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MRI plaque hemorrhage for risk stratification in carotid artery disease with moderate risk under current medical therapy

MRIPH predicts stroke in moderate carotid disease

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**Abstract.**

Background and Purpose

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 optimised medical secondary prevention in those with moderate risk.

Methods

151symptomatic patients with 30-99% 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 (CAR) 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 endpoint.

Results

55 participants showed MRIPH+ve; 47 had low, 36 intermediate and 5 high CAR scores. Cox regression showed MRIPH as a strong predictor of future infarction (HR=5.2, 95%CI=1.64–16.34, P=0.005, corrected for degree of stenosis), also in the

subgroup with 50-69% stenosis (HR=4.1, 95%CI=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 CAR 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 i.e. those with moderate degree stenosis and intermediate CAR scores, MRIPH offers additional risk stratification.

## Introduction

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 randomised controlled trial more than two decades ago has however been put in question due to improved outcomes attributed to current secondary prevention medical treatment[4]. In current practice, there is hence uncertainty when considering CEA in addition to current optimised 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 (www.ecst2.com) for patients with low to intermediate stroke risk based on a modified European Carotid Surgery Trial risk model to take modern medical management into account. However, clinical risk models have limitations[5] and there is potential for significant improvement afforded by modern imaging techniques such as MRI of the plaque to discriminate high-risk carotid plaque features previously identified by histology[6]. The presence of 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 vs. 23% in MRIPH+ve[7], MRIPH holds great promise for risk-based stratification of carotid endarterectomy. Current data is 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 due to perceived low benefit-risk ratio or patient preference. We also compared risk prediction by MRIPH and the CAR score.

## Methods

### Description of study sample

The Imaging in Carotid Artery Disease (ICAD) study was a single-center observational study between November 2010 and February 2015. None of the data presented here had been previously published, while the interrelation between brain imaging and cognitive status of the cohort are published elsewhere (Meng et al, Hosseini et al., submitted). Patients were consecutively recruited from the Fast-track TIA clinic and stroke wards at Nottingham University Hospitals NHS Trust. All the patients had been reviewed by Stroke Physicians and received optimised medical therapy for secondary stroke prevention according to current guidelines. Ultrasonographic data from vascular clinic were screened to determine eligibility for recruitment. A few participants were identified and referred from adjacent hospitals in Derby and Mansfield (Figure I-supp). Inclusion criteria were; >18 years old adults with recent anterior circulation transient ischemic attack (TIA, defined as sudden focal neurological deficits lasting less than 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 30-99%, 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 three participant-identifying centers.

**Imaging Protocol**

As part of clinical care, all participants had carotid ultrasonography prior to recruitment. The degree of carotid stenosis was assessed according to ultrasound criteria adapted from the NASCET trial[11] as used in CAVATAS[12]. Contrast-MR or CT 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 3T 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: TR 8.8ms, TE 4.1ms, FA 10°, TI 570ms, FOV 346×346 mm, matrix 384×180, slice thickness 0.9 mm, number of slices 102. The acquisition took approximately five minutes. The coded anonymous images were reformatted to axial images (1mm 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 (www.xinapse.com), by two trained researchers (AAH, RJS) and adjudicated by an experienced neuroradiologist (DPA). 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 previously validated criteria[13, 14]. Whilst blinded to the clinical data, areas of high signal were identified within the carotid artery wall within 1cm from the bifurcation. The slice with subjectively the highest signal intensity was chosen and the hyperintense area selected. A signal intensity ratio (SIR) was calculated by comparing the mean intensities of the carotid artery compared with that of adjacent sternocleidomastoid muscle ($SIR=SI_{plaque}/SI_{muscle}$). The presence of MRIPH was diagnosed if the normalized SIR between the two was at least 1.5 (MRIPH+ve).

**Clinical Assessment, Carotid Artery Risk score and Follow-up**

Clinical assessments for any cerebrovascular ischemic event, vascular risk factors, co-morbidities 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, myocardial infarction, age, sex, peripheral vascular disease, treated hypertension, and ulcerated plaque surface (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 i.e. 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 endpoint 'ipsilateral recurrent cerebral infarction' was defined as stroke (CT or MRI confirmed) or TIA with evidence of diffusion change on brain MRI corresponding to the index clinical deficit (DWI+ve TIA). Secondary endpoints were stroke alone and any ipsilateral cerebrovascular event, i.e. stroke, TIA or AmF. Further censoring endpoints were ipsilateral CEA, death or withdrawal of consent. In addition, new atrial fibrillation at the time of recurrent event, contralateral or bi-hemispheric 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 endpoint: stroke and DWI+ve TIA), as well as MRIPH and all ipsilateral cerebrovascular events (secondary endpoints: 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 endpoints.

