# Asymptomatic Carotid Artery Stenosis and the Risk of New Vascular Events in Patients With Manifest Arterial Disease

## The SMART Study

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***Background and Purpose***—The frequency of asymptomatic carotid artery stenosis (CAS) increases with age from 0.5% in individuals below 50 years of age to 5% to 10% in individuals over 65 years of age in the general population. Its prognostic value has been examined in the general population but less often in patients with clinical manifestations of arterial disease other than retinal or cerebral ischemia. We examined the relationship between asymptomatic CAS and the risk of subsequent events in this specific group of patients.

***Methods***—This study involved 2684 consecutive patients with clinical manifestations of arterial disease or type 2 diabetes mellitus, but without a history of cerebral ischemia, enrolled in the SMART study (Second Manifestations of ARTerial disease). The degree of asymptomatic CAS was assessed with Duplex scanning and defined on the basis of the blood flow velocity patterns at baseline in both carotid arteries. None of the patients underwent carotid endarterectomy or endovascular intervention. During the follow-up period, vascular events (vascular death, ischemic stroke, and myocardial infarction) were documented in detail. Data were analyzed with Cox proportional hazards regression and adjusted for age, gender, and classic vascular risk factors.

***Results***—Asymptomatic CAS of 50% or greater was present in 221 (8%) patients. During a mean follow up of 3.6 years (SD=2.3), a first vascular event occurred in 253 patients (9%). The cumulative incidence rate for the composite of subsequent vascular events after 5 years was 12.3% (95% CI=10.7 to 13.9), for cerebral infarction 2.2% (95% CI=1.4 to 2.8), and for myocardial infarction 8.0% (95% CI=6.6 to 9.4). Adjusted for age and gender, asymptomatic CAS of 50% or greater was related to a higher risk of subsequent vascular events (hazard ratio=1.5, 95% CI=1.1 to 2.1), in particular of vascular death (hazard ratio=1.8, 95% CI=1.2 to 2.6). After additional adjustment for vascular risk factors, the hazard ratios remained essentially the same.

***Conclusion***—Asymptomatic carotid artery stenosis is an independent predictor of vascular events, especially vascular death, in patients with clinical manifestations of arterial disease or type 2 diabetes but without a history of cerebral ischemia. **(*Stroke*. 2007;38:1470-1475.)**

**Key Words:** asymptomatic carotid artery stenosis ■ cardiovascular disease ■ recurrent events

Carotid artery stenosis (CAS) is defined as a narrowing of the common or internal carotid artery. Stenosis is considered symptomatic when ipsilateral retinal or cerebral ischemia has occurred and asymptomatic when these symptoms did not take place. Between 5% and 10% of the general population over 65 years of age has an asymptomatic CAS of 50% or greater.[1,2] Recently, we reported a 10% (95% CI=9 to 12) prevalence of asymptomatic CAS of 50% or greater in a cohort of patients with clinical manifestations of arterial diseases in other vascular territories than the CAS.[3] The prevalence of asymptomatic CAS 50% or greater was highest in patients with peripheral arterial disease (15%, 95% CI=13 to 18) and abdominal aortic aneurysm (12%, 95% CI=8 to 16).

Patients with asymptomatic CAS undergoing carotid endarterectomy (CEA) fared better than those treated medically for the primary outcome of perioperative stroke or death or any subsequent stroke (relative risk=0.69, 95% CI=0.57 to 0.83).[4] The absolute risk reduction, however, is small (approximately 1% per annum over the first few years of follow up). Nineteen patients with an asymptomatic CAS of at least 60% needed to undergo CEA to prevent one stroke or death in the coming 5 years, whereas 6 patients with a symptomatic

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Received November 4, 2006; accepted December 5, 2006.

