Carotid Plaque Characteristics Predict Recurrent Ischemic Stroke and TIA

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ORIGINAL RESEARCH

Carotid Plaque Characteristics Predict Recurrent Ischemic Stroke and TIA

The PARISK (Plaque At RISK) Study

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ABSTRACT

BACKGROUND Patients with symptomatic carotid stenosis are at high risk for recurrent stroke. The decision for carotid endarterectomy currently mainly relies on degree of stenosis (cutoff value >50% or 70%). Nevertheless, also, patients with mild-to-moderate stenosis still have a considerable recurrent stroke risk. Increasing evidence suggests that carotid plaque composition rather than degree of stenosis determines plaque vulnerability; however, it remains unclear whether this also provides additional information to improve clinical decision making.

OBJECTIVES The PARISK (Plaque At RISK) study aimed to improve the identification of patients at increased risk of recurrent ischemic stroke using multimodality carotid imaging.

METHODS The authors included 244 patients (71% men; mean age, 68 years) with a recent symptomatic mild-to-moderate carotid stenosis in a prospective multicenter cohort study. Magnetic resonance imaging (carotid and brain) and computed tomography angiography (carotid) were performed at baseline and after 2 years. The clinical endpoint was a recurrent ipsilateral ischemic stroke or transient ischemic attack (TIA). Cox proportional hazards models were used to assess whether intraplaque hemorrhage (IPH), ulceration, proportion of calcifications, and total plaque volume in ipsilateral carotid plaques were associated with the endpoint. Next, the authors investigated the predictive performance of these imaging biomarkers by adding these markers (separately and simultaneously) to the ECST (European Carotid Surgery Trial) risk score.

RESULTS During 5.1 years follow-up, 37 patients reached the clinical endpoint. IPH presence and total plaque volume were associated with recurrent ipsilateral ischemic stroke or TIA (HR: 2.12 [95% CI: 1.02-4.44] for IPH; HR: 1.07 [95% CI: 1.00-1.15] for total plaque volume per 100 μL increase). Ulcerations and proportion of calcifications were not statistically significant determinants. Addition of IPH and total plaque volume to the ECST risk score improved the model performance (C-statistics increased from 0.67 to 0.75-0.78).

CONCLUSIONS IPH and total plaque volume are independent risk factors for recurrent ipsilateral ischemic stroke or TIA in patients with mild-to-moderate carotid stenosis. These plaque characteristics improve current decision making. Validation studies to implement plaque characteristics in clinical scoring tools are needed. (PARISK: Validation of Imaging Techniques [PARISK]; NCT01208025) (J Am Coll Cardiol Img 2022;15:1715-1726) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CEA = carotid endarterectomy

CTA = computed tomography angiography

IPH = intraplaque hemorrhage

MES = microembolic signals

MRI = magnetic resonance imaging

NRI = net reclassification improvement

TCD = transcranial Doppler

TIA = transient ischemic attack

Ischemic stroke is a leading cause of disability and death worldwide.[1,2] Carotid atherosclerosis is one of the major contributing causes of ischemic stroke. Rupture of an atherosclerotic plaque can lead to thrombus formation and embolization of the thrombus into distally located intracranial arteries.

Randomized trials have shown that carotid endarterectomy (CEA) reduces the risk of stroke in selected patients with carotid stenosis.[3-5] The decision to perform CEA is currently based on the degree of stenosis.[6] CEA is highly beneficial for symptomatic patients with a carotid atherosclerotic plaque with 70% to 99% stenosis, whereas the beneficial effect of surgery for symptomatic patients with <70% stenosis (ie, mild-to-moderate) seems limited.[7] Yet, these patients are at a substantial risk of recurrent ipsilateral stroke as evidenced by recent studies reporting incidence rates of 2.6 to 3.0 recurrent strokes per 100 person-years.[8,9] Therefore, it is of great importance to be able to define subgroups of patients with a carotid plaque causing <70% stenosis who are at high risk of recurrent stroke.

Against this background, novel insights are challenging the strategy to solely use degree of stenosis for selecting patients for CEA. Improvements in imaging techniques enable us to visualize not only the degree of stenosis, but also specific so-called vulnerable plaque characteristics, including intraplaque hemorrhage (IPH), plaque ulcerations, relative calcification volume, and total plaque burden, which have shown to provide unique additional information on the risk of stroke recurrence.[10-17] Yet, to implement novel markers into clinical practice, it is necessary to show whether these markers improve the prediction of current clinical decision models for recurrent stroke. Currently, this evidence is still lacking. Specifically for stroke, the need for prediction studies evaluating vulnerable carotid plaque characteristics was highlighted recently to improve personalized treatment.[12,18,19]

Hence, the primary aim of the PARISK (Plaque At RISK) study is to investigate whether imaging markers of plaque vulnerability, either alone or in combination, improve the identification of patients with mild-to-moderate carotid stenosis who are at increased risk of recurrent ischemic stroke.

METHODS

STUDY POPULATION. The PARISK study (NCT01208025) is a prospective observational multicenter cohort study including patients with a recent (<3 months) cerebral or monocular transient ischemic attack (TIA) or minor stroke in the carotid artery territory and a carotid plaque in the ipsilateral internal carotid artery causing mild-to-moderate stenosis. Institutional review board approval was obtained (Medisch Ethische Commissie azM/UM, approval number NL29116.068.09/MEC 09-2-082) and all patients gave written informed consent. Further details on patient selection are provided in the Supplemental Methods.

