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ORIGINAL RESEARCH

Prediction of Stroke Risk by Detection of Hemorrhage in Carotid Plaques

Meta-Analysis of Individual Patient Data

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ABSTRACT

OBJECTIVES The goal of this study was to compare the risk of stroke between patients with carotid artery disease with and without the presence of intraplaque hemorrhage (IPH) on magnetic resonance imaging.

BACKGROUND IPH in carotid stenosis increases the risk of cerebrovascular events. Uncertainty remains whether risk of stroke alone is increased and whether stroke is predicted independently of known risk factors.

METHODS Data were pooled from 7 cohort studies including 560 patients with symptomatic carotid stenosis and 136 patients with asymptomatic carotid stenosis. Hazards of ipsilateral ischemic stroke (primary outcome) were compared between patients with and without IPH, adjusted for clinical risk factors.

RESULTS IPH was present in 51.6% of patients with symptomatic carotid stenosis and 29.4% of patients with asymptomatic carotid stenosis. During 1,121 observed person-years, 66 ipsilateral strokes occurred. Presence of IPH at baseline increased the risk of ipsilateral stroke both in symptomatic (hazard ratio [HR]: 10.2; 95% confidence interval [CI]: 4.6 to 22.5) and asymptomatic (HR: 7.9; 95% CI: 1.3 to 47.6) patients. Among patients with symptomatic carotid stenosis, annualized event rates of ipsilateral stroke in those with IPH versus those without IPH were 9.0% versus 0.7% (<50% stenosis), 18.1% versus 2.1% (50% to 69% stenosis), and 29.3% versus 1.5% (70% to 99% stenosis). Annualized event rates among patients with asymptomatic carotid stenosis were 5.4% in those with IPH versus 0.8% in those without IPH. Multivariate analysis identified IPH (HR: 11.0; 95% CI: 4.8 to 25.1) and severe degree of stenosis (HR: 3.3; 95% CI: 1.4 to 7.8) as independent predictors of ipsilateral stroke.

CONCLUSIONS IPH is common in patients with symptomatic and asymptomatic carotid stenosis and is a stronger predictor of stroke than any known clinical risk factors. Magnetic resonance imaging might help identify patients with carotid disease who would benefit from revascularization. (J Am Coll Cardiol Img 2020;13:395–406)

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ABBREVIATIONS AND ACRONYMS

AER = annualized event rate

AFx = amaurosis fugax

CI = confidence interval

HR = hazard ratio

IPH = intraplaque hemorrhage

MRI = magnetic resonance imaging

TIA = transient ischemic attack

Atherosclerotic stenosis of the internal carotid artery is present in 1% to 2% of the adult population and is the cause of ~10% to 15% of ischemic strokes (1,2). Randomized trials showed that carotid endarterectomy reduces the risk of stroke in patients with recently symptomatic carotid stenosis (3,4) and, to a lesser degree, in patients with asymptomatic carotid stenosis (5,6). Carotid artery stenting is an option to surgery in selected patients with symptomatic (7) and asymptomatic (8,9) carotid stenosis. However, the risk of stroke in patients with carotid disease has decreased owing to more efficient medical management, and, in many patients, carotid revascularization may no longer offer additional benefit. Identifying patients at high risk for stroke is therefore essential for targeting invasive treatments to individual patients.

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Magnetic resonance imaging (MRI) is able to detect features of unstable carotid plaques such as intraplaque hemorrhage (IPH), lipid-rich necrotic core, and thin or ruptured fibrous cap with good histopathological correlation (10–13). Several cohort studies and 4 meta-analyses have reported a 4- to 12-fold increased risk for ipsilateral ischemic events (including stroke, transient ischemic attack [TIA], and amaurosis fugax [AFx]) in patients with IPH under medical therapy (14–17). However, the studies were limited by small sample sizes (25 to 179 individuals) and variations in MRI protocols to detect and classify IPH. Reliable quantification of stroke risk, especially for symptomatic patients with low-grade stenosis, is lacking. Finally, it remained unclear if detection of IPH adds prognostic value to existing, validated clinical risk models. To overcome these limitations, we pooled data of individual patients who were examined by using plaque MRI for the presence of IPH and prospectively followed up in several cohort studies that used similar designs, methods, and outcomes.

METHODS

SEARCH STRATEGY AND STUDY SELECTION CRITERIA. Two experienced authors (A.S. and T.S.) identified potentially eligible studies by electronic literature searches on Ovid MEDLINE, EMBASE, and Cochrane from inception until December 2016 (Supplemental Appendix, Supplemental Tables 1 to 5). Further eligible studies were identified by screening of bibliographies of retrieved original papers, review articles, and published meta-analyses. Finally, we contacted experts in the field to identify any additional relevant studies. Disagreements on study inclusion were solved by discussion between the 2 reviewers.

The pre-defined eligibility criteria for studies were: 1) inclusion of ≥10 patients; 2) assessment of carotid IPH on MRI at baseline (as defined later) at ≥1.5-T; 3) evaluation of the degree of carotid stenosis; and 4) prospective clinical follow-up under conservative therapy (patients in whom revascularization was initially planned were excluded). IPH had to be determined on T1-weighted fat-suppressed images by the investigators of the original studies and was defined as an area of hyperintense signal in the plaque compared with the sternocleidomastoid muscle or the normal vessel wall.

