Carotid endarterectomy (CEA) reduces the risk of stroke in symptomatic carotid disease of significant severity; however, not all patients with symptomatic carotid stenosis benefit equally from CEA.1 Recent guidelines recommend surgical intervention for stenosis of at least 50% 2,3 without specifying any restrictions to avoid unnecessary CEA in lower risk patients such as women with moderate degree stenosis and late presentation. The underpinning evidence from randomized controlled trial >2 decades ago has, however, been put in question because of improved outcomes attributed to current secondary prevention medical treatment.4 In current practice, there is hence uncertainty when considering CEA in addition to current optimized medical therapy resulting in practice variation especially in the moderate-risk group. It is conceivable but unknown whether and to which degree early and optimal initiation of medical therapy may have reduced the benefit and cost-effectiveness of CEA for patients with low–intermediate risk. To address these concerns, a randomized controlled trial is underway (http://www.ecst2.com) for patients with low to intermediate stroke risk based on a modified ECST (European Carotid Surgery Trial) risk model to take modern medical management into account.

Background and Purpose—Magnetic resonance imaging (MRI)–defined carotid plaque hemorrhage (MRIPH) can predict recurrent cerebrovascular ischemic events in severe symptomatic carotid stenosis. It is less clear whether MRIPH can improve risk stratification despite optimized medical secondary prevention in those with moderate risk.

Methods—One-hundred fifty-one symptomatic patients with 30% to 99% carotid artery stenosis (median age: 77, 60.5% men) clinically deemed to not benefit from endarterectomy were prospectively recruited to undergo MRI and clinical follow-up (mean, 22 months). The clinical carotid artery risk score could be evaluated in 88 patients. MRIPH+ve was defined as plaque intensity >150% that of adjacent muscle. Survival analyses were performed with recurrent infarction (stroke or diffusion-positive cerebral ischemia) as the main end point.

Results—Fifty-five participants showed MRIPH+ve; 47 had low, 36 intermediate, and 5 high carotid artery risk scores. Cox regression showed MRIPH as a strong predictor of future infarction (hazard ratio, 5.2; 95% confidence interval, 1.64–16.34; \( P = 0.005 \), corrected for degree of stenosis), also in the subgroup with 50% to 69% stenosis (hazard ratio, 4.1; 95% confidence interval, 1–16.8; \( P = 0.049 \)). The absolute risk of future infarction was 31.7% at 3 years in MRIPH+ve versus 1.8% in patients without (\( P < 0.002 \)). MRIPH increased cumulative risk difference of future infarction by 47.1% at 3 years in those with intermediate carotid artery risk score (\( P = 0.004 \)).

Conclusions—The study confirms MRIPH to be a powerful risk marker in symptomatic carotid stenosis with added value over current risk scores. For patients undergoing current secondary prevention medication with clinically uncertain benefit from recanalization, that is, those with moderate degree stenosis and intermediate carotid artery risk scores, MRIPH offers additional risk stratification. (Stroke. 2017;48:678-685. DOI: 10.1161/STROKEAHA.116.015504.)

Key Words: atherosclerotic plaque ■ carotid stenosis ■ cerebral infarction ■ endarterectomy ■ magnetic resonance imaging ■ stroke
account. However, clinical risk models have limitations, and there is a potential for significant improvement afforded by modern imaging techniques such as magnetic resonance imaging (MRI) of the plaque to discriminate high-risk carotid plaque features previously identified by histology. The presence of MRI-defined carotid plaque hemorrhage (MRIPH) has previously been shown to predict recurrent ipsilateral ischemic events and stroke in patients with symptomatic carotid artery stenosis. With an estimated 0.6% annualized risk of recurrent stroke where MRIPH was absent versus 23% in MRIPH+ve, MRIPH holds great promise for risk-based stratification of CEA. Current data are, however, insufficient to confirm whether MRIPH predicts future cerebral infarction in patients with low–intermediate risk on current medical therapy.

This prospective study assessed whether MRIPH could be used reliably to stratify the future risk in symptomatic patients with carotid artery stenosis considered unsuitable for CEA and receiving optimal medical treatment alone because of perceived low benefit:risk ratio or patient preference. We also compared risk prediction by MRIPH and the carotid artery risk (CAR) score.

