Prevalence and Prognosis of Asymptomatic Vertebral Artery Origin Stenosis in Patients With Clinically Manifest Arterial Disease

Annette Compter, MD; H. Bart van der Worp, MD; Ale Algra, MD; L. Jaap Kappelle, MD; on behalf of the Second Manifestations of ARTerial disease (SMART) Study Group

Background and Purpose—The risk of ischemic stroke in patients with asymptomatic vertebral artery stenosis is unknown. We examined the incidence of posterior circulation ischemic stroke in patients with asymptomatic stenosis of the vertebral artery origin (VAo).

Methods—we studied a hospital-based cohort of 3717 patients (median age, 60 years; interquartile range, 52 to 68 years) with atherosclerotic arterial disease enrolled in the Second Manifestations of ARTerial disease (SMART) study. We included patients in whom duplex ultrasound of the carotid artery and vertebral artery had been performed. Patients with symptomatic VAo stenosis or planned revascularization of the carotid artery or vertebral artery were excluded. Data were analyzed with Cox regression; hazard ratios were adjusted for age and vascular risk factors.

Results—in 282 patients (7.6%), asymptomatic VAo stenosis >50% was diagnosed with duplex ultrasound. During a mean follow-up of 4.6 years (SD, 3.0), posterior circulation ischemic stroke occurred in 5 of the 282 patients with asymptomatic VAo stenosis at baseline (annual stroke rate, 0.4%) and in 12 of the 3435 patients without VAo stenosis (annual stroke rate, <0.1%). The risk of posterior circulation ischemic stroke was higher in patients with VAo stenosis than in patients without VAo stenosis (hazard ratio, 4.2; 95% CI, 1.4 to 13.1) and was further increased in patients with both VAo and carotid artery stenosis (hazard ratio, 10.5; 95% CI, 3.0 to 37.3). In multivariable analysis, this risk remained essentially the same.

Conclusions—Patients with atherosclerotic arterial disease and asymptomatic VAo stenosis have a higher risk of posterior circulation ischemic stroke than patients without such a stenosis, but the absolute risk remains low. (Stroke. 2011;42:2795-2800.)

Key Words: embolic stroke • vertebrobasilar

Up to 40% of ischemic strokes involve the vertebrobasilar circulation.1 Atherosclerotic stenosis >50% in the vertebrobasilar artery is found in approximately one fourth of the patients with vertebrobasilar transient ischemic attack (TIA) or stroke. This stenosis is most frequently located in the proximal vertebral artery (VA).2 The diagnosis of VA stenosis is facilitated by the increased use of MR and CT angiography after a TIA or ischemic stroke and improvements in duplex ultrasound. Nevertheless, the consequences of finding such a stenosis are uncertain, especially when this stenosis is asymptomatic. Patients with symptomatic VA stenosis probably have an increased risk of stroke.2-3 The effect of stenting of this stenosis is currently under study.4-5 The risk of stroke in asymptomatic VA stenosis is unknown let alone the benefit or harm of invasive treatment.

The aim of the present study was to assess the incidence and predictors of posterior circulation ischemic stroke in patients with clinically manifest arterial disease and asymptomatic stenosis >50% or occlusion at the origin of the VA on duplex ultrasound.

Subjects and Methods

Study Population

The present study is part of the ongoing Second Manifestations of ARTerial disease (SMART) study, of which a detailed description has been published.6 Briefly, patients aged 18 up to 80 years, newly referred to the University Medical Center in Utrecht, the Netherlands, with vascular risk factors or with clinically manifest atherosclerotic arterial disease are included (definitions, Supplemental Table I; http://stroke.ahajournals.org). Exclusion criteria for SMART are terminal malignancy, dependency in daily activities (score on the modified Rankin Scale >3),7 insufficient fluency in Dutch, and referral back to the primary or secondary care physician immediately after the first visit.
The current study is limited to patients who presented with clinically manifest atherosclerotic arterial disease and were included in SMART between January 1996 and January 2008. An additional inclusion criterion was the performance of duplex ultrasound at baseline of both the VA origin (VAo) and carotid artery (CA) with description of the peak systolic velocity (PSV) on both sides. Criteria for exclusion were the combination of a VAo stenosis and a posterior circulation stroke or TIA in the preceding 6 months or an intervention on the CA or VA planned at inclusion. Of the 7290 patients included in the SMART study, 4451 (61%) presented with clinically manifest atherosclerotic arterial disease. Of these patients, 3717 were included in the present study (Figure 1). The SMART study has been approved by the Ethics Committee of the University Medical Center Utrecht and all patients provided written informed consent.

