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JACC REVIEW TOPIC OF THE WEEK

von Willebrand Factor and Management of Heart Valve Disease

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ABSTRACT

For decades, numerous observations have shown an intimate relationship between von Willebrand factor (VWF) multimer profile and heart valve diseases (HVD). The current knowledge of the unique biophysical properties of VWF helps us to understand the longstanding observations concerning the bleeding complications in patients with severe HVD. Not only does the analysis of the VWF multimer profile provide an excellent evaluation of HVD severity, it is also a strong predictor of clinical events. Also of importance, VWF responds within minutes to any significant change in hemodynamic valve status, making it an accurate marker of the quality of surgical and transcatheter therapeutic interventions. The authors provide in this review a practical, comprehensive, and evidence-based framework of the concept of VWF as a biomarker in HVD, advocating for its implementation into the clinical decision-making process besides usual clinical and imaging evaluation. They also delineate critical knowledge gaps and research priorities to definitely validate this concept.
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Besides clinical evaluation, current management of heart valve disease (HVD) relies almost exclusively on echocardiographic assessment, which is challenging or needs refinement in numerous clinical situations. von Willebrand factor (VWF) biology has the unique feature to mirror the hemodynamic changes applied on the blood flow in most of stenotic or regurgitant HVD. Multiple studies demonstrated that VWF not only provides an excellent evaluation of HVD severity, but also serves as a marker of the quality of the therapeutic interventions and a predictor of patients' outcomes (1). Overall, this review offers an integrated framework for understanding the emerging concepts of VWF as a biomarker in HVD. We also delineate critical knowledge gaps and research priorities.

VON WILLEBRAND FACTOR: PRODUCTION AND REGULATION

VWF is a large multimeric glycoprotein involved in hemostasis via several of its structural domains allowing interactions with a-desintegrin and metalloprotease with a thrombospondin type-1 motif family (ADAMTS13) (A2 domain), platelets (A1 domain), Factor VIII (D′-D3 domain), collagen (A3 domain), or αIIbß3-integrin (C4 domain) (2). It has been further suggested that VWF contributes to the regulation of

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angiogenesis (3). VWF is produced and stored in endothelial cells and megakaryocytes as ultra-large multimers. Once released, they are enzymatically cleaved by ADAMTS13. Consequently, VWF circulates as a series of heterologous multimers, from single dimers to large multimers. In normal plasma, as many as 20 multimer bands can be distinguished, which thus have incorporated 40 monomeric VWF subunits. The largest multimers are hemostatically the most efficient, and generally multimers consisting of >20 to 30 VWF subunits (10 to 15 mers) are considered high-molecular-weight (HMW) multimers. Under low shear conditions (<1,000 s^{-1}), multimers are circulating in a globular "quiescent" form with some of the binding domains in cryptic conformation. Under high shear conditions (>2,000 s^{-1}), VWF multimers get "activated" switching toward an elongated form allowing interactions with platelets and collagen. In parallel, exposure of the A2-domain to the circulating ADAMTS13 induces a nearly immediate deactivation through enzymatic cleavage generating smaller and less efficient multimers (4).

FROM INHERITED VON WILLEBRAND DISEASE TO ACQUIRED VON WILLEBRAND SYNDROME

Inherited VWD, first described in 1926 by Erik von Willebrand, is caused by congenital decrease or dysfunction of VWF (5). Quantitative defects of VWF may either be classified as partial (type 1) or total (type 3), whereas VWD type 2 corresponds to a qualitative defect. VWD type 2A is characterized by lack of HMW multimers (and thus, reduced platelet binding), which in some cases is due to a mutation-induced increased susceptibility for ADAMTS13-mediated proteolysis (6).

The noninherited development of VWF dysfunction (i.e., acquired von Willebrand syndrome [aVWS]) has been reported initially in systemic lupus erythematosus or benign monoclonal gammopathy and subsequently in aortic stenosis (AS). As a selective deficiency of the HMW multimers was found in >80% of aVWS cases, the generic term aVWS type 2A is also frequently used (7).

Various assays are used to evaluate the activity of VWF multimers (i.e., the capacity to bind collagen and platelets) and screen for aVWS type 2A. The current gold standard for the diagnosis of aVWS type 2A relies on the electrophoretic analysis of VWF multimers, which is done manually, is time-consuming, and is very demanding regarding technical expertise (Online Figure 1). The point-of-care testing PFA-100/200 (Platelet Function Analyzer, Siemens, Germany) is sensitive for the presence of HMW multimers defect and provides nearly immediate results (5 to 10 min) (Online Appendix).

FROM HEYDE'S SYNDROME TO ACQUIRED VON WILLEBRAND SYNDROME TYPE 2A

In 1958, Heyde reported the eponym syndrome associating unexplained gastrointestinal bleedings (GIB) and AS in 10 patients. The causal link between both entities was further suggested by reports of clinical cases in which the GIB (mainly from angiodysplasia) disappeared after surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) (Online Tables 1 and 2). The most convincing evidence was provided in 1987 with the report of the long-term follow-up outcomes (>8 years) of a cohort of 87 patients experiencing AS and GIB (or anemia) according to treatment modality. Although after SAVR (n = 14), 93% of patients were free from recurrent bleeding, this was only the case in 3% of those who had digestive surgery (n = 37) and none of those who were treated medically (n = 40) (8).

