The risk and extent of neurologic events are equivalent for high-risk patients treated with transcatheter or surgical aortic valve replacement

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ABSTRACT

Objectives: This study was designed to characterize the incidence of new clinically detectable neurologic events, or any comparative change in indices of higher cognitive function following transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) within the framework of a prospective, randomized clinical trial for high-risk patients.

Methods: High-risk patients (predicted SAVR mortality 15%) with severe aortic stenosis (n = 750) were randomized 1:1 to TAVR or SAVR and underwent evaluation using the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale assessment at each follow-up and any suspected event. Neurologic outcomes were ascertained by a neurologist and further evaluated by Mini-Mental State Examination (MMSE), visual fields testing, gait assessment, hand function, writing evaluation, and drawing assessment.

Results: The 30-day, 1-year, and 2-year stroke rates were 4.9%, 8.7%, and 10.9%, respectively, for TAVR and 6.2%, 12.5%, and 16.6%, respectively, for SAVR ($P = .46$, $.11$, and $.05$, respectively). All-cause mortality in patients with a major stroke was 83.3% for TAVR and 54.5% for SAVR at 2 years ($P = .29$). Late major stroke was disproportionately higher (23.8% at 2 years) among patients with poor iliofemoral access randomized to SAVR. Peripheral vascular disease and falls within 6 months predicted early stroke, and severe aortic calcification and high Charlson score (≥ 5) predicted 1-year stroke post-TAVR. NIHSS and MMSE scores trended higher after SAVR than after TAVR. Lack of dual antiplatelet therapy use during and after TAVR was associated with early stroke.

Conclusions: This study defines an equivalent postprocedural stroke risk, stroke extent, and degree of cognitive change after TAVR or SAVR in a high-risk population, and also defines several predictors of stroke after TAVR. (*J Thorac Cardiovasc Surg* 2016;152:85-96)

Kaplan-Meier analysis for major stroke after TAVR or SAVR.

Central Message

This study demonstrates equivalent neurologist-adjudicated stroke risk and extent following TAVR or SAVR in a high-risk population.

Perspective

This study demonstrates equivalent postprocedural, neurologist-adjudicated stroke risk and extent of neurologic injury after TAVR or SAVR in a high-risk population. Several risk factors appear to be predictors of stroke after TAVR, and dual antiplatelet therapy appears to have a protective effect with TAVR. The 2-year mortality rate after TAVR- or SAVR-associated stroke is exceedingly high.

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Stroke is a potentially devastating consequence of aortic valve replacement, regardless of method—surgical aortic valve replacement (SAVR) or transcatheter aortic valve

replacement (TAVR)—that negatively impacts both health-related quality of life and mortality.¹ The present investigation sought to clearly define the stroke rate and

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Abbreviations and Acronyms

CVA	= cerebrovascular accident
DAPT	= dual antiplatelet therapy
NIHSS	= National Institutes of Health Stroke Scale
MMSE	= Mini-Mental State Examination
mRS	= modified Rankin Scale
SAVR	= surgical aortic valve replacement
TAVR	= transcatheter aortic valve replacement
TIA	= transient ischemic attack
VARC	= Valve Academic Research Consortium

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extent of impairment/deficits of all neurologic events following TAVR or SAVR within the framework of a prospective, randomized clinical trial among patients at high risk for mortality.

Disabling stroke is only one potential neurologic outcome measure that has been well defined. There are other, less obvious neurologic injuries that may or may not have clinical consequences and may be apparent only on detailed neuropsychological testing in the postoperative period.² Brain deficits in cognition, vision, ambulation, and other neurologic-mediated functions are potentially disabling, especially in older individuals. One major finding of previous TAVR trials has been a higher stroke rate in patients undergoing TAVR compared with those undergoing SAVR. Early strokes occurred more frequently in those with a smaller aortic valve area index.³ However, other neurologic indices were not prospectively evaluated and neurologist-adjudicated, but rather were evaluated by source document review by a clinical events committee.

Alternatively, the CoreValve US High-Risk Pivotal Trial was designed for prospective, neurologist-adjudicated stroke ascertainment by Valve Academic Research Consortium (VARC)-defined criteria.⁴ Because the 2 most commonly used scores, the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS), do not adequately assess some important brain functions, the neurologic substudy within the High-Risk Pivotal Trial, reported here for the first time, aimed to more comprehensively evaluate the neurologic effects and/or complications of TAVR and SAVR in high-risk patients.

In addition to clinically overt cerebrovascular accidents (CVAs), asymptomatic silent cerebral infarcts have been frequently observed with transcranial Doppler and diffusion-weighted magnetic resonance imaging (MRI). The prevalence of these radiologic findings is found in greater than two-thirds of patients,⁵⁻⁸ and there is some evidence to suggest they may be associated with an increased risk of neurocognitive decline.^{9,10}

Despite the penetrance of the Society of Thoracic Surgeons Database, there appears to be discrepant postoperative neurologic event rates depending on the neurologic definition used and on the comprehensive nature of the postoperative evaluation. In addition, despite the standardized definition of stroke by the VARC criteria, there appears to be a knowledge gap in the rates of neurologic injuries between patients treated with TAVR and those treated with SAVR. With continued exponential growth in the use of TAVR combined with the potential expansion into lower-risk patient subsets, better understanding of neurologic events is critical.

