Association between Carotid Plaque Features on CTA and Cerebrovascular Ischemia: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: CTA is a widely available imaging examination that may allow the evaluation of high-risk carotid plaque features.

PURPOSE: Our aim was to evaluate the association between specific carotid plaque features on CTA and ipsilateral cerebrovascular ischemia.

DATA SOURCES: We performed a systematic review of Ovid MEDLINE, Ovid Embase, Scopus, and the Cochrane Library from inception to March 2016 for articles that evaluated the relationship between CTA-detected carotid plaque features and ischemic events, defined as ipsilateral ischemic stroke or transient ischemic attack.

STUDY SELECTION: Sixteen studies were ultimately included after screening 12,557.

DATA ANALYSIS: Two readers recorded data from each study and assessed the study quality with all disagreements resolved by a third reader. A random-effects OR was used to evaluate the association between cerebrovascular ischemia and each of the evaluated plaque features.

DATA SYNTHESIS: We found significant positive relationships with cerebrovascular ischemia for the presence of soft plaque (OR, 2.9; 95% CI, 1.4–6.0), plaque ulceration (OR, 2.2; 95% CI, 1.4–3.4), and increased common carotid artery wall thickness (OR, 6.2; 95% CI, 2.5–15.6). We found a significant negative relationship between calcified plaque and ipsilateral ischemia (OR, 0.5; 95% CI, 0.4–0.7).

LIMITATIONS: We found heterogeneity in the existing literature secondary to lack of standardized plaque features and clinical definitions.

CONCLUSIONS: Soft plaque, plaque ulceration, and increased common carotid artery wall thickness on CTA are associated with ipsilateral cerebrovascular ischemia, while calcified plaque is negatively associated with downstream ischemic events.

ABBREVIATION: US = ultrasound

Given recent improvement in medical treatment, patients with asymptomatic carotid artery stenosis receiving modern intensive medical therapy now face an annual risk of stroke of ~1%.[1] Given the limitations of stenosis measurements alone in identifying patients at highest risk of ischemic stroke, recent investigations using vessel wall imaging techniques have attempted to provide more detailed characterization of vulnerable plaque features. Specific plaque features, such as intraplaque hemorrhage on MR imaging and echolucent plaque on ultrasound (US), have been identified as risk factors for future ischemic stroke, which, when considered along with stenosis severity and other factors, may help to identify those patients most likely to benefit from surgical revascularization procedures.[2,3]

CTA is a potentially attractive tool for plaque imaging because it is less operator-dependent than US and is more quickly performed and more widely available than MR imaging.[4] Easily identifiable plaque

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features on CTA such as the presence of low attenuation, calcification, and plaque ulceration have been histopathologically validated as markers of high-risk plaque features.[4-6] Although CTA has significant potential to evaluate plaque features, small studies have not reached a consensus regarding plaque features, and high-resolution 3T MR imaging techniques have been favored. We aimed to perform a systematic review and meta-analysis to evaluate the association between multiple specific carotid artery plaque features seen on CTA and cerebrovascular ischemic events.

MATERIALS AND METHODS

We performed this systematic review and meta-analysis according to the guidelines from the Meta-Analysis of Observational Studies in Epidemiology group[7] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8]

Data Searches

A medical librarian performed a comprehensive literature search in multiple electronic databases, including Ovid MEDLINE, Ovid Embase, Scopus, and the Cochrane Library from inception to March 9, 2016. We searched first in Ovid MEDLINE and then adapted subject headings and key words for other databases and identified additional records using the "Cited by" and "View references" features in Scopus (see On-line Appendix for search methodology details).

Study Selection and Eligibility

We included studies evaluating the association between various plaque features on CTA and symptomatic cerebrovascular ischemic events, defined as either prior or future transient ischemic attack or stroke in the vascular territory supplied by the index carotid artery. Specific inclusion criteria were the following: 1) studies that evaluated patients with plaque in the extracranial internal carotid artery; 2) studies using CTA of the common and cervical internal carotid arteries to assess specific plaque features; 3) studies that correlated the questioned plaque features with symptomatic status, defined as either stroke or transient ischemic attack in the vascular territory supplied by the index carotid artery; 4) studies that included asymptomatic control carotid arteries, either by comparing with the asymptomatic contralateral carotid artery (within-subject controls) or asymptomatic subjects (between-subject controls). If it appeared that authors published data from a single cohort or medical center more than once, the article with the largest sample size was included to minimize duplicate or overlapping samples. We attempted to contact the corresponding authors for additional details when necessary.

