

Association Between Carotid Plaque Characteristics and Subsequent Ischemic Cerebrovascular Events

A Prospective Assessment With MRI—Initial Results

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Background and Purpose—MRI is able to quantify carotid plaque size and composition with good accuracy and reproducibility and provides an opportunity to prospectively examine the relationship between plaque features and subsequent cerebrovascular events. We tested the hypothesis that the characteristics of carotid plaque, as assessed by MRI, are possible predictors of future ipsilateral cerebrovascular events.

Methods—A total of 154 consecutive subjects who initially had an asymptomatic 50% to 79% carotid stenosis by ultrasound with ≥ 12 months of follow-up were included in this study. Multicontrast-weighted carotid MRIs were performed at baseline, and participants were followed clinically every 3 months to identify symptoms of cerebrovascular events.

Results—Over a mean follow-up period of 38.2 months, 12 carotid cerebrovascular events occurred ipsilateral to the index carotid artery. Cox regression analysis demonstrated a significant association between baseline MRI identification of the following plaque characteristics and subsequent symptoms during follow-up: presence of a thin or ruptured fibrous cap (hazard ratio, 17.0; $P \leq 0.001$), intraplaque hemorrhage (hazard ratio, 5.2; $P = 0.005$), larger mean intraplaque hemorrhage area (hazard ratio for 10 mm² increase, 2.6; $P = 0.006$), larger maximum %lipid-rich/necrotic core (hazard ratio for 10% increase, 1.6; $P = 0.004$), and larger maximum wall thickness (hazard ratio for a 1-mm increase, 1.6; $P = 0.008$).

Conclusions—Among patients who initially had an asymptomatic 50% to 79% carotid stenosis, arteries with thinned or ruptured fibrous caps, intraplaque hemorrhage, larger maximum %lipid-rich/necrotic cores, and larger maximum wall thickness by MRI were associated with the occurrence of subsequent cerebrovascular events. Findings from this prospective study provide a basis for larger multicenter studies to assess the risk of plaque features for subsequent ischemic events. (*Stroke*. 2006;37:818-823.)

Key Words: atherosclerosis ■ carotid arteries ■ cerebrovascular disorders ■ magnetic resonance imaging

The vulnerability of an atherosclerotic plaque to rupture is believed to be related to its intrinsic composition such as the size of the lipid core and presence of intraplaque hemorrhage.^{1,2} Several prospective studies using ultrasound have shown that echolucent carotid plaques are associated with increased risk for cerebrovascular events.³⁻⁶ Echolucent plaques are known to have a higher content of lipid and hemorrhage than do echogenic plaques, which contain more calcification and fibrous tissue. However, B-mode ultrasound is still challenged when distinguishing between hemorrhage and lipid content of the plaque.⁷ A number of studies have shown that multicontrast-weighted MRI is able to distinguish

these critical plaque tissue characteristics and the surface status of plaque in the carotid artery, using histology as the gold standard.⁸⁻¹¹ In addition, improved technology and resolution have resulted in the capacity to quantify plaque components.^{12,13} This combination of accurate detection and quantification produced a recent study showing that hemorrhage into the carotid atherosclerotic plaque is significantly associated with more rapid progression in wall and lipid-rich necrotic core (LR/NC) size, as well as more rapid progression in luminal stenosis.¹⁴

The current challenge for MRI is to predict cerebrovascular events among asymptomatic patients with hemodynamically

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significant carotid stenosis using plaque composition as the determinant of vulnerability to stroke. The aim of this study was to test the hypothesis that MRI identification of specific plaque characteristics, such as the presence of intraplaque hemorrhage, a large LR/NC, or a thinned/ruptured fibrous cap, is associated with the development of subsequent ipsilateral carotid cerebrovascular events.

Subjects and Methods

Study Population

A total of 183 consecutive cases with ≥ 12 months of follow-up were selected from an ongoing prospective serial carotid MRI study referred to as PRIMARI. Subjects for PRIMARI were recruited from the diagnostic vascular ultrasound laboratories at the University of Washington Medical Center, Veterans Affairs Puget Sound, and the Virginia Mason Medical Center after obtaining informed consent. The study procedures and consent forms were reviewed and approved by the institutional review board of each site. Inclusion criteria for PRIMARI include: (1) 50% to 79% carotid stenosis by duplex ultrasound; and (2) asymptomatic with regard to their carotid artery disease within the 6 months before enrollment in PRIMARI. One side was chosen for serial MRI follow-up, referred to as the index carotid artery. Exclusion criteria included: (1) previous carotid endarterectomy on the index side; (2) previous neck irradiation; and (3) contraindication for MRI.