We invited all corresponding, first, and last authors of publications from eligible cohorts to share anonymized data at the individual patient level. No imaging

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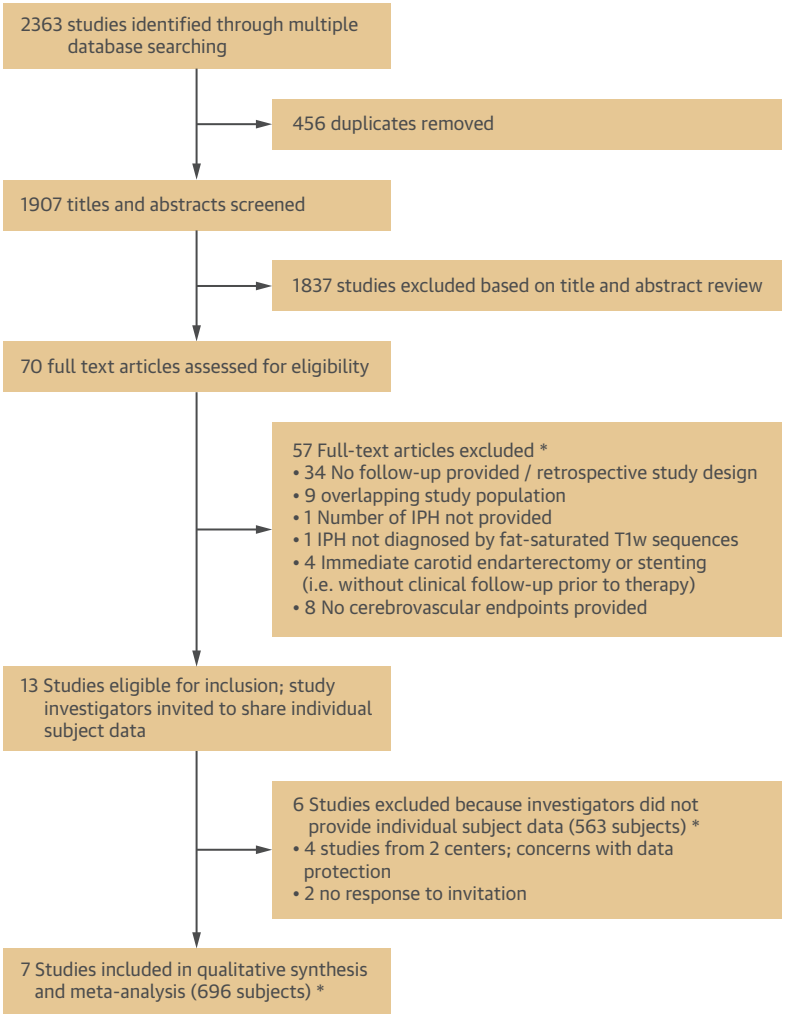
FIGURE 1 Study Flowchart



Study selection flow diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group statement (41). *Supplemental Appendix. IPH = intraplaque hemorrhage.

raw data were collected. The local ethics committee waived the need for individual consent or specific approval for this analysis.

DATA COLLECTED. Data on the following baseline patient characteristics were collected: symptomatic versus asymptomatic stenosis, presence or absence of IPH, degree of stenosis, age, sex, diabetes, smoking status, hypertension, and statin medication. Symptomatic carotid stenosis was defined by occurrence of ipsilateral ischemic symptoms in the past 6 months (retinal ischemia including retinal infarction and AFx, TIA, or ischemic stroke).

Carotid stenosis was assessed by duplex ultrasound (n = 6), computed tomography angiography (n = 2), or magnetic resonance angiography (n = 2). Degree of stenosis was expressed according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria (18). In a single study (19) reporting stenosis according to ECST (European Carotid Surgery Trial) criteria, values were transformed to NASCET values by using a published formula (20). Degree of stenosis was categorized into mild (<50%), moderate (50% to 69%), or severe (70% to 99%) concordant with NASCET (3). Patients with asymptomatic carotid stenosis were only included in the current analysis if the degree of stenosis was ≥50%.

The primary outcome event in the current study was ipsilateral hemispheric ischemic stroke

TABLE 1 Baseline Characteristics

	Symptomatic Carotid Stenosis (n = 560)	Asymptomatic Carotid Stenosis (n = 136)	Total (N = 696)
Age at baseline, yrs	72.8 ± 9.7	73.4 ± 8.9	73.0 ± 9.5
Male	387 (69.1)	115 (84.6)	502 (72.1)
Diabetes	125 (22.3)	31 (22.8)	156 (22.4)
Hypertension	370 (66.1)	105 (77.2)	475 (68.2)
Any smoking (former or current)	270 (48.2)	90 (66.2)	360 (51.7)
Statin treatment	370 (66.1)	109 (80.1)	479 (68.8)
Type of qualifying event			
Stroke	285 (50.9)	–	285 (40.9)
TIA	201 (35.9)	–	201 (28.9)
AFx	74 (13.2)	–	74 (10.6)
Asymptomatic	–	136 (100)	136 (19.5)
Presence of IPH on baseline carotid MRI	289 (51.6)	40 (29.4)	329 (47.3)
Degree of stenosis			
<50%	187 (33.4)	–	187 (26.9)
50%–69%	192 (34.3)	128 (94.1%)	320 (46.0)
70%–99%	181 (32.3)	8 (5.9)	189 (27.2)
Time between qualifying event and MRI, days	34.7 ± 38.4	–	–

Values are mean ± SD or n (%). Some percentages do not add up to 100 because of rounding.

AFx = amaurosis fugax; IPH = intraplaque hemorrhage; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

(i.e., occurring in the territory of the index carotid artery) at any time after the MRI scan. Ischemic stroke was clinically defined as a rapidly developing syndrome of focal cerebral dysfunction lasting >24 h or leading to earlier death, with no other apparent cause than cerebral ischemia. The secondary outcome event was the composite of ipsilateral ischemic stroke, TIA, and retinal ischemia.

In 1 study, IPH status and ipsilateral symptoms during follow-up were reported for each side separately in a minority of patients with bilateral carotid stenosis (21). In these patients, if outcome events occurred in both carotid territories or if no outcome events occurred at all, we arbitrarily chose the right carotid artery as the index artery; if outcome events occurred only in 1 carotid territory, the ipsilateral artery was chosen as the index artery. Patients with simultaneous bilateral strokes were excluded to rule out bias due to high likelihood of cardioembolic origin (n = 2) (22).