Methods

Description of Study Sample

The ICAD study (Imaging in Carotid Artery Disease) was a single-center observational study between November 2010 and February 2015. None of the data presented here had been previously published, whereas the interrelation between brain imaging and cognitive status of the cohort are published elsewhere. Patients were consecutively recruited from the Fast-track transient ischemic attack (TIA) clinic and stroke wards at Nottingham University Hospitals National Health Service Trust. All the patients had been reviewed by Stroke Physicians and received optimized medical therapy for secondary stroke prevention according to the current guidelines. Ultrasonographic data from vascular clinic were screened to determine the eligibility for recruitment. A few participants were identified and referred from adjacent hospitals in Derby and Mansfield (Figure 1 in the online-only Data Supplement). Inclusion criteria were >18 years old adults with recent anterior circulation TIA (defined as sudden focal neurological deficits lasting <24 hours), amaurosis fugax (AmF; painless transient monocular visual loss), or ischemic stroke (sudden focal neurological deficits lasting at least 24 hours), as confirmed by a Stroke Physician, in the previous 6 months and an ipsilateral carotid stenosis of 30% to 99%, life expectancy of >3 years, and competency to consent. MRI contraindications and planned ipsilateral CEA were exclusion criteria. All participants provided written informed consent as approved by the local Ethics Committee, and Research and Development Departments at all 3 participant-identifying centers.

Imaging Protocol

As part of clinical care, all participants had carotid ultrasonography before recruitment. The degree of carotid stenosis was assessed according to the ultrasound criteria adapted from the NASCET trial (North American Symptomatic Carotid Endarterectomy Trial) as used in CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study). Contrast MR or computed tomographic angiography was used when carotid ultrasound was unable to determine the degree of stenosis.

At recruitment, participants were assessed for cardiovascular risk factors and had brain and carotid MRI at Nottingham University Hospital, performed on a 3-T Achieva (Philips; version 3.1.2 software). For carotid wall imaging, a single coronal T1-weighted 3-dimensional gradient echo sequence was performed using blood nulling and a water excitation pulse that excludes signal from fat. The sequence parameters were as follows: repetition time, 8.8 ms; echo time, 1.1 ms; fractional anisotropy, 0.1°; inversion time, 570 ms; field of view, 346×346 mm; matrix 384×180; slice thickness, 0.9 mm; and number of slices, 102. The acquisition took ∼5 minutes. The coded anonymized images were reformatted to axial images (1 mm slice thickness, 150 slices) and transferred to a locally held secure server.

Quantitative analysis of the MR images was then performed using JAVA imaging (JIM) software (http://www.xinapse.com), by 2 trained researchers (A.A.H., R.J.S.) and adjudicated by an experienced neuroradiologist (D.P.A.). Although the presence of carotid plaque hemorrhage (MRIPH+ve) is easily visible in most cases (Figure 1), the presence of MRIPH in this study was diagnosed quantitatively according to the previously validated criteria. While blinded to the clinical data, areas of high signal were identified within the carotid artery wall within 1 cm from the bifurcation. The slice with subjectively the highest signal intensity was chosen, and the hyperintense area was selected. A signal intensity ratio was calculated by comparing the mean intensities of the carotid artery compared with that of adjacent sternocleidomastoid muscle (signal intensity ratio \( \frac{S_{\text{lumen}}}{S_{\text{muscle}}} \)). The presence of MRIPH was diagnosed if the normalized signal intensity ratio between the 2 was at least 1.5 (MRIPH+ve).

Clinical Assessment, CAR Score, and Follow-Up

Clinical assessments for any cerebrovascular ischemic event, vascular risk factors, comorbidities, and medications were recorded at recruitment and follow-up reviews.

CAR scores were defined based on degree of carotid stenosis using NASCET criteria, time since last event, primary symptomatic event,
diabetes mellitus, myocardial infarction, age, sex, peripheral vascular disease, treated hypertension, and ulcerated plaque surface (http://www.ECST2.com).