Data Extraction

All potentially eligible titles and abstracts were reviewed by a single reader. Two independent readers screened articles in their entirety to determine eligibility for inclusion. Data were extracted by 2 independent readers using a prespecified data-collection template. A third reader resolved any disagreements about data extraction. The readers extracted the following data: study design; basic study demographics for included patients, including risk factors for stroke; definitions of ischemic stroke; specific CTA imaging techniques; and definitions of plaque features.

We also answered specific questions to evaluate potential selection, detection, reporting, or confounding bias using a risk-of-bias assessment like that in previously published meta-analyses.[2,9] The risk of bias was assessed by consensus among 3 readers.

Data Analysis

Meta-analyses of the individual study odds ratios were conducted with StatsDirect statistical software (Version 2.7.9; July 9, 2012; http://www.statsdirect.com). Each pooled OR was calculated with a random-effects (DerSimonian and Laird) model, and forest plots were generated to display the individual study odds ratios and the pooled OR. Random-effects models were used to combine the studies because of the potential of variability in the outcome of interest among the studies. To assess the combinability of the OR, we calculated the P value from the Cochrane Q and I^2 statistical heterogeneity tests. The results of each study were expressed as an OR with a 95% confidence interval. For each meta-analysis with >3 studies, the presence of publication bias was evaluated through a funnel plot. The Begg and Mazumdar rank-correlation test was used to statistically assess the presence of publication bias. All P values $< .05$ were considered significant.

RESULTS

Study Characteristics

After screening 12,557 titles and abstracts, we identified 20 studies that were ultimately included in the systematic review (On-line Fig 1).[6,10-28] Of the 20 articles meeting the inclusion criteria for systematic review, 13 were retrospective, cross-sectional studies[6,10-12,14-18,20,21,24,28] and 7 were prospective, cross-sectional studies.[13,19,22,23,25-27] The time interval between the onset of ischemic symptoms and CTA ranged from 2 weeks to 6 months for those studies that provided these data (On-line Table 1).[14,20,22,23] We found no studies evaluating the association between CTA plaque features and future ischemic events. Seven studies were performed in the United States[6,10,11,18,20,24,28]; 3, in Japan[14,22,23]; 3, in Italy[15-17]; 2, in the Netherlands[19,27]; and 1 each, in Canada,[21] France,[13] China,[26] Germany,[25] and Spain.[12] The mean age of patients in the included studies ranged from 62 to 75.1 years. All studies had a preponderance of male subjects with a percentage range of men from 53.7% to 92.3%. There was a range of degree of ICA stenosis, with 6 studies requiring patients to have at least 50% stenosis,[11,13,14,16,23,25] 2 studies requiring patients to have at least 60% stenosis,[10,12] and 2 studies requiring patients to have at least 70% stenosis.[20,29] Six studies evaluated all patients with CTA examinations regardless of their degree of stenosis,[15,18,19,21,24,26] while 2 studies focused only on patients with mild-to-moderate (30%–69%) stenosis,[22,27] and 1 study focused only on patients with moderate (50%–69%) stenosis.[28] An additional study included those patients with at least 70% stenosis, symptomatic patients with at least 50% stenosis, and all symptomatic patients with evidence of plaque ulceration regardless of the degree of stenosis (On-line Table 2).[11]

Twelve studies were performed on at least a 16–detector row helical CT scanner,[11,14,18-20,22-24,26-29] while only 7 studies included patients who may have been scanned on a 4– or 8–detector row CT scanner.[10,12,13,15-17,21] One study did not provide the relevant number of rows (On-line Table 3).[25]

Of those 20 studies included for systematic review, 16 studies were eligible for meta-analysis in which 2624 patients with 3933 unique carotid arteries were analyzed. The 4 studies excluded from the meta-analysis were not amenable to calculating pooled standardized mean differences because of methodologic differences in calculating volumes, variability in plaque-feature definitions, and small sample sizes for each calculation and included studies that quantitatively evaluated the volume of soft/noncalcified plaque, the volume of calcified plaque, and Hounsfield units (On-line Table 4).

