Stroke in Patients With Aortic Stenosis

The Simvastatin and Ezetimibe in Aortic Stenosis Study

Anders M. Greve, MD, PhD; Morten Dalsgaard, MD, PhD; Casper N. Bang, MD, PhD; Kenneth Egstrup, MD; Simon Ray, MD; Kurt Boman, MD; Anne B. Rossebø, MD; Christa Gohlke-Baerwolf, MD; Richard B. Devereux, MD; Lars Køber, MD; Kristian Wachtell, MD, PhD

Background and Purpose—There are limited data on risk stratification of stroke in aortic stenosis. This study examined predictors of stroke in aortic stenosis, the prognostic implications of stroke, and how aortic valve replacement (AVR) with or without concomitant coronary artery bypass grafting influenced the predicted outcomes.

Methods—Patients with mild-to-moderate aortic stenosis enrolled in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Diabetes mellitus, known atherosclerotic disease, and oral anticoagulation were exclusion criteria. Ischemic stroke was the primary end point, and poststroke survival a secondary outcome. Cox models treating AVR as a time-varying covariate were adjusted for atrial fibrillation and congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years and female sex (CHA2DS2-VASc) scores.

Results—One thousand five hundred nine patients were followed for 4.3±0.8 years (6529 patient-years). Rates of stroke were 5.6 versus 21.8 per 1000 patient-years pre- and post-AVR; 429 (28%) underwent AVR and 139 (9%) died. Atrial fibrillation (hazard ratio [HR], 2.7; 95% confidence interval [CI], 1.1–6.6), CHA2DS2-VASc score (HR 1.4 per unit; 95% CI, 1.1–1.8), diastolic blood pressure (HR, 1.4 per 10 mm Hg; 95% CI, 1.1–1.8), and AVR with concomitant coronary artery bypass grafting (HR, 3.2; 95% CI, 1.4–7.2, all P≤0.026) were independently associated with stroke. Incident stroke predicted death (HR, 8.1; 95% CI, 4.7–14.0; P<0.001).

Conclusions—In patients with aortic stenosis not prescribed oral anticoagulation, atrial fibrillation, AVR with concomitant coronary artery bypass grafting, and CHA2DS2-VASc score were the major predictors of stroke. Incident stroke was strongly associated with mortality.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00092677.


Key Words: aortic valve stenosis □ cardiac surgical procedures □ risk factors □ stroke

The most recent US and European guidelines for treatment of valvular heart disease recommend oral anticoagulation (OAC) for stroke prophylaxis in all patients with aortic stenosis (AS) complicated by atrial fibrillation (AF).1–3 This recommendation differs from nonvalvular AF, where the decision to start OAC is guided by the CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years and female sex) risk scheme.4 The guideline discrepancy is based on observational studies indicating that calcific AS is an independent risk factor for stroke,4 which may predict stroke even in the absence of AF.5 However, limited evidence exists on the effectiveness of the CHA2DS2-VASc scores in AS populations, and particularly in less severe AS where data are equivocal with regards to an increased stroke risk per se.6

We hypothesized that calcific AS is associated with the same pathobiology underlying an increase in the CHA2DS2-VASc score and that the latter, therefore, could be particularly useful for stratifying risk of stroke in earlier stages of AS. This study was, therefore, undertaken to examine the ability of the CHA2DS2-VASc score to predict ischemic stroke in asymptomatic patients with AS with and without coexisting AF. Because risk of new-onset AF and thromboembolism may differ substantially in relation to aortic valve replacement (AVR) with or without coronary artery bypass grafting (CABG), the primary study hypothesis was stratified by AVR with and

DOI: 10.1161/STROKEAHA.114.005296

© 2014 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

1939
without concomitant CABG. A secondary end point was the effect of incident stroke on subsequent all-cause mortality in the operated and nonoperated patients, respectively. Thus, this study examined rates, predictors, and prognostic implications of ischemic stroke before and after AVR during extended follow-up in initially low-risk patients with asymptomatic AS not receiving OAC.

