for a single unit of red cells is estimated to be well over $600 Canadian dollars (2). In a patient who is bleeding profusely following surgery, the indication for red cell transfusion is clear. In this setting, red cell transfusion helps to maintain oxygen delivery and reverse the oxygen supply-demand imbalance. However, in the anemic patient who is not actively bleeding, the risks and benefits of this costly intervention remain uncertain.

The last five years has seen the reporting of a significant number of randomized-controlled trials (RCTs) comparing liberal and restrictive hemoglobin transfusion thresholds in cardiac surgical patients that attempt to address this uncertainty. A meta-analysis published in 2015 by our group demonstrated no difference in mortality between patients randomized to a restrictive or liberal transfusion threshold, though the point estimate numerically favoured the latter (3). We concluded that additional and larger well-designed trials in high-risk cardiac surgical patients were required.

The recently published Transfusion Requirements in Cardiac Surgery (TRICS) III trial was an international multicentre, randomized, controlled, non-inferiority, single-blinded trial that randomized over 5000 adult cardiac surgical patients to a restrictive or liberal transfusion threshold (4). Patients assigned to the restrictive transfusion arm received a red cell transfusion if their hemoglobin concentration was **<** 7.5 g/dL and those in the liberal transfusion arm received a red cell transfusion if their hemoglobin was **<** 9.5 g/dL intraoperatively or postoperatively **in the intensive care unit (or 8.5 g/dL on the postoperative ward).** Patients had a EuroSCORE-**I ≥** 6 indicative of a cohort with a relatively high **mortality** risk. The primary outcome was a composite of death, nonfatal myocardial infarction, stroke or new-onset renal failure requiring dialysis, occurring from the start of surgery until either discharge or 28 days after surgery. Groups were well-balanced at baseline. In the restrictive group, 52.3% of patients received a red cell transfusion after randomization, as compared to 72.6% of those in the liberal transfusion group. The trial showed that restrictive transfusion was non-inferior, and therefore as safe as a liberal transfusion strategy with respect

to the composite outcome. The primary outcome occurred in 11.4% of patients in the restrictive transfusion group and 12.5% of those in the liberal transfusion group (odds ratio [OR], 0.90; 95% CI, 0.76 to 1.07).

The TRICS III trial has many strengths. It is the largest trial comparing transfusion thresholds in cardiac surgical patients and its multicentre recruitment included patients from 73 sites across 19 countries. It also used a pragmatic trial design, allowing the transfusion protocol to be temporarily suspended in patients experiencing rapid blood loss and be resumed as soon as hemostasis was achieved. The pragmatic approach taken by the investigators provided a "real world" evaluation of the intervention. In addition, the primary analysis was a *per protocol* analysis, as opposed to an *intention to treat* analysis in an attempt to mitigate bias. Unlike conventional superiority RCTs, **most non-inferiority RCTs utilize a *per protocol* analysis as *intention to treat* analyses tend to falsely favour non-inferiority.** Importantly, a sensitivity analysis revealed no difference in outcomes between the two analytical methods.

Does TRICS III change practice?
The TRICS III trial contributes significantly to the expanding evidence surrounding red cell transfusion thresholds. Figure 1 is a forest plot of all trials of red cell transfusion thresholds in cardiac surgical patients for the outcome of in-hospital or 30-day mortality (4-10). This demonstrates that in over 8000 adult cardiac surgical patients, restrictive transfusion is as safe as liberal transfusion (**OR, 0.98; 95% CI, 0.77 to 1.25**). The TRICS III trial shifts the effect estimate to the midline, which contrasts to the findings of our recent meta-analysis that suggested that their maybe a trend towards benefit with liberal transfusion (3). These results also refute findings from observational studies that liberal thresholds for red cell transfusion are associated with a substantially increased risk of mortality and morbidity (11), and provide strong evidence that restrictive practice may be safe, at least in the short-term. It remains unclear whether there may be longer-term adverse effects from this strategy. The Transfusion Indication Threshold Reduction (TITRe 2) trial (6) also 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. Longer-term follow up from the TRICS III should help address this

