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)

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Background—Prior studies of stroke and transient ischemic attack (TIA) after transcatheter aortic valve replacement (TAVR) are limited by reporting and follow-up variability. This is a comprehensive analysis of time-related incidence, risk factors, and outcomes of these events.

Methods and Results—From April 2007 to February 2012, 2621 patients, aged 84±7.2 years, underwent transfemoral (TF; 1521) or transapical (TA; 1100) TAVR in the PARTNER trial (Placement of Aortic Transcatheter Valves; as-treated), including the continued access registry. Stroke and TIA were identified by protocol and adjudicated by a Clinical Events Committee. Within 30 days of TAVR, 87 (3.3%) patients experienced a stroke (TF 58 [3.8%]; TA 29 [2.7%]; P=0.09), 85% within 1 week. Instantaneous stroke risk peaked on day 2, then fell to a low prolonged risk of 0.8% by 1 to 2 weeks. Within 30 days, 13 (0.50%) patients experienced a TIA (TF 10 [0.67%]; TA 3 [0.27%]; P>0.17). Stroke and TIA were associated with lower 1-year survival than expected (TF 47% after stroke versus 82%, and 64% after TIA versus 83%; TA 53% after stroke versus 80%, and 64% after TIA versus 83%). Risk factors for early stroke after TA-TAVR included more postdilatations, pure aortic stenosis without regurgitation, and possibly more pacing runs, earlier date of procedure, and no dual antiplatelet therapy; high pre-TAVR aortic peak gradient was a risk factor for stroke early after TF-TAVR.

Conclusions—Risk of stroke or TIA is highest early after TAVR and is associated with increased 1-year mortality. Modifications of TAVR, emboli-prevention devices, and better intraprocedural pharmacological protection may mitigate this risk.


Key Words: stroke ■ transapical ■ transcatheter aortic valve replacement ■ transfemoral ■ transient ischemic attack

Transcatheter aortic valve replacement (TAVR) has revolutionized management of elderly patients with severe aortic stenosis, but post-TAVR neurological events remain a concern for patients and physicians. Although occurrence of post-TAVR stroke has fallen from ≈5% in initial trials to 3% in recent reports, reducing this risk is essential for advancing this technology into lower-risk patient cohorts.

Understanding the mechanisms of neurological events is critical for developing strategies for reducing their occurrence. Despite several attempts to identify procedure and patient characteristics that may lead to neurological events, the field remains somewhat controversial. One controversy is the timing of neurological events and its relationship to procedural embolization. Different reports have suggested that up to half of the events may be unrelated to procedural embolization, although small numbers of patients and events,
WHAT IS KNOWN

- Stroke after transcatheter aortic valve replacement (TAVR) is an important clinical problem; however, the reported stroke rate in current era is lower than that in the past, especially in lower-risk patients, and with use of newer devices.
- Stroke rate after TAVR is not higher compared with surgical aortic valve replacement; in fact, recent studies suggest that it may be lower than surgical aortic valve replacement.
- Stroke after TAVR results in significantly higher morbidity and mortality.

WHAT THE STUDY ADDS

- Risk of stroke or transient ischemic attack is highest early after TAVR. Importantly, risk of strokes after the initial periprocedural period is not high. This finding provides rationale for the use of emboli prevention strategies at time of procedure.
- Transient ischemic attack after TAVR also increases risk of mortality, highlighting adverse implications of any periprocedural emboli to the brain.
- More balloon post dilatation and lack of dual anti-platelet therapy before procedure were associated with higher risk of early stroke. Strategies to minimize these may help to reduce the risk of stroke.

variability in their diagnosis, and use of different analytical methods make it difficult to reach firm conclusions.6–8

The PARTNER trial (Placement of Aortic Transcatheter Valves) provides a well-characterized patient population undergoing TAVR using a balloon-expandable device, for which the incidence, timing, risk factors, and outcomes of neurological events occurring ≤5 years have been described.9–12

Our previous publication examining incidence, risk factors, and outcomes of neurological events in the high-risk randomized cohort of the PARTNER trial was based on early follow-up and few events, which necessitated combining stroke and transient ischemic attack (TIA) as a composite.7 In the present study, all TAVR patients from all PARTNER cohorts have been included, follow-up has been extended, and the number of events has permitted in-depth insight into timing, risk factors, and outcomes of neurological events after TAVR, with stroke and TIA analyzed separately.