METHODS**CoreValve US High-Risk Pivotal Randomized Cohort**

The CoreValve US High-Risk Pivotal Trial was a prospective, multicenter, randomized, controlled study performed at 45 clinical sites in the United States. Each site's Institutional Review Board approved the study protocol ([ClinicalTrials.gov](https://clinicaltrials.gov) no. NCT01240902), and all patients provided written informed consent. Patients with severe symptomatic aortic stenosis and an increased risk of mortality (as determined by 2 cardiac surgeons and 1 interventional cardiologist at the investigative site estimated that the risk of death within 30 days after surgery was $\geq 15\%$, and the risk of death or irreversible complications within 30 days after surgery was $< 50\%$)¹¹ were randomized to TAVR or SAVR. According to trial protocol, the TAVR patients were strongly recommended to take aspirin (81-325 mg) and an additional antiplatelet agent (most commonly clopidogrel 75 mg) starting 3 days before the procedure unless medically contraindicated and for at least 3 months after implantation. All TAVR patients not receiving anticoagulant therapy (eg, warfarin or a novel oral anticoagulant) also received a clopidogrel load (300 mg) on the day of the procedure. There were no specified recommendations for aspirin or antiplatelet use in the SAVR patients, although these data were recorded. Any abnormality in the neurologic evaluation triggered a neurology consultation and imaging. Transient ischemic attack and stroke were defined in accordance with VARC-1 criteria.¹²

Modified Rankin Scale (mRS) assessments were required for all suspected neurologic events. The mRS scores range from 0 to 6, correlating with perfect health without symptoms to death.¹³ To ensure uniformity of evaluation, directions for evaluation and items to consider in separating mRS scores of 2 to 4 were distributed to all neurologic investigators. The NIHSS assessment was performed at all scheduled follow-up visits in all patients.

Neurologic Substudy

Patients enrolled in the High-Risk Pivotal Trial were eligible to also participate in a neurologic substudy (Figure 1). The inclusion and exclusion criteria for the substudy were the same except for the added exclusion of roll-in patients. The purpose of the substudy was to further evaluate the

FIGURE 1. Patient disposition. TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

neurologic effects of the CoreValve System in the treatment of symptomatic severe aortic stenosis in patients necessitating aortic valve repair, and all patients were evaluated by the NIHSS and mRS and subjected to a battery of tests.

The Mini-Mental State Examination (MMSE) was used to quantify cognitive abilities.^{14,15} Writing ability was analyzed along with tests of drawing and copying ability, and visual field, gait, and hand strength and functional assessments were performed.

Endpoints. The primary endpoint for the neurologic substudy was the rate of Clinical Events Committee–adjudicated strokes (of any severity) and transient ischemic attacks (TIAs) at 1 year. Secondary endpoints included periprocedural neurologic injury (stroke, TIA, and encephalopathy), which was evaluated at discharge or at 7 days postprocedure, whichever occurred first. Additional endpoints included quantification and qualification of neurologic deficits seen after TAVR or SAVR. Encephalopathy was defined as episodes of confusion, agitation, and/or combativeness; alterations and fluctuations in levels of consciousness; and acute problems with cognition, including memory and changes in perception, including hallucinations.¹⁶

Patient assessment. Stroke events were defined based on the original VARC-1 definitions.⁴ In addition to the procedures required for the CoreValve Trial,¹⁷ the neurologic substudy patients were clinically evaluated by a neurologist at baseline, at discharge or 7 days after the index procedure (whichever occurred first), and at 1 year postprocedure. Patients were also assessed at baseline, discharge, and 1 year postprocedure using the following measures: NIHSS, MMSE,^{14,18} visual fields testing, gait assessment, hand function assessment, and writing and drawing evaluation. For the purpose of our study, a neurologic deficit was defined as an increase in NIHSS score of ≥ 2 or a decrease in the MMSE score by >4 .

Visual field testing was performed individually and bilaterally in each of the 4 visual quadrants using finger counting or a visual threat. Any abnormalities in target detection warranted more precise testing. Gait assessment included asking the patient to walk down the corridor (if ambulatory) under observation while noting any visually apparent abnormalities of gait (eg, ataxia, lateralized hemiparesis, shuffling steps). Muscle power is typically graded on a scale of 0 to 5¹⁹; however, we used a scale of 0 to 10, to enable documentation of subtleties in potential deficits.²⁰ On the 0 to 10 scale, 0 represents no muscle contraction and 10 represents normal strength. A deficit was noted when a normal assessment at baseline found a decrease of ≥ 2 .

A writing evaluation was performed by asking the patient to write 2 sentences about a given subject. A deficit was noted if the patient passed at baseline and failed at follow-up assessment. For the drawing assessment, the patient was asked to draw a clock face, put the numbers in the correct positions, and draw the hands to indicate a particular time. The assessment was scored on a scale of 0 to 4, with 1 point for drawing a closed circle, 1 for including the correct 12 numbers, 1 for placing the numbers in the correct positions, and 1 for placing the hands in the correct positions. A deficit was noted to have occurred if a patient who passed at baseline failed (missed at least 1 item) at follow-up assessment. The Clinical Events Committee that participated in the overall CoreValve Trial adjudicated the neurologic events for the substudy.

Statistical analyses. Continuous variables are presented as mean $\pm$ standard deviation and were compared using the Student *t* test. Categorical data were compared using the χ^2 or Fisher exact test. Kaplan-Meier analysis using the log-rank test was used to compare time to events. A Cox proportional hazards model was used for the univariable and multivariable analyses. Multivariable predictors of stroke were identified from univariable predictors with a *P* value $< .05$. Stepwise multivariable analyses were performed. The significance level thresholds for entry and exit of independent variables were set at 0.10. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

High-Risk Pivotal Trial

Baseline characteristic and primary clinical outcomes of the CoreValve Trial through 2 years have been reported previously.^{17,21} The rates of neurologic events at 30 days, 1 year, and 2 years are shown in Table 1. Overall, the rate of stroke events was higher in the patients treated with SAVR compared with those treated with TAVR (16.6% vs 10.9%; *P* = .05). Kaplan-Meier estimates of stroke or TIA and major stroke through 2 years are shown in Figure 2. The distribution of strokes occurring within the first 30 days are clustered in the first few days, but become more evenly distributed beyond 30 days out to 2 years (Figure 3).

Starting at the time stroke was observed (day 0), mortality in patients with any stroke was twice as high in the TAVR group compared with the SAVR group (Figure 4, A). Among patients who sustained a major stroke during the first 30 days postprocedure, mortality was high through 2 years in both groups, 83.3% for TAVR and 54.5% for SAVR (log-rank *P* = .29) (Figure 4, B).

Predictors of neurologic events. We evaluated predictors of neurologic events that occurred early, between day 0 and day 30 postprocedure, and at 1 year postprocedure. Predictors of neurologic events for the patients treated with TAVR and SAVR are presented in Table 2.

