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ORIGINAL RESEARCH

Imaging Biomarkers and Prevalence of Complex Aortic Plaque in Cryptogenic Stroke: A Systematic Review

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BACKGROUND: Complex aortic plaque (CAP) is a potential embolic source in patients with cryptogenic stroke (CS). We review CAP imaging criteria for transesophageal echocardiogram (TEE), computed tomography angiography (CTA), and magnetic resonance imaging and calculate CAP prevalence in patients with acute CS.

METHODS AND RESULTS: PubMed and EMBASE databases were searched up to December 2022 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. Two independent reviewers extracted data on study design, imaging techniques, CAP criteria, and prevalence. The Cochrane Collaboration tool and Guideline for Reporting Reliability and Agreement Studies were used to assess risk of bias and reporting completeness, respectively. From 2293 studies, 45 were reviewed for CAP imaging biomarker criteria in patients with acute CS (N=37 TEE; N=9 CTA; N=6 magnetic resonance imaging). Most studies (74%) used ≥4 mm plaque thickness as the imaging criterion for CAP although ≥1 mm (N=1, CTA), ≥5 mm (N=5, TEE), and ≥6 mm (N=2, CTA) were also reported. Additional features included mobility, ulceration, thrombus, protrusions, and assessment of plaque composition. From 23 prospective studies, CAP was detected in 960 of 2778 patients with CS (0.32 [95% CI, 0.24–0.41], I^2=94%). By modality, prevalence estimates were 0.29 (95% CI, 0.20–0.40; I^2=95%) for TEE; 0.23 (95% CI, 0.15–0.34; I^2=87%) for CTA and 0.22 (95% CI, 0.06–0.54; I^2=92%) for magnetic resonance imaging.

CONCLUSIONS: TEE was commonly used to assess CAP in patients with CS. The most common CAP imaging biomarker was ≥4 mm plaque thickness. CAP was observed in one-third of patients with acute CS. However, high study heterogeneity suggests a need for reproducible imaging methods.

Key Words: aorta ■ atherosclerosis ■ biomarker ■ imaging ■ stroke

Despite advancements in cerebrovascular imaging, the stroke mechanism remains undetermined in nearly 35% of patients with ischemic stroke.[1,2] These patients with stroke not attributable to cardioembolism, large artery atherosclerosis, or small artery disease after conventional workup are categorized as having "cryptogenic stroke."[2] A potential contributor to cryptogenic stroke (CS) is complex aortic plaque (CAP).[3,4] Studies suggest associations between ischemic stroke and CAP features such as plaque thickness, ulceration, or mobility.[3,5–7] However, the diagnostic accuracy by imaging modality to detect CAP features varies.

Prevalence rates in CS for CAP range from <10% to >50%[8,9] likely due to variability in imaging methods. Inconclusive results from the Aortic Arch Related Cerebral Hazard Trial may be due to limitations in detecting and

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CLINICAL PERSPECTIVE

What Is New?

- In patients with cryptogenic stroke, nearly a third of the patients have complex aortic plaque, which is potentially an embolic stroke source.
- There is wide variability in which features are evaluated to define complex aortic plaque based on imaging modality type.

What Are the Clinical Implications?

- It is important to evaluate the aortic arch for complex aortic plaque in patients with cryptogenic stroke.
- There is a need for consensus in how complex aortic plaque is detected and defined by imaging.

Nonstandard Abbreviations and Acronyms

CAP	complex aortic plaque
CS	cryptogenic stroke
CTA	computed tomography angiography
TEE	transesophageal echocardiogram

measuring CAP using transesophageal echocardiogram (TEE), which is often operator-dependent.[10] To offer precision and accuracy in the diagnostic stroke workup, recognizing the capabilities and limitations of each modality for evaluating aortogenic stroke causes is critical before classifying a patient as cryptogenic. For example, although TEE evaluates for cardiogenic/aortogenic stroke causes, its invasiveness and operator-dependence limit its utility. Although computed tomography angiography (CTA) cannot assess plaque mobility and has radiation risks, neck CTAs are routinely performed for stroke evaluation and may be leveraged to screen the aortic arch. Magnetic resonance imaging (MRI) of the aorta can evaluate unstable plaque components but use is restricted by cost and specialized expertise.

To better understand how to detect CAPs by imaging, this systematic review compares CAP imaging biomarker criteria by TEE versus noninvasive cross-sectional modalities such as CT and MRI. Additionally, we estimate CAP prevalence in patients with CS by imaging modality.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Search Strategy

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered with the International Prospective Register of Systematic Reviews (CRD42022300865). PubMed and EMBASE were searched from January 1, 1980 to November 14, 2021 with an updated search on December 5, 2022. Search strategy is shown in Table S1. Institutional review board approval or written informed consent was not required due to the literature-based nature of the study.

Inclusion and Exclusion Criteria

Two sets of inclusion/exclusion criteria were defined (Tables S2 and S3) and 2 independent raters screened studies (Data S1). First, to review imaging modalities and CAP imaging biomarker criteria in patients with CS, studies that used TEE/CT/MRI to assess aortic arch plaque in adults (≥18 years old) meeting criteria for cryptogenic/embolic stroke of undetermined source were included. Second, to estimate prevalence, only prospective studies with sufficient reporting of at least 10 patients with CS were included. Foreign language articles were included. Citations of the full texts and 2 meta-analyses were reviewed for eligibility.[11,12]

Data Extraction

Two independent reviewers (Y.S., J.W.S.) extracted data, and discrepancies were resolved by consensus. Study characteristics, study design, patient demographic data, imaging strategy, rater details, CAP imaging criteria, and study results/limitations were extracted (Data S1). Risk of bias and reproducibility were assessed by 2 independent reviewers (Y.S., J.W.S.) using a modified Cochrane Collaboration's tool[13] and modified version of the Guidelines for Reporting Reliability and Agreement Studies (Tables S4 and S5),[14] respectively.