STATISTICAL ANALYSIS. Statistical analyses were performed by an independent statistician (R.S.) using SAS version 9.4 for Windows (SAS Institute, Inc., Cary, North Carolina). We compared outcome events occurring during follow-up between patients with IPH and those without IPH at baseline in the entire study population and separately in patients with any degree of symptomatic stenosis; patients with symptomatic stenosis <50%, 50% to 69%, and 70% to 99%; and patients with 50% to 99% asymptomatic stenosis. Annualized event rates were calculated from the sum of events and duration of follow-up. A Kaplan-Meier analysis was performed comparing time-to-event between patients with and without IPH by using the log-rank test, and obtaining cumulative risks after 3 months and 1, 2, 3, and 4 years, starting at the time of the baseline plaque MRI scan and terminating at the earliest occurrence of an outcome event. If no outcome event occurred, analyses were censored at the time of last available follow-up, revascularization by carotid endarterectomy or stenting, or death, whichever came first.

Cox regression models were used to calculate unadjusted hazard ratios (HRs) of outcome events. Frailty models were calculated modeling the time-to-event adjusted for available clinical patient characteristics, which had previously been identified as independent predictors of ipsilateral stroke in patients with symptomatic carotid stenosis in the ECST: age group, sex, diabetes, hypertension, degree of stenosis, and symptoms at inclusion (23,24). Near occlusion, time since last event, previous myocardial infarction, peripheral vascular disease, and irregular/ulcerated plaque (which are also part of the ECST risk model) were not included because these variables were not consistently available from the included studies. To account for random effects of the individual studies, frailty models were preferred to a regular Cox regression.

All analyses were repeated for the secondary composite outcome. A p value <0.05 was considered to indicate statistical significance.

RESULTS

Thirteen studies including 1,259 patients met the inclusion criteria (**Figure 1**). Individual patient data were provided by researchers from 7 cohort studies (n = 696; Europe, n = 4; Asia, n = 2; North America, n = 1). Two of these studies included only patients with asymptomatic carotid stenosis (19,21), 4 studies included only patients with symptomatic stenosis (16,25-27), and 1 study included both symptomatic and asymptomatic patients (of which only the symptomatic subset had been published) (22). In all but 2 cohorts (21,25), follow-up for neurological symptoms was prospective. Stroke was assessed as clinical endpoint in all studies according to clinical diagnosis and confirmed by using neuroimaging in all but 1 study (chart review only; 75 asymptomatic male subjects) (21). Stroke and TIA were evaluated in all studies and AFx in all but 2 studies (21,25). One study used a 3.0-T MR scanner (22), and all other studies

TABLE 2 Annualized Rates for Ipsilateral Stroke During FU in Patients With and Without IPH at Baseline

	IPH in the Baseline MRI Scan											
	No				Yes				Total			
	Events	n	Mean Follow-Up Duration, months	AER, %	Events	n	Mean Follow-Up Duration, months	AER, %	Events	n	Mean Follow-Up Duration, months	AER, %
Symptom status at baseline												
Asymptomatic	2	96	33.3	0.8	4	40	22.4	5.4	6	136	30.1	1.8
Symptomatic	7	271	19.8	1.6	53	289	13.8	15.9	60	560	16.7	7.7
Stenosis category (symptomatic patients)												
<50%	1	103	15.8	0.7	13	84	20.5	9.0	14	187	18.0	5.0
50%–69%	5	97	30.1	2.1	25	95	17.4	18.1	30	192	23.8	7.9
70%–99%	1	71	11.6	1.5	15	110	5.6	29.3	16	181	8.0	13.3
Sex												
Female	4	126	22.7	1.7	9	68	11.0	14.4	13	194	18.7	4.3
Male	5	241	23.6	1.1	48	261	15.9	13.9	53	502	19.6	6.5
Age, yrs												
<65	2	87	19.5	1.4	7	40	12.8	16.5	9	127	17.3	4.9
65-74	2	114	23.0	0.9	17	110	16.8	11.0	19	224	19.9	5.1
>74	5	166	25.6	1.4	33	179	14.1	15.7	38	345	19.7	6.7
Total	9	367	23.3	1.3	57	329	14.9	14.0	66	696	19.3	5.9

AER = annualized event rate; IPH = intraplaque hemorrhage; MRI = magnetic resonance imaging.

were performed on 1.5-T MR scanners. A multisequence protocol (for detecting features additional to IPH) and dedicated surface coils for imaging of the vessel wall were used in 2 studies (19,26). MRI readers were blinded to the clinical status in all studies. During follow-up, subjects of all studies received best medical treatment with antithrombotic therapy and statins as applicable.

In the pooled study population (n = 696), the mean age at study inclusion was 73.0 ± 9.5 years, 502 (72.1%) patients were male, and 560 (80.5%) had symptomatic carotid stenosis (**Table 1**). Among patients with symptomatic carotid stenosis, the mean interval between the event and plaque MRI was 34.7 days. IPH was detected at baseline in 51.6% (n = 289) of patients with symptomatic stenosis and in 29.4% (n = 40) of patients with asymptomatic stenosis. Among patients with symptomatic and asymptomatic carotid stenosis combined, IPH was present in 26.9%, 46.0%, and 27.2% of patients with a degree of stenosis <50%, 50% to 69%, and 70% to 99%, respectively.

