



**HAL**  
open science

# Paradoxical Increase of Stroke in Patients with Defect of High Molecular Weight Multimers of the von Willebrand Factors following Transcatheter Aortic Valve Replacement

Kensuke Matsushita, Benjamin Marchandot, Antonin Trimaille, Marion Kibler, Joe Heger, Marilou Peillex, Sebastien Hess, Lelia Grunebaum, Antje Reydel, Michel Kindo, et al.

► **To cite this version:**

Kensuke Matsushita, Benjamin Marchandot, Antonin Trimaille, Marion Kibler, Joe Heger, et al.. Paradoxical Increase of Stroke in Patients with Defect of High Molecular Weight Multimers of the von Willebrand Factors following Transcatheter Aortic Valve Replacement. *Thrombosis and Haemostasis*, 2020, 120 (09), pp.1330-1338. 10.1055/s-0040-1713424 . hal-04380277

**HAL Id: hal-04380277**

**<https://hal.science/hal-04380277v1>**

Submitted on 8 Jan 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## **Paradoxical Increase of Stroke in Patients with Defect of High Molecular Weight Multimers of the von Willebrand Factors following Transcatheter Aortic Valve Replacement**

Kensuke Matsushita<sup>1,2</sup> Benjamin Marchandot<sup>1</sup> Antonin Trimaille<sup>1</sup> Marion Kibler<sup>1</sup> Joe Heger<sup>1</sup> Marilou Peillex<sup>1</sup> Sebastien Hess<sup>1</sup> Lelia Grunebaum<sup>3</sup> Antje Reydel<sup>1</sup> Michel Kindo<sup>1</sup> Minh Tam Hoang<sup>1</sup> Chisato Sato<sup>1</sup> Fabien De Poli<sup>4</sup> Pierre Leddet<sup>4</sup> Mickael Ohana<sup>5</sup> Laurence Jesel<sup>1,2</sup> Patrick Ohlmann<sup>1</sup> Sophie Susen<sup>6,7</sup> Olivier Morel<sup>1,2</sup>

1 Pôle d'Activité Médico-Chirurgicale Cardio-Vasculaire, Nouvel Hôpital Civil, Centre Hospitalier Universitaire, Université de Strasbourg, Strasbourg, France 2UMR1260 INSERM, Nanomédecine Régénérative, Faculté de Pharmacie, Université de Strasbourg, Illkirch, France 3Department of Haemostasis, Centre Hospitalier Universitaire, Strasbourg, France 4Department of Cardiology, Centre Hospitalier de Haguenau, Haguenau, France 5Department of Radiology, Nouvel Hôpital Civil, Centre Hospitalier Universitaire, Strasbourg, France 6 INSERM U1011 - EGID, Institut Pasteur de Lille, University of Lille, Lille, France 7Hematology Transfusion, CHU Lille, Lille, France Thromb Haemost

Address for correspondence Olivier Morel, MD, PhD, Pôle d'Activité Médico-Chirurgicale Cardio-Vasculaire, Nouvel Hôpital Civil, Centre Hospitalier Universitaire, 1 Place de l'Hôpital - 67091 Strasbourg Cedex, France (e-mail: [olivier.morel@chru-strasbourg.fr](mailto:olivier.morel@chru-strasbourg.fr)).

**Abstract** Background Stroke is a major cause of disability after transcatheter aortic valve replacement (TAVR) and stroke prediction models and data are crucially needed. Following TAVR, high molecular weight (HMW) multimers defect of von Willebrand factor (VWF) as assessed by closure time of adenosine diphosphate (CT-ADP) value > 180 seconds is an independent predictor of bleeding events. This study sought to identify predictors of ischemic neurological events in patients who underwent TAVR and the specific impact of HMW multimers defect of VWF. Methods Patients were prospectively enrolled between November 2012 and May 2018 at our institution. The CT-ADP, a point-of-care measure of hemostasis, was assessed the day before and 24 hours after the procedures. The rate of ischemic stroke and transient ischemic attack (TIA) was recorded up to 30 days after the procedures. Results Of 565 TAVR patients, ischemic stroke/TIA was observed in 21 (3.7%) patients within 30 days. Ischemic stroke/TIA was associated with major/life-threatening bleeding complications (MLBCs) (9 [43%] vs. 88 [16%],  $p = 0.002$ ) and postprocedure CTADP > 180 seconds (10 [48%] vs. 116 [21%],  $p = 0.01$ ). By multivariate analysis, MLBCs (odds ratio [OR]: 3.58; 95% confidence interval [CI]: 1.45–8.84;  $p = 0.006$ ) and postprocedure CT-ADP > 180 seconds (OR: 3.38; 95% CI: 1.38–8.25;  $p = 0.008$ ) were evidenced as independent predictors of ischemic stroke/TIA. Conclusion MLBCs and CT-ADP > 180 seconds were identified as predictors for ischemic stroke or TIA. The present study suggests that the defects of HMW multimers of the VWFs may contribute not only to bleeding events but also to thrombotic events.

Keywords ► transcatheter aortic valve replacement ► ischemic stroke ► closure time of adenosine diphosphate ► bleeding

