Editorial

Von Willebrand factor multimers during transcatheter aortic valve replacement—an additional clue for detecting post-procedural aortic regurgitation?

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Severe aortic valvular stenosis is among the most common forms of valvular heart disease, with disabling symptoms and a poor prognosis if left untreated (1). Parallel to the ageing of the general population and the rise of overall life expectancy, an increasing prevalence of the disease can be observed, and a growing need to treat patients who are deemed unsuitable for traditional valve replacement owing to high calculated surgical risk or general frailty.

Transcatheter aortic valve replacement (TAVR), first introduced in human medicine in 2002 (2) with the aim to treat this surgically inoperable or extremely high risk patient group, proved to have promising early and mid-term results when compared to surgical aortic valve replacement (SAVR) (3,4) or medical therapy alone (5). On this basis, there is a growing enthusiasm for extending the indications of TAVR towards the intermediate risk profile patient groups (6).

Despite its undisputed attractiveness, some important issues regarding TAVR such as post-procedural aortic regurgitation (ppAR), stroke, vascular complications, and the still unknown long-term durability are yet to be addressed.

Among those, ppAR, which has been observed at a relatively high incidence (7,8) and has a demonstrated correlation with increased early mortality following TAVR (8-10), is of particular importance. As ppAR is termed, by some, as the potential "Achilles heel" of TAVR (11), it should be noted that there is an extensive effort in the development of newer generation prostheses to eliminate this issue, with a reported ppAR of 2.7% with the SAPIEN 3 at 1 year (12).

As outlined previously, significant (more-than-mild) ppAR has a negative effect on outcome, thus it should be detected and dealt with early in the operating room—although the evaluation of ppAR even with transesophageal echocardiography (TEE) is not always straightforward.

Von Willebrand factor (vWF), required to promote adhesion of platelets to the site of vessel injury has a major role in hemostasis. Acquired von Willebrand disease (AVWD) is a bleeding disorder characterized by rapid removal but normal or excessive synthesis of vWF compared to the inherited form, and could be observed under various hematologic, immunologic and cardiovascular conditions, with different underlying mechanisms (13).

In AVWD associated with cardiovascular diseases, the high blood shear stress induced unfolding, consequential proteolysis and loss of high molecular weight vWF (HMW) multimers plays the key role.

The role of AVWD has been investigated in relation to bleeding events associated with continuous flow mechanical circulatory assist devices (14), in some congenital cardiac defects (15), aortic stenosis (16,17), mitral regurgitation (18) and even in some cases of aortic regurgitation.

The reasons for this growing interest lies not only in the potentially deleterious consequences of an AVWD related bleeding event—not every AVWD patient bleeds, and the bleeding is not always proportional to the severity of the defect—but also in the hypothesis, that as the loss and recovery of HMW multimers rapidly follows the changes in blood shear stress, its measurement can serve as a biological sensor of pathological blood flow in various clinical scenarios (19), such as ppAR following TAVR.

As direct vWF multimeric analysis is cumbersome, time consuming and is therefore of limited use in an acute clinical setting, in their study, Van Belle and colleagues (20) investigated the feasibility of utilizing a widely available and rapid point-of-care testing method to observe the hemostatic alterations influenced by elimination or presence of high shear stress flows related to pre-procedural aortic stenosis or ppAR during TAVR. Closure-time with adenosine diphosphate (CT-ADP) analysis with the platelet function analyzer (PFA)-100, the test used for von Willebrand disease screening, was chosen for this purpose.

In their primary cohort, all 183 patients received the SAPIEN XT valve through femoral arterial access under general anesthesia with intraprocedural TEE monitoring. Severity of ppAR was evaluated by TEE and graded according to the VARC-2 criteria. If more than mild ppAR was noted after initial valve deployment [46], a corrective attempt was made either by post-dilation [46] or by the implantation of a second valve [2]. During the procedure, values of PFA-100 CT-ADP and HMW multimer ratio were measured alongside repeated TEE examinations at three time points: after initial valve implantation (T1), after additional dilation or second valve implantation (T2), and finally 15 minutes after the conclusion of the procedure (T3). Three subgroups were then identified based on the degree of ppAR at T3-no-regurgitation group [137], corrected regurgitation [20] and a persistent regurgitation group [26]. The values of HMW multimer ratio and CT-ADP were measured in each group at the three time points, and the sequence of time related changes were noted. Based on that, receiver-operating characteristic curves were generated for CT-ADP and HMW multimer ratio detecting more-than-mild ppAR as measured by TEE, AUCs calculated, and the optimal thresholds for detecting ppAR were determined on the basis of the Youden index. This threshold of CT-ADP was tested in a validation cohort of 201 patients undergoing TAVR with the same method.

Based on their findings, it has been demonstrated that parallel to decreased HMW multimer ratio, elongation of CT-ADP could be observed not only in aortic stenosis, but also in ppAR, and the values of HMW multimer ratio and CT-ADP were significantly different between the no- or corrected regurgitation and the persistent regurgitation group. The time-related changes of HMW multimer ratio and CT-ADP also quickly followed the altered hemodynamics. With both methods, thresholds determined based on ROC analysis, showed remarkably good specificity, sensitivity, and negative predictive value for detecting more-than-mild ppAR, as confirmed by TEE. The optimal threshold value for CT-ADP identified in the primary cohort was tested in their validation cohort with regard of the presence of ppAR as observed by TEE, with the same good results. Furthermore, the presence of ppAR indicated by the altered haemostatic parameters showed correlation with 1 year mortality.

