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Carotid stenosis and cryptogenic stroke

Luca Saba, MD,[a] Riccardo Cau, MD,[a] Giacomo Spinato, MD,[b] Jasjit S. Suri, PhD,[c] Marta Melis, MD,[d] Gianluca De Rubeis, MD,[e] Pierluigi Antignani, MD,[f] *and* Ajay Gupta, MD,[g] *Cagliari and Treviso, Italy; Roseville, CA; Roma and Rome, Italy; and New York, NY*

ABSTRACT

Objectives: Cryptogenic stroke represents a type of ischemic stroke with an unknown origin, presenting a significant challenge in both stroke management and prevention. According to the Trial of Org 10,172 in Acute Stroke Treatment criteria, a stroke is categorized as being caused by large artery atherosclerosis only when there is >50% luminal narrowing of the ipsilateral internal carotid artery. However, nonstenosing carotid artery plaques can be an underlying cause of ischemic stroke. Indeed, emerging evidence documents that some features of plaque vulnerability may act as an independent risk factor, regardless of the degree of stenosis, in precipitating cerebrovascular events. This review, drawing from an array of imaging-based studies, explores the predictive values of carotid imaging modalities in the detection of nonstenosing carotid plaque (<50%), that could be the cause of a cerebrovascular event when some features of vulnerability are present.

Methods: Google Scholar, Scopus, and PubMed were searched for articles on cryptogenic stroke and those reporting the association between cryptogenic stroke and imaging features of carotid plaque vulnerability.

Results: Despite extensive diagnostic evaluations, the etiology of a considerable proportion of strokes remains undetermined, contributing to the recurrence rate and persistent morbidity in affected individuals. Advances in imaging modalities, such as magnetic resonance imaging, computed tomography scans, and ultrasound examination, facilitate more accurate detection of nonstenosing carotid artery plaque and allow better stratification of stroke risk, leading to a more tailored treatment strategy.

Conclusions: Early detection of nonstenosing carotid plaque with features of vulnerability through carotid imaging techniques impacts the clinical management of cryptogenic stroke, resulting in refined stroke subtype classification and improved patient management. Additional research is required to validate these findings and recommend the integration of these state-of-the-art imaging methodologies into standard diagnostic protocols to improve stroke management and prevention. (J Vasc Surg 2024;79:1119-31.)

Keywords: Cryptogenic stroke; Carotid imaging; CT; MRI; Plaque vulnerability

Acute ischemic stroke poses a significant global burden, leading to substantial morbidity and mortality.[1] It contributes to approximately 5% of the world's disability-adjusted life-years and is responsible for >10% of global deaths.[2] In Europe and the United States, the current incidence of stroke is approximately 200 per 100,000 population per year. Multinational epidemiologic studies have indicated an increasing trend in stroke incidence, especially in developing nations.[3-5]

Among the various subtypes of stroke, cryptogenic stroke remains a challenging category. This form of stroke refers to cases where the precise cause of the cerebrovascular event cannot be ascertained, despite a comprehensive evaluation.[6] In this context, a crucial aspect to consider is carotid stenosis, which has been regarded as a leading parameter for stratifying the risk of cerebrovascular events for the past four decades.[7] The degree of stenosis is commonly considered a reliable surrogate marker for atherosclerotic risk of cerebrovascular disease, assuming that vessel narrowing result from plaque accumulating in the artery lumen. However, recent scientific evidence emphasizes that other factors may predict the clinical behavior of atherosclerotic plaques. Specifically, some features of plaque vulnerability could be independent risk factors, irrespective of the degree of stenosis, in triggering cerebrovascular events.[8]

From the Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), Cagliari[a]; the Department of Neurosciences, Section of Otolaryngology and Regional Centre for Head and Neck Cancer, University of Padova, Treviso[b]; Stroke Monitoring and Diagnostic Division, AtheroPoint™, Roseville[c]; Department of Neurology, Azienda Ospedaliero Universitaria (A.O.U.), Cagliari[d]; AO San Camillo/Forlanini, Roma[e]; Vascular Centre, Nuova Villa Claudia, Rome[f]; and Weill Cornell Medicine, New York.[g]

Correspondence: Luca Saba, MD, Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), di Cagliari – Polo di Monserrato s.s, 554 Monserrato, Cagliari 09045, Italy (e-mail: lucasaba@tiscali.it).