Methods

Patients

From April 2007 to February 2012, 2621 high-risk or inoperable patients with severe aortic stenosis were enrolled in PARTNER. Based on a patient’s arterial anatomy, delivery was allocated in a transfemoral (TF) first strategy, with transapical (TA) access reserved for those with iliofemoral impediments to valve delivery and insertion. A total of 1521 patients underwent TF-TAVR and 1100 TA-TAVR using 22- or 24-French sheaths to insert 23 mm or 26 mm SAPIEN prosthetic aortic valves (Edwards Lifesciences, Irvine, CA). This as-treated study included all PARTNER trial cohorts: 62 roll-in patients (19 TA and 43 TF), 344 randomized cohort A (high risk) patients (104 TA and 240 TF), 175 randomized cohort B (inoperable) TF patients, 40 randomized continuing access TF patients, and 2000 nonrandomized continuing access patients (977 TA and 1023 TF). PARTNER trial selection criteria and design, along with technical details of the TAVR procedure, have been previously reported.11,12

Patients who underwent TA-TAVR had more comorbidities than those who underwent TF-TAVR, including cerebrovascular disease (prior stroke, TIA, dementia, carotid disease) in 43% versus 32% and a carotid procedure in 16% versus 7.6%, but had similar prevalence of pre-TAVR stroke and dementia (Table 1). Peripheral arterial disease was more common in TA-TAVR patients (98%) than in TF-TAVR patients (49%) and more had prior coronary interventions. Procedure time, fluoroscopy time, and volume of contrast media were greater in TF-TAVR than in TA-TAVR patients (Table 2).

End Points

The primary end points of the study were stroke or TIA occurring during or after TAVR. Stroke was defined as a focal neurological deficit lasting 24 hours or longer or a focal neurological deficit lasting <24 hours with imaging findings of acute cerebral infarction or hemorrhage. Stroke was further classified as ischemic, hemorrhagic (epidural, subdural, and subarachnoid), or ischemic with hemorrhagic conversion. TIA was defined as a focal neurological deficit fully reversible within 24 hours in the absence of any new imaging findings of infarction or other primary medical cause (eg, hypoglycemia or hypoxia). In-hospital neurological events were identified by clinicians caring for patients after TAVR. At each follow-up visit, patients were assessed according to the National Institutes of Health stroke scale, and any increase from baseline was reported as a potential adverse event. The independent Clinical Events Committee, which included a neurologist, reviewed imaging studies, neurology consults, and discharge reports, laboratory reports, and all notes for type and duration of symptoms.

Secondary end points were the competing risk of death before these neurological events, death after them, and their mortality cost.

Because TA-TAVR was not performed initially during the PARTNER trial, follow-up is described separately for each group. For TF-TAVR, median follow-up was 1 year (mean±SD 1.6±1.1 years). A total of 2389 patient-years of data were available for analyses; 25% of survivors were followed >2 years and 10% >3 years. For TA-TAVR, median follow-up was 1 year (mean±SD 1.2±0.84 years). A total of 1282 patient years of data were available for analyses; 25% of survivors were followed >2 years and 10% >2.5 years.

Data Analysis

Data analysis was based on the as treated TAVR population. Data used were from a December 2012 locked data set provided to the PARTNER Publications Office by Edwards Lifesciences. Data analysis was performed by PARTNER Publications Office investigators, with no sponsor involvement in substudy proposal, design, analysis, interpretation, or decision to publish. The Institutional Review Board at each participating site approved the trial, and all patients provided written informed consent. Data were analyzed using SAS statistical software (SAS v9.2; SAS Inc, Cary) and R software version 2.15.3.

Time-Related Events

Time-related events were estimated nonparametrically by the Kaplan–Meier method and parametrically by a multiphase nonproportional hazards model,13 by which a smooth representation of instantaneous risk (hazard function) was estimated across time. Estimates were made for stroke and TIA, both overall and for TF- and TA-TAVR groups. Although a neurological event can occur more than once, this happened only 6 times, so all analyses were performed using the first event rather than repeating events.

