Atherosclerosis in the carotid arteries is an important cause of ischemic stroke. Treatment decisions for carotid artery stenosis are currently based on the degree of luminal narrowing and the presence or absence of recent ipsilateral stroke or transient ischemic attack (TIA). However, there is increasing evidence that additional factors may be useful in stratifying a patient’s risk of stroke recurrence. A potent strategy may be the identification of so-called vulnerable plaque features, that is, intraplaque hemorrhage (IPH), a large lipid-rich necrotic core and a thin or ruptured fibrous cap.1–4 Plaques with these characteristics are associated with an increased risk of plaque rupture and subsequent embolization. A key feature of vulnerable plaques is IPH, which can be studied in vivo with high-resolution carotid magnetic resonance imaging (MRI). In cohort studies, IPH has shown to be a predictor of ipsilateral stroke and TIA in patients with symptomatic and to a lesser extend with asymptomatic carotid stenosis.3,5

Associations between clinical patient characteristics and vulnerable plaque characteristics have not been widely studied.6–9 It would be important to learn more about clinical determinants of IPH because it can give us information on the mechanism of vulnerable plaque development and risk stratification remains to be determined. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.008906.)

Key Words: carotid stenosis ■ ischemic attack, transient ■ magnetic resonance imaging ■ risk factors ■ stroke
may provide targets for prevention of vulnerable plaques. In this analysis, we investigated the association between clinical patient characteristics and carotid IPH in patients with recently symptomatic, mild to moderate carotid stenosis. The characteristics we studied are risk factors for atherosclerotic arterial disease, history of symptomatic arterial disease, and previous use of prophylactic medication.

Methods

Study Sample

For this analysis, we used baseline data from 100 patients included in the Plaque at Risk (PARISK) study (clinical.trials.gov NCT01208025) between August 2010 and December 2012. This prospective, multicenter cohort study investigates the hypothesis that the assessment of carotid plaque characteristics using noninvasive or minimally invasive imaging techniques improves identification of patients with symptomatic carotid artery stenosis <70%, who have an increased risk of recurrent TIA or ischemic stroke. Ultimately, this might result in better selection of patients with mild to moderate symptomatic carotid stenosis for carotid intervention. The study design has been described in detail elsewhere.10 In short, imaging of the carotid arteries was performed in patients diagnosed with a recent (<3 months) amaurosis fugax, hemispheric TIA, or nondisabling stroke in the internal carotid artery territory and an ipsilateral carotid stenosis of <70%, who were not scheduled for a carotid revascularization procedure. The intended sample size is 240 patients. The degree of stenosis was determined with clinically obtained Doppler ultrasound or computed tomographic angiography. The upper cutoff value of 70% was based on the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.11 The lower cutoff value was an atherosclerotic plaque with a thickness of ≥2 mm.10 Patients with a possible cardiac source of embolism or a clotting disorder were excluded from participation, as well as patients with standard contraindications for MRI, a documented allergy for MRI contrast agent or a renal clearance of <60 mL/min, or a 2-hour postload glucose level of >11.0 mmol/L or the use of antidiabetic medication. Hypercholesterolemia was defined as a serum total cholesterol of >5.0 mmol/L or the use of lipid-lowering drugs. History of ischemic heart disease was defined as a clinical diagnosis of myocardial infarction, angina pectoris, or coronary artery bypass grafting or stenting. Peripheral vascular disease was defined as typical intermittent claudication complaints or peripheral vascular surgery or amputation because of ischemia.

MRI Acquisition and Analysis

Patients underwent a high-resolution MRI scan of the carotid arteries, performed on a 3-T scanner (Achieva or Ingenia; Philips Healthcare, Best, The Netherlands, or Discovery MR750 system; GE Healthcare, Milwaukee, WI) using a phased-array carotid surface coil (Shanghai Chenguang Medical Technologies Co, Shanghai China or Machnet B.V., Roden, The Netherlands). A standardized protocol for carotid plaque MRI was used as previously described.10 In short, for determination of IPH, a T1-weighted inversion recovery transient field echo or spoiled gradient echo images (Figure). This method to visualize IPH has been histologically validated before.11 After training on a test set and achieving good interobserver agreement with experts, 2 independent observers scored the artery ipsilateral to the side of the index event. Disagreement was resolved by a third observer. The contralateral artery was scored by 1 trained observer.

