JACC: CARDIOVASCULAR INTERVENTIONS

VOL. 8, NO. 5, 2015

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcin.2015.02.008

Treatment of Acquired von Willebrand Syndrome in Aortic Stenosis With Transcatheter Aortic Valve Replacement

Tobias Spangenberg, MD,* Ulrich Budde, MD,† Dimitry Schewel, MD,* Christian Frerker, MD,* Thomas Thielsen, MD,* Karl-Heinz Kuck, MD,* Ulrich Schäfer, MD*‡

ABSTRACT

OBJECTIVES This study sought to investigate the prevalence of abnormal von Willebrand multimers (AbM) in patients undergoing transcatheter aortic valve replacement (TAVR) and the impact of TAVR on the underlying factor variances.

BACKGROUND An association between the acquired von Willebrand syndrome (aVWS) and valvular aortic stenosis (AS) has been established in the past and surgical aortic valve replacement (SAVR) shown to lead to factor recovery. Prevalence and course of AbM in patients treated with TAVR though has not yet been described comprehensively.

METHODS Ninety-five consecutive patients underwent TAVR at our institution. Hemostaseologic testing was performed before and up to 1 week after TAVR. Transvalvular and right heart hemodynamics as well as bleeding episodes were recorded and analyzed with descriptive statistics.

RESULTS Baseline prevalence of AbM was 42% with an average high-molecular-weight multimer (HMWM) count of 16.2 ± 3.3%. Pressure gradients correlated significantly with the extent of HMWM deficiency ($r = -0.63$ [$p < 0.0001$]). Following valve implantation, HMWM increased proportional to the drop in mean pressure gradient and normalized in most of the patients. However, residual aortic regurgitation/leakage led to inferior HMWM recovery but prosthesis-patient mismatch (PPM) was rare and left HMWM uninfluenced. We saw no association of transfusion with AbM and 1-year mortality was unaffected by AbM.

CONCLUSIONS AbM in patients with AS undergoing TAVR is frequent. However, TAVR is capable of correcting AbM and therefore possibly aVWS in patients with AS. As opposed to SAVR, bleeding and transfusion requirement in TAVR patients was not associated with severe HMWM deficiency; PPM was rare and HMWM were uninfluenced by the procedure. Aortic regurgitation after TAVR adversely influenced HMWM recovery. (J Am Coll Cardiol Intv 2015;8:692–700)

Aside from the primary repercussions of aortic stenosis (AS), shear stress gives rise to hemostaseologic alterations subsequently leading to an acquired von Willebrand syndrome (aVWS) (1). Gastrointestinal bleeding can be a clinical companion and forms Heyde's syndrome (2,3). A common element of aVWS is a diminished von Willebrand factor (VWF), altered structure and/or limited function thereof as a consequence of a primary disorder. In case of high shear stress (e.g., aortic valvular stenosis, hypertrophic cardiomyopathy) (4), proteolysis of the large multimers is induced by the metalloproteinase ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs) (5). A high prevalence of the aVWS (decreased VWF collagen-binding activity and loss of the largest multimers, or a combination of both in 67% to 92%) in a study population of 50 patients with AS undergoing surgical aortic valve replacement (SAVR) has been shown previously (6). But interestingly, a significant correlation between a

From the *Division of Cardiology, Asklepios Klinik St. Georg Hospital, Hamburg, Germany; †Medilys Laborgesellschaft mbH, Hemostaseology, Hamburg, Germany; and the ‡Division of Cardiology, University Heart Center Eppendorf, Hamburg, Germany. Dr. Kuck has served as a consultant for St. Jude Medical, Abbott Vascular, and Medtronic. Dr. Schäfer has served as a proctor for Medtronic, Edwards Lifesciences, and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 8, 2014; revised manuscript received February 2, 2015, accepted February 27, 2015.

decreased content of the high-molecular-weight multimers (HMWM) and severity of the AS, along with a correction of the multimer content 1 day after SAVR (6,7) was described. Currently transcatheter aortic valve replacement (TAVR) is an alternative to SAVR for selected patients (8) with superior outcomes in specified populations (9). Nevertheless, the influence on a shear stress-induced loss of HMWM in patients undergoing TAVR has not been investigated comprehensively. However, greater age, multimorbidity, and the necessity of dual antiplatelet therapy possibly leading to a substantial increase in bleeding risk are characteristic of patients envisaged for TAVR (10). Hence, a comprehensive understanding of the prevalence and the impact of TAVR on the hemostaseologic peculiarities in this population was the aim of the present work.

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METHODS

STUDY DESIGN AND PATIENT POPULATION. Between November 2011 and June 2013, a total of 95 patients with severe AS underwent a transfemoral TAVR at our institution. Written informed consent was obtained and the registry was approved by the local ethics committee. Exclusion criteria for participation were to be within 1 month of resuscitation, systemic shock, transfusion of fresh frozen plasma/factor concentrates and patients treated by left ventricular assist devices. All data were prospectively collected as a single-center registry. Inclusion criterion was native AS with an aortic valve area ≤1.0 cm^2 (≤0.6 cm^2/m^2) as determined by echocardiography. The individual baseline risk of the patients was estimated by the logistic EuroSCORE.