Statistical Analysis

Categorical and continuous variables were reported in counts/percentages and means, respectively. Interrater agreement was calculated with an unweighted Cohen's κ. In anticipation of between-study heterogeneity, prevalence of CAP was calculated with a random-effects model using a logit transformation with 95% CIs. To identify sources of heterogeneity, subgroup analyses were performed by pooling groups with at least 3 studies. A priori hypotheses for potential sources of heterogeneity were modality type, CAP criterion, and plaque location (ascending, arch, descending aorta). Statistical heterogeneity was assessed by I^2 statistics.[15] The I^2 statistic quantifies extent

of between-study heterogeneity. An I^2 value ≥50% was considered significant for heterogeneity. Sources of heterogeneity across studies were investigated by subgroup analyses based on imaging modalities, CAP imaging biomarker criteria, arch anatomy, study location, and higher grade of reproducibility (Guidelines for Reporting Reliability and Agreement Studies score ≥3). Bias secondary to small study effects was assessed by a funnel plot and the Egger's test. A P value of <0.05 was used as a threshold for statistical significance. Analyses were conducted using R (R Core Team, 2022), RStudio (RStudio Team, 2022), and SPSS v19 (IBM, Chicago, IL).

RESULTS

Literature Search

From 2293 articles, title/abstract and full-text screens by 2 raters (κ=0.62 [95% CI, 0.55–0.70], P<0.001) resulted in 45 articles for qualitative review and 23 prospectively designed studies to calculate CAP prevalence in patients with CS (Figure 1 and Tables S6 and S7).

Qualitative Review of Imaging Biomarker Criteria of CAPs

Thirty-seven TEE, 9 CTA, and 6 MR studies were included. Most studies were prospective (N=29), used a cross-sectional (N=36) study design and were single-center (N=39). Studies were conducted in Europe (N=21), Asia (N=15), and North America (N=8), and 1 study comprised an international cohort.[4] Most studies specified a cryptogenic stroke (N=25) or undetermined source (N=17) sample based on institutional stroke workups. When reported, exclusion of stroke causes that were most frequently specified included >50% cervical carotid (N=14), intracranial stenosis (N=13) or atrial fibrillation (N=16). Ischemic stroke was confirmed by imaging (N=20), clinical assessment (N=3), both (N=2), or not reported (N=20). The ascending, arch, and descending aorta were evaluated in 32, 42, and 21 studies, respectively. The ascending aorta was defined as ending at the brachiocephalic/innominate trunk (N=4), the arch ended at the left subclavian artery outlet (N=11), and the descending aorta ended distal to the left subclavian artery origin (N=4).

TEE Technique and CAP Imaging Criteria

Eighteen of 37 TEE studies reported when the TEE was performed, which ranged from within 5 to 60 days of symptom onset. Twenty-one studies reported technical details including specific views. Twenty-seven studies reported the transducer frequency and 5 MHz was most commonly used (N=21). When reported, multiplane (ability to rotate or electronically steer the ultrasound beam; enables image acquisition in different angles; N=13), omniplane (fixed wide-angle imaging plane; N=10), or biplane (capture images from 2 orthogonal planes; N=7) probes were used. Eight studies specified using Doppler flow. Ten studies reported using a topical anesthetic (N=4) or both topical anesthetic and mild/conscious sedation (N=6). Twenty studies identified the experience level of the sonographer (10=echocardiographer, 10=cardiologist) and 17 studies reported the experience-level of the TEE interpreter (9=echocardiographer, 8=cardiologist). Four studies reported an echocardiographer performed and interpreted the TEE. TEE interpretations were blinded to clinical/imaging data in 6 studies. Technical limitations included operator dependence,[16,17] semi-invasive procedure,[18] decreased sensitivity to small ulcerations,[18] and blind spots when imaging the ascending aorta due to the left bronchus[6] or tracheal air column.[16,19,20]

Most common TEE-based imaging biomarker for CAP was a plaque thickness criterion of ≥4 mm (N=29). Five studies used a higher threshold of plaque thickness ≥5 mm.[18,21–24] Other complex features included mobility (N=27) and ulceration (65%, N=24). Ulceration was defined in 9 studies[16,18,25–31] as a discrete indentation of the luminal surface measuring ≥2 mm in width and depth. Plaque protrusion (N=8),[16,21–24,26,32,33] plaque thrombus (N=6),[23,28,34–37] and surface irregularity (N=4)[23,35,38,39] were also reported as complex features. Two studies assessed calcifications but did not consider them as complex features.[34,39] Examples of TEE-based CAP imaging biomarkers are shown in Figure 2A and 2B (Videos S1 and S2), showing mobile plaque/thrombus.

CTA Technique and CAP Imaging Criteria

Nine studies used CTA to evaluate the aortic arch (N=3 ECG-gated cardiac CTA,[19,40–42] N=2 head/neck CTA,[43,44] N=2 CTA aortography with ECG-gating[42] and no mention of gating,[45] N=1 contrast-enhanced whole-body CT and aortography,[46] N=1=not reported[47]). Patients were imaged within 48 hours[40] to within 1 month[44] of symptom onset. When reported, studies used 16-slice (N=1), 64-slice CT (N=3), or 256-slice (N=1) CT scanners. Two studies used both 16-slice/64-slice[43] or 64-slice/128 slice CT scanners.[19] Reconstruction intervals ranged from 0.625 mm to 0.9 mm. CTAs were scored by radiologists in 6 studies,[19,40–42,44,45] among which 2 studies specified cardiovascular-trained radiologists.[40,41] Raters were blinded to clinical data in 4 studies.[19,40,44,45] Reported technical limitations included detector coverage and temporal resolution when using a 64-slice multidetector CT.[41]

Eight studies reported a CAP plaque thickness criterion[19,40,41,43–47] (N=5, ≥4 mm; N=2, ≥6 mm; N=1,

