Plaque Components in Symptomatic Moderately Stenosed Carotid Arteries Related to Cerebral Infarcts
The Plaque At RISK Study

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Background and Purpose—Carotid plaque composition is a major determinant of cerebrovascular events. In the present analysis, we evaluated the relationship between intraplaque hemorrhage (IPH) and a thin/ruptured fibrous cap (TRFC) in moderately stenosed carotid arteries and cerebral infarcts on MRI in the ipsilateral hemisphere.

Methods—A total of 101 patients with a symptomatic 30% to 69% carotid artery stenosis underwent MRI of the carotid arteries and the brain, within a median time of 45 days from onset of symptoms. The presence of ipsilateral infarcts in patients with and without IPH and TRFC was evaluated.

Results—IPH was seen in 40 of 101 plaques. TRFC was seen in 49 of 86 plaques (postcontrast series were not obtained in 15 patients). In total, 51 infarcts in the flow territory of the symptomatic carotid artery were found in 47 patients. Twenty-nine of these infarcts, found in 24 patients, were cortical infarcts. No significant relationship was found between IPH or TRFC and the presence of ipsilateral infarcts.

Conclusions—MRI detected IPH and TRFC are not related to the presence of old and recent cortical and subcortical infarcts ipsilateral to a symptomatic carotid artery stenosis of 30% to 69%.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01208025.

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Key Words: cerebral infarction ■ carotid stenosis ■ plaque, atherosclerotic

Large randomized controlled trials have demonstrated that patients with a symptomatic 70% to 99% stenosis of the carotid artery benefit most from carotid endarterectomy.1 In line with these results, decision making for patients with a symptomatic carotid artery stenosis is currently based on the degree of stenosis. Nevertheless, in the past decades, research has demonstrated that atherosclerotic plaque components may also play a role in risk assessment of these patients.2

Previous MRI studies suggest a correlation between specific carotid plaque components and the presence of cerebral infarcts on MRI, as well as clinical events during follow-up.3-6 The aim of the present cross-sectional study is to evaluate the association between intraplaque hemorrhage (IPH) and a thin/ruptured fibrous cap (TRFC) and the presence of infarcts on MRI in patients with a symptomatic 30% to 69% carotid artery stenosis. Vulnerable plaque components, such as IPH, remain detectable in the plaque even after 18 months.7 Therefore, we hypothesize that both old and recent infarcts might be related to vulnerable carotid plaque components as assessed on MRI. Because not all subcortical infarcts are considered to be a result from large-vessel disease, in contrast to cortical infarcts, we evaluate both cortical and total amount of infaracts.

Methods

Study Population
The current study was based on the Plaque At RISK (PARISK) study, a prospective diagnostic cohort study.4 Inclusion and exclusion criteria...
are previously described. A detailed description of the stenosis calculation can be found on http://stroke.ahajournals.org. Institutional review board approval was obtained, and all patients gave a written informed consent.

Imaging

Brain and carotid imaging were performed on the same day. Imaging was performed on 3.0 Tesla whole-body MRI scanners, with an imaging protocol described previously. A brief description of the imaging protocol can be found on http://stroke.ahajournals.org.

Image Analysis

Two trained readers (M.T. and A.D.), blinded for the brain MRI results, performed the carotid MRI analysis in VesselMASS (Leiden University Medical Center, Leiden, the Netherlands). Analysis was performed according to previously published criteria, which demonstrated a moderate to good intra- and interobserver reproducibility ($\kappa$ coefficient=0.60–1.00).

All brain MRI scans were evaluated for the presence of infarcts. Of all scored infarcts, the localization in the brain (cortical or subcortical) and the flow territory was subsequently determined. Brain images were assessed by a single experienced neuroradiologist (J.H.), blinded for the carotid MRI and clinical characteristics.

Statistical Analysis

The association between plaque components and the presence of infarcts on MRI was evaluated with a Fisher exact test. Statistical analyses were performed in IBM SPSS Statistics version 20 (IBM Corporation, Armonk, NY).