Effect of access route on neurologic events. Of the 750 patients in the as-treated cohort, 124 patients were deemed to have unsuitable anatomy for TAVR implantation via the iliofemoral access route. There were significantly more neurologic events in patients without iliofemoral access in the SAVR group compared with the TAVR group (Table 3).

Anticoagulation and/or antiplatelet use. A significantly higher percentage of TAVR patients than SAVR patients

TABLE 1. Clinical outcomes to 2 years for the as-treated cohort from the High-Risk Pivotal Trial

Outcome	Kaplan-Meier rate (no. of patients)								
	30 d			1 y			2 y		
	TAVR	SAVR	P	TAVR	SAVR	P	TAVR	SAVR	P
Any stroke or TIA	5.7 (22)	6.5 (23)	.67	10.3 (39)	14.1 (47)	.14	13.2 (48)	17.8 (56)	.13
Stroke	4.9 (19)	6.2 (22)	.46	8.7 (33)	12.5 (42)	.11	10.9 (40)	16.6 (52)	.05
Major stroke	3.9 (15)	3.1 (11)	.55	5.8 (22)	6.9 (23)	.61	6.8 (25)	9.8 (30)	.25
Ischemic	3.6 (14)	2.5 (9)	.39	5.0 (19)	5.4 (18)	.87	5.7 (21)	6.7 (21)	.70
Hemorrhagic	0.3 (1)	0.0 (0)	.34	0.8 (3)	0.9 (3)	.88	1.2 (4)	1.8 (5)	.58
Undetermined	0.0 (0)	0.6 (2)	.14	0.0 (0)	0.6 (2)	.14	0.3 (1)	1.4 (4)	.13
Minor stroke	1.0 (4)	3.4 (12)	.03	3.0 (11)	6.0 (20)	.047	4.2 (15)	7.3 (23)	.08
Ischemic	0.8 (3)	3.1 (11)	.02	2.7 (10)	5.4 (18)	.06	4.0 (14)	5.8 (19)	.20
Hemorrhagic	0.0 (0)	0.3 (1)	.30	0.0 (0)	0.6 (2)	.13	0.0 (0)	1.5 (4)	.03
Undetermined	0.3 (1)	0.0 (0)	.34	0.3 (1)	0.0 (0)	.34	0.3 (1)	0.0 (0)	.34
TIA	0.8 (3)	0.3 (1)	.36	1.6 (6)	1.6 (5)	.92	2.6 (9)	1.6 (5)	.41
ICH	0.0 (0)	0.0 (0)	—	0.8 (3)	0.7 (2)	.78	1.2 (4)	0.7 (2)	.52
Encephalopathy*	9.6 (37)	17.1 (61)	.003	13.2 (50)	19.6 (69)	.01	13.9 (52)	20.6 (72)	.01

TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; TIA, transient ischemic attack; ICH, intracranial hemorrhage. *Patients with nonfocal global encephalopathy were not reported as a stroke without unequivocal evidence based on neuroimaging studies.

were treated with an antiplatelet agent in addition to aspirin, and this differences also held for TAVR and SAVR patients who experienced a stroke up to the 2-year mark (Tables 4 and 5). Differences between the groups in the use of warfarin or another novel oral anticoagulant along with

aspirin were not as marked, although all 3 drug classes (aspirin, clopidogrel, and warfarin or novel oral anticoagulant) were used in a greater percentage of TAVR patients compared with SAVR patients, including those who experienced a stroke. Among TAVR patients, nonuse of dual antiplatelet therapy (DAPT) was associated with experiencing a stroke within 3 months of the procedure; however, this association was not true among SAVR patients (Table 6). Interestingly, among patients who had a stroke within 1 year of the procedure, SAVR patients were less likely than TAVR patients to have received DAPT at discharge; a similar trend was seen at the 3-month mark (Table 7).

FIGURE 2. Kaplan-Meier analysis for (A) stroke or TIA and (B) major stroke in the TAVR and SAVR arms of the High-Risk Pivotal Trial through 2 years. TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; TIA, transient ischemic attack.

Neurologic Substudy

The substudy cohort included 199 high-risk patients (111 undergoing TAVR and 88 undergoing SAVR). Baseline demographic data, clinical characteristics, and data on frailty, disabilities, and comorbidities are provided in Table 8. The rate of any stroke and TIA at 1 year was 11.2% for the TAVR group and 13.2% for the SAVR group. The rate of major stroke at 1 year was 2.7% for the TAVR group and 6.1% for the SAVR group.

NIHSS. Eleven patients (3 in the TAVR group [3.5%] and 8 in the SAVR group [12.7%]) exhibited signs of cognitive impairment (NIHSS score increase ≥ 2) at discharge compared with baseline. Of these, all 3 TAVR patients and 3 of the 8 SAVR patients had a neurologic event. At 1 year, 1 TAVR patient (1.5%) and 2 SAVR patients (4.9%) had a NIHSS score increase of ≥ 2 compared with baseline, and all 3 of these patients had a neurologic event reported before assessment (Table 9).

MMSE. Of the 134 patients (79 in the TAVR group and 55 in the SAVR group) with documented MMSE scores at

FIGURE 3. Distribution of the occurrences of TIAs and major and minor strokes through (A) 30 days and (B) 2 years. TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; TIA, transient ischemic attack.

discharge, 2 TAVR patients (2.5%), and 6 SAVR patients (10.9%) had a decrease of >4 points over baseline. Both of the TAVR patients and 2 of the 6 SAVR patients had a documented neurologic event before assessment. At 1 year, among the 102 patients (62 in the TAVR group and 40 in the SAVR group) with recorded MMSE scores, 5 TAVR patients (8.1%) and 1 SAVR patient (2.5%) had a decrease of >4 points. One of the TAVR patients and the SAVR patient had a documented neurologic event before assessment.

Visual field testing. Of the 172 patients (95 in the TAVR group and 77 in the SAVR group) without any field defect at baseline, 1 TAVR patient and 1 SAVR patient had a reported defect at discharge. The TAVR patient had encephalopathy, whereas the SAVR patient had no neurologic event reported. At 1 year, 2 SAVR patients had a visual field defect, 1 with a minor stroke and the other with no neurologic event reported.