ASSESSMENT OF PLAQUE CHARACTERISTICS. We included 4 plaque characteristics of the carotid artery ipsilateral to the recent event in the main analyses: 1) presence of IPH as assessed on magnetic resonance imaging (MRI); 2) plaque ulceration as assessed on computed tomography angiography (CTA); 3) the proportion of calcifications with respect to the total carotid plaque volume as assessed on CTA; and 4) plaque volume as assessed on MRI (**Figure 1**). In accordance with the analyses plan, we restricted the analyses to these 4 characteristics to prevent data-driven testing. We performed contrast-enhanced CTA using a standardized protocol. MRI image acquisition of the carotid arteries was performed on a 3-T MRI system, using a multisequence contrast-enhanced protocol. We additionally

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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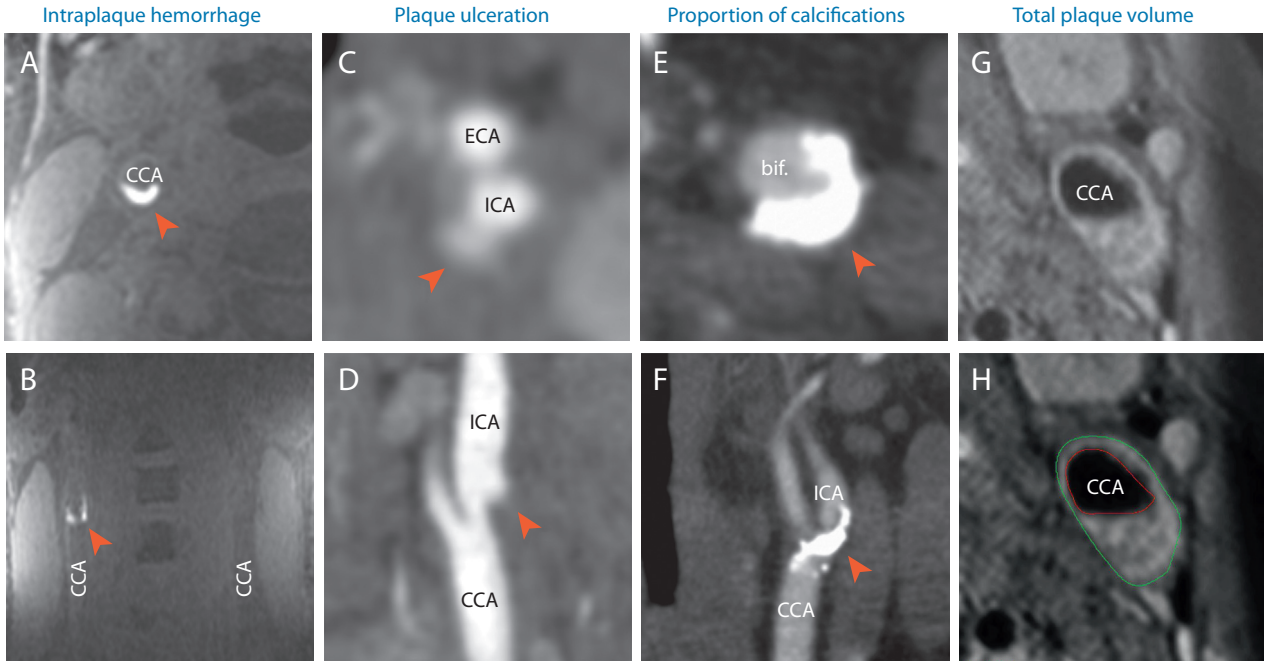
FIGURE 1 Imaging of Plaque Characteristics of Interest



Images of the predefined plaque characteristics of interest in the PARISK (Plaque At RISK). **(A and B)** 3-dimensional (3D) T_1-weighted fast spoiled gradient echo magnetic resonance images (MRIs) showing a hyperintense signal in the bulk of the plaque **(orange arrowheads)** indicative of intraplaque hemorrhage in axial view **(A)** and coronal view **(B)**. **(C and D)** Computed tomography angiography (CTA) images showing contrast material reaching into a carotid plaque **(orange arrowheads)**, which indicates plaque ulceration. **(E and F)** CTA images showing a relatively large bulk of calcification **(orange arrowheads)** at the level of the bifurcation. **(G and H)** 3D T_1-weighted precontrast quadruple inversion recovery turbo spin echo MRIs showing an axial view of a carotid plaque, which is delineated on each slice **(H)** to measure the total plaque volume. bif. = bifurcation; CCA = common carotid artery; ECA = external carotid artery; ICA = internal carotid artery.

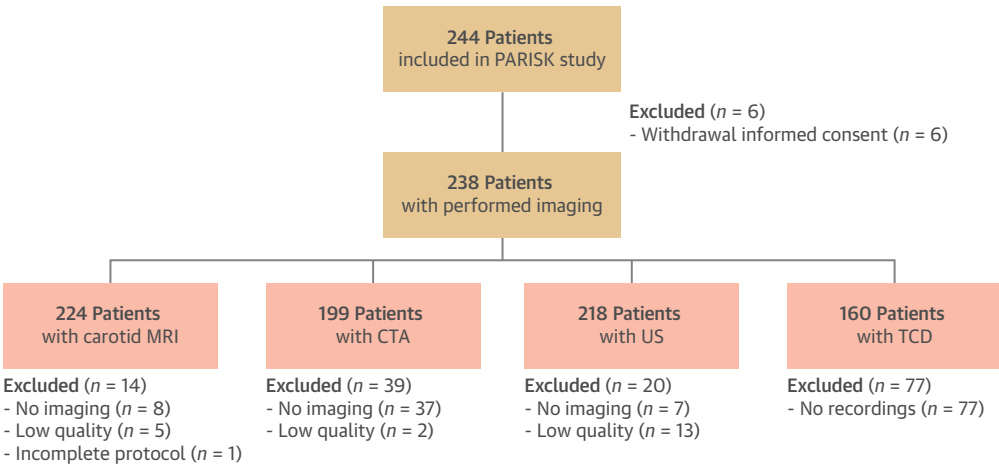
performed ultrasound imaging of the plaques and microembolus detection by means of transcranial Doppler (TCD) monitoring. For details on the imaging protocols, see the Supplemental Methods and study design paper.[20]

Symptomatic carotid arteries were evaluated by trained readers blinded for clinical data and other imaging tests. Both presence of IPH and plaque volume were scored using dedicated vessel wall analysis software (VesselMASS, Leiden University Medical Center). IPH was defined as a hyperintense signal in the bulk of the plaque compared with the adjacent sternocleidomastoid muscle using inversion recovery transient field echo or spoiled gradient echo MRIs.[10,21] We defined plaque ulceration as an extension of contrast material of >1 mm into the atherosclerotic plaque on at least 2 orthogonal slices.[11,22] The proportion of calcifications related to the total plaque volume on CTA was assessed using a semiautomated software package for atherosclerotic plaque imaging analysis (vascuCAP Research Edition, Elucid Bioimaging).[23]

ASSESSMENT OF ENDPOINTS. For the detection of new ischemic events, patients were interviewed by a medical doctor after 3 months and thereafter yearly until 5-year follow-up using structured case record forms. In case the patient could not be reached, the general practitioner was contacted for information. All diagnoses of a recurrent ischemic event were verified by medical records of the hospital and/or the general practitioner, and evaluated by 2 experienced vascular neurologists (P.J.K. and P.N.) who were blinded for imaging data.

