Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods

Transcranial Doppler Ultrasound Examination of Intracranial Arteries

Stenosis ≥50% was defined as a peak systolic velocity increase >150 cm/s for proximal middle cerebral artery (MCA), >120 cm/s for vertebral artery (VA) or basilar artery (BA), and >100 cm/s for carotid artery (CA) or a difference >30% compared with the contralateral artery. MCA occlusion was diagnosed if all other basal arteries were detectable or if the asymmetry index of the symptomatic MCA was <−21% compared with that of the contralateral MCA. CA occlusion was diagnosed if all basal arteries except the CA and the ipsilateral MCA were not detected. BA occlusion was diagnosed if there was a high-resistance flow pattern at depths of 85 to 95 mm in the BA, possibly combined with a sudden loss of flow signals when increasing the examination depth, or retrograde flow in the distal BA. Intracranial VA occlusion was diagnosed if there was a resistance flow profile in 1 side whereas normal or even compensatory elevated flow velocity was seen on the other side.

Outcome

Vascular death included fatal stroke, fatal myocardial infarction, and other cardiovascular death. Other cardiovascular death included any sudden death, including unobserved and unexpected death (e.g., while sleeping) unless proven otherwise by autopsy; death after a vascular surgery, vascular procedure, or amputation (except for trauma or malignancy); death ascribed to heart failure; death after a visceral or limb infarction. Any myocardial infarction or stroke followed by death, whatever the cause, in the subsequent 28 days was considered as a fatal myocardial infarction or fatal stroke. Cardiac events included myocardial infarction, resuscitation after cardiac arrest, and hospitalization for unstable angina or cardiac insufficiency. Major peripheral events included all events related to noncoronary or cervicocerebral artery disease leading to hospitalization or revascularization (e.g., new or worsening of claudication leading to revascularization, surgery for ruptured aneurysm, cholesterol emboli syndrome).
<table>
<thead>
<tr>
<th>Severity</th>
<th>Anterior Circulation</th>
<th>Posterior Circulation</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Infraclinoid</td>
<td>Supraclinoid</td>
</tr>
<tr>
<td>Non-significant, No. (%)</td>
<td>299 (74.2)</td>
<td>377 (93.5)</td>
<td>396 (98.3)</td>
</tr>
<tr>
<td>Stenosis ≥50%, No. (%)</td>
<td>51 (12.7)</td>
<td>17 (4.2)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Occlusion, No. (%)</td>
<td>25 (6.2)</td>
<td>9 (2.2)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Stenosis ≥50% or occlusion, No. (%)</td>
<td>76 (18.9)</td>
<td>26 (6.4)</td>
<td>7 (1.7)</td>
</tr>
</tbody>
</table>

Abbreviations: BA, basilar artery; ICAD, intracranial atherosclerotic disease; MCA, middle cerebral artery; PCA, posterior cerebral artery; VA, vertebral artery.

No. of patients = 403.
**eTable 2. Baseline Characteristics of Patients with Symptomatic and Asymptomatic Significant ICAD**

