Stroke is a potential complication of treating patients with aortic stenosis via surgical aortic valve replacement (AVR), transcatheter aortic valve replacement (TAVR), and balloon aortic valvuloplasty (BAV). Although its occurrence is rare, stroke significantly affects survival and quality of life. Based on recent randomized data from the PARTNER (Placement of Aortic Transcatheter Valves) trial, TAVR has recently emerged as the preferred therapy for inoperable patients and as an alternative to surgical AVR in high-risk patients (1,2). Importantly, increased neurologic events associated with TAVR have raised concerns (2). We reviewed the available literature to better understand the frequency, predictors, and clinical impact of post-procedure stroke during different aortic valve therapies for aortic stenosis.

Potential Sources of Embolization

Although strokes during either AVR or TAVR are undoubtedly multifactorial, the dominant etiology is likely intraprocedure embolic events. A transcranial Doppler study during TAVR demonstrated that the majority of procedural embolic events occurred during balloon valvuloplasty, manipulation of catheters across the aortic valve, and valve implantation (3). During AVR, evidence of emboli from transcranial Doppler imaging was mainly seen during insertion of an aortic cannula at the start of cardiopulmonary bypass and after declamping the aorta with the heart beating while empty (4). Late embolic events post-AVR are presumably caused by debris from the prosthesis (5).

Stroke in Surgical AVR Patients

The overall rate of stroke for isolated AVR in the global U.S. population is approximately 1.5% based on the Society of Thoracic Surgeons (STS) database (6,7). The incidence of stroke for blacks and whites among 34,510 isolated AVR procedures performed between 1999 and 2002 was 1.5% (26 of 1,762) and 1.7% (550 of 32,748), respectively (6). Similarly, O’Brien et al. (7) reviewed 67,292 isolated AVRs between 2002 and 2006 in the United States and found a cumulative stroke rate of 1.5%.

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Several studies have specifically examined the outcomes of high-risk elderly patients undergoing heart surgery (Table 1). In these multiple small series, the stroke frequency in high-risk patients undergoing AVR was increased (to as high as 4%), and important predictors were age (older than 80 years) and mean logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) (8–16). In the largest single-center study including 249 octogenarians (STS score: 10.5%) who had a mini AVR (hemi-upper sternotomy), there was a 3% perioperative mortality, but 4% of patients had strokes (15). A multicenter group retrospectively evaluated the outcomes of 159 high-risk AVR patients (mean STS score of 16.3%) and fulfilling other criteria of the PARTNER AVR vs. TAVR trial, treated in 2002 through 2007 in 4 U.S. hospitals (17). The early mortality rate was 16.4%; 4.4% of patients had permanent strokes and an additional 2.5% had transient neurologic events.

The addition of coronary artery bypass graft (CABG) or other procedures to AVR in octogenarians appears to significantly increase the risk of neurologic events. Sundt et al. (18) reported a 4% risk of stroke among 133 patients with AVR; 67% had an AVR-CABG and 11.3% had concomitant mitral valve replacement or repair. A single-center experience with AVR in octogenarians (28% with concomitant CABG) reported strokes in 5.8% (6 of 104) (19), and Alexander et al. (20) observed a 4.9% incidence (17 of 345) of stroke after AVR-CABG among octogenarians.

### Table 1 Stroke After Isolated AVR in Moderate- and High-Risk Patients

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Type of Study</th>
<th>n</th>
<th>STS</th>
<th>Mean EuroSCORE</th>
<th>Death</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk feature: &gt;80 yrs of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thourani et al. (8)</td>
<td>Retrospective, single-center</td>
<td>88</td>
<td>—</td>
<td>—</td>
<td>5.7%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Leontyev et al. (9)</td>
<td>Retrospective, single-center</td>
<td>282</td>
<td>—</td>
<td>16.2%</td>
<td>10.6%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Culliford et al. (10)</td>
<td>Retrospective, single-center</td>
<td>35</td>
<td>—</td>
<td>—</td>
<td>5.7%</td>
<td>0%</td>
</tr>
<tr>
<td>Akins et al. (11)</td>
<td>Retrospective, single-center</td>
<td>105</td>
<td>—</td>
<td>—</td>
<td>8.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Kolh et al. (12)</td>
<td>Retrospective, single-center</td>
<td>70</td>
<td>—</td>
<td>—</td>
<td>8.5%</td>
<td>2.0%*</td>
</tr>
<tr>
<td>Ennker et al. (13)</td>
<td>Retrospective, single-center</td>
<td>62</td>
<td>—</td>
<td>—</td>
<td>4.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Ferrari et al. (14)</td>
<td>Retrospective, single-center</td>
<td>124</td>
<td>—</td>
<td>12.6%</td>
<td>6.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Elbardissi et al. (15)†</td>
<td>Retrospective, single-center</td>
<td>249</td>
<td>10.5%</td>
<td>11.0%</td>
<td>3%</td>
<td>4.0%</td>
</tr>
<tr>
<td>High-risk feature: STS &gt;10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thourani et al. (17)</td>
<td>Retrospective, multicenter</td>
<td>159</td>
<td>16.3%</td>
<td>—</td>
<td>16.4%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