At baseline and after 2-year follow-up, patients underwent brain MRI to detect ischemic brain lesions, using a 3-T scanner and dedicated head coils.[20] These MRIs were evaluated by an experienced neuroradiologist (J.H.) who was blinded for clinical data and outcomes. New cortical and subcortical infarcts compared to baseline MRI were assessed.

FIGURE 2 Flowchart of the PARISK Study



TCD = transcranial Doppler; US = ultrasound; other abbreviations as in Figure 1.

The primary endpoint of the PARISK study was the composite of a clinical ipsilateral recurrent cerebral or monocular ischemic stroke or TIA during 5 years follow-up, and/or new ipsilateral (silent) infarcts on follow-up brain MRI at 2-year follow-up. For the sake of the statistical analyses, we distinguish the primary endpoint in a clinical endpoint (a clinical ipsilateral recurrent cerebral or monocular ischemic stroke or TIA during 5-years follow-up) and an imaging-based endpoint (new ipsilateral [silent] infarcts on follow-up brain MRI at 2-years follow-up).

POPULATION FOR ANALYSIS. Between September 2010 and December 2014, 244 patients were included in the PARISK study; in 238 patients, carotid imaging was performed (Figure 2).

STATISTICAL ANALYSIS. The cumulative incidence of study endpoints over time was analyzed using the Kaplan-Meier method, and log-rank tests were performed to study differences in relation to plaque characteristics. Cox proportional hazards models were then used to determine the association of the plaque characteristics with the clinical endpoint. Logistic regression models were used to assess the association of plaque characteristics with the 2-year imaging-based endpoint. We performed unadjusted analyses (models 1), and analyses that adjusted for age and sex (models 2) and additionally for cardiovascular risk factors (models 3). Results are presented as HRs with corresponding 95% CIs for the Cox proportional hazards models, and as odds ratios (ORs) with corresponding 95% CIs for the logistic regression models. For the analysis of the proportion of calcifications, the values were natural logarithmic transformed to deal with the skewed distribution.

Next, we investigated the predictive value of plaque characteristics. To this end, we took the ECST (European Carotid Surgery Trial) risk score (also called "carotid stenosis tool"), which is designed for predicting recurrent stroke risk and frequently used in clinical practice, as base model.[24] Subsequently, we added (separately and simultaneously) the plaque characteristics that were statistically significantly associated with the study endpoints. We assessed the discriminative ability of the extended ECST models compared to the base ECST model through calculating and comparing the C-statistics. We also assessed the calibration of the base and extended models by calculating calibration plots. Finally, we calculated the net reclassification improvement (NRI) using 500 bootstrap samples. More details on the statistical methods can be found in the Supplemental Methods.

Missing covariables were imputed using 5-fold multiple imputations (R package "aregImpute"). Outcome variables were not imputed. All results of the Cox and logistic regression models are the results of the pooled analysis of the 5 imputed data sets. All statistical analyses were performed using R statistical software (version 3.6.1, R Foundation for Statistical

Computing). A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

BASELINE CHARACTERISTICS. Mean age of the study participants was 68 ± 9 years and 169 (71%) participants were men. Baseline clinical and imaging characteristics are presented in **Table 1** and Supplemental Table 1. In 87 (39%) patients, IPH was present in the ipsilateral carotid artery. Ulcerations were present in 53 (27%) patients. The mean total carotid plaque volume and median proportion of calcifications were 1,281.5 ± 418.7 μL and 7.3% (IQR: 3.7%-12.5%), respectively.

FOLLOW-UP AND ENDPOINTS. Median follow-up time was 5.1 (IQR: 3.1-5.8) years. A total of 182 participants underwent brain MRI after a 2-year follow-up. Reasons of no follow-up MRI are reported in the Supplemental Results. During follow-up, 37 of 238 individuals reached the clinical endpoint including cerebral ischemic stroke (n = 14), cerebral TIA (n = 17), and monocular ischemia (n = 6). Nineteen of 238 individuals had new ipsilateral infarcts on brain MRI at 2-year follow-up. Three patients had a recurrent ipsilateral event during the interval between index event and plaque imaging. Two patients also experienced a second recurrent event after the plaque imaging.

RISK OF RECURRENT STROKE AND TIA. Kaplan-Meier curves and tables (**Figure 3**) show that the cumulative incidence of the clinical endpoint was higher among patients with IPH in the ipsilateral carotid plaque compared to those without IPH (23% vs 11% at 5-year follow-up; $P = 0.004$). Patients with ulceration in the symptomatic carotid plaque were not statistically significant at higher risk than those without plaque ulceration (17% vs 12% at 5-year follow-up; $P = 0.23$).

Table 2 presents the Cox and logistic regression models. We found that IPH presence and larger total plaque volume increased the risk of the clinical endpoint (HR: 2.59 [95% CI: 1.31-5.09] for IPH; and HR: 1.10 [95% CI: 1.04-1.17] for total plaque volume per 100 μL increase) (**Central Illustration**). After adjustments for cardiovascular risk factors, both plaque characteristics remained significant determinants (HR: 2.12 [95% CI: 1.02-4.44] for IPH; and HR: 1.07 [95% CI: 1.00-1.15] for total plaque volume per 100 μL increase). Neither presence of ulceration nor the proportion of calcifications was statistically significant associated with the clinical endpoint.

Presence of IPH and larger total plaque volume also significantly increased the occurrence of the imaging-based endpoint, having new ipsilateral ischemic MRI brain lesions at 2-year follow-up (OR: 2.97 [95% CI: 1.14-8.29] for IPH; and OR: 1.11 [95% CI: 1.00-1.22] for total plaque volume per 100 μL increase). After adjustments for cardiovascular risk factors, both plaque characteristics were no longer statistically significant associated. Neither presence of ulceration nor the proportion of calcifications was statistically significant associated with the imaging-based endpoint.