## **Introduction**

Transcatheter aortic valve replacement (TAVR) has emerged as a therapeutic alternative for patients with symptomatic severe aortic stenosis (AS) in all levels of surgical risk.<sup>1–3</sup> Indeed, the increasing experience of the heart teams has translated into significant reductions in mortality and periprocedural complications.<sup>4</sup> Despite improvements in TAVR device technology, rates of neurological events appear to be consistent over time with 30-day stroke rate ranging from 1.4 to 3.7%,<sup>4–9</sup> and consistently associated with increased mortality.<sup>10</sup> On a pathophysiological point of view, the vast majority of periprocedural neurological events following TAVR relies on debris embolization from either aortic valve leaflets or the aortic wall unlikely to be efficiently targeted by antithrombotic drugs.<sup>11,12</sup> Numerous potential predictors for neurological events have been highlighted by reviews,<sup>13,14</sup> and only a few dedicated studies identified independent risk factors that appear to differ from one study to another.<sup>6,15</sup> Interestingly, the ADVANCE study demonstrated that strokes occurring after the periprocedural period (day 2–30) were significantly related to major vascular complications, while no specific patient profiles nor procedural characteristics could be evidenced as predictors for periprocedural strokes (day 0–1).<sup>10</sup> Although it seems certain that bleeding events during TAVR are significantly related to stroke after procedures,<sup>10,16</sup> the underlying mechanisms remain uncertain. Consequently, a thorough understanding of the pathophysiology of both thrombotic and bleeding complications is required for the development of tailored strategies aimed to improve this balance. Closure time of adenosine diphosphate (CT-ADP) is a primary hemostasis point-of-care test used as a surrogate marker of high molecular weight (HMW) multimers defect of von Willebrand factor (VWF). The value of CT-ADP can be influenced by hematologic parameters and antiplatelet therapies.<sup>17</sup> We previously described that in the case of TAVR complicated by significant paravalvular leak (PVL), HMW multimers defect was not corrected.<sup>18</sup> Moreover, CTADP > 180 seconds was identified as an independent predictor of PVL and associated with early- and late-bleeding events and increased 1-year mortality among patients undergoing TAVR.<sup>17–19</sup> However, the question of whether hemostasis dysfunction through ongoing loss of HMW multimers could favor thrombotic events remains unsolved. Therefore, in the present study, we aimed to characterize the incidence, timing, and predictors of early ischemic neurological events following TAVR and evaluate the impact of ongoing primary hemostasis disorders, as assessed by CT-ADP > 180 seconds.

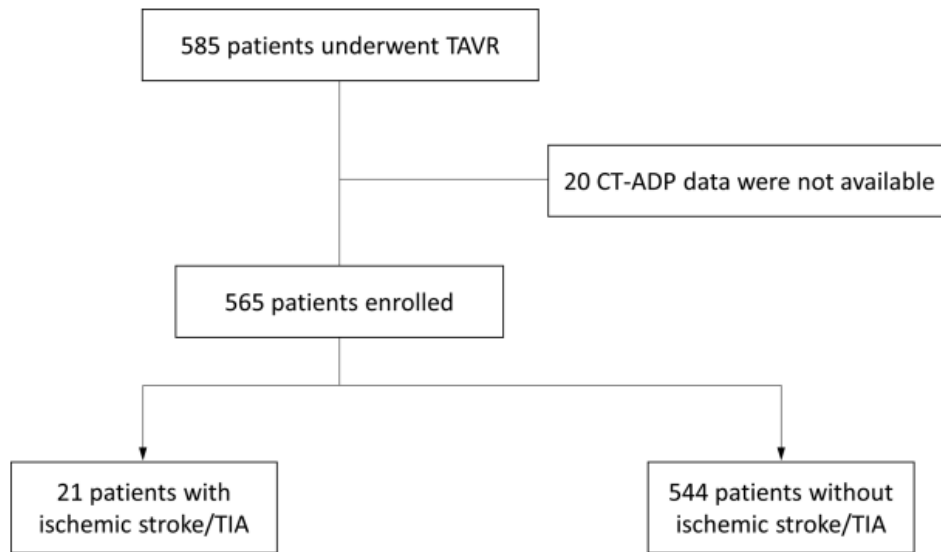
## **Methods**

**Study Design and Patients** A total of 585 consecutive patients with symptomatic severe AS who underwent TAVR were enrolled in a prospective registry at our institution (Nouvel Hôpital Civil, Université de Strasbourg, Strasbourg, France) between November 2012 and May 2018. Indications for TAVR and procedural approaches were assessed by the local heart team composed of interventional cardiologists and cardiac surgeons. The logistic EuroSCORE, as well as other nontraditional risk factors such as comorbidities or frailty, were considered when determining patients' specific risk profiles. All patients signed informed consent before the procedure and agreed to the anonymous processing of their data (France 2 and France TAVI Registries). We studied 565 patients who underwent CT-ADP assessments. The TAVR procedures were performed using balloon-expandable Edwards SAPIEN XT or S3 prosthesis (Edwards Lifesciences, Irvine, California, United States) and self-expandable CoreValve or Evolut R (Medtronic, Minneapolis, Minnesota, United States). Patients received intravenous unfractionated heparin to achieve an activated clotting time of 250 to 350 seconds during the procedures. Heparin was antagonized with 100 IU/kg of protamine at the end of the procedure. All patients received aspirin (75–160 mg) and clopidogrel (300 mg for loading dose and 75 mg/day for maintenance dose) before TAVR, with ongoing dual antiplatelet therapy (DAPT) after the procedure for 3 months. Clopidogrel was not administered when the patients were treated with oral anticoagulant (OAC). **Blood Collections** Whole blood samples were obtained by venipuncture the day before and 24 hours after TAVR. The CT-ADP assay was performed with the use of PFA-100 (Siemens Healthcare, Marburg, Germany). In the setting of TAVR, this hemostatic point-of-care assay is mainly used as a surrogate marker of HMW multimers defect of VWF. The extent of P2Y<sub>12</sub> inhibition by clopidogrel was evaluated by the analysis of vasodilator-stimulated phosphoprotein phosphorylation by flow cytometry as previously described.<sup>20</sup> **Clinical Follow-Up** Clinical follow-up data including neurological events during the first 30 days after TAVR were collected from all patients. We sought to determine if the timing of the first neurological event after TAVR was related to unique or competing causes by evaluating the incidence and predictors of the composite of ischemic stroke and transient ischemic attack (TIA) at two distinct time intervals: periprocedural (day 0–1) and early (day 2–30) as previously described.<sup>10</sup> The suspicion of a new neurological event triggered examination by a neurologist or stroke specialist. It was recommended to have imaging (multislice computed tomography or diffusion-weighted magnetic resonance imaging) to support the diagnosis of stroke. Disabling stroke was defined as a modified Rankin Score (mRS)  $\geq 2$  at 90 days postevent and an increase in at least 1 mRS category from baseline. Nondisabling stroke was defined as a mRS  $< 2$  at 90 days after the event, or as a stroke that does not result in an increase of at least 1 mRS category from baseline. TIA was defined as a new focal neurological deficit lasting  $< 24$  hours without neuroimaging evidence of tissue injury. Stroke/TIA and bleeding events were assessed according to the Valve Academic Research Consortium-2 (VARC-2) definitions. We added to the VARC-2 classification the occurrence of bleeding requiring red blood cell transfusion of two or more units. **Statistical Analysis** Categorical variables are expressed as numbers (percentage), and continuous variables are expressed as mean standard deviation (SD) or median and