Gait assessment. Of the 135 patients with recorded gait assessment data (77 in the TAVR group and 58 in the SAVR group), abnormal findings were found in 6 TAVR

FIGURE 4. Kaplan-Meier estimates of mortality for (A) patients with any stroke and (B) patients with major stroke within 30 days for the TAVR and SAVR arms of the High-Risk Pivotal Trial through 2 years. This time-to-event analysis assigned the day on which the stroke event occurred as day 0. TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

patients (7.8%) and 9 SAVR patients (15.5%). One TAVR patient had associated encephalopathy, and 2 SAVR patients had a neurologic event reported before assessment (1 with minor stroke and 1 with encephalopathy). At 1 year, 6.8% of the TAVR patients and 7.7% of the SAVR patients had abnormal gait assessment findings. Only 1 TAVR patient had a neurologic event (minor stroke) reported before assessment.

Motor assessment. Of the 97 patients with normal left motor assessment findings at baseline, the rate of weakness at discharge was 7.2% in the TAVR group and 6.5% in the SAVR group. None of the affected patients had a neurologic event before assessment. At 1 year, no TAVR patients and 2 of 35 SAVR patients (5.7%) had with notable weakness; 1 of these patients had a neurologic event. In patients with normal right motor assessment findings at baseline, the prevalence of weakness at discharge was 7.2% in the TAVR group and 10.4% in the SAVR group. A neurologic event was documented before assessment in 2 of the TAVR patients and none of the SAVR patients. At 1 year, none of the TAVR patients and 2 of 37 SAVR patients had

TABLE 2. Predictors of early and late stroke after aortic valve replacement

Predictor	Kaplan-Meier rate, % [95% CI], n	Univariable analysis			Multivariable analysis		
		HR	95% CI	P value	HR	95% CI	P value
Predictors of early (0-30 d) stroke after TAVR							
Peripheral vascular disease	8.3 [4.9-13.9], 159	3.21	1.22-8.44	.02	3.16	1.18-8.44	.02
Nocturnal bipap	13.8 [5.4-32.7], 29	3.32	1.10-10.0	.03			
Falls in past 6 mo	9.9 [4.8-19.6], 72	2.91	1.13-7.51	.03	3.18	1.23-8.21	.02
Predictors of 1-y stroke after TAVR							
Peripheral vascular disease	12.4 [8.1-18.7], 159	2.06	1.03-4.10	.04			
Severe aortic calcification	17.7 [9.2-32.3], 47	2.42	1.09-5.36	.03	2.37	1.07-5.26	.03
History of hypertension	7.8 [5.4-11.1], 372	0.28	0.11-0.73	.009	0.26	0.10-0.68	.006
Charlson Comorbidity Score ≥5	13.3 [9.3-18.9], 211	3.95	1.63-9.57	.002	3.91	1.61-9.48	.003
Predictors of 1-y stroke after SAVR							
NYHA class III/IV	11.1 [7.9-15.3], 312	0.47	0.23-0.96	.04			
Angina	6.0 [2.5-13.9], 91	0.38	0.15-0.97	.04	0.38	0.15-0.97	.04

No univariable or multivariable predictors of early stroke were found for the SAVR group. An α value of 0.05 was used to select univariable predictors, and a value of 0.10 was used for multivariable predictors. *CI*, Confidence interval; *HR*, hazard ratio; *TAVR*, transcatheter aortic valve replacement; *SAVR*, surgical aortic valve replacement; *NYHA*, New York Heart Association.

documented weakness; both of these patients had a neurologic event.

Writing evaluation. Of the 79 patients who underwent a writing evaluation, the failure rate was 5.1% in the TAVR group and 8.5% in the SAVR group, although all patients had passed at baseline. Only 1 patient in each group had a neurologic event. At 1 year, 1.6% of the TAVR group and 10% of the SAVR group failed the test; of these, 1 SAVR patient had an event.

Drawing assessment. Of the 90 patients who underwent a drawing assessment, 23.5% of the TAVR patients and 25.6% of the SAVR patients failed at least 1 portion of the assessment, although all patients had passed all portions at baseline. There were 2 patients with a neurologic event in

each group. At 1 year, 10.9% of the TAVR patients and 11.1% of the SAVR patients failed the test. A neurologic event was noted in 2 of the SAVR patients.

DISCUSSION

The first reported results of the “inoperable” risk cohort (cohort B) from the seminal Placement of Aortic Transcatheter Valves (PARTNER) Trial served as a bellwether for stroke risk associated with TAVR, revealing a higher stroke rate at 30 days in the TAVR arm compared with medical therapy (6.7% vs 1.7%; $P = .04$).²² This report was followed by an evaluation of the high-risk cohort (PARTNER cohort A), which showed a 2-fold higher stroke rate in the TAVR arm compared with the SAVR arm (4.6%

TABLE 3. Neurologic events in the High-Risk Pivotal Trial by access route and treatment cohort

