Carotid Atherosclerosis and Progression of Brain Atrophy: The SMART-MR Study

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Objective: Atherosclerosis has been implicated in the development of brain atrophy. However, support for this association comes from cross-sectional studies.

Methods: Within the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, a prospective cohort study among patients with symptomatic atherosclerotic disease (mean age ± standard deviation, 58 ± 10 years; 80% men), magnetic resonance imaging of the brain was performed in 1,232 patients at baseline (2001–2005) and in 663 patients at follow-up (2006–2009). Brain segmentation was used to quantify total brain volume, cortical gray matter volume, and ventricular volume as indicators of global, cortical, and subcortical atrophy. At baseline, measurements of carotid intima–media thickness (CIMT) and carotid stenosis were performed. Carotid stenosis was classified into groups 0 of 50%, 50 of 70% (moderate), and >70% (severe) and into unilateral or bilateral stenosis.

Results: Cross-sectional regression analyses showed that both increased CIMT and carotid stenosis were associated with decreased relative total brain and cortical gray matter volume. Our prospective findings showed that after a mean follow-up of 3.9 years (range, 3.0–5.8 years), CIMT and moderate stenosis were not related to progression of brain atrophy. Only severe or bilateral carotid stenosis was related to progression of global atrophy (β [95% confidence interval (CI)], −0.52% [−0.84 to −0.20%], −0.94% [−1.45 to −0.43%]), cortical atrophy (β [95% CI], −0.75% [−1.37 to −0.13%], −1.34% [−2.32 to −0.35%]), and subcortical atrophy (β [95% CI], 0.06% [−0.02 to 0.16%], 0.13% [0.01 to 0.28%]).

Interpretation: In a study of patients with atherosclerotic disease with 4 years of follow-up, only severe or bilateral carotid stenosis, and not moderate carotid stenosis and increased CIMT, were associated with progression of brain atrophy.

Over the past decade, evidence has accumulated that vascular risk factors and vascular disease play an important role in the etiology of dementia and cognitive impairment.1 Evidence exists that atherosclerotic processes underlie the association of vascular risk factors and dementia. Previous studies have shown that carotid atherosclerosis is associated with dementia and its subclinical markers.2–8 This association may be mediated by cerebrovascular disease, such as embolic stroke or cerebral small-vessel disease.7,9,10 The relation between carotid atherosclerosis and dementia could also be explained by hemodynamic changes in the cerebral circulation. Recent studies have shown that patients with carotid atherosclerosis have an increased risk of cerebral hypoperfusion,11,12 which subsequently may cause brain atrophy and dementia.13–15

Limited evidence exists on the direct relation between carotid atherosclerosis and brain atrophy. Cross-sectional studies have shown that increased carotid intima–media thickness (CIMT) and carotid stenosis are associated with decreased total brain volume,6,8 as well as with ventricular and sulcal widening.7 However, only 1 cross-sectional study used quantitative brain volume measurements,6 and no studies examined the longitudinal association of carotid atherosclerosis with progression of brain atrophy.
The objective of this study was to investigate whether presence and severity of carotid atherosclerosis was related to presence and progression of global, cortical, and subcortical atrophy using quantitative brain volume measurements in individuals with symptomatic atherosclerotic disease.

Patients and Methods
SMART-MR Study
Data were used from the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study, a prospective cohort study aimed at investigating brain changes on magnetic resonance imaging (MRI) in 1,309 independently living patients with symptomatic atherosclerotic disease. Details of the design and participants have been described elsewhere.16,17 In brief, between May 2001 and December 2005, all patients newly referred to the University Medical Center Utrecht with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease, or an abdominal aortic aneurysm, and without MR contraindications, were invited to participate. Excluded were patients with a terminal disease, those not independent in daily activities, and those referred back to the referring specialist immediately after 1 visit. During a 1-day visit to our medical center, an MRI of the brain was performed, in addition to a physical examination, ultrasonography of the carotid arteries, and blood sampling. Risk factors, medical history, and functioning were assessed with questionnaires that the patients completed before their visit to the medical center. Between January 2006 and May 2009, all participants still alive (n = 1,238) were invited for follow-up measurements, including MRI of the brain, a physical examination, blood sampling, risk factors, and medical history. In total, 754 of the surviving cohort (61%) gave written informed consent and participated. The SMART-MR study was approved by the ethics committee of our institution, and written informed consent was obtained from all participants.