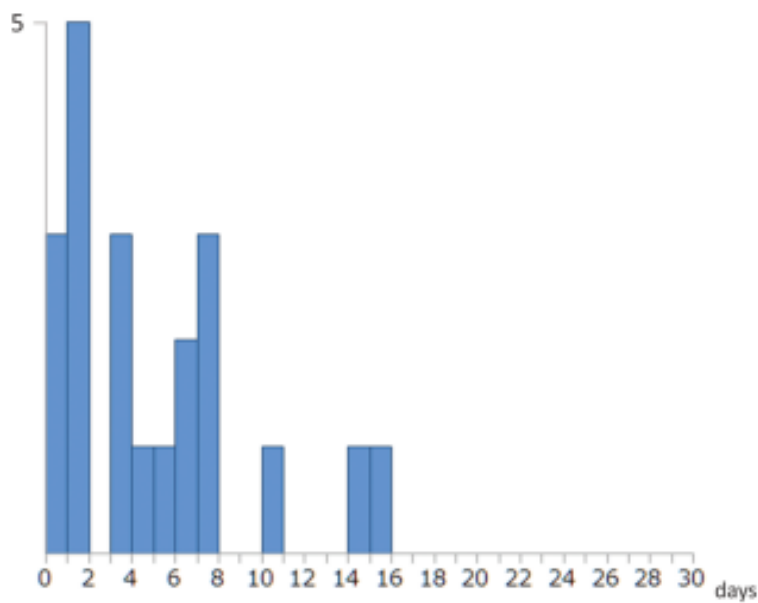
interquartile values. Differences between the two groups, consisting of patients with and without ischemic stroke or TIA, were assessed with chi-square tests for categorical variables. Unpaired Student's t-test was used to analyze continuous variables with normal distributions, and the Wilcoxon test was used to analyze continuous variables with skewed distributions. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of ischemic stroke/TIA events. Factors associated with a p-value of  $< 0.1$  in univariate analysis were implemented into a backward stepwise model using removal criteria of 0.10. To prevent expected collinearity between CT-ADP  $> 180$  seconds after TAVR and major/life-threatening bleeding complications (MLBCs), two separate multivariate analyses were performed. Additional sensitivity analyses for both CT-ADP  $> 180$  seconds after TAVR and MLBCs were performed with hemoglobin levels and platelet count, which are known to impact CT-ADP levels. Propensity score matching was performed to adjust the hemoglobin levels and platelet counts between patients with and without CT-ADP  $> 180$  seconds and patients with and without MLBCs. The propensity score model was developed using logistic regression and the model included hemoglobin levels and platelet counts as covariates. A nearest-neighbor algorithm was used to match patients with and without CT-ADP  $> 180$  seconds after TAVR and patients with and without MLBCs in a 1:1 ratio, with a caliper width equal to 0.2 of the SD of the logit of the propensity score. p-Values of  $< 0.05$  were considered to indicate statistical significance. All analyses were performed using JMP 13 software (SAS Institute, Cary, North Carolina, United States).

## Results

A total of 565 patients who underwent CT-ADP assessments were enrolled in the present study (► Fig. 1). Twenty-four patients (4.2%) developed neurological complications during the first month after TAVR. Twenty-one patients presented with ischemic neurological events (ischemic stroke or TIA) (3.7%), and the remaining 3 patients had cerebral hemorrhage (0.5%). The incidences of postprocedural ischemic neurological events are outlined in ► Supplementary Table S1 (available in the online version). The risk of ischemic stroke or TIA peaked within 1 day after TAVR and all the events occurred within 15 days (► Fig. 2).



**Fig. 1** Study flowchart. CT-ADP, closure time of adenosine diphosphate; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.



**Fig. 2** Timing of ischemic neurological events after transcatheter aortic valve replacement. TIA, transient ischemic attack.

**Baseline Characteristics** In a general elderly TAVR population, the ischemic stroke/TIA group disclosed less OAC therapy requirement at baseline (4 [19%] vs. 219 [40%],  $p = 0.049$ ) (► Table 1), while pre-TAVR CT-ADP was similar between the two groups (187 ————— 82 vs. 192 77 seconds,  $p = 0.77$ ). **Intraprocedure and Postprocedural Characteristics** Procedural and postprocedural characteristics are depicted in ► Table 2. No difference was observed in procedure time, approach site, valve size, or pre- and postdilatation between patients with and without ischemic stroke or TIA. Rates of MLBCs and bleedings requiring red blood cell transfusion of two or more units were greater in patients who developed ischemic stroke or TIA (9 [43%] vs. 88 [16%],  $p = 0.002$  and 9 [43%] vs. 100 [18%],  $p = 0.01$ , respectively). The bleeding events were related to the access site-related injury and associated bleedings after the TAVR procedures. The incidence of patients with postprocedure CT-ADP > 180 seconds was significantly higher in the ischemic stroke/TIA group (10 [48%] vs. 116 [21%],  $p = 0.01$ ) (► Fig. 3). **Predictors of Ischemic Neurological Events** In univariate analysis, postprocedure CT-ADP > 180 seconds (odds ratio [OR]: 3.35; 95% confidence interval [CI]: 1.39–8.09;  $p = 0.007$ ), MLBCs (OR: 3.89; 95% CI: 1.59–9.50;  $p = 0.003$ ), and bleedings requiring red blood cell transfusion of two or more units (OR: 3.33; 95% CI: 1.37–8.17;  $p = 0.008$ ) were significant predictors of ischemic stroke or TIA (► Table 3). Previous stroke history (OR: 2.46; 95% CI: 0.93–6.55;  $p = 0.07$ ), OAC at baseline (OR: 0.35; 95% CI: 0.12–1.04;  $p = 0.06$ ), and 24 hours postprocedural white blood cell (WBC) count (OR: 1.11; 95% CI: 0.99–1.25;  $p = 0.09$ ) tended to be associated with ischemic stroke or TIA. Two multivariate models were performed owing to the collinearity between postprocedure CT-ADP > 180 seconds and MLBCs (► Table 4). In the first model including post-procedure CT-ADP > 180 seconds, previous stroke history, OAC therapy at baseline, and WBC count after TAVR, CT-ADP > 180 seconds (OR: 3.38; 95% CI: 1.38–8.25;  $p = 0.008$ ) was the sole independent predictor of ischemic stroke or TIA. In the second model including MLBCs, previous stroke history, OAC therapy at baseline, and WBC count after TAVR, MLBCs (OR: 3.58; 95% CI: 1.45–8.84;  $p = 0.006$ ) was the only independent predictor of ischemic stroke or TIA. Results of our sensitivity analyses are shown in ► Supplementary Table S2 (available in the online version). After propensity score matching, 122 patients with CTADP > 180 seconds were compared with 122 patients with CT-ADP ————— 180 seconds (► Supplementary Tables S3 and S4, available in the online version). Likewise, 190 patients were included in the matched cohort of patients with and without MLBCs (► Supplementary Tables S5 and S6 available in the online version). A weaker relationship between CTADP > 180 seconds after TAVR and ischemic stroke/TIA was observed after adjusting hemoglobin levels and platelet counts (OR: 3.54; 95% CI: 0.95–13.2;  $p = 0.06$ ), suggesting that the anemia and thrombopenia induced by bleeding complications may have influenced the CT-ADP assessments (► Supplementary Table S2, available in the online version). There was no relationship between MLBCs and ischemic stroke/TIA