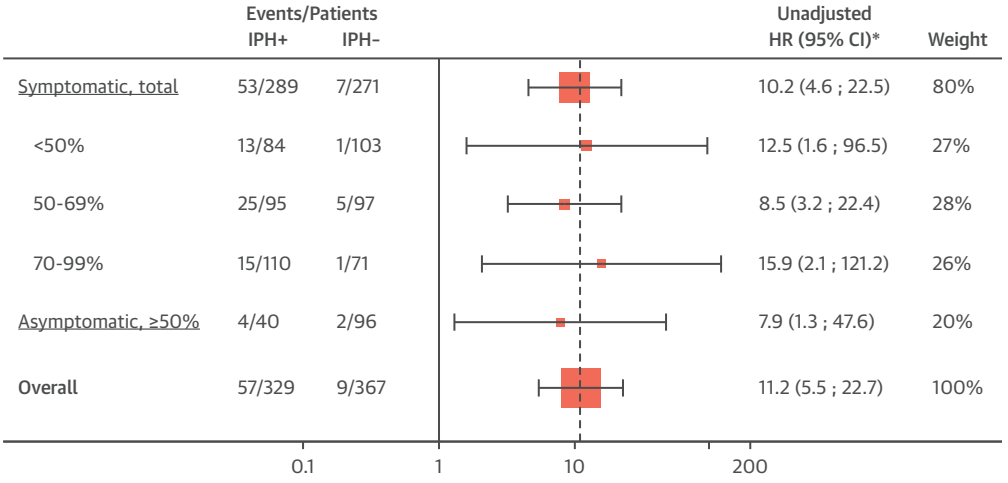
There were 1,121 person-years of follow-up in the entire cohort, with a mean duration of 19.3 months (16.7 months in patients with symptomatic stenosis and 30.1 months in patients with asymptomatic stenosis). Thirty-four patients died during follow-up without occurrence of the primary or secondary outcome event, and 7 patients were censored at the point where they underwent carotid revascularization.

During follow-up, 66 ipsilateral strokes occurred, 60 in patients with symptomatic stenosis (annualized event rate [AER]: 7.7%) and 6 in patients with asymptomatic stenosis (AER: 1.8%) (**Table 2**). Presence of IPH at baseline was associated with a significantly higher risk of ipsilateral stroke during follow-up, both among patients with symptomatic stenosis (AER: 15.9% vs. 1.6%; unadjusted HR: 10.2; 95% confidence interval [CI]: 4.6 to 22.5) and among patients with asymptomatic stenosis (AER: 5.4% vs. 0.8%; unadjusted HR: 7.9; 95% CI: 1.3 to 47.6) (**Figures 2 and 3**). Cumulative risks are provided in **Figure 3**. In patients with symptomatic carotid stenosis, the absolute difference in risk for ipsilateral stroke between patients with and without IPH was 14.0%, 26.6%, and 33.5% at 1, 2, and 4 years, respectively.

The presence of IPH increased stroke risk in patients with symptomatic stenosis at all degrees: AER of ipsilateral stroke in those with IPH versus without IPH were 9.0% versus 0.7% in patients with <50% stenosis, 18.1% versus 2.1% in patients with 50% to 69% stenosis, and 29.3% versus 1.5% in patients with 70% to 99% stenosis (**Table 2**). Unadjusted HRs for ipsilateral stroke in patients with IPH versus those without IPH in those categories of stenosis were 12.5 (95% CI: 1.6 to 96.5), 8.5 (95% CI: 3.2 to 22.4), and 15.9 (95% CI: 2.1 to 121.2), respectively (**Figure 2, Central Illustration**).

The IPH-related increase in risk of ipsilateral stroke among patients with symptomatic carotid disease

FIGURE 2 Associations Between Presence of IPH at Baseline and Ipsilateral Stroke During Follow-up



Plots show pooled estimates of associations between presence of intraplaque hemorrhage (IPH) at baseline and outcome during observed follow-up. The area of each shaded box is proportional to the weight of the cohort it represents. *Estimated from a trial-stratified Cox regression model. CI = confidence interval; HR = hazard ratio; IPH+/- = IPH at baseline present/absent.

remained similar after multivariate adjustment for known clinical risk predictors with an HR of 11.0 (95% CI: 4.8 to 25.1) (**Table 3**). In the multivariate model, only severe degree of stenosis predicted ipsilateral stroke in addition to IPH (HR: 3.3 [95% CI: 1.4 to 7.8] for 70% to 99% vs. <50% stenosis). No additional clinical risk predictors were identified after removing IPH from the model (Supplemental Table 6). After inclusion of patients with asymptomatic carotid stenosis and symptom status as an additional covariate in the model, IPH remained significantly associated with ipsilateral stroke risk (HR: 10.4; 95% CI: 4.9 to 21.9); in addition, severe degree of stenosis (HR: 3.0; 95% CI: 1.3 to 7.2) and diabetes (HR: 2.0; 95% CI: 1.2 to 3.5) were positively associated and asymptomatic status at baseline (HR: 0.3; 95% CI: 0.1 to 1.0) negatively associated with the risk of ipsilateral stroke (Supplemental Table 7).

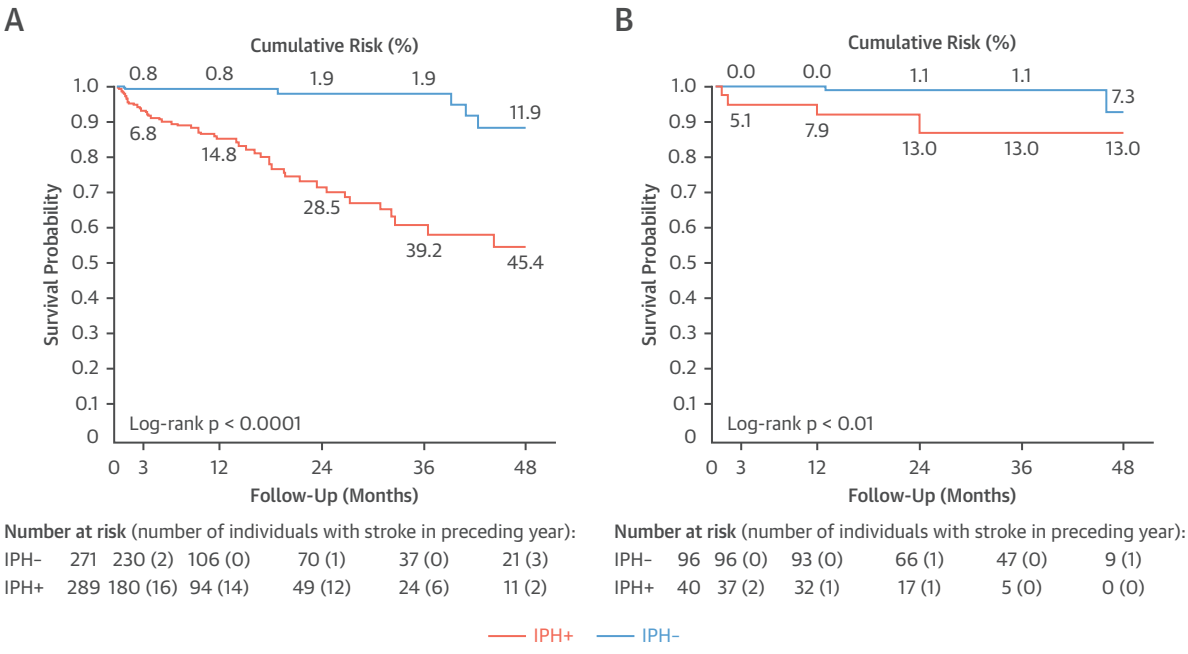
The secondary outcome event, the composite of ipsilateral ischemic stroke, TIA, or AFx, occurred in 117 patients with symptomatic carotid stenosis and in 10 patients with asymptomatic carotid stenosis (Supplemental Table 8). Presence of IPH resulted in a significantly increased risk of the secondary outcome event, with unadjusted HRs of 6.5 and 14.5 for patients with symptomatic and asymptomatic stenosis, respectively (Supplemental Figure 1). IPH remained a significant predictor of the secondary outcome event after multivariate adjustment (Supplemental Tables 9 and 10).