Carotid Atherosclerosis
Presence of atherosclerosis in the carotid arteries was assessed at baseline by measuring CIMT and carotid artery stenosis. Ultrasonography was performed with a 10MHz linear-array transducer (ATL Ultrasound 9) by well-trained and certified ultrasonographers at the Department of Radiology, University Medical Center Utrecht. Mean CIMT (in millimeters) was calculated for each patient based on 6 far-wall measurements of the left and right common carotid arteries as previously described.18 The degree of the carotid artery stenosis at both sides was assessed with color Doppler-assisted duplex scanning. The severity of carotid artery stenosis was evaluated on the basis of blood flow velocity patterns.19 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. Carotid artery stenosis $\geq 50\%$ was defined as peak systolic velocity $>150$ cm/s, and a carotid artery stenosis $>70\%$ was defined as peak systolic velocity $>210$ cm/s.19 We classified carotid stenosis into groups of 0 to 50% (no or limited), 50 to 70% (moderate), and $>70\%$ (severe). In addition, we classified carotid stenosis $>50\%$ into unilateral or bilateral stenosis.

Magnetic Resonance Protocol and Brain Segmentation
At baseline and follow-up, the MR investigations were performed on a 1.5T whole-body system (Gyroscan ACS-NT, Philips Medical Systems, Best, the Netherlands). The protocol consisted of transversal T1-weighted (repetition time [TR]/echo time [TE], 235/2 milliseconds), T2-weighted (TR/TE, 2,200/11 milliseconds and 2,200/100 milliseconds), fast fluid-attenuated inversion recovery (FLAIR; TR/TE/inversion time [TI], 6000/100/2000 milliseconds), and inversion recovery (IR; TR/TE/TI, 2900/22/410 milliseconds) sequences (field of view [FOV], 230 $\times$ 230mm; matrix size, 180 $\times$ 256; slice thickness, 4.0mm; no gap; 38 slices).16 Next, on the basis of a localizer MR angiographic slab in the sagittal plane, a 2-dimensional (2D) phase-contrast section was positioned at the level of the skull base to measure the volume flow in the internal carotid arteries (ICAs) and the basilar artery (BA).14 The 2D phase-contrast section was positioned through the ICAs and the BA (TR/TE, 16/9 milliseconds; flip angle, 7.5°; FOV, 250 $\times$ 250mm; matrix size, 256 $\times$ 256; slice thickness, 5.0mm; 8 acquired signals; velocity sensitivity, 100cm/s).

We used the T1-weighted gradient-echo, IR sequence and FLAIR sequence for brain segmentation. The probabilistic segmentation technique has been described elsewhere, and has been proven to be very reliable, with similarity indices $>0.8$ for all segmented tissue and cerebrospinal fluid (CSF) volumes.20,21 The segmentation program distinguishes cortical gray matter, white matter, sulcal and ventricular CSF, and lesions. The results of the segmentation analysis were visually checked for the presence of infarcts and adapted if necessary to make a distinction between white matter lesion (WML) and infarct volume. Total brain volume was calculated by summing the volumes of gray matter, white matter, WMLs, and infarcts. Total intracranial volume (ICV) was calculated by summing the total brain volume and the volumes of the sulcal and ventricular CSF. In 188 patients, the IR and T1-weighted sequences were missing due to a temporary change in MRI protocol, and the brain segmentation in these patients was based on the FLAIR sequence. Intraclass correlation coefficients between the segmentation using all 3 sequences and FLAIR only based on a subset of 740 patients were 0.995, 0.996, 0.961, 0.996, and 0.985 for ICV, total brain volume, CSF, ventricular volume, and WML volume, respectively.