after adjusting hemoglobin levels and platelet counts (OR: 1.88; 95% CI: 0.61–5.85;  $p = 0.27$ ) (► Supplementary Table S2, available in the online version). Timing of Ischemic Neurological Events after TAVR Overall, eight patients had an ischemic stroke or TIA during the periprocedural period (day 0–1). During the early period (day 2–30), an additional 13 patients experienced ischemic stroke or TIA (► Supplementary Table S1, available in the online version). The incidence of MLBCs and postprocedure CTADP > 180 seconds were comparable between patients with and without periprocedural ischemic stroke/TIA (1 [13%] vs. 96 [17%],  $p = 1.00$  and 2 [25%] vs. 124 [22%],  $p = 1.00$ , respectively). On the contrary, the patients with early ischemic stroke/TIA had a significantly higher incidence of periprocedural MLBCs (8 [62%] vs. 89 [16%],  $p < 0.001$ ) and postprocedure CT-ADP > 180 seconds (8 [62%] vs. 118 [21%],  $p = 0.002$ ) (► Fig. 3) than patients without early ischemic stroke/TIA. The incidence of significant PVL 1 month after TAVR tended to be more than twofold higher in patients with early ischemic stroke or TIA (4 [31%] vs. 70 [13%],  $p = 0.08$ ).

## Discussion

The current study drawn from a cohort of 565 patients who underwent TAVR is the first study to specifically evaluate the impact of ongoing primary hemostasis disorders as assessed by a postprocedure CT-ADP > 180 seconds on ischemic neurological events. The principal findings of this study can be summarized as follows: First, postprocedure CT-ADP > 180 seconds and periprocedural MLBCs served as independent predictors of ischemic neurological events following TAVR. Second, the incidence of postprocedure CT-ADP > 180 seconds was threefold higher in patients with early (day 2–30) ischemic neurological events, whereas no impact of CT-ADP was observed in the periprocedural period of day 0 to 1. Third, 89% of patients experienced neurological events several days after the periprocedural bleeds. These findings suggest that the defects of HMW multimers of the VWF may contribute not only to bleeding events but also to early ischemic events. Incidence and Possible Predictors of Stroke Events after TAVR Recent studies have demonstrated that the rates of 30-day stroke were 1.4 to 3.7%.<sup>4–6,11</sup> In the present real-life registry, we included patients mainly treated with early-generation valves, which may have slightly contributed to the increase of the 30-day stroke rate. Fibrin, amorphous calcium, and connective tissue from either the native aortic wall have been considered as the embolic nature of periprocedural stroke.<sup>12</sup> In our analysis, no specific patient profile or procedure-related characteristics could be identified as a significant predictor of periprocedural stroke (day 0–1).

This finding was consistent with the result of the ADVANCE trial which failed to identify predictors of stroke events during 0 to 1 day after TAVR.<sup>10</sup> Altogether, it is likely that periprocedural stroke is due to embolization of aortic debris caused by catheter manipulations within the calcified aortic valve and aortic arch. Currently, no specific patient or procedure-related characteristics is identified as a significant predictor for periprocedural stroke. Despite the recognized early risk of stroke, considerable numbers of neurological complications still occur > 24 hours after TAVR<sup>10,21,22</sup> and are less likely to be explained



by devices manipulations. Consistent with these previous observations, more than 50% of ischemic strokes or TIAs occurred after the first 2-day window in the present study. Besides procedural aspects, these observations strongly suggest that other determinants, may contribute to adverse neurological outcomes. The ADVANCE study has indicated that prior atrial fibrillation (AF) and more surprisingly major vascular complication were highlighted as independent predictors of stroke or TIA. Consistent with this paradoxical finding, patients with ischemic stroke or TIA were in our experience, more likely to have MLBCs and blood transfusions than patients without ischemic neurological events.