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*Stroke* **is available at http://www.strokeaha.org** **DOI: 10.1161/STROKEAHA.106.477091**

CAS of 70% to 99% needed to undergo CEA to prevent one event in 5 years.[5]

The degree of asymptomatic CAS is related to various vascular risk factors, including age, smoking, systolic blood pressure, and cholesterol.[6] A higher degree of asymptomatic CAS was predictive for future stroke in patients with large artery or small vessel atherosclerotic disease but not in patients with a cardioembolic stroke in a study among 1820 patients.[7] Moreover, asymptomatic CAS has been related to future myocardial infarction (MI) and vascular death.[8–11] Most of these studies have been performed in the general population. Two small studies, restricted to patients with coronary heart disease (CHD) or abdominal aortic aneurysm (AAA), also reported an increased risk of vascular death or MI in patients with asymptomatic CAS.[12,13]

The aim of the present large prospective cohort study was to examine the relation between asymptomatic carotid artery stenosis and the risk of vascular events in patients with various clinical manifestations of arterial disease or presence of type 2 diabetes mellitus but without a history of cerebrovascular disease.

## Methods

### Study Population

This study is part of the Second Manifestations of ARTerial disease (SMART) study. Patients aged 18 to 79 years, newly referred to the University Medical Center Utrecht, The Netherlands, with risk factors for arterial disease (hypertension, hyperlipidemia, diabetes mellitus) or with symptomatic arterial disease (CHD, cerebrovascular disease, AAA, or peripheral arterial disease) were included in the SMART study. A detailed description of the study was published previously.[14] Briefly, patients who gave their written informed consent underwent a standardized vascular screening, including a health questionnaire, laboratory assessment, and ultrasonography to investigate the prevalence and incidence of additional vascular diseases. The Ethics Committee of the University Medical Center Utrecht approved the study.

For the current study, the data of 3722 consecutive patients presenting with symptomatic arterial disease or type 2 diabetes mellitus were available. Of those patients, 996 were excluded from the analysis because of a history of cerebrovascular disease. Forty-two patients had missing values on the carotid artery duplex scanning (attributable to logistic reasons) and were excluded. Thus, 2684 patients without cerebrovascular disease at baseline remained in the study.

### Vascular Screening

All patients visited the hospital after an overnight fast of at least 8 hours and underwent total vascular screening within 2 hours. Patients completed questionnaires on history of vascular disease (CHD, peripheral arterial disease, AAA, and cerebrovascular disease), risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking, alcohol consumption, physical activity, and familial vascular history), and current medication use. Height, weight, waist circumference, and blood pressure were measured according to a standardized diagnostic protocol. Fasting blood was sampled to determine serum glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, creatinine, and homocysteine levels. Low-density lipoprotein cholesterol was calculated according to Friedewald's formula. An early morning urine sample was collected to measure albumin and creatinine concentrations.

### Carotid Artery Stenosis

Ultrasound examinations were performed by well-trained and certified ultrasound technicians at the Department of Radiology. The degree of the asymptomatic CAS at both sides was assessed with color Doppler-assisted Duplex scanning. The severity of CAS was evaluated on basis of the blood flow velocity patterns.[15] The greatest stenosis observed on the right or the left side of the common or internal carotid artery was taken to determine the severity of carotid artery disease. Accordingly, all patients were classified into one of the following categories: absence of stenosis; mild stenosis (<50% diameter stenosis, peak systolic velocity [PSV] >100 to ≤150 cm/s); moderate stenosis (≥50% to 69% diameter stenosis, PSV >150 to ≤210 cm/s); severe stenosis (≥70% to 99% diameter stenosis, PSV >210 cm/s or preocclusion PSV >210 cm/s and distal PSV <40 cm/s or subtotal PSV <50 cm/s and severe plaque); and occlusion (100% diameter stenosis, no flow).[15]

