Transcatheter Aortic Valve Implantation, Atrial Fibrillation, and Bleeding: A Surprisingly Fatal Attraction

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The treatment of severe aortic stenosis (AS) has been transformed by the advent and widespread adoption of transcatheter aortic valve implantation (TAVI). Initially indicated for the management of severe AS in patients considered an unacceptably high surgical risk, there is now growing evidence that TAVI has a role in the management of AS across a spectrum of patients ranging from low to high surgical risk.[1,2] The clinical importance of AS is ever increasing with the aging of the population, since the prevalence of AS exponentially increases with age such that approximately 10% of the population aged 80 to 89 have AS.[3] This rapidly evolving field has already ushered in new improvements regarding the application of advanced imaging modalities for preprocedure planning, the development of new generation devices, in addition to greater operator experience.[4] These have led to improvements in TAVI safety and efficacy. Nevertheless, there remains an ongoing debate, and pressing clinical need, regarding the optimal antithrombotic strategy for patients undergoing TAVI given the Janus face of antithrombotic therapy helps prevent the high rates of ischemic stroke, yet endows a significant risk of bleeding complications.[5] Indeed, while the optimal antithrombotic strategy for patients undergoing TAVI remains to be defined, it is sobering that the 1 year incidence of stroke is approximately 8 to 10%, while the rate of bleeding approximates 30% at 5 years, with similar proportions of access site- and nonaccess site-related bleeding.[6–8] Current consensus guidelines (European Society of Cardiology and American College of Cardiology), recommend dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for 3 to 6 months post-procedure, followed by long-term aspirin.[1,9] However, the data supporting these recommendations remain limited, and are largely empiric, having been derived from recommendations for patients undergoing percutaneous coronary intervention (PCI). But notably, despite the larger extent of data available in the PCI population, the optimal antithrombotic strategy for elderly patients undergoing PCI similarly remains contentious given the elderly cohort represents a unique challenge given the association between advancing age and the heightened risk of both thrombosis and bleeding risk.[10–12] Pleasingly, this important knowledge gap has begun to be addressed with the just recently published POPular TAVI trial demonstrating that aspirin, compared with DAPT for 3 months, for patients undergoing TAVI was associated with a significant reduction in bleeding rates (all bleeding events over 1 year: aspirin 15.1%, aspirin + clopidogrel 26.6%, $p = 0.001$), without significant difference in the incidence of thromboembolic complications.[13]

A critical aspect regarding antithrombotic therapy post-TAVI is the issue of patients with preexisting atrial fibrillation (AF). Indeed, up to 45% of high-risk patients undergoing TAVI have preexisting AF, and thus have a compelling indication for anticoagulation.[14] As such, defining the optimal antithrombotic strategy that threads the needle of antithrombotic efficacy and safety in the TAVI patient cohort with AF is fundamentally important. This represents a major challenge as risk prediction both for thromboembolic and bleeding events in patients with AF, independent of TAVI, remains a challenge.[15–17] In this context, the article in this issue by Lother et al sheds further light on the interplay

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between preexisting AF and outcomes in patients undergoing transfemoral TAVI (TF-TAVI).[18] Using extensive registry data from over 55,000 patients, the authors demonstrate that in patients with AF undergoing TF-TAVI, bleeding was the strongest predictor of in-hospital mortality after adjustment for EuroSCORE and age (odds ratio [OR] 18.00, 95% confidence interval [CI] 15.22–21.30, $p < 0.001$). These findings are particularly striking given these data demonstrated that while stroke was also associated with increased mortality (OR 3.35, 95% CI 2.61–4.30, $p < 0.001$), this risk was significantly outweighed by the adverse prognostic effects of bleeding. Moreover, it is noteworthy that this study highlights the adverse effects of preexisting AF on TF-TAVI outcomes with this patient group displaying a 1.35 increase of in-hospital mortality compared with patients without AF.

While the data presented by Lother et al[18] should be interpreted with usual caveats associated with a retrospective analysis, the reported findings are consistent with previous data emphasizing the prognostic significance of TAVI-associated bleeding. Indeed, early (< 30 days) major bleeding complications occur in 10 to 15% of patients undergoing TAVI, and are associated with adverse cardiovascular outcomes and increased mortality.[19] Likewise, late bleeding complications are associated with a threefold increase in mortality.[20] Against this back drop, it is significant that several studies now implicate AF as an adverse prognostic factor for patients undergoing TAVI.[21] Although data regarding the specific antithrombotic therapy in the study by Lother et al was not available, it seems likely that more intense antithrombotic approaches incorporating anticoagulation in patients with AF is a central reason for the bleeding complications. However, whether AF, independent of antithrombotic regimen, confers an increased risk of bleeding in TAVI patients remains to be investigated.

