JACC: ADVANCES VOL. 3, NO. 10, 2024


ORIGINAL RESEARCH

# Von Willebrand Factor Activity Association With Outcomes After Transcatheter Edge-to-Edge Mitral Valve Repair

Sandra Hadjadj, MSc, Philippe Pibarot, DVM, PhD, Caroline Gravel, RN, Marie-Annick Clavel, DVM, PhD, Ons Marsit, PhD, Dounia Rouabhia, MD, Benoît M. Labbé, MD, Kim O'Connor, MD, Mathieu Bernier, MD, Erwan Salaun, MD, PhD, Julio Farjat, MD, MSc, Jorge Nuche Berenguer, MD, Josep Rodés-Cabau, MD, Jean-Michel Paradis, MD, Jonathan Beaudoin, MD

## ABSTRACT

**BACKGROUND** Residual mitral regurgitation (MR) is associated with worse outcomes after transcatheter edge-to-edge mitral valve repair (TEER). Shear stress induced by MR leads to altered von Willebrand factor activity (vWF:Act) and increased closure time with adenosine diphosphate (CT-ADP).

**OBJECTIVES** The purpose of this study was to investigate the use of CT-ADP to monitor MR during TEER and the association between the vWF, residual MR, and clinical events post-TEER.

**METHODS** Sixty-five patients undergoing TEER were enrolled. CT-ADP was measured at baseline, after each clip deployment, 1 hour and 24 hours post-TEER. CT-ADP values were related to vWF:Act/vWF antigen (vWF:Ag) ratio at the same time points, and MR severity was assessed by echocardiography at 1 month. Combined events of all-cause mortality and heart failure hospitalizations were evaluated at 1 year.

**RESULTS** At 1 month, 32 (49%) patients had residual MR > mild (of those, 14% had MR > moderate). There was no significant change in CT-ADP values during the procedure. However, CT-ADP significantly decreased 1-hour post-TEER ($P < 0.001$). Patients with corrected MR demonstrated an increase in vWF:Act/vWF:Ag ratio 1-hour post-TEER. Elevated baseline vWF:Act/vWF:Ag ratio and the periprocedural percentage changes of the vWF:Act/vWF:Ag ratio (1 hour post-TEER – baseline values) were associated with the combined clinical outcome.

**CONCLUSIONS** CT-ADP evolution in time was not quick enough to provide real-time monitoring of MR severity during TEER. However, vWF:Act/vWF:Ag ratio at baseline and its variations following the procedure were associated with clinical outcomes. Those findings will need external validation. (JACC Adv. 2024;3:101242) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the Quebec Heart and Lung Institute - Laval University, Quebec, Quebec, Canada

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 27, 2023; revised manuscript received July 11, 2024, accepted July 26, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101242

**ABBREVIATIONS AND ACRONYMS**

**CT-ADP** = closure time with adenosine diphosphate

**HF** = heart failure

**HMW** = high molecular weight

**MR** = mitral regurgitation

**TEER** = Transcatheter Edge-to-Edge Mitral Valve Repair

**vWF:Act** = von Willebrand factor activity

**vWF:Ag** = von Willebrand factor antigen

Persistent mitral regurgitation (MR) after transcatheter edge-to-edge mitral valve repair (TEER) is associated with increased rates of heart failure (HF) hospitalizations and mortality.[1-5] Procedural decisions regarding adding multiple clips are led by echocardiographic and hemodynamic evaluation of residual MR and mitral gradient. However, MR assessment during TEER can be difficult, with potential multiple/eccentric jets and variable hemodynamic conditions under general anesthesia.[6]

High shear stress induced by MR leads to excessive cleavage of von Willebrand factor (vWF) multimers,[7-9] resulting in a qualitative change in vWF, decreasing its activity (vWF:Act) without affecting the levels of vWF antigens (vWF:Ag). The ratio of vWF:Act/vWF:Ag has been used to document changes in turbulent flow associated with valvular regurgitation.[8] However, comorbidities such as hypertension or atherosclerosis, which are common in patients considered for a TEER, can be confounders by affecting the clearance of vWF.[10-12] Elevated plasma levels of vWF in patients with MR and comorbidities were previously associated with cardiovascular events.[11,13-15]

Closure time with adenosine diphosphate (CT-ADP) is a point-of-care measure of hemostasis strongly influenced by vWF:Act. CT-ADP can be assessed easily and serially during TEER and is known to normalize swiftly after the correction of turbulent flow. Its use has been described to screen for paravalvular leak during transcatheter aortic valve replacement,[16] and could also represent a potential way to assess residual MR during TEER.[8,17,18] Serial intraprocedural data of CT-ADP during TEER are, however, lacking.

The aims of the present study were to explore whether acute changes of CT-ADP and vWF:Act/vWF:Ag ratio (representing correction of turbulent flow) can be associated with residual MR and clinical events at 1 year postintervention. We also sought to investigate the association between baseline vWF levels (influenced by MR and comorbid conditions) and prognosis after TEER.

