Carotid atherosclerosis is an important cause of stroke. Because stroke results in considerable morbidity and mortality,1 prevention is pivotal. At present, degree of stenosis and symptomatology are the main grounds to perform carotid endarterectomy (CEA). Pooled analysis of large randomized controlled trials showed that CEA is highly beneficial for symptomatic patients with high-grade (>70%) stenosis, reducing the 5-year absolute risk of ipsilateral ischemic stroke with 16%.2 However, in symptomatic patients with moderate (50% to 69%) carotid stenosis, the 5-year absolute risk reduction of ipsilateral stroke is only 4.6%, whereas CEA has no effect in symptomatic patients with mild (30% to 49%) carotid stenosis.2 Differences in benefit from CEA may be explained by a higher prevalence of vulnerable plaques (ie, plaques with a high tendency to cause future thromboembolic events) in patients with high-grade stenosis.

Histopathologic studies suggest that vulnerable plaques are characterized by the presence of a large lipid-rich necrotic core (LRNC) with a thin and/or ruptured fibrous cap (FC) and intraplaque hemorrhage (IPH).3,4 These plaques are histologically also referred to as complicated or Type VI plaques according to criteria of the American Heart Association5 and can be noninvasively identified by MRI.6–10 When unoperated, the 5-year risk of ipsilateral stroke for the group of symptomatic patients with mild or moderate stenosis approaches as much as 20%.2 In this group, it would be very useful to identify high-risk patients so that selection

Symptomatic Patients With Mild and Moderate Carotid Stenosis

Plaque Features at MRI and Association With Cardiovascular Risk Factors and Statin Use

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Background and Purpose—The objectives of this study were to assess plaque characteristics in symptomatic patients with mild and moderate carotid stenosis and to explore associations with cardiovascular risk factors and statin use.

Methods—One hundred patients with transient ischemic attack or stroke with ipsilateral mild and moderate carotid stenosis underwent MR plaque imaging.

Results—Patients with moderate stenosis had plaques with a higher prevalence of intraplaque hemorrhage (48.7% versus 19.7%, \(P=0.002\)) and a thin and/or ruptured fibrous cap (61.5% versus 36.1%, \(P=0.013\)), and larger lipid-rich necrotic core percentage (12.3% versus 6.8%, \(P=0.042\)) and smaller fibrous tissue percentage (82.7% versus 88.4%, \(P=0.024\)). Increasing age was positively associated with intraplaque hemorrhage (OR [per year]=1.08; 95% CI, 1.02 to 1.14; \(P=0.011\)). Statin use was negatively associated with intraplaque hemorrhage (OR=0.30; 95% CI, 0.10 to 0.93; \(P=0.038\)), a thin and/or ruptured fibrous cap (OR=0.34; 95% CI, 0.13 to 0.89; \(P=0.028\)), and with lipid-rich necrotic core percentage (B=−7.91; 95% CI, −13.60 to −2.22; \(P=0.007\)). Statin use was positively associated with fibrous tissue percentage (B=7.77; 95% CI, 2.40 to 13.14; \(P=0.005\)).

Conclusions—We found that symptomatic patients with moderate stenosis have a higher prevalence of complicated plaques than patients with mild stenosis. Exploratory analysis showed that increasing age was positively associated with intraplaque hemorrhage, whereas statin use was negatively associated with complicated plaque features. (Stroke. 2010; 41:1389-1393.)

