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EDITORIAL COMMENT

Real Dilemmas Regarding Blood Transfusion*

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In transfusing patients with red blood cells, physicians and surgeons aim to enhance the circulatory oxygen-carrying capacity that has been compromised due to blood loss or a hematological disorder. In general, bleeding and transfusion strongly correlate with adverse outcomes in patients undergoing percutaneous coronary intervention (PCI) (1,2). Understandably, these negative reports have culminated in a higher threshold among physicians to prescribe blood transfusion (3). Nonetheless, there is considerable variation in transfusion practices in U.S. hospitals, and current transfusion guidelines reflect the uncertainty stemming from the available evidence (3,4). The field of interventional cardiology is no exception to this, and the ideal place of blood transfusion around the time of PCI is unclear.

SEE PAGE 436

In this issue of *JACC: Cardiovascular Interventions*, Kwok et al. (5) describe a meta-analysis of 19 studies and 54,000 transfusion events in 2,258,711 patients undergoing PCI, for clinical outcomes of major adverse cardiac events and death at any time point. Follow-up varied from in-hospital to 5 years. In the absence of patient-level data, the authors report the crude mortality at any time point in transfused patients (based on available data from 8 of 19 studies) at 12.6% versus 1.2% in nontransfused patients. Likewise, the crude major adverse cardiac events rate (based on available data from 5 of 19 studies) was 17.4% versus 3.1% in nontransfused patients. The primary limitation with a meta-analysis on this subject is the inherent difficulty in separating mortality resulting from bleeding, particularly in the very early time frame of the index hospitalization. In an attempt to address this issue, the authors provide mortality outcomes adjusted for baseline hematocrit (2 studies), baseline anemia (5 studies), and bleeding based on a hematocrit drop (3 studies). The adverse influence of transfusion on mortality remained independently of these factors. Furthermore, the authors also show that the mortality risk increased with the number of units transfused, particularly for patients receiving more than 3 units. Correspondingly, they emphasize the importance of bleeding avoidance strategies to preclude the need for blood transfusion in the first place.

However, are these statistical adjustments able to adequately account for the propensity of physicians to transfuse patients for acute or life-threatening reasons? Is any statistical adjustment adequate to demonstrate that transfused patients would in fact have survived bleeding in the absence of transfusion had they been managed with a more conservative approach instead? The answer to both of these questions is "no" because these subjects are deeply clinical and not purely statistical, often related to variables that are not collected and analyzed in research databases. The same holds true for the decision of how many units to transfuse and how this may be reflected as a gradient of risk and benefit; this variable was not comprehensively analyzed by Kwok et al. (5) (as only 2 of 19 studies provide relevant data). Additionally, the potential outcome differences with whole blood versus packed red cell transfusion versus transfusion of other blood substitutes warrant future investigation.

The risks of transfusion are related not only to transmission of infections but also to transfusion reactions, acute lung injury, circulatory overload, and immunosuppression (6). The mechanism by which

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TABLE 1 Patient Classification Based on Circulatory Oxygen Delivery Supply-Demand Mismatch

Supply-Demand Mismatch	Clinical Features	Transfusion Indication	Risk-Benefit Ratio
Hyperacute	Symptomatic, acute blood loss, hemodynamically unstable	Life threatening	Risk of death > risk of transfusion
Acute/subacute	Recent slow blood loss or symptomatic chronic anemia (fatigue), hemodynamically stable	Intermediate	Risk of clinical deterioration ≅ risk of transfusion
Chronic	Asymptomatic chronic anemia	Elective	Risk of clinical deterioration < risk of transfusion

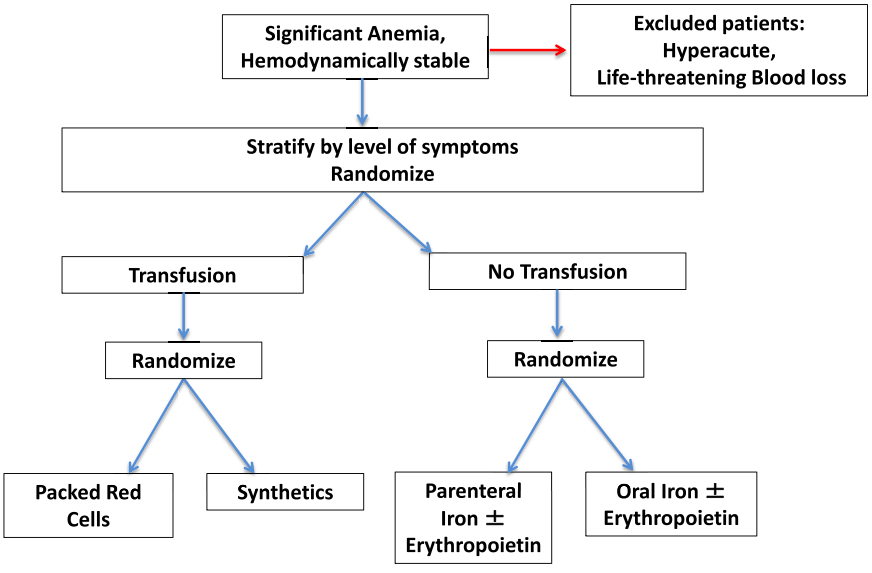
transfusion may cause cardiovascular adverse events is thought to be by reducing circulating levels of nitric oxide and subsequently reduced circulatory oxygen-carrying capacity, development of hyperdynamic circulatory physiology (and high output heart failure in certain instances), an increase in platelet reactivity and proportion of procoagulant proteins, impaired small-vessel vasodilation, and deformation of red cell shapes in storage resulting in small-vessel plugging and ischemia (7).

