LESS IS MORE

Association of Blood Transfusion With Increased Mortality in Myocardial Infarction

A Meta-analysis and Diversity-Adjusted Study Sequential Analysis

Saurav Chatterjee, MD; Jørn Wetterslev, MD, PhD; Abhishek Sharma, MD; Edgar Lichstein, MD; Debabrata Mukherjee, MD, MS

Background: The benefit of blood transfusion in patients with myocardial infarction is controversial, and a possibility of harm exists.

Methods: A systematic search of studies published between January 1, 1966, and March 31, 2012, was conducted using MEDLINE, EMBASE, CINAHL, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials databases. English-language studies comparing blood transfusion with no blood transfusion or a liberal vs restricted blood transfusion strategy were identified. Two study authors independently reviewed 729 originally identified titles and abstracts and selected 10 for analysis. Study title, follow-up period, blood transfusion strategy, and mortality outcomes were extracted manually from all selected studies, and the quality of each study was assessed using the strengthening Meta-analysis of Observational Studies in Epidemiology checklist.

Results: Studies of blood transfusion strategy in anemia associated with myocardial infarction were abstracted, as well as all-cause mortality rates at the longest available follow-up periods for the individual studies. Pooled effect estimates were calculated with random-effects models. Analyses of blood transfusion in myocardial infarction revealed increased all-cause mortality associated with a strategy of blood transfusion vs no blood transfusion during myocardial infarction (18.2% vs 10.2%) (risk ratio, 2.91; 95% CI, 2.46-3.44; P < .001), with a weighted absolute risk increase of 12% and a number needed to harm of 8 (95% CI, 6-17). Multivariate meta-regression revealed that blood transfusion was associated with a higher risk for mortality independent of baseline hemoglobin level, nadir hemoglobin level, and change in hemoglobin level during the hospital stay. Blood transfusion was also significantly associated with a higher risk for subsequent myocardial infarction (risk ratio, 2.04; 95% CI, 1.06-3.93; P = .03).

Conclusions: Blood transfusion or a liberal blood transfusion strategy compared with no blood transfusion or a restricted blood transfusion strategy is associated with higher all-cause mortality rates. A practice of routine or liberal blood transfusion in myocardial infarction should not be encouraged but requires investigation in a large trial with low risk for bias.


T HROMBOLYSIS, ANTICOAGULATION, and antiplatelet drugs have revolutionized the therapeutic approach to acute coronary syndrome, with significant improvements in clinical outcomes.1-7 However, such therapy may concomitantly increase the risk for bleeding, leading to the development of anemia during the hospital stay and to subsequent blood transfusion.8-10 Despite advancement in reperfusion therapy, patients with low hemoglobin levels continue to have more postoperative complications and higher mortality rates.11-14 and the presence of anemia in acute myocardial infarction has been associated with worse prognosis.15-19

In patients with significant coronary occlusion, low oxygen-carrying capacity secondary to anemia may further compromise the myocardial oxygen supply, worsening the ischemia. By increasing the oxygen-carrying capacity, blood transfusion might be beneficial, especially in anemia secondary to acute blood loss.
However, inappropriate blood transfusion may lead to circulatory overload and increased thrombogenicity, which can worsen the clinical outcomes. Furthermore, elevated hemoglobin levels have been shown to be associated with increased mortality.11,14 In post hoc analyses of a multicenter randomized controlled trial, Hébert et al20 reported no mortality benefits of liberal blood transfusion in maintaining hemoglobin levels of at least 10 mg/dL in critically ill patients with cardiovascular disease. However, because patients receiving blood transfusion tend to be older and have advanced disease and more associated comorbid conditions, these variables may act as confounding factors when determining mortality and morbidity rates.21-23 Because of conflicting results reported in various investigations, the benefits and harm of blood transfusion in myocardial infarction remain controversial. In the present meta-analysis, we systematically evaluated the potential risk-benefit of blood transfusion in patients with myocardial infarction.