Based on these results can we state that we can use CT-ADP as a reliable, point-of-care biological sensor for detecting ppAR? Their findings are promising, however there are several questions to be answered first, before we could make this statement.

Firstly, can we state that virtually all patients with significant aortic stenosis (or regurgitation) have a detectable hemostatic defect? Data obtained from previous studies (16,17) seem to support the presence of a strong, but not a universal correlation.

Secondly, originally CT-ADP is a non-specific screening test of hemostasis. As outlined by the authors, there are several other factors, drugs and conditions capable to influence CT-ADP. Among others included in the multivariable analysis, anemia and thrombocytopenia have also been reported to affect PFA-100 results (21), and could be expected in patients with aortic stenosis. Their role has not been investigated in this study, but if taken into account, potentially could have some influence on the results.

A further concern is, that the patients in the primary and the in validation cohort share the same characteristics in terms of good left ventricular ejection fraction [LVEF (%), 54.5±11.5 and 52.0±12.3] and relatively normal-sized aortic annulus (22.7±1.9 and 22.8±2.5 mm) as measured by pre-procedural TTE, and close-to-normal BMI (27.6±5.8 and 27.2±6.1). The peri-procedural sequence of changes in CT-ADP might be different or less pronounced in patients with different flow characteristics, such as in cases of relatively small aortic annulus (persistent high shear stress due to a smaller prosthesis) or with low-flow low-gradient

aortic stenosis (less or no pre-procedural high shear stress).

Nevertheless, there is an explicit need towards further improving the diagnostic acuity in relation to ppAR (22). This attractive point-of-care testing method as suggested by the authors should be further investigated and evaluated on larger patient groups with different characteristics. It could potentially evolve into a useful additional tool in detecting significant ppAR following TAVR.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Carabello BA, Paulus WJ. Aortic stenosis. Lancet 2009;373:956-66.
2. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006-8.
3. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477-84.
4. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.
5. Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2485-91.
6. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2016;374:1609-20.
7. Svensson LG, Tuzcu M, Kapadia S, et al. A comprehensive review of the PARTNER trial. J Thorac Cardiovasc Surg 2013;145:S11-6.
8. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol 2013;61:1585-95.
9. Kodali S, Pibarot P, Douglas PS, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. Eur Heart J 2015;36:449-56.
10. Van Belle E, Juthier F, Susen S, et al. Postprocedural aortic regurgitation in balloon-expandable and self-expandable transcatheter aortic valve replacement procedures: analysis of predictors and impact on long-term mortality: insights from the FRANCE2 Registry. Circulation 2014;129:1415-27.
11. Généreux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature. J Am Coll Cardiol 2013;61:1125-36.
12. Herrmann HC, Thourani VH, Kodali SK, et al. High-Risk and Inoperable Patients With Severe Aortic Stenosis. Circulation 2016;134:130-40.
13. James AH, Eikenboom J, Federici AB. State of the art: von Willebrand disease. Haemophilia 2016;22 Suppl 5:54-9.
14. Nascimbene A, Neelamegham S, Frazier OH, et al. Acquired von Willebrand syndrome associated with left ventricular assist device. Blood 2016;127:3133-41.
15. Gill JC, Wilson AD, Endres-Brooks J, et al. Loss of the largest von Willebrand factor multimers from the plasma of patients with congenital cardiac defects. Blood 1986;67:758-61.
16. Vincentelli A, Susen S, Le Tourneau T, et al. Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med 2003;349:343-9.
17. Blackshear JL, Wysokinska EM, Safford RE, et al. Indexes of von Willebrand factor as biomarkers of aortic stenosis severity (from the Biomarkers of Aortic Stenosis Severity [BASS] study). Am J Cardiol 2013;111:374-81.
18. Blackshear JL, Wysokinska EM, Safford RE, et al. Shear stress-associated acquired von Willebrand syndrome in patients with mitral regurgitation. J Thromb Haemost 2014;12:1966-74.
19. Van Belle E, Rauch A, Vincentelli A, et al. Von Willebrand factor as a biological sensor of blood flow to monitor percutaneous aortic valve interventions. Circ Res 2015;116:1193-201.
20. Van Belle E, Rauch A, Vincent F, et al. Von Willebrand Factor Multimers during Transcatheter Aortic-Valve

Replacement. N Engl J Med 2016;375:335-44.
21. Tiede A, Priesack J, Werwitzke S, et al. Diagnostic workup of patients with acquired von Willebrand syndrome: a retrospective single-centre cohort study. J Thromb Haemost 2008;6:569-76.
22. Abdelghani M, Spitzer E, Ren B, et al. Real-world feasibility of the VARC-recommended multiparametric approach for the assessment of post-TAVI aortic regurgitation. Int J Cardiol 2016;223:220-1.

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