DISCUSSION

This study yielded several key findings. First, IPH detectable by plaque MRI is common; in our study population, it was present in 52% of patients with previously symptomatic stenosis and in 29% of patients with asymptomatic carotid stenosis. Second, IPH significantly increased the risk of future ipsilateral stroke in patients with symptomatic and asymptomatic carotid stenosis, with unadjusted HRs of 10.2 and 7.9, respectively. Third, in patients with symptomatic carotid stenosis, IPH was associated with an increased risk of stroke at any degree of stenosis, even among patients with plaques causing <50% narrowing. Fourth, among previously symptomatic patients, only IPH and severe degree of stenosis (70% to 99%) independently predicted ipsilateral stroke in multivariate analysis, whereas other known risk factors did not.

Carotid disease is an important cause of stroke. Current guidelines, which are based on the results of large trials conducted in the 1980s and 1990s, recommend carotid endarterectomy in patients with recently symptomatic severe (70% to 99%) carotid stenosis and to consider carotid endarterectomy in patients with symptomatic moderate (50% to 69%) stenosis (28). Advances in medical therapy since then, most notably the widespread use of statins, more intensive antiplatelet regimens, lower targets for blood pressure control, and increased awareness

FIGURE 3 **Ipsilateral Stroke During Follow-Up in Patients With Symptomatic and Asymptomatic Carotid Stenosis With and Without IPH at Baseline**



Kaplan-Meier plots show the proportion of patients free of ipsilateral ischemic stroke. **(A)** All patients with symptomatic carotid stenosis. **(B)** Patients with ≥50% asymptomatic carotid stenosis. Numbers adjacent to plots indicate cumulative risks of ipsilateral stroke. Beyond 48 months, 4 more strokes occurred in patients with symptomatic carotid stenosis (3 of which occurred in IPH+ patients). Abbreviations as in Figure 2.

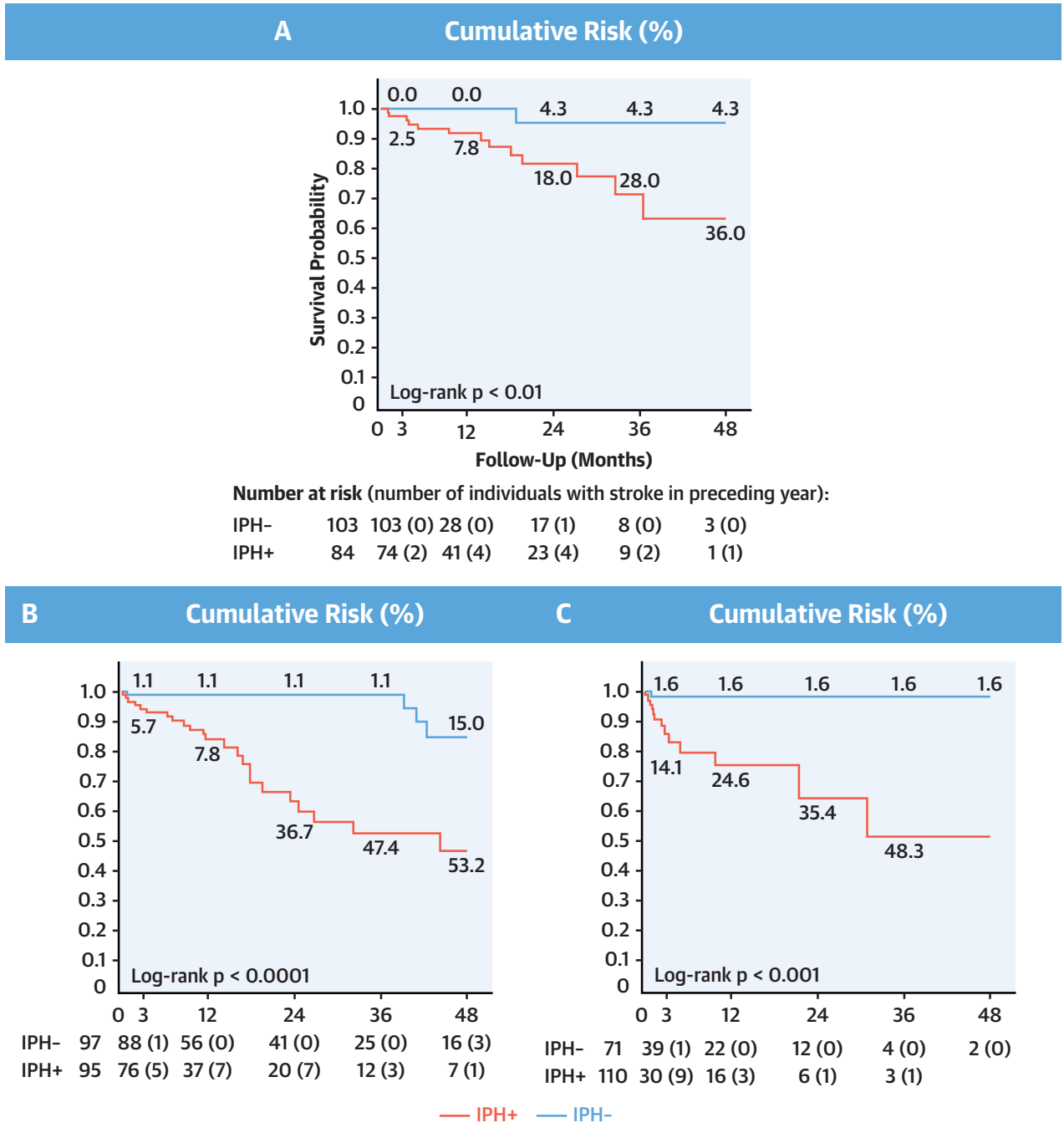
of vascular risk factors, have led to a decrease in stroke risk in patients with carotid disease. Accordingly, the risk of stroke after a TIA due to large artery atherosclerosis has dropped from as high as 20% after 3 months (29,30) to only 6% (31). Consequently, the numbers of patients needed to revascularize to prevent one stroke are likely higher today than they used to be. Thus, identifying patients at risk has become paramount to avoid unnecessary procedures.