DEVICE DESCRIPTION AND PROCEDURE. Transcatheter heart valves such as the Medtronic CoreValve (CV Luxembourg, S.a.r.l.) (n = 31), the Edwards Sapien XT valve (Edwards Lifesciences, Irvine, California) (n = 51), the Edwards Centera valve (n = 13) and St. Jude Portico valve (St. Jude Medical, St. Paul, Minnesota) (n = 1) were used as previously described (11–14). After valve deployment, the final transvalvular gradient was measured invasively (i.e., simultaneous recording with a pigtail in the left ventricle and a second pigtail in the ascending aorta) and a standardized root angiography (30 cc/ 15 cc/s) was performed to assess the extent of aortic regurgitation. All patients received acetylsalicylic acid 100 mg, before the procedure and continued indefinitely. A 600 mg loading dose of clopidogrel was administered the day before the procedure, followed by 75 mg daily for 3 months (Medtronic CoreValve) or 4 weeks (Edwards Sapien XT valve and Edwards Centera valve), respectively. During the intervention, 100 international units/kg of unfractionated heparin were administered to achieve an activated clotting time of 250 to 300 s. All procedures were performed under analgosedation.

ECHOCARDIOGRAPHY, ROUTINE LABORATORY DATA, AND FOLLOW-UP. A transthoracic and transesophageal echocardiographic study from all patients was obtained before and after implantation of the transcatheter heart valve. Transvalvular pressure gradients including mean transvalvular gradient (dPmean) were calculated with the modified Bernoulli equation, aortic orifice area was calculated with the continuity equation and indexed to the patient's body surface area (15). Left ventricular ejection fraction as well as the grade of mitral and tricuspid regurgitation were estimated by echocardiography before TAVR and after. Moreover, creatinine, glomerular filtration rate, and mortality were determined.

INVASIVE HEMODYNAMIC DATA. Quantification of the AS was performed utilizing combined left and right heart catheterization (7-F Swan-Ganz catheter; Edwards Lifesciences, Irvine, California) before and after TAVR. Right atrial pressure; pulmonary artery systolic, diastolic, and mean pressures; mean aortic pressure; left ventricular end-systolic pressure (LVESP) and end-diastolic pressure; and pulmonary capillary wedge pressure (PCWP) were recorded. Cardiac output (CO), cardiac index, stroke volume, stroke volume index, systemic vascular resistance, systemic vascular resistance index, pulmonary vascular resistance, and pulmonary vascular resistance index, were determined using the thermodilution method. Finally, the aortic valve area using the Gorlin formula (15,16) and the valvuloarterial impedance (Zva), the systemic arterial compliance (SAC) (17), and the transpulmonary gradient were calculated immediately before and after TAVR.

DATA COLLECTION AND DEFINITIONS. All baseline and follow-up variables were recorded and entered into a database. Technical success was defined as stable device placement and function as assessed by angiography and echocardiography. Device success was defined according to Valve Academic Research Consortium-2 (VARC-2) (18). Invasive hemodynamic data were obtained before and after TAVR (see previous text). N-terminal pro-B-type natriuretic peptide

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

aVWS = acquired von Willebrand syndrome

dPmean = mean transvalvular gradient

HMWM = high-molecular-weight multimer

LVESP = left ventricular end-systolic pressure

PCWP = pulmonary capillary wedge pressure

PPM = prosthesis-patient mismatch

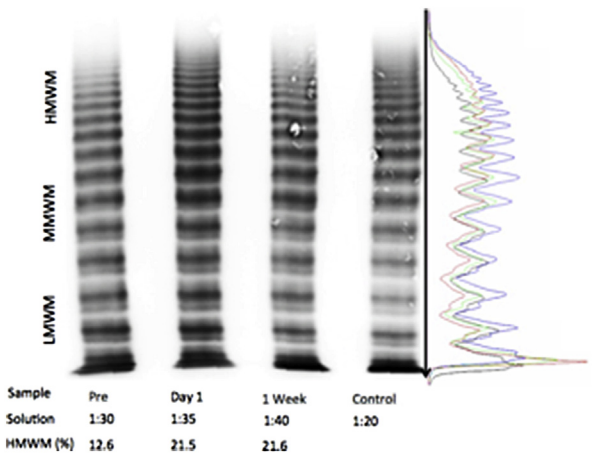
PVL = paravalvular leak

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

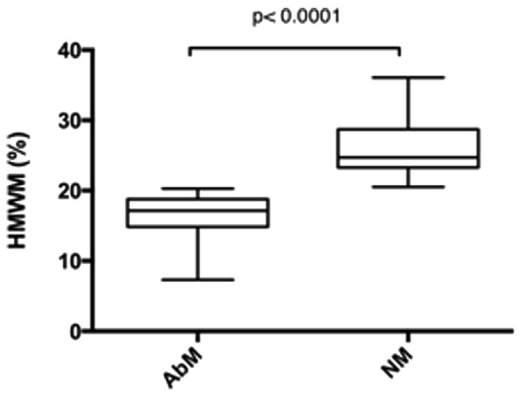
VWF = von Willebrand factor

FIGURE 1 Multimer Analysis and Quantification



Exemplary illustration of the multimer analysis by gel electrophoresis and quantitative densitometry. HMWM = high-molecular-weight multimer; LMWM = low-molecular-weight multimer; MMWM = medium-molecular-weight multimer.

