Commentary

Marker or mediator? Is the link between anemia and outcomes in patients with coronary artery disease growing any clearer?

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Continued advances in the medical and interventional management of coronary artery disease (CAD) have driven substantial improvements in long-term morbidity and mortality over recent years (1-3). However, the population of patients with chronic CAD has also grown older and more complex, and the burden of comorbidities among these patients also continues to rise. As clinicians strive to identify high-risk patients with the goal of further improving care, the prognostic impact of these non-cardiac conditions on patients' outcomes has been highlighted by a host of publications. One common comorbidity, anemia, has been linked to poorer survival, greater rehospitalization rates, poorer physical function and reduced health-related quality-of-life (4-9). Whether present at presentation to the hospital or developing during hospital stays, anemia has been shown to increase short and long-term mortality and clinical event rates (8,10). These studies leave little doubt that anemia is a predictor of poor outcomes. The key translational questions, however, remain largely unanswered—is anemia a marker or a mediator of poor outcomes? Is there any targeted intervention to treat anemia, beyond standard therapy for coronary disease, that we can leverage improve outcomes for CAD patients with anemia?

The present study by Wang and colleagues is another attempt to further clarify the relationship between anemia and outcomes (11). They examined a consecutive series of percutaneous coronary intervention (PCI) patients treated at a high-volume center in China, with 3-year follow-up of clinical events after the index procedure. As the authors point out, confounding has been a significant limitation of observational studies attempting to identify the impact of anemia on outcomes. In an effort to better reduce the impact of confounding, they used propensity matching to identify patients with and without anemia who appear to be comparable, and examined the outcomes after PCI among the matched cohort. Most previous studies of anemia and outcomes have used multivariable adjusted regression analyses to reduce confounding. The regression approach has several limitations in comparison to propensity score methods, a more robust technique to balance confounding related to measured covariates. Moreover, the authors selected a propensity matching approach which is generally regarded as the most robust propensity technique (12), essentially balancing observed covariates between exposure groups in the analytic cohorts in an attempt to mimic randomization. Using these methods, the authors found that the significant unadjusted association between anemia and both 3-year mortality and ischemic events remained strongly associated with both outcomes after propensity matching.

Several limitations of this investigation should be considered. The authors matched patients in a 1:1 fashion, accordingly only 872 of the 8,825 patients analyzed in the pre-matching cohort were included in the propensity matched analysis. It is unclear based on the data published in this report whether this reflects that many patients without anemia had characteristics (and thus propensity scores) that differed greatly from those with anemia, precluding a large number of patients from being matched, or that more non-anemic patients could have been matched if one-to-many matching was used. If the majority of patients simply could not be matched, it suggests that even the most advanced analytic techniques may fail to adequately address confounding. For example, in a prior study of the relationship between blood transfusion and outcomes in patients with AMI, our group found that the majority of patients who were treated with a blood transfusion where so dissimilar to those who did not receive a transfusion that

they could not be propensity matched (13). In this setting, regardless of analytic technique selected, the risk of residual and unmeasured confounding remains substantial, and likely obscures the true relationship between risk factor and outcome. While the analytic technique employed by the authors is appropriate and is likely the ideal method to analyze these data, the strong risk of residual and unmeasured confounding remains strong limitation of any observational study, including the present report.

What is the next step to better defining the impact of anemia on outcomes in patients with CAD? The clear goal of future research examining the relationship of anemia and outcomes should be to identify actionable risk factors for poor outcomes that can serve as novel treatment targets. Although propensity analyses, instrumental variable analyses or inclusion of falsification end points in analyses may effectively reduce the impact of confounding, it cannot be eliminated completely using any observational design (12,14-16). Instead, it will be necessary to identify new interventions to treat or prevent anemia and then translate these insights into randomized studies to test the hypothesis that treating anemia improves outcomes. Attempts to proceed down this path have thus far led to disappointing results. Outcomes trials of erythropoietin analogues in other populations, such as patients with heart failure or chronic kidney disease (17,18), have failed to show benefit. For example, the RED-HF trial randomized patients with systolic heart failure to darbepoetin alfa or placebo, examining a primary endpoint of death or hospitalization with worsening heart failure. Unfortunately, despite achieving the target hemoglobin threshold of 13 g/dL in the majority of patients in the darbepoetin arm, there was no difference in the primary endpoint between groups over a median follow-up of 28 months, and little clinically meaningful difference in health status between groups as assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) (17).

Similarly, observational data examining the relationship of acute correction of severe anemia with blood transfusion for hospitalized patients undergoing PCI or with myocardial infarction have been mixed, also most likely reflecting residual confounding (4,13,19). Consistent with findings in the erythropoietin analogue literature, trials suggest little benefit from aggressive transfusion in populations studied to date, finding no significant difference between conservative and liberal transfusion thresholds in critically ill patients, those undergoing cardiac surgery or patients with cardiac history of high cardiac risk undergoing surgery for a hip fracture (20-22). While these findings may reflect the adverse effects of the interventions themselves—erythropoietin analogues and packed red blood cell transfusions both carry potential downsides—and despite theoretical mechanisms that link diminished oxygen carrying capacity to ischemic events, there remains no clear evidence of causality in the link between anemia and outcomes in patients in CAD. Whether or not these results reflect the shortcomings of the interventions studied to date, a critical review of the literatures suggests that, at present, anemia is best considered a marker for general illness rather than an actionable mediator of adverse cardiac events.

New studies are needed to help settle these challenging questions. Whether future trials testing treatment of new therapeutic targets, or using approaches to prevent hospital acquired anemia in the first place, bear fruit remains to be seen. For instance, aggressive iron repletion could be studied in iron deficient patients given the high incidence of abnormal iron indices in CAD patients (23). Another approach may focus on randomization of patients (or centers in a cluster randomized trial) to prevention of hospital-acquired anemia by limiting blood loss during inpatient management (24,25). In the mean time, we must view the findings of Wang and coworkers as another well-conducted observational study that reminds us of two key challenges. First, recognizing anemia in patients with CAD is important, because anemia is a clear indicator of a high-risk patient who may benefit from closer follow-up with hopes of maximizing health status, preventing hospitalization and perhaps even preventing ischemic events. Second, despite significant advances in analytic technique, confounding remains a significant limitation of observational studies linking anemia to outcomes in patients with CAD. Results of these studies should be considered with appropriate skepticism of potential causal relationships until randomized data suggest treatment of anemia improves clinical outcomes or health status in patients with CAD.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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