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A High-Risk Period for Cerebrovascular Events Exists After Transcatheter Aortic Valve Implantation

CME

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CME Objective for This Article: After reading this article, the reader should be able to: discuss the risk factors for cerebrovascular events after transcatheter aortic valve implantation (TAVI), recognize the time course and types of cerebrovascular events after TAVI, and assess the impact of post-TAVI cerebrovascular events on outcomes.

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A High-Risk Period for Cerebrovascular Events Exists After Transcatheter Aortic Valve Implantation

Objectives This study assesses if there exists a high-risk period for cerebrovascular events (CeV) after transcatheter aortic valve implantation (TAVI).

Background Even though acute strokes after TAVI have been described, it is uncertain if stroke rates continue to remain high in the early months after TAVI. Furthermore, the optimal dose and duration of thromboprophylaxis is unclear.

Methods Patients who underwent TAVI were evaluated at baseline, at discharge, at 1 and 6 months, and yearly. Risk factors for CeV events, procedural details, and antithrombotic therapy were recorded. Outcomes assessed were CeV events and death. The timing of such events, predictors, and impact on survival were analyzed.

Results A total of 253 patients were assessed. Median age was 85 years. The median Society of Thoracic Surgeons score was 8.1% (interquartile range [IQR]: 5.5% to 12.0%). Risk factors included smoking (47%), hypertension (70%), dyslipidemia (66%), and diabetes mellitus (25%). Twenty-three percent had known cerebrovascular disease and 39% had atrial fibrillation. Median follow-up was 455 days (IQR: 160 to 912 days) at which time 23 patients experienced a CeV event. The incidence was highest in the first 24 h but remained high for 2 months. In-hospital mortality rate after a CeV event was 21%. A prior history of CeV disease was an independent predictor of an event (hazard ratio: 4.23, 95% CI: 1.60 to 11.11, $p = 0.004$).

Conclusions The incidence of CeV events is highest within 24 h of TAVI, but this risk may remain elevated for up to 2 months. A prior history of cerebrovascular disease is an independent predictor. This may have implications for patient selection and antithrombotic strategies. (J Am Coll Cardiol Intv 2011;4:1290–7) © 2011 by the American College of Cardiology Foundation

Transcatheter aortic valve implantation (TAVI) has been used increasingly to treat symptomatic patients with severe aortic stenosis, who are deemed to be high-risk patients for conventional surgery. Although mortality rates have been declining with increasing operator experience and device improvements, cerebrovascular event (CeV) complications continue to occur (1,2). The pathophysiology, timing, types, and prognosis of these events after TAVI are unclear. Most studies have focused on the immediate CeVs after TAVI, but there may be a residual period of high risk after an initially successful procedure.

Moreover, addressing CeV after TAVI is important for several reasons. Strokes occurring immediately after surgical bioprosthetic implants have devastating consequences; apart from high mortality rates (3), the supposed benefits of TAVI in improving quality of life in these patients is abolished (4). The cost-effectiveness of TAVI may also be lost. Most importantly, understanding these events may facilitate development of risk reduction strategies.

Methods

Patients. All patients with symptomatic severe valvular aortic stenosis who underwent TAVI between January 2005 and November 2009 were assessed. Patients enrolled in the PARTNER (Placement of Aortic Transcatheter Valves) trial were excluded from this study. Acceptance for TAVI required a consensus among a team of senior cardiac surgeons and interventional cardiologists that the risk of conventional surgery was excessive. Informed consent was obtained. Standard transfemoral or transapical TAVI techniques were used (5,6). Before 2008, antiplatelet therapy was not standardized for TAVI although most transfemoral procedure patients received dual antiplatelet agents adopted from coronary stenting recommendations. After 2008, unless contraindicated, it was recommended to managing physicians that all patients should receive a loading dose of clopidogrel (300 mg) or aspirin (325 mg) before TAVI and then 75 mg (of clopidogrel) and 81 mg (of aspirin) as maintenance therapy for 6 months (PARTNER trial protocol and recommendations from Medtronic CoreValve [Medtronic CV Luxembourg S.a.r.l., Luxembourg] [7]). Most transapical cases did not receive clopidogrel because of concerns of bleeding. Intraprocedural anticoagulation was achieved using intravenous heparin with activated clotting time maintained above 250 s. Baseline characteristics, including known risk factors for strokes were assessed. Prior cerebrovascular disease was defined as a history of a >50% stenosis on carotid

ultrasound, carotid endarterectomy, previous strokes, or transient ischemic attacks (TIA). Intraprocedural events, as well as post-procedure antiplatelet and antithrombotic therapy were recorded. In this study, antithrombotic therapies refer to the use of heparin or vitamin K antagonists (VKA), such as warfarin. In patients who experienced a CeV, the type of antiplatelet or antithrombotic agent received before the event was also documented.