FIGURE 2 High-Molecular-Weight Multimer Disparity



Differentiation of abnormal multimers (AbM) and normal multimer (NM) patients by high-molecular-weight multimers (HMWM).

TABLE 1 Demographics, Comorbidities, and Baseline Data

	Total (n = 95)	NM (n = 55)	AbM (n = 40)	p Values
Demographic data				
Male	36 (37)	24 (43)	12 (30)	0.20
Age	82.4 ± 6.5	81.8 ± 6.9	83.3 ± 6.1	0.29
EuroSCORE, %	21.7 ± 18.3	23.1 ± 18.1	19.9 ± 18.6	0.44
Arterial hypertension	89 (93)	52 (94)	37 (92)	0.69
Coronary artery disease	55 (57)	35 (63)	20 (50)	0.21
Previous cardiac surgery	11 (11)	7 (12)	4 (10)	0.75
Chronic kidney disease	34 (35)	17 (30)	17 (42)	0.28
Diabetes mellitus	32 (33)	17 (30)	15 (37)	0.51
Atrial fibrillation	43 (45)	25 (45)	18 (45)	1.0
History of bleeding	18 (20)	10 (18)	8 (20)	1.0
History of GI bleeding	11 (11)	7 (13)	4 (10)	0.75
History of stroke	11 (11)	9 (16)	2 (5)	0.11
TTE	1.	2.	3.	4.
LVEF, %	54.9 ± 11.2	54.4 ± 11.3	55.6 ± 11.1	0.59
Aortic regurgitation ≥2	14 (15)	6 (10)	8 (20)	0.25
Mitral regurgitation ≥2	45 (47)	24 (43)	21 (52)	0.41
Tricuspid regurgitation ≥2	30 (31)	19 (34)	11 (27)	0.59
Biomarkers				
Creatinine, mg/dl	1.1 ± 0.6	1.2 ± 0.7	1.0 ± 0.4	0.17
eGFR, ml/min	58.7 ± 19.3	56.6 ± 20.9	61.9 ± 16.8	0.26
NT-proBNP, ng/dl	4,771 ± 7,397	4,882 ± 6,448	4,602 ± 8,755	0.47

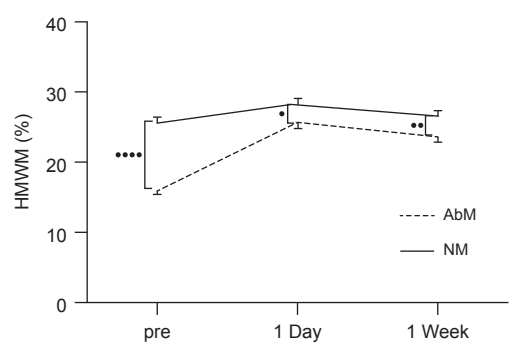
Values are n (%) or mean ± SD.

AbM = abnormal multimer; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; LVEF = left ventricular ejection fraction; NM = normal multimer; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TTE = transthoracic echocardiography.

was measured by chemiluminescence immunoassay (e411; Roche Diagnostics GmbH, Grenzach-Wyhlen, Germany). Estimated glomerular filtration rate was calculated by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula.

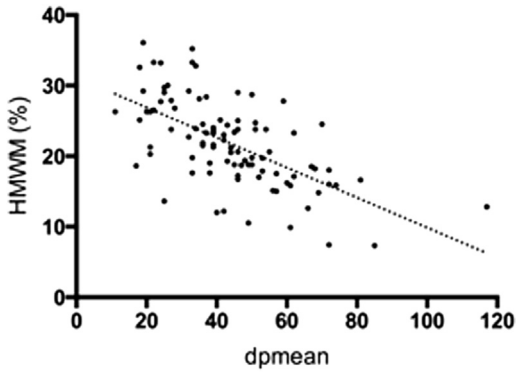
SPECIFIC BLOOD COLLECTION AND LABORATORY ASSAYS. Hemostaseologic data was gathered and analyzed before 1 day after, and 1 week after TAVR. Multimer analysis was performed as described before (19) in gels of low (1.2%) and medium resolution (1.6%; LGT agarose type VII, Sigma, Munich, Germany). Plasma samples were classified as either

FIGURE 3 High-Molecular-Weight Multimer Course



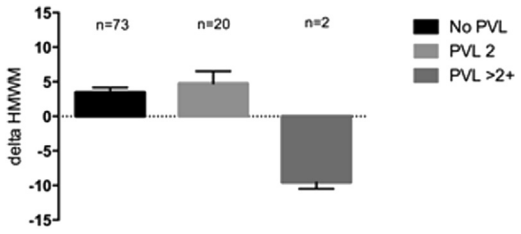
Change of high-molecular-weight multimers (HMWM) in abnormal multimer (AbM) and normal multimer (NM) patients over time. Abbreviations as in Figure 2.

FIGURE 4 Correlation of dPmean to High-Molecular-Weight Multimer



Connection of high-molecular-weight multimers (HMWM) to mean transvalvular gradient (dPmean) in the study population. Abbreviations as in Figure 2.