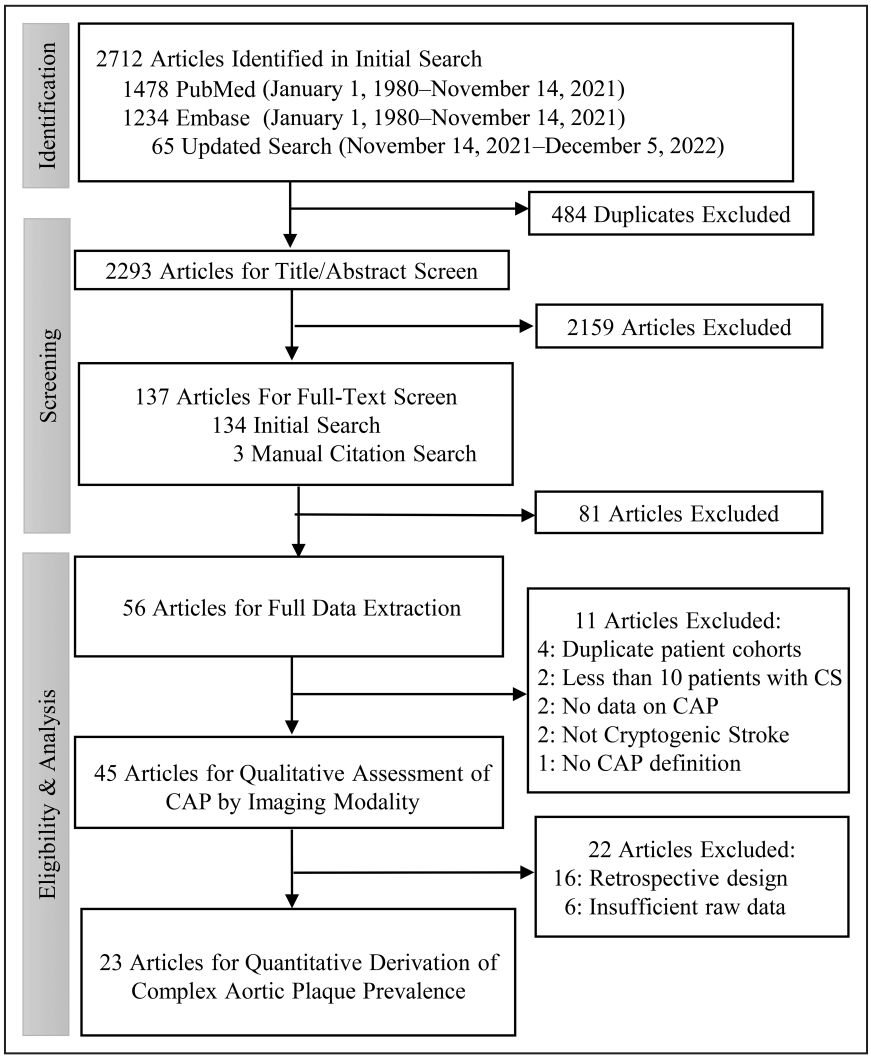

Figure 1. Search strategy.
Between January 1980 and December 2022, 2293 articles were identified from which 45 were qualitatively reviewed for imaging technique and modality-specific CAP imaging biomarkers, and 23 were quantitatively analyzed for CAP prevalence in patients with CS. CAP indicates complex aortic plaque; and CS, cryptogenic stroke.

≥1 mm with a subjective mild/severe grading[45]). Ulceration was reported as a complex feature in 6 studies.[19,40,41,43,44,47] Reported definitions in 3 studies varied as (1) intravenous contrast filling a hypodense component of plaque,[43] (2) contrast extending beyond the vascular lumen into a wide ≥3 mm orifice,[40] or (3) plaque with crater ≥2 mm in depth/width.[44] Soft plaque was included as a complex feature in 3 studies[19,41,43] and defined as plaque ≤80 Hounsfield units[19,41] or ≤180 Hounsfield units.[40] Calcifications were assessed in 4 studies[40,42,43,46] but variably included as a complex feature.[42] Two studies highlighted the lack of validation of CT-based CAP criteria.[19,40] Examples of CTA-based CAP imaging biomarkers are shown in Figure 2C and 2D.

MRI Technique and CAP Imaging Criteria

Among 6 MR studies,[8,9,17,28,48,49] 5 reported when patients were imaged (within 24 hours[9] to 1 week[49] of symptom onset). Four studies imaged at 3 Tesla,[8,9,28,48] 1 at 1.5 Tesla[49], and 1 used both 1.5 and 3 Tesla[17]. Techniques included 4-dimensional flow to assess extent of retrograde aortic blood flow,[9,48] aortic vessel wall/plaque signal,[9,17,28,48,49] Cine of plaques ≥4 mm to detect mobile plaque components,[28] and aortic lumenography with contrast-enhanced or dynamic time-resolved magnetic resonance angiography with interleaved stochastic trajectories techniques.[8,28] Two studies concurrently performed cardiac MRI.[8,49] Four studies reported scan duration (range: 45–59 minutes[8,9,28,49]). Intravenous contrast was used for contrast-enhanced magnetic

