Stroke after Aortic Valve Surgery: Results from a Prospective Cohort

Running title: Messè et al.; Stroke after aortic valve surgery

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Journal Subject Codes: Cardiovascular (CV) surgery: [38] CV surgery: valvular disease, Stroke: [44] Acute cerebral infarction, Imaging of the brain and arteries: [58] Computerized tomography and magnetic resonance imaging

DOI: 10.1161/CIRCULATIONAHA.113.005084
Abstract

**Background**—The incidence and impact of clinical stroke and silent radiographic cerebral infarction complicating open surgical aortic valve replacement (AVR) are poorly characterized.

**Methods and Results**—We performed a prospective cohort study of subjects ≥ 65 years of age undergoing AVR for calcific aortic stenosis. Subjects were evaluated by neurologists pre-operatively and post-operatively, and underwent post-operative magnetic resonance imaging (MRI). Over a 4 year period, 196 subjects were enrolled at 2 sites. Mean age = 75.8 ± 6.2 years, 36% female, 6% non-white. Clinical strokes were detected in 17%, Transient Ischemic Attack in 2%, and in-hospital mortality was 5%. The frequency of stroke in the Society for Thoracic Surgery (STS) database in this cohort was 7%. Most strokes were mild; the median National Institutes of Health Stroke Scale (NIHSS) was 3 (interquartile range 1 – 9). Clinical stroke was associated with increased length of stay, median 12 vs 10 days, \( p = 0.02 \). Moderate or severe stroke (NIHSS ≥10) occurred in 8 (4%) and was strongly associated with in-hospital mortality, 38% vs 4%, \( p = 0.005 \). Of the 109 stroke-free subjects with post-operative MRI, silent infarct was identified in 59 (54%). Silent infarct was not associated with in-hospital mortality or increased length of stay.

**Conclusions**—Clinical stroke after AVR was more common than previously reported, more than double for this same cohort in the STS database, and silent cerebral infarctions were detected in over half of patients undergoing AVR. Clinical stroke complicating AVR is associated with increased length of stay and mortality.

**Key words:** stroke, aortic valve replacement, magnetic resonance imaging
Introduction

Calcific aortic valve stenosis is an increasingly common disorder due to the aging of the population and reduction in mortality from other causes such as coronary artery disease and cancer.\(^1\sim3\) The prevalence of moderate to severe aortic stenosis (AS) in patients \(\geq\) 75 years of age approaches 3\% and about half of those with severe AS are referred for replacement\(^3,\ 4\) Stroke is considered a rare but potentially devastating complication of surgical aortic valve replacement (AVR) with risk dependent on patient characteristics and concomitant procedures. Stroke rates after surgical AVR for AS have ranged widely, from 1\% to 10\%, although most series have reported rates at the lower end of this range.\(^5\sim10\) The rate of stroke associated with Transcatheter Aortic Valve Replacement (TAVR) is more than double that of surgical AVR.\(^11,\ 12\)

Studies of clinical stroke complicating cardiac surgeries, not specific to AVR, have reported increased duration and cost of hospitalization, dramatically elevated in-hospital mortality, and a high rate of severe disability in survivors.\(^7,\ 13,\ 14\) The reduction of neurologic complications of surgery has become a priority and several technological and therapeutic innovations have been proposed to reduce perioperative stroke. However, designing adequately powered, cost efficient studies of these interventions is challenging when an accurate assessment of the outcome has not been available.\(^15\sim18\) In addition, small studies of patients who undergo MRI post-cardiac surgery have reported a high rate of subclinical infarcts, although the incidence has varied as well and the short and long term implications of silent infarcts noted on MRI are unknown.\(^19\sim23\)

There are a number of reasons to believe that the risk for stroke due to AVR is likely higher in clinical practice than what has been reported in the literature. Most of the existing estimates of clinical stroke and radiographic infarct have come from single centers, clinical trials,
or self reported outcomes from large administrative databases. In general, complications tend to be greater in clinical practice compared to the carefully controlled clinical trial environment and tend to be underestimated in self-reported quality assurance databases. Most patients are not evaluated by neurologists, who are more sensitive to subtle but potentially meaningful findings. Finally, there is evidence that the rate of ischemic neurologic complications following surgery has been increasing recently, likely due to the willingness of surgeons to operate on higher risk patients. This study addresses these gaps in the current literature by characterizing the prevalence, predictors, and impact of clinical stroke and radiographic cerebral infarction complicating surgical AVR in a prospective cohort of patients with detailed and standardized assessments.