Brain Atrophy
The brain volumes that were used for this analysis were total brain volume, cortical gray matter volume, and ventricular volume as indicators of global, cortical, and subcortical atrophy. All brain volumes were normalized for ICV.22
Brain Infarcts, WMLs, Cerebral Blood Flow
At baseline and follow-up, the whole brain was visually searched for infarcts by an investigator and a neuroradiologist. Discrepancies in rating were re-evaluated in a consensus meeting. Raters were blinded regarding the history and diagnosis of the patient. Infarcts were defined as focal hyperintensities on T2-weighted images of at least 3mm in diameter. Hyperintensities located in the white matter also had to be hypointense on T1-weighted and FLAIR images to distinguish them from WMLs. Dilated perivascular spaces were distinguished from infarcts on the basis of their location, form, and the absence of gliosis. The location, affected flow territory, and type were scored for every infarct. Brain infarcts were categorized as cortical infarcts, large subcortical infarcts, infarcts in the cerebellum and brainstem, and lacunar infarcts. We defined lacunar infarcts as infarcts sized 3 to 15mm in diameter and located in the subcortical white matter, thalamus, or basal ganglia. Large subcortical infarcts had the same characteristics as lacunar infarcts, but were sized >15mm and were located exclusively in subcortical areas.

Volumes of WMLs obtained with the segmentation program consisted of deep and periventricular WML volumes and were summed to obtain the total volume of WMLs. WML volumes were normalized for ICV.22

Postprocessing of the flow measurements was performed by 1 investigator.14,23 The flow through the left and right ICAs and BA was summed to calculate the total cerebral blood flow (tCBF; ml/min). We expressed tCBF per 100ml brain parenchymal volume to obtain a measure of cerebral perfusion (pCBF).23

Vascular Risk Factors
During the patient’s baseline visit to the medical center, height and weight were measured without shoes and heavy clothing, and the body mass index (BMI) was calculated (kg/m²). Smoking habits and alcohol intake were assessed with questionnaires. Pack years of smoking were calculated, and alcohol intake was categorized as never, former, or current. Systolic blood pressure (SBP; mmHg) and diastolic blood pressure (DBP) were measured twice with a sphygmomanometer, and the average of the 2 readings was recorded for every infarct. Brain infarcts were categorized as cortical infarcts, large subcortical infarcts, infarcts in the cerebellum and brainstem, and lacunar infarcts. We defined lacunar infarcts as infarcts sized 3 to 15mm in diameter and located in the subcortical white matter, thalamus, or basal ganglia. Large subcortical infarcts had the same characteristics as lacunar infarcts, but were sized >15mm and were located exclusively in subcortical areas.

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Study Sample
Of the 1,309 patients, 19 had no MRI, and 14 had no FLAIR sequence. In addition, in 44 patients, brain volume data were missing due to motion or artifacts. As a result, baseline MRI data were available in 1,232 patients. Of the 1,232 patients, 718 patients participated in the follow-up exam. Of these, 38 had no MRI, and in 17 patients brain volume data were missing due to motion or artifacts. As a result, the analyses for the prospective analysis were performed in 663 patients.

Data Analysis
Missing data rarely occur completely at random, and a complete case analysis (deletion of all participants with 1 or more missing values) leads to loss of statistical power and to biased results.24,25 We therefore used multiple imputation (10 datasets) to address the missing values,26 using the statistical program R (aregImpute; version 2.10.0). Data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL), by pooling the 10 inputted datasets. Subject characteristics were calculated for the baseline SMART-MR cohort (n = 1,232) and for the SMART-MR sample with follow-up measurements (n = 663).