Procedures
As part of the SMART protocol, patients underwent standardized vascular screening, including a health questionnaire on their history of vascular disease and current medication use (antithrombotic, antihypertensive, and lipid-lowering drugs), assessment of vascular risk factors, laboratory investigations, and ultrasonography of the aorta, kidneys, common and internal CA, and extracranial VA.

The extracranial VA and CA were assessed with color Doppler ultrasonography. Ultrasound examinations were performed by well-trained and certified ultrasound technicians. The first part of the VA (V1) starts at its origin and ends at the entrance of the transverse foramen of the seventh cervical vertebra. The second part (V2, intertransverse segment) is the course of the artery in the intervertebral foramina.

First, the direction of flow in the VA and its waveform were assessed in the intertransverse (V2) segment (indirect visualization). A diminished peak systolic amplitude with a delayed systolic upstroke or rounded systolic peak was considered indicative of proximal VA stenosis, after which the origin of the VA was examined (direct visualization).

VAo stenosis >50% was defined as a PSV >100 cm/s. A PSV of 0 cm/s was considered indicative of an occlusion of the VA. In the extracranial internal CA, a PSV >210 cm/s was indicative of a stenosis >70% in the period between 1996 and 2001 (n=1157).

From 2001, a PSV >270 cm/s was considered indicative of a CA stenosis >70% (n=1560).10

Follow-Up
Follow-up was prospectively obtained biannually until March 2008 by a questionnaire on hospitalizations and outpatient clinic visits. We assessed the occurrence of ischemic stroke, death, and endovascular or surgical interventions of the CA or VA. If the patient or a family member recorded the occurrence of a possible outcome event, hospital discharge letters and relevant radiology examinations were retrieved. Outcome events were assessed independently by 3 members of the SMART study End point Committee, including neurologists, cardiologists, and internists.

Outcome Measures
The primary outcome measure in the present study was ischemic stroke of the posterior circulation, defined as clinical features indicative of stroke of the brainstem, cerebellum, or occipital lobe with or without a new ischemic lesion on a repeat brain scan. Secondary outcome measures were vascular mortality, ischemic stroke, myocardial infarction, and the composite of these outcome measures (definitions, Supplemental Table I).

Data Analysis
Relative risks were calculated for differences in baseline characteristics between patients included in the current study and those excluded. Results from direct and indirect visualization of the VAo were compared to evaluate the accuracy of the indirect duplex scanning method. The presence of vascular risk factors was compared between patients with and without asymptomatic VAo stenosis by Poisson regression analysis and described as relative risks with corresponding 95% CIs.

The cumulative risk of posterior circulation ischemic stroke was estimated by the Kaplan-Meier method. For this analysis, the study population was subdivided into 3 groups: no VAo stenosis, VAo stenosis only, and both VAo and CA stenosis. Comparison between these groups was performed by the log rank test. Hazard ratios (HRs) and corresponding 95% CIs for the occurrence of posterior circulation ischemic stroke in these groups were calculated by performing Cox proportional regression analyses. In
multivariable analysis, adjustments were made for age, sex, vascular risk factors (smoking, hypertension, diabetes, coronary heart disease, peripheral arterial disease, and previous stroke) and medication use. Additional analyses were performed for ischemic stroke of the anterior circulation and CA stenosis with or without VAo stenosis. If a patient had multiple ischemic strokes during follow-up, only the first event was used in the analyses. Patients were censored at the time of an intervention on the CA or VA.

Results

Study Population
In this study, 3717 patients were included with a median age of 60 years (interquartile range, 52 to 68 years). Compared with excluded patients, included patients were younger and less often had CA stenosis, previous ischemic stroke, or TIA (Supplemental Table II).

Asymptomatic VAo stenosis >50% or occlusion was found in 282 patients (7.6%; 95% CI, 6.8 to 8.5%) of whom 43 (1%) had bilateral VAo stenosis or occlusion. Reversed flow in 1 VA was found in 35 patients (1%). Three (1%) of the 282 patients with VAo stenosis had had a previous TIA or stroke of the posterior circulation earlier than 6 months before inclusion.

