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Joke M. Dijk, Yolanda van der Graaf, Diederick E. Grobbee, Michiel L. Bots and on behalf of the SMART Study Group

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# Carotid Stiffness Indicates Risk of Ischemic Stroke and TIA in Patients With Internal Carotid Artery Stenosis

## The SMART Study

Joke M. Dijk, MD; Yolanda van der Graaf, MD, PhD; Diederick E. Grobbee, MD, PhD; Michiel L. Bots, MD, PhD; on behalf of the SMART Study Group

**Background and Purpose**—Patients with a carotid artery stenosis, including those with an asymptomatic or moderate stenosis, have a considerable risk of ischemic stroke. Identification of risk factors for cerebrovascular disease in these patients may improve risk profiling and guide new treatment strategies. We cross-sectionally investigated whether carotid stiffness is associated with previous ischemic stroke or transient ischemic attack (TIA) in patients with a carotid artery stenosis of at least 50%.

**Methods**—Patients were selected from the Second Manifestations of ARterial disease (SMART) study, a cohort study among patients with manifest vascular disease or vascular risk factors. Arterial stiffness, measured as change in lumen diameter of the common carotid arteries during the cardiac cycle, forms part of the vascular screening performed at baseline. The first 420 participants with a stenosis of minimally 50% in at least 1 of the internal carotid arteries measured by duplex scanning were included in this study. Logistic regression analysis was used to determine the relation between arterial stiffness and previous ischemic stroke or TIA.

**Results**—The risk of ischemic stroke or TIA in the highest quartile (stiffest arteries) relative to the lowest quartile was 2.1 (95% CI, 1.1 to 4.1). These findings were adjusted for age, sex, systolic blood pressure, minimal diameter of the carotid artery, and degree of carotid artery stenosis.

**Conclusion**—In patients with a  $\geq 50\%$  carotid artery stenosis, increased common carotid stiffness is associated with previous ischemic stroke and TIA. Measurement of carotid stiffness may improve selection of high-risk patients eligible for carotid endarterectomy and may guide new treatment strategies. (*Stroke*. 2004;35:2258-2262.)

**Key Words:** atherosclerosis ■ carotid arteries ■ carotid stenosis ■ cerebrovascular disorders ■ elasticity

It is well established that a stenosis of the carotid artery increases the risk of symptomatic cerebrovascular disease. The 15.3% reduction in 5-year risk of ischemic stroke in patients with a symptomatic internal carotid artery stenosis (ICAS) of 70% to 99% is usually considered large enough to perform carotid endarterectomy.<sup>1</sup> Nevertheless, patients with a lower degree of stenosis or with an asymptomatic stenosis also have a considerable risk of developing a stroke. The 5-year risk of stroke for symptomatic 50% to 69% stenosis is 22.2%,<sup>2</sup> whereas patients with an asymptomatic 60% to 99% stenosis have a 5-year risk of 16.2%.<sup>3</sup> Although carotid endarterectomy has proven to decrease the risk of ischemic stroke in these patients, this procedure is usually not performed because the absolute reduction in risk is low; thus, the number of patients needed to treat to prevent 1 stroke is considered too high.<sup>2-4</sup> Identification of new risk factors may improve the selection of high-risk subgroups for whom endarterectomy may be beneficial and may guide new (pre-

ventive) therapies.<sup>5,6</sup> We investigated whether increased common carotid stiffness, which has been shown to be an independent risk factor for ischemic stroke,<sup>7,8</sup> is related to the presence of cerebrovascular disease in patients with a carotid artery stenosis of  $\geq 50\%$ .

## Patients and Methods

### Study Population

In this study, we used data from patients enrolled in the Second Manifestations of ARterial disease (SMART) study. The SMART study is an ongoing prospective single-center cohort study in patients with manifest vascular disease or vascular risk factors. Starting in 1996, consecutive patients aged 18 to 80 years, referred to the University Medical Center Utrecht (UMCU) with manifest vascular disease (including transient ischemic attack [TIA], stroke, peripheral arterial disease, abdominal aortic aneurysm, angina pectoris, myocardial infarction, and renal artery stenosis) or a vascular risk factor (hyperlipidemia, hypertension, diabetes mellitus, and renal insufficiency), were invited to participate in the SMART study. Participants

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From the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands.

Members of the SMART study are listed in the Appendix.