The association of AS and bleeding (►**Fig. 1**) has been well appreciated for over 50 years since the initial description of the association of calcific AS and gastrointestinal bleeding by Dr. E.C. Heyde.[22] Indeed, Heyde's syndrome, as it became eponymously named, was later demonstrated to involve the intricate interplay between alterations in blood flow induced by the stenotic aortic valve, proteolysis of von Willebrand factor (vWF) high molecular weight multimers, and gastrointestinal angiodysplasia.[23] More recently it has been elucidated that the high shear stress, imparted upon circulating vWF as it traverses the severely stenotic aortic valve, results in "unfolding" of vWF multimers making it more prone to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13-mediated cleavage.[24] While vWF multimers may normalize quickly post-TAVI,[25] it is striking that recent reports have highlighted that this hemostatic abnormality may persist post-TAVI, even without significant post-TAVI paravalvular aortic regurgitation (PAVR). This raises the prospect that prosthetic valve design and/or placement may influence the hemostatic system.[26] Importantly, there appears to be a direct link between hemostatic changes in AS and clinical outcomes, with a recent report detailing patients who underwent TAVI with DAPT and exhibited low platelet reactivity, had a nearly twofold increase in rates of bleeding.[27] Moreover, a prolonged closure time with adenosine diphosphate using the point of care PFA-100 assay, is a strong predictor of TAVI-associated PAVR and also correlates with the risk of bleeding and mortality.[28,29] As such, there appears a perilous balance to be struck between the requisite platelet inhibition to prevent thrombotic complications and the dreaded risk of bleeding.[30,31] Indeed, the fact that current DAPT recommendations includes clopidogrel rather than more potent P2Y12 inhibitors, such as prasugrel and ticagrelor, reflects the caution toward stronger platelet inhibition and the associated higher bleeding risk, which is also reflected in the approach to use single antiplatelet therapy in TAVI patients deemed a high risk of bleeding.[30,32]

One aspect that surprisingly remains understudied in AS, is the effect of increased shear on blood cells passing through the stenotic aortic valve. Recently, it has been shown that monocytes, which play an important role in coagulation, exhibit an activated phenotype in AS patients which reverses post-TAVI.[33] Although it is well accepted that platelets can be activated and desensitized by shear stress, there is a lack of data currently available regarding the effects of AS, and indeed TAVI, on platelet function. Therefore, mechanistic studies on the role of shear stress-induced effects on circulating blood cells will likely provide additional insights into the links between the potential prothrombotic effects and bleeding risk observed in patients undergoing TAVI.

Given the intimate relationship between severe AS and the hemostatic system, the implications of these findings presented by Lother et al are significant given the relative lack of randomized, controlled trials in the AF TAVI patient cohort. While current guidelines support the recommendation for concurrent oral anticoagulation (OAC) with either a direct oral anticoagulant or vitamin K antagonist (VKA) in addition to aspirin for patients with AF undergoing TAVI, there is a yearning need for prospective data to confirm such a therapeutic paradigm confers benefit. In this regard, recent data has challenged the benefit of antiplatelet therapy for patients already on VKAs, while highlighting such an approach is associated with a twofold risk of major and/or life-threatening bleeding.[34] These findings have been reiterated by the recent POPular trial which investigated antithrombotic regimes for patients with a preexisting indication for anticoagulation (96% AF) undergoing TAVI. Of note, patients that received anticoagulation alone had a significant reduction in bleeding complications when compared with those receiving OAC plus clopidogrel for 3 months (21.7% vs. 34.6%, $p = 0.01$).[35] Thus, results from prospective trials such as the ENVISAGE-TAVI AF and AVATAR trials are eagerly awaited and will hopefully shed more light and provide further data on an optimal antithrombotic strategy. However, similar to the PCI domain, we may be observing the limits of our current antithrombotic strategies that have inherent limitations in their ability to straddle the risk of stroke, leaflet thrombosis, and bleeding.[36] Therefore, in an era with an array of novel antithrombotic strategies in preclinical and early clinical development, the application of new antithrombotics may hold the ultimate promise for safer and more effective strategies for patients undergoing TAVI.[36,37]