Baseline characteristics of patients with and without asymptomatic VAo stenosis are presented in Table 1. In 685 patients, both origins of the VA were directly visualized by duplex ultrasound. Separate analyses for direct and indirect

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Presence of Vertebral Artery Origin Stenosis or Occlusion (n=3717)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Characteristic Present (%) [No.]</td>
</tr>
<tr>
<td>Age &gt;60 y (median)</td>
<td>9.7 (177/1819)</td>
</tr>
<tr>
<td>Male sex</td>
<td>7.4 (208/2823)</td>
</tr>
</tbody>
</table>

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| Baseline Characteristic | Present (%) [No.] | Baseline Characteristic Absent* (%) [No.] | Relative Risk (95% CI) | Age- and Sex- Adjusted Relative Risk (95% CI) |
|-------------------------|---------------------------------------------------------------|
| Age >60 y (median)      | 9.7 (177/1819) | 5.5 (105/1898) | 1.76 (1.39–2.22) | 1.76 (1.39–2.22) |
| Male sex               | 7.4 (208/2823) | 8.3 (74/894)    | 0.89 (0.69–1.15) | 1.11 (0.86–1.44) |

Results

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Baseline characteristics of patients with and without asymptomatic VAo stenosis are presented in Table 1. In 685 patients, both origins of the VA were directly visualized by duplex ultrasound. Separate analyses for direct and indirect
patients with VAo stenosis only, and patients with combined VAo and CA stenosis. In univariable analysis, patients with VAo stenosis at baseline had a higher risk of posterior circulation ischemic stroke during follow-up than patients without VAo stenosis (HR, 4.2; 95% CI, 1.4 to 13.1). This risk was further increased in patients with combined VAo and CA stenosis.

Table 3. Cox Regression Analysis: Hazard Ratios for Independent Predictors of Posterior Circulation Ischemic Stroke (n=3421)

<table>
<thead>
<tr>
<th></th>
<th>VAo Stenosis* vs No VAo Stenosis</th>
<th>VAo Stenosis Only vs No VAo Stenosis</th>
<th>VAo Stenosis and CA Stenosis vs No VAo Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute risk</td>
<td>4/270 vs 12/3302</td>
<td>1/186 vs 12/3302</td>
<td>3/84 vs 12/3302</td>
</tr>
<tr>
<td>Hazard ratios</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>4.2 (1.4–13.1)</td>
<td>1.5 (0.2–11.5)</td>
<td>10.5 (3.0–37.3)</td>
</tr>
<tr>
<td>Age, y</td>
<td>4.3 (1.4–13.5)</td>
<td>1.5 (0.2–11.8)</td>
<td>10.8 (3.0–39.7)</td>
</tr>
<tr>
<td>Male sex</td>
<td>4.2 (1.4–13.1)</td>
<td>1.5 (0.2–11.7)</td>
<td>10.4 (2.9–36.7)</td>
</tr>
<tr>
<td>Smoking</td>
<td>4.2 (1.4–13.0)</td>
<td>1.5 (0.2–11.5)</td>
<td>10.6 (3.0–37.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.1 (1.3–12.7)</td>
<td>1.5 (0.2–11.6)</td>
<td>10.2 (2.8–36.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.1 (1.3–12.7)</td>
<td>1.5 (0.2–11.3)</td>
<td>10.0 (2.8–35.4)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>4.2 (1.4–13.1)</td>
<td>1.5 (0.2–11.8)</td>
<td>10.3 (2.9–36.4)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>4.3 (1.4–13.5)</td>
<td>1.5 (0.2–11.8)</td>
<td>10.7 (3.0–38.6)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>3.9 (1.3–12.3)</td>
<td>1.6 (0.2–12.5)</td>
<td>8.9 (2.4–33.5)</td>
</tr>
<tr>
<td>Antithrombotic drugs†</td>
<td>4.2 (1.4–13.0)</td>
<td>1.5 (0.2–11.6)</td>
<td>10.3 (2.9–36.4)</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>4.2 (1.4–13.1)</td>
<td>1.5 (0.2–11.8)</td>
<td>10.4 (2.9–37.1)</td>
</tr>
<tr>
<td>Lipid lowering drugs</td>
<td>4.2 (1.3–12.9)</td>
<td>1.5 (0.2–11.5)</td>
<td>10.1 (2.8–35.9)</td>
</tr>
<tr>
<td>3 factors‡</td>
<td>4.1 (1.3–13.0)</td>
<td>1.5 (0.2–11.7)</td>
<td>10.3 (2.8–38.2)</td>
</tr>
<tr>
<td>2 factors§</td>
<td>4.2 (1.3–13.2)</td>
<td>1.5 (0.2–11.6)</td>
<td>10.4 (2.8–38.4)</td>
</tr>
</tbody>
</table>

Additional adjustment for sex in multivariable analysis did not change the results. VAo indicates vertebral artery origin; CA, carotid artery.