Methods
We performed a prospective observational cohort study of subjects ≥ 65 years-old undergoing open surgical aortic valve repair for calcific moderate-to-severe aortic stenosis at two hospitals within the University of Pennsylvania Health System (Hospital of the University of Pennsylvania and Penn Presbyterian Medical Center). The medical and surgical histories of all patients presenting for AVR were reviewed by study coordinators to determine eligibility. Subjects were excluded if they had undergone carotid stenting or carotid endarterectomy within the previous 6 weeks, had active major psychiatric disease, severe visual, auditory, or learning impairment, any MRI incompatibility, or any significant neurological disease, defined as incidence of stroke or TIA within the preceding 6 months, symptomatic or asymptomatic severe occlusive carotid disease requiring concomitant CEA/stenting, neurodegenerative or other progressive neurological disease, or history of significant head trauma followed by persistent neurologic
defaults or known structural brain abnormalities. A separate comparison cohort of age- and sex-matched patients with non-surgical aortic valve disease was also recruited to assess the cognitive impact of aortic valve surgery in this aged cohort and will be presented in a subsequent manuscript. The institutional review board at the University of Pennsylvania approved this study.

**Surgery**

The anesthetic, surgical, and perfusion management was dictated by the treating anesthesiologist and surgeon and the study provided no guidance or protocol to the clinical team. Nine surgeons participated. In all cases the aortic cannulation site was the ascending aorta. Epiaortic ultrasound was performed prior to cannulation in 83% of cases under the guidance of a cardiothoracic anesthesiologist and data were provided to the surgeon to guide cannulation and clamping and avoidance of mobile or protruding atheromatous plaques.

**Clinical outcomes**

Surgical patients underwent post-operative MRI, and were evaluated by neurologists pre-operatively and on post-operative days 1, 3, and 7. At each time point, subjects received complete neurological examinations including a National Institutes of Health Stroke Scale (NIHSS) score. The NIHSS is a validated tool used to quantify stroke severity across a variety of neurologic domains. An NIHSS of 0 indicates a normal, or near normal, evaluation and higher numbers indicate increasing impairment and severity. Early NIHSS after stroke is highly predictive of hospital disposition and long term stroke outcomes. Study neurologists were asked to determine if there was a change in exam from the prior evaluations and whether this change was due to suspected stroke. When a clinical stroke was suspected by the neurologist, the clinical team was alerted. If the clinical team suspected a neurologic event after day 7, the study coordinator was informed and the study neurologist evaluated the patient again. Possible strokes
were independently adjudicated by two vascular neurologists and discordances were resolved with consensus. Clinical stroke was defined as new focal neurologic symptoms lasting > 24 hours determined to be of vascular origin or symptoms lasting < 24 hours with radiographic evidence of infarction in the appropriate territory. TIA was defined as neurologic symptoms lasting < 24 hours and without evidence of infarction. Severe stroke was defined as NIHSS ≥ 10. Silent infarct was defined as imaging evidence of acute infarct without clinical symptoms reported by the patient or detected by the neurologist. Patient outcomes from this cohort recorded in the Society for Thoracic Surgery (STS) database were also assessed for comparison. Per institutional practice, patients are identified for inclusion in the STS database by staff review of admissions to CT surgery and the operating room schedule. Charts are then reviewed in detail by trained staff to abstract established data elements. The only neurologic complication included in the STS aortic valve dataset is "permanent stroke", defined as any confirmed neurological deficit of abrupt onset caused by a disturbance in cerebral blood supply) that did not resolve within 24 hours.