The paradoxical relationship between bleeding and ischemic stroke events has been extensively described in percutaneous coronary intervention studies. Among various explanations, it is likely that blood transfusions are associated with an increased risk of stroke through transfusion-enhanced systemic inflammatory reaction, causing a prothrombotic environment.<sup>23</sup> In line with this paradigm, a relationship between transfusion rates and ischemic neurological events after TAVR could be evidenced in the present study. Primary Hemostasis Disorders and Stroke Events after TAVR Among various factors that could favor early bleeding events, special attention was given to the role played by primary hemostasis disorders and acquired von Willebrand syndrome, especially when flow turbulence persists after TAVR owing to significant PVL. Severe AS induces a very turbulent blood flow at the vicinity of the aortic valve, causing high shear stress that promotes deployment and cleavage of VWF's HMW multimers. Several groups including ours have demonstrated that TAVR could efficiently resolve HMW multimer defects within minutes and normalize primary hemostasis dysfunction.<sup>18,24</sup> We have recently demonstrated that CT-ADP > 180 seconds, a surrogate marker of HMW-VWF defect, as measured during the time course of the procedure allows an accurate identification of PVL in patients undergoing TAVR and is a major predictor of early but also late bleeding.<sup>17–19</sup> In addition, we could also identify that elevated CT-ADP values were associated with the presence of low hemoglobin levels, low platelet count, and appropriate platelet inhibition by P2Y<sub>12</sub> inhibitors, suggesting that CT-ADP can reflect a broad spectrum of pathologies.<sup>17</sup> Challenging the sole role of prolonged CT-ADP as a marker of bleeding risk, we could demonstrate a threefold higher incidence of postprocedure CT-ADP > 180 seconds among patients with early ischemic stroke or TIA. Likewise, the incidence of significant PVL (a potent determinant of prolonged CT-ADP) among patients with early ischemic stroke or TIA tended to be 2.5-fold higher. Moreover, our sensitivity analysis (► Supplementary Table S2, available in the online version) indicated that CT-ADP levels after TAVR was influenced by the hemoglobin levels and platelet counts. The anemia and thrombopenia following bleeding complications may have been related to both the elevated CT-ADP levels and the ischemic neurological events. Altogether, the present findings highlighted that VWF defect promoted by PVL may represent an important mechanism underlying the high bleeding diathesis observed in patients with stroke after TAVR. The present study is the first to our knowledge to show that CT-ADP > 180 seconds, as a surrogate marker of VWF defects, is a strong predictor of not only MLBCs but also ischemic neurological events. Optimal Treatment to

Prevent Ischemic Stroke Up to now, important criticisms on routine DAPT as the gold standard during TAVR rely on the followings: (1) most of cerebrovascular events occur in the early phase and are related to debris embolization, a process unlikely to be efficiently targeted by antiplatelet therapy, and (2) DAPT is associated with increased bleeding events without providing any benefit in the reduction of ischemic events.<sup>25,26</sup>

The recent demonstration that the development of bioprosthetic valve thrombosis is mainly platelet-independent emphasizes a primary role for contact phase and more likely to be efficiently targeted by OACs.<sup>27,28</sup> Initial enthusiasm for a liberal use of OACs was damped by the early discontinuation of the GALILEO study.<sup>29</sup> In this trial, efficacy and tolerance evaluation of rivaroxaban 10 mg/day combined with aspirin 75 mg/day for 3 months compared with conventional DAPT for 3 months showed an increase in all-cause mortality, thromboembolic, and bleeding events in the rivaroxaban group. In the present study, a significantly lower incidence of OAC administration at baseline was observed in the ischemic stroke/TIA group compared with the no ischemic stroke/TIA group, whereas the rate of prior AF was similar between the two groups. The discontinuation of OAC might have been due to the hemorrhagic diathesis of the patients; however, this information was not systematically collected in our study. Further studies are required to confirm whether the discontinuation of OAC can impact the neurological outcomes of AF patients undergoing TAVR. On a pragmatic approach, the present data clearly evidenced the existence of a noxious relationship between ongoing primary hemostasis disorders, early bleeds, transfusion, and ischemic stroke. This new paradigm reinforces the view that early bleeding events should be considered as potent risk factors for thrombotic processes. In line with this paradigm, strategies aimed at reducing the risk of early bleeding constitute an important area of patient's care improvement, including paradoxical reduction in ischemic cerebrovascular events. Study Limitations We acknowledge the following limitations: First, the analyses were performed on the basis of a single-center data set with uncertain generalizability. However, the registry was of prospective design. Second, the patients enrolled in the present study did not undergo mandated neurological assessment, which may have resulted in underreporting part of neurological events. Third, the present study included patients treated with various TAVR devices and changes in devices technology over time may have influenced the occurrence of stroke and incidence of PVL 1 month after TAVR. Since the prevalence of bleeding events and PVL have been dramatically reduced with newer generation valves, further studies with those valves are warranted to confirm our findings. Forth, the measurements of HMW-VWF defect were not directly performed. Fifth, CT-ADP prolongation is not specific of HMW-VWF defect and could be influenced by various other hematologic parameters and antiplatelet therapies. Sixth, the antiplatelet therapies may have been discontinued after the bleeding events in several patients, but the data were not available in the present study. Seventh, given the limited size of the cohort, multivariate analysis should be interpreted with caution. Of note, the present study was not powered to detect certain differences. The effect of the low event rate might have been more pronounced when analyzing small subgroups. As

with similar evaluation of registry data, there are inherent limitations in this type of study, mainly related to unknown confounding factors.

Conclusion MLBCs and CT-ADP are potential predictors of early postTAVR neurological events. The present study suggests that the defects of HMW of the VWF may contribute not only to bleeding events but also to thrombotic events. What is known about this topic? • Stroke is a major cause of disability after TAVR. • High-molecular weight multimers defect of VWF assessed by adenosine diphosphate closure time is an independent predictor of paravalvular leak and associated with early- and late-bleeding events among patients undergoing TAVR. What does this paper add? • The present study suggests that the defects of highmolecular weight multimers of the VWF may contribute not only to bleeding events but also to ischemic cerebrovascular events. Funding This study was supported by Groupe pour l'Enseignement, la prévention et la Recherche Cardiologique en Alsace. Conflict of Interest K.M. has received scholarship from Uehara Memorial Foundation. Other authors have reported that they have no relationship to disclose.