*2 of 100 cases (70 isolated aortic valve regurgitation [AVR] and 30 AVR/coronary artery bypass graft); †Mini AVR.

**EuroSCORE** = European System for Cardiac Operative Risk Evaluation; **STA** = Society of Thoracic Surgeons; **STS** = Society of Thoracic Surgeons.

### Stroke and TAVR

**Observational data with Edwards SAPIEN: transfemoral approach.** Five registries and 1 randomized trial reported stroke outcomes with the Edwards SAPIEN transcatheter heart valve (Edwards Lifesciences, Irvine, California) using a transfemoral (TF) approach (1,2,21–25). Reported strokes in these 5 registries ranged from 2.4% to 6% (Table 2) (21–25). In the SAPIEN Aortic Bioprosthesis European Outcome registry, the largest registry of Edwards SAPIEN TF cases, strokes were observed in 2.5% of patients (23). Similarly, the Multicenter Canadian experience reported a 30-day stroke rate of 3.0% for TF cases (22).

**Observational data with Edwards SAPIEN: transapical approach.** Two feasibility trials evaluating only the transapical (TA) approach using the Edwards SAPIEN valve reported strokes in 2% and 5% of patients (26,27). The larger TRAVERSE trial (the initial multicenter feasibility trial for TA-AVI) included 168 patients, and the rates of stroke at 30 days and 1 year were 2% and 5%, respectively (26). In the 5 registries discussed previously (21–25) that also included TA patients, strokes were noted in as many as 2.8% of the TA cases (Table 2). In a small retrospective matched study comparing the outcomes of TAVR and AVR with a TA approach via a partial upper sternotomy (28), there were no strokes in the TAVR patients and 1 (3%) in the AVR group.

**Observational data with CoreValve.** Four registries reported stroke-related clinical outcomes with the self-expanding CoreValve system (Medtronic, Minneapolis, Minnesota) (Table 2) (21,29–31). In 1 registry looking at outcomes with the first 3 generations of devices, the overall procedure rate of stroke was 4.4% (6 of 136), but was lower with the third-generation device (2.9% [3 of 102]) (29). In the other registries, 30-day strokes ranged between 1.9% and 4.5% with the TF approach with the 18-F device (21,30,31). There are limited data on the subclavian approach with the CoreValve (Medtronic) and the largest cohort of subclavian patients reported a 1.9% in-hospital stroke rate (30).
In a multidevice series of 697 patients treated with TAVR, the overall rate of in-hospital stroke was 2.8% (32); a TF approach was used in most patients (92.4%) and most were treated with the CoreValve (84.4%).

**Difficulties in Interpreting Stroke Data Across AVR and TAVR Studies**

In much of the current AVR literature, stroke is poorly defined and usually is not independently adjudicated. The majority of studies reported in-hospital mortality, and stroke is included among an overall assessment of in-hospital morbidity. Definitions (when they are available) have varied from crude determinations of a new neurologic deficit to more sensitive discriminations of stroke severity (33). In contrast, most TAVR studies have 30-day and often 1-year follow-up and attempt to apply a more consistent definition of stroke, but with varying ascertainment and adjudication. It is likely that without prospective assessment and follow-up, dedicated neurologic evaluations to adjudicate events, and confirmatory neuroimaging studies, strokes were systematically underreported in these registries. This limitation renders cross-study comparisons of published observational data problematic. In a recent effort to better define endpoints after TAVR, the Valve Academic Research Consortium proposed standardized endpoint definitions for a number of endpoints including stroke (Table 3) that should help to standardize and make future TAVR and AVR study methodologies more rigorous (33).

Another barrier to the interpretation of available data relates to discrepancies in the treated population across studies as well as the type of surgery performed (e.g., AVR, AVR-CABG). Also, the presence or absence of important comorbidities and other high-risk features is variably reported, such as atrial fibrillation. Only a minority of papers have included some form of presurgical risk assessment (e.g., STS or EuroSCORE) (9,34).