Key Words: cardiovascular risk factors ■ carotid atherosclerosis ■ MRI ■ statins ■ stroke

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.109.575670

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was defined as reported use of medication for diabetes mellitus or
angiotensin II receptor antagonists, or calcium antagonists. Diabetes mellitus
also recorded whether patients were already using statins before the
event. We did not assess cholesterol levels, because in practice,
many patients are already on statin therapy, irrespective of the initial
lipid profile.14,15

MRI Protocol
The MRI protocol and method to analyze MR images has been
described previously.9,10 MRI examinations were performed on a
1.5-T whole-body imager (Intera 11.1.4.4; Philips Healthcare, Best,
The Netherlands). A dedicated 47-mm-diameter surface coil (Philips
Healthcare) was used for unilateral plaque imaging at the symptomatic
side. Nine transverse 3-dimensional T1-weighted turbo field
echo, 3-dimensional time-of-flight, 2-dimensional T2-weighted
turbo spin-echo, and pre- and postcontrast 2-dimensional T1-
weighted turbo spin-echo images (double inversion-recovery black
blood technique) were obtained. Slice thickness was 3 mm (including
a 0.5-mm gap for the 2-dimensional sequences). The postcontrast
T1-weighted turbo spin-echo sequence was obtained 7 to 8 minutes
after intravenous administration of 0.1 mmol/kg body weight of
gadopentate dimeglumine (Magnevist; Bayer Schering Pharma AG,
Berlin, Germany). All scanning was performed by 1 experienced
investigator (R.M.K.). Images were viewed immediately after acqui-
sition. When an image was of insufficient quality to be analyzed, the
sequence was repeated.

MR images were evaluated by 1 investigator with 2 years of
experience in plaque analysis by MRI (R.M.K.) blinded to the
clinical characteristics as listed previously. MR images were evalu-
ated using dedicated software (VesselMASS; Department of Radi-
ology, Leiden University Medical Center, The Netherlands).10 Re-

gions of interest were drawn around identified plaque components
(Figure) using previously published criteria.6,7,9,10 The software
calculated total plaque volume and volumes of LRNC, calcifications,
and fibrous tissue. In the present study, LRNC, calcifications, and
fibrous tissue were expressed as percentage of total vessel wall
volume. IPH was identified as a carotid plaque signal hyperintensity
on T1-weighted turbo field echo9 or on the time-of-flight images9
(Figure). Using postcontrast T1-weighted turbo spin-echo images,
FC status was classified as “thin and/or ruptured” (Figure) or “intact
and thick.”9

Reproducibility data are not part of the present study but have
been published previously in a different setting.9,10 Interobserver
reproducibility of volumetric measurements of individual plaque
components was good (intraclass correlation coefficient=0.64 to
0.92).10 Interobserver reproducibility for the detection of IPH was

Cardiovascular Risk Factors and Statin Use
Sex and age were recorded. Patients were categorized into current,
former, and never smokers. Hypertension was defined as a systolic
blood pressure ≥140 mm Hg and/or a diastolic blood pressure
≥90 mm Hg or treatment with antihypertensive medication (diuret-
ics, β-blockers, angiotensin-converting enzyme inhibitors, angioten-
sin II receptor antagonists, or calcium antagonists). Diabetes mellitus
was defined as reported use of medication for diabetes mellitus or
fasting plasma glucose level ≥126 mg/dL. History of ischemic heart
disease was defined as a clinical diagnosis of myocardial infarction,
angina pectoris, or coronary artery bypass grafting or stenting. We
also recorded whether patients were already using statins before the

Patients and Methods

Patients
Patients who were diagnosed by a neurologist as having recent (<3
months) amaurosis fugax, transient ischemic attack, or minor stroke in
the carotid territory and an ipsilateral carotid plaque causing mild or
moderate stenosis were eligible for inclusion. Mild carotid
stenosis was defined as a peak systolic velocity <125 cm/s at the site of
maximal luminal narrowing on B-mode duplex ultrasonography11
and a luminal diameter reduction of at least 30% on transverse
B-mode duplex ultrasonography images.12 Moderate stenosis was
defined as a peak systolic velocity of 125 to 230 cm/s at the site of
maximal luminal narrowing.11 Exclusion criteria were atrial fibrilla-
tion or another potential cardiac source of embolism, contraindic-
tions for MRI,13 and a renal clearance <30 mL/min/1.73 m². This
study was approved by our Institutional Review Board. All patients
gave written informed consent.

