“TITRe”ing the Approach to Transfusions after Cardiac Surgery
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Cardiac surgery is a common, high-risk procedure performed on patients who are vulnerable to ischemic complications, including myocardial infarction, sepsis, stroke, and death. These patients often have myriad coexisting conditions that further raise their risk. Given the underlying clinical circumstances warranting cardiac surgery in the first place, the goal of maximizing oxygenation by maintaining adequate hemoglobin levels seems straightforward. Anemia is readily correctable by means of transfusion, which gives clinicians an immediate sense of satisfaction as they see hemoglobin levels rise and makes clinical sense. However, previous observational studies suggest that transfusion is associated with increased rates of infection, ischemic complications, costs, and death, although such observational studies are prone to confounding. Thus, the Society of Thoracic Surgeons (STS) has made the noncommittal recommendation that “transfusion is reasonable in most postoperative patients whose hemoglobin level is less than 7 g per deciliter.”

Given the paucity of evidence regarding the best possible transfusion levels, there is great variability in the use of transfusion after cardiac surgery. In an analysis from the STS database performed the year after the STS guidelines were published, the variability among hospitals in the use of transfusion was extraordinary, ranging from less than 5% to more than 90% among patients undergoing coronary-artery bypass graft surgery. To address this need for evidence and to establish the benefits of transfusion in postoperative patients with anemia, several clinical trials of alternative transfusion thresholds have been conducted. A Cochrane review indicated that only three randomized trials, together involving fewer than 1000 patients, reported that a more liberal transfusion strategy was of no benefit to clinical outcomes. In this issue of the Journal, Murphy and colleagues report the results of the Transfusion Indication Threshold Reduction (TITRe2) trial, which directly compared outcomes in 2007 patients randomly assigned to one of two transfusion strategies, one with a threshold of 9 g per deciliter (liberal strategy) and the other with a threshold of 7.5 g per deciliter (restrictive strategy). Not only does this study triple the size of the available database of patients who have participated in randomized trials, but it was exceedingly well conducted, with a good separation of transfusion rates (53.4% vs. 92.2%), a significant difference in postrandomization hemoglobin levels, excellent follow-up, and a good strategy for ensuring that patients were unaware of treatment assignments.

No significant difference between the transfusion strategies was observed in the primary outcomes of periprocedural ischemic complications, costs, or health status. The latter is particularly surprising given that the patient questionnaire used (the EuroQoL Group 5-Dimension Self-Report Questionnaire, or EQ-5D) explicitly inquires about difficulty with self-care, performance of usual activities, and mobility, all of which might be improved with higher hemoglobin levels. The study also reported no benefit in any of the prespecified subgroups, but these analyses examined only one risk factor at a time, and the authors chose not to model the heterogeneity of treatment benefit, which may have identified some groups of patient characteristics for which a better (or worse) outcome was associated with higher transfusion thresholds. Although a statistically significant difference in
90-day (but not 30-day) mortality was observed (mortality was higher with the restrictive strategy than with the liberal strategy), this finding was a secondary end point not presaged by any of the periprocedural complications. Despite the authors’ discussion of the theoretical advantages of more liberal transfusion policies and their call for further investigation, they have provided compelling evidence that there is no benefit (or harm) in providing transfusions for patients with hemoglobin levels higher than 7.5 mg per deciliter who are undergoing cardiac surgery, although there is the possibility of a longer-term survival benefit.

Given these data, how are the results to be interpreted, and what is the next step toward supporting the more rational use of blood transfusions in patients undergoing cardiac surgery? There is sure to be debate about the potential benefit of the liberal strategy in terms of mortality, even though this benefit was unanticipated rather than predicted and may not be replicable, given the failure to adjust for multiple comparisons and the possibility that its occurrence was due to chance alone. From my perspective, data such as these represent a great opportunity for debate among clinicians and for the development of a consensus on how to best care for postoperative patients. The center-level variability identified by the STS undoubtedly masks substantial variations in the ways in which different doctors within the same institution approach transfusion after surgery. Cardiac surgery departments should review the findings of the TITRe2 trial and decide which threshold they deem to be most appropriate for transfusion. Protocols should be developed to minimize deviation from the agreed-upon approach, and feedback should be provided to hold operators accountable to the institution’s standard of care. The STS could even provide feedback according to center and provider on the proportions of patients who received transfusions as a function of the nadir of their hemoglobin level. Having clinicians actively debate the evidence provided by TITRe2 investigators, creating transparent interpretations, developing protocols, and holding themselves accountable represent important steps toward improving the quality of cardiac surgery.

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