Methods

Study Settings

The study cohort consisted of participants in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study, a multicenter, randomized, double-blind, placebo-controlled study, investigating whether intensive lipid lowering with simvastatin/ezetimibe combination versus placebo could reduce the need for AVR and risk of cardiovascular morbidity and mortality in 1873 patients. Inclusion criteria were age 45 to 85 years, asymptomatic mild-moderate AS (defined by the European Society of Cardiology guidelines as echocardiographic aortic valve thickening accompanied by Doppler-measured aortic peak flow velocity 22.5 and ≤4.0 m/s), and normal left ventricular (LV) systolic function. The most important exclusion criteria were systolic heart failure, diabetes mellitus, and clinically apparent vascular atherosclerosis. The main outcome including other specifics about study design, organization, and clinical measures has been published.14

Design and Study Population

This study uses post hoc analysis of prospectively collected data from all patients with AF status documented by systematically read baseline ECGs (n=1563) in the SEAS study to examine predictors and prognostic implications of ischemic stroke before and after AVR in initially asymptomatic patients with mild-to-moderate baseline AS not receiving OAC (Figure I in the online-only Data Supplement). Because of exclusion of diabetes mellitus, established vascular atherosclerosis, and heart failure, a CHA2DS2-VASC score of 4 was by default the highest value (concomitant hypertension, age ≥75 years and female sex). Informed consent was obtained from each patient, and the SEAS study protocol, covering also this study subset, conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the participating countries’ human research ethics committees.

Electrocardiography

ECG study protocol reading procedures and reproducibility have been published.1 In short, ECGs were recorded at the local study centers at a paper speed of 25 or 50 mm/s, after which they were sent to the SEAS electrocardiographic core lab at Rigshospitalet, Copenhagen, Denmark. AF (paroxysmal, persistent, or permanent), defined by the standard ECG criteria (Minnesota code 8-3), was determined by a physician blinded to the randomization and all clinical data.10

Echocardiography

Echocardiographic study protocol, reading procedures, and reproducibility have been published.11 In short, transthoracic echocardiograms were read blinded at the SEAS echocardiography core laboratory located at Haukeland University Hospital in Bergen, Norway. Aortic valve area was calculated by the continuity equation,2 in accordance with recent recommendations,12 averaged over 10 consecutive beats in patients with AF. LV dimensions and wall thicknesses were measured on 2-dimensional images following the American Society of Echocardiography guidelines, and LV mass calculated using an anatomically validated formula.13-14 Left atrial volumes were measured in LV end diastole and end systole by the modified Simpson mono-plane method in the apical 4-chamber view.15 Mitral regurgitation was assessed by color Doppler using the previously described 4-point grading scale, grade ≥2 corresponding to a moderate-to-severe mitral regurgitation.16

Stroke Definitions

Ischemic stroke before and after AVR was classified by an independent End point Committee, according to an end point manual pre-specified by the SEAS Steering Committee. Diagnosis of stroke required evidence of a neurological deficit, usually localized, lasting ≥24 hours or until death (if death occurred <24 hours after onset of neurological symptoms) and confirmation by diagnostic testing (eg, computed tomography or MRI). The clinical characteristics of stroke included the sudden onset of a deficit typically manifested as reduced consciousness, disturbed vision, paresis or paralysis of ≥1 extremities, sensory impairment, speech impairment, central cranial nerve dysfunction, memory defect, ataxia, and movement disorder. Strokes that fulfilled the above clinical criteria were classified as ischemic unless the stroke was clearly hemorrhagic judged by a cranial computed tomography, MRI, and blood in spinal fluid. Hemorrhagic strokes were not included in this study’s end point.