Clinical Variables

Before the baseline MRI examination, study subjects were asked to complete a detailed health questionnaire and physical examination. The clinical end point for the study was a cerebrovascular event including stroke or transient ischemic attack (TIA) in the region supplied by the index carotid artery or ipsilateral amaurosis fugax. Only events related to the index arteries were evaluated in the present study. Follow-up continued after nonfatal events occurred. The date of symptoms of clinical end points were ascertained every 3 months by telephone interviews and confirmed through review of hospital records. Subjects who gave a history suggestive of an ischemic event were evaluated by a vascular surgeon (T.S.H.), and in suspected cases, examined by a neurologist in a timely manner. Stroke was considered to be of ischemic origin when cerebral hemorrhage was excluded by neuroimaging. TIA was defined as a new-onset focal neurological abnormality lasting < 24 hours. Amaurosis fugax was defined as acute onset of transient partial or complete monocular loss of vision. Cardioembolic stroke was diagnosed according to Rochester criteria.

MRI Protocol and Review

All patients were imaged at the University of Washington in a 1.5-T GE Signa Scanner (Horizon EchoSpeed, version 5.8; General Electric Healthcare) using a phased-array surface coil (Pathway Medical Technologies Inc). A previously published standardized protocol was used to obtain 4 different contrast-weighted images (time of flight [TOF], T1-weighted [T1W], proton density-weighted [PDW], and T2-weighted [T2W]) of the carotid arteries centered at the common carotid bifurcation on the index side.¹² MRI parameters were: T1W, double inversion-recovery, black-blood, 2D fast spin-echo, repetition time (TR)/effective echo time (TE)=800/10 ms, echo train length (ETL)=8; PDW and T2W, fast-spin echo, cardiac-gated, TR=3 or 4 cardiac R-R intervals, effective TE=20 ms for PDW and 40 ms for T2W, ETL=6; and 3D TOF, TR/TE 23/3.8 ms, flip angle 25°. Fat suppression was used for T1W, PDW, and T2W images to reduce signals from subcutaneous fat. Images were obtained with a field of view of 13 to 16 cm, matrix size of 256, slice thickness of 2 mm, and 2 signal averages.

Image quality was rated per artery for each contrast-weighted image on a 5-point scale (1=poor, 5=excellent) and cases in which image quality ≤ 2 were excluded from the study. Two experienced reviewers who were blinded to clinical outcome reviewed all

magnetic resonance images, and a consensus decision was reached for each plaque feature.

Area measurements of the lumen, outer wall, and the tissue components (LR/NC, calcium, and hemorrhage) were obtained using a custom-designed imaging analysis tool.¹² Wall area was calculated as the difference between outer wall and lumen area. The carotid bifurcation was used as a landmark for matching the 4 different contrast-weighted images at each slice location. Areas of hemorrhage, LR/NC, and calcification were identified using previously published criteria that have been validated compared with histology.^{12,15}

Mean areas per artery were calculated for lumen, wall, intraplaque hemorrhage, LR/NC, and calcification. The mean area was defined as the sum of areas from each cross-sectional location divided by the number of cross-sectional locations analyzed. Slice-based analysis was also performed for the minimum lumen area and maximal wall thickness. The most diseased cross-sectional location, defined as the site with the maximum proportion of the wall occupied by a LR/NC (Max %LR/NC), was also calculated (%LR/NC=100×(LR/NC area/wall area)). Fibrous caps status was categorized as either “thick” versus “thin or ruptured” using previously published, histologically validated criteria.¹¹

Statistical Analysis

The association of the time to a cerebrovascular event with carotid artery characteristics as ascertained by MRI and other atherosclerotic

TABLE 1. Baseline Clinical Characteristics and MRI Measurements (n=154 patients)