DATA SOURCES AND SEARCHES

A systematic search of studies published between January 1, 1966, and March 31, 2012, was conducted using MEDLINE, EMBASE, CINAHL, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials databases. Studies were identified that evaluated mortality outcomes and compared blood transfusion with no blood transfusion or a liberal vs restricted blood transfusion strategy. The search terms used were transfusion, myocardial infarction, and mortality. Pertinent trials were also searched for in clinicaltrials.gov and in proceedings from major international cardiology meetings (American College of Cardiology, American Heart Association, European Society of Cardiology, and Transcatheter Cardiovascular Therapeutics). References of original and review articles were cross-checked. Study selection was performed by 2 of us independently (S.C. and A.S.), with disagreement resolved by consensus among all the authors. Citations were first reviewed at the title and abstract level. Studies that were short-listed were then retrieved in full text.

STUDY SELECTION

Studies were considered suitable for inclusion if they met the following criteria: (1) they reported the effect of blood transfusion or a liberal blood transfusion strategy (blood transfusion levels at which there was no blood transfusion in the comparator arm) on mortality, (2) they had a comparator group with no blood transfusion or a restricted blood transfusion strategy and identified a mean hemoglobin level for both groups, and (3) they used statistical methods to minimize confounding between the groups (matching, covariate adjustment, or propensity-based adjustment). Our search was restricted to studies in the English language. Full texts of 16 potentially relevant articles were independently reviewed by at least 2 of us (S.C. and A.S.) to establish eligibility according to the inclusion criteria. To avoid confounding, we excluded studies assessing the effect of transfusion of components other than whole blood or red blood cells.

DATA EXTRACTION AND QUALITY ASSESSMENT

Data abstraction and study appraisal were performed by 2 of us (S.C. and A.S.) independently, with disagreement resolved by consensus among all authors. Key study and patient characteristics were extracted, including the outcomes of all-cause mortality and myocardial infarction reported at the longest available follow-up periods. Prespecified subgroup analyses were planned for patients with ST-segment elevation myocardial infarction (STEMI) and for patients with a hematocrit of less than 30% (to convert hematocrit to a proportion of 1.0, multiply by 0.01).

Data analyses were performed using commercially available software (RevMan 5.1 [Cochran IMS], TSA version 0.9 [Copenhagen Trial Unit], and STATA version 11 [StataCorp LP]). Outcomes were assessed using random-effects models to exclude the presence of significant heterogeneity (evaluated and quantified with the I² statistic), and then pooled random-effects risk ratios (RRs [95% CIs]) were calculated following the method by DerSimonian and Laird.

The quality of the studies was assessed on the basis of elements from the strengthening Meta-analysis Of Observational Studies in Epidemiology checklist for cohort studies. We did not assign a threshold for study inclusion. All the studies included in the analyses met at least 15 variables in the checklist.

DATA SYNTHESIS AND ANALYSIS

When available, odds ratios (ORs) reported in the articles were used to determine event rates, and unadjusted ORs (95% CIs) were used preferentially over adjusted ORs to avoid biases from different types of adjustments in the various studies.21 If ORs were not reported, we calculated them using the event and sample size frequencies. If frequencies were not given, ORs were estimated from percentages and were rounded to the nearest integer. If any cell had a 0 count, ORs were calculated by adding 0.5 to all cell counts from the study to avoid division by 0. The I² statistic was used to examine the heterogeneity of effect sizes in the overall aggregations: I² of less than 25% indicates low heterogeneity, and I² exceeding 75% indicates high heterogeneity. Publication bias was evaluated using a combination of a funnel plot–based method, the regression test by Egger, and the trim-and-fill method to estimate the number of missing studies and to calculate a corrected OR as if these studies were present. The effect of potential outliers was examined by comparing the pooled estimate with estimates obtained after iterations using k minus 1 findings (each study is left out, and the effect is restimated), where k is the number of studies. Studies were treated as statistical outliers if the k minus 1 estimate produced a 95% CI that did not overlap with the 95% CI of the aggregated estimate. P < .05 was considered statistically significant.