**TABLE 1. Definitions of Fatal/Nonfatal Events**

| | |
|---|---|
| Vascular death | Sudden death: unexpected cardiac death occurring within 1 hour after onset |
| | of symptoms or within 24 hours given convincing circumstantial evidence |
| | Death from ischemic stroke |
| | Death from intracerebral hemorrhage (hemorrhage on CT scan) |
| | Death from congestive heart failure |
| | Death from myocardial infarction |
| | Death from rupture of AAA |
| | Vascular death from other cause such as sepsis after stent placement |
| Ischemic stroke | Definite: relevant clinical features that have caused an increase in impairment of at least one grade on the modified Rankin scale accompanied by a fresh ischemic infarction on a repeat brain scan |
| | Probable: clinical features that have caused an increase in impairment of at least one grade on the modified Rankin scale without a fresh ischemic infarction on a repeat brain scan |
| MI | Fatal or nonfatal MI: at least two of the following criteria |
| | 1. Chest pain for at least 20 minutes, not disappearing after administration of nitrates |
| | 2. ST elevation more than 1 mm in 2 following leads or a left bundle branch block on the electrocardiogram |
| | 3. CK elevation of at least 2 times the normal value of CK and a MB fraction more than 5% of the total CK |

CK indicates creatinine kinase; MB, myocardial band.

### Follow Up

Patients were biannually asked to complete a questionnaire on hospitalizations and outpatient clinic visits. The end point of interest for this study was a composite of first occurrence of a vascular event, namely vascular death, ischemic stroke, and myocardial infarction. Definitions of events are given in Table 1. If patients or family recorded such an event, we retrieved hospital discharge letters and the results of relevant laboratory and radiology examinations. Three members of the SMART study Endpoint Committee independently audited all events on the basis of available information. This committee consisted of physicians from different departments. In case of disagreement, consensus was reached by consulting other members of the Endpoint Committee.

### Data Analysis

The baseline characteristics were adjusted for age between patients with and without asymptomatic CAS with covariance analysis (general linear model procedure). Differences between patients with and without asymptomatic CAS were tested with $\chi^2$ (categorical

variables), unpaired *t* test (continuous normal distributed variables) or Mann–Whitney *U* test (continuous skewed variables).

Cox proportional hazard analysis was performed to estimate hazard ratios and 95% CIs for the occurrence of vascular events (composite vascular outcome and separate for vascular death, ischemic stroke, and MI) associated with the presence of asymptomatic CAS. If a patient had multiple events, the first was used in the analysis. The unadjusted association of asymptomatic CAS of 50% or greater and vascular events was examined in model I. In model II, this association was adjusted for age and gender. In model III, additional adjustments were made for systolic and diastolic blood pressure, current smoking, diabetes, use of antiplatelet agents, blood pressure-lowering agents, and lipid-lowering agents at baseline.

Furthermore, the extent of asymptomatic CAS (30% to 49%, 50% to 69%, 70% to 99%, 100% versus no asymptomatic CAS in that category as the reference group) was examined in relation to the composite vascular outcome and separate for vascular death, ischemic stroke, and MI.

Analyses were performed in SPSS version 12.0.1. (SPSS).

## Results

### Study Population

The age-adjusted baseline characteristics of the study population are presented in Table 2. Asymptomatic CAS of 50% or greater was present in 221 (8%) of the 2684 patients. Patients with asymptomatic CAS were older (mean age=65 versus 57 years), had a higher systolic blood pressure (144 versus 139 mm Hg), had higher total cholesterol (5.5 versus 5.3 mmol/L) and low-density lipoprotein cholesterol levels (3.4 versus 3.2 mmol/L), were more often ever-smokers (90% versus 78%), had higher serum creatinine levels (102 versus 97 μmol/L), and more often had a history of peripheral arterial disease (45% versus 26%) and AAA (20% versus 12%).

