Magnetic Resonance Imaging Plaque Hemorrhage for Risk Stratification in Carotid Artery Disease With Moderate Risk Under Current Medical Therapy

Akram A. Hosseini, MD, PhD; Richard J. Simpson, PhD; Nishath Altaf, MBChB, PhD; Philip M. Bath, DSc, FMedSci; Shane T. MacSweeney, MAMB, MChir; Dorothee P. Auer, MD

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

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

Received October 27, 2016; final revision received December 15, 2016; accepted December 21, 2016.

From the Radiological Sciences, Division of Clinical Neuroscience (A.A.H., R.J.S., N.A., D.P.A.); Stroke Trials Unit, Division of Clinical Neuroscience (P.M.B.), University of Nottingham, United Kingdom; and Department of Vascular Surgery, Nottingham University Hospital NHS Trust, United Kingdom (R.J.S., N.A., S.T.M.).

Current address for N. Altaf: Department of Vascular Surgery, Royal Perth Hospital, Western Australia.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.015504/-/DC1.

Correspondence to Dorothee P. Auer, MD, Radiological Sciences, University of Nottingham, Room WB1441, Queens Medical Centre, Nottingham NG7 2UH, United Kingdom. E-mail dorothee.auer@nottingham.ac.uk

account. However, clinical risk models have limitations,[5] 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.[6] 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.[7–10] With an estimated 0.6% annualized risk of recurrent stroke where MRIPH was absent versus 23% in MRIPH+ve,[7] 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.[11] 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 I 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)[12] as used in CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study).[13] 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, 4.1 ms; fractional anisotropy, 10°; 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 anonymous 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.[14,15] 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 $=SI_{plaque}/SI_{muscle}$). 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,

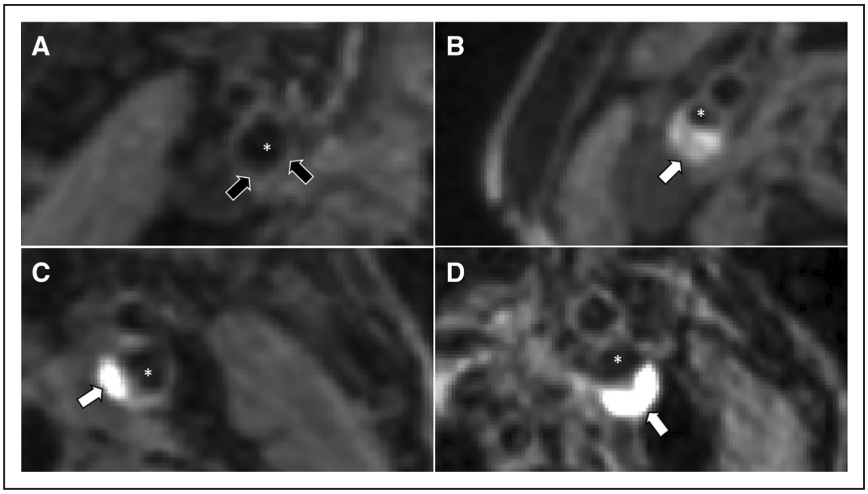

Figure 1. Axial views of T1-weighted magnetic resonance imaging (MRI) to detect plaque hemorrhage. Hyperintense signals (**B**–**D**, white arrows) show carotid plaque hemorrhage on 3-T MRI scanner; black arrows (**A**) show absence of plaque hemorrhage; asterisks indicate the lumen of internal carotid artery. **A**, No signal hyperintensity, MRIPH−ve; (**B**) large moderately MRIPH+ve; (**C**) small strongly hyperintense MRIPH+ve; and (**D**) large strongly hyperintense MRIPH+ve. MRIPH+ve indicates presence of hyperintense signal on MRI; and MRIPH−ve, absence of hyperintense signal on MRI.

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 AmF. 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 AmF). 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 scores 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 (χ^2=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 AmF. 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, 1.64–16.34; *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 CEA, 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)

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

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).