#### References

- 1 Smith CR, Leon MB, Mack MJ, et al; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high risk patients. *N Engl J Med* 2011;364(23):2187–2198
- 2 Thyregod HG, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers notion randomized clinical trial. *J Am Coll Cardiol* 2015;65(20):2184–2194
- 3 Popma JJ, Deeb GM, Yakubov SJ, et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019; 380(18):1706–1715
- 4 Wendler O, Schymik G, Treede H, et al. Source 3 registry: design and 30-day results of the European Postapproval Registry of the latest generation of the Sapien 3 transcatheter heart valve. *Circulation* 2017;135(12):1123–1132
- 5 Manoharan G, Van Mieghem NM, Windecker S, et al. 1-year outcomes with the Evolut R self-expanding transcatheter aortic valve: from the international forward study. *JACC Cardiovasc Interv* 2018;11(22):2326–2334
- 6 Durko AP, Reardon MJ, Kleiman NS, et al. Neurological complications after transcatheter versus surgical aortic valve replacement in intermediate-risk patients. *J Am Coll Cardiol* 2018;72(18): 2109–2119

- 7 Kapadia SR, Huded CP, Kodali SK, et al; PARTNER Trial Investigators. Stroke after surgical versus transfemoral transcatheter aortic valve replacement in the PARTNER trial. *J Am Coll Cardiol* 2018;72(20):2415–2426
- 8 Kapadia S, Agarwal S, Miller DC, et al. Insights into timing, risk factors, and outcomes of stroke and transient ischemic attack after transcatheter aortic valve replacement in the partner trial (placement of aortic transcatheter valves). *Circ Cardiovasc Interv* 2016;9(09):e002981
- 9 Kochar A, Li Z, Harrison JK, et al. Stroke and cardiovascular outcomes in patients with carotid disease undergoing transcatheter aortic valve replacement. *Circ Cardiovasc Interv* 2018; 11(06):e006322
- 10 Bosmans J, Bleiziffer S, Gerckens U, et al; ADVANCE Study Investigators. The incidence and predictors of early- and mid-term clinically relevant neurological events after transcatheter aortic valve replacement in real-world patients. *J Am Coll Cardiol* 2015; 66(03):209–217
- 11 Kapadia SR, Kodali S, Makkar R, et al; SENTINEL Trial Investigators. Protection against cerebral embolism during transcatheter aortic valve replacement. *J Am Coll Cardiol* 2017;69(04):367–377
- 12 Van Mieghem NM, Schipper ME, Ladich E, et al. Histopathology of embolic debris captured during transcatheter aortic valve replacement. *Circulation* 2013;127(22):2194–2201
- 13 Freeman M, Barbanti M, Wood DA, Ye J, Webb JG. Cerebral events and protection during transcatheter aortic valve replacement. *Catheter Cardiovasc Interv* 2014;84(06):885–896
- 14 Fanning JP, Walters DL, Platts DG, Eeles E, Bellapart J, Fraser JF. Characterization of neurological injury in transcatheter aortic valve implantation: how clear is the picture? *Circulation* 2014; 129(04):504–515
- 15 Tchetché D, Farah B, Misuraca L, et al. Cerebrovascular events post-transcatheter aortic valve replacement in a large cohort of patients: a FRANCE-2 registry substudy. *JACC Cardiovasc Interv* 2014;7(10):1138–1145
- 16 Tchetché D, Van der Boon RM, Dumonteil N, et al. Adverse impact of bleeding and transfusion on the outcome post-transcatheter aortic valve implantation: insights from the Pooled-RotterdamMilano-Toulouse In Collaboration Plus (PRAGMATIC Plus) initiative. *Am Heart J* 2012;164(03):402–409
- 17 Kibler M, Marchandot B, Messas N, et al. CT-ADP point-of-care assay predicts 30-day paravalvular aortic regurgitation and bleeding events following transcatheter aortic valve replacement. *Thromb Haemost* 2018;118(05):893–905
- 18 Van Belle E, Rauch A, Vincent F, et al. Von Willebrand factor multimers during transcatheter aortic-valve replacement. *N Engl J Med* 2016;375(04):335–344

- 19 Kibler M, Marchandot B, Messas N, et al. Primary hemostatic disorders and late major bleeding after transcatheter aortic valve replacement. *J Am Coll Cardiol* 2018;72(18):2139–2148
- 20 Morel O, El Ghannudi S, Jesel L, et al. Cardiovascular mortality in chronic kidney disease patients undergoing percutaneous coronary intervention is mainly related to impaired P2Y12 inhibition by clopidogrel. *J Am Coll Cardiol* 2011;57(04):399–408
- 21 Rodés-Cabau J, Dauerman HL, Cohen MG, et al. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. *J Am Coll Cardiol* 2013;62(25):2349–2359
- 22 Kleiman NS, Maini BJ, Reardon MJ, et al; CoreValve Investigators. Neurological events following transcatheter aortic valve replacement and their predictors: a report from the CoreValve trials. *Circ Cardiovasc Interv* 2016;9(09):e003551
- 23 Bahrainwala ZS, Grega MA, Hogue CW, et al. Intraoperative hemoglobin levels and transfusion independently predict stroke after cardiac operations. *Ann Thorac Surg* 2011;91(04): 1113–1118
- 24 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(07):1193–1201
- 25 Matsushita K, Marchandot B, Kibler M, et al. P2Y12 inhibition by clopidogrel increases periprocedural bleeds in patients undergoing transcatheter aortic valve replacement. *J Am Coll Cardiol* 2019;74(21):2707–2708
- 26 Rodés-Cabau J, Masson JB, Welsh RC, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon expandable valve: the arte (aspirin versus aspirin þ clopidogrel following transcatheter aortic valve implantation) randomized clinical trial. *JACC Cardiovasc Interv* 2017;10(13): 1357–1365
- 27 Jimenez C, Ohana M, Marchandot B, et al. Impact of antithrombotic regimen and platelet inhibition extent on leaflet thrombosis detected by cardiac MDCT after transcatheter aortic valve replacement. *J Clin Med* 2019;8(04):E506
- 28 Chakravarty T, Søndergaard L, Friedman J, et al; RESOLVE; SAVORY Investigators. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. *Lancet* 2017;389(10087):2383–2392
- 29 Dangas GD, Tijssen JGP, Wöhrle J, et al; GALILEO Investigators. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med* 2020;382(02):120–129