Participants were followed up at every 6-month interval until the end of study (range, 132–1587 days; median, 710 days) or terminating points, that is, death or ipsilateral CEA (range, 3–1333 days; median, 461 days). A stroke or neurology physician verified recurrent ischemic events, and ipsilateral stroke was defined as neurological deficits ipsilateral to the indexed carotid stenosis lasting at least 24 hours. The primary end point ipsilateral recurrent cerebral infarction was defined as stroke (computed tomography or MRI confirmed) or TIA with evidence of diffusion change on brain MRI corresponding to the index clinical deficit (DWI+ve TIA). Secondary end points were stroke alone and any ipsilateral cerebrovascular event, that is, stroke, TIA, or AfM. Further censoring end points were ipsilateral CEA, death, or withdrawal of consent. In addition, new atrial fibrillation at the time of recurrent event, contralateral or bihemispheric stroke, and myocardial infarction were noted during the follow-up period.

Statistical Analysis
To assess the independent effects of MRIPH and degree of carotid stenosis, we aimed to record at least 20 new ipsilateral events over the entire study period to empower bivariate regression analysis for MRIPH and degree of stenosis.

Kaplan–Meier (KM) survival analysis and log-rank tests were used to assess the associations between MRIPH and the rate of new ipsilateral clinically manifest cerebral infarctions (primary end point: stroke and DWI+ve TIA), as well as MRIPH and all ipsilateral cerebrovascular events (secondary end points: stroke, TIA, and AfM). Cerebrovascular ischemic event rates per 100 person-years were calculated for each outcome. KM analysis was also performed to examine the CAR score associations with the rates of primary and secondary end points.

Time to ipsilateral infarction or any cerebrovascular ischemic event was analyzed for MRIPH using a bivariate Cox proportional hazard model adjusted for degree of carotid artery stenosis (subgroups of ≥50% and <50% stenosis). Univariate Cox models for MRIPH were calculated for the subgroups of moderate (50% to 69%) and mild (30% to 49%) degree of stenosis. Similarly, time to event was tested for CAR scoring using univariate and bivariate Cox models, including MRIPH. SPSS Statistics was used; *P value <0.05 was considered significant.

Results
A total of 152 subjects fulfilled all inclusion and exclusion criteria (Figure I in the online-only Data Supplement). Sixty (39.5%) were women with median age of 79±12 years (men: 76±12 years; *P=0.42). Fifty-five participants (36.2%) were identified to have MRIPH ipsilateral to the indexed ischemic event, and 97 did not have ipsilateral MRIPH (MRIPH−ve; Table 1). In line with previous findings,7,14 MRIPH was again more likely to be present in men (*χ²=9.05; *P=0.003).

During the follow-up period (range, 3–1587 days), 20 ipsilateral events occurred including 15 primary end points (14 strokes, 1 DWI+ve TIA), as well as 3 TIAs, 2 AfM. The recurrent strokes were classified as large artery atherosclerotic in 11, lacunar stroke in 3 (of which 1 was bilateral), and cardioembolic in 2. One patient was lost to follow-up and therefore excluded from the survival analysis. Twenty-two participants died during the follow-up (mean, 602±353 days), and there were 9 ipsilateral CEAs, following a reconsideration of surgical intervention by the clinical team. Further events included 1 contralateral stroke, 1 contralateral TIA, and 1 bilateral stroke, which were excluded from the survival analysis as per study protocol.

MRIPH Predicts Future Ipsilateral Ischemic Events in Patients Managed by Medical Treatment
Univariate Cox regression analysis confirmed that MRIPH was significantly associated with future ipsilateral clinically manifest infarction (stroke or DWI+ve TIA, hazard ratio [HR], 5.1; 95% confidence interval [CI], 1.6–16; *P=0.005). When controlled for ≥50% or <50% stenosis, the HR was 5.2 (95% CI, 1.6–16.34; *P=0.005; Figure 2A). Similarly, MRIPH significantly predicted future stroke alone (univariate Cox analysis; HR, 5.1; 95% CI, 1.6–15.9; *P=0.006 and bivariate Cox analysis adjusted for carotid stenosis; HR, 5.12; 95% CI, 1.63–16.3; *P=0.005; Figure 2B) and all recurrent ipsilateral ischemic events (univariate Cox analysis; HR, 3.6; 95% CI, 1.4–9.1; *P=0.006 and bivariate Cox analysis adjusted for carotid stenosis; HR, 3.7; 95% CI, 1.5–9.2; *P=0.006; Figure II in the online-only Data Supplement).