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Hence, a critical question arises: How reliable is the conventional approach of relying solely on the degree of carotid stenosis to stratify cerebrovascular risk, given the emerging scientific evidence highlighting the significance of carotid plaque vulnerability? The accumulating research suggests that the mere assessment of stenosis may not capture the underlying pathophysiology associated with cryptogenic stroke and the potential risk of embolic events fully.

In this context, it becomes imperative to explore and clarify the role of carotid plaque characteristics and vulnerability as key determinants of cerebrovascular events, beyond the traditional stenosis-based stratification. Understanding the intricate relationship between carotid plaque features and the risk of embolic events has the potential to revolutionize our approach to cryptogenic stroke management and risk assessment.

In this article, our aim was to explore the evolving understanding of cryptogenic stroke etiology and highlight the pivotal role of carotid plaque vulnerability in shaping cerebrovascular risk.

DEFINITIONS AND WORKUP

Definitions. Ischemic stroke is an acute neurological event resulting from the interruption of cerebral blood supply. This interruption can be attributed to either a thromboembolic event or to the occlusion of a cerebral vessel. Despite a comprehensive investigation, the cause of the stroke can remain unidentified. In medical terms, strokes with an unknown cause are classified as cryptogenic strokes.[9] A cryptogenic stroke is classified as such when the causative etiology of the stroke remains elusive despite thorough diagnostic investigations. The term cryptogenic is derived from the Greek terms *kryptos* and *genic*, which, when combined, translate to "of obscure or unknown origin."

Etiologies. Cryptogenic stroke is a diagnosis of exclusion, used only after all other possible etiologies have been eliminated.[6,9] The potential etiologies of cryptogenic stroke are heterogeneous in origin, encompassing (1) cardioembolism owing to congenital heart disease (eg, patent foramen ovale), and acquired heart diseases (eg, cardiomyopathy, endocarditis, atrial cardiopathy, valve disease); (2) vascular diseases (eg, vasculitis, arterial dissection, nonstenosing carotid plaque, aortic arch atheroma); (3) thrombophilia; and (4) occult malignancy.[10]

An embolic stroke of undetermined source (ESUS) represents a subtype of cryptogenic stroke. The term ESUS is used to characterize strokes that are thought to have an embolic origin, yet the source of the embolus remains elusive even after comprehensive investigation.[11]

The distinction between a cryptogenic stroke and ESUS lies in the hypothesized mechanism of the stroke. An embolic cause is proposed in ESUS, whereas in cryptogenic stroke, the cause is entirely undetermined. The concept of ESUS was introduced to identify patients who might benefit from anticoagulant treatment, in contrast to antiplatelet therapy, which is typically administered for strokes of unidentified etiology.[11]

Therefore, although all cases of ESUS are cryptogenic strokes, not all cryptogenic strokes are ESUS. Other cryptogenic strokes might be caused by etiologies other than embolism, such as unrecognized small vessel disease or even nonvascular causes. ESUS is not synonymous with cryptogenic stroke, because cryptogenic stroke also includes patients with multiple potential etiologies, such as, patients with atrial fibrillation and significant atherosclerotic plaque ipsilateral to the infarct, as well as patients with incomplete diagnostic workup. In essence, cryptogenic stroke is a broader term encompassing all strokes of undetermined source, whereas ESUS pertains to a specific subset of cryptogenic strokes in which an embolic source is suspected but remains unidentified.[6]

Diagnostic workup. Determining the exact cause in a patient with cryptogenic stroke can frequently be an intricate process, as various pathologies of heart or vessel could underlie the etiologies of the stroke. Moreover, in the majority of cryptogenic stroke cases, several potential conditions often overlap, adding an additional layer of complexity in the search for the source and subsequently casting uncertainty on clinical decisions. It frequently becomes a matter of debate whether a cryptogenic stroke in a specific patient can be ascribed to a carotid atherosclerotic plaque with low-grade stenosis, a moderately sized patent foramen ovale, a significantly dilated left atrium, a regionally akinetic enlarged left ventricle, a calcified aortic valve, or even an underlying metastatic cancer.[9] The difficulty of firmly linking these potential sources to the stroke event heightens the complexity of managing cryptogenic strokes.

