Stroke After Aortic Valve Surgery
Results From a Prospective Cohort

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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 who were undergoing AVR for calcific aortic stenosis. Subjects were evaluated by neurologists preoperatively and postoperatively and underwent postoperative magnetic resonance imaging. Over a 4-year period, 196 subjects were enrolled at 2 sites (mean age, 75.8±6.2 years; 36% women; 6% nonwhite). 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 database in this cohort was 7%. Most strokes were mild; the median National Institutes of Health Stroke Scale was 3 (interquartile range, 1–9). Clinical stroke was associated with increased length of stay (median, 12 versus 10 days; \(P=0.02\)). Moderate or severe stroke (National Institutes of Health Stroke Scale ≥10) occurred in 8% and was strongly associated with in-hospital mortality (38% versus 4%; \(P=0.005\)). Of the 109 stroke-free subjects with postoperative magnetic resonance imaging, 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 reported previously, more than double for this same cohort in the Society for Thoracic Surgery database, and silent cerebral infarctions were detected in more than half of the patients undergoing AVR. Clinical stroke complicating AVR is associated with increased length of stay and mortality.  

Key Words: aortic valve ■ magnetic resonance imaging ■ surgical procedures ■ stroke

Calcific aortic valve stenosis is an increasingly common disorder attributed to the aging of the population and reduction in mortality from other causes, such as coronary artery disease and cancer.1–3 The prevalence of moderate-to-severe aortic stenosis in patients ≥75 years of age approaches 3%, and approximately half of those with severe aortic stenosis are referred for replacement.4,5 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 aortic stenosis have ranged widely, from 1% to 10%, although most series have reported rates at the lower end of this range.5–10 The rate of stroke associated with transcatheter AVR is more than double that of surgical AVR.11,12

Studies of clinical stroke complicating cardiac surgeries that are 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 periprosthetic stroke. However, designing adequately powered, cost-efficient studies of these interventions is challenging when an accurate assessment of the outcome has not been available.15–18 In addition, small studies of patients who undergo magnetic resonance imaging (MRI) postcardiac 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.19–23 There are a number of reasons to believe that the risk for stroke attributed 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
with 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 after surgery has been increasing
recently, likely because of 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 of age who were undergoing open surgical aortic valve
repair for calcific moderate-to-severe aortic stenosis at 2 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 of the patients presenting
for AVR were reviewed by study coordinators to determine eligibil-
ity. 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 impair-
ment; had any MRI incompatibility or any significant neurological
disease, defined as incidence of stroke or transient ischemic attack
(TIA) within the preceding 6 months; had symptomatic or asympto-
matic severe occlusive carotid disease requiring concomitant carotid
endarterectomy/stenting; had neurodegenerative or other progressive
neurological disease; or had a history of significant head trauma fol-
lowed by persistent neurologic defaults or known structural brain
abnormalities. A separate comparison cohort of age- and sex-matched
patients with nonsurgical 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 article. 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 of the cases, the aortic cannulation site was the ascending aorta.
Epi-aortic ultrasound was performed before 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 for avoidance of mobile or protruding atheromatous plaques.