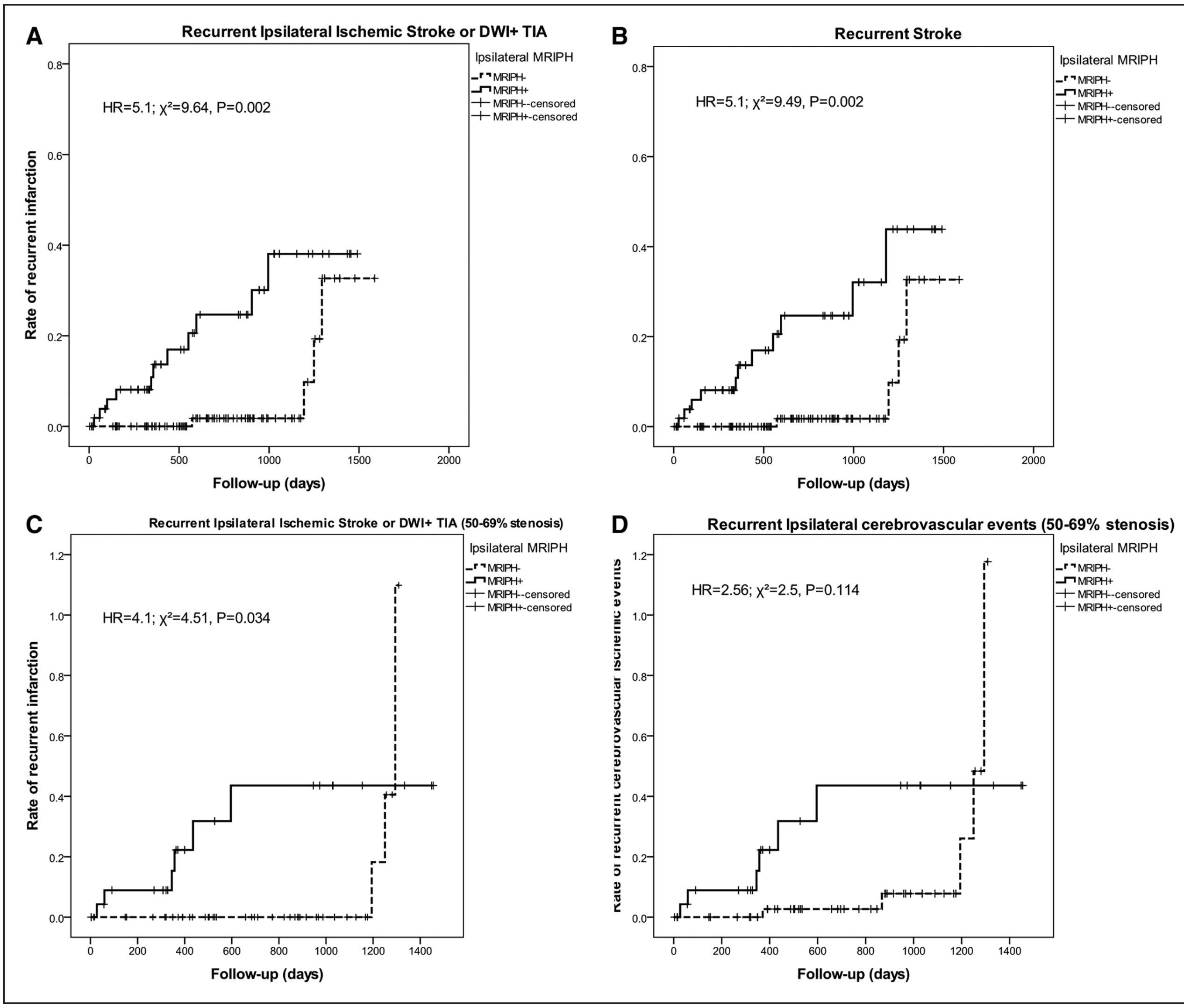

Figure 2. A, Kaplan–Meier (KM) plot showing stroke or DWI+ve transient ischemic attack (DWI+TIA) survival analysis for all study participants (30%–99% stenosis) by the presence or absence of magnetic resonance imaging–defined carotid plaque hemorrhage (MRIPH; χ^2=9.64; *P*=0.002). **B**, KM plot representing recurrent stroke for all study participants by the presence or absence of MRIPH (χ^2=9.49; *P*=0.002). **C**, KM plot showing stroke or DWI+ TIA survival analysis for participants with 50% to 69% ipsilateral carotid stenosis by the presence or absence of MRIPH (χ^2=4.51; *P*=0.034). **D**, KM plot showing recurrent ipsilateral survival analysis for participants with 50% to 69% ipsilateral carotid stenosis by the presence or absence of MRIPH (χ^2=2.5; *P*=0.114). DWI indicates diffusion-weighted imaging; HR, hazard ratio; MRIPH+, presence of hyperintense signal on MRI; MRIPH−, absence of hyperintense signal on MRI; and TIA, transient ischemic attack.