We placed stroke and TIA into the context of the ongoing competing risk of death before these neurological events.14 Finally, we assessed mortality following a neurological event.
Risk Factors for Neurological Events

Incremental risk factors for stroke were identified simultaneously within each hazard phase, with a 2-sided \( P \) value criterion for retention of variables in the model of 0.05, using the 56 variables shown in Appendix E1 in the Data Supplement. Initial variable selection used bagging (bootstrap aggregation),\(^{15,16}\) a method suited to screening a
large number of variables compared with number of events that avoids both the prematurity of a priori variable selection in this TAVR trial and the possibility of Type II error by analyzing only univariable statistically significant variables. This unsupervised machine-learning method reduces the majority of variables to the level of noise and reveals variables contributing to signal by averaging over the results of a multitude of individual analyses of bootstrap samples. Thus, for this analysis and others mentioned subsequently, patients were randomly selected from the original data set to form 1000 bootstrap data sets of equal size. Risk factors were identified for each of these data sets using automated forward stepwise selection. Occurrence of variables selected in these models was tabulated (the aggregation step), and those appearing in at least 50% of models were retained in the final analysis (Appendix E1 in the Data Supplement). This median rule tends to balance Type I and Type II error. Results were verified using Random Forests for Survival, a nonparametric machine-learning method that permitted graphical display of relationships of continuous variables to survival (partial dependency plots), adjusted for 56 variables without model assumptions.\textsuperscript{17,18} We then performed several focused investigations of additional variables identified as risk factors in other studies.

### Competing Risks of Death and Neurological Events
Actuarial and parametric estimates of stroke or TIA describe the isolated probability of experiencing these events. However, as time passes, patients die, and the method of competing risks was used to estimate the likelihood that patients would still be alive and free of a neurological event.

For this, a common interval was defined as the earliest of either death or neurological event. Patients were then transitioned from being alive without a neurological event into 2 mutually exclusive states: neurological event or death before such an event. Freedom from each event was estimated by the nonparametric product-limit method, with variances based on the Greenwood formula. Because of the difference in neurological event risk according to TF or TA stratum, the TAVR group was analyzed according to as-stratified access, recognizing that access is indicative of more generalized atherosclerotic burden.

### Survival after a Neurological Event
Survival after stroke or TIA was estimated nonparametrically and parametrically, with time zero as time of the first event. Mere depiction of survival after a neurological event does not address mortality cost. For this, we need to estimate survival had the event not occurred. Thus, we first estimated survival before a neurological event for all patients from the time of the procedure. Next, we used the parametric equation for survival before a neurological event to generate a survival curve for each patient who experienced a neurological event after the time the event occurred. This is known as conditional survival, which starts at 100% at the time of a neurological event. We then computed the average of all curves, which is the expected survival beyond the time of the neurological event had it never occurred. We then compared the actual survival curve from the time of neurological event to the expected survival curve had the event not occurred.

### Missing Values
During unsupervised bagging for variable selection, we used simple means imputation for missing values. However, to develop final models, we used multiple imputation based on all 56 covariates (not the outcome). Of the 12 variables in the final models, 2 had no missing data, 5 had 4% missing data, 4 had 1% to 3% missing data, and 1 had 6.4% missing data. The pattern of missing data appeared arbitrarily, so we assumed missing at random. Therefore, we performed 5-fold multiple imputation using a Markov chain Monte Carlo technique (SAS PROC MI)\textsuperscript{19} to yield final regression coefficient estimates, the variance–covariance matrix, and P values (SAS PROC MIANALYZE).

### Presentation
Continuous variables are summarized as mean±standard deviation or as equivalent 25th, 50th (median) and 75th percentiles when distribution of values is skewed. Categorical variables are summarized by frequencies and percentages. Both nonparametric (actuarial) and parametric estimates of time-to-event occurrence are presented with asymmetrical 95% confidence intervals.