Figure. Coregistered T1-weighted turbo field echo (TFE), time-of-flight,
T2-weighted turbo spin-echo, pre- and postcontrast T1-weighted turbo spin-echo
images of a transverse section of a carotid plaque. The right bottom panel
displays the regions of interest: black, lumen; white, LRNC; dark gray, calcifica-
tions; light gray, fibrous tissue. Intraplaque hemorrhage was scored as
being present (asterisks in T1-weighted TFE and time-of-flight images) and the FC
was designated as thin and/or ruptured (arrow in postcontrast T1-weighted turbo
spin-echo image). In addition to deep calcifications, there is a small nodular-
shaped juxtaluminal calcification (arrowheads).
very good (κ coefficient = 0.86.10) Interobserver reproducibility of FC status assessment was good (κ = 0.60 to 0.71).9

Statistical Analysis
Statistical analysis was performed using SPSS 11.5 (SPSS Inc, Chicago, Ill). Correlations between plaque composition and time after symptoms, and between clinical characteristics, were assessed by Pearson rank correlation tests. Very weak, weak, moderate, strong, and very strong correlation were defined as Pearson ρ of 0 to 0.19, 0.20 to 0.39, 0.40 to 0.59, 0.60 to 0.79, and 0.80 to 1.00, respectively.16 Differences in plaque characteristics between patients with mild and moderate carotid stenosis were assessed by independent-samples t tests and Pearson χ² tests for continuous and dichotomous measures of plaque composition, respectively. Scatterplots were generated to visually explore relationships between age (which is a continuous variable) and continuous measures of plaque composition (percentages LRNC, calcifications, and fibrous tissue). In case a nonlinear relationship was observed, continuous measures of plaque composition were natural log-transformed. Relations between clinical characteristics and plaque characteristics were explored by multivariate logistic (OR) and linear (regression-coefficient B) analyses for dichotomous and continuous plaque composition. Results of exploratory regression analyses are displayed in Table 3. Increasing age was positively associated with the presence of IPH (OR [per year] = 1.08; 95% CI, 1.02 to 1.14; P = 0.011). The use of statins before the event was negatively associated with the presence of IPH (OR = 0.30; 95% CI, 0.10 to 0.93; P = 0.038) and a thin and/or ruptured FC (OR = 0.34; 95% CI, 0.13 to 0.89; P = 0.028). The use of statins before the event was negatively associated with LRNC percentage (B = −0.79; 95% CI, −13.60 to −2.22; P = 0.007) and positively associated with fibrous tissue percentage (B = 0.77; 95% CI, 2.40 to 13.14; P = 0.005).

Discussion
In the present study, we assessed plaque characteristics in patients with transient ischemic attack and minor stroke with ipsilateral mild to moderate carotid stenosis in whom the balance between benefit and risk of CEA is small. All patients were defined symptomatic ipsilateral to the atherosclerotic lesion according to North American Symptomatic Carotid Endarterectomy Trial and European Carotid Surgery Trial criteria.17,18 Plaques with IPH and a thin and/or ruptured FC (complicated plaque features) were identified in 31% and 46% of patients with mild and moderate stenosis, respectively. Although there were no significant differences in total plaque volume, patients with moderate stenosis had a higher prevalence of plaques with IPH and a thin and/or ruptured FC and larger LRNC percentage and smaller fibrous tissue percentage. Exploratory analysis showed that increasing age was positively associated with the presence of IPH. It also

### Table 1. Cardiovascular Risk Factors of the 100 Patients Analyzed

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean± SD or Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>64%</td>
</tr>
<tr>
<td>Age, (years)</td>
<td>69.2±10.3</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>20%</td>
</tr>
<tr>
<td>Former smokers</td>
<td>46%</td>
</tr>
<tr>
<td>Never smokers</td>
<td>34%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26%</td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
<td>23%</td>
</tr>
<tr>
<td>Use of statins before event</td>
<td>42%</td>
</tr>
</tbody>
</table>