STUDY SEQUENTIAL ANALYSIS

In a single study, interim analyses increase the risk for type I error. To avoid an increase of overall type I error, monitoring boundaries can be applied to decide whether a single study could be terminated early because the P value is sufficiently small. Because no reason exists why the standards for a meta-analysis should be less rigorous than those for a single study, analogous study sequential monitoring boundaries can be applied to meta-analysis as study sequential analysis.25-28 Cumulative meta-analyses of studies are at risk for producing random errors because of few data12 and repetitive testing of accumulating data and because the requirement for the amount...
of information analogous to the sample size of a single optically powered clinical study might not be met.25,26

The underlying assumption for study sequential analysis is that significance testing and calculation of the 95% CIs are performed each time a new study is published. Study sequential analysis depends on the quantification of the required amount of information. In this context, the smaller the required amount is, the more lenient is the trial sequential analysis and the more lenient are the criteria for significance.25,26 A required diversity ($D^2$)–adjusted information size was calculated, with $D^2$ being the relative variance reduction when the meta-analysis model is changed from a random-effects model to a fixed-effects model.28 $D^2$ is the percentage of the variability between trials to the within-trial variance and constitutes the percentage of the variability between trials to the total variance in the meta-analysis.

Study sequential analysis was performed with an intent to maintain an overall 5% risk for type I error, which is the standard in most meta-analyses and systematic reviews, and we calculated the required information size (ie, the meta-analysis information size needed to detect or reject an intervention effect of a 20% relative risk increase for harm, with a risk for type II error of 10%, at a power of 90%).25,26 Study monitoring boundaries were constructed with the conventional test boundary and using methods by O’Brien and Fleming.29

RESULTS

Our MEDLINE search returned 720 studies. After elimination of duplicate results, EMBASE, Cochrane Central Register of Controlled Trials, and the other registries returned 9 additional studies, leaving 729 studies for evaluation. Through a review of titles and abstracts, 705 studies were rejected for relevance. The remaining 24 articles were reviewed and assessed for satisfaction of the inclusion and exclusion criteria. Ten studies that met all criteria were included in this analysis (Figure 1).

STUDY CHARACTERISTICS

Studies were fairly homogeneous for inclusion and exclusion criteria, with a few key differences. These results are summarized in Table 1.

STUDY QUALITY

We used the published strengthening Meta-analysis Of Observational Studies in Epidemiology40 checklist to select the studies for this review (Figure 1). The included studies reported statistically adjusted effect estimates for the outcome of mortality. Among 10 studies included, all except one (low-bias risk) were intermediate-bias risk studies as assessed by the Newcastle-Ottawa Scale41 for quality assessment risk evaluation of adequacy of selection, comparability, and outcomes assessment for individual studies (Table 2).

PRIMARY OUTCOME

We identified 10 studies, including 203,665 study participants, that met our inclusion and exclusion criteria. Only one study31 was a randomized trial; the others were observational studies. Analyses of blood transfusion in myocardial infarction revealed increased all-cause mortality associated with a strategy of blood transfusion vs no blood transfusion during myocardial infarction (18.2% vs 10.2%) (RR, 2.91; 95% CI, 2.46-3.44; $P = .001$), with a weighted absolute risk increase of 12% ($P = .001$) and a number needed to harm of 8 (95% CI, 6-17). The risk remained unchanged even on exclusion of the only randomized study.31 Pooled analysis using adjusted rates of mortality instead of the actual number of events yielded an effect largely similar to that of the primary analysis (eFigure 1; http://www.jamainternalmed.com). However, the mortality risk with blood transfusion was found to be mitigated when restricted to studies that included patients with STEMI (RR, 2.89; 95% CI, 0.54-15.58; $P = .22$) and patients with a baseline hematocrit of less than 30% (RR, 1.72; 95% CI, 0.39-7.63; $P = .47$) (eFigure 2 and eFigure 3). Multivariate meta-regression were performed using the log of the RR as the dependent variable and adjusting for the following variables as covariates: follow-up period, history of bleeding, baseline creatinine level, baseline hemoglobin level, nadir of hemoglobin level, and change in hemoglobin level during the hospital stay, as well as the use of glycoprotein IIb or IIa, thrombolytics, or antiplatelets. The meta-regression showed that blood transfusion is associated with higher mortality after adjustment for all these variables. However, we could not adjust for demographic variables in the multivariate model because we did not have patient-level data. Significant heterogeneity was noted among the outcomes ($I^2 = 93%$) (Figure 2). A sensitivity analysis performed by sequentially excluding one study at a time and performing a cumulative evaluation identified no single study as the source of heterogeneity. No significant publication bias was noted among the out-
comes with visual inspection of the funnel plot, the regression test by Egger ($P = .40$), or with trim-and-fill adjustment ([Figure 3]).