Although specific definitions varied, patients were symptomatic if they had a prior ischemic stroke or TIA in the vascular territory supplied by the carotid artery in question (On-line Table 1). Strokes were generally defined as the patient having had a persistent episode of neurologic dysfunction with confirmatory imaging in the distribution of the carotid artery, while TIAs were defined as brief episodes (<24 hours) of neurologic dysfunction, also within the carotid artery distribution.

Definitions of Plaque Features

From the included studies, we were able to collect the actual number of cerebrovascular events for patients with each plaque feature to calculate pooled odds ratios expressing the strength of association between recent ischemic events and the following 4 plaque features: 1) the presence of low attenuation or "soft" plaque, 2) the presence of calcified plaque, 3) plaque ulceration, and 4) common carotid artery wall thickness (On-line Table 5). Soft plaques were defined as having low density or lipid-rich cores, with 4 studies using a specific threshold of Hounsfield units of <50 or 60.[10,17,25,26] The presence of calcified plaque was defined as extensively calcified plaque with Hounsfield units of >120 or 130.[10,17,25,26] Specific definitions for plaque ulceration varied among studies, but it was generally defined as extension of contrast material beyond the vascular lumen into the plaque. Last, common carotid artery wall thickness was defined as thickening of the common carotid artery wall and was dichotomized by the authors of the included studies using various thresholds.

Meta-Analysis Results

We performed 4 separate meta-analyses. For the meta-analyses evaluating the association between low-attenuation plaque, plaque ulceration, and increased common carotid artery wall thickness, we included 1801, 2883, and 307 arteries in each meta-analysis, respectively (On-line Table 6). We found a significant positive association between soft or low-attenuation plaque, plaque ulceration, and increased common carotid artery wall thickness and the presence of recent ipsilateral stroke or TIA, with pooled ORs of 2.92 (95% CI, 1.41–6.04; $P = .004$), 2.20 (95% CI, 1.43–3.40; $P < .001$), and 6.19 (95% CI, 2.47–15.55; $P < .001$), respectively (Fig 1). We also analyzed 2004 arteries to determine the association of the presence of a calcified plaque and downstream cerebrovascular ischemic symptoms and found a negative association with a pooled OR of 0.536 (95% CI, 0.384–0.749; $P <$. 001) (Fig 1). Measures of study heterogeneity and publication bias for the included meta-analyses (Table) demonstrated moderate heterogeneity. Publication bias (On-line Fig 2) was only statistically significant for plaque ulceration studies.

Assessment of the Quality and Bias of the Included Studies

Our quality and bias assessment questionnaire (On-line Table 7) demonstrated that the inclusion and exclusion criteria were adequately described in all the included studies. All except 1 study included in the meta-analysis had investigators blinded to the symptomatic status of the artery in question, with that single study failing to describe the blinded status of the investigators.[19] Thirteen of the included studies had >1 investigator evaluating the questioned plaque feature, while 3 studies were aided by computer algorithms to assess plaque features.[18,22,24] Half of the studies reported measures of interreader reproducibility with κ values ranging from 0.46 to 1, depending on the specific plaque feature.[11,13,15-17,19,20,27-29] Twelve studies evaluated the degree of stenosis in addition to evaluating specific plaque features.[6,11,13,14,17-22,24,28]

DISCUSSION

In this systematic review and meta-analysis, we found that patients with carotid artery atherosclerotic disease demonstrating CTA evidence of low-attenuation plaque, increased common carotid artery wall thickness, or plaque ulceration are highly associated with the presence of recent ipsilateral ischemic events, while those patients with calcified plaques are associated with fewer ipsilateral ischemic events. Our findings are compatible with studies performed on histopathologic carotid endarterectomy specimens. Low-attenuation or soft plaque on CTA is thought to correspond to the histologically described lipid-rich necrotic core and intraplaque hemorrhage[4] and has been shown to be associated with increased risk of future stroke on both MR imaging and US.[2,3] Additionally, plaque ulceration on histopathologic samples and on high-resolution MR imaging has also been associated with symptomatic plaque.[2,30,31] Increased common carotid artery wall thickness, traditionally measured as intima-media thickness on US, is thought to reflect arterial inflammation and is a predictor of cerebrovascular events in prospective studies.[32] Conversely, histopathologic studies evaluating echogenic calcified plaque on US have found that densely calcified plaques are less frequently associated with ischemic events and may be a protective plaque feature, perhaps by preventing thrombus aggregation or by affording additional mechanical stability to a plaque surface.[3,33] Additionally, a previously published systematic review has shown that symptomatic plaques have less calcification than asymptomatic plaques.[34]

