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EDITORIAL COMMENT

Unexplained Hemoglobin Drops After TAVR

A Call for Vigilant Monitoring

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Bleeding has long been recognized as a major driver of adverse outcomes after transcatheter aortic valve replacement (TAVR). Despite major improvements in valve technology, operator skill, and periprocedural management, bleeding complications remain a key determinant of prognosis. The importance of bleeding is reflected in every iteration of the Valve Academic Research Consortium (VARC) definitions, which have progressively expanded their scope to capture clinically meaningful events. The most recent update, VARC-3, broadened the definition of "overt" bleeding to include any clinically visible source or evidence confirmed by imaging or diagnostic testing, as well as procedure-related blood loss without an identifiable source.[1] Under this updated definition lies the recognition that a substantial hemoglobin decrease is clinically meaningful, whether or not a bleeding site can be identified. In addition, blood loss occurring during the procedure, even when no source is identified, now falls within the scope of overt events. The prognostic impact of hemoglobin decline in the absence of overt bleeding, however, has not been thoroughly evaluated. In a study reported in this issue of *JACC: Cardiovascular Interventions*, Avvedimento et al[2] addressed this important gap in knowledge by analyzing data from a rigorously collected TAVR multicenter registry of nearly 10,000 patients treated with contemporary valves between 2014 and 2023. This represents one of the largest contemporary data sets exploring hemoglobin dynamics after valve implantation, and its focus on declines without visible or confirmed bleeding provides timely data on prevalence, predictors, and outcome associations in this overlooked domain.

The investigators found that more than one-half of patients experienced measurable hemoglobin decreases without overt bleeding, and 1 in 5 had declines of ≥3 g/dL. These "silent" events were not benign: both minor (3-5 g/dL) and major (≥5 g/dL) declines were independently associated with higher 1-year mortality, with a threshold effect identified around 2.7 g/dL. These findings strongly argue against dismissing hemoglobin decline as an incidental or trivial occurrence. Predictors of significant hemoglobin decline reported in this study are also instructive. Female sex, chronic kidney disease, dual antiplatelet therapy, and higher baseline hemoglobin were associated with greater risk, while the use of radial secondary access emerged as protective. Such associations are clinically intuitive and echo patterns established in percutaneous coronary intervention, where minimizing invasiveness and simplifying antithrombotic therapy reduce both overt and covert blood loss.

By establishing a clear association between hemoglobin decline and mortality, the study advances the field beyond anecdotal impressions. It complements the recent work of Nienaber et al,[3] who demonstrated a graded relationship between bleeding severity (as defined by VARC-3) and outcomes. The present study extends those findings by showing similar associations in patients with nonovert bleeding. It reinforces the VARC-3 concept that any significant blood loss, regardless of whether it is externally apparent, adversely influences outcomes and warrants clinical attention.

The pathophysiology of nonovert hemoglobin decline is complex and multifactorial. Subclinical

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bleeding is likely more common than recognized, including small retroperitoneal hematomas, access-site oozing, or intrathoracic collections that escape clinical detection. Inflammatory activation after valve deployment, hemodilution from intravenous fluids, or repetitive blood draws may also contribute. Valve-related factors, such as paravalvular leak or prosthesis-patient mismatch, can cause low-grade hemolysis, further reducing hemoglobin levels. Each of these processes may have limited impact alone, but in combination they can significantly reduce hemoglobin. Distinguishing among these mechanisms remains challenging without standardized imaging or laboratory work-up, and in most patients, multiple mechanisms likely coexist. Nevertheless, regardless of mechanism, a significant decline in hemoglobin appears to identify patients with less physiological reserve and greater vulnerability to adverse outcomes.

