Editorial

Shedding blood: anemia and adverse events after percutaneous coronary intervention (PCI)

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Substantial evidence from epidemiological studies suggests strong association between baseline anemia and worse outcomes following percutaneous coronary intervention (PCI) for both stable coronary artery disease (CAD) and acute coronary syndromes (ACS) (1-3). The existing data, almost exclusively from prospective analysis of clinical cohorts or retrospective post-hoc analysis of data from large randomized clinical trials designed to investigate other specific endpoints, point to anemia as a strong independent predictor of major adverse cardiac outcomes (MACE), major bleeding and mortality in patients undergoing PCI (4-6). Some of the published studies have utilized rigorous statistical methods to adjust for all known and measurable variables that can interact with anemia, nevertheless the associations inferred from these studies, while providing valuable insights, remain hypothesis generating.

Anemia is a clinical syndrome with a multitude of underlying etiologies, which can independently have negative impacts on major clinical outcomes including mortality (7). Integration of anemic patients secondary to heterogeneous etiologies into one group poses major challenges on studies that attempt to establish a causative relationship between this clinical syndrome and clinical outcomes after PCI. Unrecognized and unmeasured factors, such as subclinical malignancies and inflammation, may remain unaccounted for if the study protocols do not include dedicated pathways to investigate the underlying cause of anemia and stratify anemic patients in different groups based on the underlying etiologies. Moreover, contrary to assumptions of proportionality of risk with time in statistical models used for univariate and multivariate analysis, anemia is a dynamic process the severity of which may significantly vary over time; so would its direct and indirect effects on the cardiovascular system. Thus, studies dedicated on this subject need to prospectively monitor the severity of anemia as well as the underlying biological processes driving it.

The associations shown by epidemiological studies regarding the negative impacts of anemia on adverse outcomes have nevertheless strong biological plausibility. The effects of anemia on the cardiovascular system have been well described, including a compensatory increase in cardiac output for adequate systemic oxygen delivery, with the chronic tachycardia leading to adverse myocardial remodeling in chronic moderate to severe anemia (8). In the context of CAD, anemia, especially in more severe forms, can result in repeated myocardial ischemia especially under states with higher metabolic demands such as exertion (9), and can particularly compound the already jeopardized oxygenation of the myocardium during ACS (10). For patients undergoing PCI, anemia can be a marker for existence of multiple co-morbidities such as advanced age, chronic kidney disease, diabetes and autoimmune disease (4,5), all of which have firmly established negative impacts on MACE and mortality. Moreover, anemia, as the consequence of certain specific underlying etiologies, may worsen by PCI and the pharmacotherapy initiated peri-procedurally and after PCI. Dual anti-platelet therapy (DAPT) can unmask or exacerbate underlying processes such as occult gastrointestinal bleeding and bleeding diatheses, leading to substantially increased bleeding frequency and severity. The significant adverse effects of bleeding on outcomes in patients undergoing PCI,

particularly if blood transfusions become necessary, have been firmly established (4,11,12). Interestingly, in addition to bleeding, the incidence of atherothrombotic events is also higher in patients with anemia who undergo PCI (6). One obvious cause for this enhanced propensity is premature discontinuation of DAPT secondary to bleeding, which, particularly after implantation of drug-eluting stents (DES), is associated with higher incidence of probable or definite stent thrombosis (5,6). Furthermore, anemia secondary to subclinical malignancy or inflammatory processes is associated with other blood dyscrasias (13-15), which may predispose anemic patients to more ischemic events. Finally, intravascular imaging studies have shown an association of anemia with presence of more vulnerable coronary plaques as evidenced by a higher burden of necrotic core and thin-cap fibroatheroma (16).