*With or without CA stenosis.
†Anticoagulant or antiplatelet drugs.
‡Adjusted for age, history of diabetes, and history of hypertension.
§Adjusted for age and history of diabetes.
CA stenosis (HR, 10.5; 95% CI, 3.0 to 37.3). After adjustment for age and vascular risk factors, the strengths of the relations for posterior circulation stroke remained essentially the same. Patients with CA stenosis had a higher risk of anterior circulation stroke than patients without CA stenosis. After adjustment for age and vascular risk factors, the HR was 2.4 (95% CI, 1.0 to 6.2) in the subgroup of patients with combined CA and VAo stenosis.

During follow-up, 50 (1%) of the 3435 patients without VAo stenosis and 11 (4%) of the 282 patients with asymptomatic VAo stenosis underwent an intervention of the cervical arteries. Carotid endarterectomy was performed in 49 patients, CA stenting in 8 patients, and extracranial–intracranial bypass in 4 patients.

Discussion
We found that 7.6% (95% CI, 6.8% to 8.5%) of the patients with clinically manifest atherosclerotic arterial disease have an asymptomatic VAo stenosis or occlusion on duplex ultrasound. Furthermore, patients with VAo stenosis have a higher risk of posterior circulation ischemic stroke than patients without such a stenosis. Nevertheless, the absolute risk of ischemic stroke remains low. The risk of posterior circulation ischemic stroke is highest in the subgroup of patients with both VAo and CA stenosis (adjusted HR, 10.3; 95% CI, 2.8 to 38.2).

The prevalence of VAo stenosis we found is comparable with that reported in a 1980s study of 375 patients with peripheral arterial disease, of whom 7% had either a stenosis or retrograde flow in an extracranial VA. In the present study, posterior circulation ischemic stroke incidence rates were low for patients with asymptomatic VAo stenosis (annual rate, 0.4%) and in line with the annual risk of first-ever stroke in the Dutch population aged 60 to 64 years. This low stroke rate may be partly explained by the intensive contemporary medical treatment for the prevention of cardiovascular disease. The prevalence rates might be influenced by the exclusion of patients with revascularization of the CA or VA planned at study inclusion. Excluded patients were older than included patients. In contrast to previous studies, our study was performed in a large prospective cohort of patients with well-defined diagnostic inclusion criteria of clinically manifest arterial disease.

The relatively high stroke rates in patients with combined VAo and CA stenosis are in concordance with observations in patients with VAo stenosis in the 1980s. The combination of VAo and CA stenosis may serve as a source of embolism or result in generalized cerebral hypoperfusion. Several studies have suggested that patients with impaired cerebral perfusion have an increased risk of ischemic stroke as compared with those with normal perfusion. Unfortunately, the small number of strokes during follow-up and the lack of MRI in some patients did not allow a subclassification for lacunar and nonlacunar strokes.

In recent years, treatment of VA stenosis by percutaneous transluminal angioplasty and stenting has been introduced as an attractive treatment option for patients with symptomatic VA stenosis. However, in observational studies, endovascular treatment of vertebrobasilar artery stenosis has been associated with a 6.4% risk of TIA, stroke, or death in the first 30 days. The safety and benefit of stenting of symptomatic VA stenosis as compared with best medical therapy are currently under study in 2 randomized clinical trials. The effect of stenting in patients with asymptomatic VA stenosis is completely uncertain. Given the low risk of posterior circulation stroke on best medical treatment compared with the considerable risk of procedural stroke or death in patients treated with stenting, invasive treatment of asymptomatic VAo stenosis appears not warranted.

The gold standard for diagnosing VA stenosis is intra-arterial angiography; however, this procedure is associated with a small risk of stroke. Studies of sufficient quality validating the accuracy of diagnosing and grading VA stenosis with noninvasive methods against the gold standard of intra-arterial angiography are scarce. Duplex ultrasound has a high specificity (93% to 98%) but a relatively low sensitivity (70%) for diagnosing extracranial VA stenosis. There is no consensus on the ultrasound criteria for a stenosis >50%. In previous studies, a PSV >100 cm/s was considered indicative of a proximal VA stenosis >50%.

The present study is limited by the use of duplex ultrasound for the assessment of the VAo. Consequently, risk ratios and relations found in this study might be an underestimation. Second, in the SMART study, the first assessment of the VA origin was indirect in the V2 segment. The origin was only examined directly, when hemodynamic evidence of a proximal stenosis was found in the V2 segment. After comparing patients with indirect and direct examination of the VAo, no difference in the risk implications of VAo stenosis was found. In the SMART study, no data were obtained on the presence of more distal VA stenoses.