### Table 2. Carotid Plaque Features at MRI for All Patients and for Patients With Mild and Moderate Carotid Stenosis Only

<table>
<thead>
<tr>
<th>Carotid Plaque Features at MRI</th>
<th>Mean±SE or Percent</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients (n=100)</td>
<td>Patients With Mild Stenosis (n=61)</td>
</tr>
<tr>
<td>Total plaque volume, mm³</td>
<td>1027±33</td>
<td>1022±38</td>
</tr>
<tr>
<td>LRNC, %</td>
<td>9.0±1.3</td>
<td>6.8±1.5</td>
</tr>
<tr>
<td>Calcifications, %</td>
<td>4.8±0.4</td>
<td>4.7±0.5</td>
</tr>
<tr>
<td>Fibrous tissue, %</td>
<td>86.2±1.2</td>
<td>88.4±1.4</td>
</tr>
<tr>
<td>Intraplaque hemorrhage</td>
<td>31.0%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Thin and/or ruptured fibrous cap</td>
<td>46.0%</td>
<td>36.1%</td>
</tr>
</tbody>
</table>
showed that the use of statins was negatively associated with the presence of IPH and a thin and/or ruptured FC and with LRNC percentage, whereas it was positively associated with fibrous tissue percentage.

Several studies have shown that the presence of IPH, a thin and/or ruptured FC, and larger LRNC percentage are associated with the occurrence of future ipsilateral transient ischemic attack and stroke. In the present study, these plaque features were found to be more prevalent in patients with moderate carotid stenosis and may explain why these patients have more benefit from CEA than patients with mild stenosis. Exploratory analysis showed that increasing age is positively associated with the presence of IPH, whereas the use of statins is negatively associated with complicated plaque features, which were present in several of the included patients, are associated with the occurrence of ipsilateral ischemic stroke. Second, we did not prospectively assess effects of statins on plaque characteristics by comparing plaque features before and after initiation of statin medication. Third, this was an exploratory study and because of the relatively small sample size (n = 100), we did not correct for the multiple comparisons performed. Although the observed relationships were plausible, they should be verified in an independent study. Fourth, in patients who were on statin therapy, there was a large variation in type, dosage, and duration of statin use before the event. Therefore, we could not explore the association between each of these individual parameters and plaque characteristics. Last, because we only performed unilateral plaque imaging, we could not investigate the relation between clinical characteristics and plaque composition at the contralateral (asymptomatic) side.

In conclusion, we found that major cardiovascular risk factors (ie, sex, tobacco use, hypertension, diabetes mellitus, and history of ischemic heart disease) and plaque composition, which is in accordance with the findings of the CT study by Rozie et al.25

Our study has several limitations. First, we did not perform clinical follow-up, which is needed to assess whether complicated plaque features, which were present in several of the included patients, are associated with the occurrence of ipsilateral ischemic stroke. Second, we did not prospectively assess effects of statins on plaque characteristics by comparing plaque features before and after initiation of statin medication. Third, this was an exploratory study and because of the relatively small sample size (n = 100), we did not correct for the multiple comparisons performed. Although the observed relationships were plausible, they should be verified in an independent study. Fourth, in patients who were on statin therapy, there was a large variation in type, dosage, and duration of statin use before the event. Therefore, we could not explore the association between each of these individual parameters and plaque characteristics. Last, because we only performed unilateral plaque imaging, we could not investigate the relation between clinical characteristics and plaque composition at the contralateral (asymptomatic) side.

In conclusion, we found that symptomatic patients with moderate carotid stenosis have a higher prevalence of complicated plaques compared with patients with mild stenosis. Exploratory analysis showed that increasing age is positively associated with the presence of IPH, whereas the use of statins is negatively associated with complicated plaque features.

Source of Funding
Supported by Dutch Heart Foundation grant 2006B061.

Disclosures
None.

References


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*Stroke*. 2010;41:1389-1393; originally published online May 13, 2010; doi: 10.1161/STROKEAHA.109.575670

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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