Transfusion in Ischemic Heart Disease
Correlation, Confounding, and Confusion*

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Few therapies in medicine are as controversial or have as much conflicting data as blood transfusions and their role in managing critically ill patients, especially those with acute myocardial infarction (MI). Despite almost 200 years of research, advancements in transfusion medicine, and an estimated 13.8 million units of red blood cells transfused annually in the United States (1), current guidelines for transfusing red blood cells among hospitalized patients are ill-defined. The most recently published American College of Cardiology/American Heart Association guidelines for managing patients with non-ST-segment elevation acute coronary syndromes (ACS) (2) give a class III (no benefit) recommendation for routine blood transfusion in MI patients with a hemoglobin value >8 g/dl. The American Association of Blood Banks, in contrast, offers no recommendation either for or against transfusion in this population (3). However, these recommendations are based almost exclusively on observational data.

In this issue of the Journal, Ding et al. (4) provide additional insight into differential transfusion thresholds in the presence of cardiac disease. In an observational analysis of >250,000 patients admitted to 108 Veterans Affairs hospital intensive care units (ICUs), they report an association between transfusion and lower adjusted mortality at a baseline hemoglobin level <7.7 g/dl among all patients. This threshold was higher among patients with comorbid cardiac conditions (transfusion threshold of 8.7 g/dl) and approximately 10 g/dl among patients for whom the primary ICU diagnosis was acute MI.

This analysis adds to a remarkably consistent body of knowledge, especially in the observational literature, that describes the hazard of blood transfusion in critically ill patients (5) and a higher transfusion threshold among patients presenting with acute MI. Despite the available data, it is difficult to offer clear guidance regarding the appropriate transfusion threshold among patients with ischemic heart disease in the absence of a prospective, well-powered randomized trial. Treatment selection bias remains the largest limitation for even large-scale observational studies, and currently used methods to address these concerns have proved incomplete.

Therefore, while awaiting a definitive randomized trial, the challenge in designing future observational studies may be to use robust methodologies to overcome the shortcomings of traditional observational research. One such technique, propensity matching, is used frequently to account for comparator group differences. However, a recent study by Salisbury et al. (6) that evaluated the association between transfusion and mortality among acute MI patients demonstrated that >90% of the 34,937 patients in their study had nonoverlapping propensity scores, making them unsuitable for direct comparison.

In the current analysis, the investigators used a well-described, although infrequently used technique, called principal component analysis (PCA), which creates a set of artificial variables (principal components) based on correlations from a much larger dataset. Ostensibly, these principal components can be used more manageably in subsequent analyses. PCA is most helpful in situations that involve highly correlated variables and can potentially deal with the issue of collinearity. This technique may prove useful in future observational studies.
valuable in future observational studies, especially those that use large electronic health record databases, by reducing a large set of comorbid diagnoses into a small number of variables (the principal components) to study interactions between diagnoses and treatment or to adjust for multidimensional comorbidities that the treatment effect may be confounding. However, it is useful only in a very limited context; specifically, one in which the variables being composited are not themselves the true confounders, but instead are highly correlated versions of the true confounder. The primary statistical concern with PCA is that it may unnecessarily complicate an analysis by creating nonsensical components (or new confounders) that no longer adequately adjust for the original measured confounders. As such, PCA’s utility in an observational analysis comparing therapies remains unclear.

Instrumental variables offer another technique that may address confounding in determining the association between transfusion and outcome (7). An instrumental variable is associated with the treatment but not the outcome, and instrumental variable analysis attempts to “simulate” randomization in the context of an observational dataset by overcoming the effect of unmeasured confounding. An example of an instrumental variable analysis is a study by Federspiel et al. (8), which evaluated the association between drug-eluting stents (DES) and mortality and revascularization among 62,309 Medicare beneficiaries treated between May 2003 and February 2004. In the randomized trials that compared drug-eluting and bare-metal stents, DES reduced the rate of repeat revascularization, but they did not affect mortality (9), even in the setting of acute MI (10). A large observational analysis of a statewide registry used propensity matching and demonstrated an association between DES and reduced mortality among patients with acute MI (11), which was a finding that contrasted with the randomized trials and was likely subject to residual confounding. The analysis by Federspiel et al. (8) used multivariate adjustment, propensity matching, and instrumental variables. A “month of percutaneous coronary intervention” (PCI) was used as the instrument because it affected whether the patient received a DES (patients treated later were more likely to receive DES due to rapid DES adoption), but it did not affect the outcomes. In the multivariate and propensity analyses, DES use was associated with reduced mortality; in the instrumental variable analysis, DES use was associated with reduced repeat revascularization, but had no effect on mortality, directly replicating the results of the randomized trials. Instrumental variables may provide several advantages to conventional methods of dealing with confounding, but the challenge is picking the right instrument.

Ultimately, randomized trials present the only definitive way to address the role of a therapy. In the context of blood transfusion, the stage has been long set for an adequately powered trial comparing transfusion strategies in ACS patients. To date, there have been only 2 small, randomized pilot studies (total n = 155) (12,13), but they yielded conflicting results. Recently published randomized trials in other clinical situations continue to strengthen the rationale for a decisive study. Steiner et al. (14) cast doubt on the so-called “storage lesion” in transfusion, finding no substantial difference in outcomes between transfused blood stored for <10 days than blood stored for >21 days. Another recent study highlighted the role of transfusion strategy among patients who underwent cardiac surgery; although there was no observed difference in the primary composite outcome between a restrictive and liberal strategy, there was an unexpected signal for increased mortality with the restrictive strategy (15).

Despite publication of the TRICC (Transfusion in Critical Care) trial (16) 15 years ago and repeated calls for a definitive randomized trial to address the optimal transfusion strategy for patients with acute MI, the fact that a trial has not been completed speaks to the challenges associated with designing and implementing such a trial, including logistics, generalizability, and cost. However, recent developments in clinical trial design may mitigate some of these issues. One strategy is the registry-based randomized trial, which was used in the TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) (17) and SAFE-PCI (Study of Access Site for Enhancement of PCI for Women) (18) trials. The registry-based trial potentially reduces the cost and complexity associated with data management by embedding randomization within a large ongoing registry, such as the National Cardiovascular Data Registry’s CathPCI or ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry. These registries routinely collect some data elements that are relevant for a transfusion trial (baseline hemoglobin, comorbidities, cardiac catheterization, PCI, coronary artery bypass graft surgery) and in-hospital outcomes. Leveraging this data collection reduces site-level workload and costs. Another strategy, used by PCORNet (Patient-Centered Clinical Research Network) to evaluate optimal aspirin dosing for secondary prevention (19), would be to embed the trial within traditional care pathways and use electronic health records to capture events. Because of the site
level variations in the use of transfusion in ACS patients (6,20), a cluster-based randomized trial may also be feasible. This technique previously has been used effectively to generate informative data in the cardiovascular (21) and noncardiovascular (22,23) arenas. All of these strategies represent novel ways to perform rigorous, randomized trials for a fraction of the traditional trial cost and complexity by leveraging either ongoing data collection or patterns of care in clinical practice.

Until observational studies effectively deal with confounding, the correlations they find will only add to the confusion at the bedside. Instead, the way forward may be a combination of approaches: using novel statistical techniques in observational datasets to glean additional insights while incorporating recent advances in clinical trial methodology to design a simple, pragmatic trial to determine the optimal transfusion strategy among acute MI patients.

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**REFERENCES**


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