Correspondence to Dr J.M. Dijk, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Huispostnummer Str. 6.131, Postbus 85060, 3508 BA Utrecht, The Netherlands. E-mail j.m.dijk@jc.azu.nl

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**TABLE 1. Classification Degree of Internal Carotid Artery Stenosis<sup>10</sup>**

Diameter Reduction	Peak Systolic Velocity (PSV)
50–69%	150 >PSV ≤210 cm/s
≥70%	PSV >210 cm/s
Preocclusion	PSV >210 cm/s and distal PSV <40 cm/s
Subtotal	PSV <50 cm/s and severe plaque
Occlusion	No flow

underwent a vascular screening including a questionnaire, blood chemistry, and ultrasonography. Written informed consent was obtained from all participants. The study was approved by the medical ethics committee of the UMCU. The rationale and design of the SMART study have been described in detail elsewhere.<sup>9</sup>

For the current study, the data of the consecutive first 3950 participants were considered. The 590 participants, who on duplex scanning of the carotid arteries had a ≥50% to subtotal (99%) stenosis of 1 of the internal carotid arteries, were selected for the current study (for definitions see Table 1). Patients with an occlusion were not selected, unless they had a ≥50% stenosis in the contralateral carotid artery. The 37 participants with a history of carotid endarterectomy were excluded from the analysis. In 4 patients it was unknown whether they had had a TIA or ischemic stroke. Stiffness measurements were missing because of equipment failure or logistical problems in 46 participants. Measurements of 29 patients were excluded from the analysis because the intraindividual variance in stiffness measurements was considered out of range because of an irregular cardiac rhythm or inability not to move or not to breathe during the assessment. Finally, of 474 participants with a ≥50% to subtotal ICAS data on arterial stiffness of at least 1 of the carotid arteries and on the presence of a history of TIA or ischemic stroke were available. In 420 of these participants the stiffness measured in the carotid artery with the highest degree of stenosis was known.

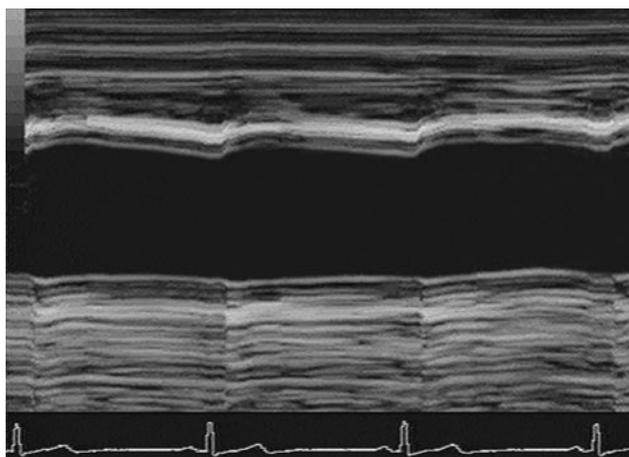
## Measurements

### Internal Carotid Artery Stenosis

Color Doppler-assisted duplex scanning of the carotid arteries was performed to detect ICAS and define the degree of stenosis. The degree of ICAS was classified based on blood flow velocities as shown in Table 1.<sup>10</sup>

### Carotid Artery Stiffness

Stiffness was assessed by measurement of distension of the common carotid arteries. The distension of an artery is the change in diameter in systole relative to the diastolic diameter during the cardiac cycle.



**Figure 1.** Distension of the common carotid artery during the cardiac cycle.

(Figure 1) Lower distension implies a stiffer artery. The displacement of the walls of the left and right common carotid artery was measured ultrasonographically with a wall track system (Scanner 200, Pie Medical) equipped with a 7.5 MHz linear array transducer and the vessel wall moving detector system. Patients were examined in supine position, with the head turned 45° away from the side examined. The left and right carotid arteries were examined separately. Measurements were performed in the distal common carotid artery 2 cm proximal to the origin of the carotid bulb. Details of the measurements have been described in detail elsewhere.<sup>11</sup> In short, at the right carotid artery, 5 assessments were performed. Each assessment lasted 4 seconds and comprised several cardiac cycles. For 1 patient the procedure lasted ≈20 minutes, including 5 minutes rest in supine position previous to the assessment. The measured distension per cardiac cycle was automatically computed during the assessment and immediately available.