Cerebrovascular events included TIA and clinical strokes (ischemic or hemorrhagic). A TIA was defined as a brief episode of neurological dysfunction (lasting <24 h) resulting from focal cerebral ischemia and not associated with evidence of cerebral infarction on imaging (computed tomography or magnetic resonance imaging). Clinical strokes were defined as acute neurological dysfunction that lasted more than 24 h with evidence of infarction on computed tomography or magnetic resonance imaging. A neurologist or internist made the diagnoses in all patients.

In this study, peripheral vascular disease was defined as the presence of claudication at rest or exertion, previous amputations for peripheral artery disease, angioplasties, bypasses, or detection of disease on noninvasive testing. Hemodynamic instability was defined as hypotension refractory to inotropic support alone requiring cardiopulmonary resuscitation, intra-aortic balloon pump insertion, or extracorporeal membrane oxygenation.

Abbreviations and Acronyms

CeV = cerebrovascular event(s)
CI = confidence interval
HR = hazard ratio
IQR = interquartile range
TAVI = transcatheter aortic valve implantation
TIA = transient ischemic attack(s)
VKA = vitamin K antagonist(s)

Mortality and CeV during the initial hospitalization were prospectively recorded. This was similarly done for those who were readmitted to the TAVI heart center. Post-discharge events were evaluated by clinical review of patients' charts via telephone calls made to patients, their families, or their physicians (internist, neurologist, cardiologists) that occurred at 1 and 6 months and yearly.

Statistical analysis. Categorical variables were expressed as numbers (percentages) and continuous variables as mean ± SD or medians and first or third quartiles when not normally distributed. Shapiro-Wilks goodness-of-fit test was used to test normality. Comparisons were made between patients who developed CeV and those who did not using Student *t* test or Mann-Whitney *U* test and chi-square or Fisher exact test as appropriate. Univariate analyses were performed to identify predictors of CeV. A stepwise backward multivariable analysis was then performed to determine independent predictors. Finally, an adjusted Cox proportional hazards regression model with stroke as a time-dependent covariate on survival was constructed and analyzed. Its effect was quantified using the hazard ratio (HR) estimate and its 95% confidence interval (CI). All statistics were performed using SPSS (version 15.0, SPSS Inc., Chicago, Illinois).

Results

A total of 253 patients underwent TAVI from January 2005 to November 2009. The median age was 85 years and 51% were men (Table 1). Overall surgical risks of these patients were high with a median logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) and Society of Thoracic Surgeons score of 28% (interquartile range [IQR]: 16% to 40%) and 8.1% (IQR: 5.5% to 12.0%), respectively. Significant proportions of patients were smokers (47%) and had risk factors of hypertension (70%), dyslipidemia (66%), and diabetes mellitus (25%). Twenty-three percent of patients had a history of prior cerebrovascular disease and more than one-third had atrial fibrillation.

The median follow-up for this study was 455 days (IQR: 160 to 912 days). During this time, 23 patients experienced CeV. Patients with CeV had a higher incidence of baseline cerebrovascular disease (48% vs. 20%, p = 0.007). There was no significant difference in the prevalence of atherosclerotic risk factors or known embolic risk factors, such as concomitant atrial fibrillation or reduced ejection fraction. Other known risk factors of stroke after surgical aortic valve replacement, such as renal function, hemoglobin, and coexistent peripheral artery disease, were not significantly different between those who had CeV versus those that did not. A higher percentage of patients undergoing the transfemoral procedure versus the transapical procedure had CeV, but this was not statistically significant (10.7% vs. 5.9%, p = 0.24). With regard to antiplatelet therapy, two-thirds of the patients (n = 168) were on clopidogrel before TAVI. One hundred thirty-four patients received a loading dose 6 h before the procedure, whereas 34 were already on a steady dose of 75 mg daily for >1 week. Patients undergoing the transapical procedure did not receive clopidogrel before TAVI and 8 had their maintenance dose of clopidogrel discontinued for 5 days before TAVI. Two hundred thirty-four (93%) patients were on aspirin before TAVI. Overall use of aspirin (89%), clopidogrel (59%), and antithrombotic therapy (heparin or warfarin) (33%) were high at discharge. Among patients who developed CeV, 91% were on aspirin, 61% were on clopidogrel, and 35% were receiving antithrombotic therapy at the time of the event.