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 infarcts 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).

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+)

	Cumulative Risk (KM Estimate), 1 y, %	Cumulative Risk (KM Estimate), 3 y, %	Risk Difference (vs MRIPH− Group), 1 y, %	Risk Difference (vs MRIPH− Group), 3 y, %	No. of Events/ Person-Years	Event Rate per 100 Person-Years
50% to 60% stenosis and MRIPH+ve	20%	35.3%	+20	+35.3	6/38.9	15.4
50% to 69% stenosis and MRIPH−ve	0	0			3/92.4	3.2
30% to 99% stenosis and MRIPH+ve	12.8%	31.1%	+12.8	+29.3	11/97.1	11.3
30% to 99% stenosis and MRIPH−ve	0	1.8%			4/184.3	2.2

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.

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, MRI-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%[16]), 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 that 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 (NASCET[12]). In the future, it will be desirable to develop a modified enhanced CAR score accounting for the evidenced 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 stenosis[8,19–21] 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 3. Recurrent Events During the Follow-Up Period

	Total Ips. Ischemic Events	Ips. Stroke or DWI+ TIA	Ips. Large Artery Atherosclerotic Stroke*	Ips. Lacunar Stroke*	Ips. Cardioembolic Stroke*	Contralateral Ischemic Event
50% to 69% stenosis and MRIPH+	6	6	6	0	0	0
50% to 69% stenosis and MRIPH−	5 (1 DWI−ve TIA, 1 AmF)	3	1	1	1	2 (1 stroke, 1 TIA)
30% to 99% stenosis and MRIPH+	13 (1 DWI-ve TIA, 1 AmF)	11 (10 strokes)	11	0	0	0
30% to 99% stenosis and MRIPH−	7 (2 DWI−ve TIA, 1 AmF)	4 strokes	1	2	1	2

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.[7,19,24] 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.

Acknowledgments

We thank Dr Daniel Rodriguez and Magnetic Resonance Imaging Radiographers for quality image acquisition, Dr Solomon Akwei for supporting the study recruitment, and Dr Peter Nightingale for statistical advice and analysis.

Sources of Funding

This paper presents independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Program (Grant Reference Number PB-PG-0107-11438). The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health. None of the sponsors had any role in study design, data collection, data analysis, data interpretation, writing the report, or in decision making to submit the article for publication.

Disclosures

A.A.H. is funded by the National Institute for Health Research (NIHR) and is partly sponsored by UCB Pharma for her PhD tuition fees. R.J.S. is funded by Stroke Association United Kingdom, NIHR, and Nottingham Vascular Surgery Research Fund. P.M.B. is Stroke Association Professor of Stroke Medicine. The other authors report no conflicts.