Results

IPH was present in 40 of 101 patients. In 15 patients, the fibrous cap status could not be assessed because no postcontrast MRI was obtained (n=6) or the postcontrast series had inferior image quality (n=9). Consequently, the fibrous cap status could be evaluated in 86 patients, and a TRFC was present in 49 of these patients. In 8 patients, both a TRFC and IPH were present (Figure 1). In total, 51 infarcts in the flow territory of the symptomatic carotid artery were found in 47 patients. Twenty nine of these infarcts, found in 24 patients, were located in the cortical region (Figure 2). An overview of baseline characteristics is given in the Table. In Table I in the online-only Data Supplement, a distribution of infarcts compared with the classification of the index event is demonstrated.

Figure 1. Overview of T$_1$ turbo spin echo (TSE) before and after gadolinium (Gd) administration, time-of-flight (TOF) sequence and a T$_1$ TFE sequence. Internal carotid artery (ICA), external carotid artery (ECA), and jugular vein (JV) are marked. The intraplaque hemorrhage is pointed out with an open arrowhead, visible as a high signal intensity relative to the signal intensity of the sternocleidomastoid muscle (*) and a thin/ruptured fibrous cap is pointed out with a white arrowhead. No infarct was visible on MRI of the brain (not demonstrated).

Figure 2. T$_2$ fluid-attenuated inversion recovery (FLAIR) sequence of the brain. A cortical infarct in the ipsilateral hemisphere is pointed out with a white arrow. Overview of the T$_1$ turbo spin echo (TSE) sequence before and after gadolinium (Gd) administration, time-of-flight (TOF) sequence and a T$_1$ turbo field echo (TFE) sequence of the symptomatic carotid artery. The internal carotid artery (ICA), external carotid artery (ECA), and jugular vein (JV) are marked. No intraplaque hemorrhage or thin/ruptured fibrous cap was present in this patient.
In the current study, imaging of the carotid plaque and the brain was performed on the same day, which implies that both MRI of the carotid plaque and MRI of the brain were obtained after the acute phase. Although histology studies demonstrated that vulnerability stabilizes after the acute phase, literature on in vivo imaging of this process is controversial. On the one hand, MRI enables to visualize different stages of plaque vulnerability. On the other hand, however, previous MRI studies have demonstrated that the presence of IPH and TRFC on MRI does not change significantly over time within 1 year. In addition, infarct volume on FLAIR images is found to decrease over time within 1 month, but disappearance of infarcts on FLAIR has, to the best of our knowledge, never been reported. These results suggest that the absence of a relationship between a high-risk plaque with IPH or TRFC components and the presence of infarcts on FLAIR images could not be explained by the rather long time interval between index event and imaging (median, 45 days; range, 7–100 days). Nevertheless, because FLAIR images also show infarcts older than the index event, this might explain why in the current study the presence of IPH and TRFC does not correlate with cerebral infarcts on MRI, in contrast to previously published studies on diffusion-weighted imaging positive infarcts in an early phase after the ischemic symptoms.

Conclusions
The current study demonstrates that MRI detected IPH and TRFC are not related to the presence of both old and recent cortical and subcortical infarcts ipsilateral to a symptomatic carotid artery stenosis of 30% to 69%.

Appendix
Participating centers: Academic Medical Center, Amsterdam (P.J. Nederkoorn); Atrium Medisch Centrum, Heerlen (A.H.C.M.L. Schreuder); Erasmus Medical Center, Rotterdam (A. van der Lugt, P.J. Koudstaal); Flevoziekenhuis, Almere (M. Limburg); Kennemer Gasthuis, Haarlem (M. Weisfelt); Laurentius Ziekenhuis, Roermond (A.G.C.C. Korten); Maasstad Ziekenhuis, Rotterdam (R. Saxena); Maastricht University Medical Center (M.E. Kooi, R.J. van Oostenbrugge, W.H. Mess); Orbis Medisch Centrum, Sittard (N.P. van Orshoven); Sint Antonius Ziekenhuis, Nieuwegein (S.C. Tromp); Sint Franciscus Gasthuis, Rotterdam (S.L.M. Bakker); Slotervaartziekenhuis, Amsterdam (N.D. Kruyt); Tergooi Ziekenhuizen, Hilversum/Blaricum (J.R. de Kruijk); University Medical Center Utrecht (J. Hendriks, J.G. de Borst); Vlaams Medisch Centrum, Venlo (B.J. Meems); Vlietland Ziekenhuis, Schiedam (J.C.B. Verhey); IJsselland Ziekenhuis, Capelle a/d IJssel (A.D. Wijnhoud).