## MATERIAL AND METHODS

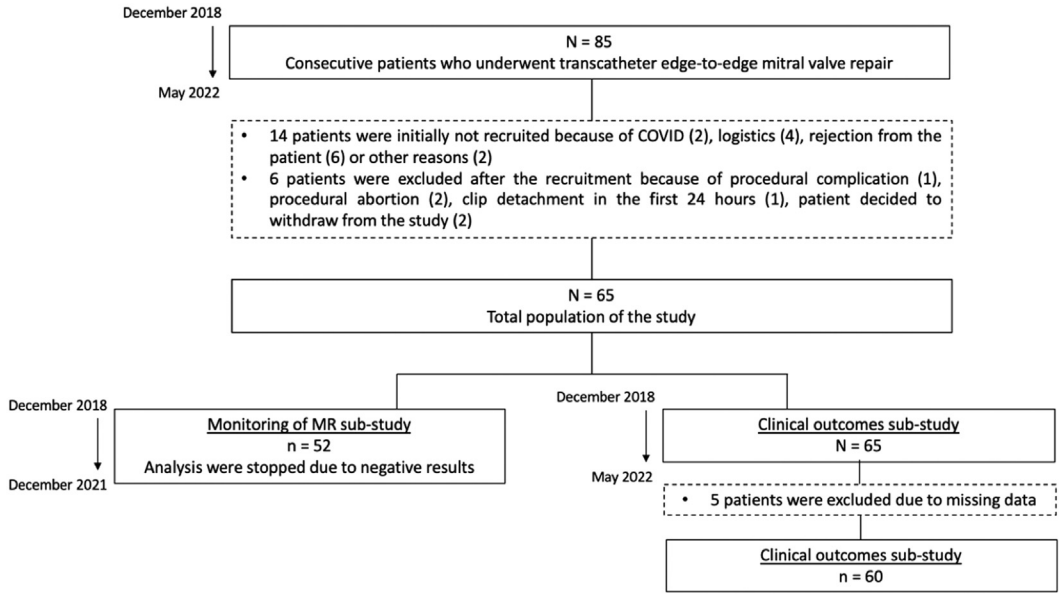
**STUDY DESIGN.** Consecutive patients with symptomatic MR who underwent TEER using MitraClip (Abbott) or Pascal device (Edwards Lifesciences) from December 2018 to May 2022 at the Quebec Heart and Lung Institute were prospectively included in the study (Figure 1). TEER procedures were performed per clinical protocol[19,20] under anticoagulation with intravenous unfractionated heparin. Antithrombotic therapy after TEER was left at the physician's discretion.

**CLINICAL AND IMAGING FOLLOW-UP.** Transthoracic and transeosophageal echocardiography were performed using commercially available equipment VIVID E95 (GE Healthcare) and EPIQ7 (Philips Healthcare). Transthoracic and transeosophageal echocardiography were performed at baseline and 1-month post-TEER. MR severity was assessed according to current guidelines using a multiparametric approach.[21,22] Residual MR was defined as MR grade > mild at 1 month. All echocardiography images were reviewed by a single level 3 reader (unaware of the biomarkers results or clinical events) for MR grade. In case of discrepancy between this assessment and the clinically reported MR grade, a third reader was involved and final MR grade was determined by consensus. All patients had a clinical visit or a follow-up call 12 months after TEER. The endpoints were defined according to the Mitral Valve Academic Research Consortium criteria.[23] The primary objective was to explore the changes in CT-ADP and vWF levels, reflecting the evolution of turbulent flow during and after the procedure. We also looked at the combined event of all-cause mortality or HF hospitalizations and its association with biomarker values. This study was approved by the local institutional review board.

**LABORATORY ANALYSIS.** Samples for measurements of von Willebrand factor activity (vWF:Act) and von Willebrand factor antigen (vFW:Ag) were collected at baseline (during the admission), 1 hour, and 24 hours (before discharge) after the procedure and were available in 60 patients. VWF:Act was analyzed using the INNOVANCE VWF Ac System (Siemens Healthineers), and vWF:Ag was measured by immunoturbidimetry (CA-5100, Sysmex). Rapid platelet function tests (CT-ADP) were performed at baseline (under anesthesia, before the femoral vein puncture), 8 minutes after the deployment of each clip, 1 hour and 24 hours after the procedure. Periprocedural serial measurements were available for 52 patients. CT-ADP tests were performed using the Platelet Function Analyzer 100 (PFA-100, Siemens Healthineers). The device aspirates blood from a sample into a membrane coated with collagen and adenosine diphosphate (ADP); platelet aggregation occludes an orifice in the membrane mimicking a vascular breach; and CT-ADP is the time to occlusion.

**STATISTICAL ANALYSIS.** Categorical variables are presented as absolute or relative frequencies.

**FIGURE 1** Population and Exclusions




MR = mitral regurgitation.

Continuous variables are expressed as mean ± SD or as median (IQR) according to the variable distribution. The procedural evolution of vWF:Act/vWF:Ag ratio and CT-ADP are expressed as percentage change vs baseline. Biomarker levels were compared between patients who experienced or not a clinical event (mortality or HF hospitalization) using the Wilcoxon rank-sum test. The evolution of CT-ADP and vWF levels after TEER was analyzed with a linear mixed model with repeated measures. One fixed factor (time effect) with three levels (baseline, first, and last clip) was defined. A random intercept (subject effect) was added to the model. A second fixed factor (residual MR effect) was added to compare patients with residual vs corrected MR with an interaction term between the two fixed factors. The dependence between repeated measurements was modeled using an unstructured covariance matrix of correlation as some observations were missing. Posteriori comparisons were performed using the Tukey's method. The normality assumption was verified with the Shapiro-Wilk test using residuals from the statistical model and transformed by the Cholesky's metric. The graphical representation of marginal linear predictor with studentized residuals suggested the homogeneity of variances. Some of the variables were log-transformed to fulfill these assumptions. Logistic regression analyses were performed to identify potential parameters that could be associated with residual MR[24] and adjusted for age, sex, Society of Thoracic Surgeons score, and blood type separately as the number of patients was limited. Continuous variables were checked for the assumption of linearity in the logit using graphical representations. Cox proportional hazard regression analyses were performed to model event-free (all-cause mortality or HF hospitalization) follow-up. Variables from univariate analyses with a probability value $<0.20$ as well as those with biological plausibility were tested in multivariable analyses. Baseline vWF:Act/VWF:Ag and ΔvWF:Act/VWF:Ag% were adjusted for age, female sex, STS score, O blood type, tricuspid regurgitation (TR) > mild, and residual MR > mild in separate models as the number of events was small. The martingale residuals were used to examine the functional form of continuous variables (no transformation was necessary). Artificial time-dependent covariates ($X[t] = \log[t] \cdot$ baseline vWF:Act/VWF:Ag and $X[t] = \log[t] \cdot \Delta$vWF:Act/VWF:Ag%) were added to the univariate models to test the proportionality assumption. The proportional hazards assumption was not rejected as local test linked to the time-dependent covariates was not significant. Receiver operating characteristic analysis was performed for significant variables, with optimal threshold values determined by the Youden Index. Kaplan-Meier