References

1. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915–924. doi: 10.1016/S0140-6736(04)15785-1.
2. Royal College of Physicians. National Clinical Guideline for Stroke. Prepared by the Intercollegiate Stroke Working Party. Fifth edition, 2016. http://guideline.ssnap.org/2016StrokeGuideline/html5/index.html?page=1&noflash. Accessed November 9, 2016.
3. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2011;57:1002–1044. doi: 10.1016/j.jacc.2010.11.005.
4. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388:2532–2561. doi: 10.1016/S0140-6736(16)31357-5.
5. Rothwell PM, Mehta Z, Howard SC, Gutnikov SA, Warlow CP. Treating individuals 3: from subgroups to individuals: general principles and the example of carotid endarterectomy. *Lancet*. 2005;365:256–265. doi: 10.1016/S0140-6736(05)17746-0.
6. Bitar R, Moody AR, Leung G, Symons S, Crisp S, Butany J, et al. *In vivo* 3D high-spatial-resolution MR imaging of intraplaque hemorrhage. *Radiology*. 2008;249:259–267. doi: 10.1148/radiol.2491071517.
7. Hosseini AA, Kandiyil N, Macsweeney ST, Altaf N, Auer DP. Carotid plaque hemorrhage on magnetic resonance imaging strongly predicts recurrent ischemia and stroke. *Ann Neurol*. 2013;73:774–784. doi: 10.1002/ana.23876.
8. Teng Z, Sadat U, Huang Y, Young VE, Graves MJ, Lu J, et al. *In vivo* MRI-based 3D mechanical stress-strain profiles of carotid plaques with juxtaluminal plaque haemorrhage: an exploratory study for the mechanism of subsequent cerebrovascular events. *Eur J Vasc Endovasc Surg*. 2011;42:427–433. doi: 10.1016/j.ejvs.2011.05.009.
9. Lin K, Zhang ZQ, Detrano R, Lu B, Fan ZM. Carotid vulnerable lesions are related to accelerated recurrence for cerebral infarction magnetic resonance imaging study. *Acad Radiol*. 2006;13:1180–1186. doi: 10.1016/j.acra.2006.07.004.
10. Kurosaki Y, Yoshida K, Endo H, Chin M, Yamagata S. Association between carotid atherosclerosis plaque with high signal intensity on T1-weighted imaging and subsequent ipsilateral ischemic events. *Neurosurgery*. 2011;68:62–67; discussion 67. doi: 10.1227/NEU.0b013e3181fc60a8.
11. Meng D, Hosseini AA, Simpson RJ, Shaikh Q, Tench CR, Dineen RA, Auer DP. Lesion topography and microscopic white matter tract damage contribute to cognitive impairment in symptomatic carotid artery disease. *Radiology*. 2017;282:502–515. doi: 10.1148/radiol.2016152685.
12. Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, et al. The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. *Stroke*. 1999;30:1751–1758.
13. McCabe DJ, Pereira AC, Clifton A, Bland JM, Brown MM; CAVATAS Investigators. Restenosis after carotid angioplasty, stenting, or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). *Stroke*. 2005;36:281–286. doi: 10.1161/01.STR.0000152333.75932.fe.
14. Kandiyil N, Altaf N, Hosseini AA, MacSweeney ST, Auer DP. Lower prevalence of carotid plaque hemorrhage in women, and its mediator effect on sex differences in recurrent cerebrovascular events. *PLoS One*. 2012;7:e47319. doi: 10.1371/journal.pone.0047319.
15. Altaf N, MacSweeney ST, Gladman J, Auer DP. Carotid intraplaque hemorrhage predicts recurrent symptoms in patients with high-grade carotid stenosis. *Stroke*. 2007;38:1633–1635. doi: 10.1161/STROKEAHA.106.473066.
16. Brott TG, Hobson RW II, Howard G, Roubin GS, Clark WM, Brooks W, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363:11–23. doi: 10.1056/NEJMoa0912321.
17. Altaf N, Kandiyil N, Hosseini A, Mehta R, MacSweeney S, Auer D. Risk factors associated with cerebrovascular recurrence in symptomatic carotid disease: a comparative study of carotid plaque morphology, microemboli assessment and the European Carotid Surgery Trial risk model. *J Am Heart Assoc*. 2014;3:e000173. doi: 10.1161/JAHA.113.000173.
18. Altaf N, Goode SD, Beech A, Gladman JR, Morgan PS, MacSweeney ST, et al. Plaque hemorrhage is a marker of thromboembolic activity in patients with symptomatic carotid disease. *Radiology*. 2011;258:538–545. doi: 10.1148/radiol.10100198.
19. Hosseini AA, Simpson RJ, Altaf N, Auer DP. Carotid plaque hemorrhage on magnetic resonance imaging and recurrent cerebrovascular events. *J Am Coll Cardiol*. 2014;63:2172–2173. doi: 10.1016/j.jacc.2013.11.062.
20. Altaf N, Daniels L, Morgan PS, Auer D, MacSweeney ST, Moody AR, et al. Detection of intraplaque hemorrhage by magnetic resonance imaging

in symptomatic patients with mild to moderate carotid stenosis predicts recurrent neurological events. *J Vasc Surg*. 2008;47:337–342. doi: 10.1016/j.jvs.2007.09.064.
21. Kwee RM, van Oostenbrugge RJ, Mess WH, Prins MH, van der Geest RJ, ter Berg JW, et al. MRI of carotid atherosclerosis to identify TIA and stroke patients who are at risk of a recurrence. *J Magn Reson Imaging*. 2013;37:1189–1194. doi: 10.1002/jmri.23918.
22. Takaya N, Yuan C, Chu B, Saam T, Underhill H, Cai J, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI–initial results. *Stroke*. 2006;37:818–823. doi: 10.1161/01.STR.0000204638.91099.91.
23. Yamada N, Higashi M, Otsubo R, Sakuma T, Oyama N, Tanaka R, et al. Association between signal hyperintensity on T1-weighted MR imaging of carotid plaques and ipsilateral ischemic events. *AJNR Am J Neuroradiol*. 2007;28:287–292.
24. Saam T, Hetterich H, Hoffmann V, Yuan C, Dichgans M, Poppert H, et al. Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging. *J Am Coll Cardiol*. 2013;62:1081–1091. doi: 10.1016/j.jacc.2013.06.015.