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Disclosures
None.

Table. Baseline Characteristics of All Patients

<table>
<thead>
<tr>
<th>Classification index event</th>
<th>Total (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69±9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.5±3.6</td>
</tr>
<tr>
<td>TIA</td>
<td>42 (42%)</td>
</tr>
<tr>
<td>AFX</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>24 (24%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67 (66%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26 (26%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>35 (35%)</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes, statin on admission –</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Yes, statin on admission +</td>
<td>50 (50%)</td>
</tr>
<tr>
<td>Family history cerebrovascular disease &lt;60 y</td>
<td>13 (13%)</td>
</tr>
</tbody>
</table>

Data are mean±SD, median (range), or absolute number of patients (%).

Hypercholesterolemia is based on clinical history. AFX indicates amaurosis fugax; BMI, body mass index; and TIA, transient ischemic attack.

In total, 22 of the 40 patients (55%) with IPH had ≥1 infarcts on MRI, whereas 25 of the 61 patients (41%) without IPH had ≥1 infarcts on MRI (P=0.22). In total, 22 of the 49 patients (45%) with a TRFC had ≥1 infarcts on MRI, whereas 18 of the 37 patients (49%) with a thick fibrous cap had ≥1 infarcts on MRI (P=0.83). Analysis based only on cortical infarcts, resulting from large-vessel disease, did not change the significance of the results. In 13 of the 40 patients (33%) with IPH ≥1, cortical infarcts were present on MRI, whereas in 11 of the 61 patients (18%) without IPH ≥1, cortical infarcts were present on MRI (P=0.10). In 9 of the 49 patients (18%) with a TRFC ≥1, cortical infarcts were present on MRI, whereas in 10 of the 37 patients (27%) with a thick fibrous cap ≥1, infarcts were present on MRI (P=0.43).

Discussion
The current study demonstrates that the presence of IPH and a TRFC in the stenosed carotid artery is not related to the presence of old and recent infarcts in the flow territory of the symptomatic carotid artery.

The current results are in contrast with previously published studies, IPH and TRFC are demonstrated to be significantly associated with the presence of acute infarcts on diffusion-weighted imaging. About infarcts on fluid-attenuated inversion recovery imaging, which represent both old and recent infarcts, controversial associations are demonstrated. Ouhlous et al demonstrated a statistically significant correlation between the presence of a lipid core in the carotid plaque and infarcts on FLAIR. However, the presence of a lipid core lacks information about the status of a possible fibrous cap. The current study results are in line with Lindsay et al, demonstrating no statistically significant association between TRFC and infarcts on FLAIR.
References


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http://stroke.ahajournals.org/content/suppl/2015/01/30/STROKEAHA.114.008121.DC1

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SUPPLEMENTAL MATERIAL

Plaque components in symptomatic moderately stenosed carotid arteries related to cerebral infarcts; the parisk study

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Methods

Inclusion In the current study patients with a symptomatic 30-69% stenosis of the carotid artery were included. Briefly, the stenosis grade was based on both the European Carotid Surgery Trial criteria (lower cutoff value of 30%) and the North American Symptomatic Carotid Endarterectomy Trial criteria (upper cutoff value of 70%), as previously described. Measurements were determined on clinically obtained Doppler ultrasound or computed tomography angiography.

Imaging hardware Imaging was performed on 3.0 Tesla whole-body MRI scanners (Achieva or Ingenia, Philips Healthcare, Best, The Netherlands, or a Discovery MR750 system, GE Healthcare, Milwaukee, Wisconsin, United States). For carotid artery imaging dedicated phased-array carotid surface coils were used (Shanghai Chenguang Medical Technologies Co, Shanghai China or Machnet B.V., Roden, The Netherlands) and for brain imaging dedicated head coils were used.