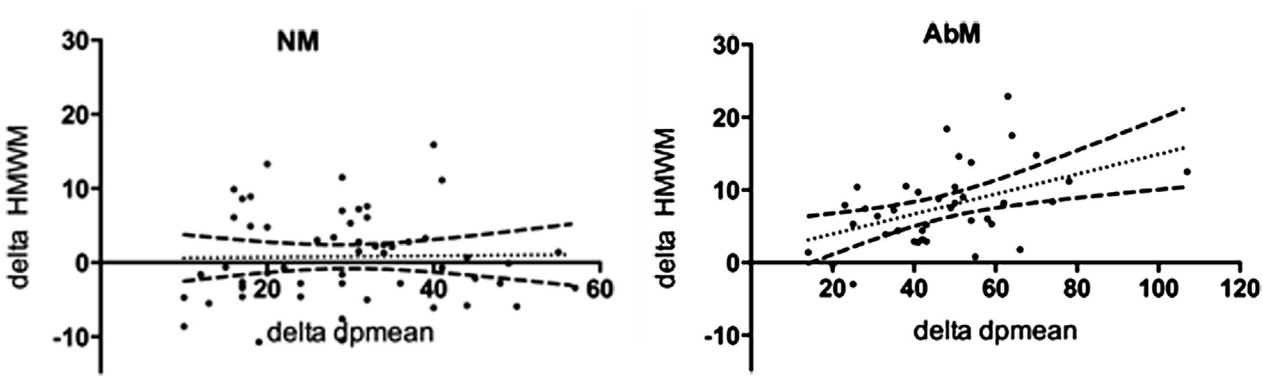
FIGURE 6 High-Molecular-Weight Multimer Alteration and PVL



Change in high-molecular-weight multimer (HMWM) content relative to paravalvular leakage after transcatheter aortic valve replacement. PVL = paravalvular leakage. Abbreviations as in Figure 2.

abnormal multimers (AbM) or normal multimers (NM) by comparison with the reference plasma (pool of 50 human control subjects). AbM were defined as a deviation from a normal distribution; either loss of HMWM or presence of larger than normal (supranormal) multimers on low-resolution gels or as abnormal migration of individual oligomers or abnormal separation into triplets/quintuplets on medium resolution gels (Figure 1). Quantitative, densitometric gel analysis was performed using software provided with the video-detection system (AlphaEaseFC Stand Alone software, Alpha Innotech Corp., San Leandro, California). Samples with the same quantity of VWF:Ag (von Willebrand factor antigen) were applied to the gels. Because VWF function is strictly dependent on it's content of large multimers, a quantitative evaluation of the multimer content was performed. Small, intermediate, and large multimers were defined as oligomers 1 to 5, 6 to 10, and >10, respectively, and evaluated by densitometry. In a survey from the Scientific Subcommittee on VWF, in 32 laboratories worldwide (19) it turned out that every laboratory used a different multimer method. Therefore, multimer results from different laboratories are not directly comparable and there is no normal reference range for the large multimer content. Our multimer method was validated from January 2011 to August 2011 (validation is ongoing for long-term stability). During the study period of 300 low-resolution gels were analyzed quantitatively. According to these results, an area under the curve of less than 20.4% for the large multimers

FIGURE 5 Pressure Drop-Related High-Molecular-Weight Multimer Alteration



High-molecular-weight multimer (HMWM) increase following transcatheter aortic valve replacement relative to reduction of mean transvalvular gradient for the abnormal multimer and normal multimer (NM) groups. dPmean = mean transvalvular gradient. Abbreviations as in Figure 2.