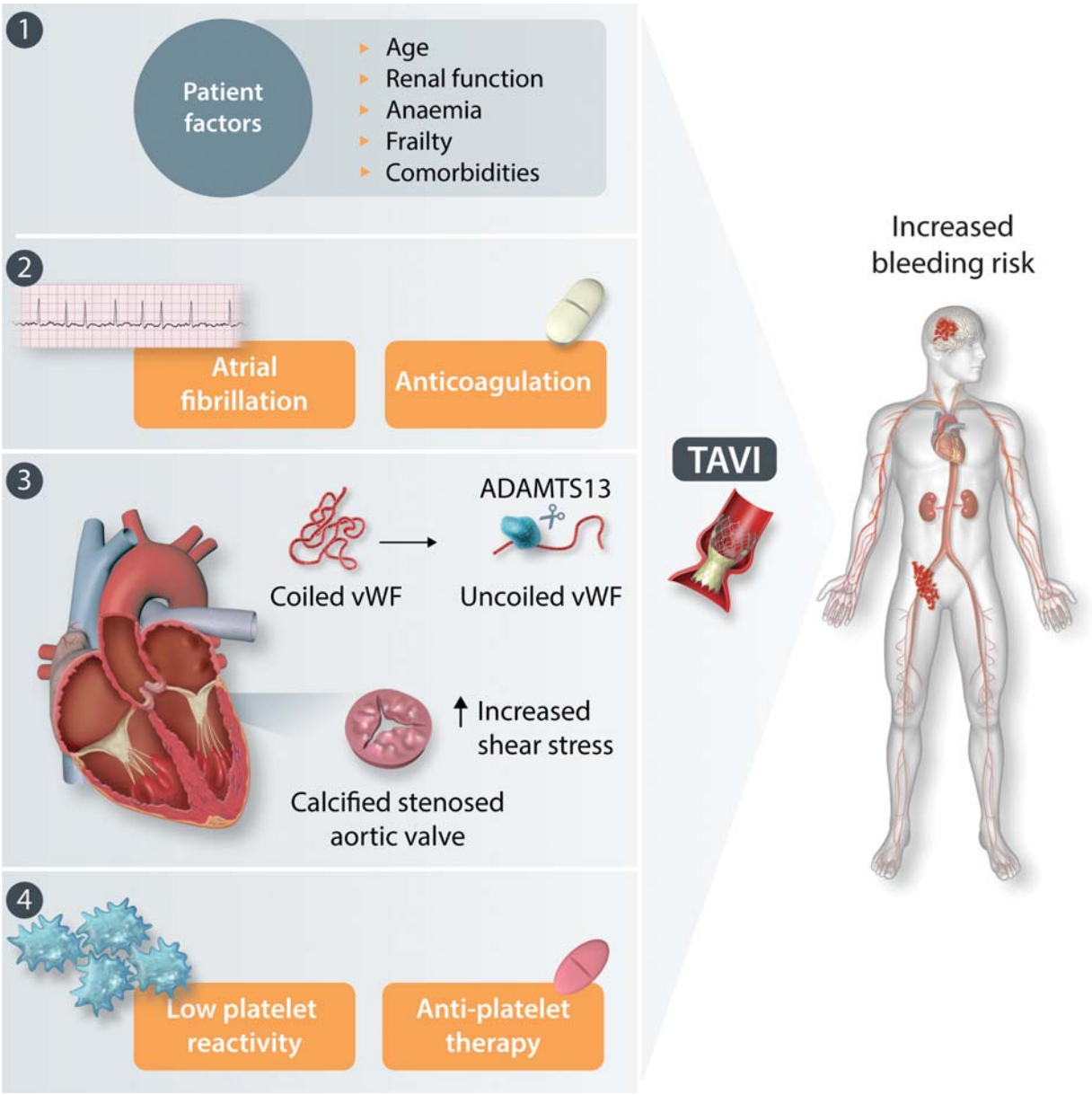

Fig. 1 Factors contributing to transcatheter aortic valve implantation (TAVI)-associated bleeding. The factors that contribute to TAVI-associated bleeding include: (1) patient factors including age, renal function, anemia, frailty, and comorbidities; (2) atrial fibrillation and the use of anticoagulation; (3) the development of acquired von Willebrand syndrome due to the effects of shear imparted on von Willebrand factor (vWF) at is traverses the stenotic aortic valve, which leads to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13)-mediated proteolysis of vWF; and (4) low platelet reactivity and the use of antiplatelet therapy. These effects on the hemostatic system predispose patients undergoing TAVI to an increased risk of bleeding at both procedure-related and nonprocedure sites.

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Conflict of Interest
None declared.

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