Liberal *versus* Restrictive Erythrocyte Transfusion Algorithms and Perioperative Outcomes: Statistical Significance and Pulmonary Complications

To the Editor:

It was with great interest that I read the recent meta-analysis by Hovaguimian and Myles[1] and the accompanying editorial by Beattie and Wijeysundera[2] regarding liberal *versus* restrictive erythrocyte transfusion triggers for surgical patients and those admitted to acute care environments. Their efforts in addressing the importance of clinical context (*e.g.*, surgical type, comorbid disease) when evaluating transfusion algorithms should be congratulated. There are, however, several additional items deserving of mention.

First, Hovaguimian and Myles[1] state that in those undergoing cardiovascular procedures, restrictive transfusion strategies increased the risk of mortality (risk ratio [RR], 1.39; 95% CI, 0.95 to 2.04) and events reflecting inadequate oxygen supply (RR, 1.09; 95% CI, 0.97 to 1.22). This statement is also highlighted in the section titled "What This Article Tells Us That Is New" and in the "Perioperative and Acute Care Transfusion Strategies" figure by Wanderer and Rathmell.[3] However, an RR crossing a threshold of 1 does not imply statistical significance and should be labeled accordingly as a nonsignificant result.

A second thing to consider when interpreting the study results is that transfusion-related pulmonary complications, including transfusion-related acute lung injury and transfusion-related circulatory overload, were not included in the analysis. As these remain the leading causes of transfusion-related morbidity and mortality and are likely more prevalent than clinically diagnosed or reported,[4,5] readers should be mindful of their exclusion and the potential implications with more liberal transfusion practices.

Again, I congratulate the authors on their tremendous contribution to this important perioperative topic. While there is much work to be done, this is a large step forward.

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Competing Interests

The author declares no competing interests.

Matthew A. Warner, M.D., Mayo Clinic, Rochester, Minnesota. warner.matthew@mayo.edu

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Rephrasing the Question of Whether Blood Transfusion Increases Risk of Adverse Outcomes after Cardiac Surgery

To the Editor:

Some studies[1,2] suggest a dose-dependent association of erythrocyte transfusion with postoperative morbidity, hospital stay, and early and late mortalities.[1,2] However, other studies[3,4] suggest that benefits of erythrocyte transfusion outweigh the risks. Recently, in a meta-analysis, using a prespecified context-specific approach and stratifying patients by characteristics and clinical settings, Hovaguimian and Myles.[5] demonstrated that restrictive transfusion strategies were associated with an increased risk of complications in high-risk patients with major surgery. Although the evidence is robust, a limitation should be noticed. Studies[3–5] usually dichotomize patients based on restrictive or liberal trigger, but hemoglobin levels within each of these groups can vary widely. As a result, hemoglobin concentration may be higher in some patients in the restrictive group than in the liberal group. Therefore, studies to stratify patients based on actual hemoglobin levels are needed. It would be nice if Hovaguimian and Myles.[5] could provide the criteria for categorizing the restrictive and liberal groups, and if their associated hematocrits in a supplemental table were added to their article. To nullify its interference on the outcome, blood transfusion should be used as a confounding factor in analyzing the effect of actual hemoglobin levels on outcome. To be robust, such subgroup analyses require adequate statistical power, so future studies should be large and preferably involving multiple centers. Such studies

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would be an important step toward personalized blood transfusion. The meta-analysis by Hovaguimian and Myles.[5] has made important progress toward this goal.

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Yan Qiu, M.D., Changwei Chen, M.M., Lei Du, M.D. Sichuan University, Chengdu, Sichuan, China (L.D.). dulei@scu.edu.cn

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In Reply:

We would like to thank Drs. Warner, Qiu, and colleagues for their valuable inputs regarding our systematic review.[1]

Dr. Warner rightly points out that CIs crossing the equality line correspond to nonsignificant results and suggests that the wording of our findings may have failed to reflect this lack of statistical significance. Although we agree that "borderline" results (*i.e.*, where one end of the CI just overlaps the null value) should be interpreted with caution, it is worth to note that the Cochrane Collaboration discourages formulations such as "nonsignificant" or "not statistically significant," since these terms are commonly misinterpreted as an indication that "the intervention has no effect."[2] Although some authors would describe such findings as a "tendency" or a "trend" toward an effect, we opted for a more moderate wording (*i.e.*, using formulations such as "seemed to" or "possible increase"), as suggested elsewhere.[3] As for the interpretation of borderline findings, it might help to remember that the true effect is more likely to lie around the point estimate (*i.e.*, around the risk ratio) than at the margins of the CI.[3] The traditionally significant $P < 0.05$ may well be suitable for testing efficacy, but CIs rather than hypothesis testing are preferred when testing safety, equivalence, or noninferiority.[4]

A second concern of Dr. Warner's is that our analysis did not include transfusion-related pulmonary complications, which may have resulted in an underestimation of potential harmful effects associated with liberal transfusion strategies. The rationale behind the exclusion of pulmonary complications was mainly related to the quality of the reported data in the original trials: in most studies, there was no distinction between transfusion-related events (such as acute lung injury or pulmonary edema due to circulatory overload) and events secondary to inadequate oxygen supply, such as left-sided heart failure due to myocardial infarction. Including outcomes with opposite etiologies could have resulted in a dilution of the intervention effects.

Qui *et al.* highlight a potential issue encountered in trials addressing transfusion strategies, *i.e.*, the fact that heterogeneity in hemoglobin levels within individual treatment groups may potentially dilute treatment effects. Their concern is based on the assumption that patients assigned to a restrictive strategy who received blood transfusions would eventually have the same (posttransfusion) hemoglobin levels as those from the liberal group. A similar issue may occur if some patients assigned to a restrictive strategy never developed anemia (*i.e.*, perioperative hemoglobin levels maintained in the range of the liberal group). This could indeed lead to an underestimation of adverse events, since only a small fraction of patients assigned to a restrictive strategy would truly be at risk of developing anemia-related complications. To address this potential source of heterogeneity, Qui *et al.* propose to stratify the analysis according to hemoglobin levels (see table 1, which provides a detailed description of hemoglobin levels across studies). Although the idea is very elegant, such exploratory analyses should be carried out with caution, since the quality of the reported data remains limited (data not extractable, heterogeneity in the frequency or duration of hemoglobin measurements, or use of inadequate statistics [*e.g.*, Student's *t* test for data correlated over time]). It is also worth noting that the randomized design used in the original studies tends to protect from bias and residual confounding. We certainly agree that large, well-designed randomized controlled trials are still needed to fully explore the effects of transfusion strategies and eagerly await the results of the ongoing Transfusion Requirements in Cardiac Surgery-III trial (NCT 02042898).

Competing Interests

The authors declare no competing interests.

Frédérique Hovaguimian, M.D., M.Clin.Res.Meth., Paul S. Myles, M.B.B.S., M.P.H., M.D., F.C.A.I., F.A.N.Z.C.A., F.R.C.A., F.A.H.M.S. Division of Anesthesiology, University Hospital of Zurich, Zurich, Switzerland (F.H.). frederique.hovaguimian@usz.ch