Given the potential heterogeneous etiologies, a comprehensive clinical and laboratory data evaluation is required. This evaluation should include an assessment for atherosclerotic and nonatherosclerotic vascular diseases,[6,10] cardiac sources of embolism (including structural and rhythm abnormalities),[12-14] and disturbances of coagulation.[15]

Limitation of current stroke classification systems. To optimize patient treatment and improve outcomes, it is imperative to discriminate between stroke etiologies. According to existing classification systems for stroke, it can be attributed to large-artery atherosclerosis (LAA) only if it results in a luminal stenosis of ≥50%.[16,17] However, this definition is arguably outdated as it is based on data and studies conducted >40 years ago that linked the risk of cerebrovascular events to the presence of high-grade carotid stenosis.

Tradition has considered the degree of carotid artery stenosis the main criterion to judge the severity of stroke

risk, mostly based on the results of a number of trials released in the 1980s and 1990s demonstrating the benefit of carotid endartrectomy in patients with moderate to severe stenosis (70%-99%), namely, the European Carotid Surgery Trial (ECST), the North American Symptomatic Carotid Endarterectomy Trial, the Asymptomatic Carotid Atherosclerosis Study, and the Asymptomatic Carotid Surgery Trial.[18,19,20,21] These studies used the degree of stenosis as a parameter to stratify risk because, at the time they were conducted, other types of information obtainable with imaging techniques that could speak to the plaque itself, rather than the degree of stenosis (which is an effect of the plaque), were not available.

In recent years, a significant body of evidence has emerged, showing that even in cases with low degrees of stenosis (<50%), there exist a potentially high risk of cerebrovascular events when plaques with characteristics of vulnerability are present.[11]

In 2017, the European Society of Cardiology highlighted the need to target revascularization in asymptomatic patients with imaging features of carotid plaque vulnerability[22] and the impact of plaque vulnerability has been emphasized in the 2020 recommendations of the American Society of Echocardiography[23] and in the clinical practice guidelines of the European Society for Vascular surgery.[24,25] This newer evidence has shifted our understanding of the potential causes of stroke reshaping and rediscussing the types of cryptogenic stroke. A recent paper by Kamel et al[26] demonstrated that the inclusion of vulnerable plaques could reclassify the etiologies of ≤15% of cases. In addition, defining LAA stroke solely based on a 50% stenosis, according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system, does not take into account some important aspects, including the compensatory enlargement of atherosclerosis vessels[27] and total carotid plaque burden. Specifically, classifying LAA based on a stenosis >50% results in overlooking 79% of patients with a high plaque burden as identified in the Subtypes of Ischaemic Stroke Classification System.[28] The inclusion of high plaque burden in the definition of LAA allows for the reclassification of stroke etiologies, identifying more patients with LAA and a lower proportion of patients with ESUS than the TOAST classification.[29]

VULNERABILITY OF CAROTID PLAQUES IN CASES WITH MILD DEGREES OF STENOSIS

The prevalence of carotid plaques with features of vulnerability in patients with cryptogenic stroke is notably higher on the side ipsilateral to the infarct in comparison to the contralateral side,[30] as demonstrated by Kamtchum-Tatuene et al.[30] In this study, the prevalence of carotid stenosis of <50% with high-risk features in the ipsilateral carotid was 32.5% (95% confidence interval [CI], 25.3-40.2) compared with 4.6% (95% CI, 0.1-13.1) in the contralateral carotid. The odds ratio (OR) of finding a plaque with high-risk features in the ipsilateral vs the contralateral carotid was 5.5 (95% CI, 2.5-12.0).[30] Furthermore, the prevalence of such complex carotid artery plaques in patients experiencing cryptogenic strokes is significantly higher compared with patients with cardioembolic or small vessel strokes.

