Asymptomatic Carotid Artery Stenosis and the Risk of Ischemic Stroke According to Subtype in Patients With Clinical Manifest Arterial Disease

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Background and Purpose—Because best medical treatment is improving, the risk of stroke in asymptomatic carotid artery stenosis (ACAS) may decline. We evaluated the risk of ischemic stroke and stratified it according to stroke subtype in patients with ACAS during long-term follow-up.

Methods—In total, 4319 consecutive patients in the Second Manifestations of Arterial disease study with clinically manifest arterial disease or specific risk factors, but without a history of cerebrovascular disease, were included. Degree of stenosis was evaluated with duplex ultrasound scanning. Strokes during follow-up were classified according to subtype. Cox-proportional hazard-regression models were used to evaluate the relationship between ACAS and future stroke.

Results—We identified 293 (6.8%) patients with ACAS 50% to 99%, of whom 193 had 70% to 99% stenosis. In these subgroups, mean follow-up was 6.2 and 6.0 years, respectively. In total, 94 ischemic strokes occurred, of which 8 in ACAS 50% to 99% patients. The any territory annual ischemic stroke risk was 0.4% in 50% to 99% ACAS and 0.5% per year for 70% to 99% ACAS patients. The risk of ischemic stroke was not significantly increased in patients with ACAS 70% to 99% (hazard ratio, 1.5; 95% confidence interval, 0.7–3.5). Patients with ACAS 50% to 99% and ACAS 70% to 99% tended to have nonsignificantly more large vessel disease strokes (hazard ratio, 1.5; 95% confidence interval, 0.5–4.2 and hazard ratio, 1.7; 95% confidence interval, 0.5–5.6).

Conclusions—Patients with clinically manifest arterial disease or type 2 diabetes mellitus have a low risk of developing ischemic stroke, irrespective of its subtype and independent of the degree of ACAS stenosis. (Stroke. 2013;44:XXX-XXX.)

Key Words: asymptomatic carotid artery stenosis ■ stroke
Methods

Design
A prospective analysis was performed on patients enrolled in SMART. The design of the SMART study has been reported in detail previously. In summary, this is a single-center prospective cohort study among patients, newly referred to the University Medical Center Utrecht with (1) clinically manifest atherosclerotic vessel disease (coronary heart disease, cerebrovascular disease, abdominal aortic aneurysm, or peripheral arterial disease, renal artery stenosis, and diabetic foot), or (2) marked risk factors for atherosclerosis (diabetes mellitus, hypertension, and hyperlipidemia). All patients, 18 to 79 years, who gave written informed consent underwent a standardized vascular screening at baseline, including a health questionnaire, laboratory assessment, and duplex ultrasonography (DUS) to investigate the prevalence and incidence of additional vascular diseases. The Ethics Committee of the University Medical Center Utrecht approved the study.

Patient Population
For the present analysis, a total of 5866 SMART patients with clinical manifestations of arterial disease (coronary heart disease, cerebrovascular disease, abdominal aortic aneurysm, or peripheral arterial disease) or risk factors for atherosclerosis (diabetes mellitus, hypertension, and hyperlipidemia) were available. From these 5866, 1473 patients with a history of cerebrovascular disease (defined as transient ischemic attack, stroke, cerebral ischemia, amaurosis fugax, or retinal infarction) before their inclusion in SMART, and 74 patients with missing DUS data were excluded. Therefore, 4319 patients remained available for analysis.

Carotid Artery Stenosis
All patients included in SMART underwent color Doppler-assisted DUS of the carotid arteries at entry. Severity of carotid artery stenosis was based on the peak systolic velocity. The observed greatest degree of stenosis was scored for analysis.

Follow-up
Biannually, patients completed a questionnaire on hospitalizations and outpatient clinic visits. Hospital discharge letters, investigations, or other correspondence were obtained to record a specific event. Therefore, all events were audited by 3 members of the Outcome Event Committee.