**TABLE 2. Age-Adjusted Baseline Characteristics of the Study Population (n=2684)**

| | CAS 50% or Greater (n=221) | No CAS (n=2463) | *P* Value |
|---|---|---|---|
| Male gender, % | 73 | 75 | 0.7 |
| Age, years | 64.5±8.3 | 56.9±11.7 | <0.001 |
| Systolic blood pressure, mm Hg | 144±20 | 139±20 | <0.001 |
| Diastolic blood pressure, mm Hg | 78±11 | 81±11 | <0.001 |
| Body mass index, kg/m$^2$ | 26.4±4.4 | 27.1±4.3 | 0.01 |
| Waist circumference, cm | 96±14 | 96±13 | 0.1 |
| Total cholesterol, mmol/L | 5.5±1.2 | 5.3±1.2 | <0.001 |
| Low-density lipoprotein cholesterol, mmol/L | 3.4±1.1 | 3.2±1.0 | <0.001 |
| High-density lipoprotein cholesterol, mmol/L | 1.2±0.4 | 1.2±0.4 | 0.7 |
| Triglycerides, mmol/L | 2.1±1.7 | 2.0±1.7 | 0,07 |
| Homocysteine, μmol/L | 14.7±7.4 | 14.0±9.7 | <0.001 |
| Fasting glucose, mmol/L | 7.2±2.8 | 6.8±2.7 | 0.3 |
| Diabetes mellitus,* % | 21 | 20 | 0.7 |
| Serum creatinine, μmol/L | 102±62 | 97±73 | <0.001 |
| Creatinine clearance (Cockroft), mL/min | 81±22 | 78±25 | <0.001 |
| Current smoking, % | 42 | 30 | <0.001 |
| Ever smoking, % | 90 | 78 | <0.001 |
| Medication use | | | |
| Antiplatelet agents, % | 63 | 54 | <0.001 |
| Blood pressure-lowering agents, % | 63 | 61 | 0.5 |
| Lipid-lowering agents, % | 45 | 42 | 0.4 |
| Angiotensin-converting enzyme inhibitor and/or AIIA, % | 29 | 23 | 0.05 |
| Vascular disease† | | | |
| CHD, % | 59 | 59 | 1.0 |
| Peripheral arterial disease, % | 45 | 26 | <0.001 |
| AAA, % | 20 | 12 | <0.001 |

Data represent mean (SD) or percentages.

*Patients on glucose-lowering agents.

†Ever or current diagnosis, a single person can be classified into more than one disease category.

### Fatal and Nonfatal Events During Follow Up

During a mean follow up of 3.6 years (SD=2.3), 239 of the 2684 (9%) patients died (147 of a vascular event), 49 (2%) patients experienced an ischemic stroke, and 165 (6%) patients had an MI. Compared with patients without an ischemic stroke during the follow up, the 49 patients who experienced an ischemic stroke were older (62 versus 57 years), had an impaired renal function (creatinine clearance 68 versus 82 mL/min), used blood pressure-lowering agents more often (82% versus 59%), and more often had a history of peripheral arterial disease (43% versus 26%) and AAA (25% versus 11%). Compared with patients without a MI during follow up, the 165 patients who had a MI were older (62 versus 57 years), had an impaired renal function (creatinine clearance 69 versus 82 mL/min), used blood pressure-lowering agents more often (84% versus 59%), and had a history of CHD (69% versus 59%), peripheral arterial disease (35% versus 26%) and AAA (24% versus 11%) more often.

The composite of ischemic stroke, MI, or vascular death occurred in 253 patients (9%). The number of events in patients with an asymptomatic CAS was higher compared with patients without an asymptomatic CAS for all outcome events (Table 3). An ipsilateral ischemic stroke occurred in 5 of the 6 patients with an asymptomatic CAS of 50% or greater. The cumulative incidence after 5 years was 12.3% (95% CI=10.7 to 13.9) for the composite of subsequent vascular events, 2.2% (95% CI=1.4 to 2.8) for cerebral infarction, and 8.0% (95% CI=6.6 to 9.4) for MI in the total study population.

Silent infarcts were present in 8 (21%) of the 38 patients with asymptomatic CAS and in 90 (15%) of the 609 patients without an asymptomatic CAS (relative risk of silent infarction=1.54, 95% CI=0.68 to 3.46). New clinical vascular events occurred in 2 (5%) of the 38 patients with asymptomatic CAS and in 29 (5%) of the 609 patients without an asymptomatic CAS. Hence, in this subsample of patients, neither silent infarcts nor new vascular events were significantly higher in those with asymptomatic CAS.