**STUDY SEQUENTIAL ANALYSIS**

The required diversity-adjusted information size ($D^2 = 97\%$) for the outcome of all-cause mortality was calculated based on analyzing a 10.2% proportion of events in the no blood transfusion or a restricted blood transfusion strategy group and evaluating for a 20% relative risk increase with blood transfusion or a liberal blood transfusion strategy at $\alpha = .05$ and $\beta = .10$ (90% power). The cumulative $z$ curves (calculated with both the conventional test boundary and the methods by O’Brien and Fleming)$^{29}$ crossed the study sequential monitoring boundary of harm, suggesting firm evidence for a 20% relative risk increase with blood transfusion or a liberal blood transfusion strategy compared with no blood transfusion or a restricted blood transfusion strategy ([Figure 4]). We also constructed a L’Abbé plot$^4$ and a small study regression graph to avoid a possible error with the effect of inclusion of small studies on the composite outcome.

**SECONDARY OUTCOME**

Blood transfusion was also significantly associated with a higher risk for subsequent myocardial infarction (RR, 2.04; 95% CI, 1.06-3.93; $P = .03$). Significant heterogeneity was present for this outcome ($I^2 = 98\%$) as well. No significant publication bias was detected ([Figure 5]).

**COMMENT**

Several important clinical findings emerged from our systematic review and meta-analysis. First and foremost, a significant mortality risk is demonstrated with a policy of liberal blood transfusion in patients with myocardial infarction, especially in those patients without STEMI or with a hematocrit of less than 30%, bringing to light a real possibility of harm with the practice of routine blood transfusion in patients with myocardial infarction. The mortality outcome was associated with statistically significant heterogeneity, likely associated with concomitant therapies, heterogeneity in the patient population, and clinical settings (which could not be adjusted for in

### Table 1. Key Features of Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Myocardial Infarction Types</th>
<th>No. of Patients</th>
<th>Mean Patient Age, y</th>
<th>Male Sex, %</th>
<th>Follow-up Period, mo</th>
<th>Baseline Hemoglobin Level, g/dL</th>
<th>Baseline Hematocrit, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronson et al,2008</td>
<td>STEMI, non-STEMI</td>
<td>2326</td>
<td>69</td>
<td>57</td>
<td>6</td>
<td>11.8</td>
<td>...</td>
</tr>
<tr>
<td>Cooper et al,2011</td>
<td>STEMI, non-STEMI</td>
<td>45</td>
<td>76.4</td>
<td>48</td>
<td>1</td>
<td>26.9</td>
<td>...</td>
</tr>
<tr>
<td>Jani et al,2007</td>
<td>STEMI, non-STEMI</td>
<td>4623</td>
<td>70.21</td>
<td>46.66</td>
<td>NA</td>
<td>10.47</td>
<td>...</td>
</tr>
<tr>
<td>Jolicoeur et al,2009</td>
<td>STEMI</td>
<td>5188</td>
<td>71</td>
<td>47</td>
<td>3</td>
<td>12.9</td>
<td>...</td>
</tr>
<tr>
<td>Nikolsky et al,2009</td>
<td>STEMI, non-STEMI</td>
<td>2060</td>
<td>67.5</td>
<td>47.6</td>
<td>12</td>
<td>13.1</td>
<td>...</td>
</tr>
<tr>
<td>Rao et al,2004</td>
<td>STEMI, non-STEMI</td>
<td>24112</td>
<td>68.9</td>
<td>58.5</td>
<td>1</td>
<td>...</td>
<td>39.9</td>
</tr>
<tr>
<td>Shishehbor et al,2009</td>
<td>STEMI</td>
<td>948</td>
<td>67</td>
<td>59</td>
<td>12</td>
<td>13.9</td>
<td>...</td>
</tr>
<tr>
<td>Singla et al,2007</td>
<td>Non-STEMI</td>
<td>370</td>
<td>70</td>
<td>99</td>
<td>1</td>
<td>8.91</td>
<td>...</td>
</tr>
<tr>
<td>Wu et al,2001</td>
<td>STEMI, non-STEMI</td>
<td>78974</td>
<td>77.8</td>
<td>45.9</td>
<td>1</td>
<td>Graded levels</td>
<td>...</td>
</tr>
<tr>
<td>Yang et al,2005</td>
<td>Non-STEMI</td>
<td>85111</td>
<td>73</td>
<td>52.9</td>
<td>NA</td>
<td>...</td>
<td>35</td>
</tr>
</tbody>
</table>