Statistical Analysis

Data were analyzed using the Statistical Analytical Software version 9.2 (SAS, Cary, NC). Continuous data are expressed as means±SD and categorical variables as proportions. Differences in discrete and continuous variables were evaluated by χ2, Fisher exact, Wilcoxon, and the Student t tests as appropriate. To isolate the predictive values of echocardiographic and clinical covariates for ischemic stroke, patients receiving OAC (n=54, of which 85% [n=46] were diagnosed with AF) were excluded (Figure I in the online-only Data Supplement). Baseline variables differing (P<0.10) between patients experiencing versus remaining free from incident ischemic stroke (CHA2DS2-VASC, body mass index, diastolic blood pressure, AF, diuretics, β-blockade, and aortic valve area index) were entered into univariate Cox regression models. Randomized treatment and LV ejection fraction were forced covariates in univariate Cox models because of clinical trial design of SEAS and importance of LV systolic function for clinical evaluation of need for AVR. Variables relating to incident stroke in the univariate Cox analyses were examined in multivariable Cox models using forward selection to eliminate nonsignificant variables. Three separate Cox proportional hazard models were used to identify the independent predictors of stroke with respect to AVR. The first model censored patients at the time of AVR provided that no stroke had occurred before the procedure. The second model assessed all strokes by including AVR as a time-dependent covariate.11 To account for perioperative strokes that may have resulted from intraoperative dislodgment of intra-aortic atheromas or of left atrial appendage thrombi, time-dependent analyses were performed with and without strokes <24 hours after AVR (n=4). A third exploratory model assessed strokes >24 hours after AVR. To evaluate if the results after AVR were sensitive to competing risks, the latter model was supplemented by an additional analysis examining the first of ischemic stroke or death after AVR. Results are given as cause-specific hazard ratios (HR) with 95% confidence intervals (CI). Time-varying modified Kaplan–Meier curves taking into account the multistate effect, that is, avoiding that the same subject appears in 2 separate survival curves at the same time point, were used to depict rates of ischemic stroke before and after AVR.17 The cumulative hazard estimate of incident stroke after AVR was calculated from the time of the first postoperative stroke (10 months after enrollment, the first patient underwent AVR after 28 days after inclusion in the SEAS trial). Outcome analyses could not be related to the presence or absence of postoperative AF because ECGs were recorded annually and no reliable estimation of perioperative AF was, therefore, available. Linear and proportional hazard assumptions were investigated by cumulative Martingale residuals (10000 random resamplings were compared with the models functional form). All covariates aside from left atrial volumes fulfilled assumptions for Cox modeling. As such, left atrial volumes were entered into the Cox model on the log2-scale (log2-scale) was chosen because an increase of 1 on the log2-scale corresponds to a doubling in left atrial volumes on the original scale and because...
log-transformation fulfilled the linear assumption). To account for the correlated prognostic information contained in left atrial volumes and AF, survival analyses using left atrial volumes were stratified by AF status. Differences in 30-day and 1-year mortality after in-study stroke were evaluated by Fisher exact test. The performance of the independent predictors of stroke in the Cox models stratified by AVR was evaluated by changes in the c-index (using the macro SURVCSTD; http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros) as described by Cook. For all hypothesis testing, a 2-tailed \( P < 0.05 \) was required for statistical significance.

