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EDITORIAL COMMENT

Postprocedural Measurement of Hemostasis to Define Long-Term Post-TAVR Bleeding Risk

Ready for Individualized Risk Assessment?

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Acquired von Willebrand factor (vWF) deficiency characterized by loss of high molecular-weight multimers (type 2A) has been described in patients with aortic stenosis with levels of multimers associated with procedural success and bleeding risk after transcatheter aortic valve replacement (TAVR).[1,2] In addition, different bleeding risk scores have been adopted to describe the short-term bleeding risk.[3,4] However, reliable tools to predict long-term bleeding risk are currently missing so far.

In this issue of *JACC: Cardiovascular Interventions*, Kikuchi et al[5] provide insights into the association between the closure time with adenosine diphosphate (CT-ADP) value, measured by the PFA-100 system (Siemens Healthineers) before and at 24 hours after the procedure, and bleeding outcomes up to 2 years after TAVR. As result, postprocedural CT-ADP >180 provided added value compared with the VARC (Valve Academic Research Consortium) criteria alone for prediction of 2-year major bleeding events.[5]

The investigators are to be commended for their efforts to monitor hemostatic function in a large, prospective TAVR cohort. The results are tempting. However, they need further confirmation before being applied to clinical practice. The use of a single hemostatic test to describe the role of platelet-dependent pathways on bleeding risk reminds us somehow of the story of on-treatment platelet reactivity after percutaneous coronary intervention.[6] Although multiple observational studies have documented an association of postprocedural platelet function within 24 hours with thrombotic and bleeding events, randomized trials to evaluate guided antiplatelet therapy failed to improve outcome. A possible explanation was that the timepoint after the procedure was too early, not reflecting the steady state of platelet function.[6] In fact, early postprocedural CT-ADP can be influenced by a number of variables, including hematocrit, platelet count, periprocedural hemostasis, and procedural success.

Some further questions remain. Can bleeding risk be modified by adjustment of the intensity and type of antithrombotic therapy? There is no detailed information about further modifications of antithrombotic therapy and possible effects on hemostatic function in the current study. Maybe antithrombotic therapy can be omitted in patients with low CT. In this context, the findings from the OCEAN-TAVI (Optimized transCathEter vAlvular iNtervention) registry in high bleeding risk patients previously demonstrated that no antithrombotic therapy was associated with similar risk of net adverse clinical events but reduced risk of bleeding events.[7] The concepts of guided antithrombotic therapy would require proof in randomized clinical trials.

In contrast to early periprocedural bleedings, detailed information on late bleeding events was not collected, and thus, important information by type and anatomical site (eg, access site, gastrointestinal, intracranial) to better determine whether prolonged

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CT-ADP reflects clinically meaningful bleeding risk beyond procedural complications is missing.

The cohort analyzed in the current paper by Kikuchi et al[5] comprised patients treated with oral anticoagulants (OAC) and antiplatelet therapy. Multivariable analysis identified OAC use as a strong negative predictor of prolonged CT-ADP (>180 seconds), which appears counterintuitive at first glimpse because OACs are not expected to directly influence platelet-mediated primary hemostasis. The circumstance that these patients have likely not received antiplatelet therapy pre- and post-TAVR sheds light on the impact of antiplatelet therapy after TAVR and the potential importance of modifying antiplatelet therapy in the further course. In addition, the group of patients with atrial fibrillation (needing OAC) and prolonged CT-ADP were at highest risk for bleeding after TAVR in another study by the same author group.[8]

The use of CT-ADP in the setting of TAVR needs to be considered in light of the pathophysiology of aortic stenosis. Increased shear stress at site of the stenotic valve leads to degradation of high molecular weight vWF multimers. TAVR relieves this shear burden, potentially reducing CT-ADP over time. By contrast, lack of procedural success, including paravalvular leakage due to anatomical features and/or underexpansion of the TAVR prosthesis can negatively impact vWF multimer degradation, thus increasing CT-ADP.[1,9] Of note, ≥ moderate paravalvular leakage (PVL) was highly significantly associated with postprocedural CT-ADP >180 seconds in the present study. Thus, serial measurements of CT-ADP after TAVR and correlation with procedural success including further cause of PVL would provide more compelling evidence of dynamic changes in primary hemostasis and its independent role in bleeding risk, and would greatly strengthen the mechanistic interpretation of the findings. A rate of PVL ≥ moderate PVL at 11.1% was relatively high in this TAVR cohort. Taking into account that PVL potentially affects postprocedural CT-ADP values, extrapolation of the findings to contemporary TAVR cohorts with ≥moderate PVL rates <2% warrants caution.[10]

In addition, more than 50% of the patients in the current study received dual antiplatelet therapy/dual antithrombotic therapy at discharge, and de-escalation to monotherapy was considered 1 to 2 months thereafter. This needs to be considered for interpretation of the findings, given that current guideline recommendations and practices suggest earlier single antiplatelet therapy (SAPT) and given the fact that intensity of dual antiplatelet therapy and use of $P2Y_{12}$ receptor inhibitors impacts CT-ADP.[11,12] Repeated evaluation of CTA-ADP after de-escalation would have given more comparable insights about its prognostic role under SAPT.

Taking together the aforementioned interplay between antiplatelet therapy, OAC in atrial fibrillation patients, PVL rates, and prolonged CT-ADP values: 1) evaluation of the prevalence of high postprocedural CT-ADP values in contemporary cohorts with low PVL rates and SAPT use; and 2) higher granularity to define postprocedural CT-ADP as an independent risk factor offering a modifiable parameter for individualized management therapies are still needed.

Besides bleeding risk, the issue of valve thrombosis (clinical and subclinical) gains increasing recognition and may contribute to valve degeneration and mortality.[13,14] Therefore, similarly to the impact of low and high platelet reactivity in patients undergoing percutaneous coronary intervention,[6] a window to define a sweet spot of any hemostatic parameter would be of even more clinical relevance.

Finally, patients with valvular disease undergoing valvular interventions display a complex interplay of components of the hemostatic system, including endothelial cells, platelets, vWF, and coagulation factors involved in thrombin generation and fibrinolysis with dynamic changes due to coagulation activation by foreign surface and flow dynamics.[15,16] Thus, platelet, coagulation, and anticoagulation pathways need to be evaluated over time to exhibit a full picture of the individual bleeding risk. Hemostatic measurement is certainly more complex than described by a single postprocedural test, a story that we have learned from personalized antiplatelet strategies. Still, the study by Kikuchi et al[5] gives us important information and perspectives that besides clinical risk evaluation we should integrate measurement of hemostasis to better define long-term bleeding risk after TAVR and further investigate individual antithrombotic management options in the future.

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