Linear regression analysis was used to investigate the cross-sectional association of CIMT and carotid stenosis with baseline relative total brain, cortical gray matter, and ventricular volume. In addition, linear regression analysis and analysis of covariance were used to investigate the prospective association of baseline carotid atherosclerosis with change in measures of brain volume by using brain volume measurements at follow-up as dependent variable and brain volume measurements at baseline as independent variable. Cross-sectional and prospective analyses were adjusted for age, sex, and follow-up time (model 1). To examine if the relation between carotid atherosclerosis and brain volume was explained by vascular risk factors, we further adjusted for smoking, alcohol consumption, BMI, hypertension, diabetes, and hyperlipidemia (model 2).

As presence of large brain infarcts is a strong confounder in the association of carotid atherosclerosis and brain volume, the above-mentioned analyses were repeated after exclusion of patients with a history of cerebrovascular disease or with 1 or more nonlacunar infarcts on MRI. Finally, to investigate whether reduced pCBF and presence of WMLs and lacunar infarcts mediate the association of carotid atherosclerosis with change in brain volume, we additionally adjusted the analyses for pCBF or for WMLs and lacunar infarcts.

Results
Mean (standard deviation [SD]) age of the total SMART-MR population (N = 1,232) was 58 (10) years. Compared with the total SMART-MR population, patients with follow-up measurements (n = 663) were younger at baseline, had hypertension and diabetes less often, had smaller CIMT, and less often had severe carotid stenosis (Table 1). The percentages of missing variables varied between 0 and 15%. Mean (SD) baseline total brain, cortical gray matter, and ventricular volumes for the total SMART-MR population were 79 (3), 36 (3), and 2.1 (1.0) %ICV and for the patients with follow-up were 79 (3), 36 (3), and 2.0 (0.8) %ICV.

Cross-sectional linear regression analyses, adjusting for age and sex, showed that an increase in CIMT of 1 SD (0.31mm) and presence of moderate, severe, or
bilateral carotid stenosis were associated with smaller total brain and cortical gray matter volume (Table 2). CIMT was also associated with larger ventricular volume. These associations were independent of cardiovascular risk factors. When repeating the cross-sectional analyses in the 663 patients with follow-up data, the results presented in Table 2 were similar (data not shown).

After a mean (SD; range) follow-up of 3.9 (0.4; 3.0–5.8) years, CIMT, moderate carotid stenosis, and unilateral stenosis were not related to change in brain volume (Fig). Only severe or bilateral carotid stenosis were related to a decrease in total brain and cortical gray matter volume and an increase in ventricular volume. Compared with patients with no or limited carotid stenosis, the differences (β, 95%
confidence interval [CI]) in change in total brain, cortical gray matter, and ventricular volume adjusted for age, sex, smoking, alcohol consumption, BMI, hypertension, diabetes, hyperlipidemia, and follow-up period were $-0.52$ (95% CI: $-0.84$ to $-0.20$), $-0.75$ (95% CI: $-1.37$ to $-0.13$), and $0.06$ (95% CI: $-0.02$ to $0.16$) %ICV for patients with severe stenosis and $-0.94$ (95% CI: $-1.45$ to $-0.43$), $-1.34$ (95% CI: $-2.32$ to $-0.35$), and $0.13$ (95% CI: $0.01$ to $0.28$) %ICV for patients with bilateral stenosis. Exclusion of patients with total occlusion of the carotid artery ($n = 32$) did not change our findings (data not shown). After exclusion of patients with nonlacunar infarcts on MRI ($n = 80$) or patients with cerebrovascular disease ($n = 153$), the associations of carotid stenosis with brain volumes did not change (data not shown).