**TABLE 1 Baseline and Procedural Characteristics of the Population (N = 65)**

| | |
|---|---|
| Clinical data | |
| Age, y | 76 ± 9 |
| Female | 24 (37) |
| Weight, kg | 79 ± 25 |
| Body surface area, $m^2$ | 1.9 ± 0.3 |
| Comorbidities | |
| Hypertension | 50 (77) |
| Dyslipidemia | 42 (65) |
| COPD | 13 (20) |
| History of AF | 33 (51) |
| CAD | 34 (52) |
| Renal failure[a] | 36 (55) |
| Surgical risk | |
| STS score MVR | 5.5 ± 3.4 |
| Frailty | |
| 6 minutes walking test, m | 284 ± 126 |
| NYHA functional class ≥ III | 50 (77) |
| Laboratory data | |
| NT-proBNP, pg/mL | 2037 (1,001-3,699) |
| eGFR, mL/min/1.73 $m^2$ | 57 (41-69) |
| O blood type | 28 (43) |
| Antithrombotic treatment | |
| Antiplatelet therapy | 23 (35) |
| Anticoagulation therapy | 37 (57) |
| Procedural characteristics | |
| Procedural timing, min | 115 ± 56 |
| Number of clip(s) | 2 ± 1 |

Values are as mean ± SD, median (25th-75th percentiles), or n (%). [a]Renal failure if eGFR <60 ml/min/1.73 $m^2$.

AF = atrial fibrillation; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; NT-proBNP = natriuretic peptide; NYHA = New York Heart Association; MVR = mitral valve replacement; STS = Society of Thoracic Surgeons risk score.

**TABLE 2 Echocardiographic Parameters at Baseline and 1-Month Post-TEER (N = 65)**

| | |
|---|---|
| Baseline | |
| LVEF, % | 46 ± 13 |
| LVEDD, cm | 5.4 ± 0.9 |
| LAVi, ml/$m^2$ | 53 ± 21 |
| PAPs, mm Hg | 46 ± 17 |
| MR etiology | |
| Functional | 25 (39) |
| Organic | 34 (52) |
| Mixed | 6 (9) |
| AR > mild | 10 (15) |
| TR > mild | 32 (49) |
| AS ≥ mild[a] | 6 (9) |
| Follow-up | |
| LVEF, % | 45 ± 11 |
| LVEDD, cm | 5.4 ± 0.9 |
| LAVi, ml/$m^2$ | 55 ± 21 |
| PAPs, mm Hg | 43 ± 15 |
| Residual MR | |
| Trace/mild | 33 (51) |
| Mild to moderate | 18 (28) |
| Moderate | 5 (8) |
| >Moderate | 9 (14) |
| TR > mild | 34 (52) |
| TMG, mm Hg | 4.7 ± 3.1 |
| TMG >5 mm Hg | 16 (25) |

Values are mean ± SD or n (%). [a]Mild corresponds to a peak velocity >2.5 m/s according to the American Society of Echocardiography guidelines.

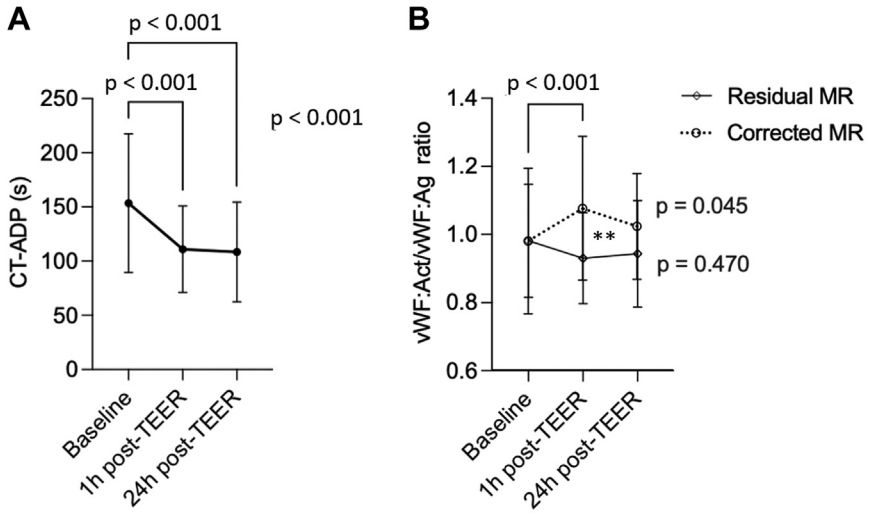
AR = aortic regurgitation; AS = aortic stenosis; LAVi = indexed left atrial volume; LVEDD = left ventricle end-diastolic diameter; LVEF = left ventricle ejection fraction; MR = mitral regurgitation; PAPs = systolic pulmonary arterial pressure; TMG = mean transmitral gradient; TR = tricuspid regurgitation.

survival curves and their associated log-rank tests were used to compare all-cause mortality or HF hospitalizations in patients who had vWF:Act/vWF:Ag ratio >1.015 and patients not improving vWF activity after the procedure (ΔvWF:Act/VWF:Ag <5.5%). The statistical analysis was not planned for multiplicity of tests for secondary outcomes. All analyses were performed using GraphPad version 9.4.1 (GraphPad Software) and SAS version 9.4 (SAS Institute Inc).