The HRs and ORs regarding the other assessed imaging and blood markers are reported in Supplemental Table 2. Maximum plaque area (assessed by MRI) and total plaque area (assessed by ultrasound) also were statistically significant determinants for recurrent events (HR: 1.12 [95% CI: 1.01-1.23] for maximum

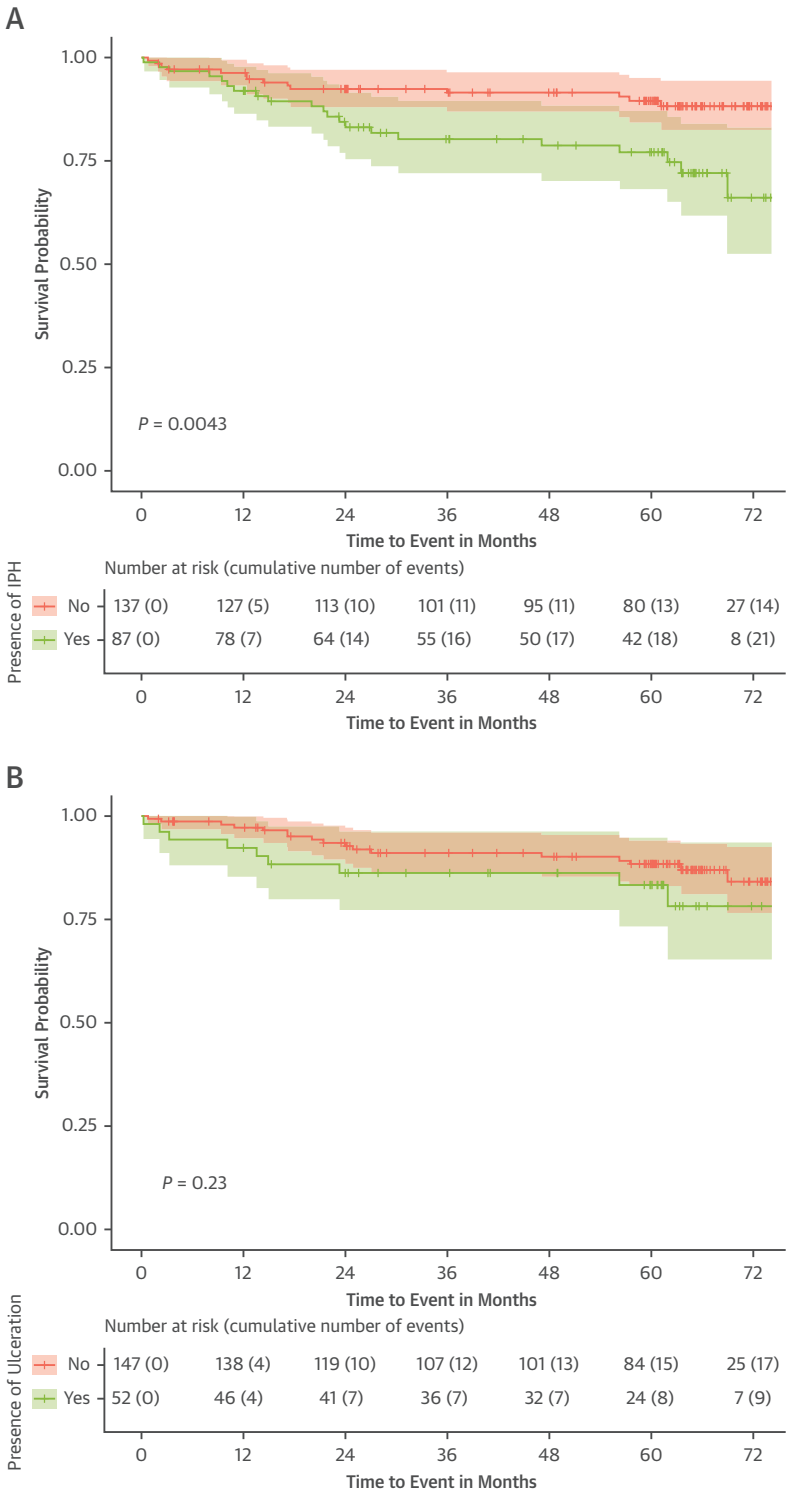
TABLE 1 Clinical Characteristics and Imaging Characteristics at Baseline[a] (N = 238)

Clinical characteristics at index event	
Age, y	69 ± 9
Men	169 (71)
Caucasian	218 (92)
Current smoking	53 (22)
BMI, kg/m^2	26.9 ± 4.5
Hypertension	176 (83)
Hypercholesterolemia	193 (85)
Diabetes mellitus	57 (26)
History of ischemic cardiovascular disease	116 (49)
Use of statins	120 (51)
Use of antihypertensive drugs	145 (61)
Use of antithrombotics	108 (46)
Classification event	
Cerebral stroke	104 (44)
Cerebral TIA	106 (45)
Monocular stroke or TIA	28 (12)
Imaging characteristics of symptomatic carotid artery	
CTA (n = 199)	
Time between index event and CTA, d	37 (16-100)
ECST degree of stenosis, %	55.0 ± 14.6
NASCET degree of stenosis, %	12.7 (0.0-31.4)
0 to 29% NASCET degree of stenosis	145 (73)
30% to 49% NASCET degree of stenosis	45 (23)
50% to 69% NASCET degree of stenosis	9 (4)
Calcification proportion, %	7.3 (3.7-12.5)
Plaque ulceration presence	53 (27)
MRI (n = 224)	
Time between index event and MRI, d	50 (33-125)
IPH presence	87 (39)
Total plaque volume, μL	1281.5 ± 418.7

Values are mean ± SD, n (%), or median (IQR). Data represent original data without imputed values. [a]Missing values were present for ethnicity (3.4%), BMI (3.4%), hypertension (10.9%), hypercholesterolemia (4.6%), diabetes mellitus (8.4%), use of statins (0.4%), use of antithrombotics (0.4%), and calcification proportion (0.5%).