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 (50-69%), and mild (30-49%) degree of stenosis. Similarly, time to event was tested for CAR scores using univariate and bivariate Cox model including MRIPH. SPSS Statistics was used; $P<0.05$ was considered significant.

**Results**

A total of 152 subjects fulfilled all inclusion and exclusion criteria (Figure I-supp). 60 (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, 13], MRIPH was again more likely to be present in men ($\chi^2$=9.05, P=0.003).

During the follow-up period (range 3-1587 days), 20 ipsilateral events occurred including 15 primary endpoints (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 three (of which 1 was bilateral), and cardioembolic in two. One patient was lost to follow-up and therefore excluded from the survival analysis. 22

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, HR=5.1, 95%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 2-A). 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 2-B) 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-supp).

A small group of patients (n=17) with severe stenosis were included as 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 less than 70% stenosis, which yielded similar results.

Using Kaplan Meier 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 one year, compared with a negligible risk for the MRIPH-ve group. The absolute risk with 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 13/100 extra infarctions at 1 year and an extra 29/100 at 3 years, compared to MRIPH-ve subjects. In our study population of patients with 30-99% carotid artery stenosis not undergoing CEA, the number needed to harm (NNH) for those with MRIPH was about 8 by 1 year, NNH=5 by 2 years and NNH=4 by 3 years compared with MRIPH-ve. The risk difference beyond 3 years did not increase; three strokes occurred after 3 years in the MRIPH-ve subgroup, of which two were likely cardio-embolic 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 50-69% 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 endpoint 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 2-C,D).

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 Kaplan Meier risk estimates for the moderate degree stenosis subgroup, the risk difference between those with and without 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 NNH in this group was 5 by 1 year, and 3 by 2 and 3 years. This means that approximately 1 in 5 patients with MRIPH in moderate degree stenosis group risked recurrent ipsilateral infarction by 1 year, while no ipsilateral infarct occurred in the subgroup without MRIPH. In moderate degree stenosis, 1 in 3 patients had future infarcts by 3 years whilst no infarct occurred in the MRIPH-ve group over the first 3 years.

*MRIPH and the carotid artery risk (CAR) score*

Of 89 participants with >50% carotid stenosis, one patient had uncertain date of indexed event and was hence excluded from CAR scores 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) due to our inclusion criteria. 14 patients in the subgroup with low or intermediate CAR scores (n=83) experienced recurrent ipsilateral ischemic events (11 stroke, 1 TIA, 2 AmF) during the follow up (mean: 657; ranged 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; i.e. 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 carotid endarterectomy.

In symptomatic moderate degree (50-69%) stenosis, carotid MRIPH carried an estimated ipsilateral stroke risk difference of +35% at 3 years, compared to those without MRIPH despite optimised medical treatment. In this group, MRIPH allowed to identify those with >15% annual risk of stroke or cerebral infarction per 100-persons year. 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 carotid endarterectomy in specialised centers (between 2.6 to 4.5%[15]), 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[16].

Clinical risk scores such as ECST/CAR are extremely helpful, quick to apply and inexpensive, but less specific to the thromboembolic risk than MRIPH[17]. ECST/CAR are necessarily based on historic actuarial data rather than the individual risk and they are not reflective of evolution in medical treatment. Nevertheless, the CAR score adjusts for the expected risk reduction due to 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[11]). 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 30-99% symptomatic carotid stenosis[7, 18]. Much of the included data for moderate degree stenosis[8, 18-20] was however limited due to heterogeneity in degree of stenosis, duration of follow up, mixed with asymptomatic carotid disease, and reflective of the past clinical practice[8, 9, 18, 19, 21, 22]. 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, 18, 23]. We believe 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 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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Table 1- Demographic characteristics and risk factors in participants with and without PH on ipsilateral carotid MRI (at recruitment):