Clinical Outcomes
Surgical patients underwent postoperative MRI and were evaluated by
neurologists prospectively and on postoperative days 1, 3, and 7. At
each time point, subjects received complete neurologic 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 impair-
ment and severity. Early NIHSS after stroke is highly predictive of hos-
pital disposition and long-term stroke outcomes. Study neurologists
were asked to determine whether there was a change in examination
from the previous evaluations and whether this change was because of
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 2 vascular neurologists, and discordances
were resolved with consensus. Clinical stroke was defined as new focal
neurologic symptoms lasting >24 hours that were determined to be of
vascular origin or symptoms lasting <24 hours with radiographic evi-
dence of infarction in the appropriate territory. TIA was defined as neu-orologic 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 admis-
sions 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 data-
set is “permanent stroke,” defined as any confirmed neurologic 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 post-
operative day 5, on a 1.5-T Siemens Magnetom Avanto (Siemens,
Erlangen, Germany) or GE Signa Excite (General Electric Medical
Systems, Milwaukee, WI) MRI scanner. The MRI modalities of mag-
netization prepared rapid acquisition gradient echo (T1 weighted),
T2-weighted, diffusion-weighted imaging (DWI), proton density
weighted, and fluid attenuation inversion recovery were acquired.
All patient Digital Imaging and Communications in Medicine images
were anonymized and converted to the Neuroimaging Informatics
Technology Initiative format. Imaging and image analysis was super-
vised by a neuroradiologist (M.B.). Acute infarcts were determined
by 2 independent trained readers who identified DWI hypertensit-
ties and compared them with Apparent Diffusion Coefficient maps
and fluid attenuation inversion recovery images 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, University of South
Carolina, Columbia, SC), and the segmented lesions were saved as
binary image datasets. Each dataset was then processed with a com-
puter program written in Matlab R2012a (Mathworks, Inc, Natick,
MA), which recorded the number and the volume of lesions and
determined their laterality and location in the brain or cerebellum.

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 sub-
jects. Descriptive statistics of the cohort, dichotomized by those who
had stroke and those who did not, and clinical outcomes of inter-
est with 95% confidence intervals (CIs) were calculated. Predictors
of clinical stroke were identified using a t test and χ2, or Wilcoxon
ranked sum for nonparametric data, as appropriate. All of the P
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 stepwise
multivariable logistic regression model forcing both age and sex
into the final model 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
quadratic-weighted κ. The correlation between MRI lesion volume
and stroke severity was evaluated using a Spearman correlation.
Statistical analyses were performed using STATA 12 (StataCorp,
College Station, TX).
Results

Postoperative Clinical Stroke Assessment

Over a period extending from April 2008 to September 2012, 721 potentially eligible patients were screened in the outpatient and inpatient settings, 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 women, and 6% were nonwhite. Clinical strokes were identified in 34 subjects (17% [95% CI, 12% to 23%]), TIA in 4 (2% [95% CI, 0% to 4%]), and in-hospital mortality occurred in 10 patients (5% [95% CI, 2% to 8%]). The 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, 1–9). Overall, 22 subjects had NIHSS <5, 4 had NIHSS ranging from 5 to 9, 3 had NIHSS ranging from 10 to 15, and 5 had NIHSS >15. There was no significant difference in clinical stroke rate between the 2 hospitals (P=0.51). Clinical strokes were most often identified early, 17 (58%) on postoperative day (POD) 1, 7 (21%) on PODs 2 or 3, 7 (21%) on PODs 4 through 7, and 3 (9%) beyond POD 7. Overall, clinical stroke was associated with an increased length of stay (median, 12 versus 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% versus 4%; P=0.28). However, moderate-to-severe stroke (NIHSS ≥10), which occurred in 8 (4%), was strongly associated with in-hospital mortality (38% versus 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. In univariate analysis, increased age, previous 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 (odds ratio, 1.07 per year [95% CI, 1.01–1.15 per year]; P=0.031), increased duration of CPB (odds ratio, 1.13 per 10 minutes [95% CI, 1.04–1.22 per 10 minutes]; P=0.005), and higher MAP nadir (odds ratio, 1.07 per mmHg [95% CI, 1.01–1.13 per mmHg]; P=0.019) were independently associated with increased odds of stroke.

Comparison With STS Database

Within this same cohort, the number of subjects with stroke reported in the STS database was 13 (6.6%). Nine of the strokes in the STS database were also documented in the Determining Neurological Outcomes From Valve Operations (DeNOVO) database, whereas 4 were not. A subsequent review of these 4 cases found that 1 subject had had alcohol withdrawal, and 3 had no clinical findings detected by the neurologist and no documented stroke symptoms beyond day 7 (2 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 POD 7. In general, subjects with stroke reported in the STS database tended to have more severe events compared with the events identified by a neurologist that were not captured in the STS database (median NIHSS, 5 versus 1; P=0.04). Figure 2 displays the distribution of NIHSS scores in patients with stroke reported in STS compared with those who were only noted in DeNOVO. In-hospital mortality rates were identical between DeNOVO and STS databases.