To examine if reduced pCBF mediated the association of severe or bilateral carotid stenosis with progression of brain atrophy, we additionally adjusted the regression analyses for pCBF. The association of severe or bilateral stenosis with a decrease in total brain and cortical gray matter volume and an increase in ventricular volume were partly explained by reduced pCBF; $\beta$s (95% CI) for severe carotid stenosis were $-0.47$ (95% CI: $-0.72$ to $-0.21$), $-0.46$ (95% CI: $-1.05$ to $0.12$), and $0.06$ (95% CI: $0.00$ to $0.13$) %ICV and for bilateral stenosis were $-0.92$ (95% CI: $-1.33$ to $-0.50$), $-0.78$ (95% CI: $-1.80$ to $0.23$), and $0.15$ (95% CI: $0.03$ to $0.27$) %ICV. Adjustment for WMLs and lacunar infarcts further attenuated the association of severe or bilateral carotid stenosis with change in brain volumes; $\beta$s (95% CI) for severe carotid stenosis were $-0.54$ (95% CI: $-0.80$ to $-0.28$), $-0.46$ (95% CI: $-1.04$ to $0.13$), and $0.06$ (95% CI: $0.00$ to $0.13$) %ICV and for bilateral stenosis were $-0.92$ (95% CI: $-1.33$ to $-0.50$), $-0.78$ (95% CI: $-1.80$ to $0.23$), and $0.15$ (95% CI: $0.03$ to $0.27$) %ICV.

| TABLE 2: Cross-Sectional Relation between Baseline Carotid Atherosclerosis Measures and Baseline Brain Volume in 1,232 Patients |
|---------------------------------|----------------|----------------|----------------|
| **Model** | **Total Brain Volume, % ICV** | **Cortical Gray Matter Volume, % ICV** | **Ventricular Volume, % ICV** |
| | $\beta^b$ | 95% CI | $\beta^b$ | 95% CI | $\beta^b$ | 95% CI |
| CIMT, per SD increase $^c$ | | | | | | |
| 1 | $-0.29$ | $-0.42$ to $-0.17^d$ | $-0.33$ | $-0.52$ to $-0.14^d$ | $0.07$ | $0.02$ to $0.12^e$ |
| 2 | $-0.20$ | $-0.33$ to $-0.08^d$ | $-0.22$ | $-0.42$ to $-0.03^e$ | $0.06$ | $0.01$ to $0.11^e$ |
| Carotid stenosis | | | | | | |
| 0 to 50%, reference | 1 | $0.00$ | $0.00$ | $0.00$ |
| Moderate, 50 to 70% | $-0.51$ | $-1.15$ to $0.14$ | $-1.15$ | $-2.12$ to $-0.17^e$ | $0.11$ | $-0.15$ to $0.37$ |
| Severe, $>70\%$ | $-0.89$ | $-1.27$ to $-0.51^d$ | $-1.42$ | $-1.99$ to $-0.84^d$ | $0.15$ | $0.00$ to $0.30$ |
| 0 to 50%, reference | 2 | $0.00$ | $0.00$ | $0.00$ |
| Moderate, 50 to 70% | $-0.29$ | $-0.93$ to $0.34$ | $-0.90$ | $-1.87$ to $0.07$ | $0.07$ | $-0.19$ to $0.33$ |
| Severe, $>70\%$ | $-0.70$ | $-1.08$ to $-0.32^d$ | $-1.22$ | $-1.79$ to $-0.64^d$ | $0.11$ | $-0.04$ to $0.26$ |
| Carotid stenosis | | | | | | |
| 0 to 50%, reference | 1 | $0.00$ | $0.00$ | $0.00$ |
| Unilateral $>50\%$ | $-0.75$ | $-1.13$ to $-0.35^d$ | $-1.33$ | $-1.93$ to $-0.73^d$ | $0.15$ | $-0.01$ to $0.30$ |
| Bilateral $>50\%$ | $-0.92$ | $-1.52$ to $-0.32^d$ | $-1.42$ | $-2.33$ to $-0.52^d$ | $0.12$ | $-0.13$ to $0.36$ |
| 0 to 50%, reference | 2 | $0.00$ | $0.00$ | $0.00$ |
| Unilateral $>50\%$ | $-0.55$ | $-0.94$ to $-0.17^e$ | $-1.12$ | $-1.72$ to $-0.52^d$ | $0.11$ | $-0.05$ to $0.26$ |
| Bilateral $>50\%$ | $-0.71$ | $-1.30$ to $-0.12^e$ | $-1.19$ | $-2.09$ to $-0.28^e$ | $0.10$ | $-0.15$ to $0.34$ |

$^a$Model 1: adjusted for age and sex; model 2: additionally adjusted for smoking, alcohol consumption, body mass index, hypertension, diabetes, and hyperlipidemia.