BMI = body mass index; CTA = computed tomography angiography; ECST = European Carotid Surgery Trial; IPH = intraplaque hemorrhage; MRI = magnetic resonance imaging; NASCET = North American Symptomatic Carotid Endarterectomy Trial; TIA = transient ischemic attack.

FIGURE 3 Kaplan-Meier Curves of Event-Free Survival for Presence of IPH and Ulcerations



The Kaplan-Meier curves show the survival probability for the clinical endpoint, defined as a clinical ipsilateral recurrent ischemic stroke or transient ischemic attack (TIA), regarding intraplaque hemorrhage (IPH) **(A)** and ulcerations **(B).** The tables show the according number at risk and cumulative number of events per year.

plaque area per 10 mm^2 increase related to the clinical endpoint; and OR: 1.15 [95% CI: 1.03-1.28] for total plaque area per 10 mm^2 increase related to the imaging-based endpoint). These associations did not change after adjustment for cardiovascular risk factors.

PREDICTIVE VALUE OF PLAQUE CHARACTERISTICS. Because we found no evidence for miscalibration of the base ECST model in our data, recalibration of the coefficients was not needed (Supplemental Figure 1). Addition of IPH presence to the ECST risk score for predicting the clinical endpoint improved the C-statistic from 0.67 to 0.75 (*P* likelihood ratio test = 0.001). For adding total plaque volume, the C-statistic improved also to 0.75 (*P* likelihood ratio test = 0.002) (**Table 3**). The combination of these plaque characteristics improved the C-statistic to 0.78 (*P* likelihood ratio test <0.001).

We also found no evidence for miscalibration for the extended models with IPH presence and/or total plaque volume at 5-, 2- and 1-year follow-up for the clinical endpoint (Supplemental Figure 1).

Finally, the continuous NRI regarding the clinical endpoint for the extended models with IPH, total plaque volume, or the combination of IPH and total plaque volume was 0.81 (95% CI: 0.25-1.28), 0.50 (95% CI: −0.01 to 1.10), and 0.85 (95% CI: 0.16-1.33), respectively (Supplemental Table 3). The net percentages of persons with a recurrent event correctly reclassified to a higher predicted risk regarding the primary endpoint were 49.5%, 5.4%, and 50.1%, respectively.

Because plaque ulceration and proportion of calcifications were not statistically significant determinants of the endpoints, and because we found no statistically significant associations between plaque characteristics and the imaging-based endpoint, these variables and this endpoint were not included in the analyses regarding prediction model performance.

TABLE 2 Adjusted Cox Proportional Hazards Models of Variables of Interest

	IPH	Ulceration	Calcification[a]	Total Plaque Volume[b]
Clinical endpoint[c]				
Model 1[d]	2.59 (1.31-5.09)	1.63 (0.73-3.66)	1.13 (0.69-1.84)	1.10 (1.04-1.17)
Model 2[e]	2.12 (1.03-4.35)	1.49 (0.66-3.38)	1.29 (0.75-2.21)	1.08 (1.00-1.16)
Model 3[f]	2.12 (1.02-4.44)	1.38 (0.60-3.20)	1.26 (0.72-2.18)	1.07 (1.00-1.15)
Imaging-based endpoint[g]				
Model 1	2.97 (1.14-8.29)	2.79 (0.99-7.73)	0.93 (0.51-1.78)	1.11 (1.00-1.22)
Model 2	2.51 (0.91-7.49)	2.61 (0.92-7.36)	0.88 (0.46-1.77)	1.08 (0.96-1.21)
Model 3	2.40 (0.87-7.19)	2.56 (0.84-7.31)	0.92 (0.47-1.91)	1.09 (0.97-1.22)

[a]The percentage of calcifications is natural log transformed. [b]The HRs of total plaque volume are expressed for an increase of 100 μL. [c]Clinical endpoint, HR (95% CI), is defined as a recurrent clinical ipsilateral ischemic stroke or TIA. [d]Model 1 is unadjusted. [e]Model 2 is adjusted for age and sex. [f]Model 3 is adjusted for age, sex, hypertension, hypercholesterolemia, current smoking, and diabetes mellitus. [g]Imaging-based endpoint, OR (95%), is defined as new ipsilateral ischemic MRI brain lesions at 2-year follow-up.

OR = odds ratio; other abbreviations as in Table 1.

DISCUSSION

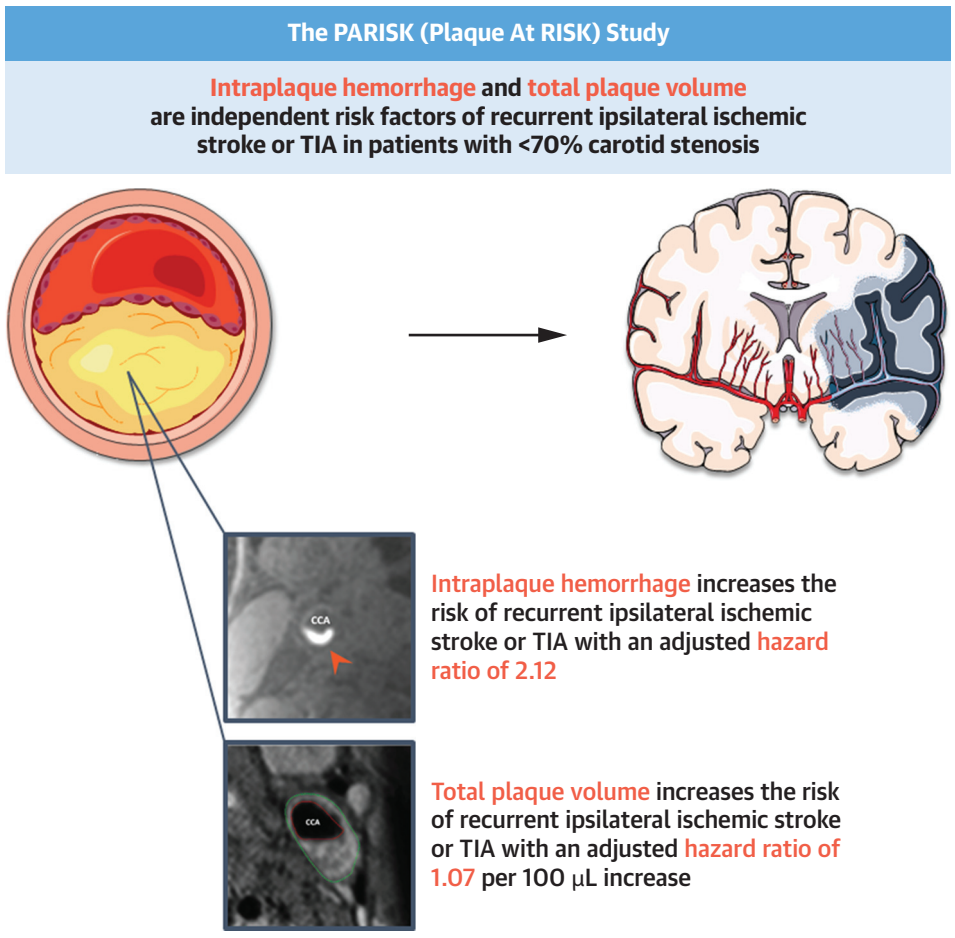
The PARISK study shows that, in patients with a symptomatic carotid plaque causing mild-to-moderate stenosis, both IPH presence and total plaque volume are independent determinants for the risk of a recurrent ipsilateral ischemic stroke or TIA. Moreover, the PARISK study shows that these imaging-derived markers improve risk prediction of stroke recurrence.