Outcome
Primary outcome was the first occurrence of any territory ischemic stroke subclassified according to laterality and subtypes. During follow-up, retinal events and hemispheric transient ischemic attack were not recorded. Stroke subtypes were determined according to the criteria summarized in Table 1 and primarily based on imaging (computed tomography or magnetic resonance imaging). If imaging was unavailable or uninformative, clinical symptoms were used to determine subtype. Stroke classification was done with knowledge on the presence of carotid stenosis. In case of multiple events or strokes, only the first event was used for analysis. This stroke subtype classification was performed by 2 independent observers (A.H. and S.A.). In case of disagreement regarding subtype, a third and fourth observer (A.A. and G.B.) were consulted to get consensus. In case of absence of imaging and unclear clinical cause, or in the absence of agreement, strokes were included in the undetermined group.

Statistical Analyses
Univariable and multivariable Cox-proportional hazard-regression models were performed to estimate hazard ratio (HR) and 95% confidence interval (CI) for the occurrence of ischemic stroke or stroke subtypes. Patients with intervention on one of the carotid arteries during follow-up were censored from this analysis at the time of carotid endarterectomy, including perioperative events. In model I, the unadjusted HR of ACAS for stroke was calculated. In model II, the HR was adjusted for age and sex. Model III, also adjusted for systolic and diastolic blood pressure, current smoking, diabetes mellitus, use of antiplatelet agents, blood pressure-lowering agents, and lipid-lowering agents at baseline.

Results

Study Population
Baseline characteristics of the 4319 patients are given in Table 2. ACAS 50% to 99% was present in 293 of 4319 (6.8%) patients, and 193 of 4319 (4.5%) patients had 70% to 99% ACAS stenosis. Thirty-nine patients had an occlusion without a contralateral stenosis of 50% to 99%.

In general, the patients with 50% to 99% ACAS were older, had a higher systolic blood pressure, and a slightly lower BMI as compared with patients without ACAS. Total cholesterol, low-density lipoprotein cholesterol, triglycerides, and homocysteine were higher in patients with ACAS. Serum creatinine levels were higher, creatinine clearance (estimated glomerular filtration rate) was worse, and ACAS patients were more often current smokers. Moreover, patients with ACAS had less often a history of coronary heart disease, but more frequently a history of abdominal aortic aneurysm and peripheral arterial obstructive disease.

Risk of Stroke
In this cohort, 94 of 4319 (2.2%) patients developed any ischemic stroke during a mean follow-up of 6.3 (SD, 3.6) years, resulting in an average any territory stroke risk of 0.35% per year.

In 88 patients with an ischemic stroke, brain imaging was available. Of these imaging showed relevant infarctions in 58 patients. For 30 patients, subtype classification was based on clinical information only because there was no relevant infarct visible on imaging. Most strokes were attributed to large vessel disease (LVD) or small vessel disease (69/94; 73%). Cardioembolic stroke was found in 16 patients and stroke of undetermined origin in 9 patients. During follow-up, 38 patients underwent an intervention on one of their carotid arteries; these patients were censored at the date of intervention.

After 1 and 5 years of follow-up the cumulative incidence of any ischemic stroke in the total cohort of 4319 patients was 0.4% (95% CI, 0.2–0.6) and 1.5% (95% CI, 1.1–1.9), respectively. The risk of ischemic stroke in the ACAS group (50%–99%) after 1 and 5 years was 0.4% (95% CI, 0.0–1.1) and 1.6% (95% CI, 0.0–3.2), respectively. Eight patients with an ischemic stroke (8/293; 2.7%) had ACAS 50% to 99% diagnosed at baseline, corresponding with an average risk of 0.4%. Five strokes occurred ipsilateral to the stenosed artery resulting in an ipsilateral stroke rate of 0.3% (Table 3).