uncertainty. Another limitation of TRICS III is that the liberal versus restrictive transfusion threshold design, which evaluates protocolized transfusion strategies, is unable to decipher how the hemoglobin threshold may vary for different patient or stages of the perioperative journey. **Although the trial does suggest that patients >75 years of age may benefit from restrictive transfusion strategy.** An individual patient-data meta-analysis may allow dissection of different patient groups to generate hypotheses which can be tested in subsequent RCTs.

Where to next?

Existing RCTs all use hemoglobin as the sole transfusion trigger, but there is no clinically meaningful physiological indication given for the need for transfusion. Arguably, the decision to transfuse should not be solely based on the hemoglobin concentration. Hemoglobin is a measure of the oxygen carrying capacity of blood, but does not indicate tissue oxygen delivery, level of tissue oxygenation, reversal of hypoxia, or improvement in oxygen debt. Coupling a physiological measurement of tissue oxygenation with hemoglobin concentration may provide a more clinically relevant personalized trigger for transfusion. Potential physiological transfusion triggers in normovolemic patients with anemia include mean arterial pressure < 60 mmHg (or < 70-80% of baseline), heart rate > 110-130 beats/min (or > 120-130% of baseline), new ST-segment depression or elevation of at least 0.1 mV in an electrocardiogram, new wall motion abnormality on transesophageal or transthoracic echocardiography, mixed venous oxygen partial pressure < 32 mmHg, oxygen extraction ratio > 40%, mixed venous oxygen saturation < 60%, or > 10% decrease in oxygen consumption (VO_2) (12). Other non-invasive measures of tissue oxygenation include the use of near-infrared spectroscopy which has been used by our group (13) as well as others (14).

The field of red cell transfusion research remains exciting; existing trials demonstrate that in the vast majority of adult cardiac surgical patients, restrictive transfusion is as safe as liberal transfusion. However, the direction of research must move further to determine physiological parameters that can be coupled with hemoglobin-based triggers to identify those patients that may truly benefit, or be harmed, from a red cell transfusion.

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Figure Legend:

Figure 1. Forest plot of randomized controlled trials comparing restrictive and liberal transfusion thresholds in cardiac surgical patients for the outcome of hospital or 30-day mortality. The data from the effect estimate of the Koch et al trial (5) reflects data for mortality or multisystem organ failure whereas the effect estimate from Murphy et al (2007) (9) reflects data for a composite outcome of death, stroke or myocardial infarction.

Study or Subgroup	Restrictive Tx Events	Total	Liberal Tx Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Year	Odds Ratio M–H, Fixed, 95% CI
Koch 2017 (Ref 5)	3	363	6	354	4.6%	0.48 [0.12, 1.95]	2017	
Mazer 2017 (Ref 4)	74	2427	87	2429	63.7%	0.85 [0.62, 1.16]	2017	
Murphy 2015 (Ref 6)	25	1000	17	1003	12.5%	1.49 [0.80, 2.77]	2015	
Shehata 2011 (Ref 7)	4	25	1	25	0.6%	4.57 [0.47, 44.17]	2011	
Hajjar 2010 (Ref 8)	15	249	13	253	9.2%	1.18 [0.55, 2.54]	2010	
Murphy 2007 (Ref 9)	10	162	7	159	5.0%	1.43 [0.53, 3.85]	2007	
Bracey 1999 (Ref 10)	3	212	6	216	4.4%	0.50 [0.12, 2.04]	1999	
Total (95% CI)		4438		4439	100.0%	0.98 [0.77, 1.25]		
Total events	134		137					

Heterogeneity: Chi^2 = 6.98, df = 6 (P = 0.32); I^2 = 14%

Test for overall effect: Z = 0.18 (P = 0.86)

Favours restrictive tx Favours liberal tx