Approximatively at the same time, 2 studies described a HMW multimers defect mimicking the biological footprint of VWD type 2A in patients with congenital cardiac defect or HVD and its correction after surgery (9,10). In particular, Weinstein et al. (10) reported that HMW multimers of patients with severe HVD (n = 43, mainly AS) were significantly reduced compared with healthy subjects or patients with coronary artery disease (Online Table 3). In this series, HMW multimers returned to normal after SAVR (10) (Online Table 2).

Based on these findings, and also due to the similarity between the GIB phenotype of patients with Heyde's syndrome and those with VWD type 2A (11), Warkentin et al. (12) were the first to suggest that Heyde's syndrome originated from aVWS type 2A induced by AS. This suggestion was further supported by the high rate of concomitant AS and HMW multimers defect (>80%) in patients with "bleeding angiodysplasia," whereas multimers were normal in patients with "nonbleeding angiodysplasia" (13), and by the report of the simultaneous correction of HMW multimers defect and GIB in 2 patients undergoing SAVR (14). In 2003, the link between AS and aVWS type 2A was definitely established by our group, demonstrating that SAVR was associated with a

ABBREVIATIONS AND ACRONYMS

aVWS = acquired von Willebrand syndrome

CT-ADP = closure time of a membrane coated with collagen and adenosine-5′-diphosphate

GIB = gastrointestinal bleeding

HMW = high molecular weight

HVD = heart valve disease

PVR = paravalvular regurgitation

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

VWD = von Willebrand disease

VWF = von Willebrand factor

parallel correction of the HMW multimers defect and a disappearance of mucosal bleeding (from 26% prior to 2% after surgery) in a series of 42 patients (15).

Overall, the correction of the HMW multimers defect and/or bleeding by aortic valve replacement was reported in 1,801 patients across >60 reports (Online Tables 1 and 2).

EPIDEMIOLOGY AND MECHANISMS OF GASTROINTESTINAL BLEEDING IN PATIENTS WITH HEART VALVE DISEASE

Bleeding from GI angiodysplasia is considered a hallmark of Heyde's syndrome even if angiodysplasia accounts for "only" 10% to 20% of all bleeding episodes in patients with AS. The first case of angiodysplasia and autopsy-proven AS was reported in 1971 (16). The exact prevalence of GIB in AS patients remains uncertain (from 2% to 5%, to 25%), but several studies have noted an increased risk of GIB (3- to 100-fold) compared with patients without AS (17). This wide estimate is related to the heterogeneity of HVD severity, to the methods and duration of data collection, and to the different bleeding definitions used across the studies (bleeding from angiodysplasia; all-cause GIB; or the combination of GIB, mucosal bleeding, and unexplained anemia altogether) (Online Table 2).

HVD patients usually do not manifest generalized bleeding diathesis because intermediate-sized multimers remain available for primary hemostasis in vessels with physiological shear rate (18). Angiodysplasia consists of clusters of submucosal arteriovenous malformations and generates pathologically increased wall shear rate (>4,000 s^{-1}). Such an environment predisposes to bleeding in patients who are lacking HMW multimers to maintain hemostasis. It is commonly found everywhere in the GI tract, but the cecum and right colon are the most affected. Bleeding from arteriovenous malformations in the nasal mucosae have also been reported (19). The bleeding risk seems intimately related to the VWF abnormalities.

CAUSAL RELATIONSHIP BETWEEN ACQUIRED VON WILLEBRAND SYNDROME AND ANGIODYSPLASIA?

Whether the relationship between aVWS type 2A and angiodysplasia in patients with AS is causative or coincidental is unclear, as both angiodysplasia and AS are associated with aging (18). Veyradier et al. (13) found that aVWS type 2A is not associated with a higher prevalence of angiodysplasia *per se*, but with a higher prevalence of "bleeding" among patients with angiodysplasia (13). Furthermore, angiodysplasia usually remains visible after SAVR, whereas GIB have stopped (Online Table 1).

Recently, the implantation of mechanical circulatory support in animals induced both aVWS type 2A and abnormal gastrointestinal vascularity, suggesting a direct causal link between VWF degradation and angiodysplasia (20). This effect may originate from the loss of the antiangiogenic effect of HMW multimers and/or to the "proangiogenic" effect of VWF-degradation products. This hypothesis is supported by the observation of capillary dilatation, tortuosity, and blood extravasation in young VWD patients (21), or the presence of angiodysplasia in young patients with aVWS type 2A related to congenital cardiopathy (9,22) (**Central Illustration**).