TABLE 2 Baseline and End-Procedural Invasive Hemodynamic Data

	Total (n = 95)	NM (n = 55)	AbM (n = 40)	p Values
Valve orifice area, cm^2	p < 0.0001	p < 0.0001	p < 0.0001	
Before TAVR	0.7 ± 0.2	0.8 ± 0.2	0.6 ± 0.2	0.008
After TAVR	2.5 ± 0.7	2.6 ± 0.8	2.5 ± 0.7	0.57
Valve orifice area index, cm/m^2	p < 0.0001	p < 0.0001	p < 0.0001	
Before TAVR	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	<0.0001
After TAVR	1.4 ± 4.2	1.4 ± 0.4	1.4 ± 0.4	0.57
Cardiac output, ml/min	p = 0.002	p = 0.06	p = 0.01	
Before TAVR	4.3 ± 1.3	4.3 ± 1.3	4.4 ± 1.2	0.76
After TAVR	4.7 ± 1.4	4.6 ± 1.5	4.8 ± 1.4	0.58
Cardiac index, $ml/min/m^2$	p = 0.003	p = 0.12	p = 0.008	
Before TAVR	2.4 ± 0.6	2.3 ± 0.6	2.5 ± 0.6	0.33
After TAVR	2.6 ± 0.7	2.5 ± 0.7	2.7 ± 0.8	0.18
Cardiac power index, W/m^2	p < 0.0001	p = 0.0001	p = 0.0002	
Before TAVR	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.42
After TAVR	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.44
Stroke volume, ml	p = 0.060	p = 0.13	p = 0.33	
Before TAVR	71.8 ± 23.7	70.2 ± 23.1	73.9 ± 24.9	0.99
After TAVR	76.6 ± 23.3	76.2 ± 23.0	76.1 ± 23.5	0.95
Stroke volume index, ml/m^2	p = 0.076	p = 0.10	p = 0.40	
Before TAVR	39.9 ± 12.2	38.4 ± 12.1	42.1 ± 12.0	0.36
After TAVR	42.5 ± 12.1	41.8 ± 11.9	43.6 ± 12.6	0.55
Zva, mm Hg*ml*m^2	p = 0.0006	p = 0.055	p = 0.002	
Before TAVR	4.4 ± 3.3	4.6 ± 4.1	4.1 ± 1.4	0.72
After TAVR	3.6 ± 1.2	3.7 ± 1.3	3.4 ± 1.2	0.19
SAC, ml/m^2/mm Hg	p < 0.0001	p < 0.0001	p < 0.0001	
Before TAVR	1.2 ± 0.6	1.2 ± 0.5	1.4 ± 0.7	0.47
After TAVR	0.9 ± 0.4	0.9 ± 0.3	1.0 ± 0.5	0.40
PCWPmean, mm Hg	p ≤ 0.0001	p = 0.0011	p = 0.13	
Before TAVR	16.7 ± 6.0	17.6 ± 7.0	16.3 ± 6.0	0.36
After TAVR	19.6 ± 8.1	20.6 ± 8.3	18.2 ± 7.6	0.17
SVRI, dyn*s*m^2cm^5	p = 0.096	p = 0.12	p = 0.47	
Before TAVR	2214 ± 1080	2277 ± 1268	2124 ± 745.0	0.90
After TAVR	2332 ± 907.5	2430 ± 1030	2193 ± 688.0	0.23
PASP, mm Hg	p = 0.01	p = 0.0088	p = 0.64	
Before TAVR	43.4 ± 12.6	43.8 ± 12.7	42.7 ± 12.6	0.69
After TAVR	46.3 ± 14.8	47.3 ± 14.4	44.9 ± 13.8	0.48
PADP, mm Hg	p = 0.046	p = 0.078	p = 0.351	
Before TAVR	16.6 ± 7.2	17.0 ± 6.4	16.1 ± 8.3	0.15
After TAVR	17.8 ± 7.3	18.5 ± 7.4	16.7 ± 7.2	0.24
PAMP, mm Hg	p = 0.014	p = 0.015	p = 0.567	
Before TAVR	27.1 ± 9.8	27.2 ± 7.9	27.0 ± 12.2	0.35
After TAVR	28.6 ± 9.6	29.5 ± 9.9	27.2 ± 9.1	0.32
PVRI, dyn*s*m^2cm^5	p < 0.0001	p < 0.0001	p < 0.0001	
Before TAVR	127.2 ± 136.7	120.1 ± 88.1	137.2 ± 185.8	0.56
After TAVR	291.4 ± 248.8	305.6 ± 272.5	271.3 ± 212.7	0.64
LVESP, mm Hg	p < 0.0001	p = 0.066	p < 0.0001	
Before TAVR	156.1 ± 33.0	146.1 ± 28.4	170.2 ± 34.2	0.0008
After TAVR	138.4 ± 23.8	139.6 ± 24.7	136.7 ± 22.6	0.72

Continued on the next page

is defined as a pathological distribution (AbM). The validity of our multimer method was reassured by comparison of the multimer pattern of an ADAMTS13 digested recombinant VWF sample and a plasma sample from a type 2A patient with our gel method and the carrier free method fluorescence correlation spectroscopy (20). The VWF:Ag was determined by a sandwich enzyme-linked immunosorbent assay with polyclonal antibodies as described (21).

STATISTICAL ANALYSIS. Continuous data were described as means and standard deviations. Differences of metric variables between 2 groups were analyzed with Student *t* tests, if the data were approximately normally distributed, and with Mann-Whitney test otherwise. Differences between 3 groups/sequential measurements were analyzed by analysis of variance for normally distributed data and the Kruskal-Wallis test otherwise with GraphPad Prism (GraphPad Software Inc., San Diego, California). Categorical data were described with absolute and relative frequencies. Differences between categorical variables were evaluated with the Fisher's exact test. In the case that the overall tests for group effects were significant, 2 group comparisons were performed using the multiple comparison adjustment of Bonferroni. Linear regression analysis was used to investigate the interrelationship of HMWM and hemodynamic variables. All p values are 2-sided. For overall tests $p \leq 0.05$ was considered significant and for multiple comparisons Bonferroni-adjusted significance levels were used.

RESULTS

BASELINE DATA. We included 36 male and 59 female subjects with a mean of 82.4 ± 6.5 years of age (Table 1). Comorbidities were dominated by hypertension (93%) and coronary artery disease (57%). Invasive dPmean averaged 43.7 ± 17.7 mm Hg with an echocardiographic mean left ventricular ejection fraction of 54.9 ± 11.2% and a pre-implantation CO of 4.3 ± 1.3 l/min.