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Magnetic Resonance Imaging Plaque Hemorrhage for Risk Stratification in Carotid Artery Disease With Moderate Risk Under Current Medical Therapy

Akram A. Hosseini, Richard J. Simpson, Nishath Altaf, Philip M. Bath, Shane T. MacSweeney and Dorothee P. Auer

Stroke. 2017;48:678-685; originally published online February 14, 2017;
doi: 10.1161/STROKEAHA.116.015504
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENT MATERIAL

Figure I-supp. Recruitment diagram for the study:

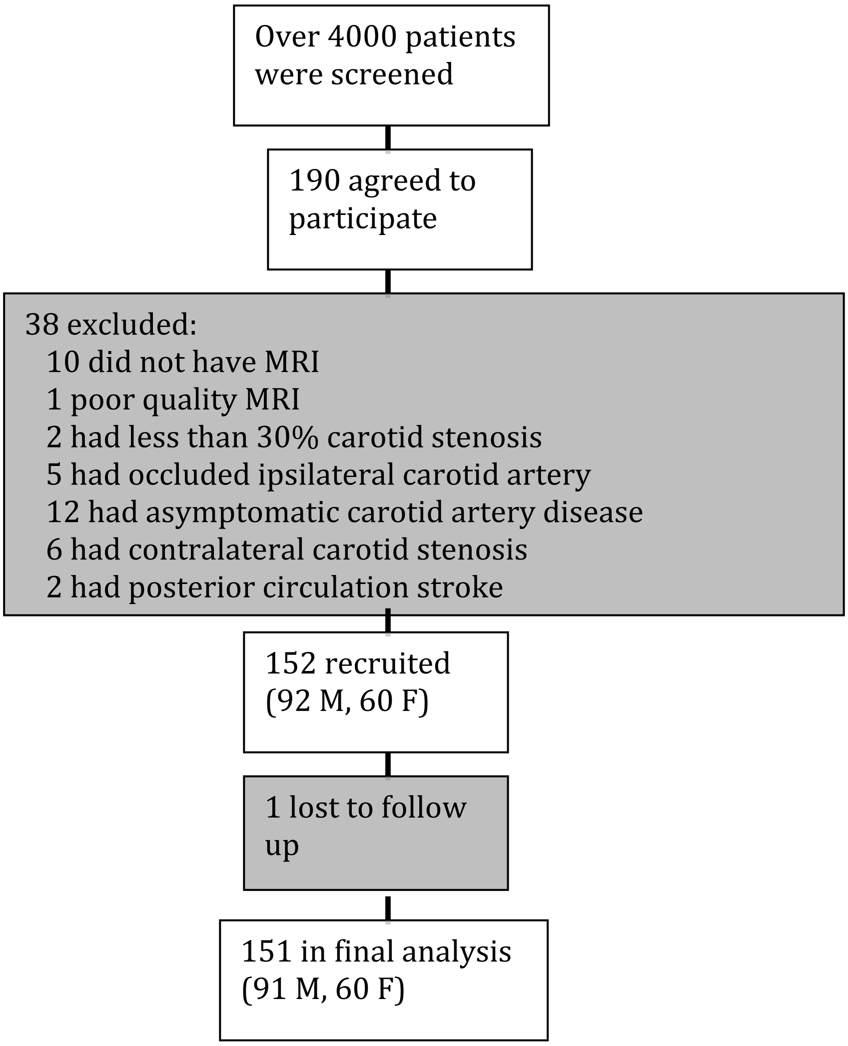

Figure II-supp. KM plot showing recurrent ipsilateral survival analysis for participants with 50-69% ipsilateral carotid stenosis by presence or absence of MRIPH (χ^2=4.51, P=0.003).