**Table 1** Clinical characteristics of participating patients

	Ischemic stroke/TIA (n = 21)	No ischemic stroke/TIA (n = 544)	p-Value
Age, y	83.6 ± 6.1	83.2 ± 7.3	0.81
Male	10 (48)	244 (45)	0.81
Body mass index, kg/m <sup>2</sup>	28.0 ± 5.5	27.4 ± 6.1	0.67
Hypertension	16 (76)	438 (81)	0.58
Diabetes mellitus	6 (29)	173 (32)	0.75
Dyslipidemia	10 (48)	300 (55)	0.50
Current smoker	0 (0)	15 (3)	1.00
Chronic kidney disease	5 (24)	102 (19)	0.57
COPD	2 (10)	90 (17)	0.55
Stroke history	6 (29)	76 (14)	0.10
AF history	7 (33)	231 (42)	0.41
Logistic EuroSCORE	17.3 ± 12.9	19.0 ± 14.1	0.58
NYHA functional class			
NYHA2	6 (29)	219 (40)	0.28
NYHA3	12 (57)	272 (50)	0.52
NYHA4	3 (14)	53 (10)	0.45
Medication			
Aspirin	12 (57)	291 (54)	0.75
DAPT	4 (19)	116 (21)	1.00
OAC	4 (19)	219 (40)	0.049
Echocardiography data			
Mean aortic gradient, mm Hg	51.4 ± 14.9	47.4 ± 12.8	0.17
Aortic valve area, cm <sup>2</sup>	0.69 ± 0.20	0.74 ± 0.20	0.23
LVEF, %	53 ± 15	54 ± 13	0.64
LVEDD, mm	49 ± 7	51 ± 8	0.40
LVESD, mm	34 ± 9	35 ± 9	0.80
Laboratory tests			
WBC, 10 <sup>3</sup> /μL	7.6 ± 2.4	7.5 ± 2.2	0.84
Hb, g/dL	12.2 ± 1.8	12.2 ± 1.7	0.94
Platelet count, 10 <sup>3</sup> /μL	231 ± 76	225 ± 73	0.72
CRP, mg/L	4.0 (4.0–7.0)	4.0 (4.0–10.9)	0.13
CT-ADP, s	187 ± 82	192 ± 77	0.77
CT-ADP > 180 s	9 (43)	250 (47)	0.73

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT-ADP, closure time of adenosine diphosphate; DAPT, dual antiplatelet therapy; Hb, hemoglobin; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NYHA, New York Heart Association; OAC, oral anticoagulant; SD, standard deviation; TIA, transient ischemic attack; WBC, white blood cell.

Note: Values are n (%), mean ± SD, or median (interquartile range).

**Table 2** Procedural and postprocedural characteristics

	Ischemic stroke/TIA (n = 21)	No ischemic stroke/TIA (n = 544)	p-Value
Procedural characteristics			
Procedural time, min	89 ± 31	82 ± 27	0.26
Femoral approach	18 (86)	486 (89)	0.49
Prosthesis diameter			0.28
23 mm	9 (43)	157 (29)	
26 mm	3 (14)	190 (35)	
29 mm	7 (33)	168 (31)	
31 mm	1 (5)	20 (4)	
34 mm	1 (5)	9 (2)	
Prosthesis type			0.75
Balloon-expandable	12 (57)	330 (61)	
Self-expandable	9 (43)	214 (39)	
Balloon predilatation	8 (38)	298 (55)	0.13
Balloon postdilatation	4 (19)	53 (10)	0.15
Postprocedural characteristics			
24-h after TAVR			
Major bleeding	4 (19)	64 (12)	0.30
Major/life-threatening bleeding	9 (43)	88 (16)	0.002
Minor bleeding	0 (0)	70 (13)	0.09
Transfusion ≥2 units	9 (43)	100 (18)	0.01
WBC, 10 <sup>3</sup> /μL	10.2 ± 4.4	9.0 ± 3.3	0.08
Hb, g/dL	10.2 ± 1.5	10.8 ± 1.6	0.11
Platelet count, 10 <sup>3</sup> /μL	179 ± 69	179 ± 59	0.99
CT-ADP, s	177 ± 82	149 ± 71	0.08
CT-ADP > 180 s	10 (48)	116 (21)	0.01
PRI-VASP, %	63 ± 18	68 ± 15	0.23
CRP, mg/L	18.0 (4.0–31.0)	12.0 (4.0–29.2)	0.64
1 mo after TAVR			
Significant PVL	5 (24)	69 (13)	0.14

Abbreviations: CRP, C-reactive protein; CT-ADP, closure time of adenosine diphosphate; Hb, hemoglobin; PRI-VASP, platelet reactivity index by VASP; PVL, paravalvular leak; SD, standard deviation; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; VASP, vasodilator-stimulated phosphoprotein; WBC, white blood cell.

Note: Values are n (%), mean ± SD, or median (interquartile range).