### Results

#### Time-Related Stroke
A total of 134 first strokes (87 in TF and 47 in TA) occurred during the follow-up period, mostly during or early after TAVR (Table I in the Data Supplement). Of strokes occurring within 30 days, 56 (64%) were diagnosed within 2 days after TAVR (TF 41 [71%]; TA 15 [52%]), and 74 (85%) were diagnosed within 7 days (TF 51 [88%]; TA 23 [79%]). Time-varying instantaneous risk of stroke peaked within 48 hours after TAVR, with a higher risk after TF than TA (Figure 1A; Figure I in the Data Supplement), then merged with a low constant risk of ≈0.8% per year. Probability of stroke at 30 days, 1 year, and 3 years was 3.8%, 5.4%, and 6.9%
Figure 1. Stroke after transcatheter aortic valve replacement (TAVR), stratified by transapical (TA; red curve, squares) versus transfemoral (TF; blue curve, circles) access. A, Stroke after TAVR. Each symbol represents a stroke; vertical bars are 95% confidence limits for nonparametric estimates. Solid lines are parametric estimates enclosed within dashed 95% confidence bands. Numbers below horizontal axis represent patients remaining at risk. Inset depicts instantaneous risk of stroke on an expanded horizontal axis. B, Competing risks after TAVR. These cumulative incidence functions for TF- and TA-TAVR combine cumulative incidence curves for stroke shown in Figures IIA and IIB in the Data Supplement. Solid lines are parametric estimates enclosed within dashed 95% confidence bands. Symbols are nonparametric estimates with 95% confidence bars. At each time point, alive without neurological event (some would call this event-free survival), death before neurologic event, and neurological event add to 100%.
for TF and 2.7%, 4.1%, and 7% for TA, respectively. After adjusting for the competing risk of death before stroke, likelihood of stroke was 3.7%, 5.1%, and 6.1% for TF and 2.6%, 3.9%, and 5.2% for TA, respectively (Figure 1B; Figure IIA and IIB in the Data Supplement). Early and late stroke risks were higher for patients with a CHA2DS2VASc score >3 compared with those with a score of ≤3 (Table II in the Data Supplement; Figure 2), although only 4.5% of patients had a CHA2DS2VASc score of ≤3.

Risk Factors for Stroke After TF-TA VR
Higher pre-TA VR aortic valve peak gradient was associated with early strokes (primarily those occurring within ≈7 days of TA VR; Table 3; Figure III in the Data Supplement). Incremental risk factors for stroke in the constant hazard phase were dementia (Figure IV in the Data Supplement) and 23-mm versus 26-mm valve size (Figure V in the Data Supplement). In focused analysis of additional variables of clinical interest, slightly more strokes occurred in patients undergoing TF-TA VR earlier in the experience and again in the latter part of the experience (Figure VI in the Data Supplement), but this observation was not reliably statistically significant (P=0.006; 48% reliable). Longer procedure time was also associated with an increased number of late strokes (Figure VII in the Data Supplement), although this observation was also not reliably statistically significant (P=0.02; 41% reliable).

Risk Factors for Stroke After TA-TA VR
Incremental risk factors for early stroke were pure aortic stenosis without regurgitation (Figure VIII in the Data Supplement) and more postdilatations (Figure IX in the Data Supplement). Other variables of clinical interest that were not reliably statistically significant included earlier date of TA-TA VR, particularly through early 2010 (Figure X in the Data Supplement; P=0.02, 32% reliable), and more rapid cardiac pacing during balloon aortic valvuloplasty (Figure XI in the Data Supplement; P=0.03, 43% reliable). Antiplatelet therapy was also possibly associated with a lower risk of early stroke (Figure XII in the Data Supplement; P=0.05, 47% reliable).

Incremental risk factors for stroke in the constant hazard phase were race other than white (Figure XIII in the Data Supplement), lower left ventricular ejection fraction (Figure XIV in the Data Supplement), and history of atrial fibrillation (Figure XV in the Data Supplement).

Table 3. Incremental Risk Factors for Stroke After Transcatheter Aortic Valve Replacement

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coefficient±SE</th>
<th>P Value</th>
<th>Reliability, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TF-TA VR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher pre-TA VR aortic valve peak gradient†</td>
<td>0.33±0.16</td>
<td>0.04</td>
<td>62</td>
</tr>
<tr>
<td>Late hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>1.2±0.48</td>
<td>0.01</td>
<td>82</td>
</tr>
<tr>
<td>Smaller prosthetic valve size: 23 mm (vs 26 mm)</td>
<td>0.62±0.34</td>
<td>0.07</td>
<td>53</td>
</tr>
<tr>
<td><strong>TA-TA VR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure aortic stenosis without regurgitation</td>
<td>0.77±0.39</td>
<td>0.05</td>
<td>55</td>
</tr>
<tr>
<td>More postdilatations‡</td>
<td>0.18±0.082</td>
<td>0.03</td>
<td>51</td>
</tr>
<tr>
<td>Late hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race other than white</td>
<td>1.7±0.57</td>
<td>0.003</td>
<td>73</td>
</tr>
<tr>
<td>Lower left ventricular ejection fraction§</td>
<td>0.82±0.40</td>
<td>0.04</td>
<td>57</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.5±0.48</td>
<td>0.002</td>
<td>75</td>
</tr>
</tbody>
</table>

SE indicates standard error; TA, transapical; TAVR, transcatheter aortic valve replacement; and TF, transfemoral.