A small group of patients (n=17) with severe stenosis were included because they were clinically felt to be unfit for surgery or were unwilling to consent to surgery. Hence, we repeated the analysis for the participants with <70% stenosis, which yielded similar results.

Using KM risk estimate, the absolute risk difference between those with and without MRIPH for recurrent infarct (stroke or DWI+ve TIA) was +12.8% at year 1 and +29.9% at year 3 (Table 2). The absolute risk of infarction in the MRIPH+ve group was 12.8% by 1 year, compared with a negligible risk for the MRIPH−ve group. The absolute risk with the presence of MRIPH was 31.7% by 3 years, compared with that of 1.8% for the MRIPH−ve. This equates to the presence of MRIPH resulting in an estimated 13 of 100 extra infarctions at 1 year and an extra 29 of 100 at 3 years, compared with MRIPH−ve subjects. In our study population of patients with 30% to 99% carotid artery stenosis not undergoing CEAs, the number needed to harm for those with MRIPH was =8 by 1 year, number needed to harm=5 by 2 years, and number needed to harm=4 by 3 years compared with MRIPH−ve. The risk difference beyond 3 years did not increase; 3 strokes occurred after 3 years in the MRIPH−ve subgroup, of which 2 were likely cardioembolic secondary to atrial fibrillation or a mechanical heart valve based on bihemispheric evidence of infarct and clinical risk assessment.

MRIPH Predicts Stroke in Moderate Degree Stenosis
A total of 72 participants with 50% to 69% stenosis suffered 11 recurrent ischemic events (Table 3), including 9 strokes. In this subgroup, MRIPH was significantly associated with future ipsilateral infarctions/strokes (HR, 4.1; 95% CI, 1.0–16.8; *P=0.049). No recurrent DWI+ve TIA was seen during the follow-up in this subgroup. For the secondary end point of all recurrent ischemic events, we found no significant association with MRIPH (HR, 2.56; 95% CI, 0.77–8.6; *P=0.128; Figure 2C and 2D).

In the subgroup with low degree stenosis (30%–49%), the imaging marker was not significantly associated with recurrence (HR, 4.3; 95% CI, 0.45–41.8; *P=0.2), but this subgroup analysis was underpowered with only 6 events.

Using KM risk estimates for the moderate degree stenosis subgroup, the risk difference between those with and without
Table 1. Demographic Characteristics and Risk Factors in Participants With and Without MRIPH on Ipsilateral Carotid MRI (at Recruitment)