Using CTA to evaluate high-risk carotid plaque features has several strengths: First, CTA can be rapidly performed and is commonly available. Unlike high-resolution plaque imaging with MR imaging, CTA plaque imaging does not require lengthy sequences or dedicated equipment such as carotid coils to evaluate plaque features. Additionally, evaluating the presence of soft or calcified plaque, plaque ulceration, or increased common carotid artery wall thickness can be easily performed with high reproducibility without requiring lengthy interpretive time or postprocessing software.

Our study illustrates some methodologic limitations of the existing literature on CTA evaluation of carotid plaque. Our analysis revealed moderate levels of heterogeneity in the meta-analy-

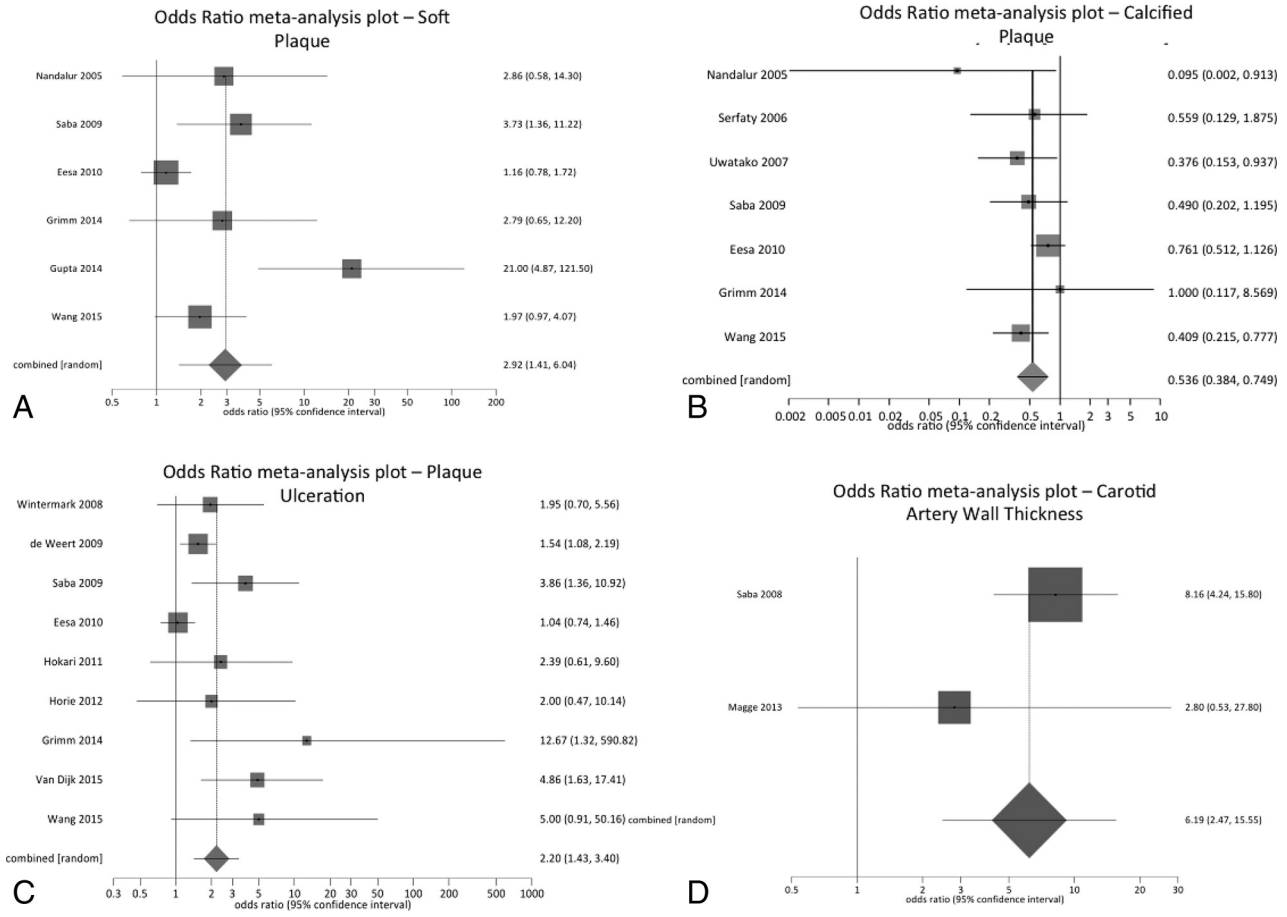

FIG 1. Four separate forest plots of the association between CT angiography–determined plaque characteristics and recent prior ipsilateral ischemic events. Each meta-analysis was calculated with a random-effects model with pooled ORs shown for each forest plot. Each *square* represents the point estimate of the effect size of the study with the square size being proportional to the inverse of the variance of the estimate and the horizontal lines representing each the 95% CI of each study. The *diamond* represents the pooled estimate with the width of the diamond representing the pooled 95% CI.

Heterogeneity and publication bias measures

	Measures of Heterogeneity			Publication Bias	
	I^2	Cochran *Q*	*P* Value	Kendall *T*	*P* Value
Soft-plaque studies	76.3%	21.13	.001	0.47	.27
Calcified-plaque studies	19.8%	7.49	.28	0.14	.56
Plaque ulceration studies	61.1%	20.56	.008	0.389	.018
Carotid artery wall thickness studies	34.6%	1.52	.22	NA	NA

Note:—NA indicates not applicable.

ses evaluating soft plaque and plaque ulceration, which may have been secondary to between-study variability in the definitions of CTA plaque features and differences in how studies adjudicated and defined stroke or TIA. Using a random-effects rather than a fixed-effects model, we could statistically account for this heterogeneity and still show strong associations between each plaque feature and cerebrovascular ischemia. We believe that increased standardization of plaque feature definitions and more consistently applied, uniform definitions of ischemic events are warranted for future studies. Additionally, risk of bias for each article was determined subjectively by consensus among 3 readers. The