First, the measured distension of the cardiac cycles within a single assessment was averaged. Next, the measurements of the 5 assessments were averaged. The process was repeated for the left carotid artery. The same procedure was followed for lumen diameter measurements. An intraobserver variability study on distension and end-diastolic lumen diameter measurements in healthy subjects showed a coefficient of variation of 6.2% and 2.1%, respectively. Between observers, this coefficient was 7.3% and 3.5%, respectively.<sup>11</sup>

### History of TIA or Ischemic Stroke

The presence of a history of TIA or ischemic stroke was assessed based on referral diagnosis and medical history. Patients who had 1 of the referral diagnoses (ischemic stroke, TIA, amaurosis fugax, retina infarction, or cerebral ischemia), or who stated a history of 1 of these diagnoses in the questionnaire) were considered to have a history of TIA or ischemic stroke.

### Vascular Screening

All elements of the vascular screening were conducted on 1 day at the UMCU. Blood samples were collected after an overnight fast. Glucose, total cholesterol, triglycerides, and HDL-cholesterol were measured. LDL-cholesterol was calculated with the Friedewald formula. Height and weight were measured without shoes and heavy clothing. Blood pressure was measured in supine position at the right brachial artery every 4 minutes during the arterial stiffness measurement, with a semiautomatic oscillometric device (Omega 1400, In Vivo Research Laboratories Inc). Medical history, use of current medication, and pack-years smoked were derived from a questionnaire described elsewhere.<sup>9</sup>

### Data Analysis

Baseline characteristics were determined for the group with and without a history of ischemic stroke and TIA. The association between carotid artery stiffness and the presence of previous ischemic stroke or TIA was determined using logistic regression models. We used the carotid distension and end-diastolic diameter measured at the common carotid artery with the highest degree of ICAS. Carotid distension was included as a continuous variable and in quartiles, comparing the quartile with the lowest distension (stiffest arteries) with that of the highest distension (more elastic arteries).

Two models were constructed, the first with adjustment for systolic blood pressure and diastolic diameter of the carotid artery (model I), because these are important determinants of distension, and the second with further adjustment for age, sex, and degree of carotid artery stenosis (model II). Other variables, including use of antihypertensive medication, lipid profile, body mass index, diabetes mellitus, and smoking behavior, were not included as confounders because they did not change the magnitude nor the direction of the association. Proper adjustment for the degree of carotid artery stenosis is important, because stenosis was associated with carotid distension at the ipsilateral side<sup>12</sup> and a strong risk factor for ischemic stroke and TIA.<sup>2,3</sup> We adjusted for the highest degree of carotid artery stenosis in a patient by including it in model II as a categorical variable. We chose to adjust for the highest degree of

**TABLE 2. Baseline Characteristics of the Study Population**

	Previous Ischemic Stroke or TIA (n=260)	No Previous Ischemic Stroke or TIA (n=160)
Sex, % (men)	79	67
Age, years	63.3 (9.1)	63.5 (9.1)
Systolic blood pressure, mm Hg	148.5 (19.7)	150.5 (21.6)
Diastolic blood pressure, mm Hg	79.6 (9.8)	78.6 (9.6)
Body mass index, kg/m <sup>2</sup>	25.9 (3.3)	25.9 (3.2)
Triglycerides, mmol/L	1.9 (1.0)	2.2 (1.5)
HDL-cholesterol, mmol/L	1.2 (0.3)	1.2 (0.4)
LDL cholesterol, mmol/L	3.6 (0.9)	3.5 (0.9)
Diabetes mellitus*, %	20	26
Pack-years	24.4 (19.7)	27.4 (22.6)
Current smoking, %	39	41
Ever smoking, %	89	88
Blood pressure-lowering medication, %	49	56
Lipid-lowering medication, %	40	36
Maximum ICAS $\geq$ 50%, %	14	37
Maximum ICAS $\geq$ 70%, %	58	53
Maximum ICAS preocclusion, %	20	9
Maximum ICAS subtotal, %	8	1
Distension common carotid artery, $\mu$ m†	411.4 (145.7)	458.0 (167.6)
Diastolic diameter common carotid artery, $\mu$ m†	8473 (1147)	8193 (1058)
History of stroke, %	60	0
Referred for cerebrovascular disease, %	87	0

Data are mean (SD) or %.

TIA indicates transient ischemic attack; ICAS, internal carotid artery stenosis.

\*Glucose-lowering medication, fasting glucose  $\geq$ 7.0 mmol/L or nonfasting glucose  $\geq$ 11.1 mmol/L.

†Measured at carotid artery with the highest degree of ICAS.

carotid artery stenosis because this is associated with the highest risk of ischemic stroke.<sup>3</sup> The analysis was repeated with the mean distension from the left and right carotid arteries.