Among these ACAS 50% to 99% patients, 4 strokes with atherothrombotic (LVD or small vessel disease) origin were identified (HR, 0.9; 95% CI, 0.3–2.4); these were all LVD strokes (HR, 1.5; 95% CI, 0.5–4.2). The other 4 strokes were classified as undetermined because these patients had more than 1 potential cause for their stroke. For patients with 70% to 99% ACAS, the cumulative incidence was 0.6% (95% CI,
In the literature, the overall risk of stroke in patients with ACAS varies from 1% to 10%. In this SMART population after a mean follow-up of 6.3 years, we found a 2.2% overall risk of stroke, and in patients with ACAS 50% to 99% this was 2.7%. The annual stroke rate was only 0.4% in 50% to 99% and 0.5% in 70% to 99% ACAS patients. Although the prevalence of ACAS in our cohort corresponds with the literature, the small number of strokes is remarkable, especially considering the long-term follow-up of our cohort. First of all, this might be caused by the fact that patients with previous cerebrovascular disease were excluded and that our patients were mostly included with transient or nondisabling manifestations of coronary heart disease. Therefore, our population might be considered relatively healthy with respect to vascular disease status. Second, we focused on patients with ACAS ≥50%, which may be considered a mild stenosis. However, even our group with 70% to 99% ACAS had a low stroke risk during long-term follow-up. Third, a recent study in patients with moderate ≥50% ACAS and contralateral transient ischemic attack or stroke on intensive medical therapy showed that the average annual risk of ipsilateral ischemic stroke or transient ischemic attack was only 0.34% (95% CI, 0.01–1.87). Obviously, the increasing number of patients on best medical treatment has reduced the stroke risk in asymptomatic patients especially in patients taking statins. The number of patients with moderate ACAS taking any dose of lipid-lowering agents at baseline and included in our study increased from 45% (2006) to 60% (2011). Most recent high-quality studies reported a decrease in average annual rate of any territory stroke of 1.5% and ipsilateral stroke of only about 0.5% (Abbott, unpublished data, 2012). With the current unique long-term follow-up (mean, 6.3 years) analysis, we confirmed that the annual ischemic stroke risk seems to stay very low in patients with moderate or severe ACAS. To emphasize, we collected our data prospectively, included a high number of patients, censored patients with carotid intervention, and performed a long-term follow-up as compared with the existing literature. The implications

### Table 1. Definitions of Stroke Categories

<table>
<thead>
<tr>
<th>Subtypes of Stroke</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large artery atherosclerosis</td>
<td>Imaging&lt;br&gt;Cortical or cerebellar infarcts &gt;15 mm in diameter&lt;br&gt;Cortical function disorder or motor or sensory deficit of one area of the face, arm or leg&lt;br&gt;Cerebellar syndromes were classified as LVD&lt;br&gt;Retinal ischemia was classified LVD</td>
</tr>
<tr>
<td>Small artery atherosclerosis</td>
<td>Imaging&lt;br&gt;Infarcts of &lt;15 mm in diameter localized in the deep regions of the brain or in the brain stem&lt;br&gt;Motor or sensory deficit of 2 or 3 areas of face, arm, and leg without cortical function disorder, ataxic hemiparesis, or a dysarthria-clumsy hand syndrome&lt;br&gt;Brain stem syndromes were classified as SVD</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>Arterial occlusions presumably attributed to an embolus from the heart</td>
</tr>
<tr>
<td>Strokes of other cause</td>
<td>Strokes attributed to none of the above-described causes and probably rare causes of strokes</td>
</tr>
<tr>
<td>Strokes of undetermined cause</td>
<td>Strokes not determined to one specific cause of stroke with confidence (eg, &gt;1 possible cause)</td>
</tr>
</tbody>
</table>

LVD indicates large vessel disease; and SVD, small vessel disease.

0.0–1.7) for 1 year and 1.9% (95% CI, 0.0–4.0) after 5 years. These patients developed 6 strokes during follow-up, which include an annual average risk of any stroke of 0.5% and 0.3% for ipsilateral stroke (n=4).

In patients without ACAS ≥50%, 64 atherothrombotic strokes were found (average stroke rate of 0.4%), of which 28 were attributed to small vessel disease and 36 by LVD. The classification of the remaining strokes was cardioembolic (n=16) and undetermined stroke (n=4).

### Strokes in Patients with ACAS

Patients with ACAS had a slightly, not statistically significant, higher risk of ischemic stroke as compared with patients without ACAS (Table 4). In the unadjusted analyses, we observed more strokes attributed to LVD in patients with ACAS 50% to 99% or with ACAS 70% to 99% (HR, 1.5; 95% CI, 0.5–4.2 and HR, 1.7; 95% CI, 0.5–5.6) compared with patients without ACAS, but not statistically significant.