Event	30 d				1 y				2 y			
	Iliofemoral		Non-iliofemoral		Iliofemoral		Non-iliofemoral		Iliofemoral		Non-iliofemoral	
	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
Any stroke or TIA	5.9 (19)	5.3 (16)	4.5 (3)	12.3 (7)	10.8 (34)	12.5 (35)	7.7 (5)*	22.3 (12)*	14.2 (42)	15.6 (41)	7.7 (5)†	30.0 (15)†
Stroke	5.0 (16)	5.0 (15)	4.5 (3)	12.3 (7)	8.9 (28)	10.7 (30)	7.7 (5)*	22.3 (12)*	11.5 (35)	14.1 (37)	7.7 (5)†	30.0 (15)†
Major stroke	3.7 (12)	2.0 (6)	4.5 (3)	8.8 (5)	5.7 (18)	4.6 (13)	6.1 (4)*	18.7 (10)*	6.9 (21)	7.1 (18)	6.1 (4)*	23.8 (12)*
Ischemic	3.4 (11)	1.7 (5)	4.5 (3)	7.0 (4)	4.8 (15)	3.6 (10)	6.1 (4)	15.4 (8)	5.5 (17)	4.6 (12)	6.1 (4)	17.8 (9)
Hemorrhagic	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	1.0 (3)	0.7 (2)	0.0 (0)	1.9 (1)	1.4 (4)	1.3 (3)	0.0 (0)	5.0 (2)
Undetermined	0.0 (0)	0.3 (1)	0.0 (0)	1.8 (1)	0.0 (0)	0.3 (1)	0.0 (0)	1.8 (1)	0.4 (1)	1.3 (3)	0.0 (0)	1.8 (1)
Minor stroke	1.3 (4)	3.0 (9)	0.0 (0)	5.3 (3)	3.2 (10)	6.1 (17)	1.6 (1)	5.3 (3)	4.7 (14)	7.1 (19)	1.6 (1)	8.3 (4)
Ischemic	0.9 (3)	2.7 (8)	0.0 (0)	5.3 (3)	2.9 (9)	5.4 (15)	1.6 (1)	5.3 (3)	4.4 (13)	5.8 (16)	1.6 (1)	5.3 (3)
Hemorrhagic	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.7 (2)	0.0 (0)	0.0 (0)	0.0 (0)	1.3 (3)	0.0 (0)	3.1 (1)
Undetermined	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)
TIA	0.9 (3)	0.3 (1)	0.0 (0)	0.0 (0)	2.0 (6)	1.9 (5)	0.0 (0)	0.0 (0)	3.1 (9)	1.9 (5)	0.0 (0)	0.0 (0)
ICH	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.0 (3)	0.8 (2)	0.0 (0)	0.0 (0)	1.4 (4)	0.8 (2)	0.0 (0)	0.0 (0)
Encephalopathy‡	7.5 (24)†	16.0 (48)†	19.7 (13)	22.9 (13)	11.5 (36)†	18.6 (55)†	21.3 (14)	25.0 (14)	12.3 (38)†	19.4 (57)†	21.3 (14)	27.5 (15)

Data are presented as Kaplan-Meier estimates (no. of patients). *TAVR*, Transcatheter aortic valve replacement; *SAVR*, surgical aortic valve replacement; *TIA*, transient ischemic attack; *ICH*, intracranial hemorrhage. * $P < .05$. † $P \leq .01$. ‡Patients with nonfocal global encephalopathy were not reported as stroke without unequivocal evidence based on neuroimaging studies.

TABLE 4. Discharge medications for the TAVR and SAVR patients

Category	TAVR (n = 391), % (n)	SAVR (n = 359), % (n)	P value
Patients discharged on aspirin	94.1 (368)	93.3 (335)	.6504
Patients discharged on antiplatelet	90.5 (354)	35.9 (129)	<.0001
Patients discharged on anticoagulant	59.6 (233)	68.8 (247)	.0087
Patients discharged on both aspirin and antiplatelet	87.5 (342)	34.8 (125)	<.0001
Patients discharged on both aspirin and anticoagulant	58.1 (227)	65.5 (235)	.0373
Patients discharged on both antiplatelet and anticoagulant	53.7 (210)	24.0 (86)	<.0001
Patients discharged on aspirin and antiplatelet and anticoagulant	52.2 (204)	22.8 (82)	<.0001
Patients discharged on aspirin or antiplatelet	97.2 (380)	94.4 (339)	.0581
Patients discharged on aspirin or anticoagulant	95.7 (374)	96.7 (347)	.4757
Patients discharged on antiplatelet or anticoagulant	96.4 (377)	80.8 (290)	<.0001
Patients discharged on aspirin or antiplatelet or anticoagulant	97.2 (380)	96.7 (347)	.6745

TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

vs 2.4%; $P = .07$).²³ These pivotal preliminary findings launched international concerns about whether TAVR imparted a higher risk of stroke than SAVR, presumably due to the unprotected intravascular manipulation of wires and devices around the arch and through a calcified aortic valve.

These initial concerns were tempered somewhat by subsequent European Registry results and meta-analyses that demonstrated stroke rates ranging from 1% to 5%.²⁴⁻²⁷ The results of the CoreValve Trial further offset those of the PARTNER Trial, demonstrating equivalent stroke rates for TAVR and SAVR (4.9% vs 6.2%; $P = .46$) at 30 days.¹¹ These results provoked criticism that the stroke rate reported for the SAVR group in the CoreValve Trial was unexpectedly high, and that this apparently higher-than-expected (compared with PARTNER data) SAVR-associated stroke rate explained the noninferior statistical findings. Of note, a recent single-institution prospective observational study of patients undergoing SAVR revealed that the neurologist-adjudicated and MRI-confirmed hospital stroke rate was more than double

the stroke rate reported in the STS database (data extracted retrospectively by chart review to abstract “permanent stroke”) for the same patient cohort.² Neurologic complications in the PARTNER Trial were ascertained retrospectively by a Clinical Events Committee chart review. In contrast, in the CoreValve Trial, neurologic outcomes were ascertained prospectively with baseline neurologist-adjudicated testing for all patients, and thus there is greater confidence that all neurologic events were appropriately captured and reported. It is this discrepancy in methodology that likely explains the difference in absolute stroke rates reported by these 2 large randomized controlled trials.

In the CoreValve Trial, the combined neurologic event rates (any stroke or TIA) at 30 days, 1 year, and 2 years did not differ significantly between the TAVR and SAVR groups; however, the rate of stroke at 2 years was higher in the SAVR group. The rate of minor stroke was also significantly higher in the SAVR group at 30 days and 1 year, and the majority of these events were ischemic in origin. The rate of nonfocal, global encephalopathy was

TABLE 5. Discharge medications for TAVR and SAVR patients who had a stroke up to 2 years postprocedure

Category	TAVR (n = 40), % (n)	SAVR (n = 52), % (n)	P value
Patients discharged on aspirin	87.5 (35)	90.4 (47)	.6595
Patients discharged on antiplatelet	82.5 (33)	38.5 (20)	<.0001
Patients discharged on anticoagulant	62.5 (25)	75.0 (39)	.1965
Patients discharged on both aspirin and antiplatelet	77.5 (31)	36.5 (19)	<.0001
Patients discharged on both aspirin and anticoagulant	62.5 (25)	71.2 (37)	.3801
Patients discharged on both antiplatelet and anticoagulant	52.5 (21)	25.0 (13)	.0067
Patients discharged on aspirin and antiplatelet and anticoagulant	52.5 (21)	23.1 (12)	.0035
Patients discharged on aspirin or antiplatelet	92.5 (37)	92.3 (48)	>.9999
Patients discharged on aspirin or anticoagulant	87.5 (35)	94.2 (49)	.2877
Patients discharged on antiplatelet or anticoagulant	92.5 (37)	88.5 (46)	.7266
Patients discharged on aspirin or antiplatelet or anticoagulant	92.5 (37)	94.2 (49)	>.9999

TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement.