**Table 3** Univariate analysis for prediction of ischemic stroke or TIA

	OR (95% CI)	p-Value
Age, y	1.01 (0.95–1.07)	0.81
Male	1.12 (0.47–2.68)	0.80
Body mass index, kg/m <sup>2</sup>	1.02 (0.95–1.09)	0.67
Hypertension	0.77 (0.28–2.16)	0.63
Diabetes mellitus	0.86 (0.33–2.25)	0.76
Dyslipidemia	0.74 (0.31–1.77)	0.50
Current smoker	–	0.99
Chronic kidney disease	1.35 (0.48–3.78)	0.56
COPD	0.53 (0.12–2.32)	0.40
Stroke history	2.46 (0.93–6.55)	0.07
AF history	0.68 (0.27–1.71)	0.41
Logistic EuroSCORE	0.99 (0.96–1.02)	0.54
Medication at admission		
Aspirin	1.15 (0.48–2.76)	0.75
DAPT	0.87 (0.29–2.63)	0.80
OAC	0.35 (0.12–1.04)	0.06
Echocardiography data		
Mean aortic gradient, mm Hg	1.02 (0.99–1.05)	0.17
Aortic valve area, cm <sup>2</sup>	0.25 (0.03–2.38)	0.23
LVEF, %	0.48 (0.02–10.84)	0.64
LVEDD, mm	0.98 (0.92–1.03)	0.40
LVESD, mm	0.99 (0.95–1.04)	0.80
Procedural characteristics		
Femoral approach	0.72 (0.20–2.50)	0.60
Prosthesis type		
Balloon-expandable	0.86 (0.36–2.09)	0.75
Self-expandable	1.16 (0.48–2.79)	0.75
Predilatation	0.51 (0.21–1.25)	0.14
Postdilatation	2.18 (0.71–6.72)	0.17
Procedure time, min	1.01 (0.99–1.02)	0.26
Postprocedural characteristics		
WBC, 10 <sup>3</sup> /μL	1.11 (0.99–1.25)	0.09
Hb, g/dL	0.79 (0.59–1.05)	0.11
Platelet count, 10 <sup>3</sup> /μL	1.00 (0.99–1.01)	0.99
CRP, mg/L	1.00 (0.99–1.01)	0.83
CT-ADP > 180 s	3.35 (1.39–8.09)	0.007
PRI-VASP ≤ 50%	2.16 (0.68–6.92)	0.19
Major/life-threatening bleeding	3.89 (1.59–9.50)	0.003
Transfusion ≥ 2 units	3.33 (1.37–8.17)	0.008

Abbreviations: AF, atrial fibrillation; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT-ADP, closure time of adenosine diphosphate; DAPT, dual antiplatelet therapy; Hb, hemoglobin; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; OAC, oral anticoagulant; OR, odds ratio; PRI-VASP, platelet reactivity index by VASP; TIA, transient ischemic attack; VASP, vasodilator-stimulated phosphoprotein; WBC, white blood cell.

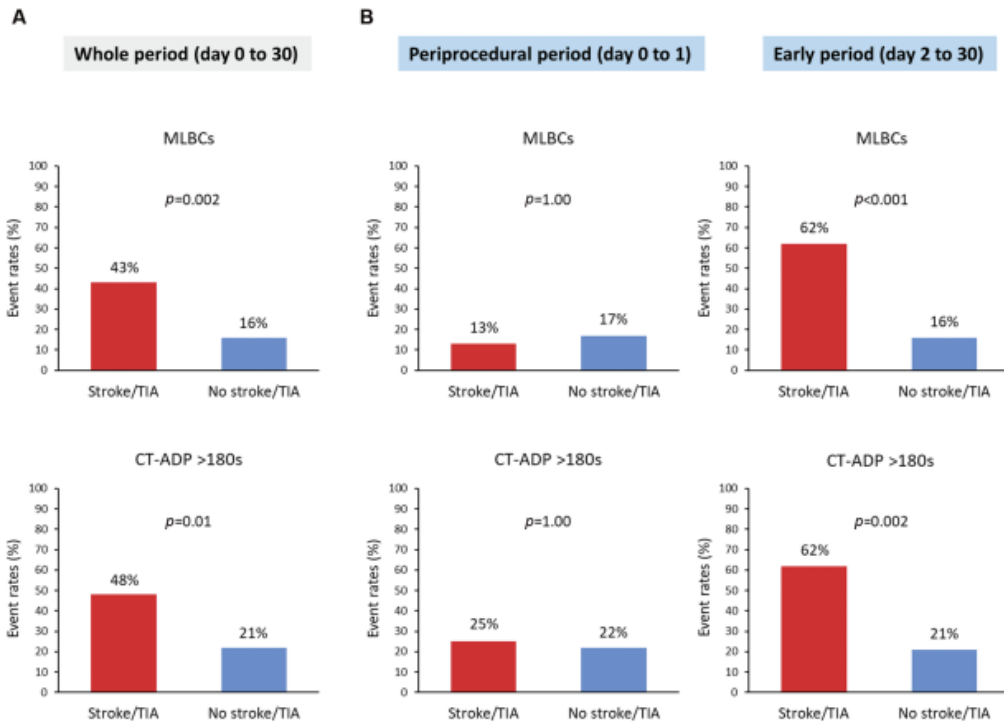


**Table 4** Multivariate analysis for prediction of ischemic stroke or TIA

	OR (95% CI)	p-Value
Model 1		
Stroke history	2.22 (0.82–6.04)	0.12
OAC at baseline <sup>a</sup>	–	–
WBC, 10 <sup>3</sup> /μL	1.12 (0.99–1.26)	0.08
CT-ADP > 180 sc	3.38 (1.38–8.25)	0.008
Model 2		
Stroke history	2.13 (0.78–5.79)	0.14
OAC at baseline	0.38 (0.12–1.15)	0.09
WBC, 10 <sup>3</sup> /μL <sup>a</sup>	–	–
Major/life-threatening bleeding	3.58 (1.45–8.84)	0.006

Abbreviations: CI, confidence interval; CT-ADP, closure time of adenosine diphosphate; OAC, oral anticoagulant; OR, odds ratio; TIA, transient ischemic attack; WBC, white blood cell.

<sup>a</sup>Excluded according to removal criteria.



**Fig. 3** Rate of major/life-threatening bleeding events and postprocedure CT-ADP > 180 seconds in patients with ischemic stroke or TIA following transcatheter aortic valve replacement (TAVR). Rates of MLBCs and postprocedure CT-ADP > 180 seconds were significantly higher in the ischemic stroke/TIA group (43% vs. 16%,  $p = 0.002$  and 48% vs. 21%,  $p = 0.01$ ) (A). The incidence of MLBCs and postprocedure CT-ADP > 180 seconds were comparable between patients with and without perioperative ischemic stroke/TIA (13% vs. 17%,  $p = 1.00$  and 25% vs. 22%,  $p = 1.00$ , respectively) (B). By contrast, patients with ischemic stroke/TIA during 2 to 30 days after TAVR had an increased incidence of perioperative MLBCs (62% vs. 16%,  $p < 0.001$ ) and postprocedural CT-ADP > 180 seconds (62% vs. 21%,  $p = 0.002$ ) (B). CT-ADP, closure time of adenosine diphosphate; MLBC, major/life-threatening bleeding complication; TIA, transient ischemic attack.