PROCEDURAL SUCCESS. Acute device success was achieved in 89% of the patients. No patient was lost during TAVR or in need of conversion to SAVR, though 1 patient converted to transapical implantation. Twenty-two patients experienced a paravalvular leakage ≥2 and 4 from a moderate but none from a severe prosthesis-patient mismatch (PPM) at the end of the procedure. PPM was considered if the effective orifice area indexed to the patient's body surface area was <0.85 cm^2/m^2 (moderate) or <0.65 cm^2/m^2 (severe) (22,23).

Periprocedural complications according to VARC-2 criteria were documented in 10 patients, 4 of which experienced a major stroke within 48 h. Eleven patients needed a permanent pacemaker due to conduction disturbances.

HEMOSTASEOLOGY AND TRANSVALVULAR HEMODYNAMICS. Defined by a densitometric HMWM content of <20.4% (24) we identified AbM in 42% of our patients. By means of multimer analysis we measured a HMWM content (% area under the curve) of 21.8 ± 6.1 before implantation, 27.2 ± 5.8 on day 1, and 25.3 ± 5.7 after 1 week in the entire study population. An additional evaluation of VWF:Ag (collagen-binding assay), VWF:CB, and GpIbM unveiled no further insights (25). The AbM group had an average HMWM content of 16.2 ± 3.3% before implantation, whereas the NM group presented with significantly higher values (25.9 ± 4.0%; $p < 0.0001$) (**Figure 2**). Though normal by then, the HMWM content remained distinctively lower in AbM patients 1 day (25.4 ± 5.8 vs. 28.5 ± 5.4; $p = 0.02$) and 1 week after TAVR compared to the NM group (23.6 ± 5.0 vs. 26.7 ± 5.8; $p = 0.008$) (**Figure 3**). Only 3 patients of the AbM group did not recover their HMWM after 1 week (HMWM 16.5 ± 0.5). However, the relative increase in HMWM was significantly greater in AbM patients (mean difference [95% confidence interval]: 9.51 [6.86 to 12.17] vs. 2.52 [0.10 to 4.94]). And contrary to the NM group, AbM patients also possessed a significantly higher HMWM content 1 week after implantation compared to their baseline (7.65 [5.00 to 10.31] vs. 0.81 [-1.59 to 3.22]). Measurements of dPmean pre-implantation were strongly correlated with HMWM content (**Figure 4**) and correlation slightly favored invasive pressure readings (noninvasive: $r = -0.56$; $p < 0.0001$; invasive: $r = -0.63$; $p < 0.0001$). The dPmean of patients with AbM was significantly higher (54.3 ± 18.6 mm Hg vs. 36.0 ± 12.4 mm Hg; $p \leq 0.0001$). The drop in dPmean after TAVR correlated significantly with the increase of HMWM in patients with AbM ($r = 0.417$; 95% confidence interval [CI]: 0.107 to 0.653; $p = 0.008$), which it did not in the NM group ($r = 0.128$; 95% CI: -0.152 to 0.389; $p = 0.356$) (**Figure 5**). Two patients of the entire population had a significant paravalvular leak (PVL >2) after TAVR and their HMWM content declined within a week. However, HMWM increased significantly if PVL was <2 ($p = 0.005$, $n = 73$) or 2 ($p = 0.0001$, $n = 20$) (**Figure 6**). Furthermore, the correlation of ARI in patients with PVL ≥2 revealed a borderline significance ($r = -0.4316$; $p = 0.050$).

HEMODYNAMICS. Hemodynamic data is presented in **Table 2**. Pre-implantation LVESP ($p < 0.0001$), dPmean ($p < 0.0001$), and dPmax ($p < 0.0001$) were significantly higher in patients with AbM compared to the NM group. Baseline systemic arterial pressures, pulmonary pressures, PCWP, CO, cardiac index, and SAC were similar in both groups. This also applied for Zva, pulmonary vascular resistance index, and transpulmonary gradient before implantation. After TAVR, the overall study population showed a significant increase in CO, cardiac index, and aortic pressures. Furthermore, we observed a significant increase in PCWP and pulmonary artery pressures as well as left ventricular end-diastolic pressure. Otherwise, there was a decrease in Zva, SAC, transvalvular gradients, and LVESP after TAVR in both groups. Post-procedural systemic arterial pressures, pulmonary pressures, PCWP, CO, cardiac index, SAC, and aortic regurgitation index again were similar in both groups. PCWP and pulmonary artery pressures remained unchanged only in the AbM group. Additionally, the drop in LVESP and increase in cardiac index after TAVR was distinctive in the AbM group.