## Results

Table 2 reflects the characteristics of the patients that did (n=260) or did not (n=160) experience a previous TIA or ischemic stroke and in whom the stiffness of the carotid artery with the highest degree of stenosis was known. The group with a previous TIA or ischemic stroke comprised more men and consisted of more patients with a higher degree of ICAS than patients without a history of symptomatic cerebrovascular disease. Of the patients with a history of symptomatic cerebrovascular disease, 60% had a history of ischemic stroke, whereas the remaining 40% of the patients had had amaurosis fugax, retina infarction, or a TIA. In the symptomatic group, 87% of the patients were referred and included in the study because of recent symptoms of cerebrovascular disease; the remaining 13% had a history of ischemic stroke or TIA and had been referred to the UMC Utrecht for other reasons.

As shown in Table 3, increasing carotid distension (implying decreasing arterial stiffness) is associated with a lower prevalence of a history of TIA or ischemic stroke, adjusted

for diastolic diameter, systolic blood pressure, degree of ICAS, age, and sex (odds ratio [distension/standard deviation of 164  $\mu$ m] 0.75 [95% CI, 0.60 to 0.94]). In quartiles, shown in Figure 2: patients in the quartile with the lowest distension (ie, stiffest arteries) have a 2.1 times (95% CI, 1.1 to 4.1) higher prevalence of a previous TIA or ischemic stroke compared with the patients in the quartile with the highest distension (Figure 2). Using the mean distension from both carotid arteries, instead of the distension measured at the

**TABLE 3. Relation of Common Carotid Artery Distension With Previous Ischemic Stroke or TIA**

	Distension Linear*	Distension in Quartiles†
	OR (95% CI)	OR (95% CI)
I	0.77 (0.62–0.94)	2.1 (1.2–3.8)
II	0.75 (0.60–0.94)	2.1 (1.1–4.1)

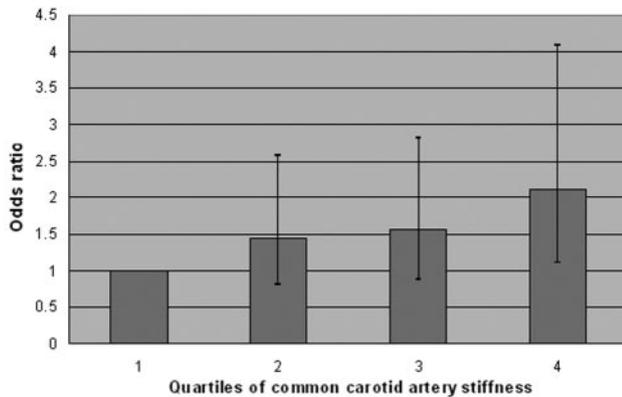
OR=Odds Ratio.

\*Distension in  $\mu$ m divided by SD (=164  $\mu$ m).

†Quartile with lowest distension (stiffest arteries) vs quartile with highest distension.

I, Adjusted for diastolic diameter carotid artery and systolic blood pressure.

II, Model I, additionally adjusted for age, sex, and maximum degree of carotid artery stenosis.



**Figure 2.** Relation of distension (in quartiles) with previous ischemic stroke or TIA. In quartile 1, the reference group, are the patients with the most elastic arteries. Bars are odds ratios with 95% CI, adjusted for age, sex, systolic blood pressure, diastolic diameter of the carotid artery, and degree of internal carotid artery stenosis.

carotid artery with the highest degree of stenosis, demonstrated similar results (odds ratio, 2.2 [95% CI, 1.1 to 4.2] for the quartile with the lowest versus the quartile with the highest distension).

## Discussion

This study shows that increased carotid stiffness is associated with a higher prevalence of previous TIA or ischemic stroke in patients with a  $\geq 50\%$  to subtotal ICAS.

We used carotid distension rather than the commonly used distensibility coefficient ( $2 \times [\text{distension}/\text{diastolic diameter}]/\text{pulse pressure}$ ) because noncombined variables were preferred. A ratio in a statistical model may obscure the impact of the separate variables. Instead of correcting for diastolic diameter and blood pressure by using a ratio as in the distensibility coefficient, we adjusted for these variables in the linear regression model.