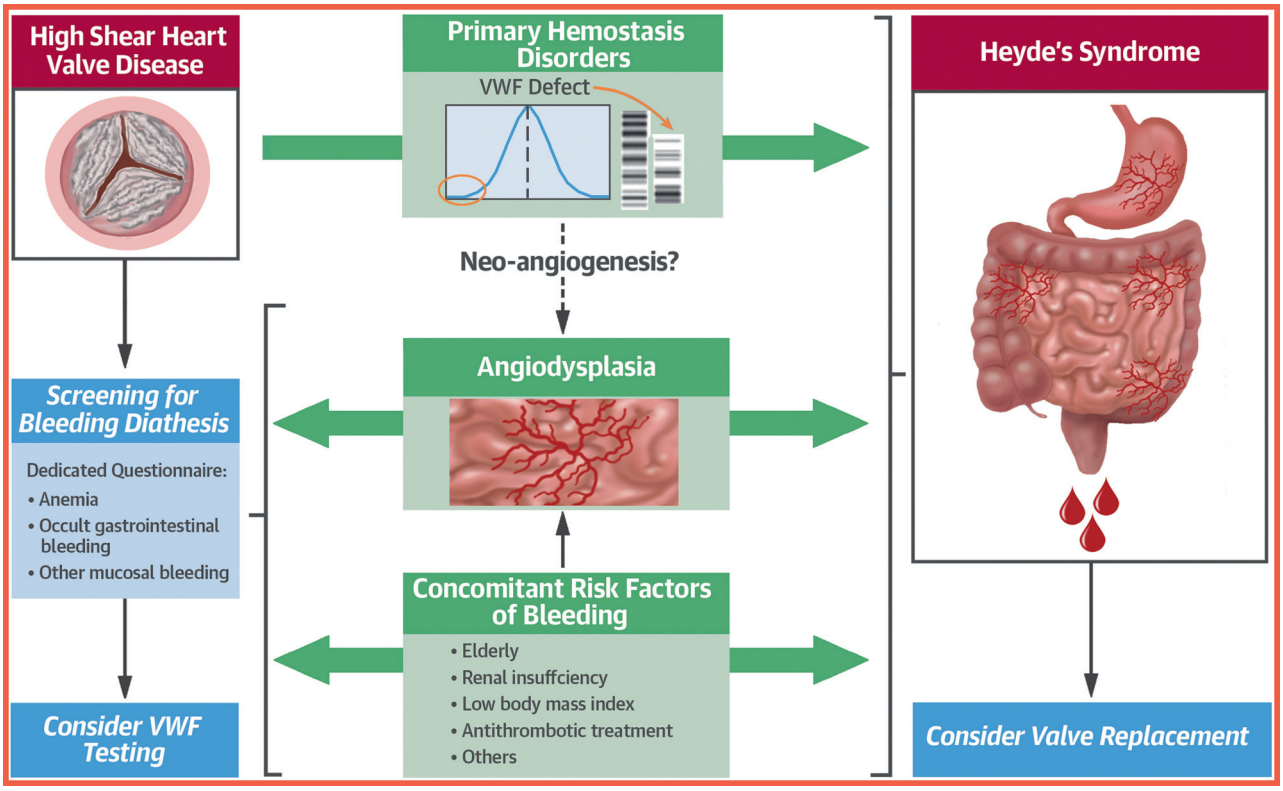
VON WILLEBRAND FACTOR MULTIMER STRUCTURE TO ASSESS THE SEVERITY OF HEART VALVE DISEASE

Steady-state measurement of the VWF multimer structure (and its quantification by closure time of a membrane coated with collagen and adenosine-5′-diphosphate [CT-ADP]) seems a reliable index of the presence and severity of several native HVDs or prosthetic valve dysfunction.

IN NATIVE STENOTIC HVD. The exact prevalence of HMW multimers defect in AS is unknown. Although most of the studies have reported a prevalence in the 65% to 85% range, much lower (33%) or higher (100%) prevalences have also been reported (Online Table 2). This may originate from different methods of quantification of HMW multimers (Online Table 2) or from the investigation of populations with different AS severity. Indeed, the seminal work of Vincentelli et al. (15) established that the percentage of HMW multimers inversely correlates with the increase of the echocardiographic transaortic gradient ($r = -0.56$; $p < 0.001$), whereas CT-ADP positively correlates ($r = 0.58$; $p < 0.001$).

This initial observation was further confirmed and repeated in 16 studies that included a total of 1,548 patients (Online Table 3). However, the correlation is not absolute, and we and others have reported that approximately 50% of patients with moderate AS have abnormal CT-ADP and HMW multimers (23,24). On the other hand, at least 20% of patients with echocardiography-based severe AS do not have a significant VWF defect (15). As it has been shown that a lower LVEF usually translates into a lower transaortic gradient and less degradation of HMW multimers, part of the previously described heterogeneity could relate to differences in ventricular function

CENTRAL ILLUSTRATION **von Willebrand Factor and Heart Valve Disease**



Van Belle, E. et al. J Am Coll Cardiol. 2019;73(9):1078–88.

Emerging roles for mucosal bleeding scores, VWF (von Willebrand Factor) testing, and early valve replacement in patients with HVD based on the pathophysiology of Heyde's syndrome.

(1,25). Nevertheless, a recent report has suggested that even in patients with poor LV function, the analysis of HMW multimers may be used to differentiate between patients with true or pseudosevere AS (26). No reliable data have been reported in patients with mitral or pulmonary stenosis.

IN NATIVE REGURGITANT HVD. Blackshear et al. (27,28) identified a strong correlation between the severity of the regurgitant valvulopathy (as assessed by the regurgitant volume by echocardiography) and the magnitude of the HMW multimers defect (or the CT-ADP) in 84 patients with native mitral regurgitation ($p < 0.001$) (27) or aortic regurgitation ($r = 0.74$; $p < 0.001$ for CT-ADP) (28). They also reported a prevalence of HMW multimers defect for ≈80% in patients with severe mitral or aortic regurgitation.