$^b\beta$ = coefficient of linear regression; an increase of the independent variable by 1 unit is associated with a $\beta$ increase of brain volume.

$^c$SD = standard deviation.

$^d$ICV = intracranial volume; CI = confidence interval; CIMT = carotid intima–media thickness.
CI) for severe carotid stenosis were -0.42 (-0.67 to -0.16), -0.36 (-0.95 to 0.22), and 0.05 (-0.02 to 0.12) %ICV and for bilateral stenosis were -0.84 (-1.26 to -0.41), -0.67 (-1.68 to 0.35), and 0.14 (0.01 to 0.26) %ICV.

Finally, post hoc analysis excluding patients with suspected cognitive impairment (Mini Mental State Examination < 24) did not change the results (data not shown).

Discussion

In a population with symptomatic atherosclerotic disease, we observed that increased CIMT and carotid stenosis were significantly associated with decreased relative total brain and cortical gray matter volume. However, our prospective findings showed that only severe or bilateral carotid stenosis, but not increased CIMT or moderate stenosis, were related to progression of global, cortical, and subcortical atrophy over a 4-year period of patient follow-up. This relation was independent of age, sex, and vascular risk factors, such as hypertension, hyperlipidemia, and diabetes, and was partly explained by reduced cerebral perfusion and cerebral small-vessel disease.

Our cross-sectional findings are in agreement with previous studies such as the Cardiovascular Health Study and the Framingham Study.6,7 These large-scale population-based studies reported that increased CIMT as well as moderate and severe carotid stenosis were associated with sulcal and ventricular widening7 and with smaller total brain volume.6 To our knowledge, this is the first study that also examined the prospective relation of measures of carotid atherosclerosis with progression of brain atrophy. An explanation of the disparity between the cross-sectional and prospective findings could be that carotid stenosis and CIMT reflect different stages and severity of the atherosclerotic process.18,19 Carotid stenosis and plaques are irreversible focal manifestations of atherosclerosis, whereas increased CIMT represents mainly hypertensive medial hypertrophy.27 In fact, studies have shown that CIMT could be reduced by antihypertensive and lipid-lowering treatment.28,29 However, because CIMT has proven to be a strong predictor of future cardiovascular events,30 it is unlikely that treatment could have explained the discrepancies between the cross-sectional and prospective findings. It is, however, conceivable that compared with severe or bilateral carotid stenosis, increased CIMT or moderate stenosis may require a longer follow-up time than 4 years to achieve similar effects on progression of brain atrophy. The disparity between the cross-sectional and prospective findings could not be explained by a healthy survivor effect, because the cross-sectional results were similar within the 663 patients with complete follow-up. Another explanation for the cross-sectional results could be that carotid atherosclerosis and brain atrophy are independent processes with common elements in the causal pathway, because many of the contributory factors in atherosclerosis have emerged as potential contributors in dementia.31 Common pathophysiological elements could include hypertension, hyperlipidemia, inflammation, or genetic factors.31 Although adjustment for cardiovascular risk...
Several mechanisms may explain an association between severe or bilateral carotid stenosis and progression of brain atrophy. Cerebrovascular disease may mediate the association between atherosclerosis and atrophy. Because excluding individuals with large brain infarcts on MRI did not affect the estimate, it is not likely that the association with brain atrophy is explained by cortical or large subcortical infarcts. However, adjusting the analyses for presence of cerebral small-vessel disease, such as WMls and lacunar infarcts, partly mediated the association between atherosclerosis and progression of brain atrophy. Also, severe or bilateral stenosis may induce cerebral hypoperfusion leading to cerebral hypoxia especially in individuals with reduced or impaired collateral circulation. A good collateral circulation can generate normal cerebral hemodynamics in patients with carotid stenosis. When collaterals are not adequate, the perfusion pressure distal to the lesion begins to fall, which might trigger regional brain microcirculatory disturbances that can evolve into a neurodegenerative process, eventually leading to brain atrophy. The cortical gray matter is especially vulnerable to hypoperfusion, because the gray matter has higher oxygen and glucose requirements than the white matter. This is confirmed by our findings that adjusting for pCBF, as an indicator of cerebral perfusion, only attenuated the association of carotid stenosis with progression of cortical atrophy. Future studies are needed, using measures of flow in the circle of Willis and cerebral perfusion at brain tissue level, to further elucidate the relation between carotid artery disease, collateral circulation, cerebral hypoperfusion, and neurodegeneration.