### Results

Baseline ECG data and thus AF status were available in 1563 patients (83%). Age, sex, and AS severity were not statistically different in those with and without ECG data (all \( P > 0.288 \)). Excluding those prescribed OAC, 1509 patients remained in this study (Figure I in the online-only Data Supplement). The study population consisted of 923 men (61%) and 586 women (39%) followed for a mean of 4.3 years, totaling 6529 patient-years of follow-up. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=1509)</th>
<th>No Stroke (n=1467)</th>
<th>Stroke (n=42)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.3±9.7</td>
<td>67.2±9.7</td>
<td>71.0±9.5</td>
<td>0.012</td>
</tr>
<tr>
<td>Current or ex-smokers, n (%)</td>
<td>833 (55.2)</td>
<td>811 (55.3)</td>
<td>22 (52.4)</td>
<td>0.709</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.0±4.3</td>
<td>26.9±4.3</td>
<td>28.6±5.0</td>
<td>0.015</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>145.2±20.3</td>
<td>145.1±20.3</td>
<td>149.0±17.2</td>
<td>0.217</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>82.1±10.5</td>
<td>82.0±10.5</td>
<td>85.6±10.6</td>
<td>0.031</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.56±0.88</td>
<td>3.56±0.89</td>
<td>3.69±0.86</td>
<td>0.357</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.51±0.43</td>
<td>1.51±0.43</td>
<td>1.47±0.32</td>
<td>0.385</td>
</tr>
<tr>
<td>Estimated GFR, mL/min per 1.73 m²</td>
<td>68.3±12.1</td>
<td>67.9±12.9</td>
<td>68.3±12.1</td>
<td>0.822</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, mU/L</td>
<td>1.87±1.21</td>
<td>1.87±1.21</td>
<td>1.82±1.05</td>
<td>0.785</td>
</tr>
<tr>
<td>Baseline atrial fibrillation, n (%)</td>
<td>96 (6.4)</td>
<td>90 (6.1)</td>
<td>6 (14.3)</td>
<td>0.046</td>
</tr>
<tr>
<td>Left bundle branch block, n (%)</td>
<td>42 (2.8)</td>
<td>41 (2.8)</td>
<td>1 (2.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>64.9±11.0</td>
<td>64.9±11.0</td>
<td>66.9±12.8</td>
<td>0.241</td>
</tr>
<tr>
<td>CHA2DS2-VASc (score)</td>
<td>1.8±1.2</td>
<td>1.8±1.2</td>
<td>2.1±1.3</td>
<td>0.066</td>
</tr>
<tr>
<td>Baseline hypertension, n (%)</td>
<td>784 (52.0)</td>
<td>759 (51.7)</td>
<td>25 (59.5)</td>
<td>0.319</td>
</tr>
<tr>
<td>Age 65–74 y, n (%)</td>
<td>566 (37.5)</td>
<td>548 (50.4)</td>
<td>18 (75.0)</td>
<td>0.017</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>586 (38.8)</td>
<td>572 (39.0)</td>
<td>14 (33.3)</td>
<td>0.458</td>
</tr>
</tbody>
</table>

**Echocardiographic parameters**

- Peak aortic jet velocity, m/s: 3.0±0.55
- Aortic valve area index, cm²/m²: 0.61±0.19
- Mean gradient, mmHg: 22.7±8.7
- Bicuspid aortic valve, n (%): 67 (5.5)
- Aortic regurgitation grade ≥2, n (%): 226 (16.6)
- Mitral regurgitation grade ≥2, n (%): 147 (10.6)
- LA systolic volume index, mL/m²: 35.8±16.4
- LA diastolic volume index, mL/m²: 18.9±11.9
- LV mass index, g/m²: 99.9±30.5
- LV ejection fraction, %: 65.9±8.2
- Stroke volume index, mL/m²: 5.3±6.3
- Cardiac index, L/min per m²: 2.65±0.75

**Medicine**

- Simvastatin/ezetimibe, n (%): 755 (50.3)
- Aspirin, n (%): 289 (19.2)
- Diuretics, n (%): 689 (45.7)
- β-Blockade, n (%): 749 (49.6)
- Renin–angiotensin system blocker, n (%): 619 (41.0)

CHA2DS2-VASc indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years and female sex; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LA, left atrial; LDL, low-density lipoprotein; and LV, left ventricular.

*Defined as continuous prescription during the course of the study.
Entire Follow-Up and Pre-AVR Strokes

A total of 47 (3%) strokes occurred, 42 (3%) patients had ischemic strokes, of which 10% had a fatal outcome, incident AF was detected in 84 (6%) patients without baseline AF, a total of 139 (9%) died, and 429 (28%) underwent A VR, of which 30% (n=129) had A VR combined with CABG (Figure I in the online-only Data Supplement). Of the 42 ischemic strokes, 62% (n=26) occurred before A VR, which translated to 5.6 versus 21.8 strokes per 1000 patient-years pre- and post-A VR (P<0.001), respectively.