Magnetic Resonance Imaging

Subjects were imaged after the AVR procedure, with a target of postoperative day 5, on 1.5 Tesla Siemens Magnetom Avanto (Siemens, Erlangen, Germany) or GE Signa Excite (General Electric Medical Systems, Milwaukee, WI) MRI scanners. The MRI modalities of Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE, T1-weighted), T2-weighted, diffusion-weighted imaging (DWI), proton density-weighted (PD), and Fluid Attenuation Inversion Recovery (FLAIR) were acquired. All patients’ DICOM (Digital Imaging and Communications in Medicine) images were anonymized and converted to the Neuroimaging Informatics Technology Initiative (NIfTI) format. Imaging and image analysis was supervised by a
neuroradiologist (M.B.). Acute infarcts were determined by two independent trained readers who identified DWI hyperintensities and compared them to ADC maps and FLAIR images in order to exclude chronic lesions and false positives. Discrepancies were resolved by a third independent reader. Acute infarcts were then manually segmented using a viewing and segmenting tool (MRIcron) and the segmented lesions were saved as binary image datasets. Each dataset was then processed with a computer program written in Matlab R2012a (Mathworks, Inc) which identified DWI hyperintensities and compared them to ADC maps and FLAIR images in order to exclude chronic lesions and false positives. Discrepancies were resolved by a third independent reader. 

Statistics

Sample size calculations performed for this study assumed an expected rate of stroke of 10% and an incidence of infarct on MRI of 40%, resulting in a minimum of 7% precision (with 95% confidence) in the estimates of the actual incidence rates with 180 enrolled subjects. Descriptive statistics of the cohort, dichotomized by those who had stroke and those who did not, and clinical outcomes of interest with 95% confidence intervals were calculated. Predictors of clinical stroke were identified using t-test and chi-squared, or Wilcoxon ranked sum for non-parametric data, as appropriate. All probability values are 2-sided, with values of p<0.05 considered statistically significant. Missing variables were dropped from the analysis, and no imputation was performed. Factors potentially associated with stroke in univariate analysis (p<0.20) were evaluated in a step-wise multivariable logistic regression model forcing both age and gender into the final model in order to determine factors independently associated with clinical stroke. The impact of clinical stroke and silent infarct on length of stay and in-hospital mortality were evaluated using chi-squared, Fisher exact, and Wilcoxon rank sum. Interrater agreement on the number of infarcts identified on MRI was evaluated using quadratic- weighted kappa. The correlation
between MRI lesion volume and stroke severity was evaluated using Spearman correlation. Statistical analyses were performed using STATA 12 (College Station, TX)

Results

Post-operative Clinical Stroke Assessment

Over a period extending from April 2008 to September 2012, 721 potentially eligible patients were screened in the outpatient and inpatient setting and 196 enrolled subjects received AVR (57% at the Hospital of the University of Pennsylvania and 43% at Penn Presbyterian Medical Center). Figure 1 presents a diagram describing why screened patients were excluded from the trial. The average age of subjects enrolled was 75.8 ± 6.2 years, 36% were female, and 6% were non-white. Clinical strokes were identified in 34 (17%, 95% confidence interval [CI], 12 – 23%) subjects, TIA in 4 (2%, 95% CI, 0 – 4%), and in-hospital mortality occurred in 10 (5%, 95% CI, 2 – 8%) patients. The vast majority of clinical strokes were ischemic, only 2 subjects (6% of strokes, 1% overall) were found to have intracerebral hemorrhage on neuroimaging. Most strokes were mild; the median NIHSS was 3 (interquartile range [IQR] 1 – 9). Overall, 22 subjects had NIHSS < 5, 4 had NIHSS ranging from 5 - 9, 3 had NIHSS ranging from 10-15, and 5 had NIHSS > 15. There was no significant difference in clinical stroke rate between the two hospitals (p=0.51). Clinical strokes were most often identified early, 17 (58%) on post-operative day (POD) one, 7 (21%) on PODs two or three, 7 (21%) on PODs four through seven, and 3 (9%) beyond POD seven. Overall, clinical stroke was associated with an increased length of stay, median 12 vs 10 days, p=0.02 which remained significant after excluding subjects who died in the hospital, p=0.007. Overall, clinical stroke was not significantly associated with in-hospital mortality, 9% vs 4%, p=0.28. However, moderate-to-severe stroke (NIHSS≥10) which occurred
in 8 (4%), was strongly associated with in-hospital mortality 38% vs 4%, p =0.005.