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TABLE 6. Medication at discharge for TAVR and SAVR patients who had a stroke or not within 3 months postprocedure

Category	TAVR			SAVR		
	Stroke (n = 21)	No stroke (n = 354)	P value	Stroke (n = 27)	No stroke (n = 302)	P value
DAPT at discharge, % (n/N)	66.7 (14/21)	90.4 (320/354)	.0007	40.7 (11/27)	36.4 (110/302)	.6558
Anticoagulation at discharge, % (n/N)	57.1 (12/21)	60.2 (213/354)	.7833	77.8 (21/27)	70.2 (212/302)	.4065

TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; DAPT, dual antiplatelet therapy.

significantly higher in the SAVR group at all time points out to 2 years. Stroke rates were highest (by more than 3-fold) in the patients who were judged to have inadequate iliofemoral access for TAVR on preoperative evaluation and were then randomized to the SAVR group compared with those randomized to non-iliofemoral TAVR. This is consistent with previous publications reporting worse outcomes in patients with significant large-vessel lower extremity peripheral artery disease compared with the general population.²⁸

The neurologic substudy findings are consistent with those of the whole CoreValve High-Risk Trial results showing a trend toward higher NIHSS scores and a greater drop in MMSE scores at discharge in patients undergoing SAVR compared with those undergoing TAVR. The extent and frequency of neurologic deficits as otherwise measured by visual field, gait abnormality, left or right hand motor function, writing evaluation, or drawing evaluation were similar in the TAVR and SAVR groups. The small study group size may have resulted in a lack of statistical significance, considering that both the gait assessment and the writing evaluation suggested a trend toward worse outcomes with SAVR. Overall, these detailed neurologic evaluations of the substudy uncovered more changes in indices of higher cognitive function than neurologic events adjudicated simply by the VARC definitions. How these changes impact quality of life are not yet clear, but the results of the substudy suggest that physician-reported

neurologic outcome assessments underestimate true neurologic event rates.

Univariate and multivariate analysis revealed multiple predictors of neurologic events (Table 2). The presence of peripheral vascular disease and a history of previous fall predicted a higher incidence of stroke at 30 days among the TAVR patients. A Charlson Comorbidity Index score of ≥ 5 and severe aortic calcification predicted a higher incidence of stroke at 1 year. One surprising finding was that new-onset atrial fibrillation was not an independent predictor for stroke, in disagreement with a previous retrospective report.²⁹

According to the CoreValve Trial design, there is no requirement to discharge SAVR patients on aspirin or an antiplatelet agent (eg, clopidogrel), and there is only a strong recommendation to discharge TAVR patients on DAPT unless medically contraindicated. Consequently, and as expected, a significantly higher percentage of TAVR patients (88%) than SAVR patients (35%) were discharged on an antiplatelet agent in addition to aspirin. The lack of use of DAPT after TAVR was associated with a greater risk of stroke; however, this same association did not hold for the SAVR patients, suggesting that DAPT may have a more defined role for TAVR but not necessarily for SAVR. It must be emphasized that despite differing medication regimens, this study provides some evidence that DAPT may lead to a reduced stroke rate, particularly with TAVR.

A limitation of the neurologic substudy is that only 27% of the entire trial enrollment participated in it, reducing the statistical power of the dataset. With respect to the whole CoreValve Trial, medication use extending beyond the first several months postdischarge was not collected, and so the exact duration of DAPT in each arm is not known. Moreover, the medication data were based on case report forms, and thus were dependent on site-reporting accuracy. Thus, the points in the discussion pertain to a planned 3- to 6-month duration of DAPT in those patients who received TAVR.

CONCLUSIONS

The neurologic outcomes analyses of the CoreValve Trial and neurologic substudy show that the neurologist-adjudicated stroke rate is at least equivalent following either

TABLE 7. Medications for the TAVR and SAVR patients who experienced stroke within 3 months and 1 year postprocedure

Category	TAVR, % (n/N)	SAVR, % (n/N)	P value
TAVR (n = 21) and SAVR (n = 27) patients who experienced stroke within 3 months postprocedure			
DAPT at discharge	66.7 (14/21)	40.7 (11/27)	.0745
Anticoagulation at discharge	57.1 (12/21)	77.8 (21/27)	.1260
TAVR (n = 33) and SAVR (n = 42) patients who experienced stroke within 1 year postprocedure			
DAPT at discharge	75.8 (25/33)	35.7 (15/42)	.0006
Anticoagulation at discharge	63.6 (21/33)	76.2 (32/42)	.2359

TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; DAPT, dual antiplatelet therapy.