Abbreviations: Ellipsis, not known; NA, not applicable (in-hospital mortality rates reported); STEMI, ST-segment elevation myocardial infarction.

SI conversion factors: To convert hematocrit to a proportion of 1.0, multiply by 0.01; to convert hemoglobin level to grams per liter, multiply by 10.0.

### Table 2. Newcastle-Ottawa Scale of Bias Risk for Individual Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Adequacy of Selection</th>
<th>Outcomes Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronson et al,2008</td>
<td>** * * * * *</td>
<td>* * * * *</td>
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<tr>
<td>Cooper et al,2011</td>
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<td>Jani et al,2007</td>
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<td>Jolicoeur et al,2009</td>
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<td>Nikolsky et al,2009</td>
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<td>Rao et al,2004</td>
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<td>Shishehbor et al,2009</td>
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<td>Singla et al,2007</td>
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<tr>
<td>Wu et al,2001</td>
<td>** * * * * *</td>
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<tr>
<td>Yang et al,2005</td>
<td>** * * * * *</td>
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</tbody>
</table>

All studies demonstrated that the outcome of interest was not present at the start of the study. Asterisks are the star ratings per the Newcastle-Ottawa Scale; * and ** indicates the highest ratings for these categories.
In our analysis because of the unavailability of patient-level data, but might also be due to the precision of the large observational studies, conferring an artificially high $I^2$ statistic. Also notable was the fact that the results remained unchanged with meta-regression adjusting for certain variables, including the follow-up period, a history of bleeding, baseline hemoglobin level, nadir of hemoglobin level, and change in hemoglobin level during the hospital stay, indicating a significant risk for blood transfusion over and above that associated with bleeding (and anemia) in myocardial infarction.47,48 The single randomized trial included in our analysis, the Conservative Versus Liberal Red Cell Transfusion in Acute Myocardial Infarction Trial,31 had a small sample size and was underpowered to make any relevant conclusions regarding clinically important intervention effects. We attempted to overcome the risk for increased random error due to sparse data and repetitive testing in our analysis by constructing study sequential monitoring boundaries, and our results indicated that random error was not the greatest risk in our meta-analysis. However, confounding by indication may be an important problem because the patients liberally transfused may also be the patients with the most serious disease and at the greatest risk for mortality as estimated by prognostic factors at baseline independent of the interventions subsequently used. We also drew a regression plot to avoid overestimating the effects of small studies on the overall outcomes. Our 95% CIs were narrow, with a large sample size, indicating at least a possibility of real harm with liberal and indiscriminate blood transfusion practices.

Of even greater concern was our finding of a significantly greater risk for myocardial reinfarction with blood transfusion. This finding seems to conform to recent findings of detrimental effects on platelet aggregation with blood transfusion.44 Overall, our findings are consistent with recent recommendations by the AABB (formerly the American Association of Blood Banks)49 and in a prior Cochrane review50 for a restrictive blood transfusion policy in critically ill patients. Our analysis attempts to address the lacuna in the knowledge about blood transfusion practices among patients with acute coronary syndromes as expressed in the aforementioned guidelines by providing an updated meta-analysis on the topic in the absence of an adequately powered randomized trial.

We also found that the risks for blood transfusion became mitigated during our subgroup analyses in patients with STEMI and in patients with a baseline hematocrit of less than 30%. This suggests a future direction of further research in identifying specific subgroups that may accrue a real benefit from blood transfusion (ie, are less with) transfusion; when they are to the right of the midline, representing a risk ratio of 1, it means that the risks of dying favor (ie, are less with) transfusion; when they are to the left of the midline, representing a risk ratio of 1, it means that the risks of dying are comparable for transfusion and the comparators.