<table>
<thead>
<tr>
<th></th>
<th>Intracranial Stenosis ≥50% or Occlusion</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic (n = 74)</td>
<td>Symptomatic (n = 72)</td>
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<tr>
<td>Age, mean (SD), y</td>
<td>64 (14)</td>
<td>65 (13)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>55 (74.3)</td>
<td>53 (73.6)</td>
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<td>Body mass index, mean (SD), kg/m²</td>
<td>27.1 (4.5)</td>
<td>26.3 (4.4)</td>
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<tr>
<td>Medical history, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>58 (78.4)</td>
<td>63 (87.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (21.6)</td>
<td>16 (22.2)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>33 (44.6)</td>
<td>37 (51.4)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>24 (32.4)</td>
<td>29 (40.3)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>7 (9.5)</td>
<td>8 (11.1)</td>
</tr>
<tr>
<td>History of coronary heart disease</td>
<td>14 (18.9)</td>
<td>12 (16.7)</td>
</tr>
<tr>
<td>History of peripheral artery disease</td>
<td>6 (8.1)</td>
<td>9 (12.5)</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>11 (14.9)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Examination findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mean (SD), mm Hg</td>
<td>142 (22)</td>
<td>142 (18)</td>
</tr>
<tr>
<td>Diastolic BP, mean (SD), mm Hg</td>
<td>79 (12)</td>
<td>78 (11)</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>199 (42)</td>
<td>197 (49)</td>
</tr>
<tr>
<td>LDL-C, mean (SD), mg/dL</td>
<td>121 (38)</td>
<td>120 (44)</td>
</tr>
<tr>
<td>HDL-C, mean (SD), mg/dL</td>
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<td>51 (15)</td>
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<td>TG, median (IQR), mg/dL</td>
<td>110 (88-139)</td>
<td>128 (93-175)</td>
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<td>TG/HDL-C ratio, median (IQR)</td>
<td>2.1 (1.5-3.4)</td>
<td>2.4 (1.8-3.9)</td>
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<td>Glucose, median (IQR), mg/dL</td>
<td>97 (88-108)</td>
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<td>HbA1c, median (IQR), %</td>
<td>5.7 (5.4-6.4)</td>
<td>5.8 (5.4-6.4)</td>
</tr>
<tr>
<td>Metabolic syndrome, No. (%)</td>
<td>14 (20.9)</td>
<td>18 (29.5)</td>
</tr>
<tr>
<td>Atherogenic dyslipidemia, No. (%)</td>
<td>5 (6.8)</td>
<td>10 (13.9)</td>
</tr>
<tr>
<td>ASCOD grade, No. (%)</td>
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<td></td>
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<tr>
<td>A0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>A3</td>
<td>28 (37.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>A2</td>
<td>9 (12.2)</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>A1</td>
<td>37 (50.0)</td>
<td>68 (94.4)</td>
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<td>Cardiac pathology</td>
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<td>27 (36.5)</td>
<td>38 (52.8)</td>
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<tr>
<td>C3</td>
<td>9 (12.2)</td>
<td>12 (16.7)</td>
</tr>
<tr>
<td>C2</td>
<td>8 (10.8)</td>
<td>9 (12.5)</td>
</tr>
<tr>
<td>C1</td>
<td>28 (37.8)</td>
<td>8 (11.1)</td>
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</table>
eTable 2. Baseline Characteristics of Patients with Symptomatic and Asymptomatic Significant ICAD (continued)

<table>
<thead>
<tr>
<th>Intracranial Stenosis ≥50% or Occlusion</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Asymptomatic (n = 74)</strong></td>
<td><strong>Symptomatic (n = 72)</strong></td>
</tr>
<tr>
<td>Small vessel disease</td>
<td></td>
</tr>
<tr>
<td>S0</td>
<td>12 (16.2)</td>
</tr>
<tr>
<td>S3</td>
<td>54 (73.0)</td>
</tr>
<tr>
<td>S2</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>S1</td>
<td>4 (5.4)</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; ICAD, intracranial atherosclerotic disease; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides.

*Calculated after log-transformation of data.

ASCOD phenotyping assigns a degree of causality between the index stroke and each category as follows: 1 = potential cause; 2 = causality is uncertain; 3 = the disease is present but is unlikely a direct cause; 0 = the disease is absent.
### eTable 3. Baseline Characteristics According to Localization of Significant ICAD