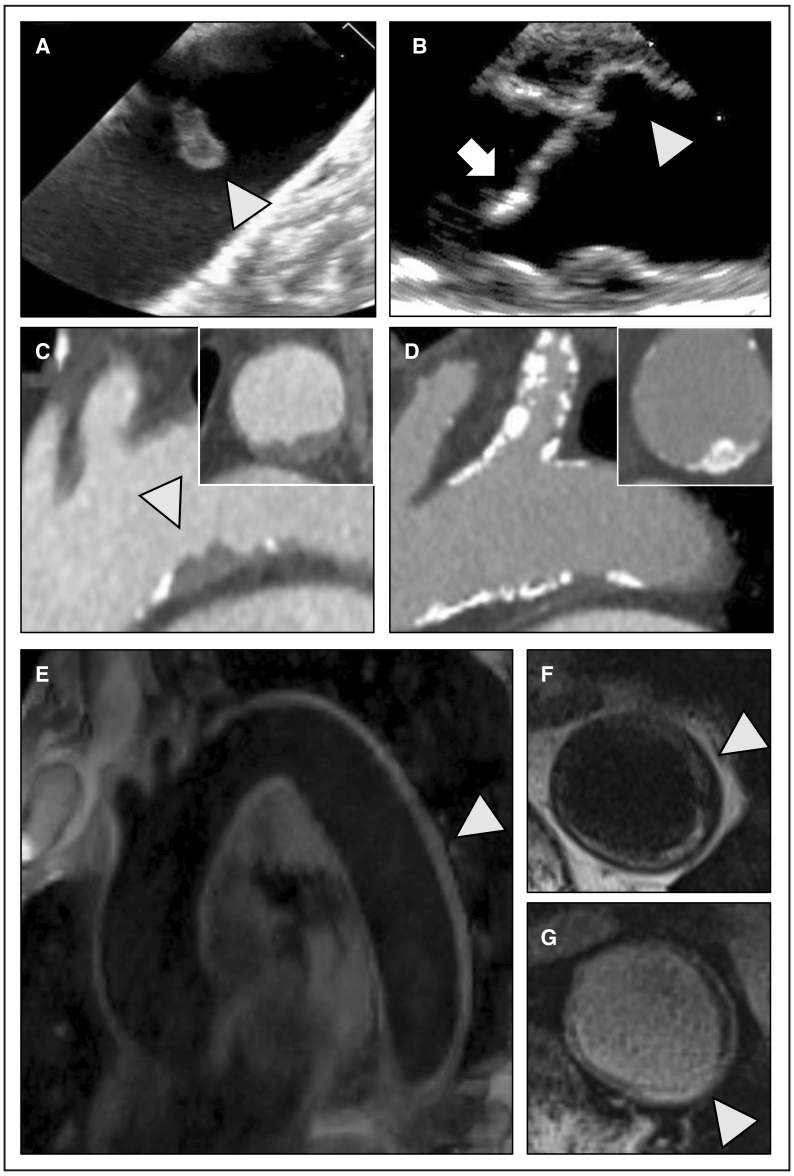

Figure 2. Examples of complex aortic plaque by imaging modality.
Aortic plaque imaging biomarkers by transesophageal echocardiogram shows a mobile component (arrowhead) at the ascending aorta (see also Video S1) (**A**) and ulcerated (arrowhead) aortic plaque with adjacent mobile component (arrow; see also Video S2) (**B**). Examples of arch plaque imaging features on a computed tomographic angiography neck show plaque thickness with surface irregularity (arrowhead, inset) (**C**) and irregular plaque calcifications (**D**). Aortic vessel wall magnetic resonance images (**E**) show wall thickening in dark-blood imaging (arrowhead, measured 4.491 mm in thickness. Reproduced from Hu et al[62] with permission. Copyright © 2020, John Wiley and Sons. Other magnetic resonance imaging features include wall thickness with heterogeneous T2 vessel wall/plaque signal (arrowhead) on T2-weighted imaging (**F**) or wall enhancement (arrowhead) on postcontrast T1-weighted fat suppressed imaging (**G**).

resonance angiography in 2 studies.[8,28] Raters were identified as cardiologists (N=2) with fellowship/cardiovascular imaging training,[8,49] neurologists (N=1),[17] or experienced readers (N=3).[9,28,48] Raters were blinded to clinical or other imaging data in 3 studies.[9,28,49] Reported MR limitations included potentially over-/underestimating plaque thickness due to volume averaging, limited spatial resolution, motion artifact or differences in tissue contrast from flowing blood,[17,28] costs,[28] long scan times,[9,28] and patient-related MR-contraindications.[8,28]

All MR studies defined CAP as plaque thickness ≥4 mm. Ulcerated plaque was a criterion in 2 studies[8,28]

Study	Modality	Aortic Segment	Patients with CAP	Total Patients with CS	Prevalence [95% CI]
Haeusler et al., 2017[8]	TEE	Asc, Arch	6	89	0.07 [0.03–0.14]
Ryoo et al., 2016[47]	TEE	Asc, Arch, Desc	40	321	0.12 [0.09–0.17]
Mohammad et al., 2020[49]	TEE	NR	3	24	0.12 [0.03–0.32]
Dúbrava et al., 2006[51]	TEE	Asc, Arch	29	218	0.13 [0.09–0.19]
Mendel et al., 1998[24]	TEE	Asc, Arch, Desc	14	104	0.13 [0.08–0.22]
Harloff et al., 2006[37]	TEE	Asc, Arch	37	212	0.17 [0.13–0.23]
Castellanos et al., 2001[20]	TEE	Arch	10	49	0.20 [0.10–0.34]
Kim et al., 2012[19]	CTA	Asc, Arch, Desc	15	63	0.24 [0.14–0.36]
Conti et al., 2000[50]	CTA	Asc, Arch, Desc	5	20	0.25 [0.09–0.49]
Chatzikonstantinou et al., 2012[42]	CTA	Asc, Arch, Desc	22	71	0.31 [0.21–0.43]
Chatzikonstantinou et al., 2012[45]	TEE	Arch, Desc	21	64	0.33 [0.22–0.46]
Yahia et al., 2004[34]	TEE, CTA	Asc, Arch	79	237	0.33 [0.27–0.40]
Kessler et al., 1996[22]	MRI	Asc, Arch, Desc	34	100	0.34 [0.25–0.44]
Viguier et al., 2001[39]	TEE	Asc, Arch	14	40	0.35 [0.21–0.52]
Di Tullio et al., 1996[18]	TEE	Asc, Arch, Desc	15	40	0.38 [0.23–0.54]
Rundek et al., 1999[26]	TEE	Arch	24	62	0.39 [0.27–0.52]
Shimada et al., 2013[29]	TEE	Asc, Arch, Desc	74	178	0.42 [0.34–0.49]
Wehrum et al., 2014[48]	TEE, MRI	Arch	31	67	0.46 [0.34–0.59]
Wehrum et al., 2017[9]	TEE, MRI	Asc, Arch	22	40	0.55 [0.38–0.71]
Anan et al., 2021[52]	TEE	Asc, Arch, Desc	147	267	0.55 [0.49–0.61]
Strecker et al., 2020[36]	TEE	Arch	198	329	0.60 [0.55–0.66]
Fujimoto et al., 2011[53]	TEE	Asc, Arch	80	127	0.63 [0.54–0.71]
Mahfouz et al., 2018[33]	MRI	Asc, Arch, Desc	40	56	0.71 [0.58–0.83]
Total (95% CI)			960	2778	0.32 [0.24–0.41]
Prediction interval					[0.07–0.74]