*Percent of times variable appeared in 1000 bootstrap models.
†[Aortic valve peak gradients/70]², squared transformation.
‡[Number of postdilatations+1]², squared transformation.
§[55/left ventricular ejection fraction], inverse transformation.
Survival After Stroke
Patients who experienced a stroke had lower 1-year survival than patients who did not (TF, 47% after stroke versus 82%; TA, 53% after stroke versus 80%; Figure 3A and 3B).

Time-Related TIA

Risk of TIA
A total of 35 TIAs (21 in TF and 14 in TA) occurred during the follow-up period. Of 13 TIAs occurring within 30 days after TAVR, 10 occurred after TF-TAVR (0.67%) and 3 after TA-TAVR (0.27%; P>0.17). Time-varying instantaneous risk of TIA was higher after TF-TAVR than after TA-TAVR, followed by a lower constant late risk after TF-TAVR and slightly increasing late risk after TA-TAVR (Figures XVI and XVII in the Data Supplement). Estimated probability of TIA at 30 days, 1 year, and 3 years was 0.67%, 1.3%, and 1.9% for TF and 0.27%, 1.3%, and 2.9% for TA, respectively.

Survival After TIA
Patients who experienced a TIA had lower 1-year estimated survival than patients who did not (TF, 64% after TIA versus 83%; TA, 64% after TIA versus 83%; Figure 4A and 4B).

Discussion

Principal Findings
This study demonstrates that risk of stroke and TIA was highest in the first week after TAVR, highlighting the importance of procedural modifications to curtail this risk. Without adjusting for baseline characteristics, risk was less after TA- than after TF-TAVR. Risk factors also differed between these groups, with possibly more effect of a learning curve in TA and of procedure time in TF. TIA posed a significant mortality risk, albeit smaller than stroke.

Findings in Context
Our previous publication of neurological events in the randomized high-risk cohort A of PARTNER focused on a comparison of TAVR with surgical aortic valve replacement. Only 31 events (23 strokes and 8 TIAs) occurred among TAVR patients, limiting multivariable analysis. In the present study, not only were there sufficient events to study stroke and TIA separately, but we were able to separately identify risk factors according to access—TA or TF. Increased severity of aortic stenosis and history of cerebrovascular disease were early risk
Factors identified previously in cohort A (all cases) and in this study only after TF-TAVR.

The timing of stroke after TAVR is an important factor when considering periprocedural modifications that may mitigate risk. Strokes within the first 7 days may be considered procedural because recognition of stroke may not be immediate and symptom onset may be delayed until the thrombus forms on the embolized particles. Early risk of stroke occurred after both TF- and TA-TAVR, suggesting that emboli-prevention devices and appropriate pharmacotherapy may substantially reduce this risk. An emboli-protection device have been evaluated in single center randomized clinical trial (CLEAN-TAVI [Claret Embolic Protection and TAVI Trial]) and 2 multicenter randomized trials are ongoing (SENTINEL [Cerebral Protection in Transcatheter Aortic Valve Replacement; clinicaltrials.gov/ct2/show/NCT02214277] and REFLECT [Cerebral Protection to Reduce Cerebral Embolic Lesions After Transcatheter Aortic Valve Implantation; clinicaltrials.gov/ct2/show/NCT02536196]).20,21 In addition, nonendothelialized valve stent struts or stagnant eddy flow in the niches behind the native calcified cusps may present a thrombogenic surface, thus, increasing the risk of delayed stroke.22

Access-related differences in stroke risk are still debated. In PARTNER, unadjusted stroke risk was higher after TA- than after TF-TAVR; however, after adjusting for baseline characteristics, risk was similar.23 Other studies and meta-analyses have shown no difference in stroke risk based on access site.24 Risk of stroke after TAVR has decreased over time, though less pronounced in the TF group,3,25 where evolution of the delivery system and refined patient selection may have contributed to a decrease. Late hazard for stroke appeared to be slightly higher after TA-TAVR, potentially pointing to the higher vascular risk in this population and highlighting the need for better long-term pharmacotherapy.