<table>
<thead>
<tr>
<th></th>
<th>MRIPH+ve (n=55)</th>
<th>MRIPH−ve (n=97)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median y (interquartile range)</td>
<td>76 (13)</td>
<td>77 (11)</td>
<td>0.28</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>13 (23.6)</td>
<td>47 (48.5)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (18.2)</td>
<td>23 (23.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>45 (81.8)</td>
<td>78 (80.4)</td>
<td>0.83</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>14 (25.5)</td>
<td>27 (27.8)</td>
<td>0.75</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12 (21.8)</td>
<td>21 (21.6)</td>
<td>0.98</td>
</tr>
<tr>
<td>Statin use before indexed ischemic event, n (%)†</td>
<td>33 (60.0)</td>
<td>45 (46.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>Use of statin after indexed ischemic event</td>
<td>55 (100)</td>
<td>92 (94.8)‡</td>
<td>0.16</td>
</tr>
<tr>
<td>Smoking habit, n (%)</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Smokers</td>
<td>12 (21.8)</td>
<td>26 (26.8)</td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>11 (20.0)</td>
<td>34 (35.1)</td>
<td></td>
</tr>
<tr>
<td>Exsmokers§</td>
<td>32 (58.2)</td>
<td>37 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet/anticoagulant agent(s) used before indexed ischemic event, n (%)</td>
<td></td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>14 (25.5)</td>
<td>19 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>17 (30.9)</td>
<td>36 (37.1)</td>
<td></td>
</tr>
<tr>
<td>Dual (aspirin and [dipyridamole or clopidogrel])</td>
<td>11 (20.0)</td>
<td>9 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>4 (7.3)</td>
<td>7 (7.2)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9 (16.4)</td>
<td>26 (26.8)</td>
<td></td>
</tr>
<tr>
<td>Use of antiplatelet or anticoagulation after indexed ischemic event</td>
<td>55 (100)</td>
<td>96 (100)</td>
<td></td>
</tr>
<tr>
<td>Degree of stenosis, n (%)¶</td>
<td>0.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30% to 49%</td>
<td>22 (40.0)</td>
<td>41 (42.3)</td>
<td></td>
</tr>
<tr>
<td>50% to 69%</td>
<td>25 (45.5)</td>
<td>47 (48.5)</td>
<td></td>
</tr>
<tr>
<td>70% to 99%</td>
<td>8 (14.5)</td>
<td>9 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Type of symptom on presentation, n (%)</td>
<td>0.073</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>35 (63.6)</td>
<td>41 (42.3)</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>15 (27.3)</td>
<td>42 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>3 (5.5)</td>
<td>11 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Retinal stroke</td>
<td>2 (3.6)</td>
<td>3 (3.1)</td>
<td></td>
</tr>
<tr>
<td>CAR score, total number of participants (mean scores)</td>
<td>33 (9.7)</td>
<td>55 (7.1)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Low CAR scores, ie, 0% to 7.5% risk, n</td>
<td>12</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Intermediate CAR scores, ie, 7.5% to 15% risk, n</td>
<td>17</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>High CAR scores, ie, &gt;15% risk, n.</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Time between presenting symptom and MRI, median d (interquartile range)</td>
<td>23 (33)</td>
<td>26 (33)</td>
<td></td>
</tr>
<tr>
<td>Number of carotid endarterectomy, n (%)</td>
<td>4 (7.3)</td>
<td>5 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Follow-up until any end point, median d (interquartile range)#</td>
<td>552 (665)</td>
<td>674.5 (610.25)</td>
<td></td>
</tr>
</tbody>
</table>

CAR indicates carotid artery risk; MRI, magnetic resonance imaging; MRIPH+, presence of hyperintense signal on MRI; MRIPH−, absence of hyperintense signal on MRI; and TIA, transient ischemic attack.

*Significantly different (<0.05) between MRIPH+ and MRIPH− groups.
†Patients were on regular statin therapy >6 mo before inclusion onto the study.
‡All patients were given statin immediately after the ischemic event, but 5 patients stopped taking statin because of the intolerance during the follow-up.
§Exsmokers were defined as stopped smoking for >6 mo.
||All patients were given antiplatelet or anticoagulation according to the guidelines, but 1 patient stopped taking antiplatelet within a few weeks because of personal preference and against the medical advice.
¶Based on the ultrasound criteria described in the Methods.
#Follow-up period from the entry point until the end of study period, ipsilateral carotid endarterectomy, or death if did not meet the primary end point (recurrent event).
MRIPH for future stroke or DWI+ve TIA was +20% and +35.3% at years 1 and 3, respectively. The annualized risk of recurrent stroke or DWI+ve TIA in this group in the presence of MRIPH was 14.3%, compared with 3.2% in the MRIPH−ve subgroup. The number needed to harm in this group was 5 by 1 year and 3 by 2 and 3 years. This means that ≈ 1 in 5 patients with MRIPH in moderate degree stenosis group risked recurrent ipsilateral infarction by 1 year, whereas no ipsilateral infarct occurred in the subgroup without MRIPH. In moderate degree stenosis, 1 in 3 patients had future infaracts by 3 years, whereas no infarct occurred in the MRIPH−ve group over the first 3 years.

**MRIPH and the CAR Score**

Of 89 participants with >50% carotid stenosis, 1 patient had uncertain date of indexed event and was hence excluded from CAR score evaluation (Table 1). Mean and categorical CAR scores were significantly higher in MRIPH+ve group compared with MIRPH−ve (P=0.001 and P=0.005, respectively).