**TABLE 3. Number of Events in Patients With and Without CAS During Follow Up**

| | Asymptomatic CAS 50% or Greater (n=221) | No Asymptomatic CAS (n=2463) |
|---|---|---|
| Nonvascular death | 17 (8) | 74 (3) |
| Vascular death | 34 (15) | 114 (5) |
| MI | 28 (13) | 137 (6) |
| Ischemic stroke | 6 (3) | 43 (2) |
| All first vascular events | 44 (20) | 209 (9) |
| CEA | 13 (6) | 4 (0) |
| Endovascular intervention | 2 (1) | ... |

Data represent number of patients with percentages in parentheses.

## Vascular Events in Patients With Asymptomatic Carotid Artery Stenosis

In Table 4, the hazard ratios of different vascular events are given for asymptomatic CAS of 50% or greater and of 70% or greater. Adjusted for age and gender, the presence of asymptomatic CAS of 50% or greater and of 70% or greater was related to a higher risk of subsequent vascular events (hazard ratio [HR]=1.5, 95% CI=1.1 to 2.1) and (HR=1.5, 95% CI=1.0 to 2.1), respectively. When the vascular events were separated into vascular death, ischemic stroke, and MI, the relative risk of vascular death (HR=1.8, 95% CI=1.2 to 2.6 and HR=1.5, 95% CI=1.0 to 2.4) was associated with the presence of asymptomatic CAS of 50% or greater and of 70% or greater was slightly higher. After adjustment for vascular risk factors known to be associated with the degree of CAS and with vascular risk, the strength of the relations for any vascular event, vascular death, ischemic stroke, and MI remained essentially the same. Relationships of asymptomatic CAS with outcomes were similar in patients with and without peripheral arterial disease (data not shown). The 857 patients with diabetes mellitus and the presence of asymptomatic CAS of 50% or greater and of 70% or greater had the highest increased risk of vascular death (HR=3.2, 95% CI=1.6 to 6.4 and HR=2.6, 95% CI=1.1 to 6.1, respectively) compared with patients without diabetes. The extent of asymptomatic CAS and the risk of a subsequent event adjusted for age and gender are presented in Table 5. Patients with 30% to 49% asymptomatic CAS had a 1.2 increased risk of MI (HR=1.2, 95% CI=0.7 to 1.9), those with 50% to 69% CAS had the highest risk of vascular death (HR=2.1, 95% CI=1.1 to 3.8), and those with 70% to 99% CAS had a hazard ratio of 1.7 (95% CI=0.9 to 2.8) of MI. Patients with an occlusion of one of the carotid arteries detected at screening had a 2.6 increased risk of ischemic stroke (HR=2.6, 95% CI=0.8 to 8.4). The strength of the relations for any vascular event remained essentially the same after adjustment for vascular risk factors.

**TABLE 4. Relation Between Asymptomatic CAS and Vascular Events**

| | | HR (95% CI) | |
|---|---|---|---|
| Vascular Event | Model | CAS 50% or Greater to 99% (n=221) | CAS 70% or Greater to 99% (n=147) |
| All first vascular events (n=253) | I | 2.0 (1.5–2.8) | 2.1 (1.5–3.1) |
| | II | 1.5 (1.1–2.1) | 1.5 (1.0–2.1) |
| | III | 1.5 (1.1–2.1) | 1.5 (1.0–2.2) |
| Vascular death (n=147) | I | 2.8 (1.9–4.2) | 2.6 (1.7–4.1) |
| | II | 1.8 (1.2–2.6) | 1.5 (1.0–2.4) |
| | III | 2.0 (1.3–3.0) | 1.7 (1.1–2.8) |
| Ischemic stroke (n=49) | I | 1.3 (0.6–3.1) | 1.7 (0.7–4.2) |
| | II | 1.1 (0.5–2.6) | 1.3 (0.5–3.4) |
| | III | 1.2 (0.5–3.0) | 1.6 (0.6–4.2) |
| MI (n=165) | I | 2.0 (1.3–3.0) | 2.0 (1.2–3.2) |
| | II | 1.5 (1.0–2.3) | 1.4 (0.9–2.3) |
| | III | 1.5 (1.0–2.3) | 1.4 (0.8–2.3) |

Model I, unadjusted; model II, adjusted for age and gender; model III, additionally adjusted for systolic and diastolic blood pressure, current smoking, diabetes, use of antiplatelet agents, blood pressure-lowering agents, and lipid-lowering agents at baseline.