Timing and types of events. Most CeV (n = 20, 87%) occurred within 2 months of TAVI, of which, one-half (n = 11) occurred within the first 24 h of the procedure (Fig. 1). These early events were mostly ischemic strokes (n = 9), of which 2 occurred after documented episodes of prolonged hypotension requiring resuscitation during TAVI. Two patients experienced TIA.

Table 1. Clinical Characteristics: Only Advanced Age and a Prior History of Cerebrovascular Disease Were Univariate Predictors of Stroke

	All (N = 253)	CeV (n = 23)	No CeV Event (n = 230)	p Value
Age, yrs	85 (79–89)	87 (83–92)	85 (79–89)	0.05
Weight, kg	71.0 ± 16.3	71.3 ± 15.0	71.4 ± 16.3	0.97
Height, cm	166.2 ± 10.3	165.7 ± 11.1	166.3 ± 10.2	0.81
Male	129 (51)	11 (48)	118 (51)	0.82
Diabetes	64 (25)	8 (35)	56 (24)	0.31
Hypertension	177 (70)	17 (74)	160 (70)	0.81
Dyslipidemia	166 (66)	16 (70)	150 (65)	0.82
Atrial fibrillation	98 (39)	11 (49)	87 (38)	0.38
Smoking	118 (47)	10 (44)	108 (47)	0.83
Coronary artery disease	191 (76)	17 (74)	174 (76)	0.80
Previous stroke	43 (17)	7 (30)	36 (16)	0.08
Previous cerebrovascular disease	58 (23)	11 (48)	47 (20)	0.007
Prior carotid imaging	35 (14)	7 (30)	28 (12)	0.025
Peripheral vascular disease	83 (33)	7 (30)	76 (33)	1.00
Transfemoral	168 (66)	18 (78)	150 (65)	0.24
Delivery systems				0.27
RF 1 and 2	127 (50)	14 (61)	113 (49)	
RF 3/Novaflex	36 (14)	3 (13)	33 (14)	
CoreValve 18-F	5 (2)	1 (4)	4 (2)	
Ascendra	85 (34)	5 (22)	80 (35)	
Activated clotting time, s	267.1 ± 85.2	269.3 ± 52.4	266.8 ± 89.5	0.87
Hemodynamic instability	12 (5)	2 (9)	10 (4)	0.30
Redilation	47 (19)	6 (26)	41 (18)	0.43
Clopidogrel pre-treatment				0.42
Naive with loading dose	134 (53)	13 (56)	121 (53)	
Continued stable dose	34 (14)	5 (22)	29 (13)	
Discontinued	8 (3)	0(0)	8 (3)	
Naive with no loading	77 (30)	5 (22)	72 (31)	
Aspirin pre-treatment				0.79
Loading dose	57 (23)	6 (26)	51 (22)	
Continued stable dose	177 (70)	16 (70)	161 (70)	
No aspirin	19 (7)	1 (4)	18 (7.8)	
Clopidogrel at time of event	148 (59)	14 (61)	134 (58)	0.35
Aspirin at time of event	224 (89)	21 (91)	203 (88)	1.00
Antithrombotic therapy at time of event	84 (33)	8 (35)	76 (33)	0.83
Glomerular filtration rate, ml/kg/min	57.7 ± 24.2	50.5 ± 22.0	58.5 ± 24.3	1.00
Left ventricular ejection fraction, %	54.8 ± 14.1	59.6 ± 11.0	54.4 ± 14.3	0.04
Hemoglobin, g/dl	121.9 ± 16.0	124.9 ± 21.5	121.6 ± 15.4	0.49
Logistic EuroSCORE, %	28 (16–40)	18 (14–32)	28 (16–41)	0.15
Society of Thoracic Surgeons score, %	8.1 (5.5–12.0)	10.6 (5.1–13.8)	7.9 (5.5–11.9)	0.19

Values are median (interquartile range), mean ± SD, or n (%). Novaflex and Ascendra are products of Edwards Lifesciences Inc. (Irvine, California). CoreValve is a product of Medtronic CV Luxembourg S.a.r.l. (Luxembourg).

CeV = cerebrovascular event(s); EuroSCORE = European System for Cardiac Operative Risk Evaluation; RF = Retroflex.