Risk factors for stroke differ between TA- and TF-TAVR groups. In the TA-TAVR group, possibly more pacing runs and reliably more postdilatations were associated with higher risk of stroke, suggesting that procedural modification may be important in reducing these events. Recently, operators have minimized pacing runs by avoiding balloon dilatation before valve implantation and reduced postdilatation through proper valve sizing. Higher stroke risk in patients with pure aortic stenosis without regurgitation could be because of more severe aortic stenosis, as seen in the TF-TAVR group.

Figure 4. Survival after transient ischemic attack (TIA) compared with expected survival had a TIA not occurred (green curve). Format is as in Figure 3. A, TA-TAVR; B, TF-TAVR. TA indicates transapical; TAVR, transcatheter aortic valve replacement; and TF, transfemoral.
and documented in the previous study." Although we did not have quantification of valve calcification, we interpret the risk factor, higher pre-TAVR aortic valve peak gradient, as a surrogate for more severe aortic stenosis.

Clinical Implications
Most TAVR patients are not on antiplatelet therapy because of increased risk of bleeding. In the current literature, there is controversy regarding the safest and most effective antithrombotic or antiplatelet regimen in the periprocedural period. Several studies have indicated that dual antiplatelet therapy may simply increase risk of major bleeding without affecting the occurrence of cerebrovascular events.2,6-28 Further studies are needed to determine whether periprocedural dual antiplatelet therapy can reduce the risk of stroke without increasing risk of bleeding.

Postprocedural warfarin could also be beneficial for these patients. According to the latest American College of Cardiology/American Heart Association valvular heart disease guidelines,29 anticoagulation with warfarin is considered reasonable within the first 3 months after bioprosthetic AVR (Class IIb recommendation). This recommendation is based on the results of the Danish National Patient Registry, which demonstrated (albeit controversially) that discontinuation of warfarin within the first 6 months after AVR was associated with increased risk of cardiovascular death.30 Whether warfarin will reduce cerebrovascular events after TAVR awaits further clinical studies.

Improvements in the TAVR procedure may decrease risk of post-TAVR stroke. We observed that longer procedure time and more pacing runs and postdilatations were associated with a higher risk of stroke after TAVR (with variable reliability). Advances in valve and delivery-system design, along with increasing experience, may reduce procedure times and, thereby, reduce occurrence of stroke.

Long-term stroke risk is associated with thromboembolism from atrial fibrillation, thrombus formation around the native calcified cusps, or aortic arch manipulation. A higher CHA2DS2-VASc score may be associated with long-term stroke, though it was not an independent risk factor and may have less discriminating power in elderly patients with multiple comorbidities.29

TIA was associated with a smaller but significant risk of mortality. This is the first time that such an association has been described in a prospective TAVR trial.

Limitations
Periprocedural neurological assessment was not routinely performed; therefore, occurrence of neurological events may have been underestimated.30 Clinical Events Committee adjudication of events could be limited because of lack of information; however, this data set contains a large number of well-characterized patients from multiple institutions. With the advent of transaortic TAVR and smaller TAVR delivery systems, TA-TAVR has become less common.

Conclusions
Risk of stroke or TIA was highest early after TAVR, though this risk decreased over the study period. These events are associated with increased risk of 1-year mortality, highlighting the need for antiplatelet therapy and emboli-prevention devices, along with procedural modifications, that may mitigate this risk.

Sources of Funding
This study was funded by Edwards Lifesciences. Data analysis was performed by PARTNER Publications Office investigators, with no sponsor involvement in study proposal or design, analyses, interpretation, or the decision to publish.

Disclosures
Dr Miller consults with Abbott Vascular Structural Heart, GenTAC, Medtronic Cardiovascular Division, and Edwards Lifesciences PARTNER trial and is an investigator for the PARTNER trial. Dr Webb consults with Edwards Lifesciences and is an executive committee member and investigator for the PARTNER trial. Dr Mack is a PARTNER trial executive committee member for Edwards Lifesciences. Dr Ellis consults with Boston Scientific, Abbott Vascular, and Medtronic. Dr Herrmann receives research funding from and is a consultant for Edwards Lifesciences. Dr Pichard is a proctor for Edwards Lifesciences. Dr Svensson is on executive committees for Edwards Lifesciences’ PARTNER and COMMENCE trials. Dr Smith is a PARTNER trial investigator for Edwards Lifesciences. Dr Kodali is a consultant for Edwards and a member of the Scientific Advisory Board for Thubrikar Aortic Valve. Dr Makkar has research support from Edwards Lifesciences and St Jude Medical, consults with Abbott Vascular, Cordis, and Medtronic, and has equity in Entourage Medical. Dr Thourani consults with Edwards Lifesciences. Dr Blackstone is on executive committees for Edwards Lifesciences’ PARTNER and COMMENCE trials and leads the Cleveland Clinic PARTNER Publications Office, which carries out and publishes independent analyses of PARTNER data. The other authors report no conflicts.