Postoperative Brain MRI

Postprocedure in-hospital MRI was performed on 129 subjects (66%), which occurred on a median POD 6 (interquartile range, POD 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% to 70%]). The lesions tended to be small and multiple, and the number of lesions per patient ranged from 0 to 34. The raters had excellent agreement in determining the number of infarcts present on each MRI, with a weighted κ of 0.99. The mean number of lesions per patient was 2.3 (SD, 4.6) and the median was 1 (interquartile range, 0–3). The total volume of DWI lesions ranged from 33 to 55,871 mm³. Figure 3 displays the histogram of lesion volumes, and Figure 4 provides examples of MRIs from patients with clinical strokes and clinically silent lesions.
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 with those with clinically silent lesions (median, 284 versus 552 mm$^3$; $P=0.02$). Of the 109 clinical stroke-free subjects with postoperative MRI, silent infarct was identified in an additional 59 (54% [95% CI, 45% to 64%]). No significant association was identified between clinically silent infarct and in-hospital mortality ($P=0.33$) or increased length of stay ($P=0.99$). Postoperative MRI was not obtained in 67 subjects because of 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, previous stroke or TIA, history of coronary artery disease, higher severity of New York Heart Association congestive heart failure class, and TIA, transient ischemic attack.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=196)</th>
<th>Stroke (n=34)</th>
<th>No Stroke (n=162)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>75.8±6.2</td>
<td>78.0±6.1</td>
<td>75.3±6.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Women</td>
<td>71 (36.4)</td>
<td>16 (47.1)</td>
<td>55 (34.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>11 (5.6)</td>
<td>3 (8.8)</td>
<td>8 (4.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>Never</td>
<td>72 (37.3)</td>
<td>12 (36.4)</td>
<td>60 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>116 (60.1)</td>
<td>20 (60.0)</td>
<td>96 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>5 (2.6)</td>
<td>1 (3.0)</td>
<td>4 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>168 (85.7)</td>
<td>30 (88.2)</td>
<td>138 (85.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>62 (31.6)</td>
<td>10 (29.4)</td>
<td>52 (32.1)</td>
<td>0.76</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>172 (87.8)</td>
<td>31 (91.2)</td>
<td>141 (87.0)</td>
<td>0.77</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>7 (3.6)</td>
<td>2 (5.9)</td>
<td>5 (3.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>67 (34.2)</td>
<td>9 (26.5)</td>
<td>58 (35.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>Previous stroke or TIA</td>
<td>25 (12.8)</td>
<td>8 (23.5)</td>
<td>17 (10.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>138 (70.4)</td>
<td>25 (73.5)</td>
<td>113 (69.8)</td>
<td>0.66</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>54 (27.6)</td>
<td>11 (32.4)</td>
<td>43(26.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>NYHA CHF classification</td>
<td></td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>Class I</td>
<td>5 (3.1)</td>
<td>1 (3.1)</td>
<td>4 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>81 (50.0)</td>
<td>16 (50.0)</td>
<td>65 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>68 (42.0)</td>
<td>14 (43.8)</td>
<td>54 (41.5)</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>8 (4.9)</td>
<td>1 (3.1)</td>
<td>7 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>57.5±11.9</td>
<td>57.6±11.9</td>
<td>57.5±11.9</td>
<td>0.91</td>
</tr>
<tr>
<td>Mean aortic valve gradient (N=188)</td>
<td>45.7±15.8</td>
<td>47.1±14.4</td>
<td>45.5±16.1</td>
<td>0.41</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Operative characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic atherosclerosis†</td>
<td>139/162 (86%)</td>
<td>25/29 (86%)</td>
<td>114/133 (86%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Bioprosthetic replacement valve</td>
<td>191 (97.5)</td>
<td>33 (97.1)</td>
<td>158 (97.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>CPB time, min</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>Postoperative 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>

Data are mean±SD or n (%) unless otherwise specified. CABG indicates coronary artery bypass graft; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; MVR, mitral valve repair; NYHA CHF, New York Heart Association congestive heart failure; and TIA, transient ischemic attack.