**Table 1** presents the clinical and demographic characteristics of the overall cohort and in subjects dichotomized by whether a clinical stroke was detected or not. In univariate analysis, increased age, prior history of stroke or TIA, longer cardiopulmonary bypass (CPB) time and higher mean arterial pressure (MAP) nadir were associated with clinical stroke (p<0.05). In multivariable logistic regression modeling, older age (OR 1.07 per year, 95%CI 1.01 –1.15, p=0.031), increased duration of CPB (OR 1.13 per 10 minutes, 95% CI, 1.04 –1.22, p=0.005) and higher MAP nadir (OR 1.07 per mmHg, 95%CI 1.01 –1.13, p=0.019) were independently associated with increased odds of stroke.

**Comparison to STS Database**

Within this same cohort, the number of subjects with stroke reported in the Society for Thoracic Surgery (STS) database was 13 (6.6%). Nine of the strokes in the STS database were also documented in the DeNOVO database, while four were not. A subsequent review of these four cases found that one subject had had alcohol withdrawal and three had no clinical findings detected by the neurologist and no documented stroke symptoms beyond day 7 (two of these subjects had subclinical infarcts on MRI). Among the 25 subjects determined to have a stroke by the neurologist not reported in the STS database, 2 died in the hospital and 9 had their symptoms resolve by post-operative day 7. In general, subjects with stroke reported in the STS database tended to have more severe events compared to the events identified by a neurologist that were not captured in the STS database, median NIHSS 5 vs 1, p=0.04. **Figure 2** displays the distribution of NIHSS scores in patients with stroke reported in STS compared to those who were only noted in DeNOVO. In-hospital mortality rates were identical between DeNOVO and STS databases.
Post-operative brain MRI

Post-procedure in-hospital MRI was performed on 129 subjects (66%) which occurred on a median post-operative day 6 (interquartile range [IQR] 5-8). MRI adherence improved over time; 57% of the first 100 subjects and 75% of the last 96 subjects underwent in hospital postoperative MRI. Overall, DWI lesions were seen in 79 subjects (61%, 95% CI, 53 – 70%). The lesions tended to be small and multiple and the number of lesions per patient ranged from 0 – 34. The raters had excellent agreement in determining the number of infarcts present on each MRI with a weighted kappa of 0.99. The mean number of lesions per patient was 2.3 (SD 4.6) and the median was 1 (IQR 0-3). The total volume of DWI lesions ranged from 33 – 55,871 mm$^3$. Figure 3 displays the histogram of lesion volumes and Figure 4 provides examples of MRIs from patients with clinical strokes and clinically silent infarcts. Among the 20 subjects with clinical stroke who underwent MRI, diffusion infarct volume strongly correlated with severity based on NIHSS, rho=0.57, p=0.009. Patients with clinical stroke had significantly larger infarct volumes compared to those with clinically silent lesions, median 284 vs 552 mm$^3$, p=0.02. Of the 109 clinical stroke-free subjects with post-operative MRI, silent infarct was identified in an additional 59 (54%; 95% CI, 45 - 64%). No significant association was identified between clinically silent infarct and in-hospital mortality (p=0.33) or increased length of stay (p=0.99). Post-operative MRI was not obtained in 67 subjects due to medical instability (n=39), refusal (n=23), or time constraint (n=5). Table 2 presents the clinical, demographic, and operative characteristics of patients who did and did not receive MRI. In univariate analysis, prior stroke or TIA, history of CAD, higher severity of NYHA CHF classification, and longer duration of cardiopulmonary bypass were all associated with not obtaining an MRI. Of those without MRI, 14 (22%) had clinical strokes and 9 (14%) died. Failure to obtain an MRI was
strongly associated with in hospital mortality, 13% vs 1%, p<0.001. Among the 67 who did not receive an MRI, 26 did have a clinical head CT, of which 7 had possible or probable infarct noted on their radiology report.