References


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_Circ Cardiovasc Interv._ 2016;9:
doi: 10.1161/CIRCINTERVENTIONS.115.002981

_Circulation: Cardiovascular Interventions_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/9/9/e002981

Data Supplement (unedited) at:
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Appendix E1. Variables Considered in Multivariable Analyses

Pre-Procedural Patient and Valve Characteristics

Cohort
Cohort A (operable), Cohort B (inoperable)

Demographics
Age (years), sex, race (white, black, other), height (cm), weight (kg), body mass index (kg/m²), body surface area (m²)

Functional Health Status
Syncope not related to atroventricular block, exertional syncope, New York Heart Association functional class, CHA₂DS₂-VASc score

Aortic Valve Pathophysiology (Including Echocardiographic Studies)
Aortic valve (AV) calcification with bulky cusp nodules, AV area (EOA, cm²), AV area index (EOA, cm²/m²), AV mean gradient (mmHg), AV peak gradient (mmHg), AV regurgitation severity

Aortic Vasculopathy
Porcelain aorta, porcelain aorta with additional intravascular pathology, calcified aorta

Peripheral Arterial Disease
Peripheral arterial disease

**Cerebrovascular Disease**
Cerebral vascular disease including carotid disease, carotid disease, previous carotid endarterectomy or carotid stent, previous stroke, dementia

**Coronary Artery Disease**
Coronary artery disease

**Ventricular Function**
Myocardial infarction

**Other Cardiac Comorbidity**
Mitral valve (MV) disease, baseline MV regurgitation severity, atrial fibrillation

**Left Ventricular Outflow Tract, Including Proximal Aorta**
Left ventricular outflow tract dimension (cm)

**Pre-Procedure Echocardiogram: Left Ventricular Morphology and Function**
Visual ejection fraction (%)

**Noncardiac Comorbidity**
Diabetes mellitus, oxygen-dependent pulmonary disease, creatinine (mg/dL)
Medication
Antiarrhythmic, anticoagulant, antiplatelet, statin

Procedural Characteristics

Access
Transapical, transfemoral, date of procedure

Valve Size
23 or 26 mm, valve mismatch (none, moderate, severe)

Concomitant Procedures
Other

Support
Total procedure time (skin-to-skin) (min), device closure, volume of contrast media (mL), total fluoroscopy time (min), anesthesia duration (min), number of post-dilatations, number of rapid cardiac pacing attempts during balloon aortic valvotomy, number of rapid cardiac pacing attempts during valve deployment
Table E1. Time-Related Stroke and TIA: First Strokes and TIAs after Transcatheter Aortic Valve Replacement

<table>
<thead>
<tr>
<th>Days after TAVR</th>
<th>TA-TAVR (n=1100)</th>
<th>TF-TAVR (n=1521)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Stroke</td>
<td></td>
</tr>
<tr>
<td>0 – 2</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>3 – 7</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>8 – 30</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>First TIA</td>
<td></td>
</tr>
<tr>
<td>0 – 2</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>3 – 7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>8 – 30</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

