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EDITORIAL COMMENT

Single-Timepoint Snapshot of Hemoglobin

Is it Enough to Reflect the Dynamicity of Coronary Atherosclerosis?*

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Anemia affects nearly one-third of the global population and imposes a major socioeconomic and health burden.[1] Anemia is associated with the development of coronary artery disease (CAD), which is attributed to systemic effects such as oxidative stress and chronic inflammation. A long-term follow-up of the Framingham cohort revealed a J- or U-shaped relationship between hematocrit level and cardiovascular events.[2] A study from the ARIC (Atherosclerosis Risk in Communities) cohort proposed that anemia is an independent predictor of clinical events attributable to CAD.[3] Several trials thereafter demonstrated the association of anemia with a worse prognosis in CAD patients.[4]

Therefore, it remains to be investigated how anemia is related to the change of the coronary tree. Because coronary atherosclerosis is a dynamic process resulting from continuous time-dependent interactions between the plaque and its surrounding blood environment[5] and the hemoglobin level is intertwined with diverse disease conditions, it is obvious that a single measurement of hemoglobin level cannot fully define its role in CAD development, and data on the association between time-serial changes in hemoglobin and CAD are needed. Additionally, understanding this longitudinal association may provide valuable clinical insights into the assessment and management of CAD in a more integrated manner.

In this issue of *JACC: Asia*, Won et al[6] publish an interesting study on the relationship between the changes in hemoglobin and the annualized plaque volume changes (PVCs). Subjects who had undergone serial coronary computed tomographic angiography with an interval of ≥2 years from the PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging) registry were analyzed (n = 830), and the degree of changes in hemoglobin (Δ hemoglobin) was inversely correlated with annualized PVC (β = -2.173, P = 0.001). This association was predominant in subjects with hemoglobin <14.3 g/dL (median value) compared with those with hemoglobin ≥14.3 g/dL. Notably, the baseline total plaque volume was not different according to the baseline hemoglobin, and the baseline hemoglobin was not a predictor of PVCs. Based on these observations, the authors suggest that efforts to prevent anemia might be helpful to attenuate plaque progression, particularly in subjects with low hemoglobin.

The current analysis performed in a prospective, international, observational registry with unique longitudinal data demonstrates the significant association between changes in hemoglobin and the coronary plaque volume over a period of time and broadens prior knowledge on the relationship of hemoglobin status with CAD. Nevertheless, several limitations should be noted in interpreting the results. The changes in hemoglobin level were simplified to changes between 2 time points. Although clinical covariates including demographic profile, comorbidities, renal function, and medication history were rigorously accounted for, several confounders affecting the hemoglobin level such as iron metabolism, nutrition state, hematologic disease, and the

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Clinical Trials Investigating the Effect of Anemia Correction in Patients With Coronary Artery Disease

Methods to Correct Anemia	Publication Year (First Author)	Study Population	Intervention	Result (Primary Outcomes)
Red cell transfusion	2011 (Cooper et al)[7]	45 patients with acute MI and hematocrit ≤30%	1:1 randomized to • a liberal strategy (transfuse when hematocrit <30% to maintain 30%-33%) • a conservative strategy (transfuse when hematocrit <24% to maintain 24%-27%)	Liberal strategy vs conservative strategy: 38% vs 13% ($P = 0.046$) (composite of in-hospital death, recurrent MI, or new or worsening heart failure)
	2013 (Carson et al)[8]	110 patients with ACS or stable angina undergoing cardiac catheterization and a hemoglobin <10 g/dL	1:1 randomized to • a liberal strategy (1 or more units of blood to raise the hemoglobin level ≥10 g/dL) • a restrictive strategy (receive blood for symptoms from anemia or for a hemoglobin <8 g/dL)	Liberal strategy vs restrictive strategy: 10.9% vs 25.5% ($P = 0.054$) (composite of death, MI, or unscheduled coronary revascularization within 30 d)
	2021 (Ducrocq et al)[9]	668 patients with MI and hemoglobin level between 7 and 10 g/dL	1:1 randomized to: • a liberal strategy (transfusion triggered by hemoglobin ≤10 g/dL) • a restrictive strategy (transfusion triggered by hemoglobin ≤8 g/dL)	Liberal strategy vs restrictive strategy: 14.0% vs 11.0%, meeting the prespecified noninferiority criterion of a restrictive strategy to a liberal strategy (composite of all-cause death, stroke, recurrent MI, or emergency revascularization prompted by ischemia at 30 d)
Erythropoiesis-stimulating agents	2017 (Steppich et al)[10]	138 patients with STEMI after successful reperfusion	1:1 randomized to • epoetin-β group (33,300 U administered immediately at 24 and 48 h after percutaneous coronary intervention) • placebo group	Epoetin-β group vs placebo group: 25.0% vs 17.0% ($P = 0.26$) (composite of death, recurrent MI, stroke, coronary bypass surgery and target vessel revascularization, 5 y after randomization)
Iron supplementation	No clinical trials to date			

ACS = acute coronary syndrome; MI = myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

status of antithrombotic and anticoagulation agents during follow-up were not fully adjusted. Therefore, the causal relationship between the correction of anemia and the decrease in PVCs cannot be drawn from the results.

Currently, there is no established consensus on the optimal hemoglobin level in CAD patients, let alone whether the correction of anemia leads to a better prognosis. As in **Table 1**,[7-10] a recent randomized controlled trial showed the noninferiority of a restrictive transfusion strategy with hemoglobin ≤8 g/dL compared with a liberal transfusion strategy with hemoglobin ≤10 g/dL in myocardial infarction patients.[9] In contrast to proven benefits in heart failure, the administration of erythropoiesis-stimulating agents did not improve clinical outcomes in myocardial infarction patients.[10] There is also no trial investigating the efficacy of iron supplementation to correct iron deficiency in CAD patients. Instead, iron overload is more of a concern in CAD patients, in which iron chelation improved endothelium-dependent vasodilation.[11] All these prior intervention studies imply the delicate and complex nature of managing anemia in CAD patients, and it remains to be tested whether the correction of anemia leads to improvement of coronary atherosclerosis and a better prognosis.

Then, what is the practical message from the current study in this context? When looking at the results that Δ hemoglobin but not baseline hemoglobin was an independent predictor of PVCs and that PVCs were the highest in the low baseline or low follow-up hemoglobin group, it can be speculated that a single time point spot hemoglobin level cannot be a sole prerequisite for anemia correction. It emphasizes the importance of meticulous measures to prevent anemia and of tracing the dynamic changes of hemoglobin and the individual patient's risk profile on a regular basis to optimize primary and secondary prevention of CAD. In future studies, the benefit of anemia correction in more selected CAD patients, such as those with persistently low hemoglobin level over a certain period of time, should be investigated. This study clearly indicates that a single hemoglobin level is a snapshot of dynamic interaction between hemoglobin changes and coronary atherosclerosis. Endeavors to appreciate this process in a broadened

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view of the time-varying sequence will provide better CAD management in clinical practice.

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