TABLE 8. Baseline clinical characteristics, comorbidity, disability, and frailty assessments at baseline for patients in the high-risk neurologic substudy

Characteristic	TAVR (n = 111)	SAVR (n = 88)	P value
Age, y, mean ± SD	82.3 ± 7.4	83.7 ± 7.3	.20
Male sex	55.0 (61/111)	59.1 (52/88)	.56
NYHA class III/IV	89.2 (99/111)	87.5 (77/88)	.71
STS score, %, mean ± SD	7.0 ± 3.0	7.4 ± 3.7	.31
Logistic EuroSCORE, %, mean ± SD	17.2 ± 13.8	18.6 ± 14.1	.49
Diabetes mellitus	35.1 (39/111)	36.4 (32/88)	.86
Controlled by insulin	9.0 (10/111)	11.4 (10/88)	.58
Peripheral vascular disease	43.5 (47/108)	48.3 (42/87)	.51
Atrial fibrillation/flutter	40.5 (45/111)	42.0 (37/88)	.83
Total NIHSS score			.55
0	84.2 (85/101)	80.8 (63/78)	
1-5	15.8 (16/101)	19.2 (15/78)	
6-10	0.0	0.0	
>10	0.0	0.0	
Previous stroke	17.1 (19/111)	14.8 (13/88)	.65
NIHSS score (for the previous stroke)			.64
0	72.2 (13/18)	63.6 (7/11)	
1-5	27.8 (5/18)	36.4 (4/11)	
6-10	0.0	0.0	
>10	0.0	0.0	
mRS score (for the previous stroke)			.25
0	50.0 (9/18)	66.7 (8/12)	
1	22.2 (4/18)	25.0 (3/12)	
2	16.7 (3/18)	8.3 (1/12)	
3	5.6 (1/18)	0.0	
4	5.6 (1/18)	0.0	
5	0.0	0.0	
Previous TIA	18.0 (20/111)	15.9 (14/88)	.69
Home oxygen	9.1 (10/110)	9.1 (8/88)	>.99
Charlson Comorbidity score ≥5	51.4 (57/111)	62.5 (55/88)	.11
Anemia	14.2 (15/106)	11.1 (9/81)	.54
Albumin <3.3 g/dL	10.1 (11/109)	13.3 (11/83)	.50
Unplanned weight loss	7.2 (8/111)	8.0 (7/88)	.84
5-meter gait speed >6 s	78.4 (80/102)	79.3 (65/82)	.89
Grip strength below threshold	63.6 (70/110)	66.7 (58/87)	.66
Falls in past 6 mo	20.7 (23/111)	20.5 (18/88)	.96
Wheelchair bound	1.8 (2/111)	3.4 (3/88)	.66
Does not live independently	3.6 (4/111)	8.0 (7/88)	.22
Katz Index of activities of daily living			
≥2 deficits	0.0	2.3 (2/88)	.19
MMSE score	26.7 ± 2.6 (110)	26.4 ± 2.8 (88)	.55
Normal (≥25)	78.2 (86/110)	75.0 (66/88)	.62

(Continued)

TABLE 8. Continued

Characteristic	TAVR (n = 111)	SAVR (n = 88)	P value
Mild (21-24)	18.2 (20/110)	21.6 (19/88)	
Moderate (10-20)	3.6 (4/110)	3.4 (3/88)	
Severe (<10)	0.0	0.0	

TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; SD, standard deviation; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; TIA, transient ischemic attack; MMSE, Mini-Mental Status Examination.

TAVR or SAVR, and that the extent of neurologic impairment caused by the strokes is also similar. These findings hold out to 2 years after aortic valve replacement, and are in contrast to previous reports of a higher stroke rate associated with TAVR compared with SAVR.^{23,30-32}

The mortality rate in stroke is very high by 2 years, and more than double after TAVR compared with SAVR (Figure 4, A); thus, clearly stroke remains an important problem with any aortic valve intervention. Focus should now shift toward improving methods that will further mitigate stroke risk, including the use of less traumatic, more easily maneuverable devices or of embolic debris filters that prevent or limit embolic phenomena. In addition, results of ongoing clinical trials aimed at identifying optimal antiplatelet/anticoagulation regimens after TAVR or for patients with atrial dysrhythmias or other indications for anticoagulation should be helpful. In light of recognized deficiencies in stroke prevention and detection, more rigorous and widespread adoption of neurologist-adjudicated stroke surveillance is warranted for all cardiovascular procedures.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: [http://www.jtcvsonline.org/article/S0022-5223\(16\)00433-5/addons](http://www.jtcvsonline.org/article/S0022-5223(16)00433-5/addons).

Conflict of Interest Statement

T.G.G., J.T.S., G.M.C., and N.S.K. have received institutional research grants from Medtronic but no personal income. D.H.A. has received institutional grants and institutional royalties for patents with Medtronic, and institutional royalties for patents with Edwards Lifesciences, and serves on a medical advisory board for

TABLE 9. Changes from baseline in neurologic assessment measures for patients in the neurologic substudy

Characteristic	TAVR	SAVR	P value
NIHSS			
Discharge			
Increased by ≥ 2 , % (n/N)	3.5 (3/85)	12.7 (8/63)	.05
Without neurologic event, n/N	0/3	5/8	
With neurologic event, n/N	3/3	3/8	
1 y			
Increased by ≥ 2 , % (n/N)	1.5 (1/65)	4.9 (2/41)	.56
Without neurologic event, n/N	0/1	0/2	
With neurologic event, n/N	1/1	2/2	
MMSE			
Discharge			
Decreased by >4 , % (n/N)	2.5 (2/79)	10.9 (6/55)	.06
Without neurologic event, n/N	0/2	4/6	
With neurologic event, n/N	2/2	2/6	
1 y			
Decreased by >4 , % (n/N)	8.1 (5/62)	2.5 (1/40)	.40
Without neurologic event, n/N	4/5	0/1	
With neurologic event, n/N	1/5	1/1	
New gait abnormality			
Discharge, % (n/N)	7.8 (6/77)	15.5 (9/58)	.16
Without neurologic event, n/N	5/6	7/9	
With neurologic event, n/N	1/6	2/9	
1 y, % (n/N)	6.8 (4/59)	7.7 (3/39)	>.99
Without neurologic event, n/N	3/4	3/3	
With neurologic event, n/N	1/4	0	
Weakness in left hand motor function			
Discharge, % (n/N)	7.2 (5/69)	6.5 (3/46)	>.99
Without neurologic event, n/N	5/5	3/3	
With neurologic event, n/N	0	0	
1 y, % (n/N)	0.0 (0/56)	5.7 (2/35)	.14
Without neurologic event, n/N	0	1/2	
With neurologic event, n/N	0	1/2	
Weakness in right hand motor function			
Discharge, % (n/N)	7.2 (5/69)	10.4 (5/48)	.74
Without neurologic event, n/N	3/5	5/5	
With neurologic event, n/N	2/5	0/5	
1 y, % (n/N)	0.0 (0/55)	5.4 (2/37)	.16
Without neurologic event, n/N	0	0/2	
With neurologic event, n/N	0	2/2	
Failed writing evaluation			
Discharge, % (n/N)	5.1 (4/79)	8.5 (5/59)	.50
Without neurologic event, n/N	3/4	4/5	
With neurologic event, n/N	1/4	1/5	
1 y			
Without neurologic event, n/N	1/1	3/4	.08
With neurologic event, n/N	0	1/4	
Failed drawing evaluation			
Discharge, % (n/N)	23.5 (12/51)	25.6 (10/39)	.82
Without neurologic event, n/N	10/12	8/10	
With neurologic event, n/N	2/12	2/10	
1 y, % (n/N)	10.9 (5/46)	11.1 (3/27)	>.99
Without neurologic event, n/N	5/5	1/3	
With neurologic event, n/N	0/5	2/3	