### Discussion

In patients with clinically manifest arterial disease or type 2 diabetes mellitus, the presence of ACAS 50% to 99% was associated with an average annual stroke rate of =0.4% and 0.5% for patients with ACAS 70% to 99%. Furthermore, the presence of ACAS was related to a slightly higher risk of ischemic stroke as compared with patients without ACAS. However, this difference was not statistically significant. Half of all strokes during follow-up in patients with ACAS 50% to 99% were of the LVD subtype.

In the general population, the prevalence of ACAS ≥50% ranges from 0% to 7.5% and for ACAS ≥70% from 0% to 3.1%. A slightly increased prevalence of 7.7% (332/4319) for moderate ACAS and 5.4% (293/4319) for more severe ACAS was observed in our population. This should be attributed to our selection of patients with clinically manifest arterial disease versus a lower risk in the general community.
for routine clinical practice include a plea for a conservative approach in ACAS in general and revascularization only within the confines of well-designed randomized clinical trials.

The Trial of ORG 10172 in Acute Stroke Treatment criteria include the 3 most common subtypes of stroke, implementing large artery atherosclerosis (nonlacunar), small artery occlusion (lacunar), or stroke attributed to cardioembolism. Any ipsilateral ischemic stroke in the presence of carotid artery stenosis by definition is attributed to LVD. Lacunar strokes are more often associated with hypertension and other vascular risk factors. To the best of our knowledge, this is the first study that differentiates strokes during follow-up according to stroke subtype in patients with ACAS. In our cohort, most strokes were LVD strokes, followed by small vessel disease, and these proportions are consistent with the literature. By classifying stroke according to subtype, we showed that carotid stenosis was not the underlying cause for all strokes that occurred. A substantial number of strokes had >1 potential cause and, therefore, were classified to have an undetermined etiology (eg, attributable to a combination of lacunar syndrome, cardiac embolism, or carotid artery stenosis). An earlier report already showed that strokes in patients with contralateral ACAS cannot only be attributed to large artery disease (eg, carotid embolization). However, our data need to be interpreted with care because the total number of strokes per subtype was limited.

Atherosclerotic disease has been associated with more cerebrovascular events. We found a slightly higher stroke risk in patients with more tight (≥70%) stenosis, being in agreement with previous studies using DUS follow-up. However, we were unable to investigate the exact influence of stenosis progression on the annual stroke rates, as the design of SMART only provides a single DUS at baseline. Besides degree of stenosis, plaque vulnerability and plaque volume have been considered important in predicting future stroke risk, although mainly investigated in symptomatic patients. One study confirmed this observation in asymptomatic patients. In our analysis, we did not retrieve plaque characteristics because most of the patients did not undergo surgery, and this information was not collected at baseline DUS. Within our cohort, patients were censored from the date of intervention to allow the natural history in this truly asymptomatic cohort.