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<td>Anterior (n = 68)</td>
<td>Posterior (n = 42)</td>
<td>Both (n = 36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>63 (15)</td>
<td>65 (12)</td>
<td>68 (11)</td>
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<td></td>
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<tr>
<td>Men, No. (%)</td>
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<td>30 (83.3)</td>
<td>.02</td>
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<td>Medical history, No. (%)</td>
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<td>Hypertension</td>
<td>56 (82.3)</td>
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<td>30 (83.3)</td>
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<td>Dyslipidemia</td>
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<tr>
<td>History of coronary heart disease</td>
<td>8 (11.8)</td>
<td>8 (19.0)</td>
<td>10 (27.8)</td>
<td>.12</td>
<td></td>
<td></td>
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<tr>
<td>History of peripheral artery disease</td>
<td>8 (11.8)</td>
<td>4 (9.5)</td>
<td>3 (8.3)</td>
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<td>History of atrial fibrillation</td>
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<td>Examination findings</td>
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<td>140 (18)</td>
<td>145 (22)</td>
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<tr>
<td>Diastolic BP, mm Hg, mean (SD)</td>
<td>79 (12)</td>
<td>79 (13)</td>
<td>78 (22)</td>
<td>.83</td>
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<td>198 (39)</td>
<td>198 (56)</td>
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<tr>
<td>LDL-C, mean (SD) mg/dL.</td>
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<td>122 (34)</td>
<td>120 (53)</td>
<td>.95</td>
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<td>HDL-C, mean (SD), mg/dL.</td>
<td>52 (15)</td>
<td>53 (13)</td>
<td>52 (15)</td>
<td>.88</td>
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<td>TG, median (IQR), mg/dL</td>
<td>116 (91-165)</td>
<td>109 (81-138)</td>
<td>127 (104-164)</td>
<td>.43³</td>
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<td>TG/HDL-C ratio, median (IQR)</td>
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<tr>
<td>HbA1c, median (IQR), %</td>
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<td>6.0 (5.5-6.4)</td>
<td>6.1 (5.4-6.4)</td>
<td>.54³</td>
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<tr>
<td>Metabolic syndrome, No. (%)</td>
<td>14 (24.6)</td>
<td>9 (21.9)</td>
<td>9 (30.0)</td>
<td>.74</td>
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<tr>
<td>Atherogenic dyslipidemia, No. (%)</td>
<td>8 (11.8)</td>
<td>3 (7.1)</td>
<td>4 (11.1)</td>
<td>.77</td>
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<tr>
<td>ASCOD grade³, No. (%)</td>
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<td>Atherothrombosis</td>
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<td>A0</td>
<td>0 (0.0)</td>
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<td>0 (0.0)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>13 (19.2)</td>
<td>13 (30.9)</td>
<td>2 (5.6)</td>
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<td></td>
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</tr>
<tr>
<td>A2</td>
<td>6 (8.8)</td>
<td>5 (11.9)</td>
<td>2 (5.6)</td>
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<td></td>
<td></td>
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<tr>
<td>A1</td>
<td>49 (72.1)</td>
<td>24 (57.1)</td>
<td>32 (88.9)</td>
<td>.15</td>
<td></td>
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<tr>
<td>Cardiac pathology</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<td>29 (42.6)</td>
<td>18 (42.9)</td>
<td>18 (50.0)</td>
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<tr>
<td>C3</td>
<td>5 (7.3)</td>
<td>7 (16.7)</td>
<td>9 (25.0)</td>
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<td></td>
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<tr>
<td>C2</td>
<td>9 (13.2)</td>
<td>7 (16.7)</td>
<td>1 (2.8)</td>
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<td></td>
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<tr>
<td>C1</td>
<td>21 (30.9)</td>
<td>8 (19.0)</td>
<td>7 (19.4)</td>
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</table>
**eTable 3. Baseline Characteristics According to Localization of Significant ICAD (continued)**

<table>
<thead>
<tr>
<th></th>
<th>Anterior (n = 68)</th>
<th>Posterior (n = 42)</th>
<th>Both (n = 36)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small vessel disease</td>
<td></td>
<td></td>
<td></td>
<td>.81</td>
</tr>
<tr>
<td>S0</td>
<td>6 (8.8)</td>
<td>6 (14.3)</td>
<td>7 (19.4)</td>
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<tr>
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<td>55 (80)</td>
<td>32 (76.2)</td>
<td>26 (72.2)</td>
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</tr>
<tr>
<td>S2</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>S1</td>
<td>4 (5.9)</td>
<td>2 (4.8)</td>
<td>1 (2.8)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; ICAD, intracranial atherosclerotic disease; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides.

* Calculated after log-transformation of data.
* ASCOD phenotyping assigns a degree of causality between the index stroke and each category as follows: 1 = potential cause; 2 = causality is uncertain; 3 = the disease is present but is unlikely a direct cause; 0 = the disease is absent.
eTable 4. Prevalence of Non-Intracranial Atherosclerosis in Patients with Symptomatic and Asymptomatic Significant ICAD

<table>
<thead>
<tr>
<th>No. (%) with atherosclerosis in:</th>
<th>Intracranial Stenosis ≥50% or Occlusion</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic (n = 41)</td>
<td>Symptomatic (n = 48)</td>
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<tr>
<td>Extracranial carotid artery</td>
<td>55 (76.4)</td>
<td>52 (73.2)</td>
</tr>
<tr>
<td>Aortic arch</td>
<td>36 (60.0)</td>
<td>34 (61.8)</td>
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<tr>
<td>Descending aorta</td>
<td>15 (25.0)</td>
<td>15 (27.3)</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>22 (34.9)</td>
<td>17 (27.4)</td>
</tr>
<tr>
<td>Femoral artery</td>
<td>50 (74.6)</td>
<td>51 (78.5)</td>
</tr>
<tr>
<td>Coronary artery</td>
<td>48 (71.6)</td>
<td>55 (82.1)</td>
</tr>
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</table>