## Discussion

In patients with a previous clinical manifestation of arterial disease or type 2 diabetes mellitus, the presence of asymptomatic carotid artery stenosis (≥50%) was related to a higher risk of subsequent vascular events, in particular of vascular death. Moreover, the relative risk for any recurrent vascular event was greater when the extent of asymptomatic CAS increased. The associations were independent of age and gender.

To the best of our knowledge, only two other studies examined the prognostic value of asymptomatic CAS in patients with clinical manifest arterial disease. A study of 809 patients with stable CHD showed that asymptomatic CAS of 50% or greater was related to an increased risk of vascular death or MI in a univariate Cox regression analysis (HR=3.4, 95% CI=1.5 to 7.8).[12] After adjustment for age, sex, smoking, hypertension, diabetes mellitus, lipid status, and history of previous MI, asymptomatic CAS tended to predict vascular death or MI (HR=1.9, 95% CI=0.8 to 4.5). In another study, it was shown that in 208 patients electively operated for an AAA, the presence of an asymptomatic CAS of 50% or greater was independently associated with vascular mortality (HR=3.6, 95% CI=1.3 to 10.1) and morbidity (HR=4.0, 95% CI=1.8 to 9.0).[13] These studies and our present study indicate that, overall, in patients with clinical manifestations of arterial disease, the presence of asymptomatic CAS (≥50%) is a risk indicator of new vascular events. One of the differences between the previous studies and this study is that our study was conducted in a large prospective cohort of patients with well-defined diagnostic inclusion criteria of manifest arterial disease.

A study conducted in subjects with a mean age of 67 years showed that the death rate in 109 patients with self-reported cardiovascular disease or diabetes was only slightly higher (3.61 deaths per 100 person-years) than that in 139 patients with asymptomatic CAS who did not report cardiovascular disease or diabetes (3.14 deaths per 100 person-years).[10] The relative risks of vascular events associated with asymptomatic CAS seemed to be higher in the general population than

**TABLE 5. Risk of Any Vascular Event in Relation to the Extent of Asymptomatic CAS**

| | HRs Adjusted for Age and Gender With 95% CIs | | | |
|---|---|---|---|---|
| Asymptomatic CAS Extent* | All First Vascular Events (n=253) | Vascular Death (n=147) | Ischemic Stroke (n=49) | MI (n=165) |
| 30–49% (n=172) | 1.0 (0.6–1.5) | 0.8 (0.4–1.4) | 0.7 (0.2–2.1) | 1.2 (0.7–1.9) |
| 50–69% (n=74) | 1.4 (0.8–2.5) | 2.1 (1.1–3.8) | 0.6 (0.1–4.1) | 1.5 (0.7–3.0) |
| 70–99% (n=96) | 1.4 (0.9–2.2) | 1.5 (0.9–2.5) | 0.7 (0.2–3.0) | 1.7 (0.9–2.8) |
| 100% occlusion (n=51) | 1.5 (0.8–2.7) | 1.5 (0.7–3.2) | 2.6 (0.8–8.4) | 1.0 (0.4–2.5) |

*No carotid artery stenosis is reference category.

in patients with clinical manifestations of arterial disease. This may be caused by management of vascular risk factors and the use of antithrombotic medication, but different approaches used by investigators to define the study population and the degree of CAS may also play a role.