An important finding of this study is that the absolute risk of posterior circulation stroke in patients with asymptomatic VAo stenosis is low. For this reason, invasive treatment of asymptomatic VAo stenosis appears not warranted. Because the majority of the patients with atherosclerotic arterial disease and VAo stenosis died from a vascular cause, management of these patients should focus on reduction of the total vascular risk.

Appendix
Members of the SMART study group: A. Algra, MD, Y. van der Graaf, MD, D.E. Grobbee, MD, and G.E.H.M. Rutten, MD, Julius Center for Health Sciences and Primary Care; F.L.J. Visseren, MD, Department of Vascular Medicine; F.L. Moll, MD, Department of Vascular Surgery; L.J. Kappelle, MD, Department of Neurology; W.P.T.M. Mali, MD, Department of Radiology; and P.A. Doevendans, MD, Department of Cardiology, University Medical Center, Utrecht, the Netherlands.

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Disclosures
None.
References


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Data Supplement (unedited) at:
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**Table S1. Definitions of inclusion criteria and outcome measures**

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<tr>
<th>Vascular risk factors</th>
<th>Hypertension</th>
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<td>Hyperlipidemia</td>
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<td></td>
<td>Diabetes mellitus</td>
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<td></td>
<td>Renal insufficiency</td>
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<td>Clinically manifest atherosclerotic arterial disease</td>
<td>Transient ischemic attack</td>
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<td></td>
<td>Minor stroke</td>
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<td>Asymptomatic carotis artery stenosis</td>
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<tr>
<td></td>
<td>Peripheral arterial disease</td>
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<td></td>
<td>Diabetic foot</td>
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<tr>
<td></td>
<td>Abdominal aortic aneurysm</td>
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<td></td>
<td>Angina pectoris</td>
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<tr>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Renal artery stenosis</td>
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<tr>
<td>Posterior circulation ischemic stroke</td>
<td>Clinical features indicative of stroke of the brainstem, cerebellum, or occipital lobe with or without a new ischemic lesion on a repeat brain scan</td>
</tr>
<tr>
<td>Anterior circulation ischemic stroke</td>
<td>Clinical features consistent with stroke in the territory of the anterior cerebral artery, middle cerebral artery, or internal carotid artery, with or without a new ischemic lesion on a repeat brain scan</td>
</tr>
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<td>Vascular death</td>
<td>sudden death, death from ischemic stroke or intracerebral hemorrhage, death from congestive heart failure or myocardial infarction, death from rupture of an aortic aneurysm, or vascular death from another cause</td>
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<td></td>
<td>Included</td>
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<tr>
<td></td>
<td>N=3717</td>
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<tr>
<td>Age (median, +/- SD)</td>
<td>59.8 (10.4)</td>
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<tr>
<td>Male sex</td>
<td>75.9 (2823)</td>
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<td>Diagnosis at inclusion</td>
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<td>Coronary artery disease</td>
<td>53.5 (1987)</td>
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<td>Peripheral arterial disease</td>
<td>20.6 (765)</td>
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<td>Ischemic stroke</td>
<td>6.1 (225)</td>
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<td>Transient Ischemic Attack</td>
<td>7.2 (268)</td>
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<td>Amaurosis fugax</td>
<td>1.1 (42)</td>
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<tr>
<td>Other†</td>
<td>11.6 (430)</td>
</tr>
<tr>
<td>Hypertension‡</td>
<td>51.0 (1896)</td>
</tr>
<tr>
<td>BMI &gt;30 (kg/m2)</td>
<td>17.6 (653)</td>
</tr>
<tr>
<td>Hyperlipidemia§</td>
<td>78 (2899)</td>
</tr>
<tr>
<td>Current or recently stopped smoking†</td>
<td>27.2 (1012)</td>
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<td>Previous stroke‡</td>
<td>10.1 (375)</td>
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<td>Coronary heart disease‡</td>
<td>51.0 (1894)</td>
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<td>23.6 (876)</td>
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<td>Diabetes‡</td>
<td>15.1 (561)</td>
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<tr>
<td>Abdominal aortic aneurysm‡</td>
<td>9.1 (339)</td>
</tr>
</tbody>
</table>

CI, confidence interval; SD, standard deviation
* on direct or indirect visualisation of vertebral artery origin; †, retinal infarction, diabetic foot, renal artery stenosis, renal failure, abdominal aortic aneurysm; ‡, ever or current diagnosis; §, total cholesterol >5.0 mmol/L, or LDL cholesterol > 3.2 mmol/L, or treated with lipid lowering agents; #, definition stenosis based on peak systolic velocity criteria duplex ultrasound