Since the initial report of Weinstein et al. (10), almost 500 patients with regurgitant HVD have been characterized with the analysis of VWF-related markers (Online Table 2). To our knowledge, no data have been reported on patients with tricuspid regurgitation.

IN STRUCTURAL OR NONSTRUCTURAL DETERIORATION OF THE BIOPROSTHETIC VALVE. Hemodynamic prosthetic valve function and VWF-related markers have been studied in nearly 1,300 patients (Online Table 4).

Detection of paravalvular regurgitation. Several groups established that measurement of HMW multimers or CT-ADP could accurately identify the presence of paravalvular regurgitation (PVR) (29) (Online Tables 2 and 4). In our cohort of 183 patients undergoing TAVR (WITAVI cohort), HMW multimers and CT-ADP >180 s discriminated patients with or without moderate or severe PVR, respectively, having a negative predictive value of 98.7% and 98.6%, respectively. These results were replicated in a multicentric cohort of 201 patients showing a negative predictive value of 96.9% for CT-ADP (1).

FIGURE 1 **Proposed Models for the Quantification of HVD Severity by the Analysis of VWF Multimers Profile**

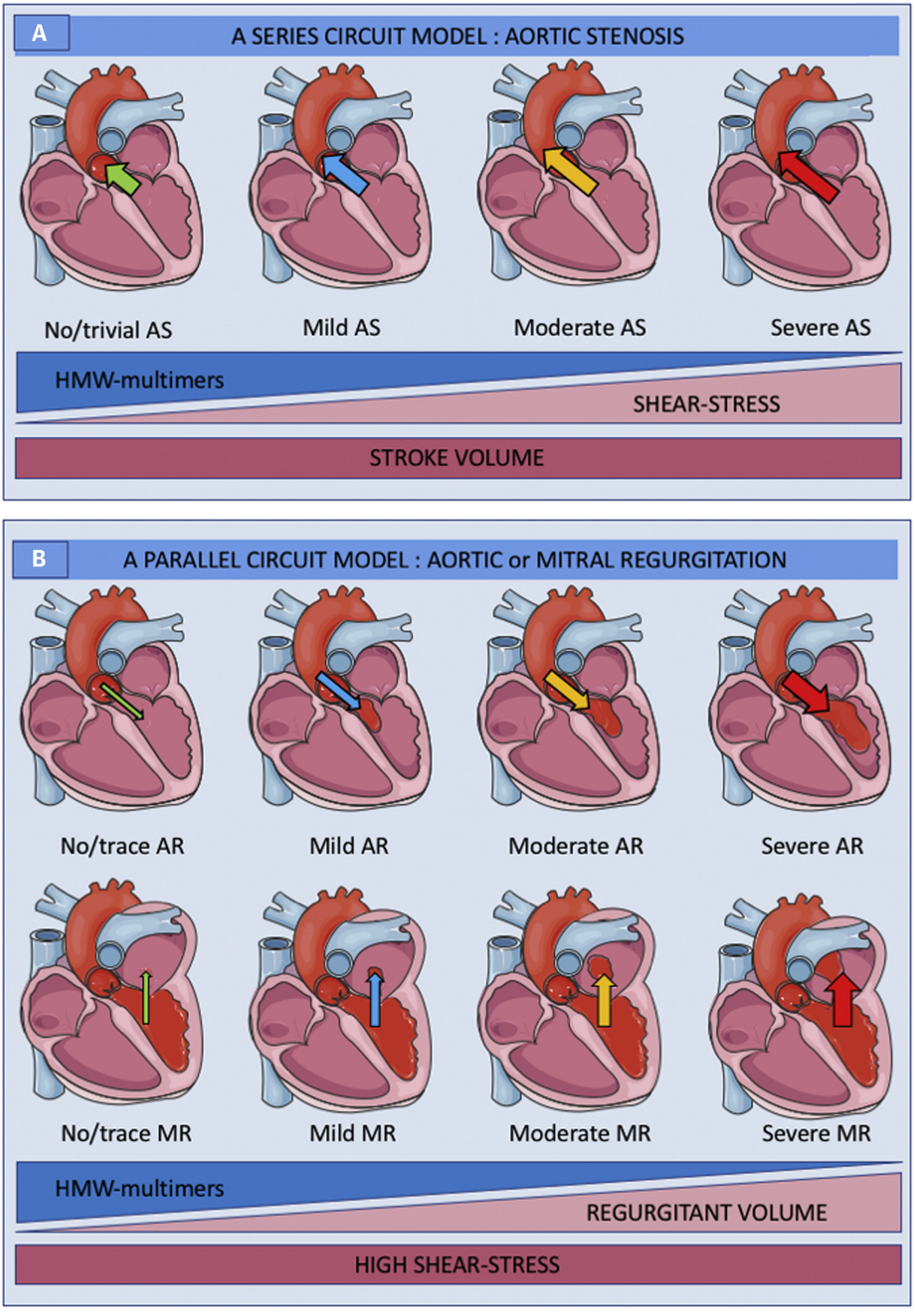


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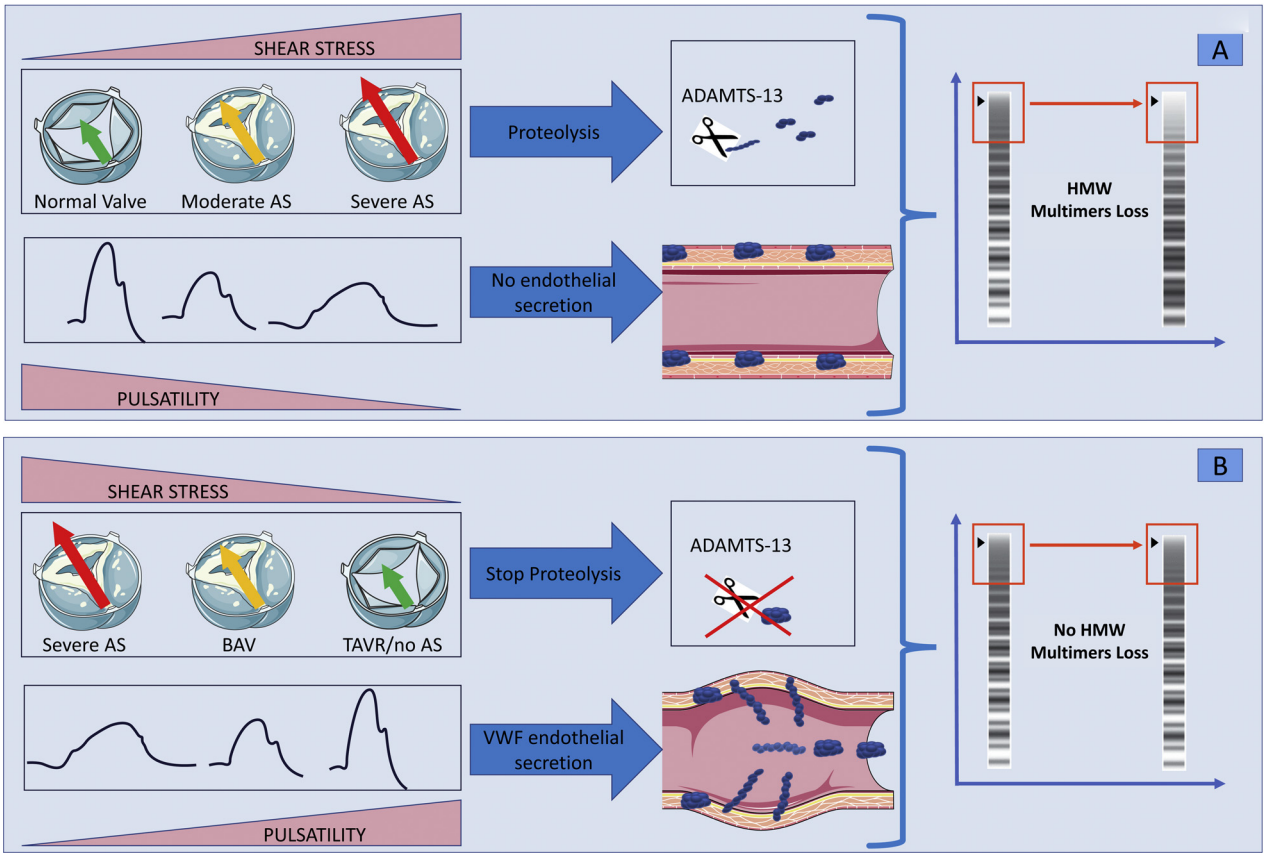
FIGURE 2 Proposed Physiopathology Model for the Dynamic Changes of VWF Multimers Profile During the Course of Aortic Stenosis and Its Repair



(A) Progression of AS disease generates HMW multimers defect by increasing shear stress–induced proteolysis and decreasing release of VWF through reduction of pulsatility. **(B)** AS treatment generates HMW multimers recovery by stopping shear stress–induced proteolysis and release of VWF through increasing of pulsatility. ADAMTS13 = a desintegrin and metalloproteases with a thrombospondin type-1 repeats-13; AS = aortic stenosis; BAV = balloon aortic valvuloplasty; TAVR = transcatheter aortic valve replacement; VWF = von Willebrand Factor; other abbreviations as in Figure 2.