TABLE 2 Continued

	Total (n = 95)	NM (n = 55)	AbM (n = 40)	p Values
LVEDP, mm Hg	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	
Before TAVR	12.4 ± 6.7	12.9 ± 6.4	11.9 ± 7.2	0.50
After TAVR	16.6 ± 7.8	16.5 ± 7.4	16.9 ± 8.4	0.98
AoPsys, mm Hg	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	
Before TAVR	110.5 ± 22.0	112.3 ± 24.9	108.1 ± 17.3	0.57
After TAVR	135.7 ± 24.3	138.0 ± 25.2	132.7 ± 23.1	0.36
AoPdias, mm Hg	$p = 0.005$	$p = 0.061$	$p = 0.029$	
Before TAVR	49.7 ± 9.9	49.4 ± 10.7	50.1 ± 8.7	0.55
After TAVR	53.0 ± 10.6	52.8 ± 11.7	53.3 ± 9.2	0.96
AoPmean, mm Hg	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	
Before TAVR	71.1 ± 12.7	71.7 ± 14.4	70.4 ± 10.0	0.76
After TAVR	81.3 ± 13.5	82.2 ± 14.8	80.1 ± 11.7	0.40
dPmax, mm Hg	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	
Before TAVR	47.6 ± 27.2	36.5 ± 21.0	62.8 ± 27.2	<0.0001
After TAVR	3.5 ± 3.6	3.2 ± 2.4	4.2 ± 4.8	0.62
dPmean, mm Hg	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	
Before TAVR	43.7 ± 17.7	36.0 ± 12.4	54.3 ± 18.6	<0.0001
After TAVR	6.4 ± 4.0	6.2 ± 3.9	6.7 ± 4.1	0.51
Aortic regurgitation index (32)	26.2 ± 8.3	26.0 ± 9.9	26.3. ± 8.1	0.89

AoPdias = diastolic aortic pressure; AoPmean = mean aortic pressure; AoPsys = systolic aortic pressure; dPmax = maximal transvalvular gradient; dPmean = mean transvalvular gradient; LVEDP = left ventricular end-diastolic pressure; LVESP = left ventricular end-systolic pressure; PADP = pulmonary artery diastolic pressure; PAMP = pulmonary artery mean pressure; PASP = pulmonary artery systolic pressure; PCWPmean = mean pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index; SAC = systemic arterial compliance; SVRI = systemic vascular resistance index; TAVR = transcatheter aortic valve replacement; Zva = valvuloarterial impedance; other abbreviations as in **Table 1**.

POST-IMPLANTATION THROMBOCYTOPENIA. Platelet counts dropped by 27% after TAVR (169.3 ± 78.8 to 126.0 ± 56.7) but recovered within the following week (157.7 ± 74.0) without differences between the AbM and NM groups. For further evaluation of the post-

implantation thrombocytopenia soluble P-selectin levels were measured by enzyme-linked immunosorbent assay, but found to be within normal limits in all patients and at all time points (data not shown).

BLEEDING, TRANSFUSION, AND OUTCOMES. Review of clinical records and patient history revealed 18% of our patients have had bleeding episodes before TAVR. Gastrointestinal bleeding was registered in 11% of the patients, with endoscopically verified angiodysplasias as the cause in 3 patients. Three patients where found to experience gastrointestinal bleeding and AbM denoting Heyde's syndrome in 7.5% of the patients with AbM. Periprocedurally our patients received 1.7 ± 3.6 packed red blood concentrate (PRBC) without significant difference in between groups ($p = 0.55$). Nevertheless, patients that were deceased within the first year received significantly more PRBC (6.6 ± 7.3 vs. 1.2 ± 2.8; $p < 0.0001$). Life-threatening or disabling bleeding (VARC-2) occurred in 3 of our patients as a result of access site complication. One of them belonged to the AbM 2 to the NM group of which 1 died within 30 days. Major vascular complications other than bleedings were encountered in 2 patients and necessitated 17% of the PRBC that were transfused in all patients. One of them was deceased within 30 days, none experienced AbM. Thirty-day mortality was 4.2% and 8 patients (8.4%) died within the first year after TAVR.

DISCUSSION

Deficiency of the HMWM and/or AbM are known to facilitate bleeding if not leading to Heyde's syndrome (2). SAVR has been proven to correct factor deficiency (5,7) and treat bleeding episodes in patients with AS (26). Nevertheless, this approach is not without risk, as SAVR does require ample access and cardiopulmonary bypass with substantial doses of heparin. And though in this context the minimally invasive TAVR without cardiopulmonary bypass may be advantageous in patients with a bleeding diathesis, little is known about the impact on von Willebrand multimers and aVWS in the TAVR population.

We discovered 42% of our patients to experience AbM with an average HMWM content of 16.2 ± 3.3%. This finding is in line with smaller investigations in patients undergoing SAVR (5,6,27), but to the best of our knowledge for the first time provides data on a larger scale for patients undergoing femoral TAVR.

After TAVR, 90% of the patients with AbM presented with a normal multimer distribution and densitometry. And although these patients significantly increased in HMWM content compared to baseline, the patients with NM did not (**Figure 3**). TAVR not only led to a normalization of HMWM content in patients with prior AbM, it also left HMWM in the remainder of the study population unaltered. Thus denoting periprocedural secretion implausible.