In the study by Sherwood et al. (3), patients transfused for hemoglobin ≤10 g/dl and bleeding derived the greatest benefit, whereas transfusion for hemoglobin >10 g/dl was associated with adverse outcomes irrespective of bleeding. Intuitively, patients who benefit the most from blood transfusion also comprise the sickest cohort with greater comorbidities and hemodynamic compromise in the context of either acute blood loss or chronic anemia. No single laboratory value (hematocrit or hemoglobin included) can therefore be an absolute "automatic" trigger for transfusion. Thus, the pertinent question remains: Who is eligible to receive a transfusion and how could a prospective clinical trial shed light on this complex subject? Earlier studies have produced inconclusive results (8,9).

Although Kwok et al. (5) recommend that physicians should "minimize" transfusions, there are currently no well-established ways to do so in the acute in-hospital scenario. To better understand the clinical decision-making process of whom to transfuse, one may derive a patient classification based on the severity of circulatory oxygen delivery supply-demand mismatch (Table 1). Of these, the intermediate group deserves closer attention: given that these are hemodynamically stable patients, could alternatives to transfusion (e.g., synthetic red cell substitutes, iron supplementation, erythropoietin) be suitable options?

Data on red cell substitutes such as recombinant hemoglobin, hemoglobin-based oxygen carriers, and fluorocarbon-based oxygen carriers is evolving, but currently, these oxygen-carrying compounds are not available for clinical use. In contrast, physicians have long-term experience with oral iron supplementation, which has proved to be safe, inexpensive, and effective. The gastrointestinal side effects of oral iron and

FIGURE 1 Potential Trial Profile



the ensuing issues with adherence may be avoided with the use of parenteral iron or erythropoietin.

Additionally, the question of whether transfusion is truly harmful can only be answered in the context of a well-designed, randomized, controlled trial. Such a trial would first of all exclude patients who would not survive without immediate transfusion and then randomize the remaining patients with a comparable level of anemia to receive a transfusion-based strategy or not. The patients not receiving transfusion could be further randomized to receive alternative forms of therapy (**Figure 1**). The main study outcomes of interest are mortality and bailout transfusion.

Although the meta-analysis by Kwok et al. (5) serves as a stark reminder of the potential adverse prognostic effects of transfusion, the wait continues for the ideal prospective, randomized trial that will definitively alter our practice and allay our fears. Until then, clinicians should continue to adopt best practice with prudent use of transfusion based on the severity of patient presentation. More importantly, it is paramount that a bleeding avoidance strategy (with upfront risk stratification as well as active procedural measures) be meticulously adopted in all invasive procedures to prevent significant acute anemia. This may be the single most important take-home message from the present comment!

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REFERENCES

1. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol 2005;96:1200–6.

2. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004;292:1555–62.

3. Sherwood MW, Wang Y, Curtis JP, Peterson ED, Rao SV. Patterns and outcomes of red blood cell transfusion in patients undergoing percutaneous coronary intervention. JAMA 2014;311:836–43.

4. Yang X, Alexander KP, Chen AY, et al., CRUSADE Investigators. The implications of blood transfusions for patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. J Am Coll Cardiol 2005;46:1490–5.

5. Kwok CS, Sherwood MW, Watson SM, et al. Blood transfusion after percutaneous coronary intervention and risk of subsequent adverse outcomes: a systematic review and meta-analysis. J Am Coll Cardiol Intv 2015;8:436–46.

6. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA 2010; 304:1559–67.

7. Doyle BJ, Rihal CS, Gastineau DA, Holmes DR Jr. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. J Am Coll Cardiol 2009;53:2019–27.

8. Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J 2013;165:964–71.e1.

9. Cooper HA, Rao SV, Greenberg MD, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). Am J Cardiol 2011;108:1108–11.

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