**Randomized Trials of TAVR**

In the inoperable cohort of the randomized PARTNER trial (1), which randomized TF-TAVR versus standard therapy with prospective ascertainment of stroke outcomes and careful event monitoring, the rate of all strokes and transient ischemic attacks at 30 days was 6.7% for the 179 patients after TAVR and 1.7% after standard therapy (p < 0.03). At 1-year follow-up, strokes and transient ischemic attacks were 10.6% and 4.5% after TAVR and standard therapy, respectively (p = 0.04). The rate of major stroke (modified Rankin Scale score of ≥2) was 5% at 30 days and 7.8% at 1 year.

In the PARTNER trial comparing TAVR and surgical AVR in high-risk patients (2) (n = 348 TAVR [TF and TA]; 351 AVR), strokes and transient ischemic attacks were more frequent after TAVR than AVR at both 30 days and 1 year (30 days: 5.5%}
TAVR vs. 2.4% AVR, p = 0.04; and 1 year: 8.3% TAVR vs. 4.3% AVR, p = 0.04). Major strokes were 3.8% after TAVR versus 2.1% with AVR (p = 0.20) at 30 days and 5.1% versus 2.4% (p = 0.07) at 1 year, whereas all-cause mortality was similar for both groups at 30 days and 1 year. The combined endpoint of all strokes (or major strokes) and mortality was similar for TAVR and AVR at early and late time points.

Stroke and BAV

With the emergence of TAVR, there has been a resurgence in BAV. In recent series of BAV, the observed stroke rates were found to be approximately 1% to 2% (35–39). The largest single-center cohort of patients (301 BAV in 262 patients) reported a stroke rate of 2% (35). In the PARTNER trial, 150 BAVs were performed in the medical therapy arm with only 2 strokes occurring (1.3%) (39).

Neuroimaging After AVR and TAVR

Three small studies used diffusion-weighted magnetic resonance imaging (DW-MRI) before and after AVR, and new imaging abnormalities (5 to 7 days after AVR) were observed in 38% (4 of 37), 40% (6 of 15), and 47% (14 of 30) of patients (40–42). Clinical strokes were less frequent (8%, 13%, and 0%, respectively), although 13% of patients had what was described as a “transient psychotic syndrome” in 1 study (42). Although several studies demonstrated a transient deterioration in neurocognitive function early after valve surgery, there was complete recovery within 4 months (42).

Similar DW-MRI studies after TAVR revealed an even greater number of new ischemic lesions (in 68% to 84% of patients), and in the vast majority of cases, these perfusion abnormalities have also not resulted in clinical strokes (43–46). Rodes-Cabau et al. (44) evaluated 29 TA and 31 TF patients treated by TAVR with the Edwards SAPIEN valve, and the proportion of patients with new DW-MRI deficits was similar for TA and TF patients (71% vs. 66%, respectively). Only 2 patients (3.3%) (1 in each group) had a stroke within 24 h of the procedure, and there were no significant differences in neurocognitive function in those with and without perfusion changes.

Neuroimaging outcomes after TAVR have been compared with an historical cohort of AVR patients (46). New ischemic lesions on DW-MRI were significantly increased with TAVR (86% [19 of 22] for the Edwards SAPIEN vs. 80% [8 of 10] for the CoreValve and 48% [10 of 21] for AVR). However, the 32 TAVR patients were older and had higher logistic EuroSCOREs and more comorbidities than the surgical patients. Moreover, although the number of lesions increased after TAVR, the lesion size was 3 to 4 times larger after surgical AVR. Despite the high proportion of abnormal neuroimaging studies, no clinical strokes were observed after TAVR, whereas 1 (4.7%) occurred in the surgical group.

Risk Factors for Post-Procedural Stroke

Limited information is available regarding risk factors for postoperative stroke after AVR and TAVR. Low ejection fraction (EF) has been identified as an independent risk factor for neurologic events (47,48). Stroke was significantly more frequent in AVR (including aortic regurgitation) in patients with an EF <40% compared with those with an EF >40% (5.5% vs. 2.0%, p = 0.005). A single-center retrospective analysis also identified low EF as an independent predictor of stroke; the stroke rate was 3% for isolated AVR and an EF <30% compared with 1% for patients with an EF >30% (48).

Extensive calcification of the ascending aorta is believed to increase the risk of neurologic complications after AVR and is frequently a high-risk feature that dissuades surgeons from performing AVR. Girardi et al. (49) reported strokes in 4% of 25 patients with a “porcelain aorta” undergoing aortic valve surgery using a no-clamp technique. Similarly, Gillinov et al. (50) reported the outcome of 62 patients with extensive calcification of the ascending aorta undergoing AVR, and the risk of permanent stroke was 10%, but differed based on the different management strategies of the ascending aorta.