*There was >50% internal carotid artery stenosis on Doppler ultrasound.
†Evidence of any aortic atherosclerosis was seen on intraoperative epiaortic ultrasound.
The STS national database reported a stroke rate of 1.5% from projects who underwent AVR plus CABG. The highest risks excluding those without infarct present. The Nationwide STS database has reported mortality rate increases of 5 to 10 fold. Overall, the mortality rate in this cohort of patients compares favorably with previous studies of patients at high risk. A 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 >67,000 isolated AVR procedures and 2.7% from >66,000 subjects who underwent AVR plus CABG. The highest risks of neurologic complications have been reported in subjects undergoing multivalue procedures, with stroke occurring in ≤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 >9-fold. This result is consistent with previous studies of stroke after aortic valve disease, which have reported mortality rate increases of 5 to 10 fold. Overall, the mortality rate in this cohort of patients compares favorably with previous studies of patients at high risk. A meta-analysis of studies of isolated AVR procedures including >13,000 patients >80 years of age reported a postoperative mortality rate of 6.7%, whereas a meta-analysis of >9,000 patients >80 years of age undergoing AVR and CABG reported a mortality rate of 9.7%. The Nationwide STS database has reported previously an in-hospital mortality rate of 6.4% from >46,000 AVR's. 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 prespecified factor in our data analysis, and we were surprised to see that higher values were independently associated with stroke risk, because we had predicted that the opposite might be true. Previous 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 with 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 >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 7 of these subjects had a recorded NIHSS ≥5, which generally implies a readily

Discussion

In this prospective cohort of older patients undergoing AVR, clinical stroke was seen in 1 of 6 subjects, and subclinical infarct on neuroimaging was detected in more than half of subjects. Both of these outcomes were considerably more common than has been described previously in the literature. Previous 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 >67,000 isolated AVR procedures and 2.7% from >66,000 subjects who underwent AVR plus CABG. The highest risks of neurologic complications have been reported in subjects undergoing multivalue procedures, with stroke occurring in ≤9.7% of subjects.

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Discussion

In this prospective cohort of older patients undergoing AVR, clinical stroke was seen in 1 of 6 subjects, and subclinical infarct on neuroimaging was detected in more than half of subjects. Both of these outcomes were considerably more common than has been described previously in the literature. Previous 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 >67,000 isolated AVR procedures and 2.7% from >66,000 subjects who underwent AVR plus CABG. The highest risks of neurologic complications have been reported in subjects undergoing multivalue procedures, with stroke occurring in ≤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 >9-fold. This result is consistent with previous studies of stroke after aortic valve disease, which have reported mortality rate increases of 5 to 10 fold. Overall, the mortality rate in this cohort of patients compares favorably with previous studies of patients at high risk. A meta-analysis of studies of isolated AVR procedures including >13,000 patients ≥80 years of age reported a postoperative mortality rate of 6.7%, whereas a meta-analysis of >9,000 patients ≥80 years of age undergoing AVR and CABG reported a mortality rate of 9.7%. The Nationwide STS database has reported previously an in-hospital mortality rate of 6.4% from >46,000 AVR’s. 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 prespecified factor in our data analysis, and we were surprised to see that higher values were independently associated with stroke risk, because we had predicted that the opposite might be true. Previous 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 with 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 >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 7 of these subjects had a recorded NIHSS ≥5, which generally implies a readily
Table 2. Demographic, Clinical, and Operative Characteristics by MRI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MRI (n=129)</th>
<th>No MRI (n=67)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Clinical characteristics and demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>75.3±6.0</td>
<td>76.7±6.4</td>
<td>0.19</td>
</tr>
<tr>
<td>Women</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>0.92</td>
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</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 mellitus</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>Previous 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>
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<td>NYHA CHF classification</td>
<td>0.02</td>
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<td></td>
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<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</td>
<td>58.4±11.1</td>
<td>55.7±13.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean aortic valve gradient</td>
<td>46.2±15.4</td>
<td>45.0±16.6</td>
<td>0.37</td>
</tr>
<tr>
<td>Internal carotid artery stenosis</td>
<td>20 (20.6)</td>
<td>8 (13.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Operative characteristics</td>
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<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, min</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±4.9</td>
<td>51.3±9.2</td>
<td>0.10</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation</td>
<td>43 (33.3)</td>
<td>23 (34.3)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Data are mean±SD or n (%) unless otherwise specified. CABG indicates coronary artery bypass graft; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; MVR, mitral valve repair; NYHA CHF, New York Heart Association congestive heart failure; and TIA, transient ischemic attack.