Clinical Assessment

At the baseline visit, participants were interviewed and examined by a physician. Details of the index cerebrovascular event, history of other symptomatic arterial diseases, and risk factors of atherosclerotic arterial disease were collected. Also the use of statins, antiplatelet agents, and coumarin derivatives before the stroke or TIA that led to inclusion in the PARISK study (ie, the index event) was documented, as well as the duration of treatment. Risk factors for atherosclerotic arterial disease, history, and medication use were considered present when (1) noted at patients medical history at admission of the index event; (2) in case of medical treatment for the condition; and (3) self-reported. Medical records were used to verify and complete clinical data. In case medical records did not suffice, the patient’s general practitioner was contacted for additional information.

Smoking status was categorized as current or noncurrent smokers. Patients were considered to be current smokers if they reported smoking on a daily basis. In all other cases, patients were considered to be former or never smokers. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg on clinical examination or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting serum glucose level of >6.9 mmol/L, or a 2-hour postload glucose level of >11.0 mmol/L or the use of antidiabetic medication. Hypercholesterolemia was defined as a serum total cholesterol of >5.0 mmol/L or the use of lipid-lowering drugs. History of ischemic heart disease was defined as a clinical diagnosis of myocardial infarction, angina pectoris, or coronary artery bypass grafting or stenting. Peripheral vascular disease was defined as typical intermittent claudication complaints or peripheral vascular surgery or amputation because of ischemia.

Statistical Analysis

Statistical analyses were performed using SPSS version 20 (IBM Corporation, Armonk, NY). For each patient, IPH was scored positive when identified in 1 or both carotid arteries. A $\chi^2$ test was used to compare categorical variables between groups with and without IPH. An unpaired t test or Mann–Whitney U test was used to compare continuous variables between these groups. The association between clinical variables and IPH was examined using multivariable logistic regression analysis. Variables that showed an association with IPH in the univariable analysis with a P value of <0.1 were included in the multivariable analysis. The association between the duration of antiplatelet therapy before the index event and IPH was assessed with

Figure. Magnetic resonance images showing an example of intraplaque hemorrhage (IPH) in the left carotid artery of a patient with an ipsilateral transient ischemic attack 7 weeks before. A, IPH is visualized as a hyperintense signal (#) on the T1-weighted (T1w) inversion recovery transient field echo sequence, compared with the sternocleidomastoid muscle (*). For comparison, less hyperintensity is seen on the precontrast and postcontrast T1w spin-echo sequences (B and C, respectively).
**Results**

Carotid MRI data were available in 100 of the first 105 patients included in the PARISK study. In 45 of these patients (45%), IPH was observed in 1 or both carotid arteries. IPH was present exclusively on the symptomatic side in 31 of 45 patients (69%), on both sides in 11 of 45 patients (24%), and exclusively on the contralateral side in 3 of 45 patients (7%). The median time from index event to MRI was 45 days (range 7–100). Clinical characteristics in relation to the presence or absence of IPH are shown in Table 1. There was a higher prevalence of IPH among men compared with women: 37 of 69 (54%) versus 8 of 31 (26%); P=0.01 and among patients who used antiplatelet agents before the index event compared with patients who did not: 23 of 37 (62%) versus 22 of 63 (35%); P=0.008. Age, risk factors for atherosclerotic arterial disease, history of symptomatic arterial disease, and type of event (stroke, TIA, or amaurosis fugax) were not related to IPH. Neither was administration of intravenous thrombolysis for the index event.

In multivariable analysis, the previous use of antiplatelet agents, sex, and current smoking was included. The use of antiplatelet agents before the index event was the only variable that remained significantly associated with IPH: odds ratio, 2.71 (95% confidence interval, 1.12–6.61; Table 2).

**Use of Antiplatelet Agents Before the Index Event**

Thirty-seven patients used antiplatelet agents before the index event. The remaining patients started antithrombotic therapy shortly after the index event (62 started antiplatelet agents and 1 started a coumarin derivate). Thus, at the time of MRI, all patients used either an antiplatelet or anticoagulant agent, but 63 of 100 patients only started recently. In the patients who used antiplatelets before the index event, the median time between the use of antithrombotic drugs and MRI was 6 years (range, 1–28). Within this group of patients, there was no association between the duration of antiplatelet therapy and IPH (P=0.94). In the patients who started antithrombotic therapy shortly after the index event, the median time was ≈45 days (range 7–100; time event to MRI).