## RESULTS

A total of 65 patients (37% women; age 76 ± 9 years) were included in the study. Baseline and procedural characteristics are listed in **Table 1**, and echocardiographic parameters are shown in **Table 2**. MR etiology was functional in 25 (39%) patients, organic in 34 (53%) patients, and mixed in 6 (9%) patients. After 1 month of follow-up, 32 (49%) patients had residual MR > mild; of those, 9 (14%) patients had MR > moderate. After a 1-year follow-up, clinical events (mortality or HF hospitalizations) occurred in 14 (22%) patients. Patients who experienced a clinical event had a higher STS score for mitral valve replacement (7.3 ± 3.2 vs 4.9 ± 3.5, $P = 0.02$) and lower 6-minute walking test results at baseline (224 ± 112 m vs 303 ± 126 m, $P = 0.043$). There was no difference in the prevalence of patients with an O blood type between groups. Patients with an O blood type demonstrated lower levels of vWF:Ag at baseline (1.64 [1.16-1.98] vs 2.08 [1.72-2.47] IU/ml; $P = 0.002$), without difference in vWF:Act/vWF:Ag ratio (0.99 [0.90-1.12] vs 0.95 [0.87-1.01]; $P = 0.178$) (Supplemental Table 1). There was significantly more TR at follow-up in patients with events (>mild: 79% vs 45%, $P = 0.036$). Otherwise, there was no statistical difference in terms of comorbidities or echocardiographic parameters between the two groups. Patients treated with antiplatelet therapies had no significant difference for CT-ADP and vWF levels at baseline (Supplemental Table 2).

**FIGURE 2** Evolution of CT-ADP and vWF Levels After TEER




(A) Closure time with adenosine diphosphate (CT-ADP) significantly decreased at 1 hour and 24 hours after transcatheter edge-to-edge mitral valve repair (TEER) compared to baseline. (B) vWF:Act/vWF:Ag ratio only increased significantly at 1 hour post-TEER in the group of patients without residual MR (**$P < 0.01$ compares vWF:Act/vWF:Ag ratio at 1 hour in patients with corrected MR vs patients with residual MR). Variables are presented as mean ± SD. MR = mitral regurgitation; vWF:Act/vWF:Ag = von Willebrand factor activity/antigen ratio.

**ACUTE EVOLUTION OF FLOW BIOMARKERS DURING TEER.** Among the 65 patients included in the study, CT-ADP values were available in 52 patients (Figure 1). CT-ADP results are presented in Supplemental Figure 1. There was no significant difference in CT-ADP between the baseline and the first or last clip (129 [108-190] vs 136 [98-187] vs 135 [99-183] seconds, $P = 0.180$). However, the CT-ADP significantly decreased 1-hour post-TEER and remained stable at 24 hours compared to baseline (129 [108-190] vs 99 [82-130] vs 94 seconds [83-116] at baseline, 1 hour, and 24 hours, $P < 0.001$) (Figure 2A).

**VARIABLES ASSOCIATED WITH RESIDUAL MR.** The vWF:Act/vWF:Ag ratio was used to document the evolution of the turbulent flow induced by MR correction. Figure 2B shows that patients with corrected MR had a significant increase of the vWF:Act/vWF:Ag ratio at 1-hour post-TEER vs baseline (+0.10 ± 0.02; $P = 0.045$). The ratio was significantly higher in patients with corrected vs residual MR (1.02 [0.99-1.12] vs 0.93 [0.85-1.01] IU/mL, $P = 0.002$). Variables associated with residual MR are listed in Table 3. Patients with residual MR were more likely to have lower vWF:Act/vWF:Ag ratio at 1-hour post-TEER and lower ΔvWF:Act/vWF:Ag. Multivariable models were performed, each adjusting for one of the following parameters: age, female sex, STS score, or O blood type (associated with lower vWF levels) (Supplemental Table 3). Only lower levels of vWF:Act/vWF:Ag ratio at 1-hour post-TEER remained significantly associated with residual MR.

**VARIABLES ASSOCIATED WITH CLINICAL OUTCOMES.** Laboratory data at baseline, 1 hour after the procedure, and the percentage changes (Δ%) are displayed in Table 4. Among the 65 patients included in the study, 60 patients had both baseline and 1-hour post-procedural variables available (Figure 1). Baseline vWF:Act/vWF:Ag ratio was significantly higher in patients who had a clinical event during follow-up (respectively, 0.93 [0.87; 1.00] vs 1.04 [1.00; 1.23]; $P = 0.003$) (Table 4). Cox univariable analyses are shown in Table 5; patients with higher baseline vWF:Act/VWF:Ag ratio had an increased risk for all-cause mortality or HF hospitalizations after the procedure (HR: 13.96 [95% CI: 1.76-75.08], $P = 0.005$). Presence of TR > mild before the procedure was also associated with clinical events (HR: 3.43 [95% CI: 1.14-12.55], $P = 0.038$).

Evolution of biomarkers: Patients without clinical event after the procedure had a significantly higher increase in vWF:Act/vWF:Ag ratio (as estimated from percentage changes vs baseline) compared to patients who had a clinical event (ΔvWF:Act/VWF:Ag: 6% [0;13] vs 0% [-11;2], $P = 0.001$) (Table 4). Patients with a higher ΔvWF:Act/VWF:Ag ratio had a decreased risk for all-cause mortality or HF hospitalizations after the

**TABLE 3 Univariable Logistic Regressions Comparing Patients With and Without MR > Mild at 1 Month Post-TEER**

| Residual MR | OR (95% CI) | *P* Value |
|---|---|---|
| End-procedural CT-ADP (n = 52) | 0.99 (0.98-1.00) | 0.155 |
| 1 h post-TEER | | |
| CT-ADP (n = 52) | 0.99 (0.97-1.01) | 0.208 |
| vWF:Act/vWF:Ag (n = 49) | 0.50 (0.27-0.81) | 0.002[a] |
| Δ (%) | | |
| ΔCT-ADP (n = 52) | 1.00 (0.99-1.02) | 0.641 |
| ΔvWF:Act/vWF:Ag (n = 44) | 0.94 (0.88-0.98) | 0.021 |

vWF:Act/vWF:Ag is presented with increments of 10. $P < 0.05$ is considered to indicate statistical significance. [a]Also significant in multivariable models, each corrected for age, female sex, STS score, and O blood type (Supplemental Table 3).

CT-ADP = closure time with adenosine diphosphate; MR = mitral regurgitation; TEER = transcatheter edge-to-edge mitral valve repair; vWF:Act/vWF:Ag = von Willebrand factor activity/antigen ratio.

procedure (HR: 0.93 [95% CI: 0.88-0.97], $P = 0.002$) (Table 5). Residual MR > mild by echo evaluation was not associated with adverse outcomes ($P = 0.708$).