Previous studies have reported a 4- to 12-fold increase in the risk of cerebrovascular events in the presence of IPH (14-16). However, these studies often reported on combined risks of stroke and TIA, precluding meaningful estimations of stroke risk. Second, single studies were too small to investigate if IPH adds prognostic value to established models based on readily available clinical and imaging characteristics (23) such as the degree of stenosis.

By pooling data at individual patient level from several prospective studies, we were able to overcome these limitations. Our study showed that if IPH was present at baseline, patients with mild (<50%), moderate (50% to 69%), or severe (70% to 99%) symptomatic carotid stenosis were at high risk of ipsilateral stroke during follow-up, with estimated annualized rates of 9.0%, 18.1%, and 29.3%, respectively. Conversely, the event rates were low if IPH was absent, irrespective of the degree of stenosis (0.7%, 2.1%, and 1.5%), and notably did not differ materially from the event rate observed among patients with asymptomatic carotid stenosis without IPH (0.8%). Hence, among patients with symptomatic carotid stenosis, IPH is a much stronger predictor of stroke risk than the degree of stenosis or symptom status and potentially a more useful marker to select patients who benefit from revascularization or, vice versa, to identify those who can safely be treated with medication alone.

Our finding of an increased future stroke risk among patients with hemorrhaged plaques causing <50% stenosis ipsilateral to the qualifying event is of particular interest. Plaque MRI would potentially allow attributing large artery atherosclerosis as the presumed cause of stroke, TIA, or AFx in patients with ipsilateral plaques causing <50% stenosis if IPH is present, provided that other etiologies have been ruled out. Current guidelines do not recommend endarterectomy or stenting in patients with carotid plaques causing <50% narrowing of the lumen, although our results suggest that some of

CENTRAL ILLUSTRATION **Ipsilateral Stroke During Follow-Up in Patients With Mild, Moderate, and Severe Symptomatic Carotid Stenosis With and Without IPH at Baseline**



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Kaplan-Meier plots show the proportion of patients free of ipsilateral ischemic stroke. **(A)** Less than 50% stenosis, **(B)** 50% to 69% stenosis, and **(C)** 70% to 99% stenosis. Numbers adjacent to plots indicate cumulative risks of ipsilateral stroke. Abbreviations as in Figure 2.

these patients might benefit from carotid revascularization, which remains to be proven in clinical trials.

Plaque-imaging studies or other ancillary investigations to estimate the risk of stroke in patients with carotid disease are only useful in clinical practice if they add prognostic value to validated (and readily available) clinical risk factors. A model to predict the risk of stroke in patients with symptomatic carotid stenosis under medical therapy derived in the ECST study population includes degree of stenosis in addition to various other clinical and demographic patient characteristics (24). When we included IPH and those variables of the aforementioned risk model that were available from the contributing studies in a multivariate model, we found that only IPH and severe degree of stenosis remained significantly associated with the occurrence of ipsilateral stroke, the association being much stronger for IPH than for severe stenosis (adjusted HRs of 11.0 and 3.3, respectively). These findings are in line with those of previous studies, in which IPH predicted recurrent cerebrovascular events, whereas the ECST risk model failed to do so (22,32). Thus, a model including both IPH and clinical variables would likely be superior in identifying patients at risk compared with a model based on clinical data alone. However, this hypothesis requires proof in a separate cohort.

Identifying those patients at risk of stroke who might benefit from revascularization is even more crucial among patients with asymptomatic carotid disease, who have a much lower risk of stroke. Trends of decreasing stroke risks over the years have been suggested in these patients by means of meta-regression (33), and it is no longer clear that the moderate benefit of revascularization in preventing stroke seen in earlier trials is still present in the context of modern medical therapy. At the same time, detection of individuals without IPH and thus lower risk for future events could prevent unnecessary revascularization and its inherent risks and costs. The potential benefits of improved patient identification for revascularization by using MRI are supported by case model-based cost-effectiveness analyses. These analyses show that an imaging-based strategy for selection of patients with asymptomatic carotid artery stenosis for surgery can be a cost-effective approach compared with intensified medical treatment alone, with the highest value in relatively younger patients (34). Our study found an increase in stroke risk among asymptomatic patients with IPH at baseline compared with those without (AER: 0.8% vs. 5.4%; unadjusted HR: 7.9). The small sample size limits comparability of our findings with the risk increase conveyed by the presence of micro-embolic signals in transcranial Doppler (HR: 6.4) (35) or juxta-luminal areas of low echogenicity in gray scale ultrasound (HR: 2.3) (36), as reported in much larger studies of asymptomatic patients. It remains to be shown in larger cohorts if a combination of these complementary imaging studies identifies patients at sufficiently high risk of stroke to justify carotid revascularization.