In the present study, we showed that the risk of vascular death is greater than the risk of stroke. This is consistent with previous studies in the general population.[1,16,17] The annual risk of stroke from asymptomatic CAS is approximately 1% per year in the general population,[11] 2% in the medical treatment group of the CEA trials,[18,19] and we found an annual stroke risk of less than 1%. This is probably attributable to the fact that our patients had no history of cerebral ischemia, had another clinical vascular disease, or were otherwise at high risk. Screening 2684 patients for detecting asymptomatic CAS resulted in a prevalence of 8%. The clinical consequence of the identification of asymptomatic CAS in patients with already clinical manifestations of arterial disease, however, is limited, and the cost-effectiveness remains to be determined. Asymptomatic CAS is an independent predictor of vascular events, in particular of vascular death, in patients with clinical manifest arterial disease as shown in this study. Management of these patients should be concentrated on a reduction of the total vascular risk rather than on the stroke risk only. Medical treatment (use of antiplatelet agents, lipid- and blood pressure-lowering agents), lifestyle changes (quit smoking, increase physical activity, appropriate diet), and close monitoring or follow-up measurements of existing vascular risk factors are essential to reduce the vascular risk in these patients. With advances in effective risk management, the benefit of CEA in patients with asymptomatic CAS may be further narrowed.

Follow up of asymptomatic CAS with duplex ultrasound for detecting progression of the degree of stenosis may identify patients with high risk for developing cerebral ischemia and may be a tool in selecting patients for CEA.[8] However, the cost-effectiveness of this strategy is unknown. New guidelines from the American Academy of Neurology support the use of CEA for patients aged 40 to 75 years with asymptomatic CAS of 60% to 99% if the patient has at least a 5-year life expectancy and if the surgery/complication rate is low (<3%).[5] The level of surgical expertise with CEA is related with the surgical risk. Surgeons with less expertise have a higher perioperative risk and this reverses the benefit of CEA.[4] So, in our view, effective treatment of the established vascular risk factors is the first treatment step to reduce vascular risk and if the degree of asymptomatic CAS progresses, then surgery may be considered. Patients with asymptomatic CAS but without cerebral ischemia do not have an increased risk of ischemic stroke but do have an increased risk of MI or vascular death, as shown in Table 4. Therefore, CEA in patients with asymptomatic CAS of 50% or greater may be of lesser benefit to reduce the risk of a recurrent vascular event. Whether this is also true for progressive asymptomatic CAS is not known.

We acknowledge some limitations of the study. The study population consisted of those patients who had survived their first vascular event, could be located, and were willing to participate. Thus, it could be that our patients were healthier than those not referred to our hospital, which may have led to an underestimation of the association between asymptomatic CAS and the risk of subsequent vascular events. Second, because in patients with asymptomatic CAS, the ipsilateral neurological event rate may be dependent on plaque characteristics,[20] we collected data about the structure of the carotid arterial wall and the characteristics of the atherosclerotic plaque. Unfortunately, these data were missing or not retrievable in approximately half of the patients. Therefore, we could not perform reliable analyses.

In conclusion, asymptomatic CAS of 50% or greater is an independent predictor of vascular events, in particular of vascular death, in patients with already clinical manifest arterial disease or type 2 diabetes but without a history of cerebrovascular ischemia.

## Appendix

Members of the SMART Study Group are: A. Algra, MD, PhD, Y. van der Graaf, MD, PhD, D.E. Grobbee, MD, PhD, and G.E.H.M. Rutten, MD, PhD, Julius Center for Health Sciences and Primary Care; F.L.J. Visseren, MD, PhD, Department of Vascular Medicine; H.A. Koomans, MD, PhD, Department of Nephrology; B.C. Eikelboom, MD, PhD, and F.L. Moll, MD, PhD, Department of Vascular Surgery; L.J. Kappelle, MD, PhD, Department of Neurology; W.P.T.M. Mali, MD, PhD, Department of Radiology; and P.A. Doevendans, MD, PhD, Department of Cardiology.

## Acknowledgments

We gratefully acknowledge the contribution of the SMART Study Group, the members of which are listed in the Appendix.

## Disclosures

None.

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