Although the investigators deserve commendation for drawing attention to a neglected aspect of post-TAVR care, the present study is not without limitations. Hemoglobin values were reported by participating sites without central laboratory adjudication, and the timing of measurements was not standardized. Frailty indexes, coagulation profiles, and inflammatory biomarkers were not systematically captured. The transfusion adjustment, although necessary, represents an approximation that may under- or overestimate the true decline. Most important, the thresholds applied were extrapolated from percutaneous coronary intervention literature rather than validated in TAVR-specific populations. Yet the consistency of findings across nearly 10,000 patients, the graded risk associations, and the identification of a prognostic cutoff around 3 g/dL make the results highly persuasive. The incorporation of the VARC-defined high bleeding risk criteria would have further enriched risk stratification but does not diminish the strength of the observations.[4]

What then should clinicians take from these findings? First, hemoglobin monitoring after TAVR must be taken seriously. A decline of ≥3 g/dL, even in the absence of overt bleeding, should not be dismissed as laboratory noise. Instead, it should trigger vigilance. Targeted vascular ultrasound, echocardiography, or computed tomography may be warranted to exclude concealed complications, while a careful review of antithrombotic therapy is advisable. The strong association between dual antiplatelet therapy and hemoglobin decline reinforces the contemporary movement toward simplified antithrombotic regimens. Trials such as POPular-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) have demonstrated the safety and efficacy of single antiplatelet therapy in most patients without another indication for oral anticoagulation.[5] Hemoglobin dynamics may provide additional clinical rationale for early de-escalation of antithrombotic therapy.

Second, the findings have implications for clinical research and endpoint definitions. VARC-3 acknowledged that any blood loss matters but did not specify quantitative thresholds. The present data suggest that a decline of ≥3 g/dL is a practical and clinically meaningful cutoff, aligning TAVR with established bleeding definitions in percutaneous coronary intervention and other interventional fields. Incorporating this threshold into consensus documents would facilitate comparability across trials, refine bleeding endpoints, and improve the calibration of risk/benefit assessments for novel devices and therapeutic strategies.

Third, the study points toward fertile ground for future research. Prospective validation of the ≥3 g/dL threshold across diverse populations and procedural settings is essential to determine its generalizability. Mechanistic investigations using systematic imaging, biomarker assays, and hemolysis testing could clarify the relative contributions of subclinical bleeding, hemodilution, and valve-related hemolysis. Interventional studies should evaluate whether systematic responses to hemoglobin decline, such as standardized imaging, iron supplementation, or adjusted transfusion thresholds, can mitigate risk and improve outcomes. Health economic analyses may also be informative, as hemoglobin decline may prolong hospitalization and increase resource use. Beyond clinical research, the integration of hemoglobin dynamics into endpoint definitions, quality metrics, and guideline recommendations will be important to ensure that safety assessment keeps pace with the expanding role of TAVR. Finally, embedding hemoglobin monitoring into patient selection and postprocedural care pathways could support a more personalized approach, particularly as TAVR expands to younger and lower risk populations in which safety margins are narrow and long-term outcomes paramount.

Providing evidence that unexplained hemoglobin decline after TAVR is not benign (a fall of ≥3 g/dL,

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even without overt bleeding, is common, clinically relevant, and independently associated with higher mortality), this study invites a cultural shift: hemoglobin decline should no longer be considered a trivial laboratory observation but a marker of risk that deserves vigilance, evaluation, and integration into standardized definitions. By refining how we monitor and respond to hemoglobin dynamics, we can further improve the safety and value of TAVR in an era when excellence in outcomes is more crucial than ever.

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REFERENCES

1. Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol*. 2021;77(21):2717–2746. https://doi.org/10.1016/j.jacc.2021.02.038

2. Avvedimento M, Cepas-Guillén P, Nuche J, et al. Clinical impact of in-hospital hemoglobin decline without overt bleeding after transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2025;18(22):2744–2757.

3. Nienaber S, Himken J, Meertens M, et al. Comparison of Valve Academic Research Consortium (VARC)-2 and VARC-3 criteria for bleeding complications after transcatheter aortic valve replacement. *J Am Heart Assoc*. 2025;14:e039342. https://doi.org/10.1161/JAHA.124.039342

4. Garot P, Morice MC, Angiolillo DJ, et al. Defining high bleeding risk in patients undergoing transcatheter aortic valve implantation: a VARC-HBR consensus document. *EuroIntervention*. 2024;20(9):536–550. https://doi.org/10.4244/EIJ-D-23-01020

5. Brouwer J, Nijenhuis VJ, Delewi R, et al. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med*. 2020;383:1447–1457. https://doi.org/10.1056/NEJMoa2017815

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