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EDITORIAL COMMENT

Bleeding in Patients With Severe Aortic Stenosis in the Era of Transcatheter Aortic Valve Replacement*

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Aortic stenosis (AS) increasingly afflicts our aging population, affecting about 0.2% in individuals 55 to 64 years of age and 2% to 3% in subjects older than 65 years of age. In up to 20% of patients with moderate-to-severe AS, mucous nasopharyngeal and cutaneous bleedings are observed, whereas gastrointestinal (GI) bleeding occurs in 1% to 3% of the patients. GI bleeds in patients with severe AS are usually associated with angiodysplasia—multifocal submucosal vascular malformations formed probably as a result of increasing wall tension during colonic contractions, which is the second most common cause of lower GI bleeding in patients >60 years of age (the so-called Heyde syndrome [HS]) (1). Compelling evidence for the pathophysiological link between AS and bleeding from angiodysplasia stems from the resolution of GI bleeding observed during the first 7 days after surgical aortic valve replacement (AVR) (2), although the abnormal vessels remained visible on colonoscopy. A major mechanism underlying increased bleeding risk in AS represents acquired type 2A von Willebrand syndrome that is characterized by a quantitative deficiency of high molecular weight multimers (HMWM) of von Willebrand factor (vWF) (3). Other mechanisms not associated with type 2A von Willebrand syndrome could also been involved in bleeding risk observed in severe AS (4).

vWF that is predominantly synthesized in endothelial cells, and megakaryocytes is a multimeric plasma glycoprotein assembled from identical ~250 kDa subunits into disulfide-linked multimers up to >20,000 kDa. vWF is essential for platelet-subendothelium adhesion and platelet-to-platelet interactions under high shear stress conditions, such as in angiodysplasia. The most effective in platelet-mediated hemostasis are the vWF HMWM, defined usually as the presence of >10 dimers of vWF, which represent ~30% of the circulating molecules in healthy individuals (5). In areas of high shear stress, the conformational structure of the vWF can be altered, leading to exposure of the bond between Tyr842 and Met843, which is cleavage-sensitive to a specific metalloprotease (ADAMTS13 [a disintegrin-like and metalloprotease with thrombospondin type 1 motif 13]) (6). It has been shown that 20% to 70% of AS patients have a marked reduction in the percentage of vWF HMWM (7,8), and this value correlates with the transvalvular gradients (8). AVR decreases GI bleeding in 93% of patients with angiodysplasia, whereas GI surgery produces a durable remission in as few as 5% of the patients (9).

In the transcutaneous aortic valve intervention (TAVI) cohort, 9.2% of elderly patients unfit for AVR had a history of GI bleeding or anemia, including 6% with GI bleeding unrelated to angiodysplasia, 1.5% with bleeding from undefined origin, and 1.7% with documented HS (10). HS was reported to increase the periprocedural bleeding risk during TAVI, which is an effective therapeutic option in the setting of GI bleeding, with severe transfusion-dependent anemia observed only for the patient in whom TAVI failed (10). Benton et al. (11) also demonstrated cessation of massive GI bleeding with post-procedural recovery of vWF HMWM after TAVI.

The study by Spangenberg et al. (12) in this issue of *JACC: Cardiovascular Interventions* performed in 95 elderly patients with severe AS undergoing transfemoral transcatheter aortic valve replacement (TAVR) increases our knowledge of the impact of

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this intervention on bleeding risk, in particular bleeding associated with abnormal vWF multimers. The authors confirmed that a high proportion (42%) of the AS patients had type 2A von Willebrand syndrome with a relatively high content of vWF HMWM of about 16% that, as expected, was strongly correlated with mean transvalvular gradients. Interestingly, only 18% of the patients reported bleeding before TAVR, including GI bleeding noted in 11% (12). In line with previous findings (1,3,7), only a subset of AS patients with type 2A von Willebrand syndrome experienced clinically overt bleeding, indicating that there are other modulators of bleeding risk in this disease, involving inherent and environmental individual hemostatic profile. What, then, might reduce bleeding risk in severe AS? Potential mechanisms that may support hemostasis despite decreased vWF HMWM

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and reduce bleeding risk in a subset of AS patients involve enhanced thrombin generation and platelet activation reflected by higher soluble CD40 ligand in circulating blood (8), formation of procoagulant microparticles (13), and impaired fibrinolysis in part mediated by increased release of plasminogen activator inhibitor-1 (14). Higher local thrombin generation is likely to potentiate platelet activation and aggregation, which might improve local hemostasis also at high shear stress in the bleeding-prone lesions. It would be of interest to look at thrombin generation and efficiency of fibrin formation and degradation before and after TAVR as the factors that might help identify subjects deficient in vWF HMWM who are prone to GI bleeding.

Spangenberg et al. (12) provided additional evidence that abnormal vWF multimer pattern related to high shear stress improves in about 90% of the patients after TAVR, with a still lower HMWM content in these subjects compared with the control group. The remaining patients comprised individuals with mild-to-moderate aortic regurgitation or paravalvular leakage 2+ or more after TAVR, who displayed a decrease in vWF HMWM within a week from the procedure. Of note, a deficiency of vWF HMWM in the TAVR population showed no association with the risk of blood transfusions during the procedure and access site bleeding despite aspirin (100 mg/day) with clopidogrel (loading dose of 600 mg followed by 75 mg/day) plus intravenous unfractionated heparin during the procedure. Of note, type 2A von Willebrand syndrome does not increase 1-year mortality following TAVR (12). This indicates that a less invasive TAVR is safer than AVR mainly due to elimination of the large chest wound and reduction in HMWM vWF during cardiovascular bypass.

From a methodological point of view, it should be highlighted that the ratio of vWF collagen-binding activity (vWF:CB) to vWF antigen (vWF:Ag), a standard diagnostic test to assess to the functionality of vWF, was not determined in this study. In patients suspected of type 2A von Willebrand syndrome or disease, this test is performed even if it is less sensitive compared with gel electrophoresis and Platelet Function Analyzer-100 (Siemens, Marburg, Germany). Moreover, multimer analysis is not standardized, and there are substantial differences between various tests, which might hamper the interpretation of the results.

It is generally acknowledged that early diagnosis and appropriate treatment of HS, which frequently manifests as obscure or recurrent GI bleeding, are essential, although clinically relevant bleeding in AS patients appears to be less common in clinical practice than would be expected based on a high incidence of type 2A von Willebrand syndrome in this disease. Growing evidence indicates that AVR and TAVR offer long-term resolution of bleeding in most patients with severe AS. The study by Spangenberg et al. (12) supports the view that TAVR is an effective and safe option in symptomatic AS patients with a history of severe GI bleeding or refractory anemia of unknown origin. It remains to be established which laboratory tests should be performed to optimally manage AS patients who are not suitable for AVR or refuse surgery.

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