Age remains a risk factor for stroke; in 1 series, it was the only multivariable predictor of neurologic events (51).
However, a more robust multivariable analysis in patients undergoing valve surgery (not only AVR) revealed 4 baseline characteristics and 2 procedural events that were associated with early post-procedure stroke: female sex (odds ratio [OR]: 2.6; 95% confidence interval [CI]: 1.5 to 4.8), EF <30% (OR: 2.3; 95% CI: 1.2 to 4.5), diabetes (OR: 2.2; 95% CI: 1.2 to 4.2), age older than 70 years (OR: 2.0; 95% CI: 1.1 to 3.6), bypass procedure time >120 min (OR: 3.7; 95% CI: 1.1 to 14.4), and calcification of the ascending aorta (OR: 2.6; 95% CI: 1.3 to 5.8) (52). Of note, atrial fibrillation was not included in the model. Among patients with an EF <40% in another study, additional multivariate predictors of stroke were peripheral vascular disease, a history of stroke or cerebrovascular disease, and diabetes (47,53). Finally, walking <300 m during a 6-min walk test has been demonstrated to be predictor of stroke after AVR (54).

Early embolic stroke after surgical AVR is also a concern. Follow-up of 2,317 patients with AVR revealed an annual rate of stroke of 1.3% for bioprostheses and 1.4% for mechanical valves (55). In comparison, the annual rate of major bleeding was 1.0% with anticoagulation and 0.4% without. Multivariate predictors of late stroke have included female sex (hazard ratio [HR]: 1.76; 95% CI: 1.26 to 2.48), age older than 75 years (HR: 1.88; 95% CI: 1.11 to 2.78), atrial fibrillation (HR: 2.21; 95% CI: 1.13 to 4.15), a history of or current smoking (HR: 2.59; 95% CI: 1.73 to 3.71 and HR: 2.96; 95% CI: 1.97 to 6.12, respectively), number of grafts performed (HR: 1.24; 95% CI: 1.02 to 1.56) and a tilting disc versus bileaflet prosthesis for the mechanical valve (HR: 1.74; 95% CI: 1.04 to 2.90). Age, previous stroke, diabetes, and carotid lesions were identified as independent predictors in patients with a stentless biological AVR (56).

In the PARTNER randomized trial of AVR versus TAVR, independent risk factors for early stroke were assignment to TAVR (vs. AVR) and a smaller aortic valve area (57). Predictors of late strokes (after 30 days) were: 1) history of stroke 6 to 12 months before the procedure; 2) non-TF candidate, reflecting a higher burden of atherosclerosis and more frequent vasculopathy; and 3) higher New York Heart Association functional class (57). There were no important differences in the frequency of late strokes between TAVR and AVR patients.

**Timing of Stroke After Procedures**

The timing of stroke among 75 events observed post-AVR in a single center over 5 years revealed that 72% occurred within 24 h post-procedure, 17% between 24 and 72 h post-procedure, and the remaining 11% occurred between days 3 and 9 (58). In another study, of 63 strokes after AVR, 55% occurred within 24 h of surgery (52). An early time course was also reported in patients after biological AVR, in which 19 of the 25 strokes (76%) recorded within 90 days occurred in the first week, and 18 of these early events (95%) were intraoperative (59). Among randomized AVR cases in the PARTNER trial, 62.5% of the major strokes (5 of 8) seen at 1 year occurred within the first 2 days, 25% (2 of 8) between 5 and 30 days, and 1 (12.5%) later than 30 days (57).

After TAVR, there appears to be a more significant proportion of early strokes occurring >24 h post-procedure (24,43), but TAVR patients with multiple comorbidities are probably at higher risk of both early and late strokes. In the inoperable patients of the PARTNER trial, 12 strokes were reported at 30 days in the TAVR group; 1 event occurred before the procedure (1). Of the 11 other events, 3 (27%) were observed within 24 h, 6 (55%) between days 1 and 5, and 2 (18%) after the first week. In the high-risk patients of the PARTNER trial who received a transcatheter valve, 12 major strokes occurred in the first 30 days; 7 (58%) were diagnosed in the first 2 days, 9 (75%) in the first 5 days, and 3 (25%) between 5 and 30 days (57). These observations parallel the Canadian experience in which only 25% of 30-day strokes were seen within 24 h of the procedure (22). In high-risk and inoperable patients of the PARTNER trial, late strokes (after 30 days) were seen in 2.8% and 3.9% of patients between 30 days and 1 year after TAVR, respectively, representing one third of the total stroke events at 1 year (1,2). It is still unclear whether these late (>30 days) stroke events are related to the procedure, the antiplatelet/anticoagulation regimen, or other comorbidities.