In this issue of *Journal of Thoracic Disease* (*JTD*), Wang *et al*. report the impact of (baseline) anemia in a prospective cohort of 851 patients selected from the population of patients undergoing PCI for any indication in a single center in China between 2008 and 2012 (17). The primary end-point of the study was the rate of ischemic events with MACE, defined as a composite of non-fatal myocardial infarction and target vessel revascularization, and all-cause mortality as the secondary end points. Using a propensity score matching approach to balance covariates observed in the study between anemic and non-anemic groups, the authors observe that anemia is associated with increased adverse events at 3-year follow-up, including ischemic events: hazard ratio (HR) =2.20 [95% confidence interval (CI), 1.61–3.00]; MACE: HR =2.88 (95% CI, 1.89–4.40); and mortality HR =3.58 (95% CI, 1.75–7.32). Kaplan-Meier curves for these endpoints separate very early and continue to diverge during the course of the 3-year follow-up (17).

The findings of this study are largely in line with previous reports (2,3,5,6) reporting anemia as an independent prognostic marker for adverse outcomes in an all-comer cohort of patients. The various limitations of the current studies, as detailed earlier, also apply to the report by Wang *et al*. Additionally, as the authors acknowledge, the observational non-randomized design of the study introduces latent, unrecognized or unmeasured variables that result in hidden bias despite attempts by the authors to reduce selection bias by the propensity matching approach. Important details that would have helped in better interpreting these data include definitions of ischemic events and how they were adjudicated and assessment for the relevant components of ischemic events such as stent thrombosis and myocardial infarction in the territory of non-culprit arteries. Furthermore, details on the pharmacotherapy used peri-procedurally, the types of stents used, the choice of anti-platelet agents and duration- and rates of premature discontinuation of DAPT would aid in identifying the presence of interaction between these variables and ischemic events. Critically, bleeding rates in anemic and non-anemic groups during the follow-up period would have also had significant interactions with ischemic events and ideally should have been included in the design of the study.

The "ideal studies" to address the various hypotheses generated by reports like the one presented by Wang *et al*. are randomized clinical trials that would have core elements including, investigation of the underlying causes of anemia and stratification of patients based on the etiology, and severity of anemia both at baseline and during the follow up period in their design. Such a design would provide the most appropriate platform to study the interaction of the underlying causes of anemia as well as the impact of clinical management guided by the underlying etiology on outcomes. Trials of sufficient statistical power to check for other specific endpoints including the effects of various management strategies such as optimal medical therapy, modes of revascularization by PCI or bypass graft surgery on outcomes are needed. With specific regards to PCI, the peri-PCI anticoagulation, the types of the stents, and the optimal duration of DAPT are areas that can be examined by this research methodology.

In the absence of data from such ideally designed studies and based on the best available data, the following strategies may be adopted to reduce the risk in anemic patients undergoing PCI. Correction of hemoglobin levels by blood transfusion prior to PCI should not be undertaken unless the levels are less than 7–8 g/dL (4). To avoid peri-PCI bleeding, potent anti-platelet agents such as glycoprotein IIb/IIIa inhibitors should not be used and anticoagulation with bivalirudin may be considered, although anemia in patients with the latter pharmacotherapy still portrayed worse outcomes (12). Where possible, PCI via the trans-radial approach should be considered since it is associated with less bleeding and improved mortality (18,19). The choice of DES versus bare metal stents (BMS) in anemic patients should be decided based on individualized evaluation of bleeding *vs*. thrombosis risk. Overall, the existing evidence suggests the safety and efficacy of DES in the presence of anemia (5). In the presence of high bleeding risk and/or requirement for shorter duration of DAPT, a

new drug-coated polymer-free stent may be chosen since it has been shown to be superior to BMS both in safety and efficacy in anemic patients with high risk of bleeding, and requires 1-month of DAPT (20). As the accumulating data from recent trials suggest, the optimal duration of DAPT would depend on multiple factors including the location and complexity of the treated lesions, the size, type and number of stents, recent ACS and estimation of bleeding *vs.* thrombosis risk in individual patients (21,22).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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