The association between arterial stiffness and the presence of a history of symptomatic cerebrovascular disease was studied cross-sectionally. In a cross-sectional study, results may be biased because the variable under study may have changed after the occurrence of the outcome. This does not seem to be the case in our study, because arterial stiffness is not likely to be influenced by the occurrence of ischemic stroke or TIA. However, some studies have shown that physically inactive people have stiffer arteries than physically active people,<sup>13,14</sup> and one may argue that people who experienced a stroke in the past may have an increased arterial stiffness because of inactivity. This does not seem to explain our results, because only people with a nondisabling disease were included in the study. In addition, the reference group largely consists of people who were referred for peripheral arterial disease or coronary artery disease, and thus probably are not extremely physically active themselves. Finally, the symptoms of cerebrovascular disease had occurred recently in 87% of the people because they entered the study because of these symptoms. Patients may have received antihypertensive treatment after the occurrence of a vascular event, and treatment with certain antihypertensive medication has been shown to reduce arterial stiffness.<sup>15</sup> As antihyper-

tensive medication did not appear to be confounding, antihypertensive treatment of one of the groups does not explain our results either.

In this study, patients with a carotid artery stenosis who had experienced an ischemic stroke or TIA had stiffer carotid arteries than those who did not experience symptoms of cerebrovascular disease. The association did not change after adjusting for potential confounders. Several mechanisms may explain our results. First, an increased arterial stiffness leads to an increase in pulse pressure by a faster recurrence of the reflected wave.<sup>16,17</sup> The resulting pulsatile stress has been shown to be a potent stimulus for carotid plaque rupture and has been associated with plaque ulceration.<sup>18,19</sup> Furthermore, the increased arterial stiffness measured in the common carotid artery may reflect an increased arterial stiffness and pulse pressure in the intracerebral vasculature. The pathological changes in the carotid arterial wall causing an increased arterial stiffness, such as fibrosis, calcifications, and breaks in elastin fibers, indeed have also been shown in intracerebral vessels.<sup>20,21</sup> Whether the increased arterial stiffness is mainly associated with intracerebral small vessel disease resulting in lacunar infarction (a relatively common cause of stroke in patients with an ICAS),<sup>22,23</sup> with an embolism from the stenosed internal carotid artery, or with both needs to be evaluated in future research. Furthermore, whether the increased arterial stiffness is mainly related to ischemic stroke or TIA in the territory of one cerebral artery cannot be concluded from this study, because the information unfortunately was not available.

Other potential risk factors for cerebrovascular disease in patients with a carotid artery stenosis, such as plaque morphology,<sup>24</sup> asymptomatic embolization,<sup>25</sup> and impaired cerebral vasoreactivity,<sup>26</sup> have been reported. The associations between these risk factors and stroke and TIA are consistent with our findings: the risk of cerebrovascular disease increases with more severely damaged arteries.

Thus, arterial stiffness appears to be associated with previous ischemic stroke and TIA in patients with a  $\geq 50\%$  to subtotal stenosis of a carotid artery. It is of interest to further establish the value of this noninvasive technique in discriminating between patients with a carotid artery stenosis at high and at low risk for symptomatic cerebrovascular disease in a prospective follow-up study. In addition, because patients with low arterial stiffness appeared to experience fewer cerebrovascular events, reduction of arterial stiffness may prevent cerebrovascular disease. Especially, angiotensin-converting enzyme-inhibitors<sup>15</sup> and advanced glycosylated end-product-breakers<sup>27</sup> have been shown to effectively reduce arterial stiffness and may provide an alternative treatment in patients with a carotid artery stenosis.

In conclusion, this study demonstrates that carotid stiffness is associated with a history of TIA or ischemic stroke in patients with a  $\geq 50\%$  to subtotal carotid artery stenosis. Measurement of carotid stiffness may improve selection of high-risk patients for whom carotid endarterectomy is beneficial. As well, reduction of carotid stiffness may be an alternative treatment option in these patients.

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## Appendix

Members of the SMART Study Group (in alphabetical order): A. Algra, MD, FAHA, Julius Center for Health Sciences and Primary Care and Department of Neurology; J.D. Banga, MD, PhD, Department of Vascular Medicine; B.C. Eikelboom, MD, PhD, Department of Vascular Surgery; Y. van der Graaf, MD, PhD, Julius Center for Health Sciences and Primary Care; D.E. Grobbee, MD, PhD, Julius Center for Health Sciences and Primary Care; P.P.Th. de Jaegere, MD, PhD, Department of Cardiology; L.J. Kappelle, MD, PhD, Department of Neurology; H.A. Koomans, MD, PhD, Department of Nephrology; W.P.T.M. Mali, MD, PhD, Department of Radiology; F.L. Moll, MD, PhD, Department of Vascular Surgery; 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; all members are from the University Medical Center Utrecht, The Netherlands.

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