Variable	Study Population mean (SD) or %
Age, y	71.1 (9.3)
Male sex, %	82
Mean follow-up, mo	38.2 (17.1)
Body mass index	27.1 (4.4)
Smoking, %	
Current	38
Former	49
Systolic blood pressure, mm Hg	144.2 (25.5)
Diastolic blood pressure, mm Hg	70.0 (12.4)
History of hypertension, %	75
History of diabetes, %	25
History of hypercholesterolemia, %	79
History of coronary artery disease, %	44
Currently on HMG-CoA reductase inhibitor, %	64
MRI measurements	
% of arteries with lipid-rich/necrotic core	72
% of arteries with intraplaque hemorrhage	28
% of arteries with thin/ruptured fibrous cap	38
Mean lumen area per slice, mm ²	61.2 (28.5)
Mean wall area per slice, mm ²	87.8 (27.6)
Mean LR/NC area per slice, mm ²	8.8 (11.6)
Mean calcium area per slice, mm ²	3.4 (4.8)
Mean IPH area per slice, mm ²	1.9 (5.2)
Maximum LR/NC area as % of wall area	20.3 (17.8)
Maximum wall thickness, mm	4.2 (1.5)
Minimum lumen area, mm ²	15.4 (9.8)

Sample size varies slightly across variables attributable to missing values. Values represent means (SD).

HMG-CoA indicates 3-hydroxy-3-methylglutaryl-coenzyme A.

risk factors was analyzed using the Cox proportional hazards model with the likelihood ratio test used to ascertain statistical significance. Only univariate analyses (using 1 independent variable) were performed with the Cox regression model. Meaningful multivariate analyses could not be performed because of the limited number of cases with an event. Results from Cox models are expressed as hazard ratios (HRs) with 95% CIs. The Kaplan–Meier product-limit method was used to estimate cumulative event-free rates in subgroups for graphical display depending on the presence of intraplaque hemorrhage and thin or ruptured fibrous cap. Data on patient and artery characteristics were expressed as mean±SD. All calculations were made with SPSS 12.0 for Windows. Statistical significance was defined as a value of $P < 0.05$.

Results

Among the 183 patients (183 arteries) available, 29 arteries were excluded because of an image quality rating of ≤ 2 . Mean age of the 154 remaining participants was 71.1 years (range 48.4 to 87.2), and 82% were male. Mean follow-up time was 38.2 months. The baseline clinical characteristics and baseline MRI findings are presented in Table 1. A total of 111 (72%) of the subjects had arteries containing an LR/NC, and 43 (28%) had intraplaque hemorrhage into the necrotic core. Thin or ruptured caps were observed in 58 subjects (38%). During follow-up, 14 of the 154 individuals experienced an ipsilateral ischemic cerebrovascular event (4 TIAs, 6 strokes, and 4 with ipsilateral amaurosis fugax). Among the

14 cases, 2 patients with a history of intermittent atrial fibrillation had a stroke during follow-up that was felt by their neurologist and cardiologist to be cardiogenic. These 2 cases were not included as events in the analysis.

Among all of the baseline clinical and MRI variables listed in Table 1, Cox regression analysis indicated that plaques with intraplaque hemorrhage (HR, 5.2; 95% CI, 1.6 to 17.3; $P = 0.005$), larger mean intraplaque hemorrhage area (HR for 10-mm² increase, 2.6; 95% CI, 1.4 to 4.6; $P = 0.006$), thin or ruptured fibrous cap (HR, 17.0; 95% CI, 2.2 to 132.0; $P < 0.001$), larger maximum %LR/NC (HR for 10% increase, 1.6; 95% CI, 1.2 to 2.0; $P = 0.004$), and maximum wall thickness (HR for a 1-mm increase, 1.6; 95% CI, 1.1 to 2.3; $P = 0.008$) were associated with the development of subsequent ischemic cerebrovascular events (Table 2). Kaplan–Meier plots for the incidence of ipsilateral cerebrovascular events demonstrated that event-free survival was higher among plaques without intraplaque hemorrhage compared with those with intraplaque hemorrhage at baseline (Figure 1) and among plaques with intact, thick fibrous caps (Figure 2). Figure 3 shows a representative case of intraplaque hemorrhage with fibrous cap rupture seen on baseline MRI examination. The subject went on to develop an ipsilateral stroke 24 months later and subsequently underwent carotid endarterectomy. Histological examination of the corresponding cross-section demonstrates intraplaque hemorrhage with surface disruption.