†Evidence of any aortic atherosclerosis was seen on intraoperative epi-aortic ultrasound.

The strengths of this study include prospective ascertainment of stroke incidence, preoperative and serial postoperative 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 2 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 black, blacks were not well represented in our study cohort. This was not likely a result of recruitment bias, because the percentage of blacks participating closely resembled the pool available and approached for participation. 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 white and 6% were nonwhite. 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 majority of subjects in this cohort received bioprosthetic valves, which is consistent with current recommendations for this age group. The clinical and radiographic risks for neurologic injury complicating placement of a mechanical valve are uncertain. Although it is unlikely that these risks would be lower, the existing literature suggests that they are likely similar. Although 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 previous 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. 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 include a large number of subjects, because the risk of stroke decreased as the time from the surgery increased up to the final neurologic evaluation on day 7.

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Data are mean±SD or n (%) unless otherwise specified. CABG indicates coronary artery bypass graft; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; MVR, mitral valve repair; NYHA CHF, New York Heart Association congestive heart failure; and TIA, transient ischemic attack.

†Evidence of any aortic atherosclerosis was seen on intraoperative epi-aortic ultrasound.

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.

A number of small cohorts have been published that have performed early postoperative MRI in subjects undergoing cardiac surgery. These studies all contained less than 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 postoperative MRI ranged from 32% to 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 postprocedure was high, because 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 on postoperative cognitive decline remains unclear. Prospective serial assessments of long-term cognitive function and quality of life are being assessed in control subjects and surgical patients in an ancillary component of this study.

The strengths of this study include prospective ascertainment of stroke incidence, preoperative and serial postoperative 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 2 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 black, blacks were not well represented in our study cohort. This was not likely a result of recruitment bias, because the percentage of blacks participating closely resembled the pool available and approached for participation. 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 white and 6% were nonwhite. 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 majority of subjects in this cohort received bioprosthetic valves, which is consistent with current recommendations for this age group. The clinical and radiographic risks for neurologic injury complicating placement of a mechanical valve are uncertain. Although it is unlikely that these risks would be lower, the existing literature suggests that they are likely similar. Although 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 previous 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. 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 include a large number of subjects, because 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.\textsuperscript{15,16,18,45} 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 transcatheter aortic valve repair (transcatheter AVR) are uncertain. Devices for transcatheter AVR 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 AVR, and these studies reported double the rate of acute stroke compared with open surgical AVR.\textsuperscript{11,12} Overall, the rates of stroke in both arms of these studies were lower than what 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 postoperatively 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 AVR should receive frequent postoperative neurologic checks so that an intervention can be made as quickly as possible when a large stroke occurs.

Clinical stroke complicating AVR was more common than previous 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 a >9-fold increased mortality risk. This study also has demonstrated that MRI-identified infarct occurs in more than half of patients without clinical evidence of stroke. Although 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.