Abbreviations: ICAD, intracranial atherosclerotic disease.
eTable 5. Prevalence of Non-Intracranial Atherosclerosis According to Localization of Significant ICAD

<table>
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<tr>
<th>No. (%) with atherosclerosis in:</th>
<th>Circulation</th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
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<td>Anterior (n = 35)</td>
<td>Posterior (n = 34)</td>
<td>Both (n = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extracranial carotid artery</td>
<td>27 (79.4)</td>
<td>25 (75.8)</td>
<td>16 (80.0)</td>
<td>.91</td>
<td></td>
</tr>
<tr>
<td>Aortic arch</td>
<td>17 (56.7)</td>
<td>14 (53.8)</td>
<td>12 (80.0)</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>Descending aorta</td>
<td>7 (23.3)</td>
<td>9 (34.6)</td>
<td>5 (33.3)</td>
<td>.61</td>
<td></td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>11 (32.3)</td>
<td>11 (39.3)</td>
<td>4 (30.8)</td>
<td>.81</td>
<td></td>
</tr>
<tr>
<td>Femoral artery</td>
<td>29 (82.9)</td>
<td>25 (83.3)</td>
<td>11 (78.6)</td>
<td>.92</td>
<td></td>
</tr>
<tr>
<td>Coronary artery</td>
<td>25 (75.8)</td>
<td>27 (84.4)</td>
<td>16 (88.9)</td>
<td>.46</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICAD, intracranial atherosclerotic disease.
eTable 6. Four-Year Risk of Recurrent Vascular Events Associated with Coexisting Diseases in Patients with Significant ICAD

<table>
<thead>
<tr>
<th></th>
<th>MACE, N (%)</th>
<th>Log-Rank P Value</th>
<th>Hazard Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 36)</td>
<td>3 (9.0)</td>
<td>.08</td>
<td>1.00 (ref)</td>
<td>.24</td>
</tr>
<tr>
<td>Yes (n = 107)</td>
<td>24 (23.4)</td>
<td></td>
<td>2.12 (0.61-7.34)</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 68)</td>
<td>8 (12.8)</td>
<td>.01</td>
<td>1.00 (ref)</td>
<td>.36</td>
</tr>
<tr>
<td>Yes (n = 66)</td>
<td>19 (29.9)</td>
<td></td>
<td>1.90 (0.48-7.53)</td>
<td></td>
</tr>
<tr>
<td>Cardiac pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C0 (n = 65)</td>
<td>7 (11.4)</td>
<td>.01</td>
<td>1.00 (ref)</td>
<td>.09</td>
</tr>
<tr>
<td>C1, 2, 3 (n = 74)</td>
<td>20 (28.2)</td>
<td></td>
<td>2.24 (0.87-5.73)</td>
<td></td>
</tr>
<tr>
<td>Small vessel disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S0 (n = 19)</td>
<td>6 (34.6)</td>
<td>.05</td>
<td>1.00 (ref)</td>
<td>.008</td>
</tr>
<tr>
<td>S1, 2, 3 (n = 120)</td>
<td>20 (17.3)</td>
<td></td>
<td>0.23 (0.08-0.68)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CI, confidence interval; ECAS, extracranial carotid artery stenosis; HR, hazard ratio; ICAD, intracranial atherosclerotic disease; MACE, major adverse cardiovascular events.

*Adjusted for age, baseline systolic blood pressure, baseline high-density lipoprotein cholesterol, body mass index, and history of atrial fibrillation.
eFigure 1. Study Flow Chart

785 patients assessed for eligibility between June 2005 and December 2008

405 patients with cerebral infarction enrolled in the AMISTAD study

2 patients excluded: no MRA, no TCD and no CTA

403 patients with intracranial arterial investigations included in the present study
289 underwent CE- and TOF-MRA
399 underwent TCD
53 underwent CTA

Abbreviations: CE, contrast enhanced; CTA, computed tomography angiography; MRA, magnetic resonance angiography; TCD, transcranial Doppler; TOF, time of flight.
eFigure 2. Mean Systolic Blood Pressure Levels and Low-Density Lipoprotein Cholesterol Concentrations at Baseline and Follow-Up Visits

A. Mean SBP levels at baseline and follow-up visits.
B. Mean LDL-C concentrations at baseline and follow-up visits.

Abbreviations: ICAD, intracranial atherosclerotic disease; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
eFigure 3. Cumulative Incidence Curves of Major Vascular Events According to the Presence of Significant ICAD

Abbreviations: ICAD, intracranial atherosclerotic disease.
eReferences