Heterogeneity: $Tau^2 = 0.7348$; $Chi^2 = 386.05$, df = 22 ($P < 0.01$); $I^2 = 94\%$

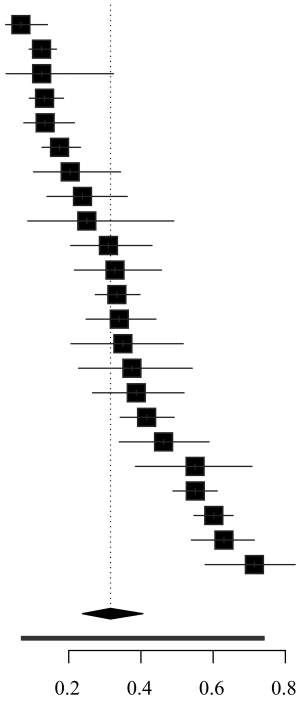

Figure 3. Forest plot for complex aortic plaque prevalence.
Asc indicates ascending aorta; CAP, complex aortic plaque; CS, cryptogenic stroke; CTA, computed tomography angiography; Desc, descending aorta; MRI, magnetic resonance imaging; NR, not reported; and TEE, transesophageal echocardiogram.

but was defined in only 1 study as plaque with ≥2 mm base-width/depth.[28] Other reported MR-based plaque characteristics included mobile components,[28] plaque protrusion,[28] plaque with thrombus,[28] calcification,[9] or signal intensity compared with a reference muscle (eg, T1-weighted signal intensity >150% than sternocleidomastoid muscle[17] and T2-weighted signal intensity compared with cardiac muscle with reference to the American Heart Association plaque classification[9]). Examples of MR-based CAP imaging features are shown in Figure 2E through 2G.

Prevalence of CAPs in Patients With Cryptogenic Stroke

Quantitative analysis was derived from 23 prospectively designed studies[1] (Table S7). Nineteen studies specified consecutive recruitment. Analysis comprised 2778 patients (N=1630 male, N=1041 female, N=107 unknown; mean age 63.8 years). When specified, authors reported stroke subtype as cryptogenic in 16 or "undetermined source" in 6 studies. Ischemic stroke was confirmed by imaging (N=11), clinical assessment (N=1), imaging/clinical assessment (N=2), or not reported (N=9). Eight studies specified including both patients with transient ischemic attack and acute ischemic stroke. Stroke topography was reported in 13 of 23 studies (N=6, embolic pattern; N=9, anterior circulation; N=7, posterior circulation). Fourteen of 23 studies reported imaging for aortic arch plaque within 2 days (N=2), 7 days (N=8), 14 days (N=3), or 30 days (N=1) from stroke onset. Data from 23 studies included 15 TEE,[2] 2 CTA,[19,42] 2 MR,[8,48] 2 TEE/CTA,[42,47] and 2 TEE/MR[8,49] studies.

CAP was identified in 960 of 2778 patients (0.32 [95% CI, 0.24–0.41], I^2=94%) (Figure 3A). Prevalence rates by imaging modality were 0.29 (95% CI, 0.20–0.40, I^2=95%) for TEE; 0.23 (95% CI, 0.15–0.34, I^2=87%) for CTA; and 0.22 (95% CI, 0.06–0.54, I^2=92%) for MR (Figure 4A through 4C). No publication bias was detected (P=0.075) (Figure S1).

Sources of heterogeneity based on CAP imaging criteria were analyzed. Figure 5A through 5C show the prevalence estimates for TEE studies that defined CAP as ≥4 mm plaque thickness (0.30 [95% CI, 0.19–0.44], I^2=96%), ≥4 mm or mobile component (0.31 [95% CI, 0.20–0.46], I^2=97%), versus ≥4 mm, mobile, or with ulceration (0.28 [95% CI, 0.18–0.42], I^2=95%). High heterogeneity remained when assessing by arch location, though prevalence was highest at the arch (0.36 [95%

[1]References 8,9,18–20,22,24,26,29,33,34,36,37,39,42,45,47–53.

[2]References 18,20,22,24,26,29,31,33,34,36,37,39,51–53.