TABLE 3 Multivariate Model of Time to Ipsilateral Stroke According to Baseline Characteristics in All Patients With Symptomatic Carotid Stenosis

	Studies	n	Adjusted Hazard Ratio (95% CI)	p Value
Age, yrs				
<65*	5	105	1.00	
65–74	5	179	0.7 (0.3–1.7)	0.44
>74	5	274	0.8 (0.4–1.9)	0.68
Sex				
Male*	5	385		
Female	4	173	1.0 (0.5–2.1)	0.95
Diabetes mellitus				
No*	5	433		
Yes	5	125	1.8 (1.0–3.2)	0.06
Hypertension				
No*	5	189		
Yes	5	369	1.1 (0.5–2.2)	0.80
Degree of stenosis				
<50%*	4	186	1.00	
50%–69%	5	191	2.0 (1.0–4.3)	0.06
70%–99%	3	181	3.3 (1.4–7.8)	0.005
Type of qualifying event				
Stroke*	5	284	1.00	
TIA	5	200	1.1 (0.6–2.0)	0.75
Retinal ischemia (including retinal infarction and AFx)	5	74	0.4 (0.1–1.2)	0.11
IPH at inclusion				
No*	4	271		
Yes	5	287	11.0 (4.8–25.1)	<0.0001

Data derived from frailty model. Individual data of 2 patients were incomplete. *Reference category.
CI = confidence interval; other abbreviations as in Table 1.

In addition to comprehensive risk factor management, current guidelines recommend a sufficient antiplatelet and lipid-lowering therapy for symptomatic and asymptomatic individuals (28). Interestingly, in our population, statin treatment at baseline was more widespread in asymptomatic individuals. A possible explanation might be that asymptomatic individuals had a higher prevalence of pre-existing cardiovascular disease (e.g., congenital heart disease) and thus already were on intensive medication at baseline. This explanation remains speculative, however, because data for concomitant vascular disease were not available in all patients.

STUDY LIMITATIONS. Only 7 of the 13 identified eligible cohort studies provided individual patient

data for a pooled analysis. Most of the included studies were not initially designed to follow up their patients for 4 years, explaining the relatively rapid decrease in the number of patients at risk. Studies differed in inclusion criteria and mode of follow-up. Furthermore, in most of the studies including patients with symptomatic carotid stenosis, the interval between the qualifying event and carotid MRI was relatively long; hence, we cannot draw any conclusions about the very early risk of recurrent stroke after the initial event. Relatively few patients with asymptomatic carotid stenosis were included, and most of them had only a moderate degree of narrowing. Hence, we cannot draw firm conclusions on the usefulness of plaque MRI in patients with asymptomatic stenosis. Finally, only the originally collected individual patient data were available for evaluation. Thus promising, yet technically and timely more demanding, parameters such as plaque volume (37) or lipid content (12) could not be evaluated.

For detection of IPH, T1-weighted sequences remain the method of choice. In recent years, 3-dimensional isotropic MR imaging sequences, which have also been applied in the majority of included studies, have been proposed for plaque imaging. Compared with two-dimensional sequences, these sequences allow for a more detailed plaque characterization and accurate quantification of plaque components at a high spatial resolution and scan times <5 min (38). Magnetization-prepared rapid gradient-echo sequences have been found to be even superior to fast-spin echo T1-weighted images (39). Further optimizations have led to simultaneous noncontrast angiography and intraplaque hemorrhage imaging sequences (40); once made commercially available, these imaging sequences might be implemented as an angiographic technique in clinical routine carotid MRI examinations with simultaneous detection of IPH at no additional cost.

CONCLUSIONS

Detection of IPH by using MRI is common and associated with an increased risk of future stroke in patients with symptomatic carotid stenosis irrespective of the degree of luminal narrowing, as well as in patients with ≥50% asymptomatic carotid stenosis. Among recently symptomatic patients, the association of IPH with future stroke risk is much stronger than that of previously known clinical risk factors and independent of these factors. Thus far, data on the additional benefit of IPH-guided surgical, interventional, or therapeutic approaches are limited, and the risk and optimal timing of carotid revascularization in high-risk plaques are unknown. Our results support the need for clinical trials selecting patients for revascularization or investigating the benefit of revascularization versus medical therapy alone based on carotid plaque MRI or other extended imaging.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: IPH detected by using carotid MRI is a marker of plaque instability that is strongly associated with the future risk of stroke irrespective of symptom status or stenosis degree and is a stronger predictor of stroke risk than previously known clinical risk factors.

COMPETENCY IN MEDICAL KNOWLEDGE 2: IPH may already be present in symptomatic vessels with <50% stenosis and increase the risk for stroke. Evaluation of carotid disease should thus extend beyond establishing the degree of stenosis.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS 1: Additional MRI of the carotid arteries in stroke patients may reveal instable atherosclerotic plaque and enable for a more individualized primary and secondary prevention of stroke.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS 2: Diagnosis of carotid IPH can readily be diagnosed by using a standard MRI neck coil in a 5-min MRI protocol that can be implemented in clinical MRI stroke protocols.

TRANSLATIONAL OUTLOOK 1: Risk models including IPH along with clinical variables are likely to improve the identification of patients who benefit most from carotid revascularization.

TRANSLATIONAL OUTLOOK 2: Further studies are needed to determine the optimal selection of patients for revascularization and to investigate the benefit of revascularization versus medical therapy alone based on carotid plaque MRI or other extended imaging.

REFERENCES

1. de Weerd M, Greving JP, Hedblad B, et al. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke 2010;41:1294–7.

2. Petty GW, Brown RD Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. Stroke 1999;30:2513–6.

3. Barnett HJ, Taylor DW, Eliasziw M, et al., North American Symptomatic Carotid Endarterectomy Trialists' Collaborative Group. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. N Engl J Med 1998;339:1415–25.

4. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351:1379–87.

5. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363:1491–502.

6. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995;273:1421–8.

7. Brott TG, Calvet D, Howard G, et al. Long-term outcomes of stenting and endarterectomy for symptomatic carotid stenosis: a preplanned pooled analysis of individual patient data. Lancet Neurol 2019;18:348–56.

8. Rosenfield K, Matsumura JS, Chaturvedi S, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. N Engl J Med 2016;374:1011–20.

9. Brott TG, Howard G, Roubin GS, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. N Engl J Med 2016;374:1021–31.

10. Chu B, Kampschulte A, Ferguson MS, et al. Hemorrhage in the atherosclerotic carotid plaque: a high-resolution MRI study. Stroke 2004;35:1079–84.

11. Moody AR, Allder S, Lennox G, Gladman J, Fentem P. Direct magnetic resonance imaging of carotid artery thrombus in acute stroke. Lancet 1999;353:122–3.

12. Chai JT, Biasiolli L, Li L, et al. Quantification of lipid-rich core in carotid atherosclerosis using magnetic resonance T2 mapping: relation to clinical presentation. J Am Coll Cardiol Img 2017;10:747–56.

13. Chu B, Ferguson MS, Chen H, et al. Magnetic [corrected] resonance imaging [corrected] features of the disruption-prone and the disrupted carotid plaque. J Am Coll Cardiol Img 2009;2:883–96.

14. Gupta A, Baradaran H, Schweitzer AD, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. Stroke 2013;44:3071–7.

15. Saam T, Hetterich H, Hoffmann V, 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;62:1081–91.

16. 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;73:774–84.

17. Jiang B, He D, Zhang L, Ye M. Risk prediction of cerebrovascular events with carotid plaque magnetic resonance analysis: a meta-analysis. J Neuroradiol 2019;46:117–23.

18. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. Stroke 1991;22:711–20.

19. Esposito-Bauer L, Saam T, Ghodrati I, et al. MRI plaque imaging detects carotid plaques with a high risk for future cerebrovascular events in asymptomatic patients. PLoS One 2013;8:e67927.

20. Rothwell PM, Gibson RJ, Slattery J, Sellar RJ, Warlow CP. Equivalence of measurements of carotid stenosis. A comparison of three methods on 1001 angiograms. European Carotid Surgery Trialists' Collaborative Group. Stroke 1994;25:2435–9.

21. Singh N, Moody AR, Gladstone DJ, et al. Moderate carotid artery stenosis: MR imaging-depicted intraplaque hemorrhage predicts risk of cerebrovascular ischemic events in asymptomatic men. Radiology 2009;252:502–8.

22. Hosseini AA, Simpson RJ, Altaf N, Bath PM, MacSweeney ST, Auer DP. Magnetic resonance imaging plaque hemorrhage for risk stratification in carotid artery disease with moderate risk under current medical therapy. Stroke 2017;48:678–85.

23. Rothwell PM, Mehta Z, Howard SC, Gutnikov SA, Warlow CP. From subgroups to individuals: general principles and the example of carotid endarterectomy. Lancet 2005;365:256–65.

24. Rothwell PM, Warlow CP. Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. European Carotid Surgery Trialists' Collaborative Group. Lancet 1999;353:2105–10.

25. 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;68:62–7.

26. Kwee RM, van Oostenbrugge RJ, Mess WH, et al. MRI of carotid atherosclerosis to identify TIA and stroke patients who are at risk of a recurrence. J Magn Reson Imaging 2013;37:1189–94.

27. Yoshida K, Sadamasa N, Narumi O, Chin M, Yamagata S, Miyamoto S. Symptomatic low-grade carotid stenosis with intraplaque hemorrhage and expansive arterial remodeling is associated with a high relapse rate refractory to medical treatment. Neurosurgery 2012;70:1143–50.

28. Naylor AR, Ricco JB, de Borst GJ, et al. Editor's choice—management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55:3–81.

29. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 2004;62:569–73.

30. Purroy F, Montaner J, Molina CA, Delgado P, Ribo M, Alvarez-Sabin J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. Stroke 2007;38:3225–9.

31. Amarenco P, Lavallee PC, Labreuche J, et al. One-year risk of stroke after transient ischemic attack or minor stroke. N Engl J Med 2016;374:1533–42.

32. 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.

33. Raman G, Moorthy D, Hadar N, et al. Management strategies for asymptomatic carotid stenosis: a systematic review and meta-analysis. Ann Intern Med 2013;158:676–85.

34. Gupta A, Mushlin AI, Kamel H, Navi BB, Pandya A. Cost-effectiveness of carotid plaque MR imaging as a stroke risk stratification tool in asymptomatic carotid artery stenosis. Radiology 2015;277:927.

35. Markus HS, King A, Shipley M, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol 2010;9:663–71.

36. Kakkos SK, Griffin MB, Nicolaides AN, et al. The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke. J Vasc Surg 2013;57:609–18.

37. Lu M, Peng P, Cui Y, et al. Association of progression of carotid artery wall volume and recurrent transient ischemic attack or stroke: a magnetic resonance imaging study. Stroke 2018;49:614–20.

38. Narumi S, Sasaki M, Natori T, et al. Carotid plaque characterization using 3D T1-weighted MR imaging with histopathologic validation: a comparison with 2D technique. AJNR Am J Neuroradiol 2015;36:751–6.

39. Ota H, Yarnykh VL, Ferguson MS, et al. Carotid intraplaque hemorrhage imaging at 3.0-T MR imaging: comparison of the diagnostic performance

of three T1-weighted sequences. Radiology 2010; 254:551–63.

40. Wang J, Bornert P, Zhao H, et al. Simultaneous noncontrast angiography and intraplaque hemorrhage (SNAP) imaging for carotid atherosclerotic disease evaluation. Magn Reson Med 2013;69:337–45.

41. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

KEY WORDS carotid, cerebrovascular event, intraplaque hemorrhage, ischemic stroke, magnetic resonance imaging, NASCET

APPENDIX For supplemental information including tables and figures, please see the online version of this paper.