The incidence of CeV remained high between days 2 and 30 after the procedure (n = 6, 2.5%) and became less frequent in the second (n = 2, 0.8%) month. Late CeV were infrequent (n = 4) and occurred at days 126, 180, 200, and 600.

The most common location of cerebral infarction was the middle cerebral artery territory followed by the posterior circulation (4 patients presented with cerebellar dysfunction, and 1 presented with cortical blindness from bilateral occipital infarcts) (Fig. 2). Fifteen percent of patients had infarction in multiple territories. Lacunar infarcts and internal capsule infarcts were less common.

Prognosis and predictors of CeV. Patients who had early, in-hospital CeV had a trend toward higher mortality rates compared with those that did not (21% vs. 8%, p = 0.08). Median follow-up was 455 days (IQR: 160 to 912 days). Treating CeV as a time-dependent covariate, CeV did not

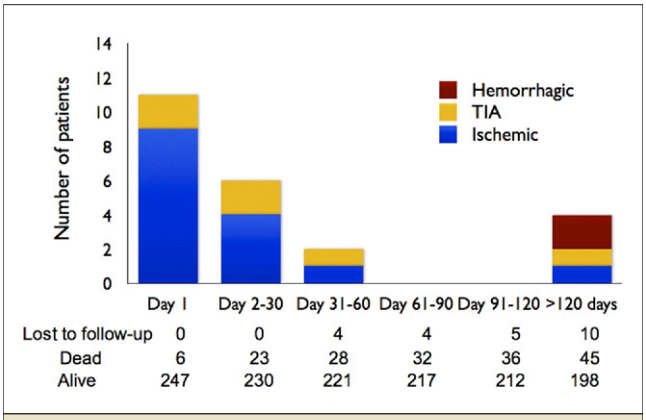

Figure 1. Timing of CeV After TAVI

Most events occur in the first 24 h. The incidence of events then diminishes after day 60. CeV = cerebrovascular event(s); TAVI = transcatheter aortic valve implantation; TIA = transient ischemic attack(s).

clearly predict increased mortality over time with the HR of 1.06 (95% CI: 0.46 to 2.46), p = 0.89. Known predictors of CeV after surgical bioprosthetic aortic valve replacement, including age, diabetes mellitus, hypertension, dyslipidemia, previous cerebrovascular disease, renal function, peripheral vascular disease, atrial fibrillation, left ventricular ejection fraction, access site chosen, redilation of the aortic valve, and the use of antiplatelet and antithrombotic therapy were assessed. On multivariate analyses, only a history of cerebrovascular disease remained an independent predictor of stroke (HR: 4.23, 95% CI: 1.60 to 11.11, p = 0.004). Although the numbers of patients having prior carotid ultrasonography was low, among those with carotid stenosis of >50%, 7 patients (20%) developed CeV on follow-up.

Discussion

This study demonstrates that CeV after TAVI occur most frequently in the first 24 h, but the incidence remains elevated through the first 2 months. Periprocedural CeV are associated with high in-hospital mortality.

Our study results are consistent with the published results of the PARTNER trial. In cohort A, the combined CeV was 5.5% at 30 days and 8.3% at 1 year, whereas in cohort B, it was 6.7% and 10.6%, respectively. This study focuses, however, on the timing of these events (8,9).

Immediate post-procedural events. No prior studies have described the timing and types of CeV after TAVI. Current information on this issue comes predominantly from experience after surgical bioprosthetic valve implants. Thromboembolic risk is high immediately after surgical valve implantation (10). Immediate post-procedural CeV may be due to disruption of atheromatous or calcific debris intraoperatively. Cerebral ischemia can also occur due to periprocedural hypotension. The similarly high incidence seen in this TAVI study in the first 24 h may be attributed to embolism of debris during valve implantation as catheters, wires, and devices traverse the aortic arch, balloon aortic valvuloplasty (11), valve deployment or redilation, or hypotensive episodes. In addition, thrombi can form on devices/wires during the procedure. The location of cerebral infarcts seen in this study is typical of embolic infarcts (12), with a large proportion localized in the middle cerebral artery territory, posterior circulatory system, or involving multiple foci. Preventive strategies for the immediate periprocedural period include meticulous care with hemodynamic support and adequate anticoagulation during the procedure. Newer devices that deflect or filter emboli are also currently being investigated.

