Symptomatic Patients With Mild and Moderate Carotid Stenosis

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

Robert M. Kwee, MD; Robert J. van Oostenbrugge, MD; Martin H. Prins, MD; Johannes W.M. ter Berg, MD; Cees L. Franke, MD; Arthur G.G.C. Korten, MD; Bé J. Meems, MD; Jos M.A. van Engelshoven, MD; Joachim E. Wildberger, MD; Werner H. Mess, MD; M. Eline Kooi, PhD

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

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 symptomatic stenosis 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 Association\(^5\) 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...
for CEA can be improved. An initial study by Saam et al demonstrated that with increasing stenosis grade, the prevalence of complicated plaques at MRI also increased. However, no analysis was performed with regard to patient symptomatology. Furthermore, little is known about the association between clinical characteristics and plaque features in symptomatic patients with mild to moderate carotid stenosis. Therefore, the present study was designed to assess carotid plaque characteristics in symptomatic patients with mild and moderate carotid stenosis, and to explore associations with cardiovascular risk factors and statin use.

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 ultrasonography and a luminal diameter reduction of at least 30% on transverse B-mode duplex ultrasonography images. Moderate stenosis was defined as a peak systolic velocity of 125 to 230 cm/s at the site of maximal luminal narrowing. Exclusion criteria were atrial fibrillation or another potential cardiac source of embolism, contraindications for MRI, 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.

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 (diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin 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 event. We did not assess cholesterol levels, because in practice, many patients are already on statin therapy, irrespective of the initial lipid profile.

MRI Protocol

The MRI protocol and method to analyze MR images has been described previously. 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 acquisition. 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 evaluated using dedicated software (VesselMass; Department of Radiology, Leiden University Medical Center, The Netherlands). Regions of interest were drawn around identified plaque components (Figure) using previously published criteria. 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 echo or on the time-of-flight images (Figure). Using postcontrast T1-weighted turbo spin-echo images, FC status was classified as “thin and/or ruptured” (Figure) or “intact and thick.”

Reproducibility data are not part of the present study but have been published previously in a different setting. Interobserver reproducibility of volumetric measurements of individual plaque components was good (intraclass correlation coefficient = 0.64 to 0.92). Interobserver reproducibility for the detection of IPH was
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 measures, respectively. Level of significance was 0.05.

Results
One hundred two consecutive patients underwent MRI scanning. Two patients were excluded because their MR images could not be used due to poor quality and incomplete examination, respectively. Eventually, 100 patients (61 with mild and 39 with moderate carotid stenosis) were analyzed. Mean time interval between last symptoms and MRI examination was 32.1 ± 19.7 days. Clinical characteristics are displayed in Table 1. Patients who were on statin therapy used atorvastatin (10 to 40 mg), pravastatin (20 to 40 mg), rosuvastatin (10 to 20 mg), and simvastatin (10 to 40 mg) for 8 months to 22 years (median 5 years) before the event. Carotid plaque features are displayed in Table 2. There was no significant correlation between plaque composition and time after symptoms (Pearson ρ = −0.118 to 0.090; P = 0.248 to 0.489). There were no strong correlations between the various clinical parameters (Pearson ρ = 0.319). Total plaque volume was not different between patients with mild and moderate carotid stenosis. Patients with moderate stenosis had a higher prevalence of plaques with IPH and a thin and/or ruptured FC. Additionally, these patients had plaques with a larger LRNC percentage and smaller fibrous tissue percentage. Scatterplots (not shown) did not reveal nonlinear relationships between age and continuous measures of 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 = 0.34; 95% CI, 0.13 to 0.89; 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 = −7.91; 95% CI, −13.60 to −2.22; P = 0.007) and positively associated with fibrous tissue percentage (B = 7.77; 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</td>
<td>Patients With Mild Stenosis</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>
features,6,7,9 we also found that the use of statins is 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,19–22 a thin and/or ruptured FC, and larger LRNC percentage22 at MRI 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 age was positively associated with the presence of IPH, which may explain why CEA is more beneficial in elderly patients.23 The relationship between statin therapy and carotid plaque composition has also been explored by others; Underhill et al24 showed that the use of statins is associated with a decrease in LRNC percentage and an increase in fibrous tissue percentage as assessed by MRI.24 Rozie et al25 performed a cross-sectional study in 100 symptomatic patients with varying degrees of stenosis, in which they assessed the relationship between carotid plaque characteristics at CT and cardiovascular risk factors. They found that patients with hypercholesterolemia had a smaller percentage of lipid in the plaque, which was explained because many of these patients were using statins.25 In accordance with the studies by Underhill et al24 and Rozie et al,25 our study also showed that the use of statins is associated with smaller LRNC percentage. At present, CT cannot reliably distinguish intraplaque hemorrhage from LRNC26 and FC status cannot be assessed. Using MRI, which enables reliable assessment of plaque features,6,7,9 we also found that the use of statins is associated with a lower prevalence of plaques with IPH and a thin and/or ruptured FC. Altogether, these studies suggest that the use of statins modifies plaque phenotype. Future studies should investigate whether the effect of statins on plaque composition, as monitored by noninvasive imaging, also reduces the risk of clinical events. We found no association between other 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.

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Disclosures
None.

References
1. Shaalan WE, Wahlgren CM, Desai T, Piano G, Skelly C, Bassiouny HS.
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