Key: TA, transapical; TAVR, transcatheter aortic valve replacement; TF, transfemoral; TIA, transient ischemic attack
Table E2. Non-Parametric Estimates of Probability of Stroke after TAVR, Stratified by CHA2DS2-VASc Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Prevalence</th>
<th>7-Day Probability of Stroke</th>
<th>1-Year Actuarial Probability of Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>TF-TAVR</td>
<td>TA-TAVR</td>
</tr>
<tr>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>1</td>
<td>5 (0.19)</td>
<td>5 (0.33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2</td>
<td>15 (0.57)</td>
<td>15 (0.99)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3</td>
<td>73 (2.8)</td>
<td>68 (4.5)</td>
<td>5 (0.45)</td>
</tr>
<tr>
<td>4</td>
<td>314 (12)</td>
<td>280 (18)</td>
<td>34 (3.1)</td>
</tr>
<tr>
<td>5</td>
<td>830 (32)</td>
<td>517 (34)</td>
<td>313 (28)</td>
</tr>
<tr>
<td>6</td>
<td>838 (32)</td>
<td>387 (25)</td>
<td>451 (41)</td>
</tr>
<tr>
<td>7</td>
<td>348 (13)</td>
<td>159 (10)</td>
<td>189 (17)</td>
</tr>
<tr>
<td>8</td>
<td>154 (5.9)</td>
<td>72 (4.7)</td>
<td>82 (7.5)</td>
</tr>
<tr>
<td>9</td>
<td>44 (1.7)</td>
<td>18 (1.2)</td>
<td>26 (2.4)</td>
</tr>
</tbody>
</table>

Key: TA, transapical; TAVR, transcatheter aortic valve replacement; TF, transfemoral
Figure E1. Stroke within 30 days after transcatheter aortic valve replacement (TAVR), stratified by transapical (TA; red curve, squares) versus transfemoral (TF; blue curve, circles) access. Format is as in Figure 1A.
Figure E2. Competing risks after transcatheter aortic valve replacement (TAVR). Solid lines are parametric estimates enclosed within dashed 95% confidence bands. Symbols are non-parametric estimates with 95% confidence bars. At each time point, “alive without neurologic event” (some would call this “event-free survival”), “death before neurologic event”, and “neurologic event” add to 100%.

A, TF-TAVR
Figure E2. Competing risks after transcatheater aortic valve replacement (TAVR). Solid lines are parametric estimates enclosed within dashed 95% confidence bands. Symbols are nonparametric estimates with 95% confidence bars. At each time point, “alive without neurologic event” (some would call this “event-free survival”), “death before neurologic event”, and “neurologic event” add to 100%.

B, TA-TAVR
Figure E3. Pre-procedure aortic valve peak gradient and risk-adjusted probability of stroke 30 days and 1 year after TF-TAVR (Random Forest for Survival partial dependency plot).
Symbols are risk-adjusted estimates. Solid lines are the loess smoother of these points.
**Figure E4.** Stroke after TF-TAVR stratified by presence of dementia. Symbols are Kaplan-Meier nonparametric estimates, with 95% confidence bars at selected time points. Numbers below the horizontal axis are patients remaining at risk.
Figure E5. Stroke after TF-TAVR stratified by prosthetic valve size 23 mm versus 26 mm.

Format is as in Figure E4.
Figure E6. Date of TF-TAVR and risk-adjusted probability of stroke 30 days and 1 year after TF-TAVR. Format is as in Figure E3.
**Figure E7.** Procedure time and risk-adjusted probability of stroke 30 days and 1 year after TF-TAVR. Format is as in Figure E3.
Figure E8. Stroke after TA-TAVR stratified by presence of pre-procedure pure aortic stenosis without regurgitation or mixed aortic regurgitation/aortic stenosis. Format is as in Figure E4.
Figure E9. Stroke after TA-TAVR stratified by number of post-dilatations. Format is as in Figure E4.
Figure E10. Date of TA-TAVR and risk-adjusted probability of stroke 30 days and 1 year after TA-TAVR. Format is as in Figure E3.
Figure E11. Stroke after TA-TAVR stratified by number of rapid cardiac pacing attempts.

Format is as in Figure E4.
Figure E12. Stroke after TA-TAVR stratified by presence of pre-procedure anti-platelet drug therapy. Format is as in Figure E4.
Figure E13. Stroke after TA-TAVR stratified by white versus non-white race. Format is as in Figure E4.
Figure E14. Ejection fraction and risk-adjusted probability of stroke 30 days and 1 year after TA-TAVR. Format is as in Figure E3.
Figure E15. Stroke after TA-TAVR stratified by presence of pre-procedure atrial fibrillation.

Format is as in Figure E4.
Figure E16. Instantaneous risk of transient ischemic attack (TIA) stratified by TF-TAVR versus TA-TAVR. Solid lines enclosed in dashed 95% confidence bands depict parametric estimates of the instantaneous risk.
Figure E17. Occurrence of transient ischemic attack (TIA) stratified by TF-TAVR versus TA-TAVR. Format is as in Figure 1.