**EDITORIAL COMMENT**

**Blood Transfusion After Myocardial Infarction**

**Friend, Foe, or Double-Edged Sword?**

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Combined mechanical and pharmacological interventions constitute the cornerstone of therapy for patients with ST-segment elevation myocardial infarction. Over the last decade, remarkable advances in primary angioplasty procedures and adjunct antithrombotic and antiplatelet therapies have led to significant improvements in procedural success and a drastic reduction in thrombotic complication rates. However, these interventions are now being used increasingly in complex patients, who frequently have severe associated comorbidities, which leads to an increased risk of bleeding (1,2). Currently, major bleeding is feared as the most important noncardiac complication in patients undergoing coronary interventions. Different studies have identified anemia as a strong “independent” predictor of adverse events and mortality in these patients (1,2). In this scenario, once prevention has failed, transfusion remains the only available therapy. However, recent systematic reviews of studies on red blood cell transfusion in patients with ischemic heart disease indicate that routine transfusion is of little clinical benefit and, in fact, may carry the potential for ischemic heart disease indicate that routine transfusion is of little clinical benefit and, in fact, may carry the potential for adverse serious consequences (3,4) (Table 1). Therefore, the appropriateness of transfusion has come under intense scrutiny and many practitioners have adopted a restrictive approach to the use of blood products, especially when prompted by “arbitrary” transfusions triggers. However, in patients with ischemic heart disease, the use of transfusion still remains rather liberal (3,4). Is transfusion a necessary evil?

In this issue of *JACC: Cardiovascular Interventions*, Nikolsky et al. (5) examined the large database of the randomized CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trial to assess the prognostic impact of blood transfusion after primary angioplasty. This is the first study assessing the implications of transfusions in this setting. These investigators found that transfusion was independently associated with major adverse events and, more importantly, with 30-days and 1-year mortality. However, is transfusion indeed a double-edged sword?

**Previous Studies**

The landmark TRICC (Transfusion Requirement in Critical Care) randomized trial (6) of critically ill patients found no benefit with the use of a liberal transfusion strategy to maintain hemoglobin levels of 10 mg/dl as compared with a restrictive approach where transfusions were only indicated to patients with a hemoglobin level <7 mg/dl. In an early study, Wu et al. (7) analyzed the large Medicare administrative database (79,000 patients with acute myocardial infarction, with and without ST-segment elevation, aged >65 years and managed largely conservatively) and suggested that anemia at admission increased early and late mortality. Transfusion was associated with a lower 30-day mortality in patients with a hematocrit ≥33% at admission, whereas transfused patients with hematocrit >36% had a higher mortality. Subsequent studies in patients with ST-segment elevation acute myocardial infarction consistently demonstrated an increased mortality after transfusion that persisted after adjustment for potential confounders (8–10).

**Data From the CADILLAC Trial**

In an early study (1), the CADILLAC investigators demonstrated that baseline anemia (hematocrit at initial presentation <39% for men and <36% for women) was frequently found (12.8%) in patients undergoing primary angioplasty and this finding was strongly associated with early and 1-year mortality (3-fold risk increase). Furthermore, after adjusting for potential confounders (patients with anemia had an adverse risk profile) either anemia or baseline hematocrit was identified as the strongest independent predictor of 1-year mortality on multivariate analysis. Of interest, when added to these models, neither nadir hematocrit value nor blood transfusions, correlated with mortality (1). Finally, when adjusted for medication use (patients with anemia were less likely to receive aspirin, beta-blockers, and statins) anemia continued to be an independent predictor of mortality. These findings are of special interest considering that the CADILLAC trial was a randomized study where patients with high hemorrhagic risks were excluded. Therefore, it is likely that baseline anemia, bleeding complications during hospitalization, and transfusion requirements will be much higher in unselected real-world patients undergoing primary angioplasty. Interestingly enough, in this initial report the CADILLAC investigators suggested that further
studies were required to assess whether “early transfusion” could improve the prognosis in these patients (1). In a subsequent report (2), the CADILLAC investigators derived a set of 7 variables that were proportionally weighted into a risk score for 1-year mortality. This score was subsequently validated against the dataset of the STENT-PAMI (Stent Primary Angioplasty in MI) trial. Again, anemia emerged as an independent predictor of 1-year mortality. Transfusion was not selected for inclusion in the “risk score” but it remained unclear whether this variable was indeed analyzed or excluded due to its interaction with anemia.

In the current analysis of the CADILLAC trial (5), blood transfusion was strongly associated with adverse clinical outcomes. Of the 4% of patients that received transfusions, roughly 1 in 4 died and 1 in 2 suffered adverse clinical events (death, myocardial infarction, target vessel revascularization, or stroke) at 1 year. Transfused patients had more adverse baseline characteristics, larger myocardial infarctions, and poorer procedural results. However, after careful statistical adjustment “transfusion”—but not anemia—was identified as an independent predictor of 1-year mortality. Transfusion was not selected for inclusion in the “risk score” but it remained unclear whether this variable was indeed analyzed or excluded due to its interaction with anemia.

### Clinical Implications

In patients with acute myocardial infarction, bleeding prevention is of paramount importance. In the past, both bleeding and transfusion were considered nuisances rather than potentially life-threatening complications. Currently, the shift toward strategies that diminish bleeding risk while maintaining efficacy in reducing ischemic complications is clear. The role of new anticoagulants, potentially safer yet equally effective, should be further investigated in these patients. Minimization of blood loss during primary angioplasty appears essential. In this context, the radial approach emerges as an attractive strategy. In a meta-analysis of randomized trials the radial access reduced major bleeding complications by 73% as compared with femoral access (11). Peripheral arterial disease is strongly associated with baseline anemia (1); therefore, the radial access appears particularly attractive in these patients (1). This route, initially reserved for elective patients, is increasingly used in selected patients undergoing primary angioplasty (12).

Once prevention has failed, how should we treat anemic patients with acute myocardial infarction? Although transfusion currently remains the only available therapy, the study of Nikolsky et al. (5) provides compelling reasons to think twice before applying this double-edged sword therapeutic strategy. First of all, optimal transfusion thresholds should be defined. In the present study, practice heteroge-
neity was highlighted because transfusion rates were 2.5 times higher in the U.S. than in non-U.S. centers. Further, more than one-half of the patients receiving transfusions did not have moderate to severe bleeding and had a nadir hematocrit >30%. In these situations, transfusion appears to have particularly adverse consequences. A holistic approach, with individualized management, should be pursued and appropriate transfusion triggers should be tailored according to the underlying clinical condition (hemodynamic instability, active bleeding, comorbidities, revascularization completeness).

As the authors have acknowledged, transfusion may simply be a predictor of a predictor of an outcome, the proverbial friend of a friend. Nevertheless, accumulated evidence strongly suggests that in patients with acute myocardial infarction transfusion may indeed become a real “foe.” Therefore, until more information is available, a conservative approach—with restrictive indications of blood products—appears warranted. Widespread adoption of restrictive transfusion strategies might significantly improve clinical outcomes in these patients, thus shifting this therapy into a trusting “friend.”

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