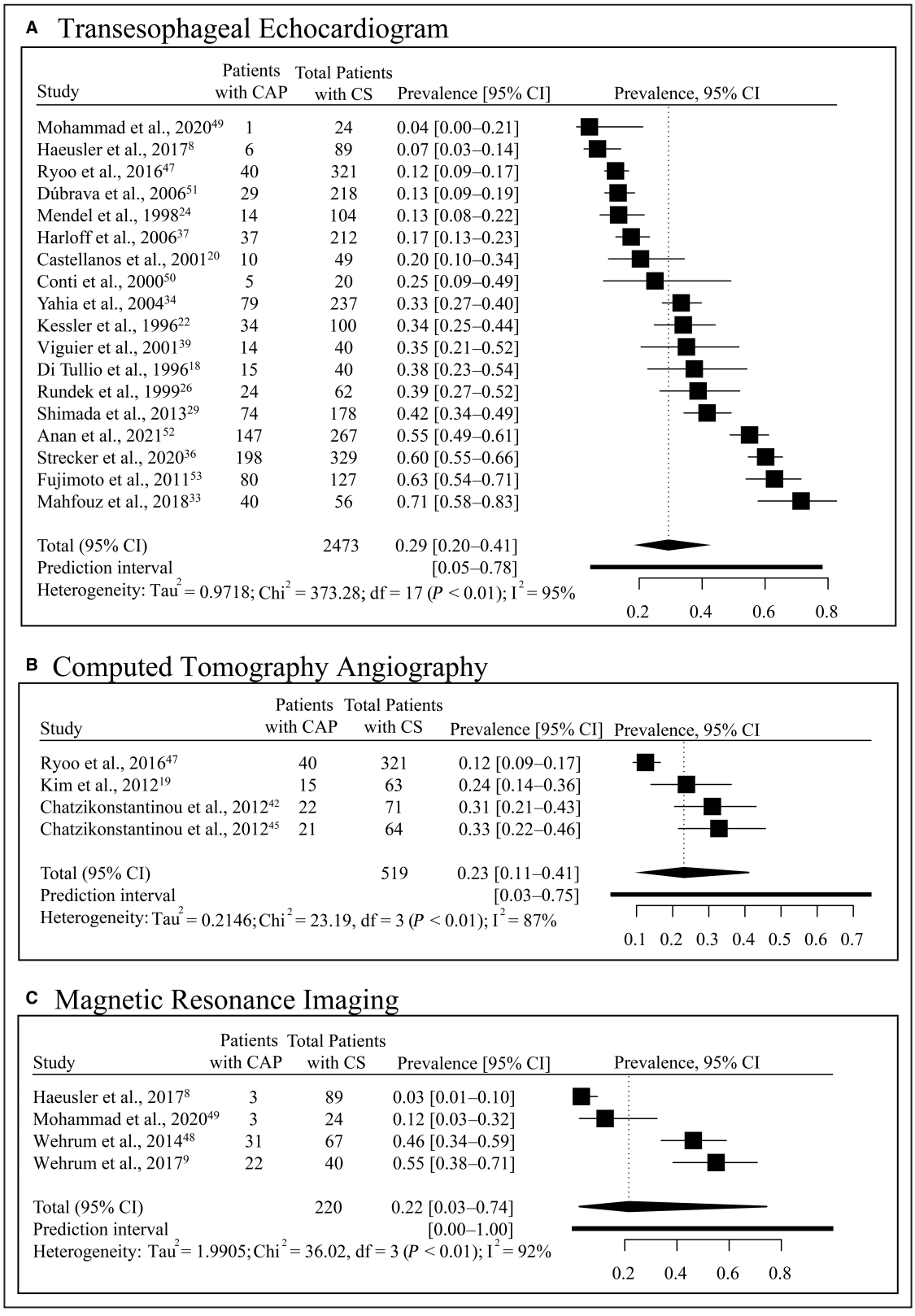

Figure 4. Forest plots for complex aortic plaque prevalence by imaging modality.
Forest plots for transesophageal echocardiogram studies (**A**), computed tomography angiography studies (**B**), and magnetic resonance imaging studie (**C**). CAP indicates complex aortic plaque; and CS, cryptogenic stroke.

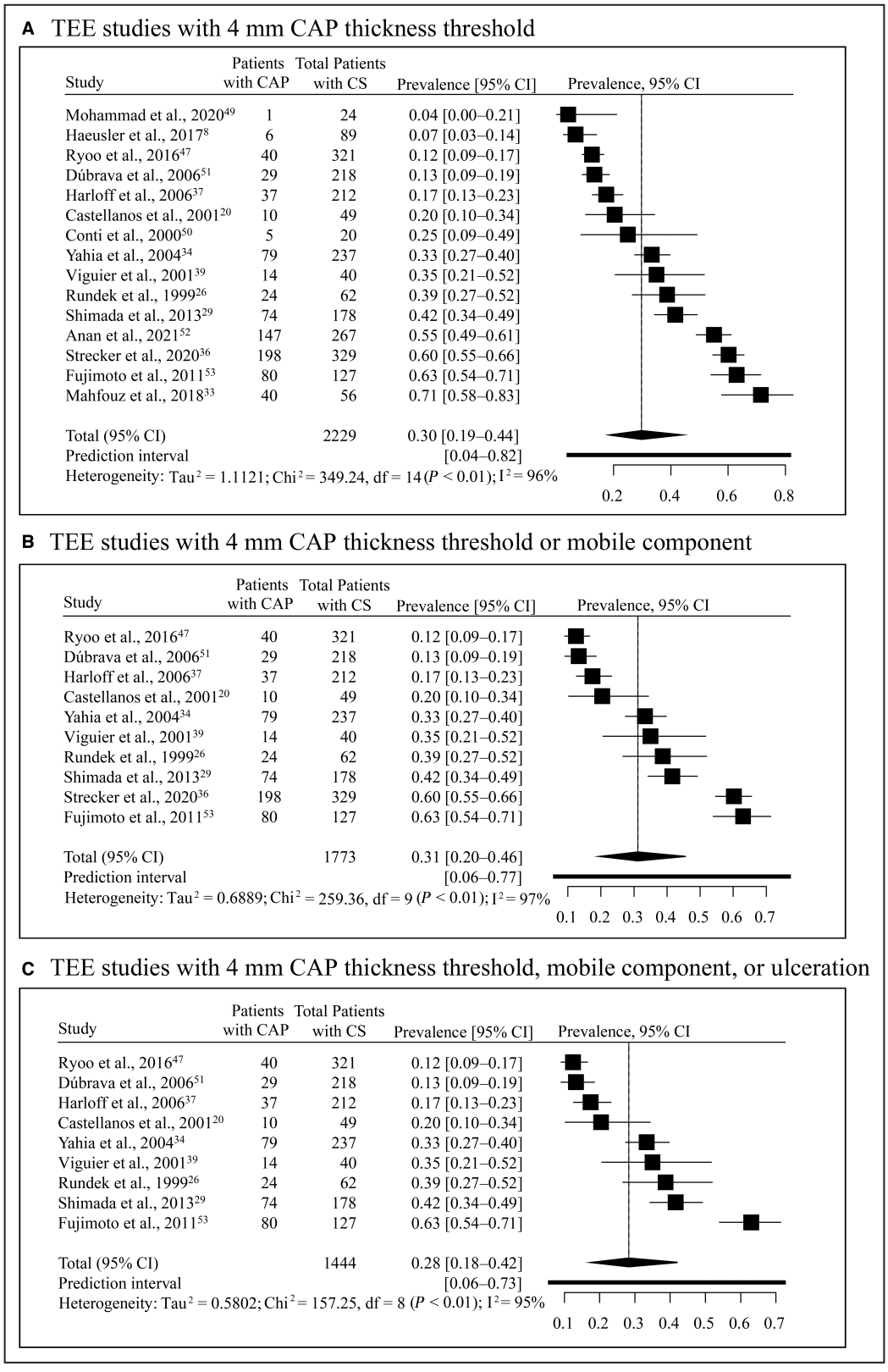

Figure 5. Complex aortic plaque prevalence by TEE-based imaging biomarker criteria.
Forest plots for ≥4 mm CAP plaque thickness (**A**), ≥4 mm CAP plaque thickness or mobile component (**B**), and ≥4 mm CAP plaque thickness, mobile component, or with ulceration (**C**). CAP indicates complex aortic plaque; CS, cryptogenic stroke; and TEE, transesophageal echocardiogram.