Presence of IPH doubled the risk of the clinical endpoint. A recent meta-analysis has also shown that IPH increased the risk of ipsilateral ischemic events (stroke, TIA, and amaurosis fugax) in symptomatic patients with carotid stenosis <70% (unadjusted HR: 3.5-5.9).[14] Most of the patients in our cohort have a NASCET (North American Symptomatic Carotid Endarterectomy Trial) degree of stenosis of 0% to 30%, suggesting that we included patients with less severe stenosis resulting in a lower HR for IPH.

Total plaque volume increased the risk of a recurrent ipsilateral ischemic neurological event with a HR of 1.1 per 100 μL increase. Most studies investigating the role of plaque volume are retrospective, but Lu et al[25] reported in a prospective study that annual progression of carotid plaque volume was significantly associated with recurrent events (adjusted HR of 1.2 per 10 μL increase), which is in alignment with our results. Plaque volume represents better than degree of stenosis plaques that grow outward into the vessel wall without causing luminal narrowing. Plaque volume, however, is less easy to assess than IPH on MRI because plaque volume is a 3-dimensional (3D) measure. The more convenient quantifiable characteristics maximum plaque thickness (1D) and maximum plaque area (2D) are comparable measures of total plaque volume. In this study, we showed that also maximum plaque area as measured by MRI, but not maximum plaque thickness, was a statistically significant determinant for the clinical endpoint.

Furthermore, our study shows that IPH and total plaque volume have added predictive value compared to currently used clinical prediction models. By adding (the combination of) these parameters to the ECST risk score, the model performance strongly improved. This finding indicates that IPH and total plaque volume are important predictors that can be used for clinical risk assessment. The high continuous NRIs of the extended models are in line with these findings

CENTRAL ILLUSTRATION **Carotid Intraplaque Hemorrhage and Total Plaque Volume Increase the Risk of Recurrent Ipsilateral Ischemic Stroke and Transient Ischemic Attack**



van Dam-Nolen DHK., et al. J Am Coll Cardiol Img. 2022;15(10):1715–1726.

Artery and brain illustrations are retrieved and edited from smart.servier.com. CCA = common carotid artery; TIA = transient ischemic attack.

and stress particularly the added value of IPH. The large positive values of the event NRI indicate that IPH improves the detection of persons with a high risk of recurrent stroke or TIA.[26] Continuous NRI does not require risk categorization and is therefore useful for evaluating recurrent stroke risk because there are no established risk categories for stroke recurrence. However, continuous NRI could be affected by miscalibration.[26] Nonetheless, the extended models for 5-year follow-up are well calibrated in our study. Therefore, in our study, continuous NRI is the best method to determine changes in risk classification by models including plaque characteristics.

The main improvement of the ECST risk score is caused by the addition of IPH. Besides this, the presence of IPH is easy to detect on MRI and can be visualized with common MRI sequences within a few minutes. Therefore, compared to total plaque volume, using IPH in clinical risk assessment will probably give the greatest benefit.

Future research should focus on developing new prediction tools including IPH and total plaque volume as imaging risk markers. The ECST risk score was developed more than 20 years ago and recalibrated in 2005.[24,27] The calibration curves in our data show that only patients with a risk ranging from approximately 0.05 to 0.55 are well predicted with the ECST risk score. This stresses the need for developing an actual scoring system including both clinical and imaging-based plaque characteristics, enabling precision medicine for secondary stroke prevention.

In the current study, we did not find statistically significant associations between plaque ulceration and calcification proportion and the endpoints. Regarding plaque ulceration, we did see a trend that patients having plaque ulceration had a higher recurrent stroke and TIA risk. Because only 27% patients had plaque ulceration, probably our study had not sufficient power to prove a significant association between plaque ulceration and the endpoints. Another limitation could be that we used only CTA to detect plaque ulceration. Previous studies have shown that 3D ultrasound can also effectively detect ulcerations and that number and volume of ulcerations are predictive for stroke in patients with moderate-to-severe atherosclerosis.[28,29] With this in mind, we recommend to also include plaque ulceration as a potential predictor in future research on developing and optimizing prediction tools. With regard to calcification proportion, we found a median of 7%, which is a low percentage. This is probably inherent to a patient population with less severe stenosis. We hypothesize that for a protective effect of calcifications, the calcification proportion must exceed a certain threshold. Previous studies that reported significant associations between calcification proportion and ischemic stroke included patients with higher values of calcification proportion.[17] A study from Shaalan et al[30] suggested a cutoff value for plaque area calcification of 30% as optimal threshold to differentiate symptomatic from asymptomatic plaques.