In our cohort, no recurrent ischemic event occurred in the subgroup with high CAR scores, but the respective subgroup was very small (n=5) because of our inclusion criteria. Fourteen patients in the subgroup with low or intermediate CAR scores (n=83) experienced recurrent ipsilateral ischemic events (11 strokes, 1 TIA, and 2 AmF) during the follow-up (mean, 657; range, 3–1491 days).

KM survival analysis for predictive value of CAR scores was insignificant (P=0.22). Bivariate regression analysis demonstrated no significant effect of CAR (P=0.49) but confirmed significant independent association of MRIPH with future cerebral infarction (HR, 6.7; 95% CI, 1.7–26; P=0.006).
Patients with intermediate CAR scores and MRIPH+ve (n=36) risked future stroke (no DWI+ve TIA event was observed) at a higher rate than expected, that is, 29.5% by 1 year and 47.1% by 3 years, but no stroke or DWI+ve TIA was observed in patients with MRIPH−ve by 3 years (P=0.004).

**Discussion**

In patients with symptomatic carotid artery disease managed with current medical treatment alone, MDR-defined plaque hemorrhage significantly predicted future ipsilateral cerebral infarction and stroke alone. Importantly, MRIPH also predicted recurrence in clinical subgroups with lower or uncertain benefit from CEA.

In symptomatic moderate degree (50%–69%) stenosis, carotid MRIPH carried an estimated ipsilateral stroke risk difference of +35% at 3 years, compared with those without MRIPH despite optimized medical treatment. In this group, MRIPH allowed to identify those with >15% annual risk of stroke or cerebral infarction per 100 person-years. In contrast, absence of MRIPH identified the subgroup with minimal risk of stroke in the first year. It is worth noting that the observed risk difference between MRIPH+ve and MRIPH−ve patients outweighs the risk of CEA in specialized centers (between 2.6% and 4.5%), thus highlighting the potential benefit of targeted surgery.

MRIPH was associated with significantly higher CAR risk, but its association with future clinical events was independent of CAR. Moreover, in our cohort, CAR scores did not predict cerebrovascular ischemic events. In contrast, MRIPH allowed to risk stratify patients with intermediate CAR scores, showing in the presence of MRIPH, nearly half will risk stroke by 3 years. This is in line with our previous findings in severe carotid stenosis for which the similar ECST score also failed to show predictive power.17

Clinical risk scores such as ECST/CAR are extremely helpful, quick to apply, and inexpensive, but less specific to the thromboembolic risk than MRIPH.18 ECST/CAR is necessarily based on historic actuarial data rather than the individual risk, and it is not reflective of evolution in medical treatment. Nevertheless, the CAR score adjusts for the expected risk reduction because of improved medical therapy. Also, plaque ulceration on ultrasonography, that is, part of ECST/CAR, may not be as reliably detected compared with historic conventional angiography (NASCET12). In the future, it will be desirable to develop a modified enhanced CAR score accounting for the evidence power of MRIPH to index the risk of future events furthering a precision medicine approach in secondary stroke prevention care.

In a previous meta-analysis, we found that carotid MRIPH significantly increased the risk of recurrent ischemic events several fold (OR, 12.2; 95% CI, 5.5–27.1) in patients with 30% to 99% symptomatic carotid stenosis.7,19 Much of the included data for moderate degree stenosis8,10–21 was, however, limited because of heterogeneity in degree of stenosis, duration of follow-up, mixed with asymptomatic carotid disease, and reflective of the past clinical practice.8,9,19,20,22,23

### Table 2. Risk Estimation for Recurrent Ipsilateral Stroke or TIA With Evidence of Restricted Diffusion on MRI (DWI+ TIA) in Patients With Symptomatic Carotid Artery Stenosis and Presence of MRIPH (MRIPH+)