All-cause mortality also tended to be higher after A VR than in nonoperated patients, although this difference did not reach statistical significance (HR, 1.5; 95% CI, 1.0–2.3; P=0.072). Of the 110 deaths in nonoperated patients, only 7% (n=8) occurred in individuals with previous stroke. In contrast, of the 29 deaths that occurred after A VR, 24% (n=7) had previous stroke of which 86% (n=6) were post-AVR strokes. Although there were few events, this translated to a tendency to increased 30-day and 1-year mortality rates in patients experiencing post-AVR stroke (30-day mortality: 22% and 1-year mortality: 36%) compared with that observed after stroke in nonoperated patients (30-day mortality: 5% and 1-year mortality: 22%, both P≥0.150 in comparison of all-cause mortality after stroke in operated and nonoperated). Combining data from operated and nonoperated patients, in-study stroke was associated with 8.1-fold (95% CI, 4.7–14.0; P<0.001) greater risk of death in the study period. When excluding patients with perioperative strokes (<24 hours after A VR, n=4), predictors of ischemic stroke stratified by A VR are given in Tables 2 to 4. There was no detectable effect of randomized treatment on the observed stroke rates before (HR, 0.7; 95% CI, 0.4–1.3) or after A VR (HR, 0.6; 95% CI, 0.2–1.7; both P≥0.326; Tables 3–4).

Important, increased body mass index (HR, 1.1; 95% CI, 1.0–1.2) and age ≥75 years (HR, 4.5; 95% CI, 1.6–12.6; both P≤0.004) were the only multivariable predictor of ischemic stroke before A VR. Adding strokes that occurred ≥24 hours after A VR CHA2DS2-VASc score (HR, 1.4; 95% CI, 1.0–1.8), greater diastolic blood pressure (HR, 1.4 per 10 mm Hg; 95% CI, 1.1–1.8), preoperative AF (HR, 2.7; 95% CI, 1.1–6.5), and AVR in itself (HR, 5.4; 95% CI, 2.5–11.8; all P≤0.026) remained as independent predictors of ischemic stroke. The latter seemed to be driven by a markedly elevated relative risk of stroke in patients undergoing AVR combined with CABG (HR, 3.2; 95% CI, 1.4–7.2; P=0.006;
Table 2). In a separate analysis adding perioperative strokes (<24 hours after AVR [n=4]), the HR for stroke after AVR was even further substantiated (HR, 6.7; 95% CI, 3.3–13.6; P<0.001). Including perioperative strokes increased relative risks of stroke 4.4-fold (95% CI, 2.1–9.2; P<0.001) in patients undergoing AVR with simultaneous CABG and increased the trend in patients undergoing isolated AVR (HR, 1.9; 95% CI, 0.9–4.0; P=0.089). c-Index analyses demonstrated intermediate prediction of incident stroke (c-index 0.71) and pointed toward AVR as a major risk factor for ischemic stroke in this population (Table 5).

Strokes Post-AVR

Incidence of stroke post-AVR was mainly driven by strokes occurring >24 hours after the procedure (Figure), although 75% (n=12) of post-AVR strokes occurred within a week of surgery (median time to post-AVR stroke was 3 days with interquartile ranges 0.5–49.5 days). Restricting the survival analyses to post-AVR follow-up in-study stroke was associated with an 11.3-fold (95% CI, 4.5–28.6; P<0.001) greater risk of in-study death in patients undergoing isolated AVR (HR, 1.9; 95% CI, 0.9–4.0; P=0.089). c-Index analyses demonstrated intermediate prediction of incident stroke (c-index 0.71) and pointed toward AVR as a major risk factor for ischemic stroke in this population (Table 5).