Discussion

In this prospective cohort of older patients undergoing aortic valve replacement, clinical stroke was seen in one out of six subjects and subclinical infarct on neuroimaging was detected in over half of subjects. Both of these outcomes were considerably more common than has been previously described in the literature. Prior reports of stroke complicating AVR have varied widely, but generally are well below 10%. A meta-analysis of 48 observational studies including 13,216 subjects ≥ 80 years old who underwent isolated AVR reported that stroke occurred in 2.4%. A separate meta-analysis of 40 studies evaluating outcome from combined aortic valve and coronary artery bypass grafting (CABG) found a higher stroke rate of 3.7%. The STS national database reported a stroke rate of 1.5% from over 67,000 isolated AVR procedures and 2.7% from over 66,000 subjects who underwent AVR plus CABG. The highest risk of neurologic complications have been reported in subjects undergoing multivalve procedures with stroke occurring in up to 9.7% of subjects.

In our cohort, clinical stroke was associated with increased length of stay and moderate-to-severe stroke was strongly associated with mortality, increasing the likelihood of dying in the hospital by more than nine-fold. This result is consistent with prior studies of stroke following aortic valve disease, which have reported mortality rate increases of five- to ten-fold. Overall, the mortality rate in this cohort of patients compares favorably to prior studies of high risk patients. A meta-analysis of studies of isolated AVR procedures including over 13,000
patients over 80 years of age reported a postoperative mortality rate of 6.7% while a meta-analysis of almost 9,000 patients over 80 years of age undergoing AVR and CABG reported a mortality rate of 9.7%. The nationwide STS database has previously reported an in-hospital mortality rate of 6.4% from over 46,000 aortic valve replacements. More recent analyses of STS data from 2002 through 2006 reported a mortality rate of 3.2% for isolated AVR and 5.6% for AVR plus CABG. We found a mortality rate of 5% in our cohort where the median age exceeded 75 years, 8% received a concomitant mitral valve replacement, and 30% received concomitant CABG.

The only patient-level predictor of clinical stroke in this cohort was age, which is a well-established risk factor for neurologic ischemic complications of surgery. Two operative factors were also associated with stroke risk; duration of CPB and higher MAP nadir. Duration of CPB has been described previously as a risk factor for stroke. Lowest recorded MAP during the procedure was a pre-specified factor in our data analysis and we were surprised to see that higher values were independently associated with stroke risk as we had predicted the opposite might be true. Prior studies have reported the opposite finding. The explanation for our contradictory finding is unclear and likely clinically irrelevant given the small absolute difference in MAPs between groups.

Comparing the clinical stroke rate in the DeNOVO cohort to the local STS database revealed that many neurologic events were not recorded. This finding is at least partially explained by the fact that STS documents "permanent stroke" defined as symptoms lasting more than 24 hours and 9 of the subjects' symptoms had resolved by the final neurologic evaluation. Predictably, the strokes that were documented in the STS database tended to be more severe than the additional events that were identified by the neurologist. However, 16 clinical strokes missed
in STS had symptoms persist until they expired or through day 7 of the hospitalization and seven of these subjects had a recorded NIHSS ≥ 5, which generally implies a readily apparent and potentially disabling deficit. This finding highlights the importance of neurologist evaluations in accurately determining stroke incidence after procedures and the potential failings of self-reported quality databases.24, 26

A number of small cohorts have been published that have performed early post-operative MRI in subjects undergoing cardiac surgery.19-23 These studies all contained <50 subjects and many did not provide extensive information about the sizes and distribution of the DWI lesions. In these studies, the incidence of acute infarct on post-operative MRI ranged from 32 - 43%, lower than in our cohort. The reason for the higher rate of radiographic infarct in our cohort is uncertain but likely is related to our focus on older patients and the fact that many of these smaller studies included non-valve procedures, which appear to have a lower risk of emboli. Importantly, it is plausible that the ischemic burden in those subjects who were not able to obtain MRI post-procedure was high, since subjects who failed to get an MRI tended to be sicker with a high rate of clinical stroke and very high mortality. The impact of clinical stroke and silent infarcts upon post-operative cognitive decline remains unclear.19, 20, 41 Prospective serial assessments of long term cognitive function and quality of life are being assessed in controls and surgical patients in an ancillary component of this study.