Strengths of our study are the large number of patients investigated and the volumetric assessment of measures of brain atrophy, which made it possible to obtain precise estimates of progression of brain atrophy, and resulted in a large power to detect associations. Volumetric segmentation methods have several advantages compared with visual rating and 2D assessment of brain atrophy. Contrary to visual rating scales, volumetric assessments are not impeded by ceiling effects. Furthermore, volumetric segmentation methods are more precise, and therefore more likely to detect small differences in brain volumes that cannot be detected by visual rating and 2D techniques. In addition, the segmentation of different brain tissue types and CSF spaces allowed us to differentiate between cortical and subcortical brain atrophy. Finally, the extensive information on markers of cerebrovascular pathology and cardiovascular risk factors allowed us to investigate whether the association between carotid atherosclerosis and brain atrophy was independent of these possible confounders or modifiers. Our interpretation of the results may be limited by a few factors. First, individuals who participated in the follow-up examination represent a relatively healthy group. If anything, however, this may have led to an underestimation of the true association. Second, because the majority of our study sample consisted of male patients with atherosclerotic disease, we do not know to what extent our results also apply to women or can be generalized to the general population. Although we adjusted for vascular risk and disease, our population consisted of patients with manifest arterial disease, and it is thus still possible that other factors than atherosclerosis may explain our findings, such as heart failure or hypoxia, which may have occurred during myocardial infarction or cardiovascular interventions. Nonetheless, our cross-sectional findings were similar to those found in population-based samples.

In summary, in this prospective study in patients with symptomatic atherosclerotic disease, only high grade or bilateral carotid artery narrowing led to progression of brain atrophy.

Acknowledgment

Supported by a program grant from the Netherlands Organization for Scientific Research-Medical Sciences (NWO-MW: project No. 904-65-095) and a grant from the Netherlands Organization for Scientific Research (NWO: project No. 917-66-311; M.I.G.).

Potential Conflicts of Interest

A.A.: grants, Netherlands Heart Foundation, Netherlands Brain Foundation, Thrombosis Foundation Holland, Netherlands Organization for Scientific Research, and Netherlands Organization for Health Research and Development; consulting fee/honorarium, Boehringer Ingelheim; other, a principal investigator of ESPRIT, the European/Australian Stroke Prevention in Reversible Ischemia Trial, a trial that was run independently of any pharmaceutical company; after completion and full analysis of ESPRIT, the study group accepted financial support from Boehringer Ingelheim for post hoc exploratory analyses of the ESPRIT trial data; for this purpose a contract was signed ensuring complete scientific freedom.

Appendix

We thank the members of the SMART Study Group of University Medical Center Utrecht: A. Algra, MD, PhD, Julius Center for Health Sciences and Primary Care, Rudolf Magnus Institute for Neurosciences, Department
of Cardiology; Y. van der Graaf, MD, PhD, Department of Epidemiology; Y. van der Graaf, MD, PhD, Department of Neurology; P. A. Doevendans, MD, PhD, Department of Vascular Medicine.

ANNALS of Neurology

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