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**Figure 2.** Risk for all-cause mortality with liberal blood transfusion. M-H indicates Mantel-Haenszel. Diamond indicates the overall summary estimate for the analysis (width of the diamond represents the 95% CI); boxes, the weight of individual studies in the pooled analysis; whiskers, the 95% CIs; when they are to the left of the midline, representing a risk ratio of 1, it means that the risks of dying favor (ie, are less with) transfusion; when they are to the right of the midline, representing a risk ratio of 1, it means that the risks of dying are comparable for transfusion and the comparators.

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**Figure 3.** Trim-and-fill adjustment for assessment of publication bias. RD indicates risk difference.
We also restricted our search to English-language sources.

Our study method also had several strengths. The magnitude and consistency of the observed effects for blood transfusion in myocardial infarction make the likelihood of random error affecting this observation unlikely. Moreover, we rigorously controlled for publication bias and used random-effects models, which are not be considered. We also restricted our search to English-language sources.

Our study method also had several strengths. The magnitude and consistency of the observed effects for blood transfusion in myocardial infarction make the likelihood of random error affecting this observation unlikely. Moreover, we rigorously controlled for publication bias and used random-effects models, which are
generally better suited when studies are gathered only from the published literature. We also evaluated for the validity of our mortality findings by constructing study sequential monitoring boundaries and inferred that our results indicated a firm evidence of harm with a practice of liberal blood transfusion in myocardial infarction.

In conclusion, this meta-analysis provides evidence that rates of all-cause mortality and subsequent myocardial infarction are significantly higher in patients with acute myocardial infarction receiving blood transfusion. Additional outcomes data are needed from randomized clinical trials that investigate important outcomes with adequate sample size and with low risk for bias.

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Correspondence: Saurav Chatterjee, MD, Division of Cardiology, Department of Medicine, Brown University, and Providence Veterans Affairs Medical Center, 40 Roger Williams Green, Providence, RI 02904 (sauravchatterjeemd@gmail.com).

Author Contributions: Dr Chatterjee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Chatterjee, Wettlerslev, and Lichstein. Acquisition of data: Chatterjee and Sharma. Analysis and interpretation of data: Chatterjee, Wettlerslev, Lichstein, and Mukherjee. Drafting of the manuscript: Chatterjee, Wettlerslev, and Sharma. Critical revision of the manuscript for important intellectual content: Chatterjee, Wettlerslev, Lichstein, and Mukherjee. Statistical analysis: Chatterjee and Wettlerslev. Administrative, technical, and material support: Chatterjee and Lichstein. Study supervision: Wettlerslev, Lichstein, and Mukherjee.

Conflict of Interest Disclosures: None reported.


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Here We Go Again—Blood Transfusion Kills Patients?

D o blood transfusions kill more patients with an acute myocardial infarction than anemia? Chatterjee and colleagues would have you believe that they do. We remain unconvinced.

In reviewing the study, we first wondered whether the authors asked the right question. As physicians, we believe that profound anemia is life threatening, and as a consequence transfusions in many patients are life saving. Therefore, we expected that more nuanced, clinically relevant questions would be addressed.

For instance, we should be asking: “What is a safe hemoglobin transfusion trigger in most patients?” Or, “Which patients experiencing an acute myocardial infarction are at greater risk for transfusions or anemia than others?”

In a synthesis of the literature focused on the issue of harms, the authors summarized results from 10 studies that included a total of 203,665 patients. The systematic review identified only one small randomized trial and went on to conduct a meta-analysis of observational studies that compared patients who underwent transfusion with patients who did not undergo transfusion. Chatterjee and colleagues documented that 18.2% of patients transfused died compared with 10.2% of patients not transfused. This represented a weighted absolute risk increase of 12% or a number needed to harm of 8.

Clinically important information is missing from this analysis. Perhaps most important, the investigators did not adequately consider the hemoglobin concentration before transfusion. The authors did analyze the study stratified by a pretransfusion hemoglobin concentration of less than 10 g/dL (to convert hemoglobin concentration to g/dL, multiply by 10). However, this analysis is incomplete and therefore remains unconvincing.