The strengths of this study include prospective ascertainment of stroke incidence, pre-operative and serial post-operative evaluations by neurologists, assessments of stroke severity using validated scales, and independent adjudication of stroke outcomes. There are multiple limitations that also deserve mention. The subjects were recruited from two hospitals and represent a single academic health system experience. Thus, it is possible that this cohort reflects
a referral bias, with more complicated and higher risk patients than are typically seen in routine clinical practice. In addition, a meaningful portion of potentially eligible patients were unable or unwilling to participate, which also may limit generalizability. In spite of the fact that both hospitals are positioned within the West Philadelphia community which is predominantly African American, African Americans were not well represented in our study cohort. This was not likely a result of recruitment bias as the percentage of African Americans participating closely resembled the pool available and approached for participation. Out of the 714 eligible patients seen in the cardiac clinics at both study sites, 653 of the patients seen in clinic had a known race of which 94% were Caucasian and 6% were non-white. Despite improvement in MRI adherence over the course of the study, it could not be obtained in a sizable minority of subjects. The most common reason for inability to obtain an MRI was patient unwillingness or medical instability, and this is reflected in the higher number of clinical strokes and increased mortality among those who did not undergo MRI. The vast majority of subjects in this cohort received bioprosthetic valves, which is consistent with current recommendations for this age group.42, 43 The clinical and radiographic risk for neurologic injury complicating placement of a mechanical valve are uncertain. While it is unlikely that these risks would be lower, the existing literature suggests that they are likely similar.44 While prospectively acquired, the cohort is relatively small and is underpowered to study a broader array of potentially important risk factors for perioperative stroke. For example, concordant with prior studies from large databases, the point estimates suggest increased stroke risk in subjects undergoing concomitant CABG or mitral valve procedures, yet these did not reach significance in our cohort.6, 7, 9, 10 Finally, the study neurologists only performed evaluations through day 7 and it is possible that additional late neurologic complications were missed, although this is unlikely to be a large number of subjects
as the risk of stroke decreased as the time from the surgery increased up to the final neurologic evaluation on day 7.

Reducing neurologic complications of surgery has become a priority and several technological and therapeutic innovations have been proposed including prophylactic neuroprotection medication and embolic protection devices. Given the high incidence of clinical and radiographic neurologic injury, AVR is a potentially high yield setting in which to test interventions that aim to reduce ischemic burden. The implications of this study regarding transcutaneous aortic valve repair (TAVR) are uncertain. Devices for TAVR have been approved and are rapidly being adopted in clinical practice. Approval of these devices was based on randomized trials of high risk subjects requiring aortic valve replacement and these studies reported double the rate of acute stroke compared to open surgical AVR. Overall, the rates of stroke in both arms of these studies were lower than we identified in our surgical cohort and this is likely related to the fact that neurologists were not routinely involved in early assessments of subjects. Finally, intra-arterial embolectomy devices are now available that can be used in patients post-operatively to recanalize intracerebral occlusions with minimal or no adjunctive thrombolytic therapy, but time from stroke onset to intervention has the greatest impact on potential for good outcome. Thus, patients undergoing aortic valve replacement should receive frequent post-operative neurologic checks so that an intervention can be made as quickly as possible when a large stroke occurs.