Other publications have emphasized the association of nonstenosing carotid artery plaques in an unrecognized percentage of cryptogenic strokes.[31,32] For instance, a study conducted by Kopczak et al[33] involving 234 patients showed that the prevalence of complicated carotid artery plaques in patients with cryptogenic stroke was significantly higher ipsilateral than contralateral to the infarct side (31% vs 12%; $P = .0005$). Complicated carotid artery plaques had a higher prevalence in cryptogenic stroke compared with cardioembolic/small vessel stroke (31% vs 15%; $P = .02$).[33] In a subsequent study, the same authors demonstrated that patients with cryptogenic stroke and a complicated non stenosing carotid plaque ipsilateral to the ischemic territory had a 5.6-fold increased risk of recurrent stroke or TIA compared with cryptogenic stroke patients without a complicated plaque at presentation (hazard ratio [HR]. 5.6; 95% CI, 1.43-21.83) with an incidence rate of transient ischemic attack (TIA)/stroke (3-year interval) of 10.92 vs 1.82 per 100 patient-years ($P = .003$).[34] These studies emphasize the correlation between the presence of complex plaques and the risk of ischemic episodes. However, there are multiple plaque features that are associated with the occurrence of cerebrovascular events,[35,36] and it is possible to explore the specific association and risk of each one. Table I summarizes previous studies regarding noninvasive imaging features and attributable risk for symptom development.

The role of carotid artery imaging. Contemporary imaging modalities, including ultrasound (US) examination, computed tomography (CT) scan, and magnetic resonance imaging (MRI), enable detailed visualization of carotid plaque composition and morphology, facilitating the identification of features of vulnerability as potential causes of ischemic stroke. In clinical practice, all patients with acute neurological symptoms undergone immediate cerebrovascular imaging using CT or MRI upon arrival for the assessment of ischemic stroke presence and to exclude any evidence of hemorrhage. Furthermore, imaging of the carotid bifurcation is crucial for all patients exhibiting symptoms of cerebral ischemia. Carotid US represents the most commonly used modality to evaluate carotid plaque atherosclerosis enabling the assessment of some morphological and compositional features of vulnerability. The use of US examination can outline some sonomorphological characteristics associated with plaque vulnerability,[37] including a large juxtaluminal hypoechogenic area,[38] heterogeneous

Table I. Overview of studies examining noninvasive imaging features and attributable risk for symptom development