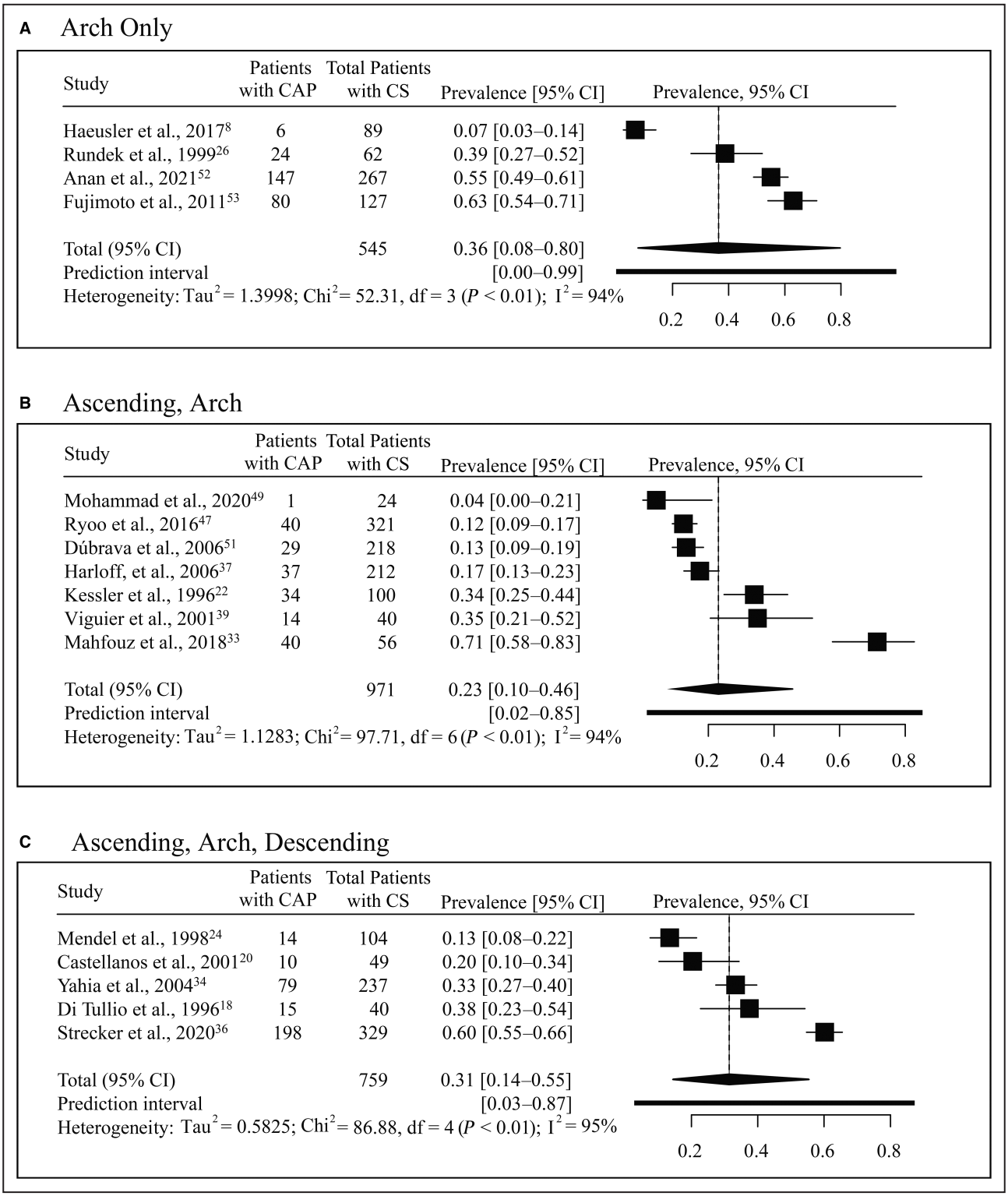

Figure 6. Complex aortic plaque prevalence by TEE based on aortic location.
Forest plots for studies that evaluated the aortic arch (**A**), ascending aorta and aortic arch (**B**), and ascending aorta, aortic arch, and descending aorta (**C**). CAP indicates complex aortic plaque; CS, cryptogenic stroke; and TEE, transesophageal echocardiogram.

CI, 0.08–0.80], I^2=94%) (Figure 6A through 6C). Post hoc analysis by study location showed no significant heterogeneity among North American studies (0.35 [95% CI, 0.25–0.47], I^2=0%) compared with Europe (0.27 [95% CI, 0.18–0.39], I^2=95%) and Asia (0.38 [95% CI, 0.18–0.62], I^2=96%) (Figure S2). Eight studies

with higher reproducibility (Guidelines for Reporting Reliability and Agreement Studies score ≥3 and ≥10 patients with CAP)[8,19,20,34,39,45,48,49] showed moderate heterogeneity (0.34 [95% CI, 0.27–0.42], I^2=63%; Figure S3).

Risk of Bias Assessment

Cochrane Collaboration tool and a modified version of the Guidelines for Reporting Reliability and Agreement Studies assessed for risk of bias and reporting completeness, respectively (Figure S4). Most studies (57%) satisfied 3 of 6 criteria of the Cochrane Collaboration tool. Few studies reported an interrater (N=2[9,34]) or intrarater (N=1[9]) reliability assessment. Rater training/experience and number of years of training were reported in 10 and 2 studies,[9,48] respectively.