Potential predictive factors were also analyzed within the subgroup of plaques that had an LR/NC (n=111 patients with 11 events). The presence of intraplaque hemorrhage (HR, 4.2; 95% CI, 1.1 to 16.0; $P = 0.022$), thin or ruptured fibrous cap (HR, 8.6; 95% CI, 2.0 to 67.5; $P = 0.007$), larger mean intraplaque hemorrhage area (HR for 10-mm² increase, 2.3; 95% CI, 1.3 to 4.2; $P = 0.017$), and maximum %LR/NC (HR

TABLE 2. Relationship Between Risk Factors and Ipsilateral Cerebrovascular Event During Follow-Up, Determined by Cox Regression

Variable	HR	95% CI	P Value
Age, y	1.1	1.0–1.1	0.1
Gender	1.0	0.2–4.5	1.0
Body mass index	1.0	0.9–1.2	0.6
Systolic blood pressure	1.0	1.0–1.0	0.7
Diastolic blood pressure	1.0	1.0–1.0	0.8
History of hypertension	1.6	0.4–7.4	0.5
History of diabetes	1.0	0.3–3.8	1.0
History of hypercholesterolemia	1.1	0.3–5.2	0.9
History of coronary artery disease	1.2	0.4–3.8	0.7
HMG-CoA reductase inhibitor use	1.0	0.3–3.4	1.0
Presence of LR/NC	4.4	0.6–33.7	0.09
Presence of IPH	5.2	1.6–17.3	0.005
Presence of thin/ruptured FC	17.0	2.2–132.0	<0.001
Mean lumen area*	1.2	0.9–1.5	0.2
Mean wall area†	1.1	0.9–1.4	0.3
Mean LR/NC area‡	1.6	1.1–2.1	0.01
Mean calcium area‡	2.4	0.9–6.1	0.1
Mean IPH area‡	2.6	1.4–4.6	0.006
Maximum %LR/NC of wall‡	1.6	1.2–2.0	0.004
Maximum wall thickness§	1.6	1.1–2.3	0.008
Minimum lumen area*	1.3	0.7–2.5	0.4

IPH indicates intraplaque hemorrhage; FC, fibrous cap; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A.

*A 10-mm² decrease; †a 10-mm² increase; ‡a 10% increase; §a 1-mm increase.

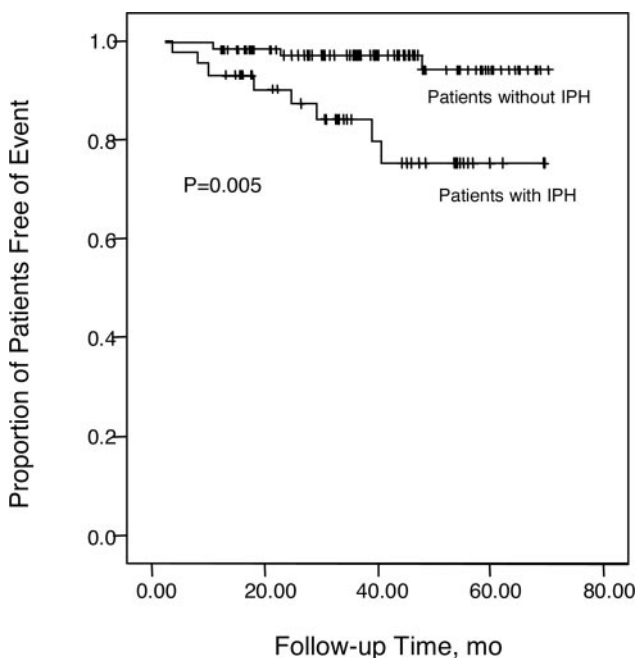


Figure 1. Kaplan–Meier survival estimates of the proportion of patients remaining free of ipsilateral cerebrovascular events for subjects with (lower curve) and without (upper curve) intraplaque hemorrhage. IPH indicates intraplaque hemorrhage.

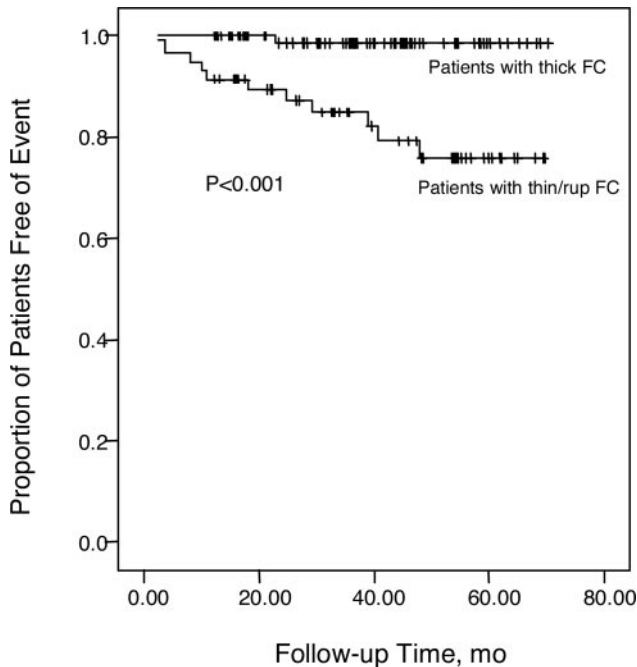


Figure 2. Kaplan–Meier survival estimates of the proportion of patients remaining free of ipsilateral cerebrovascular events for subjects with (lower curve) and without (upper curve) thin or ruptured fibrous cap.

for 10% increase, 1.5; 95% CI, 1.1 to 2.2; $P=0.021$) were significant predictors by Cox regression analysis.

Discussion

This study represents one of the first to prospectively examine the relationship between baseline carotid plaque features identified by MRI and the development of subsequent carotid cerebrovascular events. Among patients with initially asymptomatic, hemodynamically significant carotid stenosis (50%

to 79% by duplex ultrasound), Cox regression analysis showed that arteries with thin or ruptured fibrous caps, intraplaque hemorrhage, larger maximum %LR/NC, and larger maximum wall thickness had a significantly higher likelihood of developing ipsilateral cerebrovascular events during follow-up. These findings provide further evidence of the utility of MRI for identifying the high-risk atherosclerotic carotid plaque.

Intraplaque hemorrhage has long been recognized as a component of the complex atherosclerotic plaque. Histological studies published in the 1980s demonstrated an association between the presence of intraplaque hemorrhage and a history of TIA or stroke before carotid endarterectomy.^{16,17} However, the limitation of studies on excised specimens is that they are retrospective and cannot quantify the risk of future events. Several prospective ultrasound studies suggested that echolucent plaques predict an increased risk of subsequent ischemic cerebrovascular events.^{3–6} Advantages of ultrasonography include low cost and widespread availability. However, studies on the accuracy of ultrasound for identifying plaque composition have been conflicting, and ultrasound cannot reliably distinguish hemorrhage from lipid core.^{18–20} Our study found that the presence of intraplaque hemorrhage was significantly associated with subsequent carotid cerebrovascular events. However, the presence of an LR/NC, which sometimes includes an intraplaque hemorrhage, was not significantly associated with the risk of an event. An additional analysis comparing patients with an LR/NC but without a hemorrhage ($n=68$) versus all other patients ($n=86$) showed no significant association with the risk of an event (HR, 0.4; $P=0.2$). These findings suggest that the ability to distinguish the LR/NC with intraplaque hemorrhage from the LR/NC without intraplaque hemorrhage may be critical.

On the other hand, analysis of the size of the LR/NC, such as the maximum %LR/NC of wall, was associated with future events. When we evaluated the association between events

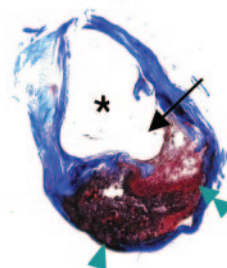
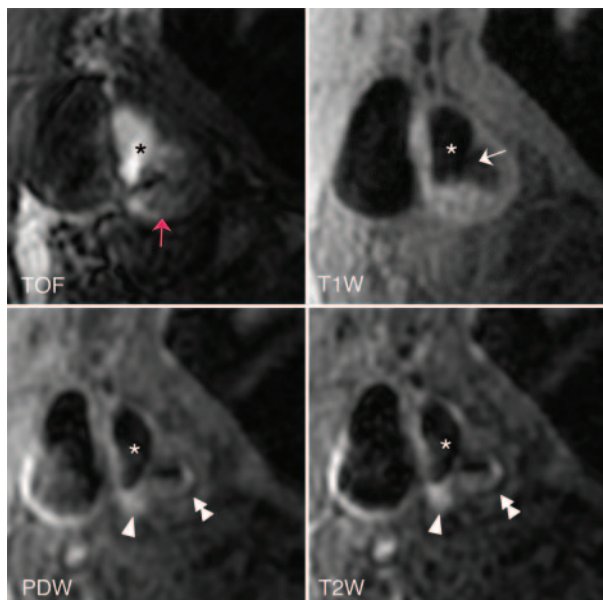


Figure 3. A representative case of fibrous cap rupture and hemorrhage into a carotid atherosclerotic plaque on baseline MRI. The subject experienced an ipsilateral stroke 24 months later and subsequently underwent CEA. Signal intensity patterns of hemorrhage (red arrow in TOF) are hyperintensity on the TOF and T1W images and hypointensity (double arrowhead) and hyperintensity (arrowhead) on the PDW/T2W images, suggesting a mixed of type I and type II intraplaque hemorrhage. A Mallery trichrome-stained matching histology section demonstrates the presence of the hemorrhage (arrowhead and double arrowhead) and surface disruption (arrow). The hemorrhage near to the disrupted surface (double arrowhead) is more recent than the hemorrhage deep in the plaque (arrowhead). Asterisks indicate the lumen.

and the presence of a larger LR/NC, defined as greater than the mean of all plaques with a LR/NC ($n=111$), Cox regression univariate analysis demonstrated a significant association with subsequent ipsilateral carotid cerebrovascular events (HR, 7.0; 95% CI, 1.9 to 26.5; $P=0.002$).

It is well known that a thin or ruptured fibrous cap is an important morphological component of the vulnerable atherosclerotic plaque.^{1,2} Previous studies have shown that MRI can distinguish thick, thin, and ruptured caps with good sensitivity and specificity in vivo.^{11,21} In a retrospective study, Yuan et al²² demonstrated that patients with thin and ruptured fibrous caps were more likely to have had a recent TIA or stroke (odds ratio, 10 and 23, respectively) compared with plaques with thick caps identified by MRI. In line with previous histological and retrospective imaging studies, findings from our prospective study confirm the importance of fibrous cap status in the development of future ischemic complications.

The Asymptomatic Carotid Atherosclerosis Study (ACAS) evaluated the efficacy of endarterectomy in patients with a >60% diameter reduction in asymptomatic carotid stenosis.²³ More recently, the largest randomized trial of endarterectomy for asymptomatic stenosis, the Medical Research Council Asymptomatic Carotid Surgery Trial (ACST), published results similar to ACAS.^{24,25} Both studies demonstrated absolute 5-year risk reductions with surgery of 5.3% and 5.1%, respectively. It is noteworthy that although there was a higher risk of stroke in the medically treated group, the overwhelming majority of subjects did not have an event. These findings highlight the need for developing improved criteria for identifying the characteristics of the high-risk carotid plaque, other than degree of stenosis, to better select those with asymptomatic carotid disease in need of surgical intervention.

In the present study, 2 cases were diagnosed as having a cardiogenic stroke and were not included as events in the analysis. However, even if we included those cases in the analysis, the results did not change. Cox regression analysis indicated that plaques with intraplaque hemorrhage (HR, 4.7; 95% CI, 1.6 to 14.0; $P=0.004$), larger mean intraplaque hemorrhage area (HR for 10-mm² increase, 2.4; 95% CI, 1.4 to 4.1; $P=0.008$), thin or ruptured fibrous cap (HR, 9.4; 95% CI, 2.1 to 42.1; $P<0.001$), larger maximum %LR/NC (HR for 10% increase, 1.4; 95% CI, 1.1 to 1.9; $P=0.01$), and maximum wall thickness (HR for a 1-mm increase, 1.6; 95% CI, 1.1 to 2.1; $P=0.007$) were associated with the events. A limitation of this study is the small number of cerebrovascular events that occurred during follow-up in our study population. The number was too small to support a multivariate analysis. Nonetheless, highly significant associations were observed, and these findings form the basis and justification for larger, prospective studies to better define the risk of specific carotid plaque features for TIA and stroke.

In conclusion, this prospective study indicates that a thin or ruptured fibrous cap, intraplaque hemorrhage, larger maximum %lipid-rich/necrotic core, and larger maximum wall thickness as identified by MRI are significantly associated with the development of subsequent ipsilateral hemispheric

TIA, stroke, or amaurosis fugax in patients with an initially asymptomatic, 50% to 79% carotid stenosis at baseline. If reproduced in larger prospective studies, MRI may provide an important tool for risk stratification and selection of candidates for invasive therapy.

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