### Table 2. Baseline Characteristics (n=4319)

<table>
<thead>
<tr>
<th></th>
<th>ACAS 50% to 99% (N=293)</th>
<th>ACAS 70% to 99%* (N=193)</th>
<th>Occlusion** (N=39)</th>
<th>No ACAS 0% to 49% (N=3987)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean±SD), y</td>
<td>65.2±8.0</td>
<td>65.9±7.8</td>
<td>62.9±9.5</td>
<td>59.1±10.2</td>
</tr>
<tr>
<td>Women</td>
<td>82 (28.0)</td>
<td>51 (26.4)</td>
<td>5 (12.8)</td>
<td>977 (24.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>148±21</td>
<td>149±22</td>
<td>148±24</td>
<td>144±62</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>79±10</td>
<td>79±10</td>
<td>83±13</td>
<td>88±79</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.4±3.4</td>
<td>26.5±3.4</td>
<td>27.2±3.7</td>
<td>27.4±4.4</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>97±10</td>
<td>98±10</td>
<td>99±11</td>
<td>97±12</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.3±1.2</td>
<td>5.3±1.3</td>
<td>4.8±1.2</td>
<td>4.9±1.3</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.2±1.0</td>
<td>3.2±1.1</td>
<td>3.0±1.1</td>
<td>2.9±1.0</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.2±0.3</td>
<td>1.2±0.4</td>
<td>1.1±0.3</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.0±1.2</td>
<td>2.0±1.3</td>
<td>1.8±0.9</td>
<td>1.9±2.3</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>14.3±6.2</td>
<td>14.1±5.8</td>
<td>13.9±6.5</td>
<td>13.2±5.7</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>6.9±2.4</td>
<td>6.9±2.5</td>
<td>6.5±2.3</td>
<td>6.7±2.3</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>86 (29.4)</td>
<td>58 (30.1)</td>
<td>14 (35.9)</td>
<td>1167 (29.3)</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>100±46</td>
<td>102±51</td>
<td>112±56</td>
<td>92±36</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>76±25</td>
<td>74±24</td>
<td>80±31</td>
<td>93±32</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>119 (40.6)</td>
<td>75 (38.9)</td>
<td>16 (41.0)</td>
<td>1294 (32.5)</td>
</tr>
<tr>
<td>Ever smoking, %</td>
<td>140 (47.8)</td>
<td>95 (49.2)</td>
<td>17 (43.6)</td>
<td>1823 (45.7)</td>
</tr>
<tr>
<td><strong>Medication use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agents, %</td>
<td>189 (64.5)</td>
<td>131 (67.9)</td>
<td>30 (76.9)</td>
<td>2663 (66.8)</td>
</tr>
<tr>
<td>Blood pressure-lowering agents, %</td>
<td>215 (73.4)</td>
<td>139 (72.0)</td>
<td>32 (82.1)</td>
<td>3048 (76.4)</td>
</tr>
<tr>
<td>Lipid-lowering agents, %</td>
<td>174 (59.4)</td>
<td>119 (61.7)</td>
<td>27 (69.2)</td>
<td>2487 (62.4)</td>
</tr>
<tr>
<td><strong>Vascular disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD, %</td>
<td>162 (55.3)</td>
<td>105 (54.4)</td>
<td>25 (64.1)</td>
<td>2606 (65.4)</td>
</tr>
<tr>
<td>PAOD, %</td>
<td>110 (37.9)</td>
<td>72 (37.3)</td>
<td>12 (30.8)</td>
<td>879 (22.0)</td>
</tr>
<tr>
<td>AAA, %</td>
<td>35 (11.9)</td>
<td>20 (10.4)</td>
<td>6 (15.4)</td>
<td>363 (9.1)</td>
</tr>
</tbody>
</table>

Data represent mean±SD or percentages in parentheses. AAA indicates abdominal aortic aneurysm; ACAS, asymptomatic carotid artery stenosis; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; and PAOD, peripheral arterial obstructive disease.

*Subset of patients with ACAS 50% to 99% and **3 patients with bilateral occlusion.
The optimal treatment for ACAS remains a matter of debate. We showed low rates of stroke, making the benefit of carotid endarterectomy questionable in this cohort.2,4,29 The Asymptomatic Carotid Surgery Trial indicated that for patients <75 years, carotid endarterectomy significantly reduced the 10-year stroke risk (10.8% versus 16.9%),14 with ACAS patients should include optimal medical therapy (eg, antiplatelet therapy, statins, and blood pressure control), and surgery should only be recommended based on individual risk stratification and probably within the confines of the lower natural risk of stroke. We think that treatment of ACAS might have been relatively low due to the healthier status of SMART patients as compared with other studies on ACAS stroke risk. Moreover, information on stenosis degree or medication were only collected at baseline. Therefore progression of stenosis neither changes in medicine could be evaluated over time. The SMART study has a hospital-based setting and, therefore, extrapolation and generalization of results beyond this setting may be limited. However, SMART is a well structured and predefined study in which all patients undergo the same treatment protocols and our long-term follow-up is unique.

In conclusion, patients with ACAS have a low risk of developing ischemic stroke, irrespective of its subtype and independent of the degree of stenosis.

### Acknowledgments

We gratefully acknowledge the contribution of the SMART Study group.

### Disclosures

None.

### References


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