Prosthesis-patient mismatch and residual gradient. Prosthesis-patient mismatch (PPM) generates elevated gradients when the effective orifice area of the normally functioning valve is too small in relation to body size. We observed the reappearance of an HMW multimers defect at 6 months after SAVR only in the 10 of 42 patients presenting with PPM in our cohort (15), and the absence of recovery of the HMW multimers defect has been reported in the only patient with PPM from another small SAVR cohort (30). Post-procedural VWF antigen has also been shown to correlate with the indexed effective orifice area (31). Mirroring the previous observations made in native aortic valve stenosis, we established the correlation between residual HMW multimers defect and the post-procedural transaortic gradient after balloon aortic valvuloplasty or TAVR ($r = -0.68$; $p < 0.0001$) (32) (Online Table 3).

Detection of structural valve deterioration. Blackshear et al. (27) reported abnormal VWF pathway in 43

FIGURE 1 Continued

(A) Series circuit: HMW multimers correlate inversely with the degree of the AS through a progressive increase of the shear stress **(length of the arrow),** which is applied to the steady stroke volume **(width of the arrow). (B)** Parallel circuit: HMW multimers correlate inversely with the degree of AR/MR through a progressive increase of the regurgitant volume **(width of the arrow)** submitted to a steady shear stress **(length of the arrow)**. AR = aortic regurgitation; AS = aortic stenosis; HMW = high molecular weight; MR = mitral regurgitation.

patients with a dysfunctional aortic or mitral prosthesis compared with 64 patients with normally functioning prosthesis. Pérez-Rodríguez et al. (33) further documented the HMW multimers defect and CT-ADP prolongation in patients with dysfunctional bioprosthetic valves and their normalization after redo-surgery (Online Tables 2 and 4).