Later events. The incidence of CeV continues to be high after the first 24 h and persists up to the first 60 days after TAVI. During this period, the bioprosthesis itself may be a source of thromboemboli before endothelialization of the prosthesis completes (13,14). Aggregation of platelet and fibrin has been known to occur on valve leaflet within a few hours after implantation. It is uncertain how much more thrombogenic a transcatheter valve is compared with a conventional surgical bioprosthesis. First, the impact of crimping the valve within a stent followed by balloon dilation on the surface characteristics of these valves is unknown. Second, a fabric, sealing cuff covering the inflow portion of the transcatheter heart valve intended to prevent paravalvular leak may not be completely opposed to the aortic wall leading to stasis and possible thrombus formation. The native valve leaflets, which may be fissured or denuded are left compressed adjacent to the stent frame, which again has unknown thrombogenic consequences. Finally, endothelialization of stent struts may not be complete (Fig. 3) (15). To reduce thromboembolic risk, most patients in this center were on dual antiplatelet agents after TAVI for up to 3 to 6 months. There is, however, little evidence to support this practice other than fact that this

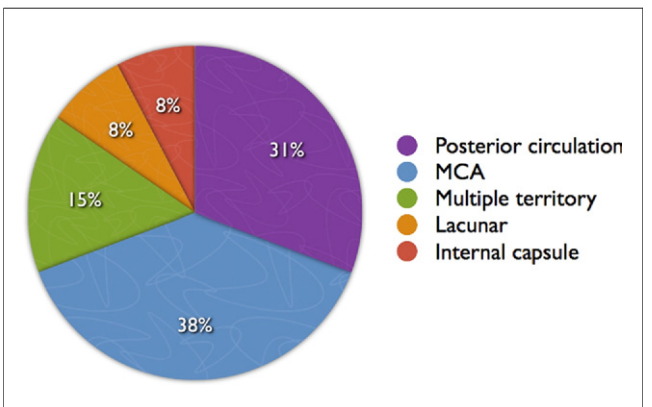

Figure 2. Location of Infarcts

Most infarcts occur in the middle cerebral artery (MCA) territory followed by the posterior circulation.

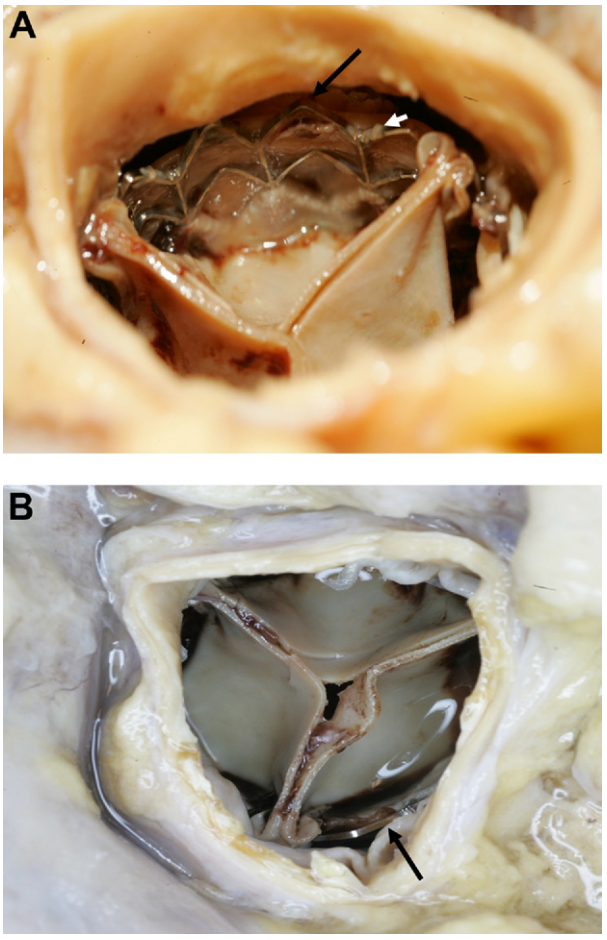

Figure 3. Pathological Images Showing Incomplete Endothelialization

(A) Postmortem of a patient who died on day 25 from pulseless ventricular tachycardia. **(B)** Postmortem of a patient who died on day 28 after implantation from stroke-related complications. Several stent struts are not endothelialized **(black arrow)** in this patient. Areas with tissue ingrowth **(white arrow)** are also shown for comparison.

approximates the time required for endothelialization over stainless steel coronary stents (16). It is also unclear if the use of antithrombotic therapies, such as VKA might reduce CeV. This study was not large enough to detect differences in CeV rates among patients who used antiplatelet agents or antithrombotic therapies.