Discussion

This study is, to the best of our knowledge, the first to examine independent predictors of ischemic stroke in initially asymptomatic mild-to-moderate AS. Several new findings add to current knowledge. First, in patients with AS with low risk of thromboembolism not prescribed OAC, components of the CHA2DS2-VASc scoring system were applicable for anticipating the risk of ischemic stroke irrespective of AF status. Second, AVR combined with CABG was independently associated with marked risks of peri- and postoperative ischemic stroke, which translated to reduced long-term survival. Third, the predictive information of left atrial volume of incident stroke was contained in AF status. Finally, randomized treatment with 40 mg of simvastatin and 10 mg of ezetimibe versus placebo did not lower the risk of stroke before or after AVR.

The observed higher incidence of all-cause mortality after stroke in post-AVR patients argues that aside from disabling
the patient postoperative stroke is also indicative of impaired long-term survival (36% died within the first year of follow-up). Recent data have suggested comparable or higher risk of stroke after transcatheter AVR compared with conventional AVR.20–23 This is concerning in the context of observational studies demonstrating an incidence of cerebrovascular lesions, as detected by MRI, of >70% after transcatheter AVR.24 Prevention of ischemic stroke is, therefore, of key importance for continued safe expansion of transcatheter AVR and conventional AVR. In long-term follow-up of 1014 patients, referred for AVR with a stentless valve, predictors of cerebrovascular events were individual risk factors and not the type of valve prosthesis in itself.25 This corresponds well with comparable occurrence of thromboembolism in randomized comparisons of bioprosthetic versus mechanical valves and suggests that comorbidities rather than intraoperative technique are the main predictors of stroke on the population level.26,27

The fact that CHA2DS2-VASc scores worked in this asymptomatic AS population with a low detected prevalence of AF concurs with data from the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) registry, suggesting that CHA2DS2-VASc scores relate to stroke also in valvular AF28 and recent studies demonstrating the ability of CHA2DS2-VASc to predict outcome also in patients without AF.29 Careful patient selection for AVR and transcatheter AVR and appropriate anticoagulation, that is, for AF status, CHA2DS2-VASc score, and presence of additional coronary artery disease, therefore seem to be the modifiable risk factors for stroke prevention in AS, which may translate to improved post-AVR survival.30 This hypothesis is further supported by reduced risk of stroke in (1) low-risk patients with AS with sinus rhythm,31 (2) sufficiently anticoagulated post-AVR patients,21 and (3) no detectable effect of intensive lipid-lowering in this study.

The fact that AVR combined with CABG was independently associated with a marked increase in the risk of stroke argues that procedure-related factors are separately predictive