subjectivity involved in assessing the risk of bias is inherent to systematic reviews and meta-analyses. We also detected the possibility of publication bias in our meta-analysis of plaque ulceration, which raises the possibility that negative studies were not published. However, the evaluation of publication bias is limited, given the small number of studies published on the CTA characterization of plaque ulceration, and future studies are warranted to examine whether such a bias exists.

Our systematic review and meta-analyses also revealed knowledge gaps that future studies should seek to clarify. First, we found that investigators have, to date, evaluated only the relationship between specific plaque features and recent prior ischemic symptoms, rather than future stroke. Although longitudinal MR imaging studies have shown that high-risk carotid plaque features such as intraplaque hemorrhage do not change significantly during a 1-year period in symptomatic patients,[35] prospective studies evaluating future stroke risk are needed if CTA plaque analysis is to play a greater role in primary stroke prevention. It is possible that a more directly applicable use of the results of our study may allow

clinicians to improve their confidence in identifying a culprit lesion after a stroke of uncertain etiology has occurred so that optimal secondary stroke prevention measures can be initiated.[36,37] Second, we found that the time interval between the onset of ischemic symptoms and CTA for the evaluation of plaque features was relatively inconsistent among included studies. Third, many studies did not include precise descriptions of how causation of ischemic stroke was attributed to a given ICA. Prospective studies with standardized protocols and definitions evaluating the predictive value of these plaque features for ischemic symptoms are warranted to improve the clinical usefulness of carotid plaque CTA.

CONCLUSIONS

Our systematic review and meta-analyses suggest that plaque features such as the presence of soft plaque, plaque ulceration, or increased common carotid artery wall thickness seen on CTA are strongly positively associated with cerebrovascular ischemic events and that the presence of calcified plaque is negatively associated with prior ischemic events. Routine assessment of these plaque features on CTA may be complementary to measuring degree of luminal stenosis and aid in identifying high-risk plaque features.

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