It may be relevant to consider recommendations for aortic surgical bioprostheses. The American College of Cardiology/American Heart Association guidelines recommend aspirin alone in patients without additional risk factors, but they state that warfarin for 3 months is reasonable (17). However, the European Society of Cardiology guidelines recommend 3 months of VKA (18). These differences have arisen as some studies suggest that VKA is effective, whereas others suggest benefit is limited to high-risk subsets (patients with low left ventricular ejection fraction or atrial fibrillation) (19). Other studies have demonstrated no significant differences between antiplatelet agents and VKA (20–22). The optimal preventive strategy in the early few months thus remains elusive for surgical bioprostheses, and even more so after TAVI. It is worthwhile to note that whereas strokes continue to occur late after 60 days, this probably reflects the background risks of this population and is unlikely to be related to the valve/procedure. When considering VKA use, it is important to note that 2 patients had a hemorrhagic stroke. In addition, the use of triple therapy (VKA, aspirin, and thienopyridines) has been associated with significantly increased bleeding risk (23).

Predictors of stroke. This study identified a prior history of cerebrovascular disease as a predictor of CeV. These patients should be made aware of their risk during the consent process and managed with greater care. Currently, it is unknown if routine screening for cerebrovascular disease (e.g., carotid or ascending aortic imaging) would have an impact on outcomes. However, the high incidence of CeV in those with carotid stenosis of >50% in this study suggests that this potential predictor should be explored in the future. It was interesting to note that atrial fibrillation was not a risk predictor of stroke in this study. In addition, the use of warfarin in patients with atrial fibrillation was not significantly different for those without (36% vs. 32%, $p = 0.50$).

Prognosis. The in-hospital mortality rate among patients who developed CeV after TAVI was high (21%). In this study, CeV and their impact on midterm survival were not statistically significant and are likely due to the small number of events in this cohort. Larger studies in the future may be required to assess this further. This reflects a sicker cohort of patients who have more comorbidities than those in previously published reports on patients treated with conventional bioprosthetic valves.

Study limitations. The incidence of CeV in prior studies varies depending on how these events were diagnosed (24). In this study, neurologists and internists diagnosed these events clinically and, therefore, an underestimation of events may be possible. Similarly, transapical patients in a surgical intensive care unit setting may be less likely to have stroke diagnosed than transarterial patients on a medical ward would. The use of Rankin scores or National Institutes of Health scores would have allowed more objective assessment of such events. This study focused predominantly on overt, clinical CeV, as most of these events occurred before the change in the guidelines. Recent studies comparing magnetic resonance imaging before and after TAVI show a much higher incidence of subclinical stroke (25,26). It is uncertain if patients who experience subclinical strokes have a similar prognosis to those who have overt symptoms. Therefore, it is imperative that future studies are done by standardizing the definitions of CeV (e.g., using the Valve Academic Research Consortium definitions [27]), the type

and modality of neuroimaging, and the timing of evaluation to allow a more precise estimate of risks. In this study, we were also unable to explore the relationship between individual components of the cerebrovascular disease (carotid stenosis, endarterectomy, and previous TIA or strokes) on the risk of further events, as the number of patients who had baseline carotid imaging was few and this was not standardized.

The exclusion of PARTNER patients was necessary, as this trial was ongoing at the time of the study. In addition, this study was also performed to understand the clinical characteristics and outcomes of patients who did not fulfill the inclusion/exclusion criteria to the PARTNER trial. However, the numbers of patients excluded was small (n = 19), and they did not affect the results when they were included in the analysis.

The small number of patients and heterogeneous use of antiplatelet agents and VKA alone or in combination does not allow determination of which strategy is more effective. Among those who received antithrombotic therapies, we were unable to determine if all patients were at therapeutic levels.

With a more standardized antiplatelet/antithrombotic protocol in future, a more meaningful comparison can be made with regards their effect on preventing CeV.

Although we have noted a relationship of CeV with a prior history of cerebrovascular disease, the small number of patients in this study leads to it being underpowered and a beta error cannot be ruled out with certainty. Also, the ability of multivariable methods to identify independent predictors with only 23 CvE is very limited. However, the clinical relationship remains highly plausible.

Conclusions

The incidence of CeV appears highest in the first 24 h after TAVI, but, importantly, it also remains elevated for 2 months. Patients with a prior history of cerebrovascular disease are at higher risk. This may have implications for patient selection and antithrombotic strategies.

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Key Words: antiplatelet therapy ■ antithrombotic therapy ■ percutaneous aortic valve replacement ■ stroke ■ transient ischemic attack(s).

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