---

### Table 4. Hazard Ratios for First-Ever Stroke in Patients After AVR: During 4.3 Years of Follow-Up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Post-AVR HR Univariate Stroke (95% CI)</th>
<th>P Value</th>
<th>Post-AVR HR Univariate Stroke/Death (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA2DS2-VASc (per 1 increase)</td>
<td>1.5 (1.0–2.2)</td>
<td>0.078</td>
<td>1.4 (1.1–1.9)</td>
<td>0.014</td>
</tr>
<tr>
<td>Baseline hypertension</td>
<td>2.5 (0.9–7.1)</td>
<td>0.096</td>
<td>1.9 (1.0–3.7)</td>
<td>0.050</td>
</tr>
<tr>
<td>Age 65–74 y</td>
<td>11.6 (1.5–90.0)</td>
<td>0.019</td>
<td>2.2 (0.9–5.5)</td>
<td>0.076</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>7.9 (0.9–70.4)</td>
<td>0.065</td>
<td>4.8 (2.0–11.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.8 (0.3–2.2)</td>
<td>0.645</td>
<td>1.9 (0.9–4.0)</td>
<td>0.100</td>
</tr>
<tr>
<td>Clinical covariates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (per 1 kg/m²)</td>
<td>1.1 (1.0–1.2)</td>
<td>0.277</td>
<td>1.1 (1.0–1.1)</td>
<td>0.169</td>
</tr>
<tr>
<td>Diastolic BP (per 10 mmHg)</td>
<td>1.1 (1.0–1.1)</td>
<td>0.158</td>
<td>1.0 (1.0–1.0)</td>
<td>0.707</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.8 (0.4–8.1)</td>
<td>0.422</td>
<td>2.1 (0.8–5.4)</td>
<td>0.126</td>
</tr>
<tr>
<td>Simvastatin/ezetimibe vs placebo</td>
<td>0.6 (0.2–1.7)</td>
<td>0.326</td>
<td>0.5 (0.2–0.9)</td>
<td>0.030</td>
</tr>
<tr>
<td>Medicine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>1.8 (0.6–5.6)</td>
<td>0.310</td>
<td>1.3 (0.7–2.6)</td>
<td>0.432</td>
</tr>
<tr>
<td>β-Blockade</td>
<td>0.2 (0.1–1.3)</td>
<td>0.089</td>
<td>1.2 (0.6–2.4)</td>
<td>0.618</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA systolic volume (per doubling)</td>
<td>1.5 (0.6–4.3)</td>
<td>0.411</td>
<td>1.8 (1.0–3.5)</td>
<td>0.067</td>
</tr>
<tr>
<td>LA diastolic volume (per doubling)</td>
<td>1.1 (0.6–2.3)</td>
<td>0.701</td>
<td>1.3 (0.8–2.0)</td>
<td>0.278</td>
</tr>
<tr>
<td>LV ejection fraction (per 10% increase)</td>
<td>1.1 (1.0–1.2)</td>
<td>0.031</td>
<td>1.0 (1.0–1.0)</td>
<td>0.606</td>
</tr>
<tr>
<td>Aortic valve area index (per 1 cm²/m²)</td>
<td>2.1 (0.1–35.3)</td>
<td>0.601</td>
<td>1.3 (0.2–9.4)</td>
<td>0.774</td>
</tr>
</tbody>
</table>

AVR indicates aortic valve replacement; BP, blood pressure; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years and female sex; CI, confidence interval; HR, hazard ratio; LA, left atrial; and LV, left ventricular.

*Univariate hazard ratios for composite end point of first of ischemic stroke or death (to account for differences in postoperative survival on the possibility of experiencing postoperative stroke).

---

### Table 5. Contributions to Incident Stroke Prediction in the SEAS Study: During 4.3 Years of Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable χ²</th>
<th>P Value</th>
<th>HR</th>
<th>c-Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke in all patients (42 events)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of adding variables to model with DBP only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP only (per 10 mmHg)</td>
<td>4.6</td>
<td>0.032</td>
<td>1.4</td>
<td>0.60</td>
</tr>
<tr>
<td>+AF</td>
<td>5.5</td>
<td>0.019</td>
<td>2.8</td>
<td>0.62</td>
</tr>
<tr>
<td>+CHA2DS2-VASc</td>
<td>4.4</td>
<td>0.035</td>
<td>1.3</td>
<td>0.64</td>
</tr>
<tr>
<td>+Time-varying AVR</td>
<td>17.9</td>
<td>&lt;0.001</td>
<td>5.4</td>
<td>0.71</td>
</tr>
</tbody>
</table>

+ indicates the addition of each variable separately to the model beginning with diastolic blood pressure only. χ² is the likelihood ratio statistic for each single covariate when added to the model. Hazard ratios are when each covariate is included in the model and display event rate ratios for diastolic blood pressure (per 10 mm Hg increments), atrial fibrillation (yes/no), CHA2DS2-VASc score (per 1 U), and time-varying aortic valve replacement (yes/no). AF indicates atrial fibrillation; AVR, aortic valve replacement; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years and female sex; DBP, diastolic blood pressure; HR, hazard ratio; and SEAS, Simvastatin and Ezetimibe in Aortic Stenosis.
of stroke. A study from the general population suggests that burden of atherosclerosis rather than age in itself is the main predictors of stroke after CABG. The high relative risk of stroke among patients undergoing AVR and CABG observed in this low-risk population is consistent with this hypothesis.