Conclusions

Clinical stroke complicating AVR was more common than prior studies have suggested. Many of these strokes were mild, yet overall they were associated with increased length of stay, and
Moderate-to-severe stroke was associated with greater than a 9-fold increased mortality risk. This study also has demonstrated that MRI-identified infarct occurs in over half of patients without clinical evidence of stroke. While these subclinical central nervous system injuries are not associated with in-hospital outcomes, the long term implications remain to be determined. The DeNOVO study is continuing to follow subjects and will provide insight into the long term cognitive and quality of life sequelae of clinical and subclinical neurologic injury.

Acknowledgments: We wish to thank Abigail Lyon, BS, Sara Heverly-Fitt, BS, and Scott Welden for their contributions to study organization and execution.

Funding Sources: This study was supported by National Institutes of Health/National Heart Lung and Blood Institute Grant R01HL084375.

Conflict of Interest Disclosures: Dr. Messé has served as a consultant (modest) for Glaxo Smith Kline and is receiving salary support as co-PI of a study of neuroprotection in high risk thoracic aortic repair sponsored by Glaxo Smith Kline.

References:


26. Veen EJ, Janssen-Heijnen ML, Bosma E, de Jongh MA, Roukema JA. The accuracy of


Table 1. Demographic, clinical, and operative characteristics overall and by stroke status

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=196)</th>
<th>Stroke (n=34)</th>
<th>No stroke (n=162)</th>
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<td><strong>Clinical characteristics and demographics:</strong></td>
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<td>Age (years)</td>
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<td>78.0±6.1</td>
<td>75.3±6.1</td>
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<td>Female</td>
<td>71 (36.4)</td>
<td>16 (47.1)</td>
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<td>Non-white</td>
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<td>Hypertension</td>
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<td>30 (88.2)</td>
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<td>62 (31.6)</td>
<td>10 (29.4)</td>
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<td>9 (26.5)</td>
<td>58 (35.8)</td>
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<td>Prior stroke or TIA</td>
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<td>54 (27.6)</td>
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<td>54 (41.5)</td>
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<td>Left ventricular ejection fraction</td>
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<td>Mean aortic valve gradient (n=188)</td>
<td>45.7±15.8</td>
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<td>45.5±16.1</td>
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<td>Internal carotid artery stenosis*</td>
<td>28/155 (18)</td>
<td>3/26 (12)</td>
<td>25/129 (19)</td>
<td>0.34</td>
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<td><strong>Operative characteristics:</strong></td>
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<tr>
<td>Aortic atherosclerosis**</td>
<td>139/162 (86%)</td>
<td>25/29 (86%)</td>
<td>114/133 (86%)</td>
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<td>Bioprosthetic replacement valve</td>
<td>191 (97.5)</td>
<td>33 (97.1)</td>
<td>158 (97.5)</td>
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<tr>
<td>CPB time(minutes)</td>
<td>118±46</td>
<td>134±52</td>
<td>115±43</td>
<td>0.03</td>
</tr>
<tr>
<td>Concomitant MVR</td>
<td>15 (7.7)</td>
<td>4 (11.8)</td>
<td>11 (6.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>59 (30.1)</td>
<td>14 (41.2)</td>
<td>45 (27.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Lowest hematocrit on CPB</td>
<td>23.6±3.4</td>
<td>22.6±3.4</td>
<td>23.8±3.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Lowest MAP during procedure</td>
<td>52.5±9.2</td>
<td>55.4±7.9</td>
<td>51.9±9.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Post-operative atrial fibrillation</td>
<td>66 (33.7)</td>
<td>11 (32.4)</td>
<td>55 (34.0)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

* >50% internal carotid artery stenosis on Doppler ultrasound
** Evidence of any aortic atherosclerosis on intraoperative epiaortic ultrasound
**Table 2. Demographic, clinical, and operative characteristics by MRI**