TAVR, Transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental Status Examination.

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Key Words: aortic stenosis, surgical aortic valve replacement, transcatheter aortic valve replacement, neurologic outcomes, stroke

Discussion

Dr J. Lawton (St Louis, Mo). Dr Gleason, excellent presentation, thank you for giving me your manuscript. I enjoyed reading it, and I enjoyed your presentation.

In this subgroup analysis of the CoreValve Pivotal Trial in 199 patients, first I have a couple of questions about how you did the trial. Were the patients randomized first, or was the iliofemoral access suitability determined first?

Dr Gleason (Pittsburgh, Pa). Thank you Dr Lawton. Access suitability was determined prior to randomization. As a point of clarity, if you're alluding to how the neuro substudy patients were chosen, this was dependent on whether a study site was participating in the neuro substudy. It was

not a requirement for a site to be in the neuro substudy to be in the overall trial, but it was mandatory for involvement and entry into the substudy to have a neurologist on site fully engaged in the trial. So for institutions that had a bona fide neurologist on the study, those were the centers that contributed to the neuro substudy.

Dr Lawton. And having said that, how do you define major stroke versus minor stroke? And encephalopathy, I take it, was a totally separate group?

Dr Gleason. That is correct. Encephalopathy was tabulated as a separate outcome; however, for the slides that you saw as "all stroke," encephalopathy was included. In other words, "all stroke" denotes major stroke, minor stroke, and encephalopathy. As far as definitions, we used VARC-1 definitions for minor and major for the Pivotal Trial and neuro substudies. VARC-1 defines minor as a Rankin score less than 2 and major greater than 2.

Dr Lawton. And for those of us who don't put in the CoreValve, could you perhaps contrast it to the previous studies comparing surgical AVR and transcatheter AVR in terms of differences in implantation in terms of blowing a balloon up, and also delivery size with respect to the risk of stroke and how you think this valve may be different?

Dr Gleason. That's a good question, and I can only give you my personal opinion on this point. We are an institution that uses several of the devices including the Sapien, and I would at this point argue that there is no difference in stroke risk; I think they are equivalent.

Not all, but most, of the patients in the High-Risk Pivotal Trial did get balloon valvuloplasty at the time of implant either prior to or after CoreValve deployment. Now, most groups, including our own do not do a predeployment valvuloplasty with the CoreValve device, and this may be one argument in favor of CoreValve for certain patients.

The short answer is that I suspect the stroke risks are equivalent.

Dr Lawton. And I appreciated the scatterplots of the strokes that occurred within 30 days versus over the 2-year period of your follow-up, and that raises the question of should we really be attributing strokes after 30 days to be related to the procedure? You demonstrated a very high risk of death in those patients that had stroke, and that could be a late stroke too. So should we include all those late strokes and attribute them to perhaps the valve, the implantation technique, or patient risk factors?

Dr Gleason. Frankly, I think all are relevant, but I also think it's important to continue to study the issue. I will point out that one of the interesting aspects about stroke adjudication and stroke reporting—it's striking, actually—is that there is likely widespread underreporting. The University of Pennsylvania group recently published a fairly comprehensive study of their own site that was NIH-sponsored and had a population of approximately 200 patients, who they followed prospectively with preoperative assessment for stroke. Every patient was adjudicated post-AVR by neurologists and by neuroimaging with MRIs. They showed that the STS-reported stroke rate in that group by that same site in the same patients using the retrospective methods of chart review from which the STS database is based was half the actual neurologist-adjudicated stroke rate.

So, in other words, when we use the STS database and claim that the stroke risk based on this dataset for an AVR is, say, 1% to 2%, this recent study clearly demonstrated that that's probably inaccurate, and this is largely due to this issue of nonneurologist and retrospectively adjudicated stroke.

Dr Lawton. And lastly, in those patients who are not suitable for the iliofemoral approach prior to randomization, those are clearly very high risk based on your data. Do you have any advice or tips for dealing with those patients, or are they just high-risk peripheral vascular disease patients for any cardiac surgery?

Dr Gleason. Well, it was an interesting finding that we did not expect. As you recall, the surgical patients, those treated surgically who had prohibitive iliofemoral disease, had a higher risk of stroke. Reconciling why this was the case is not entirely clear to me, because most of those patients were accessed either by direct aortic access or by subclavian, either of which could in theory portend a higher risk of stroke. So I don't really know why this occurred, but you may be correct, that bad iliofemoral disease is a marker for bad vascular disease throughout, and it is this fact that raised the stroke rate in the surgical AVR-treated group.

As far as advice, I think this is very much a changing game. With this study, I think we can move beyond tabulating what the risk is and move into an era focused on how we can prevent it. There are now deflection devices and filters that will likely be implemented in short order.

That's another question that we didn't quite address, but the conjecture is that most of these strokes are embolic, and thus perhaps a large percentage are preventable, particularly the early ones.

Dr Lawton. And the surgical patients included mini-access, total sternotomy, any type of surgical approach?

Dr Gleason. It was a mix, but the great majority were median sternotomy.