These data suggested that analysis of the VWF pathway could provide a warning signal of significant alterations of the hemodynamics properties of the bioprosthesis at a given time point. However, VWF-related markers cannot help to identify the underlying mechanism of bioprosthesis dysfunction (stenosis, regurgitation, or both), and dedicated larger studies are needed to further delineate its clinical utility.

TEMPORAL VARIATIONS IN VON WILLEBRAND FACTOR MULTIMER STRUCTURE AS A SENSOR OF DYNAMIC CHANGES IN HEART VALVE FUNCTION

In 1988, Weinstein et al. (10) were the first to report that the recovery of the HMW multimers defect during SAVR happens as soon as the cardiopulmonary bypass relieves the AS by shunting the blood from right cavities to ascending aorta. This milestone observation remained unnoticed until we reported in 2003 a complete normalization of VWF function at day 1 post-SAVR in a cohort of 42 patients with AS (15).

Around the same period, biophysical analysis confirmed that VWF physiological mechano-enzymatic cleavage by ADAMTS13 occurs within a few seconds (4). Based on these findings, we investigated the time-course of the HMW multimers defect recovery in 30 patients with AS undergoing TAVR or balloon aortic valvuloplasty. We noticed that VWF markers returned to normal as quickly as 5 min after successful TAVR, whereas no correction was observed after suboptimal AS correction by balloon aortic valvuloplasty (32). We further observed in the WITAVI cohort that the lack of rapid normalization of VWF markers coincided with the presence of a significant PVR after valve deployment. Overall, sequential analysis of VWF-related markers was sensitive enough to identify for 2 sequential hemodynamic status for the same patient: a first change from AS to PVR and then a second change from PVR to normal valve function, when post-dilatation was successful (1) opening the perspective of real-time monitoring of the efficacy of valves interventions (34) (see the following dedicated section).

PROPOSED PHYSIOPATHOLOGY MODELS FOR QUANTIFICATION OF HEART VALVE DISEASE SEVERITY AND ANALYSIS OF DYNAMIC CHANGES IN VALVE FUNCTION

QUANTIFICATION OF THE SEVERITY OF HVD. For an alteration of the VWF multimeric profile to become apparent in the peripheral blood, it requires that the blood volume submitted to high shear stress represents a large enough fraction of the overall blood volume.

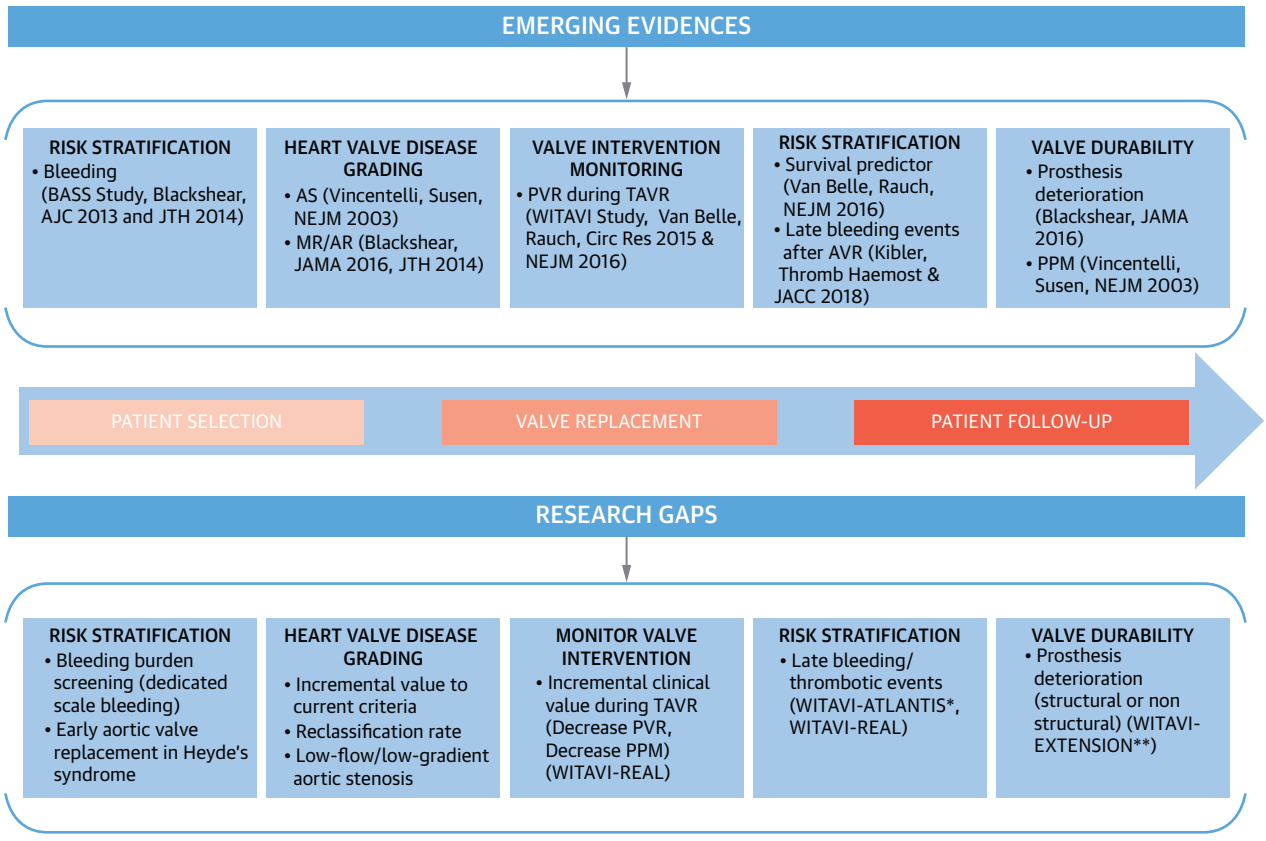
In stenotic HVD: a series circuit model. When the blood is circulating in a "series circuit," the multimeric profile is reflecting the higher level of shear stress of the circuit. This is typically the case for patients with stenotic valves generating high shear stress, where the entire bloodstream is submitted to the valve stenosis. Thus, the higher the increase in shear stress at the level of the valve (i.e., "the higher is the gradient"), the lower are the HMW multimers measured in the peripheral blood. This explains why quantification of the loss of HMW multimers correlates so well with the transvalvular gradient (**Figure 1A**, Online Table 3).