**Outcomes After Stroke**

The mortality associated with strokes after AVR is significant. A large AVR study revealed that in-hospital mortality for patients without stroke was 4.6% (127 of 2,754) compared with 31% (11 of 35) for those with an early (<24 h) stroke and 14% (4 of 28) for those with a late (>24 h) stroke (52). A multivariable analysis from another study indicated that post-operative stroke with permanent disability was a strong predictor of 30-day mortality after AVR in octogenarian patients (OR: 11.3; 95% CI: 1.7 to 75.1) (16). Other variables strongly associated with mortality were post-operative renal failure (OR: 20.9; 95% CI: 6.5 to 67.6), immunocompromised state (OR: 14; 95% CI: 1.7 to 112.3) and intra- or post-operative intra-aortic balloon pump requirement (OR: 14.9; 95% CI: 2.9 to 75.8).

The outcome of stroke after TAVR seems to be influenced by the severity of the neurologic event. In patients with stroke and no permanent deficit, data available suggest that mortality may not be affected (24). However, inoperable patients with major stroke post-TAVR in the PARTNER trial had significantly increased 1-year mortality rate (66.7% vs. 27.7%; p < 0.0001) compared with patients without a major neurologic event (60).
Discussion

Most of the surgical AVR studies are observational and lack prospectively assessed and adjudicated outcomes using standardized definitions for stroke. Therefore, the available literature on stroke related to surgical AVR is inconsistent and nondefinitive. Small prospective trials using DW-MRI have reported a much greater rate of perfusion abnormalities than clinical events; at present, the relevance of these findings is unclear and the subject of further investigation. Established risk factors for stroke after AVR include age and left ventricular dysfunction. Further data are needed to determine the incremental risks conferred by aortic calcification and atrial fibrillation.

TAVR is currently restricted to high-risk patients, and the rates of stroke after TAVR appear higher than after AVR. In a randomized trial comparing TAVR and AVR in high-risk patients, the AVR group had a 2-fold lower event rate for all neurologic events and major stroke at 30 days and 1 year (2). Importantly, the data thus far generated involved the use of early-generation high-profile TAVR devices and operators with limited case experience, which may have negatively influenced some of the periprocedure stroke results. Similar to the neuroimaging data with AVR, DW-MRI studies have demonstrated significant numbers of imaging deficits post-TAVR, but there are limited data associating these with significant clinical events.

In the setting of AVR or TAVR, the presence of a major stroke is undoubtedly associated with a poor overall prognosis, and efforts to reduce the rate of stroke after these procedures are ongoing. Because a significant percentage of these strokes appear to be procedure-related and embolic in nature, some have suggested that active protection of the cerebral circulation from embolic debris might be helpful. A small feasibility (n = 3) study suggested that a deflector device covering the right brachiocephalic trunk and the left carotid arteries may decrease neuroimaging defects post-TAVR (61). No benefit of an intra-aortic filter had been seen on neuroimaging outcomes in patients after cardiac surgery (62). However, the lack of benefit may be due to inclusion of very low risk patients in this study. The presence of atrial fibrillation in this elderly population, often not anticoagulated because of bleeding concerns, may be an additional significant factor influencing the occurrence of stroke. The role of optimal anticoagulation in these patients is another area of active investigation.

Further prospective studies with large numbers of patients undergoing TAVR and AVR with detailed neurology assessments, neurocognitive testing, and neuroimaging evaluations will need to be done to better determine the neurologic risks of these procedures. The PARTNER 2 and SURTAVI (SURgery and Transcatheter Aortic Valve Implantation) trials, including intermediate-risk patients, will address these issues in different substudies. As suggested by “Current Thinking Regarding Neurological Assessments for Transcatheter Valve Trials” by the U.S. Food and Drug Administration (FDA communication, May 25, 2011), neurologic and neurocognitive evaluations will be made by neurologists to improve the quality of clinical assessments.

Conclusions

Clinical stroke after TAVR or AVR is an important complication and is associated with a poor clinical prognosis. Recent randomized data showed that stroke rates appear to be higher with TAVR compared with AVR, but with wide CIs due the relatively low event rates. The prevalence of delayed or late strokes after the procedure is not insignificant and should generate active investigation of both devices and adjunctive pharmacotherapy to reduce the frequency and severity of strokes after AVR and TAVR in the future.

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REFERENCES


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