Appendix

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

- Michael A. Acker, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Joseph E. Bavaria, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Thomas F. Floyd, MD (Department of Anesthesiology & Critical Care, State University of New York, Stony Brook, NY);
- Tania Giovanetti, PhD (Department of Psychology, Temple University, Philadelphia, PA);
- W. Clark Hargrove III, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Scott E. Kasner, MD (Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Steven R. Messé MD (Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA);
- William H. Matthai, Jr., MD (Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Emile R. Mohler III, MD (Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Rohinton J. Morris, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Alberto A. Pochettino, MD (Department of Surgery, Mayo Clinic, Rochester, MN);
- Catherine E. C. Price, PhD (Department of Clinical and Health Psychology, University of Florida, Gainesville, FL);
- Sarah J. Ratcliffe, PhD (Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Ola A. Selnes, PhD (Department of Neurology, Johns Hopkins University Hospital, Baltimore, MD);
- Wilson Y. Szeto, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Y. Joseph Woo, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Nimesh D. Desai, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA);
- John G. Augustides, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Albert T. Cheung, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- C. William Hanson, III, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Jiri Horak, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Benjamin A. Kohl, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Jeremy D. Kukafka, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Warren J. Levy, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Thomas A. Mickler, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Bonnie L. Milas, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Joseph S. Savino, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Albert T. Cheung, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Albert T. Cheung, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- William J. Vernick, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Joseph S. Savino, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA);
- Stuart J. Weiss, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA).

Acknowledgments

We thank Abigail Lyon, Sara Heverly-Fitt, Elizabeth Stambrook, and Scott Welden for their contributions to study organization and execution.

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Disclosures

Dr Messé has served as a consultant (modest) for Glaxo Smith Kline and is receiving salary support as coprincipal investigator of a study of neuroprotection in high-risk thoracic aortic repair sponsored by Glaxo Smith Kline. The other authors report no conflicts.
References


Clinical Perspective

The Determining Neurological Outcomes From Valve Operations study was a prospective observational study of 196 patients >65 years of age who underwent aortic valve replacement for calcific aortic stenosis at 2 hospitals. Standardized assessments were performed by neurologists before surgery and on postoperative days 1, 2, and 7, and a postoperative MRI was planned for each patient. Clinical strokes were detected in 17% and transient ischemic attack in 2%, and in-hospital mortality was 5%. The frequency of stroke in the Society for Thoracic Surgery database in this cohort was 7%. Clinical stroke was associated with increased length of stay (median, 12 versus 10 days; \( P=0.02 \)). Although most of these events were associated with mild deficits, moderate or severe stroke (National Institutes of Health Stroke Scale \( \geq 10 \)) occurred in 8 (4%) and was strongly associated with in-hospital mortality (38% versus 4%; \( P=0.005 \)). Magnetic resonance imaging was performed in 129 subjects on median postoperative day 6, and 59 (54%) of 109 clinically stroke-free subjects demonstrated silent infarct. Silent infarct was not associated with in-hospital mortality or increased length of stay. The results of this study suggest that both clinical stroke and silent ischemic neurologic injury after aortic valve replacement occurs with much greater frequency than has been appreciated previously. Overall, clinical stroke is associated with increased length of stay, and severe stroke is strongly associated with in-hospital mortality.
SUPPLEMENTAL MATERIAL

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

Michael A. Acker, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA); Joseph E. Bavaria, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA); Thomas F. Floyd, MD (Department of Anesthesiology & Critical Care, State University of New York, Stony Brook, NY); Tania Giovanetti, PhD (Department of Psychology, Temple University, Philadelphia, PA); W. Clark Hargrove III, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA); Scott E. Kasner, MD (Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA); Steven R. Messé MD (Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA); William H. Matthai, Jr., MD (Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA); Emile R. Mohler III, MD (Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA); Rohinton J. Morris, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA); Alberto A. Pochettino, MD (Department of Surgery, Mayo Clinic, Rochester, MN); Catherine E. C. Price, PhD (Department of Clinical and Health Psychology, University of Florida, Gainesville, FL); Sarah J. Ratcliffe, PhD (Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA); Ola A. Selnes, PhD (Department of Neurology, Johns Hopkins University Hospital, Baltimore, MD); Wilson Y. Szeto, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA); Y. Joseph Woo, MD (Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA); Nimesh D. Desai, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); John G. Augostides, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); Albert T. Cheung, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); C. William Hanson, III, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); Jiri Horak, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); Benjamin A. Kohl, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); Jeremy D. Kukafka, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); Warren J. Levy, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); Thomas A. Mickler, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); Bonnie L. Milas, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); Joseph S. Savino, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); William J. Vernick, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA); and Stuart J. Weiss, MD (Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA)