

Carotid Plaque MRI and Stroke Risk A Systematic Review and Meta-analysis

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Background and Purpose—MRI characterization of carotid plaque has been studied recently as a potential tool to predict stroke caused by carotid atherosclerosis. We performed a systematic review and meta-analysis to summarize the association of MRI-determined intraplaque hemorrhage, lipid-rich necrotic core, and thinning/rupture of the fibrous cap with subsequent ischemic events.

Methods—We performed a comprehensive literature search evaluating the association of carotid plaque composition on MRI with ischemic outcomes. We included cohort studies examining intraplaque hemorrhage, lipid-rich necrotic core, or thinning/rupture of the fibrous cap with mean follow-up of ≥ 1 month and an outcome measure of ipsilateral stroke or transient ischemic attack. A meta-analysis using a random-effects model with assessment of study heterogeneity and publication bias was performed.

Results—Of the 3436 articles screened, 9 studies with a total of 779 subjects met eligibility for systematic review. The hazard ratios for intraplaque hemorrhage, lipid-rich necrotic core, and thinning/rupture of the fibrous cap as predictors of subsequent stroke/transient ischemic attack were 4.59 (95% confidence interval, 2.91–7.24), 3.00 (95% confidence interval, 1.51–5.95), and 5.93 (95% confidence interval, 2.65–13.20), respectively. No statistically significant heterogeneity or publication bias was present in the 3 main meta-analyses performed.

Conclusions—The presence of intraplaque hemorrhage, lipid-rich necrotic core, and thinning/rupture of the fibrous cap on MRI of carotid plaque is associated with increased risk of future stroke or transient ischemic attack in patients with carotid atherosclerotic disease. Dedicated MRI of plaque composition offers stroke risk information beyond measurement of luminal stenosis in carotid atherosclerotic disease. (*Stroke*. 2013;44:00-00.)

Key Words: carotid arteries ■ carotid artery plaque ■ ischemic attack, transient ■ MRI ■ risk ■ stroke

Carotid stenosis severity is widely used as an imaging marker for stroke risk, with the degree of stenosis used as a key inclusion criterion in several multicenter, large randomized trials of surgery versus medical treatment of carotid atherosclerotic disease.^{1,2} However, recent evidence suggests that specific elements of plaque composition are stroke risk factors independent of stenosis severity.³ Moreover, recent studies have demonstrated that MRI techniques can characterize these specific components of carotid plaque accurately in vivo compared with histopathology.^{4,5}

Given the reduction in stroke risk with advances in medical therapy during the past 2 decades, there has been increasing interest in investigating markers of plaque vulnerability to aid in selecting high-risk patients.⁶ However, MRI of plaque composition is a relatively new technique and individual studies have generally been small, thereby making it challenging to draw definite conclusions of the

value of MRI carotid plaque characterization. Furthermore, it is unclear whether there are differences in the risk profiles of specific plaque components such as intraplaque hemorrhage (IPH), lipid-rich necrotic core (LRNC), or thinning/rupture of the fibrous cap (TRFC). In addition, it is unknown whether certain techniques for plaque characterization, such as those involving high-resolution protocols with dedicated carotid surface coils, are superior to techniques that can be performed with widely available, standard MRI neck coils. For these reasons, we performed a systematic review and meta-analysis to evaluate whether MRI of plaque composition is a predictor of ipsilateral ischemic events in carotid atherosclerotic disease.

Methods

The methodology for this study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.⁷

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Study Eligibility Criteria

Studies with MRI-based characterization of carotid artery plaque composition and its association with ipsilateral stroke or transient ischemic attack (TIA) were eligible. Specific inclusion criteria were: (1) English language articles; (2) studies with ≥ 10 subjects; (3) MRI of carotid vessel plaque composition; (4) mean follow-up >1 month after plaque imaging; (5) assessment for development of ipsilateral stroke or TIA; and (6) nonsurgical management of patients. Given the emphasis on certain plaque characteristics in the American Heart Association (AHA) classification system,^{3,4} we included 3 specific plaque elements in this study: (1) IPH; (2) LRNC; and (3) TRFC. Because this was not a study of the diagnostic accuracy of MRI but rather an initial evaluation to determine if MRI characterization of plaques is associated with outcomes, studies did not require histopathologic correlation of MRI findings. In cases where testing characteristics or outcome data were not clear from the article, we attempted to contact the corresponding author for additional details.

Information Search and Data Collection

A systematic search was performed on March 13, 2013, by a medical librarian searching Ovid MEDLINE, Ovid Embase, the Cochrane Library, and AHRQ website, using additional databases for related articles searching. References were screened and data extracted by a team of 3 independent readers using a predetermined data collection template. Details of search methodology, study selection, and data collection are provided in the Methods in the online-only Data Supplement.

Assessment of Risk of Bias in Studies

We adapted bias assessment criteria used in a previously published meta-analysis⁸ of imaging findings and stroke risk: (1) risk of outcome ascertainment bias was assessed by recording whether researchers were blinded to MRI results when stroke outcomes were

assessed; (2) risk of confounding bias was assessed by recording whether potentially confounding stroke risk factors were collected and statistically analyzed; (3) completeness of follow-up data was assessed by noting the number of subjects lost to follow-up.

Statistical Analyses

All studies reporting a hazard ratio (HR) or presenting data amenable to HR calculation were included for meta-analysis. Because of the significant variation in study sizes, length of follow-up, and patient characteristics, the more conservative random-effects model was used. Heterogeneity was measured using the I^2 statistic. Publication bias was examined with the Begg–Mazumdar test. We performed subgroup analyses within each imaging group stratified by symptomatic versus asymptomatic disease. In the IPH subgroup, an additional subset analysis was performed stratifying studies by whether high-resolution imaging was performed with a dedicated surface carotid coil. All analyses were conducted using Stata version 12 software.

Results

Study Selection

A total of 3436 abstracts were initially screened, of which 17 potentially eligible articles were selected for further review (Figure 1). Of these 17 articles, 4 did not meet inclusion criteria when read in their entirety as they did not include patients followed up for development of stroke or TIA after specified MRI plaque testing, whereas 4 studies were excluded as they included subsets of cohorts published in larger studies ultimately selected for the systematic review. The remaining 9 studies^{9–17} met eligibility for the systematic review.

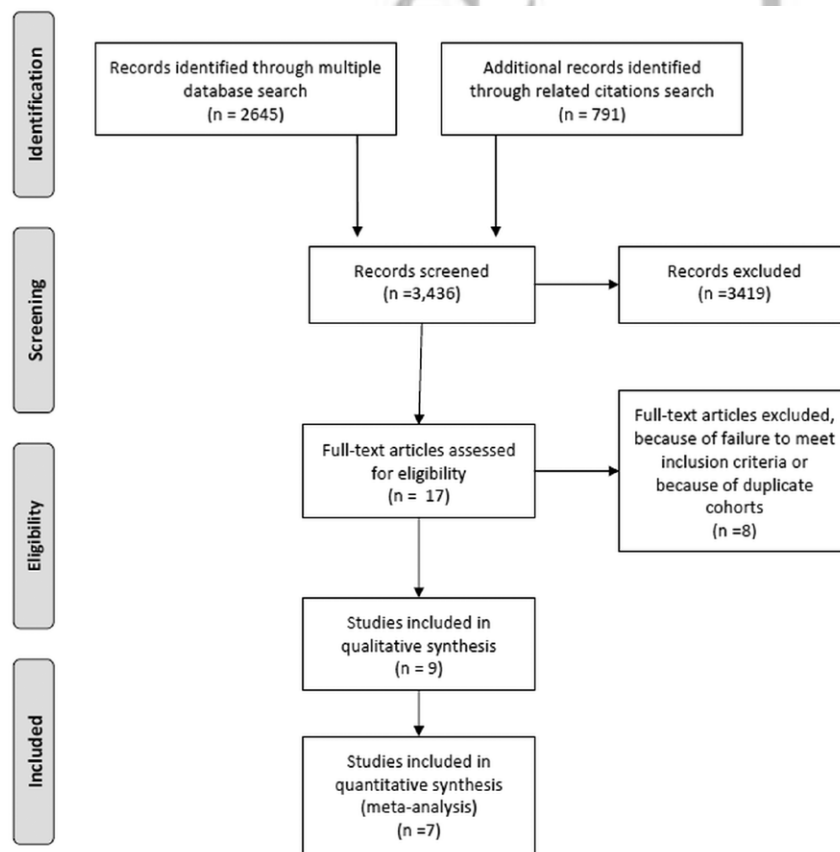


Figure 1. Study selection flow diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group statement.⁷ Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Qualitative Assessment and Study Characteristics

Of the 9 articles meeting eligibility for qualitative review (Table 1), all were cohort studies. Two studies were retrospective^{10,17} and the remaining 7 were prospective (Table 1). Three studies were conducted in Japan,^{10,16,17} 2 in the United Kingdom,^{9,13} and 1 each in Canada,¹⁴ the Netherlands,¹¹ Switzerland,¹² and the United States.¹⁵ All studies had similar subject ages (mean, 69–78 years) and a similarly higher preponderance of male subjects (range, 62.7%–100%). There were considerable differences between the studies in the degree of stenosis included: 1 study focused exclusively on high-grade ($\geq 70\%$) stenosis¹⁰; 5 studies included moderate to high-grade ($\geq 50\%$) stenosis^{9,12–15}; 3 studies^{11,16,17} included low to moderate stenosis (0%–69%). There was similar heterogeneity in patient symptoms, with 3 studies^{12,14,15} focused on asymptomatic patients, 5 studies^{9–11,13,17} on symptomatic patients, and 1 study¹⁶ with a mixed cohort. Two of the studies with symptomatic patients^{9,10} focused exclusively on patients with $\geq 50\%$ stenosis. Though most current guidelines recommend carotid intervention in such patients, in one cohort¹⁰ the medically managed patients were either poor surgical candidates or refused surgery. The other cohort⁹ was studied in the United Kingdom at a time before which symptomatic

patients with $\geq 50\%$ stenosis were offered carotid endarterectomy as routine standard of care.

All studies except one¹² were performed on 1.5-T MRI. For determination of LRNC or TRFC, high-resolution, multicontrast weighted dedicated carotid imaging was performed using carotid surface coils in all cases. In the IPH studies, 4 were performed using high-resolution dedicated carotid coils^{11–13,15} and 4 were performed with standard head/neck coils used for routine magnetic resonance angiography studies.^{9,10,14,16} MRI techniques, test results, and outcomes are summarized in Table 2. Outcomes were differentiated as ipsilateral stroke versus ipsilateral TIA in only 4 studies,^{9,10,14,16} whereas the remaining 5 studies used a composite outcome of ipsilateral stroke plus TIA. Detailed description of MRI testing methods as well as definitions of abnormal test results and outcome measures are provided in Table I in the online-only Data Supplement.

Assessment of Study Methods

In only 4 of 9 studies^{11,12,14,16} did the authors describe blinding of MRI results to researchers who assessed ischemic outcomes, whereas blinding was not reported in the remaining 5 articles. Eight of 9 studies collected and presented potentially confounding vascular risk factors, with only 1 study¹¹ not

Table 1. Overview of Patient Characteristics in Studies Evaluating the Risk of Stroke in Patients With Carotid Plaque MRI

Study No.	Study First Author and Year	Study Design	No. of Medically Managed Subjects	No. of Carotid Arteries With Follow-up Outcome Data	Mean Age, SD	Male, %	Disease Severity (All in Reference to Proximal ICA)	Symptomatic (Prior TIA or Stroke) Versus Never Symptomatic	Mean Follow-up, mo	Mean Interval Since Last Symptomatic	Imaging a Surrogate for Which Plaque Element(s)
1	Takaya et al, 2006 ¹⁵	Prospective Cohort	154	154	71.1	82	50%–79%	Asymptomatic	38.2	No symptoms for ≤ 6 mo	IPH, LRNC, thin/ruptured FC
2	Yamada et al, 2007 ¹⁶	Retrospective cohort	35	50	70	83.2	45% (mean)	Mixed population, no breakdown provided	12.0	Not provided	IPH
3	Singh et al, 2009 ¹⁴	Prospective cohort	75	98	74.8	100	50%–70%	Asymptomatic	24.9	No symptoms for ≤ 6 mo	IPH
4	Sadat et al, 2010 ¹³	Prospective cohort	61	61	74	N/A	50% (median)	Symptomatic	16.9	< 30 d	LRNC, thin/ruptured FC
5	Kurosaki et al, 2011 ¹⁰	Retrospective cohort	96 (full testing data only on 62 subjects)	62	77.8	80.6	$\geq 70\%$	Symptomatic	9.0	Not provided	IPH
6	Yoshida et al, 2012 ¹⁷	Retrospective cohort	25	0 (only IPH-positive patients followed)	74.2	92	$< 50\%$	Symptomatic	31.3	Not provided	IPH
7	Mono et al, 2012 ¹²	Prospective cohort	62	65	68.7	74	$\geq 50\%$	Asymptomatic	18.9	≤ 6 mo (32% had stroke prior to 6 mo before imaging)	IPH, LRNC, thin/ruptured FC
8	Kwee et al, 2013 ¹¹	Prospective cohort	126	126	69	62.7	30%–69%	Symptomatic	12.0	31.5 d	IPH, LRNC, thin/ruptured FC
9	Hosseini et al, 2013 ⁹	Prospective cohort	179	179	71.7	70.9	$\geq 50\%$	Symptomatic	17.5	39.6 d	IPH

ICA indicates internal carotid artery; IPH, intraplaque hemorrhage; LRNC, lipid-rich necrotic core; N/A, data not available; TIA, transient ischemic attack; and TRFC, thinned/ruptured fibrous cap.

Table 2. Overview of MRI Plaque Testing Characteristics and Risk of Ipsilateral Cerebrovascular Events

Study No.	Study First Author and Year	Plaque Element	No. of Arteries With Negative MRI	No. of Arteries With Positive MRI	Ipsilateral Ischemic Strokes in Negative Test Group	Ipsilateral Ischemic Strokes in Positive Test Group	Ipsilateral All Ischemic Events (TIA/Stroke) in Negative Test Group	Ipsilateral All Ischemic Events (TIA/Stroke) in Positive Test Group	All-Event (TIA/Stroke) HR	95% CI
1a	Takaya et al, 2006 ¹⁵	IPH	68	43	N/A	N/A	3	8	5.2	1.6–17.3
1b		TRFC	N/A	N/A	N/A	N/A	1	10	17	2.2–132.0
1c		LRNC	43	111	N/A	N/A	1	11	4.4	0.6–33.7
2	Yamada et al, 2007 ¹⁶	IPH	28	22	0	4	0	4	N/A	N/A
3	Singh et al, 2009 ¹⁴	IPH	62	36	0	2	0	6	3.59	2.48–4.71
4a	Sadat et al, 2010 ¹³	TRFC	34	27	N/A	N/A	N/A	N/A	7.39	1.61–33.82
4b		LRNC	42	19	N/A	N/A	N/A	N/A	1.75	0.55–5.54
4c		IPH	30	31	N/A	N/A	N/A	N/A	5.85	1.27–26.77
5	Kurosaki et al, 2011 ¹⁰	IPH	30	32	1	2	1	6	N/A	N/A
6	Yoshida et al, 2012 ¹⁷	IPH	0	25	N/A	N/A	N/A	11	N/A	N/A
7a	Mono et al, 2012 ¹²	LRNC	49	16	N/A	N/A	2	3	7.2	1.12–46.28
7b		TRFC	23	42	N/A	N/A	1	4	1.103	0.11–10.70
7c		IPH	49	16	N/A	N/A	5	0	0.03	0.00–86.62
8a	Kwee et al, 2013 ¹¹	LRNC	N/A	N/A	N/A	N/A	3	10	3.2	1.08–9.50
8b		TRFC	N/A	N/A	N/A	N/A	2	11	5.8	1.91–17.32
8c		IPH	N/A	N/A	N/A	N/A	6	7	3.5	1.06–11.96
9	Hosseini et al, 2013 ⁹	IPH	65	114	1	25	5	57	12	4.8–30.1

CI indicates confidence interval; HR, hazard ratio; IPH, intraplaque hemorrhage; LRNC, lipid-rich necrotic core; N/A, data not available; TIA, transient ischemic attack; and TRFC, thinned/ruptured fibrous cap.

presenting these data. Finally, in the assessment of the completeness of follow-up, in 1 study¹² 2 subjects moved from the country and were lost to follow-up. No other follow-up losses were described in the remaining 8 studies.

Meta-analysis Results

Seven of 9 studies meeting inclusion for systematic review were eligible for meta-analysis. One study was not amenable for meta-analysis¹⁷ as only IPH-positive subjects were followed to outcome, whereas another study¹⁶ did not report the association between imaging findings and event rates in the form of a HR and thereby did not provide data needed for the meta-analysis. The remaining 7 studies had data that could be included in meta-analysis, including 7 studies evaluating IPH,^{9–15} 4 studies evaluating LRNC,^{11–13,15} and 4 studies evaluating TRFC.^{11–13,15}

In the IPH-characterized group, a total of 678 patients and 702 unique carotid arteries were meta-analyzed with a mean follow-up of 20.2 months. In the LRNC-characterized group, 403 patients and 406 carotid arteries with a mean follow-up of 23.8 months were meta-analyzed. Finally, in the TRFC-characterized group, a total of 363 carotid arteries and patients with a mean follow-up of 22.1 months were meta-analyzed. No significant heterogeneity or publication bias was noted in the 3 primary analyses (Table 3). We found a significant positive relationship between IPH, LRNC, and TRFC and the risk

of future ischemic events (stroke plus TIA), with a random-effects HR of 4.59 (95% confidence interval [CI], 2.92–7.24), 3.00 (95% CI, 1.51–5.95), and 5.93 (95% CI, 2.65–13.29), respectively, for each specific plaque element (Figure 2).

Subset Analyses

No significant heterogeneity was found in any of the subset analyses with the exception of borderline heterogeneity ($I^2=68%$) present in subset analysis of the 3 IPH studies using standard neck coils. A statistically significant random-effects HR was preserved in subset analyses including symptomatic versus asymptomatic subjects in studies of IPH and LRNC,

Table 3. Heterogeneity and Publication Bias Measures of Main Study Groups

Group	Test of Heterogeneity I^2	Publication Bias (Begg and Mazumdar Rank Correlation)		
		Kendall τ	Test Statistic (Z)	P Value
All IPH studies	0.1%	−3	−0.45	0.652
All LRNC studies	0%	0.333	0.679	0.4969
All TRFC studies	0%	0	0	0.9999

IPH indicates intraplaque hemorrhage; LRNC, lipid-rich necrotic core; and TRFC, thinned/ruptured fibrous cap.

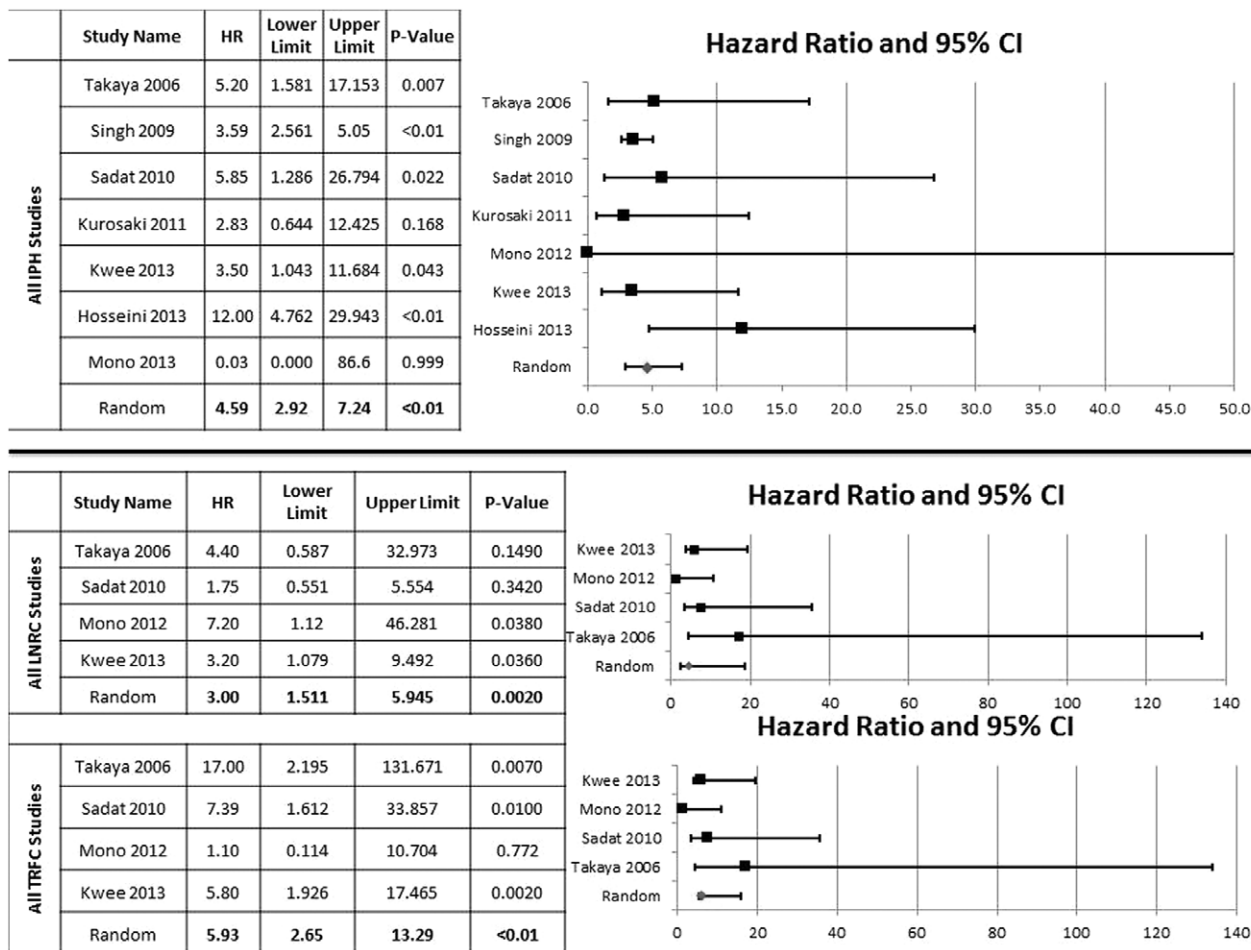


Figure 2. Individual forest plots of the association between MRI-determined intraplaque hemorrhage (IPH), lipid-rich necrotic core (LRNC), and thinning/rupture of the fibrous cap (TRFC), and ipsilateral cerebrovascular events determined by a random-effects model for all studies. Squares represent point estimates for effect size expressed as a hazard ratio (HR) with the size proportional to the inverse variance of the estimate. Diamond represents pooled estimate. Lines represent 95% confidence intervals (CIs).

and in studies of symptomatic subjects with TRFC. The single subset analysis not achieving statistical significance was the analysis of TRFC in asymptomatic subjects ($P=0.268$; Table 4). Furthermore, in the IPH studies, no significant difference in HR was found when studies were stratified by whether multisequence technique with a dedicated carotid coil was used.

Discussion

Measurement of stenosis severity has been the primary imaging-based measure of stroke risk in carotid atherosclerotic disease and plays a critical role in existing treatment guidelines.^{1,2} However, histopathologic studies have demonstrated that certain plaque elements, independent of arterial narrowing, are more likely to cause symptoms and thereby are hallmarks of unstable plaque.³ Recent developments in MRI technology have allowed accurate discrimination between the specific histological subtypes of carotid plaque as proposed by the AHA.⁴ However, studies using MRI of plaque to predict patient outcome are relatively new, with the first such study to our knowledge published in 2006.¹⁵

In our study, we found carotid plaques with IPH, LRNC, or TRFC are significantly more likely to result in ipsilateral

ischemic events, with HR ranging from ≈ 3 for LRNC to ≈ 6 for TRFC, with this increased risk present across a wide range of stenosis severity. This is the first comprehensive meta-analysis of MRI plaque characteristics and stroke prediction, though 1 recent study⁹ did present a limited meta-analysis of IPH alongside an original patient cohort, finding a pooled odds ratio of 10.02 (95% CI, 5.46–18.38) associating IPH and future stroke/TIA. In our study, we were able to calculate a HR of 4.59 with narrower CIs (95% CI, 2.92–7.23) associating IPH and future stroke/TIA, with the difference between meta-analyses partly attributable to the risk metric used in our study, the HR, a potentially more useful measure of risk taking into account time to events. Further important differences in our meta-analysis of IPH data include analyzing recent studies^{11,12} with 188 additional patients and the inclusion of larger and longer followed cohorts published more than once in the literature.¹³ One such recent study, Mono et al,¹² seems to contribute to the decreased effect size of IPH as a predictor of stroke compared with the previous meta-analysis.⁹ In this study, the only 1 performed on a 3-T MRI, there were 5 ischemic events in 65 patients, none of which occurred in the group with IPH present.

Table 4. Subgroup Analyses of Specific Plaque Element Studies

Subgroup	No. of Studies	HR (95% CI)	HR P Value	Test of Heterogeneity		Publication Bias		Test Between Groups	
				I^2	Kendall τ	Test Statistic (Z)	P Value	Test Statistic (Z)	P Value
IPH studies with asymptomatic subjects	3	3.66 (2.70–4.95)	<0.01	0%	–1	–0.52	0.602	–1.20	0.114
IPH studies with symptomatic subjects	4	5.860 (2.898–11.849)	<0.01	23.20%	–0.33	0.679	0.4969		
IPH studies using multisequence, carotid coil–dependent technique	4	4.40 (2.10–9.23)	<0.01	0%	–2	–0.68	0.497	–0.24	0.407
IPH studies using single sequence, standard neck coils	3	5.044 (2.147–11.851)	<0.01	68%	0.33	0.522	0.6015		
LRNC studies with asymptomatic subjects	2	5.739 (1.463–22.511)	0.012	0%				1.08	0.859
LRNC studies with symptomatic subjects	2	2.410 (1.092–5.319)	0.028	0%					
TRFC studies with asymptomatic subjects	2	4.54 (0.31–65.89)	0.268	3%				–0.23	0.410
TRFC studies with symptomatic subjects	2	6.304 (2.581–15.395)	<0.01	0%					

Publication bias test only performed if minimum of 3 studies available. CI indicates confidence interval; HR, hazard ratio; IPH, intraplaque hemorrhage; LRNC, lipid-rich necrotic core; and TRFC, thinned/ruptured fibrous cap.

A statistically significant HR for all plaque elements was achieved when analysis was limited to studies of symptomatic patients, as well as with subset analyses of IPH and LRNC in asymptomatic patients. Perhaps related to a small sample size of the 2 studies of asymptomatic patients with TRFC,^{12,15} this particular subset analysis did not achieve statistical significance. Additional studies may provide the statistical power needed to arrive at more definitive conclusions of the role of TRFC in predicting ischemic events in this subgroup.

Furthermore, our study demonstrated no statistically significant difference in HR between the 3 plaque elements, though the presence of LRNC showed the lowest HR (3.00) and TRFC showed the highest HR (5.93), with IPH demonstrating an intermediate HR (4.59). This rank ordering of risk, if verified via future research, is consistent with the general sequence of plaque progression in the AHA classification scheme. In this cascade of events, lipid-rich atheroma typically precedes the development of more advanced plaque in which hemorrhage can develop. This in turn can further progress to surface defects and FC rupture, ultimately precipitating embolism.³ Though 4 of the 7 studies^{11–13,15} in this meta-analysis examined >1 plaque element per patient, a multiparametric testing approach addressing the significance of each plaque element as a component of a composite plaque risk profile was not performed in any study. Furthermore, given the potential dynamic nature of plaque progression over time, the possibility that plaque elements may have changed between the time of testing and stroke/TIA outcome assessment was not evaluated by any study.

Our study also highlights potential barriers to the implementation of MRI carotid plaque imaging as a routine risk

stratification tool. For example, to determine the presence of LRNC and TRFC accurately, investigators used MRI protocols with multiple sequences, which generally take >30 minutes to complete and require a specialized carotid artery surface MRI coil not typically used in most clinical settings. However, in 3 studies, IPH was measured using standard, large field-of-view neck coils with a gradient echo–based protocol that takes <5 minutes.^{9,10,14} Prediction of future events using these gradient echo–based techniques was not significantly different from prediction using multisequence technique with a carotid coil (HR of 5.04 versus 4.41; $P=0.41$), though the small number of studies in this subset analysis resulted in borderline statistically significant heterogeneity suggesting that further work is needed to confirm that these techniques do in fact perform similarly. Furthermore, additional work is needed to assess the clinical utility of this tool, given that the ability to distinguish between acute intraluminal thrombus and IPH accurately is a known limitation of gradient echo–based techniques of IPH classification.⁹

Our study illustrates important limitations of the current literature on MRI plaque characterization. First, there is significant variation in reporting outcomes, with most studies using a composite measure of stroke/TIA, thereby preventing the accurate calculation of separate HR for stroke versus TIA. Second, because detailed raw data on test results were not provided in the majority of studies, the pooled prevalence of each specific plaque element cannot be accurately calculated in the studies included in this meta-analysis. Third, there is significant variability in MRI techniques for plaque imaging, raising questions about which technique is best for risk stratification, including whether quantitative volumetric analyses

are needed and the differences between plaque characterization on 1.5-T versus 3-T machines. Fourth, as many studies included patients with wide ranges of stenosis, more precise composite risk estimates taking into account both stenosis and plaque characteristics will require studies with less variability in the degree of stenosis included. Fifth, as only 2 subjects in total in the meta-analysis were described as being lost to follow-up, it is unclear what systematic efforts to assure follow-up were undertaken and to what extent losses to follow-up not explicitly described may have introduced bias in the ascertainment of study outcomes. Sixth, the lack of blinding in many studies also raises concerns about ascertainment bias, particularly when evaluating subjective end points of TIA. Finally, depending on local surgical practices, those patients who undergo surgical revascularization may have plaque or vascular risk factor profiles that differ from the medically managed patients eligible for this meta-analysis, thereby potentially introducing selection bias into the nonrandomized cohort studies comprising this meta-analysis.

Despite these limits, there is sufficient evidence from our systematic review and meta-analysis to conclude that MRI characterization of the specific plaque elements of IPH, LRNC, and TRFC can provide additional measures of stroke risk not provided by simple measurement of luminal stenosis. The use of carotid plaque MRI to select high-risk groups that may benefit from surgical revascularization requires continued investigation, particularly in asymptomatic carotid stenosis, with validation that may ultimately require an ancillary cohort study of the medical management arm of 1 of the modern randomized controlled trials of medical versus surgical therapy for stroke prevention.

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Disclosures

None.

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Carotid Plaque MRI and Stroke Risk: A Systematic Review and Meta-analysis Ajay Gupta, Hedyeh Baradaran, Andrew D. Schweitzer, Hooman Kamel, Ankur Pandya, Diana Delgado, Allison Dunning, Alvin I. Mushlin and Pina C. Sanelli

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SUPPLEMENTAL MATERIAL

**Carotid Artery Plaque Characterization on MRI and Stroke Risk: A Systematic
Review and Meta-Analysis**

SUPPLEMENTAL METHODS

Information Sources and Search:

Potentially relevant articles were found by searching the biomedical electronic databases Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)1946 to Present, Ovid Embase and the Cochrane Library. Relevant subject headings and free text terms were used. Published, unpublished and ongoing studies were identified by searching The Cochrane Central Register of Controlled Trials and the Agency for Healthcare Research and Quality's website. Additional records were identified by employing the Related Citations feature in PubMed and the Cited Reference Search in Web of Science®. The primary search was conducted in Ovid MEDLINE. Subject headings and key words were adapted for the other databases. In both MEDLINE and Embase, a validated search filter, developed by the Health Information Research Unit at McMaster University, to sensitively detect clinically sound prognostic studies, was applied.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)1946 to Present.Searched 03/13/13.

1. exp Carotid Stenosis/ 11027
2. Plaque, Atherosclerotic/ 1583
3. (carotid adj3 (athero\$ or stenosis\$ or ulcer\$ or plaque\$ or narrow\$ or obstruct\$ or occlus\$ or constrict\$ or bruit\$)).tw. 18774
4. (steno\$ occlus\$ or stenoocclus\$).tw. 667
5. Plaque\$.tw. 85630
6. or/1-5 104895
7. exp Magnetic Resonance Imaging/ 281263
8. magnetic resonance.tw. 190679
9. (vessel adj3 imag\$).tw. 828
10. (MR or MRI or MRIs or MRA or MRDTI).tw. 210725
11. or/7-10 422480
12. exp Stroke/ 75252
13. Stroke\$.tw. 133710
14. cerebrovascular.tw. 34776
15. ((brain or vascular or lacunar or venous or cerebral or isch?emic) adj2 (accident\$ or infarct\$ or event\$ or attack\$)).tw. 43254
16. (cva or cvas).tw. 1771
17. or/12-16 204222
18. 6 and 11 and 17 1704
19. limit 18 to "prognosis (maximizes sensitivity)" 520
20. (animals not (humans and animals)).sh. 3960085
21. 19 not 20 512

Embase via Ovid 1974 to 2013 March 13. Searched 03/13/13.

1. exp carotid artery obstruction/ 24029
2. atherosclerotic plaque/ 19450
3. (carotid adj3 (athero\$ or stenosis\$ or ulcer\$ or plaque\$ or narrow\$ or obstruct\$ or occlus\$ or constrict\$ or bruit\$)).tw. 25881

4. (steno\$ occlus\$ or stenoocclus\$).tw. 1018
5. Plaque\$.tw. 108345
6. or/1-5 142819
7. exp nuclear magnetic resonance imaging/ 472524
8. magnetic resonance.tw. 227936
9. ((vessel or plaque) adj3 imag\$).tw. 2039
10. (MR or MRI or MRIs or MRA or MRDTI).tw. 271924
11. or/7-10 586858
12. exp cerebrovascular accident/ 51716
13. Stroke\$.tw. 188909
14. cerebrovascular.tw. 47063
15. ((brain or vascular or lacunar or venous or cerebral or isch?emic) adj2 (accident\$ or infarct\$ or event\$ or attack\$)).tw. 59686
16. (cva or cvas).tw. 3053
17. or/12-16 274329
18. 6 and 11 and 17 3150
19. ((animal or nonhuman) not (human and (animal or nonhuman))).de. 4587047
20. 18 not 19 3084
21. limit 20 to "prognosis (maximizes sensitivity)" 2410

Cochrane Library via Wiley.Searched 03/13/13.

- #1 MeSH descriptor: [Carotid Stenosis] explode all trees 525
- #2 MeSH descriptor: [Plaque, Atherosclerotic] this term only 16
- #3 (carotid near/3 (athero* or stenosis* or ulcer* or plaque* or narrow* or obstruct* or occlus* or constrict* or bruit*)) 1330
- #4 (steno* occlus* or stenoocclus*) 840
- #5 Plaque* 6666
- #6 (#1 or #2 or #3 or #4 or #5) 8357
- #7 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees 4549
- #8 magnetic resonance 7074
- #9 ((vessel or plaque) near/3 imag*) 138
- #10 (MR or MRI or MRIs or MRA or MRDTI) 13410
- #11 (#7 or #8 or #9 or #10) 16910
- #12 MeSH descriptor: [Stroke] explode all trees 4179
- #13 stroke* 27172
- #14 cerebrovascular 6385
- #15 ((brain or vascular or lacunar or venous or cerebral or isch*emic) near/2 (accident* or infarct* or event* or attack*)) 5070
- #16 (cva or cvas) 335
- #17 (#12 or #13 or #14 or #15 or #16) 31403
- #18 (#6 and #11 and #17) from 2000 to 2013 165

Study Selection and Data Collection Process:

The title and abstract of all references were reviewed by a single reader who excluded studies that did not meet the inclusion criteria. After preliminary articles were identified, manuscripts were reviewed in their entirety by two independent readers to determine final inclusion, with disagreements resolved by a third reader as a tie-breaker. Study data was extracted by two independent readers using a predetermined data collection template. All disagreements were resolved by an independent third reader as a tie-breaker.

SUPPLEMENTAL TABLE

Study Number	Study First Author and Year	Plaque Element	Magnet Field Strength	MRI Technique (for Plaque Element Under Study)	MRI Coil Type	Definition of Abnormal MRI Test Result	Any Quantitative Plaque Element Assessment	Stroke or TIA Definition
1a	Takaya 2006 ¹	IPH	1.5T	High-resolution multi-contrast weighted technique (TOF, T1W FS, PD FS, T2W FS)	dedicated carotid phased-array surface coil	hyperintense T1W and TOF & isointense on T2. Recent IPH is hyperintense on all sequences	Volumetric analysis with assessment of mean areas for plaque components and wall areas	Stroke: Clinical diagnosis after evaluation by vascular surgeon & neurologist and confirmed to be of ischemic origin by neuroimaging. TIA: new-onset focal neurological abnormality lasting >24 hours.
1b		thin/ruptured FC	1.5T	High-resolution multi-contrast weighted technique (TOF, T1W FS, PD FS, T2W FS)	dedicated carotid phased-array surface coil	thin or absent dark band between lumen and plaque core	Volumetric analysis with assessment of mean areas for plaque components and wall areas	
1c		LRNC	1.5T	High-resolution multi-contrast weighted technique (TOF, T1W FS, PD FS, T2W FS)	dedicated carotid phased-array surface coil	iso- to hyperintense on T1W and PD	Volumetric analysis with assessment of mean areas for plaque components and wall areas	
2	Yamada 2007 ²	IPH	1.5T	3D IR T1WI MPRAGE; also 3D TOF pre- and post-gadolinium	Standard neck array and spine array coils	Carotid plaque with intensity on MPRAGE of 200% that of adjacent muscle with ROI placement	Plaque volume was calculated in patients with high signal intensity.	Clinical diagnosis for stroke/TIA
3	Singh 2009 ³	IPH	1.5T	3D T1 FS SPGR	8-channel neurovascular phased-array coil	SI > 50% adjacent muscle	No volumetric analysis	Clinical diagnosis for stroke/TIA determined by follow up in clinic and by phone and by medical records evaluation
4a	Sadat 2010 ⁴	thin/ruptured FC	1.5T	High-resolution multi-contrast weighted technique (T1W FS, PD FS, T2W FS, STIR)	dedicated 4-channel carotid phased-array surface coil	FC discontinuity or cavity formation in plaque (absence of low T1 signal and high STIR signal band)	Plaque component areas determined and 3D reconstructed volumes were made.	Clinical diagnosis based for stroke/TIA based on medical records and patient interviews.
4b		LRNC	1.5T	High-resolution multi-contrast weighted technique (T1W FS, PD FS, T2W FS, STIR)	dedicated 4-channel carotid phased-array surface coil	high signal on T1 relative to muscle, iso- to hypointense on T2, STIR. Large lipid content if >25% of total volume	Plaque component areas determined and 3D reconstructed volumes were made	
4c		IPH	1.5T	High-resolution multi-contrast weighted technique (T1W FS, PD FS, T2W FS, STIR)	dedicated 4-channel carotid phased-array surface coil	T1 hyperintense relative to muscle. Recent if high signal on all sequences; Fresh if iso- to hypointense on T2	Plaque component areas determined and 3D reconstructed volumes were made	
5	Kurosaki 2011 ⁵	IPH	1.5T	3D GRE black-blood T1W	standard combined neck/head coil	relative intensity of 1.2 times adjacent sternocleidomastoid muscle	No Volumetric analysis	Stroke/TIA decided by 2 physicians based on combination of clinical & imaging findings
6	Yoshida 2012 ⁶	IPH	not reported	3D GRE black blood T1W	not specified	hyperintense signal relative to sternocleidomastoid muscle with ROI placement	No volumetric analysis	Stroke/TIA defined on clinical basis
7a	Mono 2012 ⁷	LRNC	3T	High-resolution multi-contrast weighted technique (TOF, T1W, CE T1W FS, and T2W FS)	dedicated 4-channel carotid phased-array surface coil	isointense on TOF, hyperintense on T1W, of variable intensity on T2W, and hypointense on CE-T1W	Area and volume of plaque components calculated.	TIA defined as focal neurologic deficit with no correlate on imaging and stroke defined as focal neurologic deficit with evidence of acute infarction on imaging
7b		thin/ruptured FC	3T	High-resolution multi-contrast weighted technique (TOF, T1W, CE T1W FS, and T2W FS)	dedicated 4-channel carotid phased-array surface coil	thin (dark band adjacent to lumen missing on TOF, smooth luminal surface on all images) or ruptured (dark band adjacent to lumen missing or discontinuous on TOF, signal at site of presumed rupture hyperintense on TOF, and surface irregular)	Area and volume of plaque components calculated	
		IPH	3T	High-resolution multi-contrast weighted technique (TOF, T1W, CE T1W FS, and T2W FS)	dedicated 4-channel carotid phased-array surface coil	hyperintensity on TOF and T1W and hypo-/isointense on T2WI and CE-T1WI or hyperintense on all sequences	Area and volume of plaque components calculated	
8a	Kwee 2013 ⁸	LRNC	1.5T	High-resolution multi-contrast weighted technique (3D T1W, 3D TOF, T2W, T1W & CE T1W IR black blood)	dedicated 47 mm diameter surface coil	no/slight enhancement on CE T1W, no high signal on T1W/TOF	Plaque component volume calculated	Strokes defined clinically but confirmed as ischemic with imaging. TIA: acute loss of focal cerebral or monocular function <24h. Stroke: acute loss of focal cerebral or monocular function lasting >24h
8b		thin/ruptured FC	1.5T	High-resolution multi-contrast weighted technique (3D T1W, 3D TOF, T2W, T1W & CE T1W IR black blood)	dedicated 47 mm diameter surface coil	disrupted/discontinuous high signal between LRNC and lumen on CE T1W		
8c		IPH	1.5T	High-resolution multi-contrast weighted technique (3D T1W, 3D TOF, T2W, T1W & CE T1W IR black blood)	dedicated 47 mm diameter surface coil	high signal on T1W or TOF		
9	Hosseini 2013 ⁹	IPH	1.5T	3D T1 GRE black blood with FS	quadrature neck array coils	1.5x signal hyperintensity adjacent sternocleidomastoid with ROI placement	No volumetric analysis	Ischemic events determined by clinical details but confirmed by imaging.

Supplemental Table I - Overview of MRI Plaque Testing and Outcome Characteristics

N/A indicates data not available; TRFC, thinned/ruptured fibrous cap; IPH, intraplaque hemorrhage; LRNC, lipid-rich necrotic core; T, Tesla; TOF, time-of-flight; T1W, T1-weighted; T2W, T2-weighted; PD, proton density; FS, fat-saturated; IR, inversion recovery; MPRAGE, magnetization-prepared rapid acquisition with gradient echo; SPGR, spoiled gradient recalled; GRE, gradient echo; CE, contrast enhanced.

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