In regurgitant HVD: a parallel circuit model. In a "parallel circuit," the multimeric profile measured is resulting from the mixture of the multimeric profile of different blood volumes submitted to different levels of shear stress circulating in parallel along the bloodstream. This is the case for patients with regurgitant HVD generating high shear stress (i.e., mitral or aortic regurgitation) in whom only one fraction of the blood, the regurgitant fraction, is submitted to high shear stress, whereas the other fraction is not. In this model, the higher the proportion of blood submitted to high shear stress is, the lower are the HMW multimers in the peripheral blood. Thus, in regurgitant HVD, the HMW multimers defect is correlated to the "regurgitation fraction" measured by echocardiography (**Figure 1B**, Online Table 2).

These models are consistent with the absence of reports describing HMW multimers defects in patients with mitral/tricuspid stenosis or tricuspid regurgitation, because those HVD usually generate relatively low shear stress with gradient <10 mm Hg or a laminar flow. They are also consistent with the observation that patients with coronary stenosis lack VWF multimers abnormalities, because the high shear stress generated involves only a tiny fraction of the overall blood volume (10).

TEMPORAL CHANGES OF VALVE FUNCTION. Role of the endothelial release. Proteolyzed VWF multimers do not covalently remultimerize in the circulation. Consequently, the multimeric profile of

FIGURE 3 **Evidence-Based Framework and Research Gaps in the Emerging Concept of VWF as a Biomarker in HVD Clinical Course (With Landmark References and Current/Future Trials)**



*Biological substudy of ATLANTIS (NCT02664649) trial; **long-term follow-up of WITAVI-REAL (NCT03728049). PPM = patient-prosthesis mismatch; PVR = paravalvular regurgitation; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve.

circulating VWF in a peripheral blood sample depends on the steady-state between proteolysis and new VWF release.

In "acute" experimental AS (32) (**Figure 2A**) or in "acute" clinical PVR during TAVR (1), it is relatively straightforward that the acute appearance of a large circulating blood volume submitted to pathological high shear stress will almost instantaneously (within minutes) translate into a loss of HMW multimers.

A less straightforward scenario arrives when there is an "acute" recovery from a pathological high shear stress to a physiologically low shear stress. Surprisingly, this change in shear stress is associated with an acute recovery of HMW multimers, as is illustrated in analysis of samples taken after successful TAVR or after PVR treated by post-dilatation (1,32). Although the excessive proteolysis stops nearly instantaneously with normalization of shear stress, this is obviously not sufficient to provide an acute recovery of the pool of large multimers.

In our studies, we noted that the change from pathological to physiological shear stress coincides with a rapid release of VWF and VWF propeptide from endothelial storage pools. Because these storage pools are enriched in HMW multimers, it seems conceivable that the correction of the HMW multimers defect is due to this acute release of VWF from endothelial cells of the vasculature after the recovery of the physiological flow and pulse pressure (32,35) (**Figure 2B**).

To summarize, the 3 key determinants of VWF multimers profile in HVD are: 1) the degree of "pathological" shear stress locally generating the proteolysis (mainly "variable" in stenotic HVD while mainly "constant" in regurgitant HVD); 2) the fraction of the whole blood submitted to the abnormal shear stress

(mainly "variable" in regurgitant HVD while mainly "constant" as being 100% in stenotic HVD); and 3) the ability of the endothelium to release VWF multimers, depending notably on the level of pulse pressure (**Figures 1 and 2**).

THE MOST ADVANCED POTENTIAL CLINICAL APPLICATIONS OF VON WILLEBRAND FACTOR-RELATED MARKERS BEFORE, DURING, AND AFTER VALVE INTERVENTIONS

TOWARDS A BETTER RECOGNITION OF THE BLEEDING BURDEN IN HVD PATIENTS. Bleeding risk seems intimately related to VWF pathway abnormalities. There is also ample evidence that aVWS type 2A is a major predictor of GIB in the HVD population. In particular, Blackshear et al. (36) have reported that prolonged CT-ADP time is indicating a greater risk of bleeding. They also observed that among those with an apparent similar severity of mitral regurgitation, clinically significant bleedings were manifested in those with more significant VWF abnormalities (28).