<table>
<thead>
<tr>
<th>Clinical characteristics and demographics:</th>
<th>MRI (n=129)</th>
<th>No MRI (n=67)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75.3±6.0</td>
<td>76.7±6.4</td>
<td>0.19</td>
</tr>
<tr>
<td>Female</td>
<td>43 (33.6)</td>
<td>28 (41.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Non-white</td>
<td>9 (7.0)</td>
<td>2 (3.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Never</td>
<td>47 (36.7)</td>
<td>25 (38.4)</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>77 (60.1)</td>
<td>39 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>4 (3.1)</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>110 (85.3)</td>
<td>58 (86.6)</td>
<td>0.81</td>
</tr>
<tr>
<td>Diabetes</td>
<td>42 (32.6)</td>
<td>20 (29.9)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>113 (87.6)</td>
<td>59 (88.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>5 (3.9)</td>
<td>2 (3.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>43 (33.3)</td>
<td>24 (35.8)</td>
<td>0.73</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>12 (9.3)</td>
<td>13 (19.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>83 (64.3)</td>
<td>55 (82.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>31 (24.0)</td>
<td>23 (34.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>NYHA CHF classification</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Class I</td>
<td>4 (3.8)</td>
<td>1 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>61 (58.1)</td>
<td>20 (35.1)</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>35 (33.3)</td>
<td>33 (57.9)</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>5 (4.8)</td>
<td>3 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (n=193)</td>
<td>58.4±11.1</td>
<td>55.7±13.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean aortic valve gradient (n=188)</td>
<td>46.2±15.4</td>
<td>45.0±16.6</td>
<td>0.37</td>
</tr>
<tr>
<td>Internal carotid artery stenosis* (n=155)</td>
<td>20 (20.6)</td>
<td>8 (13.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Operative characteristics:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic atherosclerosis** (n=162)</td>
<td>86 (83%)</td>
<td>53 (91%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Bioprosthetic replacement valve</td>
<td>126 (97.7)</td>
<td>65 (97.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>CPB time (minutes)</td>
<td>113±44</td>
<td>129±47</td>
<td>0.01</td>
</tr>
<tr>
<td>Concomitant MVR</td>
<td>11 (9.0)</td>
<td>4 (6.0)</td>
<td>0.59</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>36 (27.9)</td>
<td>23 (34.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>Lowest hematocrit on CPB</td>
<td>23.9±3.5</td>
<td>23.4±3.2</td>
<td>0.49</td>
</tr>
<tr>
<td>Lowest MAP during procedure</td>
<td>53.1±9.2</td>
<td>51.3±9.2</td>
<td>0.10</td>
</tr>
<tr>
<td>Post-operative atrial fibrillation</td>
<td>43 (33.3)</td>
<td>23 (34.3)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

*50% internal carotid artery stenosis on Doppler ultrasound
**Evidence of any aortic atherosclerosis on intraoperative epiaortic ultrasound
Figure Legends:

**Figure 1.** A flow diagram of patients screened and enrolled in the study

**Figure 2.** Distribution of National Institutes of Stroke Scale (NIHSS) scores among patients with strokes reported in STS compared to those with strokes only in DeNOVO.

**Figure 3.** Distribution of total infarct volumes on MRI diffusion weighed imaging in mm$^3$, excluding those without infarct present.

**Figure 4.** Examples of infarcts on MRI. A. Patient with 14 clinically silent infarcts totaling 3292mm$^3$. B. Patient with 7 clinically silent infarcts totaling 2695mm$^3$ (DSHE image is moderate subcortical infarct). C. Patient with a clinical stroke (NIHSS 15) and 34 infarcts totaling 12,033mm$^3$. D. Patient with a clinical stroke (NIHSS 3) 6 small infarcts totaling 412mm$^3$. E. Patient with a single clinically silent infarct measuring 766mm$^3$. F. Patient with a clinical stroke (NIHSS 13) and 27 infarcts totaling 55,871mm$^3$. 

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Figure 1
Figure 2

No stroke in STS
n=25

Stroke in STS
n=9

NIHSS
- 0-4
- 5-9
- 10-14
- ≥15
Figure 3
Stroke after Aortic Valve Surgery: Results from a Prospective Cohort
for the Determining Neurologic Outcomes from Valve Operations (DeNOVO) investigators

Circulation. published online April 1, 2014;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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The Determining Neurologic Outcomes from Valve Operations (DeNOVO) investigators:

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