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Letters

TO THE EDITOR

von Willebrand Disease After TAVR

The Missing Link?

By abolishing the obstruction created by a highly stenotic aortic valve, transcatheter aortic valve replacement (TAVR) is an effective treatment for severe aortic stenosis, with a hemodynamic profile (mean gradient and aortic valve area) at least similar or even superior to conventional surgical aortic valve replacement (1). However, the presence of paravalvular leak (PVL) after TAVR has been shown to be associated with increased mortality (2). Although a negative impact on left ventricular recovery and remodeling has been proposed as the primary causal mechanism (3), the exact pathophysiology of PVL and its association with increased mortality remains to be completely understood.

Spangenberg et al. (4) elegantly demonstrated that although TAVR was successful in resolving the detrimental hematologic impact of aortic stenosis in most patients, PVL was associated with a persistent breakdown of high molecular weight von Willebrand factor (vWF), suggesting an increase in flow turbulence. Although this finding is extremely interesting, the low number of patients (N = 95) included in their study precludes any definitive conclusion regarding the clinical implication of acquired vWF disease after TAVR, both from a bleeding and mortality point of view.

From a large cohort of 2,401 patients in the randomized PARTNER (Placement of AoRTic TraNscathetER Valve Trial), we recently demonstrated that the strongest predictor of bleeding events between 30 days and 1 year after successful TAVR was the presence of moderate to severe PVL (5). Although some may argue that PVL may represent a marker of patients' sickness rather than a causal factor leading to mortality, we suggested that significant PVL, with persistent increased flow turbulence and shear stress, may lead to the breakdown of the large molecular weight vWF and consequently predispose patients to late bleeding events, potentially contributing to increased mortality.

Whether high molecular weight vWF could be a clinically useful surrogate marker of significant PVL (or any other states of high shear stress, such as prosthesis-patient mismatch) in the future needs to be investigated in a larger population; however, the report of Spangenberg et al. (4), paired with our previous findings (5), suggests that vWF breakdown after TAVR could be seen as the "missing link" among PVL, late bleeding events, and its association with increased mortality.

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REPLY: von Willebrand Disease After TAVR: The Missing Link?

In reply to the letter of Dr. Généreux and colleagues, we strongly agree with their continuative analysis of our data that in conjunction with their work on major late bleeding complications offer a substantiated hypothesis for the paravalvular leakage (PVL)-associated mortality after transcatheter aortic valve

replacement (TAVR). Furthermore, our study provides the asked for proof of the turbulence-induced cleavage of proaggregation proteins (1) for the TAVR population.

In summary, TAVR as well as surgical aortic valve replacement lead to a resolution of high-molecular weight multimer (HMW-MM) deficiency/acquired von Willebrand-syndrome in patients with severe aortic stenosis. However, PVL as well as prosthesis-patient mismatch lead to persistent/recurrent factor deficiency in the respective treatment modalities, with severe (i.e., HMW-MM-deficient) prosthesis-patient mismatch appearing to occur more frequently with surgical aortic valve replacement (2,3). As of now and from a pathophysiological standpoint, these findings fuel the thesis of PVL ultimately translating into a HMW-MM-associated bleeding diathesis and therefore increased mortality (4). But this applies possibly even more so to patients with atrial fibrillation/atrial flutter in need of oral anticoagulation or triple therapy after TAVR. Whether HMW-MM/PVL status after TAVR should be incorporated into the post-procedural anticoagulant strategy in order to reduce bleeding in this subset of patients, reflecting up to 40% of the TAVR population, needs to be clarified by future studies.

Furthermore, with HMW-MM deficiency as an underlying mechanism of PVL-associated mortality, efforts to sidestep PVL-induced HMW-MM deficiency are the logical primary consequence. Congruously, HMW-MM reflected by platelet function analyzer-closure time adenine DI-phosphate have just lately been suggested to be capable of guiding these efforts intraprocedural (5).

Definite evidence for the joint thesis though will only be available if future randomized trials reducing major late bleeding complications demonstrate improved survival (1) in a number of patients allowing definite conclusions. With this in mind, consolidating the work of Généreux et al. (4) providing bleeding-associated mortality as driving force and target, our work indicating HMW-MM as the missing link of bleeding associated mortality and PVL, and the work of Van Belle et al. (5) providing a technical suggestion for intraprocedural HMW-MM-guided PVL avoidance, final clarification seems to be within reach.

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Quantitative Evaluation of Residual Atrial Septal Defect Following Transseptal Catheterization for Intracardiac Interventional Procedures

Iatrogenic residual atrial septal defect (rASD) following transseptal catheterization (TC) is a risk of many interventional procedures. In a recent issue of *JACC: Cardiovascular Interventions*, Schueler et al. (1) reported a 50% rASD persistence rate after transcatheter mitral valve repair using the MitraClip system (Abbott Vascular, Abbott Park, Illinois). The assessment was made at 6-month transesophageal echocardiography (TEE) follow-up. They concluded that the persistent interatrial shunting was associated with worse clinical outcomes and increased mortality. However, there are some important deficiencies in their methodology and data presentation that require clarification.

The size of rASD and the time course for possible regression are critical parameters that will affect clinical hemodynamic and cardiac function. Previous studies using Mullins TC sheath (Medtronic,