Dozens of reports have shown that valve replacement is the only option to cure or at least relieve this bleeding diathesis (Online Tables 1 and 2).

It could therefore be suggested to measure VWF-related markers in case of chronic anemia of unknown origin or documented GIB from angiodysplasia in HVD patients to detect aVWS type 2A. The presence of detect aVWS type 2A could be incorporated in the decision-making process for prompt valve interventions in patients not meeting the conventional valve replacement criteria as suggested since 1971 (16) (**Central Illustration**).

REAL-TIME MONITORING OF VALVE INTERVENTIONS

Because of the noxious impact of PVR on a patient's prognosis, it is critical to obtain an accurate assessment of PVR at the time of the procedure to consider immediate corrective treatments (37). Transesophageal echocardiography, mainly performed under general anesthesia, is the gold standard method to assess the severity of PVR. However, mini-invasive TAVR without general anesthesia or transesophageal echocardiography has become the standard of care in two-thirds of interventions, and this trend could impair the evaluation of PVR (38,39). We have reported the capacity of VWF-related markers to detect PVR during TAVR and monitor its correction in real time, with an excellent negative predictive value of >98% compared with transesophageal echocardiography (1). The advantage of point-of-care CT-ADP testing is that it is designed as a compact instrument and is automatically calibrated, making its use by catheterization laboratory nurses after a short training possible. Including sample handling, results are available in <10 min after sampling. Practically, if CT-ADP is corrected after valve implantation, it could be proposed to terminate the procedure safely without requiring further sophisticated imaging investigations. If CT-ADP is still prolonged after valve deployment, the likelihood of PVR is high, and should encourage the use of a more comprehensive imaging technique.

This strategy, which may improve the diagnosis of PVR during mini-invasive TAVR and help to rationalize the decision of whether to perform corrective treatments, will be tested in the large-scale multicenter randomized clinical trial WITAVI-REAL (Von Willebrand Factor Point-of-care Testing to Improve Minimally Invasive TAVI Outcomes) (NCT03728049). If this trial provides confirmation, CT-ADP point-of-care testing could become the "seatbelt" of mini-invasive TAVR procedures (39).

VON WILLEBRAND FACTOR AND CT-ADP AS THE "MISSING LINK AMONG PVR, LATE BLEEDING EVENTS, AND ITS ASSOCIATION WITH INCREASED MORTALITY AFTER TAVR"

The above hypothetical statement made by Généreux et al. (40) in 2015 has been underscored by recent data. Indeed, significant PVR is both one of the main risk factors of major late bleeding complications after TAVR (2- to 3-fold increase) (41) and one of the strong predictors of mortality (42). Mirroring the clinical effect of PVR, prolonged CT-ADP has recently been highlighted as a major independent predictor of PVR, late bleeding complications (3-fold increase), and all-cause death after TAVR (1,25,43). Altogether, these findings suggest that the HMW multimers defect could partially explain the higher bleeding rate and contribute to the higher mortality risk observed in case of significant PVR. This relationship has already been established in several other cardiovascular conditions promoting HMW multimers defect, such as after implantation of mechanical circulatory support (22).

CONCLUSIONS: A CALL FOR FURTHER RESEARCH

Most of the data establishing VWF as a quantitative marker of HVD severity come from monocentric cohorts of homogenous patients (**Figure 3**). Large-scale

prospective multicentric and well-characterized longitudinal cohorts are needed to provide more definite estimates of the prevalence of aVWS type 2A and Heyde's syndrome at the various stages of HVD. Additional data are also required in patients with particular hemodynamic conditions, including those with low-flow/low-gradient AS or mixed HVD. The incremental value of VWF-related markers on top of current clinical/imaging criteria and other biomarkers (e.g., B-type natriuretic peptide) in the staging reclassification of HVD also needs to be evaluated.

The mucosal bleeding burden of HVD patients is also poorly recognized. Clinical validation of a bleeding scale dedicated to this population, such as the one developed by Tosetto et al. (44), should be considered to facilitate identification of the "bleeding pattern" by the clinician. Moreover, the association between VWF abnormalities and bleeding needs to be confirmed in larger cohorts, allowing multivariable analyses to deal with potential confounders. Finally, the clinical impact of earlier intervention in patients with Heyde's syndrome without another indication for valve replacement will have to be validated against the current conservative strategy.

Overall, although there is emerging evidence, the lack of current data leads to many uncertainties on the indications and wide application of VWF as a biomarker for all-comer HVD patients before or after intervention. We suggest that it is time to fill these research gaps. The dedicated WITAVI-REAL trial will provide thoughtful insights to better appreciate some of these issues. Many current questions could be easily answered by incorporating VWF biological substudies in upcoming transcatheter valve interventions trials or registries (**Figure 3**).

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KEY WORDS aortic stenosis, biomarker, bioprosthesis heart valve disease, mitral regurgitation, paravalvular regurgitation, point-of-care test, transcatheter aortic valve replacement, von Willebrand factor

APPENDIX For an expanded Methods section as well as a supplemental figure and tables, please see the online version of this paper.