Multivariable models were performed, each adjusting for one of the following parameters: age, female sex, STS score, O blood type, tricuspid regurgitation, or residual MR (Supplemental Table 4). Baseline vWF:Act/vWF:Ag ratio remained significantly associated with increased risk of clinical events, along with the ΔvWF:Act/VWF:Ag ratio. Patients with higher baseline vWF:Act had also higher prevalence of coronary artery disease ($P = 0.014$) and a trend for more hypertension ($P = 0.099$) and dyslipidemia ($P = 0.099$).

Kaplan-Meier curves depicting freedom from all-cause mortality or HF hospitalizations at 1 year are illustrated in Figure 3. At baseline, patients who had an elevated vWF:Act/vWF:Ag ratio >1.015 were more likely to have clinical events during the follow-up (log-rank $P < 0.001$) (Figure 3A). The lack of improvement in the von Willebrand factor activity (ΔvWF:Act/VWF:Ag < 5.5%) after the procedure was associated with worse clinical outcomes (Log-rank $P = 0.005$) (Figure 3B). Threshold values were derived from receiver operating curves and Youden tests presented in Supplemental Table 5.

**TABLE 4 Laboratory Data in Patients With vs Without Clinical Event (All-Cause Mortality or HF Hospitalization)**

| | Free From Events (n = 43, 77.0%) | Clinical Events (n = 14, 23.0%) | *P* Value |
|---|---|---|---|
| Baseline | | | |
| CT-ADP, s | 125 (108-194) | 127 (104-145) | 0.432 |
| vWF:Act/VWF:Ag | 0.93 (0.87-1.00) | 1.04 (1.00-1.23) | 0.003 |
| 1 h post-TEER | | | |
| CT-ADP, s | 100 (86-126) | 102 (87-132) | 0.830 |
| vWF:Act/VWF:Ag | 1.00 (0.93-1.07) | 1.00 (0.87-1.19) | 0.874 |
| Δ% = 1 h post-TEER – baseline | | | |
| ΔCT-ADP, % | −27 (−44 to −8) | −14 (−38 to −2) | 0.183 |
| ΔvWF:Act/VWF:Ag, % | 6 (0-13) | 0 (−11 to 2) | 0.001 |

Values are n (25th-75th percentiles). *P* values compare results in the group free from events vs the group with clinical events. $P < 0.05$ is considered to indicate statistical significance.

HF = heart failure; other abbreviations as in Table 3.

**TABLE 5 Variables Associated With All-Cause Mortality and Hospitalizations for Heart Failure**

| | Univariable Analysis | |
|---|---|---|
| | HR (95% CI) | *P* Value |
| Laboratory variables | | |
| Baseline CT-ADP | 0.99 (0.98-1.00) | 0.246 |
| End-procedural CT-ADP | 0.99 (0.98-1.00) | 0.144 |
| ΔCT-ADP | 1.00 (0.99-1.03) | 0.182 |
| Baseline vWF:Act/VWF:Ag | 13.96 (1.76-75.08) | 0.005[a] |
| ΔvWF:Act/VWF:Ag | 0.93 (0.88-0.97) | 0.002[a] |
| Clinical baseline variables | | |
| Age, years | 1.01 (0.95-1.08) | 0.836 |
| Female sex | 0.97 (0.30-2.82) | 0.962 |
| Hypertension | 3.61 (0.72-65.64) | 0.216 |
| Dyslipidemia | 0.89 (0.31-2.91) | 0.841 |
| COPD | 1.55 (0.42-4.63) | 0.460 |
| Coronary artery disease | 0.95 (0.33-2.79) | 0.930 |
| History of atrial fibrillation | 0.82 (0.27-2.37) | 0.715 |
| eGFR | 1.00 (0.98-1.03) | 0.902 |
| NT-proBNP | 2.01 (0.56-7.75) | 0.296 |
| O blood type | 0.67 (0.20-1.93) | 0.466 |
| STS Score MVR | 1.11 (0.96-1.24) | 0.093 |
| Pre-TEER echocardiographic variables | | |
| AR > mild | 2.09 (0.57-6.24) | 0.214 |
| TR > mild | 3.43 (1.14-12.55) | 0.038 |
| AS ≥ mild | 0.58 (0.03-2.93) | 0.602 |
| PAPs | 0.99 (0.96-1.02) | 0.615 |
| Post-TEER echocardiographic variables | | |
| MR > mild | 0.82 (0.27-2.35) | 0.708 |
| TMG >5 mm Hg | 2.07 (0.68-5.97) | 0.177 |

$P < 0.05$ is considered to indicate statistical significance. [a]Also significant in multivariable models, each corrected for age, female sex, STS score, O blood type, TR, and residual MR (Supplemental Table 4).

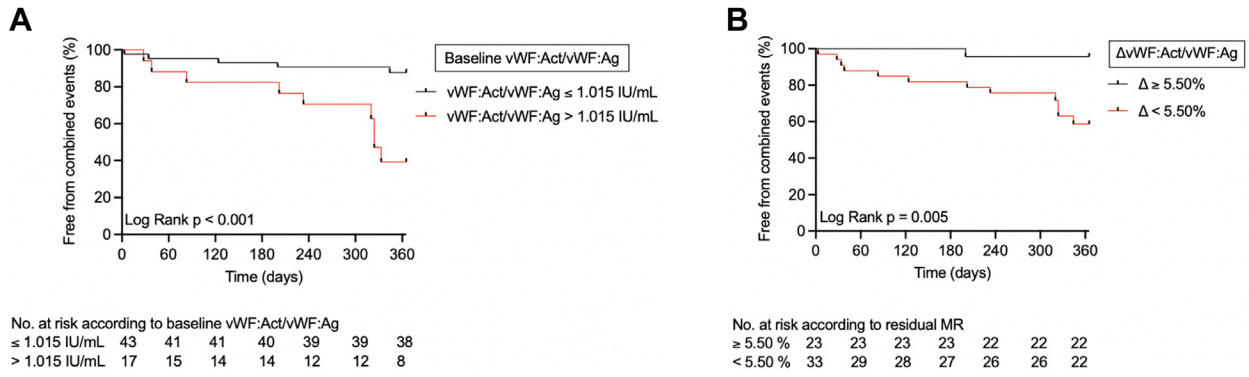
Abbreviations as in Tables 1, 2, and 3.