| | MRIPH+ (n=55) | MRIPH- (n=97) | *P* Value |
|---|---|---|---|
| Age, median years (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 prior to indexed ischemic event†, n (%) | 33 (60.0) | 45 (46.4) | 0.11 |
| Use of statin after indexed ischemic event | 55 (100) | 92 (94.8) †† | |
| Smoking habit, n (%) | | | |
| Smokers | 12 (21.8) | 26 (26.8) | 0.05 |
| Non-smokers | 11 (20.0) | 34 (35.1) | |
| Ex-smokers‡ | 32 (58.2) | 37 (38.1) | |
| Antiplatelet/anticoagulant agent(s) used prior to 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 |
| 30-49% | 22 (40.0) | 41 (42.3) | |
| 50-69% | 25 (45.5) | 47 (48.5) | |
| 70-99% | 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, i.e. 0-7.5% risk, number | 12 | 35 | |
| Intermediate CAR scores i.e. 7.5-15% risk, number | 17 | 19 | |
| High CAR scores i.e. >15% risk, number | 4 | 1 | |
| Time between presenting symptom and MRI, median days (interquartile range) | 23 (33) | 26 (33) | |
| Total number of carotid endarterectomy, n (%) | 4 (7.3) | 5 (5.2) | |
| Follow-up until any endpoint point**, median days (interquartile range) | 552 (665) | 674.5 (610.25) | |

TIA: Transient Ischemic Attack; MRIPH+: presence of hyperintense signal on MRI; MRIPH-: Absence of hyperintense signal on MRI.

*Significantly different (<0.05) between MRIPH+ and MRIPH- groups. †Patients were on regular statin therapy more than 6 months prior to inclusion onto the study. ††All patients were given statin immediately after the ischemic event, but 5 patients stopped taking statin due to intolerance during the follow-up. †††All patients were given antiplatelet or anticoagulation according to the guidelines, but one patient stopped taking antiplatelet within a few weeks due to personal preference and against medical advice. ‡Ex-smokers were defined as stopped smoking for more than 6 months. §Based on 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 endpoint (recurrent event).

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 Year, % | Cumulative Risk (KM- Estimate*), 3 Year, % | Risk Difference (vs. MRIPH- group), 1 year, % | Risk Difference (vs. MRIPH- group), 3 year, % | Number of events/person -years | Event rate per 100 person-years |
|---|---|---|---|---|---|---|
| 50-60% stenosis and MRIPH+ | 20% | 35.3% | +20 | +35.3 | 6/38.9 | 15.4 |
| 50-69% stenosis and MRIPH- | 0 | 0 | | | 3/92.4 | 3.2 |
| 30-99% stenosis and MRIPH+ | 12.8% | 31.1% | +12.8 | +29.3 | 11/97.1 | 11.3 |
| 30-99% stenosis and MRIPH- | 0 | 1.8% | | | 4/184.3 | 2.2 |

*Kaplan-Meier Estimate

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 |
|---|---|---|---|---|---|---|
| 50-69% stenosis and MRIPH+ | 6 | 6 | 6 | 0 | 0 | 0 |
| 50-69% stenosis and MRIPH- | 5 (1 DWI-ve TIA, 1 AmF) | 3 | 1 | 1 | 1 | 2 (1 stroke, 1 TIA) |
| 30-99% stenosis and MRIPH+ | 13 (1 DWI-ve TIA, 1 AmF) | 11 (10 stroke) | 11 | 0 | 0 | 0 |
| 30-99% stenosis and MRIPH- | 7 (2 DWI-ve TIA, 1 AmF) | 4 stroke | 1 | 2 | 1 | 2 |

*according to TOAST criteria. TIA: Transient Ischemic Attack; 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; AmF: Amaurosis fugax; MRIPH+ve: presence of hyperintense signal on MRI; MRIPH-ve: Absence of hyperintense signal on MRI.

Figure 1- Axial views of T1-weighted MRI to detect plaque hemorrhage.
Hyperintense signals (b-d, white arrows) show carotid plaque hemorrhage on 3T 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; d) Large strongly hyperintense MRIPH+ve.

Figure 2-A,Kaplan-Meier plot showing stroke or DWI+ TIA survival analysis for all study participants (30-99% stenosis) by presence or absence of MRIPH ($\chi^2$=9.64, P=0.002). B, KM plot representing recurrent stroke for all study participants by presence or absence of MRIPH ($\chi^2$=9.49, P=0.002). C, KM plot showing stroke or DWI+ TIA survival analysis for participants with 50-69% ipsilateral carotid stenosis by presence or absence of MRIPH ($\chi^2$=4.51, P=0.034). D, KM plot showing recurrent ipsilateral survival analysis for participants with 50-69% ipsilateral carotid stenosis by presence or absence of MRIPH ($\chi^2$=2.5, P=0.114).