Table 3 shows details on the side of IPH in patients who were and were not taking an antiplatelet agent before the index event. The proportion of ipsilateral and contralateral IPH in antiplatelet users was comparable with that in nonantiplatelet users (32% and 3% versus 30% and 3%). Interestingly, the proportion of bilateral IPH was much higher in antiplatelet users compared with that in nonusers (27% versus 2%).

The majority of patients (28/37) used a single antiplatelet agent. Of these, 26 used aspirin 80 or 100 mg, 1 used clopidogrel, and 1 used dipyridamole. Sixty-one percent of the patients on monotherapy had IPH, compared with 68% of patients on dual therapy (P=0.75).

Most patients used antiplatelet therapy for peripheral or coronary artery disease. In 2 of 37 patients, the antiplatelets were most likely prescribed as primary prevention because of a history of symptomatic arterial disease did not use antiplatelets. In only 2 of these patients, IPH was present.

**Discussion**

The results of our study suggest that the previous use of antiplatelet agents is associated with carotid IPH in patients with mild to moderate, recently symptomatic carotid stenosis. In our analysis, this could not be explained by associations with risk factors for atherosclerotic arterial disease. However, we
Table 3. Side of IPH in Patients With and Without Antiplatelet Use Before the Index Event

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral IPH, n (%)</th>
<th>Contralateral IPH, n (%)</th>
<th>Bilateral IPH, n (%)</th>
<th>No IPH, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet agent</td>
<td>12 (32)</td>
<td>1 (3)</td>
<td>10 (27)</td>
<td>14 (38)</td>
</tr>
<tr>
<td>No antiplatelet agent</td>
<td>19 (30)</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>41 (65)</td>
</tr>
</tbody>
</table>

IPH indicates intraplaque hemorrhage. *Percentage of IPH within antiplatelet agent.

might not have enough power to perform an extensive multivariate analysis of potential risk factors.

To our knowledge, the only other study that found an association between antiplatelet therapy and carotid IPH was a histopathology study.6 In this study, 154 carotid endarterectomy plaques (130 symptomatic and 24 asymptomatic) from 118 patients were studied. Plaques were categorized according to the presence of multiple hemorrhage versus single or no hemorrhage. There was multiple hemorrhage in 66 of 154 patients (43%) of carotid endarterectomy plaques. In plaques from patients who used antiplatelet therapy within 1 month before surgery, multiple hemorrhage was present in 53 of 78 (68%) compared with 13 of 76 (17%) in plaques from patients who did not (P<0.001). The authors did not report details on the total duration of antiplatelet therapy before surgery.

Some more recent studies investigated the clinical determinants of carotid IPH.7–9 In none of them, the association with antiplatelet therapy was described. One study in 100 symptomatic patients with >30% carotid stenosis found statin use to be negatively associated with IPH but did not record the use of antiplatelet agents.3 A community-based study in which 24% of 1006 participants with carotid wall thickening had IPH reported antithrombotic medication use in 309 of 1006 (30%). Hypertension and current smoking were associated with IPH, but no association with the use of antithrombotic therapy was investigated.3 A histopathology study of 794 carotid endarterectomy patients (84% symptomatic) found a prevalence of IPH as high as 81% and found no association with antiplatelet therapy.3 However, in that study, the reported rate of antiplatelet agent use was 93%. This percentage probably includes both patients who used antiplatelet therapy before the event that led to the endarterectomy and patients who only started therapy after the event, shortly before endarterectomy. Interestingly, this study did find coumarin-type anticoagulation to be associated with IPH, something we could not investigate because of the lack of patients with this type of anticoagulation. Their possible explanation that coumarin-type anticoagulants induce increased hemorrhage from the microvessels in the plaque may also be applicable to antiplatelet agents. Support for this mechanism was found in a recent histopathology study that looked at the burden of IPH in coronary arteries in relation to the use of antithromboembolic drugs.13 In that study, the use of oral anticoagulants was associated with an increased IPH burden. There was no association between IPH burden and antiplatelet agents, but the densities of intraplaque microvessels in patients on antiplatelet therapy were higher than those in nontreated patients.13

Increased microvessel density is thought to play a role in the cause of plaque hemorrhage.