We also found no associations between ultrasound measurements and TCD monitoring and the endpoints, except for total plaque area. Previous studies reported that echolucent plaques (plaques with low grey-scale median values) and microembolic signals (MES) increase the risk of recurrent stroke.[31,32] These studies included patients with severe carotid stenosis (50% to 99%), which is in contrast to our study population. In addition, MES also increase the risk of first-ever stroke in asymptomatic patients.[33,34] We suppose that, mainly in patients with severe stenosis, echolucent plaques and MES are predictive for recurrent stroke. The low proportion of patients having MES in our cohort (8%) underlines this assumption. On the other hand, it may also be that the relatively small sample size limited our findings, especially for MES because TCD monitoring was performed in a subset of patients only. Therefore, we recommend to investigate the role of echolucent plaques and MES in cohorts including patients with various levels of carotid stenosis.

Our study also shows that although all patients had <70% carotid stenosis and therefore had no clear indication for CEA, the predicted 5-year risk of recurrent ischemic stroke or TIA based on the extended ECST risk model was 40% to 50% for some patients. This is a considerably high risk, which calls for reconsideration of current treatment of these patients. IPH and total plaque volume could help deciding which patients need more advanced secondary prevention or CEA.

This finding also stresses that patients with a low NASCET stenosis have a considerable recurrent stroke risk. Most patients included in this study had a NASCET stenosis 0% to 30%. This patient category has an atherosclerotic plaque which is not well reflected in luminal narrowing, but which can consist of vulnerable plaque components and can cause outward instead of inward remodeling. We show in this study that, although patients have no or less luminal stenosis, they have an increased recurrent stroke risk. Therefore, including plaque characteristics besides the stenosis degree in prediction tools is necessary to identify these high-risk patients.

This study has several strengths. First of all, this is the first prospective multicenter study with multimodality imaging of the carotid artery. This enabled us to compare multiple plaque characteristics and to investigate which plaque characteristics have an added value for clinical use. Secondly, whereas previous studies most often were not designed to follow patients for a long time period, patients included in the PARISK study were clinically followed for 5 years, providing us the ability to investigate long-term recurrent stroke risk.[14] A third strength of the PARISK study is that the analyses are adjusted for covariables, and that we investigated the predictive performance of the plaque characteristics. Most previous studies were not able to adjust their analyses and to determine the added predictive value of their findings compared to existing clinical tools. However, this information is

TABLE 3 Performance of ECST Risk Score and Extended Models With Plaque Characteristics

Model	C-Statistic (95% CI)[a]	*P* Value for LRT
1: ECST risk score[b]	0.67 (0.54-0.80)	Ref.
2: ECST risk score + IPH presence	0.75 (0.65-0.87)	0.001
3: ECST risk score + total plaque volume	0.75 (0.64-0.87)	0.002
4: ECST risk score + IPH presence + total plaque volume	0.78 (0.66-0.90)	<0.001

[a]According to the clinical endpoint, which is a recurrent clinical ipsilateral ischemic stroke or TIA. [b]The ECST risk score refers to the scoring system developed by Rothwell et al.[24] It includes the following variables: NASCET stenosis, near occlusion, sex, age, time since last event, presenting event, diabetes, previous myocardial infarction, peripheral vascular disease, treated hypertension, and irregular/ulcerated plaque.

LRT = likelihood ratio test; Ref. = reference; other abbreviations as in Table 1.

highly important for implementing plaque characteristics in daily clinical practice.

STUDY LIMITATIONS. The lower-than-expected rate of recurrent ischemic events might be the result of improved secondary prevention. However, despite the rather low incidence rates, the statistical power was adequate for the analyses including IPH and total plaque volume. Additionally, due to a relatively small sample size and low prevalence of some plaque characteristics, we may not have been able to show a statistically significant association between specific plaque features (eg, plaque ulceration, MES, and echolucent plaques) and the endpoints, although previous studies did. Nevertheless, our study had sufficient power to prove the discriminative ability of IPH and total plaque volume stressing again the usability of these markers in patients with <70% carotid stenosis. Another limitation is that because of logistical factors (eg, referral to academic hospitals), plaque imaging could not be performed the same day of the index event, resulting in a delay between index event and plaque imaging. However, this might reflect clinical practice because patients referred by a general practitioner to an outpatient clinic usually do not receive carotid imaging the same day as their ischemic event. During this interval, 3 patients had a recurrent event in our study; however, this did not influence the results. Finally, we included both ischemic stroke and TIA in our endpoint analyses, whereas previous studies often focused on ischemic stroke alone. Because stroke and TIA could be seen as a continuum rather than as different subgroups, we decided to include all adjudicated cerebral ischemic events as primary endpoint.[35]

Over the last years, professionals have stressed the need to also take imaging characteristics of plaque vulnerability into account for treatment decisions. The PARISK study is the first prospective study showing the added value of IPH presence and total plaque volume in patients with mild-to-moderate carotid stenosis. These imaging-derived markers have an important clinical impact by enhancing risk classification for recurrent stroke. We show now that including these markers in clinical decision making could improve personalized treatment and, moreover, targeted intervention. Useless interventions can be avoided and more patients will receive better treatment. The next step is to validate our findings in other cohorts. CTA is currently the preferred diagnostic tool in patients with acute ischemic stroke and is able to assess calcifications, ulcerations, stenosis, and plaque burden.[12,18,36] An additional MRI protocol with 1 sequence for IPH detection could complete the diagnostic work-up and, in the end, result in optimal clinical decision making. Based on these new findings in the PARISK study, we advocate using both CTA and MRI for plaque imaging to improve clinical prediction of recurrent stroke.

CONCLUSIONS

IPH and total plaque volume are independent risk factors for recurrent ipsilateral ischemic stroke or TIA in patients with mild-to-moderate carotid stenosis. These plaque characteristics improve current clinical decision making. Validation studies to implement plaque characteristics in clinical scoring tools are needed.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In stroke patients having mild-to-moderate carotid stenosis, IPH and total plaque volume are important risk factors for recurrent ipsilateral ischemic events. These imaging-derived markers have clinical impact by improving risk prediction of stroke recurrence. Therefore, these plaque characteristics should be incorporated in clinical decision making to improve risk assessment and personalized treatment.