The current data set was not complete enough to ascertain whether suboptimal anticoagulation or other pathophysiological mechanisms, for example, atherosclerotic debris broken off by perioperative procedures or effects of perioperative hypotension, was the main cause. Data have suggested that left atrial appendage closure may prevent stroke in patients with AF. However, it remains controversial whether various surgical techniques, such as atrial exclusion or AF surgery in combination with AVR and CABG, could reduce risk of postoperative stroke. Notwithstanding, this study underscores the importance of recognizing careful anticoagulation in patients with a history of AF and that AVR even in the modern era is not a trivial procedure.

Limitations
Although the data were prospectively collected and end point criteria were predefined, the design was post hoc with inherent limitations. Because of several exclusion criteria, the SEAS population constituted of low-risk patients and the observed stroke rates, the performance of the CHA2DS2-VASc score may not be directly applicable to high-risk patients with AS. The SEAS end point manual did not include more refined characteristics of the neurological deficits (eg, National Institutes of Health Stroke Scale, modified Rankin Scale), stroke subtypes, the rehabilitation, and clinical management of the patients having incident stroke. Data on the types of implanted valves, such as mechanical versus bioprosthesis, were not available. The exclusion of patients receiving OAC resulted in few patients with advanced AF and severely dilated left atria, which could have underestimated their relative importance for risk of stroke. Too few data, for example, preoperative ejection fraction LV ejection fraction, diabetes mellitus, reliable post-AVR incident AF estimation, and absolute events, were available to ascertain whether the cause and thus the predictive value of nonoperative versus post-AVR AF differ. Because of limited information on implanted valves, we could not assess whether any patients with bioprosthesis had a postoperative stroke and whether they received OAC. The use of forward stepwise selection is recognized to be an unstable procedure, where small changes in the data could potentially lead to different variables being selected for the model. This is exacerbated in the presence of a small number of outcome events.

Conclusions
During extended follow-up in patients with AS not prescribed OAC, AF, AVR with concomitant CABG, and components of the CHA2DS2-VASc were the major predictors of stroke. Incident stroke was predictive of increased mortality, particularly among patients patient having post-AVR stroke. This highlights the ability of the CHA2DS2-VASc to stratify risk of stroke in patients with AS and particularly in the case of referral for AVR with combined CABG.

Sources of Funding
The Simvastatin and Ezetimibe in Aortic Stenosis study was conducted with financial support from Merck & Co, Inc, Whitehouse Station, NJ. The sponsor provided the study authors with free access to all the data; the authors were free to interpret data and write the article. The access to raw data, decision to publish, choice of analyses to include, and drafting of the article were wholly controlled by the authors.

Disclosures
Dr Boman has received honoraria and a research grant from Merck & Co, Inc, Whitehouse Station, NJ, the funding sponsor of the Simvastatin and Ezetimibe in Aortic Stenosis study. Dr Devereux has
served as a consultant to Merck & Co, Inc. Dr Egstrup has received honoraria from Merck & Co, Inc. Dr Wachtell has received a research grant from Merck & Co, Inc. The other authors report no conflicts.

References


Stroke in Patients With Aortic Stenosis: The Simvastatin and Ezetimibe in Aortic Stenosis Study

Stroke. 2014;45:1939-1946; originally published online June 5, 2014;
doi: 10.1161/STROKEAHA.114.005296
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/7/1939

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/06/05/STROKEAHA.114.005296.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
Supplemental Figure I Study Flow-Chart: During 4.3 Years of Follow-Up.

Abbreviations: AF: Atrial fibrillation, AVR: Aortic valve replacement, † Time at risk prior to surgery in operated patients is attributed to the non-aortic valve replacement group (6 patients with in-study strokes were subsequently referred for surgery, meaning that 423 patients underwent aortic valve replacement without a history of stroke). ‡ Stroke refers to non-hemorrhagic type.