## DISCUSSION

The main findings of our study are: 1) time-changes in CT-ADP evolution are not fast- or precise-enough to provide real-time monitoring of MR severity during TEER; 2) the vWF:Act/vWF:Ag ratio at 1-hour post-TEER was associated with residual MR at 1 month, but neither this metric nor residual MR assessed by echocardiography were associated with clinical outcomes at 1 year; and 3) 1-year clinical outcomes post-TEER were associated with baseline vWF:Act/vWF:Ag ratio and its improvement after the procedure.

The vWF is a glycoprotein released as a high molecular weight (HMW) multimers by endothelial cells and megakaryocytes.[25] The vWF HMW multimers play

**FIGURE 3** Kaplan-Meir Curves Depicting Freedom From All-Cause Mortality or Heart Failure Hospitalizations



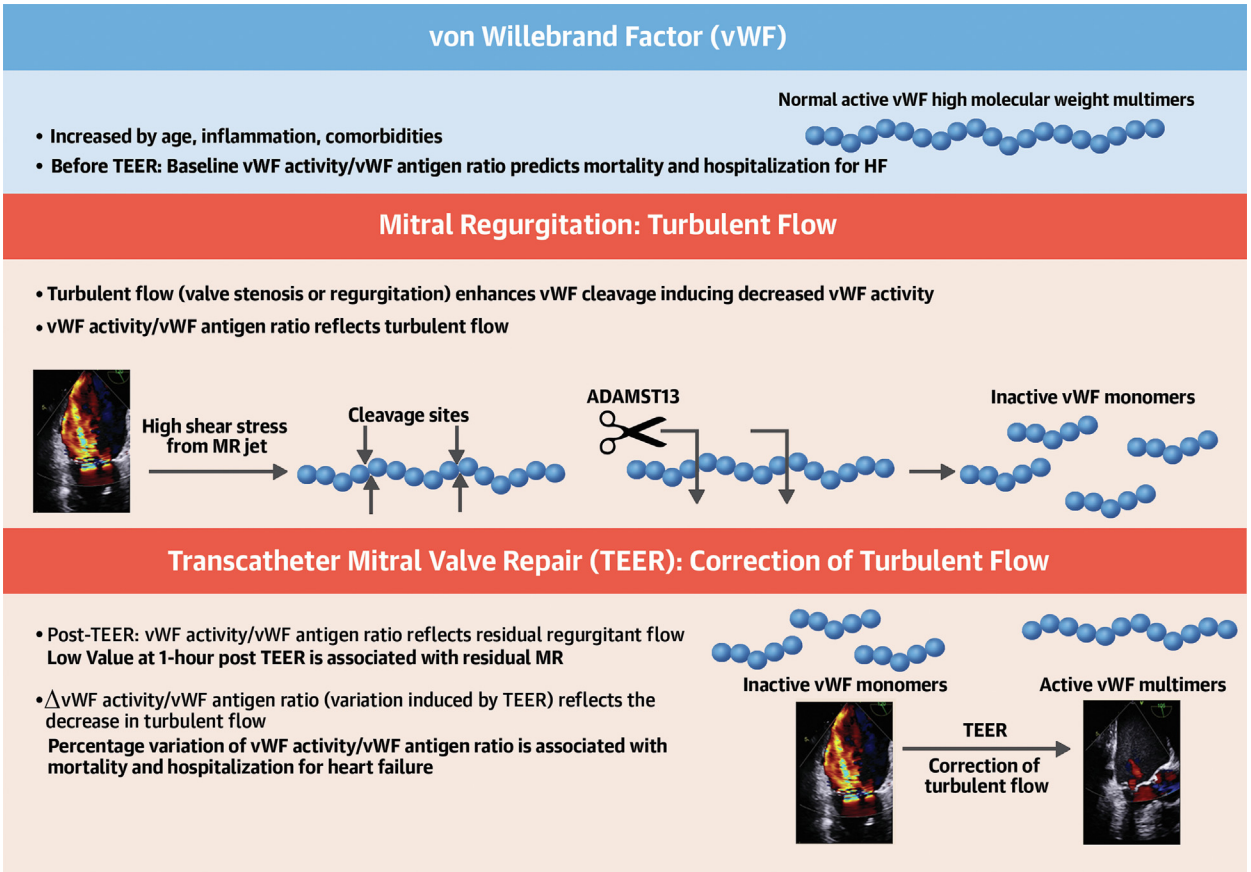

(A) Baseline levels of von Willebrand factor activity and antigen ratio (vWF:Act/vWF:Ag) ≤1.015 IU/mL vs >1.015 IU/mL. (B) Degree of improvement of vWF:Act/vWF:Ag ratio Δ ≥ 5.50% vs Δ <5.50%. MR = mitral regurgitation; vWF:Act/vWF:Ag = von Willebrand factor activity/antigen ratio.

an important role in hemostasis, particularly in platelet activation and aggregation.[26] Valvular heart diseases such as aortic stenosis or MR are associated with high turbulent blood flow inducing the proteolysis of vWF HMW multimers and cause an acquired von Willebrand syndrome.[8,9] The CT-ADP test is highly sensitive to defects in vWF HMW multimers and is increased in patients with turbulent blood flow.[17,27] Van Belle et al have demonstrated that HMW multimers defects could resolve within minutes after percutaneous aortic valve procedures, significantly associated with paravalvular leak and mortality after the intervention.[16,17] After a surgical mitral valve repair or replacement, CT-ADP was significantly decreased, and a postprocedural CT-ADP ≤121 seconds was associated with freedom of death or mitral valve surgery.[8] Little data are available regarding the use of CT-ADP in patients undergoing TEER, with conflicting results.[28,29] To our knowledge, our study is the first to describe the use of CT-ADP in a real-time procedural TEER frame. Our results suggested a normalization of CT-ADP 1 hour after the procedure. However, the dynamic changes in CT-ADP were not fast enough to enable real-time monitoring of the evolution of MR severity during the procedure. Moreover, this final CT-ADP value was not significantly linked to residual MR or clinical events. These results do not support the use of periprocedural CT-ADP monitoring in that setting. Although CT-ADP improvement has been shown as early as 5 minutes after flow correction,[17] further improvement can be seen after a longer wait time. It is possible that our negative periprocedural CT-ADP results were related to an early measure (8 minutes after each clip); however, longer wait times are likely to result in procedural delays. Residual turbulent flow from MR and TR, as well as the hemodynamic effect of anesthesia, can also potentially interfere with the dynamic of CT-ADP improvement but could not be assessed in our study because of limited sample size.

The lack of association between residual MR and clinical events is in opposition with previous reports [3,30] and is likely related to our small sample size. This also highlights the difficulty to assess residual MR after TEER with echocardiography.[6,31] Our results, however, showed that patients without significant improvement in the vWF activity 1-hour post-TEER vs baseline had more mortality and HF hospitalizations after the procedure. This metric is related to the decrease in turbulent flow, which considers the global improvement in MR rather than the final grade of MR (**Central Illustration**). Some patients can potentially benefit from TEER by going from very severe to mild or even moderate MR without being able to normalize their hemostatic parameters completely. In those patients, the amplitude of variation of MR and hemostatic markers might be potentially more important than the final MR grade or single biomarker value.

Consistent with previous studies, our results demonstrated that an elevated baseline level of vWF activity expressed as vWF:Act/vWF:Ag ratio was associated with mortality and HF hospitalizations.[11,13-15] Our results showed an association between elevated vWF:Act and coronary artery disease, which is consistent with previous reports.[32] Hence, patients showing elevated vWF:Act/vWF:Ag ratio at baseline represent a population at risk for clinical events following TEER. Whether this marker can

**CENTRAL ILLUSTRATION** **Summary of the Mechanistic Impact of Turbulent Flow on vWF Multimers and Its Association With Outcomes in Patients Undergoing TEER**




**Hadjadj S, et al. JACC Adv. 2024;3(10):101242.**

Von Willebrand factor (vWF) is a high molecular weight multimeric protein that is increased in patients with various comorbidities. An elevated von Willebrand factor activity/antigen ratio (vWF:Act/vWFAg) at baseline was found to be associated with mortality and hospitalizations for heart failure (HF) at 1 year of follow-up after transcatheter edge-to-edge mitral valve repair (TEER). In the presence of high shear stress induced by turbulent flow (mitral regurgitation), vWF multimers are cleaved by a metalloproteinase (ADAMST13), leading to a decrease in vWF:Act. Residual mitral regurgitation > mild after TEER was associated with lower values of vWF:Act/vWF:Ag ratio at 1-hour post-TEER. The percentage variation of vWF:Act/vWF:Ag ratio (Δ%) reflects the decrease in turbulent flow and was associated with mortality and hospitalization for HF after 1-year post-TEER. MR = mitral regurgitation.

potentially help to refine preintervention evaluation will require validation in a larger cohort.

**STUDY LIMITATIONS.** This was a single-center study with a limited number of patients and small number of clinical events. The statistical associations reported cannot be interpreted as cause-effect relationships. Residual MR was defined as any MR greater than mild; because of our small sample size, we could not perform analyses based on each MR grade (mild, moderate, and severe). Moreover, functional and primary MR were analyzed together in this exploratory work. The lack of association for residual MR and prognosis is in opposition with previous literature and likely related to limited power. Our results suggest that CT-ADP should not be used to monitor periprocedural MR acutely. The simultaneous presence of TR might also cause turbulence and influence our metrics. However, the influence of TR on vWF is attenuated due to the low-pressure system and the time before getting into the systemic circulation. Our study was not powered for this type of subanalysis. Because we did not control for the multiplicity in tests for secondary outcomes, the

results should be taken with caution. Although our data suggest a potential value for baseline or serial (Δ) vWF metrics, those results will need validation in larger cohorts. To establish optimal cutoff values would need further validation in larger cohorts and require a predictive analysis.

## CONCLUSIONS

This study does not support the use of intraprocedural CT-ADP to screen for residual MR during TEER. The vWF:Act/vWF:Ag ratio at 1-hour post-TEER was associated with residual MR at 1 month. The baseline vWF activity and its improvement following TEER (Δ) were associated with mortality and HF hospitalizations at 1 year after the procedure. These flow-dependent tests may have potential roles in classification and prognostication for patients undergoing TEER; however, those results will need validation in larger cohorts.

**ACKNOWLEDGMENT** The authors thank Serge Simard for statistical support.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

Ms Hadjadj and Dr Beaudoin are funded by Fonds de Recherche du Québec-Santé. This work was supported by Fondation de l'Institut Universitaire de Cardiologie et Pneumologie de Québec. Dr Rodés-Cabau holds the Research Chair "Fondation Famille Jacques Larivière" for the Development of Structural Heart Disease Interventions. Dr Pibarot has received institutional funding from Edwards Lifesciences, Medtronic, Pi-Cardia, and Cardiac Success for echocardiography core laboratory analyses and research studies in the field of interventional and pharmacologic treatment of valvular heart diseases, for which he received no personal compensation. Dr Beaudoin received research support from JAMP-Pharma, not related to the current work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr Jonathan Beaudoin, Institut Universitaire de Cardiologie et de Pneumologie de Québec - Université Laval, 2725 Chemin Ste-Foy, Québec G1V 4G5, Canada. E-mail: jonathan.beaudoin@criucpq.ulaval.ca.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** While CT-ADP variations were observed after TEER, intraprocedural measurements were not useful to monitor acute changes in MR. vWF:Act/vWF:Ag ratio at 1-hour post-TEER was associated with residual MR, and the degree of improvement of vWF activity following TEER was associated with mortality and HF hospitalizations at 1 year.

**TRANSLATIONAL OUTLOOK:** These flow-dependent tests may have potential roles in classification and prognostication for patients undergoing TEER and other valvular procedures but will require validation in larger cohorts.

## REFERENCES

**1.** Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–2318.

**2.** Mack M, Carroll JD, Thourani V, et al. Transcatheter mitral valve therapy in the United States: a report from the STS/ACC TVT registry. *Ann Thorac Surg*. 2022;113:337–365.

**3.** Ailawadi G, Lim DS, Mack MJ, et al. One-year outcomes after MitraClip for functional mitral regurgitation. *Circulation*. 2019;139:37–47.

**4.** Nickenig G, Estevez-Loureiro R, Franzen O, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. *J Am Coll Cardiol*. 2014;64:875–884.

**5.** Sugiura A, Kavsur R, Spieker M, et al. Recurrent mitral regurgitation after MitraClip: predictive factors, morphology, and clinical implication. *Circ Cardiovasc Interv*. 2022;15:e010895.

**6.** Zoghbi WA, Asch FM, Bruce C, et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American society of echocardiography developed in collaboration with the society for cardiovascular angiography and interventions, Japanese society of echocardiography, and society for cardiovascular magnetic resonance. *J Am Soc Echocardiogr*. 2019;32:431–475.

**7.** Federici AB, Rand JH, Bucciarelli P, et al. Acquired von Willebrand syndrome: data from an international registry. *Thromb Haemostasis*. 2000;84:345–349.

**8.** Blackshear JL, Wysokinska EM, Safford RE, et al. Shear stress-associated acquired von Willebrand syndrome in patients with mitral regurgitation. *J Thromb Haemostasis*. 2014;12:1966–1974.

**9.** Loscalzo J. From clinical observation to mechanism–Heyde's syndrome. *N Engl J Med*. 2012;367:1954–1956.

**10.** Atiq F, Meijer K, Eikenboom J, et al. Comorbidities associated with higher von Willebrand factor (VWF) levels may explain the age-related increase of VWF in von Willebrand disease. *Br J Haematol*. 2018;182:93–105.

**11.** Morange PE, Simon C, Alessi MC, et al. Endothelial cell markers and the risk of coronary heart disease: the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study. *Circulation*. 2004;109:1343–1348.

**12.** Folsom AR, Wu KK, Shahar E, Davis CE. Association of hemostatic variables with prevalent cardiovascular disease and asymptomatic carotid artery atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) study investigators. *Arterioscler Thromb*. 1993;13:1829–1836.

**13.** Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European concerted action on thrombosis and disabilities angina pectoris study group. *N Engl J Med*. 1995;332:635–641.

**14.** Prakash R, Horsfall M, Markwick A, et al. Prognostic impact of moderate or severe mitral regurgitation (MR) irrespective of concomitant comorbidities: a retrospective matched cohort study. *BMJ Open*. 2014;4:e004984.

**15.** Simpson TF, Kumar K, Samhan A, et al. Clinical predictors of mortality in patients with moderate to severe mitral regurgitation. *Am J Med*. 2022;135:380–385.e3.

**16.** Van Belle E, Rauch A, Vincent F, et al. Von Willebrand factor multimers during transcatheter aortic-valve replacement. *N Engl J Med*. 2016;375:335–344.

**17.** 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;116:1193-1201.

**18.** Blackshear JL, Kusumoto H, Safford RE, et al. Usefulness of von Willebrand factor activity indexes to predict therapeutic response in hypertrophic cardiomyopathy. *Am J Cardiol*. 2016;117:436-442.

**19.** Silvestry FE, Rodriguez LL, Herrmann HC, et al. Echocardiographic guidance and assessment of percutaneous repair for mitral regurgitation with the Evalve MitraClip: lessons learned from EVEREST I. *J Am Soc Echocardiogr*. 2007;20:1131-1140.

**20.** Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol*. 2009;54:686-694.

**21.** Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. *J Am Soc Echocardiogr*. 2017;30:303-371.

**22.** Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14:611-644.

**23.** Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. *Eur Heart J*. 2015;36:1878-1891.

**24.** Gammie JS, Grayburn PA, Quinn RW, Hung J, Holmes SD. Quantitating mitral regurgitation in clinical trials: the need for a uniform approach. *Ann Thorac Surg*. 2022;114:573-580.

**25.** Stockschlaeder M, Schneppenheim R, Budde U. Update on von Willebrand factor multimers: focus on high-molecular-weight multimers and their role in hemostasis. *Blood Coagul Fibrinolysis*. 2014;25:206-216.

**26.** Schneider SW, Nuschele S, Wixforth A, et al. Shear-induced unfolding triggers adhesion of von Willebrand factor fibers. *Proc Natl Acad Sci U S A*. 2007;104:7899-7903.

**27.** 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;111:374-381.

**28.** Gragnano F, Crisci M, Bigazzi MC, et al. Von Willebrand factor as a novel player in valvular heart disease: from bench to valve replacement. *Angiology*. 2018;69:103-112.

**29.** Meindl C, Paulus M, Koller T, et al. Acquired von Willebrand syndrome and factor VIII in patients with moderate to severe mitral regurgitation undergoing transcatheter mitral valve repair. *Clin Cardiol*. 2021;44:261-266.

**30.** Kar S, Mack MJ, Lindenfeld J, et al. Relationship between residual mitral regurgitation and clinical and quality-of-life outcomes after transcatheter and medical treatments in heart failure: COAPT trial. *Circulation*. 2021;144:426-437.

**31.** Pozo OE, Salinas Gallegos A, Gordillo X, et al. Correlation of intraprocedural and follow up parameters for mitral regurgitation grading after percutaneous edge-to-edge repair. *J Clin Med*. 2022;11:2276.

**32.** Yan B, Wang Q, Du W, et al. Elevated Plasma von Willebrand Factor Antigen and Activity Levels Are Associated With the Severity of Coronary Stenosis. *Clin Appl Thromb Hemost*. 2020;26:1076029619900552.

**KEY WORDS** **CT-ADP, MitraClip, transcatheter mitral valve repair, von Willebrand diseases, von Willebrand factor**

**APPENDIX** **For supplemental tables and a figure, please see the online version of this paper.**