Authors	Type of study	Patient population	Modalities	Features	Risk of cerebrovascular events
Kurosaki et al[25]	Retrospective	1190	MRI	IPH	HR, 4.2; 95% CI, 2.48-4.71
Van Dam-Nolen et al[26]	Prospective	244	TCD, US, CT, MRI	IPH	HR, 2.12; 95% CI, 1.02-4.44
McNally et al[27]	Retrospective	726	MRI	IPH	OR, 25.2; 95% CI, 10.1-57.0.
McNally et al[27]	Retrospective	726	MRI	Intraluminal thrombi	OR, 103.6; 95% CI, 8.64-710.8.
Eesa et al[33]	Retrospective	674	CT	Intraluminal thrombi	OR, 4.33; $P = .01$
Kwee et al[34]	Prospective	126	MRI	Thin/ruptured FC	HR, 5.76; 95% CI, 1.91-17.32
Yuan et al[35]	Prospective	53	MRI	Thin/ruptured FC	Thin FC (OR, 10; 95% CI, 1-104)
					Ruptured FC (OR, 23; 95% CI, 3-210
Sadat et al[36]	Prospective	61	MRI	Ruptured FC	HR, 7.39; 95% CI, 1.61-33.82
Baradaran et al[37]	Meta-analysis	2624	CT	LRNC	OR, 2.92; 95% CI, 1.41-6.04
Xu et al[38]	Prospective	120	MRI	LRNC	LRNC >40% wall area were prone to rupture of the FC in comparison with patients with a LRNC <40%
Gupta et al[39]	Meta-analysis	403	MRI	LRNC	OR, 3; 95% CI, 1.51-5.95
Sajedi et al[43]	Retrospective	33	CTA	Carotid web	OR, 16.7; 95% CI, 2.78-320.3; $P =$ .01
Coutinho et al[44]	Retrospective	62	CTA	Carotid web	OR, 8.0, 95% CI, 1.2-67; $P = .032$
Mathiesen et al[48]	Retrospective	6584	US	MPT	(95% CI, 1.09-1.38; $P = .0009$) in men and 1.19 (95% CI, 1.01-1.41; $P = .04$) in women
Sillesen et al[49]	Prospective	5808	US	MPT	After adjusting f OR, risk factors, HRs for maximum plaque thickness and carotid plaque volume with primary major ASCVD events as an end point were 1.96 [95% CI ,0.91-4.25; $P = .015$] for primary MACE and 3.13 (95% CI, 1.80-5.51; $P < .001$) for secondary MACE
Coutinho et al[50]	Retrospective	85	CTA	MPT	>3-mm plaque thickness of the noncalcified component was present ipsilateral to stroke in 35% of patients (vs 15% of the contralateral; $P =$ .01)
Zhao et al[51]	Prospective	1047	MRI	MTP	Maximum wall thickness was found to be a stronger discriminator than stenosis for HRP (AUC, 0.93 vs 0.81; $P <$ .0001).
Qiao et al[56]	Retrospective	47	MRI	Intraplaque neovascularization	Neovascularization, associated with cerebrovascular events (OR, 51.7; 95% CI, 3.40-469.80; $P = .004$) after controlling for age, sex, cardiovascular risk factors, wall thickness, and stenosis

Table I. Continued.

Authors	Type of study	Patient population	Modalities	Features	Risk of cerebrovascular events
Song et al[57]	Prospective	155	US	Intraplaque neovascularization	Intraplaque neovascularization is associated with recurrent cerebrovascular events (HR, 4.5; 95% CI, 1.9-10.90; $P = .001$) independent of the severity of carotid stenosis (HR, 3.5; 95% CI, 1.4-8.6; $P = .007$)

ASCVD, *AUC*, area under the curve; *CI*, confidence interval; *CT*, computed tomography; *CTA*, computed tomography angiography; *FC*, fibrous cap; *HR*, hazard ratio; *HRP*, high-risk plaque; *IPH*, intraplaque hemorrhage; *LRNC*, lipid-rich necrotic core; *MACE*, major adverse cardiac event; *MRI*, magnetic resonance imaging; *MPT*, maximum plaque thickness; *OR*, odds ratio; *TCD*, transcranial Doppler; *US*, ultrasound.

echotexture,[39,40] and plaque echogenicity.[41] In addition, transcranial Doppler US examination can detect circulating emboli that appears as short duration, high-intensity embolic signals accompanied by a distinctive chirping sound.[36,42,43] Detection of symptomatic embolization on transcranial Doppler US examination is an independent predictors of future stroke risk.[44]

Although carotid US is widely available, cost effective, and radiation free, CT scans and MRI are often required in clinical practice to assess extracranial and intracranial vessels for atherosclerosis diseases.[6,10] In clinical practice, the choice of an imaging modality should depend on the available technology and the inherent pros and cons of each specific imaging method, as well as local expertise.