DISCUSSION

Detection and measurement of CAP in patients with CS vary by imaging modality. Most studies used a ≥4 mm plaque thickness criterion as a CAP imaging biomarker regardless of TEE, CTA, or MR imaging strategy. However, variability in measurement technique, thresholds and specific morphologic plaque features by modality for detecting CAP were present. For example, TEE more commonly assessed plaque mobility, CTA incorporated calcification features and MR used 4-dimensional flow and vessel wall imaging to assess retrograde flow within the descending aorta and plaque composition/signal, respectively. Reported technical limitations varied by modality type and were primarily related to site expertise and resources, such as operator skill for TEE, use of ECG-gated cardiac versus head/neck CTAs and MR access. The pooled prevalence of CAP in patients with CS was 32%. Subgroup analyses based on modality type, CAP imaging biomarker criteria, and aortic arch segment for prevalence estimates ranged from 22% to 36%, though heterogeneity remained high. High heterogeneity highlights a need for consensus on imaging strategies and measurement methods as well as awareness of the limitations of each modality to detect CAP, a potential cause of embolic strokes in a third of patients with CS.

There is no established guideline for assessing aortic plaque by imaging in patients with CS. The Atherosclerosis, Small-Vessel Disease, Cardiac Pathology, Other Causes, Dissection Phenotyping of Ischemic Stroke considers mobile thrombus in the aortic arch as potentially causal (highest causality grade) of stroke and aortic plaque ≥4 mm without a mobile lesion as uncertain.[7] Yet, plaque mobility was not assessed in 27% and 83% of TEE and MR studies, respectively. Only 1 MR study using Cine methods evaluated plaque mobility.[28] Additionally, an autopsy study showed a prevalence of 60% of ulcerated aortic plaque in patients with ischemic stroke with no known stroke cause versus 22% in patients with known stroke cause, suggesting ulceration to be an important CAP feature.[54] Despite this association, plaque ulceration was assessed in only 65%, 67%, and 33% of TEE, CTA, and MR studies, respectively. Moreover, definitions for ulceration were variably reported, limiting reproducibility. Instead, the most common imaging criterion for CAP among all studies was ≥4 mm plaque thickness and was used in 92%, 89%, and 100% of TEE, CTA, and MR studies, respectively. Indeed several studies show a higher prevalence of aortic ≥4 mm plaque thickness in patients with CS compared with patients with other stroke causes and in patients without stroke.[55] Using the ≥4 mm plaque thickness criterion and additional plaque features of mobility and ulceration did not substantially change the CAP prevalence estimate for TEE studies although analyses were limited by high heterogeneity.

TEE is traditionally used to evaluate cardiogenic and aortogenic stroke causes. It offers high spatial resolution and dynamic imaging with maneuvers permitting assessment of plaque mobility as well as cardiac sources, such as a left atrial thrombus or septal defects. However, it is semi-invasive often requiring anesthesia, is operator dependent, has limited sensitivity for small ulcerated plaques[18,56] and up to 2% of ascending aortic plaques are reportedly missed due to poor insonation windows from air in the trachea and bronchus.[57] A suprasternal window approach with transthoracic echocardiography can image the ascending/proximal arch but is limited for the descending aorta,[58] which may have a higher prevalence of CAP.[36] In a TEE versus CTA study, CTA detected more plaques in all aortic segments.[42,59] A study comparing ECG-gated cardiac CTA against transthoracic echocardiography showed CTA was also able to assess cardiac thrombi. However, CTA was suboptimal for evaluating valvular disease and endocarditis and showed a lower diagnostic yield for septal defects such as patent foramen ovales.[60] Other disadvantages of CTA include inability to evaluate plaque mobility, risks associated with radiation and iodinated intravenous contrast and uncertainty regarding whether it can adequately measure cardiac chamber volumes and left ventricular ejection fractions.[59,60] It is worth highlighting that assessment of both the aortic arch and cervical vasculature on CTA neck exams could reduce additional diagnostic testing. Investigating the added diagnostic value of an ECG-gated cardiac CTA compared with leveraging diagnostic aortic arch information on routinely performed CTA head/neck exams is a future direction.

Advantages of CTA and MRI also include plaque composition analysis. Three CTA studies defined soft plaque as a complex plaque feature. However, the Hounsfield unit thresholds differed for defining

complexity.[19,40,41] Four studies assessed plaque calcifications with variable descriptive morphologic criteria.[40,42,43,46] Given the lack of validated CT-based CAP imaging biomarker criteria, this remains an area of potential innovative research especially with recent technical advancements of photon-counting CT technology.[61] Also advanced MR techniques now enable thoracic aorta multicontrast imaging of the lumen and vessel wall through a single 10-minute acquisition.[62] Such MR innovations can be synergistic with photon-counting CT to validate CAP imaging biomarkers for vulnerable features, such as T1-weighted hyperintense signal for intraplaque hemorrhage. Additional advantages of noninvasive cross-sectional imaging modalities are the minimization of operator dependence and comprehensive anatomic assessment.

This study has several limitations. First, studies may have been missed despite a comprehensive literature review including a manual citation search and inclusion of foreign language articles. Second, studies were published between 1980 and 2022, during which the definition of cryptogenic stroke evolved and the term "embolic stroke of unknown source" was introduced in 2014.[63] Studies were included if the authors reported using a cryptogenic or undetermined stroke cohort based on their institutional workup. Studies that specified excluding 2 or more sources of stroke during the clinical workup were also included. Differences in stroke subtyping may explain the heterogeneity seen in the quantitative analyses. Some authors reported confirming ischemic stroke with imaging whereas others used either imaging or clinical assessment. Variability in patient inclusion can introduce a selection bias, including patients' tolerance for a semi-invasive TEE or lengthy MR exam. Third, for prevalence calculation, only prospective studies were included. Detection of cardiac sources after performing a TEE in patients identified as cryptogenic/undetermined based on initial workup may have introduced a selection bias and may overestimate the pooled prevalence. Fourth, most studies did not report intra- and interrater reliability measures or the training/experience level of the echocardiographer or exam interpreter. Use of reporting guidelines should improve methodological rigor and reproducibility.

CONCLUSIONS

The prevalence of complex aortic plaque is approximately one-third of patients with CS. There is a need for consensus in imaging strategy, imaging criteria for CAP detection and measurement, and directed efforts in standardized and reproducible reporting.

ARTICLE INFORMATION

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Supplemental Material

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