Antiplatelet agents reduce the risk of clot formation and are therefore used in the prevention of ischemic attacks, including stroke. Our results suggest an association between antiplatelet use and IPH, whereas IPH is related to occurrence of future stroke. This seems paradoxical and may prompt concern over potential risks of antiplatelet agent use. However, one should realize that the overall beneficial effect of antiplatelet medication may be the net effect of the reduction of clot formation, including the potential risks of increased occurrence of IPH. Indeed, the benefit of aspirin in preventing stroke is small.14 The 37 patients in our cohort who previously used antiplatelet agents had a cerebrovascular event despite taking an antiplatelet agent. Moreover, in a recent cohort study in patients with 50% to 69% asymptomatic carotid stenosis, the use of dual antiplatelet therapy was an independent risk factor of progression to severe >70% stenosis.15

Our results imply that antiplatelet agents should be used with care and should not be prescribed when there is no evidence of clinical benefit, for example, in patients with asymptomatic atherosclerosis, that is, without a history of any previous symptoms of arterial disease. Also, the question arises whether we should be careful with antiplatelet agents in the specific patient group with signs of a vulnerable plaque. However, before this can be answered, prospective studies need to examine whether increased risk of IPH because of antiplatelet use also increases the risk of ipsilateral stroke symptoms.

Confounding by indication may play a role in our results. It would be present if the initial indication for antiplatelet agents, that is, a history of symptomatic arterial disease, would be a risk factor for IPH. In our analysis, a history of symptomatic arterial disease was not associated with IPH. However, this finding may be unreliable because of the low numbers in this study.

When we looked at the subgroup of previous antiplatelet users in more detail, we found that antiplatelet therapy had the largest effect on the proportion of patients with bilateral IPH. This indicates that it was associated with IPH in both ipsilateral (symptomatic) and contralateral (asymptomatic) plaques and suggests a systemic effect of antiplatelet therapy. We did not find a difference in the frequency of IPH between single and dual antiplatelet users, although numbers may have been too small to test an association. Also, we found no relation between the duration of previous antiplatelet use and IPH. Of note, the patients on antiplatelet therapy used it >1 year before the index event, so all were long-term users. However, the remaining patients, who started antiplatelet therapy shortly after the index event, were short-term users with a median of 45 days (time event to MRI).

Several limitations need to be discussed. PARISK included only patients with mild to moderate symptomatic stenosis; of whom, many will be at low risk of recurrent events.

We cannot make causal inference because this is a cross-sectional study, and the small sample size limits thorough analyses of associations. Although medication use was
self-reported, we do not know if patients were compliant with the antiplatelet therapy. IPH on MRI was not validated histologically because patients did not undergo surgery.

Finally, this is a cross-sectional analysis in the context of a risk-stratification study. In studies of IPH and risk, it is worth mentioning that because of the substantial increase in quality of medical treatment of patients with carotid stenosis during the past decades, the future risk of stroke is generally low. The trials that previously showed benefit from carotid surgery were done before the improvements in medical treatment.16,17 The risk of stroke may currently be low enough to obviate a carotid revascularization procedure in most patients. This stresses the importance of stratifying risk in the context of modern medical treatment, enabling to select only those patients who benefit from procedural revascularization. Present observational studies, such as PARISK, will provide insight in the up-to-date stroke risk and in the usefulness of plaque characteristics in risk stratification.

To conclude, our finding is hypothesis generating and needs to be validated in other cohorts. Whether IPH is related to future TIA or ischemic stroke in the patients in this cohort is unclear. Although not yet available, a clinical follow-up will be done in all patients of the PARISK study, finishing in 2016. By that time, we can study associations between antiplatelet use, carotid IPH, and clinical events during follow-up.

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.G.C. Koren); 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 Kruijf); University Medical Center Utrecht (J. Hendrikse, G.J. de Borst); Verecuri Medisch Centrum, Venlo (B.J. Meems); Vlietland Ziekenhuis, Schiedam (J.C.B. Verhey); Usselland Ziekenhuis, Capelle a/d IJssel (A.D. Wijnhoud).

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Disclosures

None.

References

Use of Antiplatelet Agents Is Associated With Intraplaque Hemorrhage on Carotid Magnetic Resonance Imaging: The Plaque at Risk Study

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