Imaging protocols Carotid arteries. The imaging protocols for carotid artery imaging have been described previously. Briefly, a pre- and post-contrast $T_1$-weighted ($T_1$) quadruple inversion recovery (QIR) turbo spin echo (TSE) or a $T_1$-weighted double inversion recovery (DIR) Fast Spin Echo (FSE) sequence, on respectively Philips or GE scanners, was used for
assessment of the fibrous cap status. Post-contrast images were acquired 6 minutes after administration of 0.1 mmol/kg gadolinium based contrast agent with an injection rate of 0.5 mL/min. A time-of-flight (TOF) sequence and a T1-weighted inversion recovery turbo field echo (TFE) or a T1-weighted spoiled gradient echo (SGR) sequence, on respectively Philips or GE scanners, were used to identify IPH.

**Brain.** The imaging protocols for brain imaging have been described previously as well. Briefly, the sequences used for infarct detection are a T2-weighted fluid attenuated inversion recovery (FLAIR) sequence and a T2-weighted TSE or FSE sequence.

**Image analysis** All imaging data were evaluated by trained readers blinded to the results of other imaging modalities, clinical data, and baseline characteristics. Firstly, each reader was trained on a test set of 15 patients. Secondly, trained readers could only perform final data analyses after achieving acceptable interobserver agreement with experts on another test set of 15 patients. Since this test set was rather small a cut-off value of kappa ≥ 0.4 was used. The interobserver agreement of IPH was good (both readers kappa = 0.7). The interobserver agreement for TRFC was good for one observer (kappa = 0.7) and fair for the other reader (kappa = 0.4).

**Carotid arteries** In all patients the presence or absence of IPH in the ipsilateral carotid artery was determined and the fibrous cap status was scored binary as thick or thin/ruptured. The presence of IPH was scored as a region of hyperintense signal, relative to the adjacent sternocleidomastoid muscle, in the bulk of the plaque on the TOF sequence or on the T1-weighted TFE or SGR sequence, according to previously published criteria. Fibrous cap status was determined on pre- and post-contrast T1-weighted images. The fibrous cap was scored as thick in case of a continuous signal enhancement between lumen and lipid rich
necrotic core (LRNC) and as thin/ruptured in case of an interrupted or absent signal enhancement between lumen and LRNC.

The carotid images were analyzed by two independent readers (MT and AD), with three years of experience in carotid MRI reading. Each patient was analyzed once. In case of doubt a third reader, with >10 years of experience in carotid MRI reading, was consulted (MK or AL).

**Statistical analysis** Since there is a large variety in delay between symptoms and imaging (median 45 days, range 7-100) the relationship between plaque components, presence of infarcts and time between symptoms and imaging was evaluated with an unpaired samples T-test. Additionally, patients were divided in imaged before 45 days and imaged after 45 days. A Fisher’s Exact test was used to evaluate the difference in plaque components between these two groups.

**Results**

The mean time between symptoms and imaging in patients with ≥1 infarcts in the flow territory of the symptomatic carotid artery was 44 days, compared to 52 days in patients without infarcts in the flow territory of the symptomatic carotid artery. This difference was, based on a unpaired samples t-test not statistically significant.

IPH was present in 20 patients imaged before 45 days, compared to 20 patients imaged after 45 days. IPH was absent in 32 patients imaged before 45 days, compared to 29 patients imaged after 45 days. TRFC was present in 25 patients imaged before 45 days, compared to 24 patients imaged after 45 days. A thick fibrous cap was present in 16 patients imaged before 45 days, compared to 21 patients imaged after 45 days. Both, the prevalence of IPH (p = 0.84) and TRFC (p = 0.52), were not significantly different in patients imaged before and after 45 days.
Discussion

In histological literature a fibrous cap of <200 µm is considered to be a thin fibrous cap. In a previous MRI study, however, is demonstrated that the accuracy of measurements of fibrous caps <310 µm decreases significantly.\(^6\) Besides, a good reproducibility for fibrous cap assessment based on the differentiation between thin/ruptured and thick fibrous caps is demonstrated in previous literature.\(^5\) This classification also seems to be useful for risk assessment in patients with a high risk on recurrent cerebral ischemia.\(^7\) For this reason we decided to classify the plaques between a thin/ruptured or a thick fibrous cap.

Supplemental table

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Infarcts (cortical + subcortical)</th>
<th>Cortical infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke (minor)</td>
<td>49</td>
<td>34</td>
</tr>
<tr>
<td>TIA</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>AFX</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are number of patients; TIA = transient ischemic attack; AFX = amaurosis fugax

References