Condensing the hemostaseologic and hemodynamic findings disclosed further information. Correlation of HMWM count to dPmean in our population ($r = -0.63$; $p < 0.0001$) matches previous reports ($r = -0.76$; $p < 0.001$; and $r = -0.56$; $p < 0.001$) (6,27). However, 2 patients experienced a PVL >2+ after TAVR and their HMWM content declined substantially within a week whereas the HMWM of patients *with* AR/PVL<2 increased instead ($p = 0.003$). Also, all 4 patients that did not recover from their AbM experienced mild-moderate AR/PVL after TAVR. Appropriately enough, the correlation of ARI to HMWM in patients with PVL ≥2 after TAVR was borderline significant (-0.4316; $p = 0.050$). Indistinguishable by HMWM, however, PPM occurred in 4% of the patients. Thus, compared to SAVR (up to 20%) PPM is rare and does not seem to have the same bearing. In conclusion, and as they are reciprocally affected by the transvalvular gradient, HMWM can be proposed as a (hemostaseologic) marker of the severity of aortic valvular stenosis. These results, moreover, emphasize persistent and recurrent shear stress as the cause of multimer deficiency. Because AR/PVL after TAVR is associated with mortality (28), HMWM quantification could theoretically serve as a prognostic biomarker once a consensus on the cutoff (% area under the curve) is established. Future studies are needed to clarify whether HMWM and their quantitative analysis in low-resolution gels can perform as an adjunct to established grading systems.

Patients with AbM presented with significantly higher transvalvular pressure gradients and LVESP. The valve orifice area was significantly smaller (**Table 2**). A pertinent finding in view of a presumably shear stress–induced genesis of the aVWS. Significant increase of cardiac index in the AbM patients and their lower Zva with its prognostic capabilities (29) probably identify AbM patients as more severely obstructed and particularly appreciative for TAVR.

Because severe aVWS (i.e., low content of HMWM and bleeding episodes) as well as prior bleeding episodes have been associated with excessive bleeding/transfusion needs in patients undergoing SAVR (6) we examined the rate of transfusion and bleeding. The incidence of PRBC transfusion in our study was 37% including 30 days after TAVR. In contrast, SAVR without blood conservation strategy has recently been assigned a transfusion rate of 82.9% and with blood conservation strategy 68% of the patients still needed transfusion (30). Although we observed a

rather high incidence of transfusion for TAVR, the quantity did not differ in between patients belonging to the AbM and the NM group and it was nearly one-half of what patients undergoing SAVR with blood conservation strategy required lately (1.7 ± 3.6 PRBC/patient vs. 2.9 ± 4.3 PRBC/patient) (30). Bleeding under TAVR being unaffected by an AbM distribution might be explained by the fact that it was access site related and rather caused by anatomical than hemostatic elements. In contrary, wound surfaces and drainage sites of SAVR are understandably subject to an aVWS or AbM. Narrowing the view to the well-known transfusion-associated increase in mortality, these findings argue in favor of TAVR for patients with AbM or aVWS.

STUDY LIMITATIONS. This single-center study combines 4 different devices for TAVR and whether the correlational data is applicable to other collectives remains uncertain. Prior bleeding episodes were incompletely detected because we did not use a bleeding questionnaire and owed to the fact that spontaneous bleeding is rather infrequent among aVWS patients. Finally, blood sampling during a long-term follow-up would have been of additional value.

CONCLUSIONS

We describe a significant prevalence of AbM in patients with AS undergoing TAVR, and a close relationship of transvalvular pressure gradients and the extent of HMWM deficiency. And although an excellent correction of hemostaseologic as well as hemodynamic pathology takes place, about one-half the rate of transfusions compared to SAVR are needed. And opposed to SAVR, there was no increase in bleeding or transfusion needs in patients with severe VWF deficiency undergoing TAVR. We hypothesize this to be reasoned by the fact that severe bleeding in our population involved access site complications and was not attributable to large wound surfaces as in SAVR patients. Therefore, bleeding and transfusion is not as conditional to factor deficiencies and AbM therefore does not bring about the same undesirable consequences in TAVR. Moreover, the intervention itself does not adversely affect beforehand normal HMWM, whereas extracorporeal life support as cardiopulmonary bypass is known to consume HMWM (31), probably even more so in patients with aVWS, who have been shown to be at an increased risk of bleeding/transfusion with SAVR. In view of the minimal invasive, less sanguineous but hemostaseologic proficient approach, TAVR deserves consideration as the primary approach for patients with severe aVWS or AbM. But in view of the significant correlation of dPmean decrease with HMWM increase as well as recurrence of factor deficiency in patients with AR/PVL, HMWM seem to reach beyond and our study exposes HMWM content as a marker of shear stress and therefore stenosis severity. Whether HMWM content is capable of distinguishing between groups with discriminable prognostic properties or could act as a biomarker for procedural success remains to be proven by future investigations.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Tobias Spangenberg, Asklepios Klinik St. Georg, Department of Cardiology, Lohmuehlenstrasse 5, 20099 Hamburg, Germany. E-mail: t.spangenberg@asklepios.com.

PERSPECTIVES

Deficiency of HMWM and/or AbM are known to facilitate bleeding, if not leading to Heyde's syndrome, in patients with aortic stenosis and SAVR having been proven to correct this deficiency. Although transcatheter aortic valve replacement leads to a normalization of HMWM content in patients with prior AbM (42%), residual aortic regurgitation/leakage leads to inferior HMWM recovery. As HMWM content is strongly correlated with mean transvalvular gradient and aortic regurgitation results in inferior factor recovery, future studies need to determine whether HMWM content is capable of distinguishing between groups with discriminable prognostic properties or could act as a biomarker for procedural success.

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KEY WORDS aortic stenosis, transcatheter aortic valve replacement, von Willebrand syndrome