TRANSLATIONAL OUTLOOK: New prediction tools should be developed including both clinical and imaging characteristics. Furthermore, randomized trials are needed to investigate whether patients with mild-to-moderate carotid stenosis having IPH do benefit from intensive medical therapy or carotid revascularization.

REFERENCES

1. 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.

2. Katan M, Luft A. Global Burden of Stroke. *Semin Neurol*. 2018;38:208–211.

3. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339:1415–1425.

4. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet*. 1998;351:1379–1387.

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;363:1491–1502.

6. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236.

7. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361:107–116.

8. Karlsson L, Kangefjard E, Hermansson S, et al. Risk of recurrent stroke in patients with symptomatic mild (20-49% NASCET) carotid artery stenosis. *Eur J Vasc Endovasc Surg*. 2016;52:287–294.

9. Singh N, Marko M, Ospel JM, Goyal M, Almekhlafi M. The risk of stroke and TIA in non-stenotic carotid plaques: a systematic review and meta-analysis. *AJNR Am J Neuroradiol*. 2020;41:1453–1459.

10. Yuan C, Mitsumori LM, Ferguson MS, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation*. 2001;104:2051–2056.

11. Lovett JK, Gallagher PJ, Hands LJ, Walton J, Rothwell PM. Histological correlates of carotid plaque surface morphology on lumen contrast imaging. *Circulation*. 2004;110:2190–2197.

12. Saba L, Saam T, Jager HR, et al. Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications. *Lancet Neurol*. 2019;18:559–572.

13. Homburg PJ, Rozie S, van Gils MJ, et al. Atherosclerotic plaque ulceration in the symptomatic internal carotid artery is associated with nonlacunar ischemic stroke. *Stroke*. 2010;41:1151–1156.

14. Schindler A, Schinner R, Altaf N, et al. Prediction of stroke risk by detection of hemorrhage in carotid plaques: meta-analysis of individual patient data. *J Am Coll Cardiol Img*. 2020;13:395–406.

15. Takaya N, Yuan C, Chu B, et al. Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: a prospective assessment with MRI — initial results. *Stroke*. 2006;37:818–823.

16. Baradaran H, Al-Dasuqi K, Knight-Greenfield A, et al. Association between carotid plaque features on CTA and cerebrovascular ischemia: a systematic review and meta-analysis. *AJNR Am J Neuroradiol*. 2017;38:2321–2326.

17. Kwee RM. Systematic review on the association between calcification in carotid plaques and clinical ischemic symptoms. *J Vasc Surg*. 2010;51:1015–1025.

18. Bos D, van Dam-Nolen DHK, Gupta A, et al. Advances in multimodality carotid plaque imaging: AJR expert panel narrative review. *AJR Am J Roentgenol*. 2021;217:16–26.

19. Nies KPH, Smits LJM, Kassem M, Nederkoorn PJ, van Oostenbrugge RJ, Kooi ME. Emerging role of carotid MRI for personalized ischemic stroke risk prediction in patients with carotid artery stenosis. *Front Neurol*. Published online August 3, 2021. https://doi.org/10.3389/fneur.2021.718438

20. Truijman MT, Kooi ME, van Dijk AC, et al. Plaque At RISK (PARISK): prospective multicenter study to improve diagnosis of high-risk carotid plaques. *Int J Stroke*. 2014;9:747–754.

21. Cappendijk VC, Cleutjens KB, Heeneman S, et al. In vivo detection of hemorrhage in human atherosclerotic plaques with magnetic resonance imaging. *J Magn Reson Imaging*. 2004;20:105–110.

22. de Weert TT, Cretier S, Groen HC, et al. Atherosclerotic plaque surface morphology in the carotid bifurcation assessed with multidetector computed tomography angiography. *Stroke*. 2009;40:1334–1340.

23. Sheahan M, Ma X, Paik D, et al. Atherosclerotic plaque tissue: noninvasive quantitative assessment of characteristics with software-aided measurements from conventional CT angiography. *Radiology*. 2018;286:622–631.

24. Rothwell PM, Mehta Z, Howard SC, Gutnikov SA, Warlow CP. Treating individuals 3: from subgroups to individuals: general principles and the example of carotid endarterectomy. *Lancet*. 2005;365:256–265.

25. 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;49:614–620.

26. Leening MJ, Vedder MM, Witteman JC, Pencina MJ, Steyerberg EW. Net reclassification improvement: computation, interpretation, and controversies: a literature review and clinician's guide. *Ann Intern Med*. 2014;160:122–131.

27. 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;353:2105–2110.

28. Madani A, Beletsky V, Tamayo A, Munoz C, Spence JD. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound vs TCD microemboli. *Neurology*. 2011;77:744–750.

29. Kuk M, Wannarong T, Beletsky V, Parraga G, Fenster A, Spence JD. Volume of carotid artery ulceration as a predictor of cardiovascular events. *Stroke*. 2014;45:1437–1441.

30. Shaalan WE, Cheng H, Gewertz B, et al. Degree of carotid plaque calcification in relation to symptomatic outcome and plaque inflammation. *J Vasc Surg*. 2004;40:262–269.

31. Gronholdt ML, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation*. 2001;104:68–73.

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. 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;9:663–671.

34. Spence JD, Tamayo A, Lownie SP, Ng WP, Ferguson GG. Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis. *Stroke*. 2005;36:2373–2378.

35. Koudstaal PJ, van Gijn J, Frenken CW, et al. TIA, RIND, minor stroke: a continuum, or different subgroups? Dutch TIA Study Group. *J Neurol Neurosurg Psychiatry*. 1992;55:95–97.

36. Saba L, Moody AR, Saam T, et al. Vessel wall-imaging biomarkers of carotid plaque vulnerability in stroke prevention trials: a viewpoint from the Carotid Imaging Consensus Group. *J Am Coll Cardiol Img*. 2020;13:2445–2456.

KEY WORDS carotid atherosclerosis, computed tomography angiography (CTA), magnetic resonance imaging (MRI), plaque imaging, recurrent stroke risk, symptomatic carotid artery disease

APPENDIX For expanded Methods and Results sections as well as supplemental tables and a figure, please see the online version of this paper.