<table>
<thead>
<tr>
<th>Stenosis Level</th>
<th>MRIPH+</th>
<th>MRIPH−</th>
<th>Risk Difference vs CAR</th>
<th>Risk Difference vs CAR</th>
<th>No. of Events/ Person-Years</th>
<th>Event Rate per 100 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% to 60% stenosis and MRIPH+ve</td>
<td>20%</td>
<td>35.3%</td>
<td>+20</td>
<td>+35.3</td>
<td>6/38.9</td>
<td>15.4</td>
</tr>
<tr>
<td>50% to 69% stenosis and MRIPH−ve</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td>3/92.4</td>
<td>3.2</td>
</tr>
<tr>
<td>30% to 99% stenosis and MRIPH+ve</td>
<td>12.8%</td>
<td>31.1%</td>
<td>+12.8</td>
<td>+29.3</td>
<td>11/97.1</td>
<td>11.3</td>
</tr>
<tr>
<td>30% to 99% stenosis and MRIPH−ve</td>
<td>0</td>
<td>1.8%</td>
<td></td>
<td></td>
<td>4/184.3</td>
<td>2.2</td>
</tr>
</tbody>
</table>

**Notes:** DWI indicates diffusion-weighted imaging; KM, Kaplan–Meier; MRI, magnetic resonance imaging; MRIPH+ve, presence of hyperintense signal on MRI; MRIPH−ve, absence of hyperintense signal on MRI; and TIA, transient ischemic attack.

### Table 3. Recurrent Events During the Follow-Up Period

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>50% to 69% stenosis and MRIPH+ve</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50% to 69% stenosis and MRIPH−ve</td>
<td>5 (1 DWI−ve TIA, 1 AmF)</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1 (1 stroke, 1 TIA)</td>
</tr>
<tr>
<td>30% to 99% stenosis and MRIPH+ve</td>
<td>13 (1 DWI−ve TIA, 1 AmF)</td>
<td>11 (10 strokes)</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30% to 99% stenosis and MRIPH−ve</td>
<td>7 (2 DWI−ve TIA, 1 AmF)</td>
<td>4 strokes</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Notes:** AmF indicates Amaurosis fugax; DWI, diffusion-weighted imaging; DWI+ve TIA, TIA with evidence of restricted diffusion on MRI brain; DWI−ve TIA, TIA with no evidence of restricted diffusion on MRI brain; Ips., ipsilateral; MRI, magnetic resonance imaging; MRIPH+, presence of hyperintense signal on MRI; MRIPH−, absence of hyperintense signal on MRI; and TIA, transient ischemic attack.

*According to TOAST criteria (Trial of Org 10172 in Acute Stroke Treatment).
Our new observational study overcomes these issues and provides evidence that the current risk models and risk management can be improved for patients with expected low–moderate risk.

The presented results are from a single center limiting their generalizability into local standard practice. Nevertheless, multiple studies across diverse populations, scanner platforms, and protocols have consistently shown that carotid plaque hemorrhage is associated with future or recurrent cerebrovascular ischemic events in symptomatic carotid artery stenosis. We think that there is now sufficient evidence to justify refinement of clinical risk assessment scores with individualized data using MRIPH. Whether the proven added value of MRIPH for risk prediction will translate into predictive value of risk–benefit from CEA or carotid stenting remains to be demonstrated in the ongoing (ECST-2, MRI substudy) and the future randomized control trials using MRIPH defined risk stratification.

Summary

MRIPH is a significant predictor of future cerebral infarction and stroke in patients with symptomatic carotid artery stenosis. MRIPH status affords clinically useful risk stratification in those with moderate carotid stenosis or intermediate CAR scores.

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References


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Figure I-sup. Recruitment diagram for the study:

Over 4000 patients were screened

190 agreed to participate

38 excluded:
10 did not have MRI
1 poor quality MRI
2 had less than 30% carotid stenosis
5 had occluded ipsilateral carotid artery
12 had asymptomatic carotid artery disease
6 had contralateral carotid stenosis
2 had posterior circulation stroke

152 recruited (92 M, 60 F)

1 lost to follow up

151 in final analysis (91 M, 60 F)
Figure II-supp. KM plot showing recurrent ipsilateral survival analysis for participants with 50-69% ipsilateral carotid stenosis by presence or absence of MRIPH ($\chi^2=4.51$, $P=0.003$).