Intraplaque hemorrhage. Intraplaque hemorrhage (IPH) is characterized by an extravasation of blood constituents within the atherosclerotic plaque, and it is recognized as a critical feature of plaque vulnerability. In recent years, several longitudinal and cross-sectional studies have shown that IPH is a strong risk factor for developing symptoms. A longitudinal study of 1190 patients with asymptomatic carotid stenosis, followed for a mean period of 53 months, showed that IPH detected by MRI was significantly associated with subsequent cerebrovascular ischemic events (HR, 4.2; 95% CI, 1.0-17.1; $P = .04$).[45]

In some cases, the impact of IPH in patients with mild carotid stenosis has been explored: A recently published meta-analysis performed on 7 cohorts involving 560 patients with symptomatic carotid stenosis and 136 patients with asymptomatic carotid stenosis showed that IPH was a more potent predictor of stroke than any established clinical risk factor. The annualized event rates of stroke on the ipsilateral side were 9.0% for patients with IPH and 0.7% for those without, in cases of stenosis of <50%.

In the recent prospective Plaque At RISK (PARISK) study of 244 patients with a recent symptomatic mild-to-moderate carotid stenosis who were followed up for a mean period of 5.1 years using transcranial Doppler examination, US examination, MRI, and CT scan, the presence of IPH was associated with recurrent cerebrovascular events (HR, 2.12; 95% CI, 1.02-4.44) with an improvement of predictive performance by adding these imaging markers to the ECST risk score (C-statistic increase from 0.67 to 0.75; $P = .001$).[46]

An important point is related to the IPH according to the time of occurrence, either as recent/acute (less than a week), intermediate (1-6 weeks), or chronic/old (>6 weeks). The likelihood of cerebrovascular events is at its highest with recent/acute IPH; however, it continues to be increased for >18 months.

MRI is largely considered the most sensitive modality for IPH detection, because its appearance depends on the oxidative state of hemoglobin: in particular, strongly T1-weighted images, with an inversion prepulse to suppress the signal of blood show IPH as a focus of hyperintense signal in the bulk of the plaque[47] (Fig 1). A CT scan is generally considered less sensitive because of a substantial overlap in the Hounsfield unit of fibrous, lipid, and IPH components. US examination is generally considered unsuitable,[48] although recent studies suggest otherwise with experienced operators.[49,50] It is important to remember that, among the different imaging techniques, MRI allows for classification of IPH according to the time of occurrence.

Intraluminal thrombus. Another feature of vulnerability, that is associated with cryptogenic stroke is the presence of carotid intraluminal thrombus, an uncommon condition that was shown to present with neurological symptoms in ≤92% of cases.[51] In a retrospective cross-sectional study, published in 2015 performed on 726 carotid-brain MRI examinations, the strongest predictor of carotid-source stroke was intraluminal thrombus.[52] In another CT angiography-based study of 674 patients, the presence of intraluminal thrombi was highly predictive of the symptomatic side in carotid disease.[53] CT angiography is a sensitive modality, which may demonstrate a filling defect within the lumen surrounded by contrast material[54] (Fig 2). Contrast-enhanced US examination and MRI are also accurate noninvasive imaging modalities to delineate intraluminal thrombus.[54]

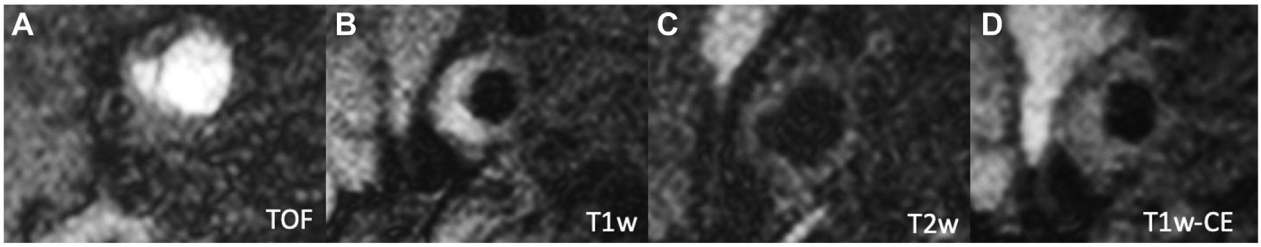

Fig 1. Example of intraplaque hemorrhage (IPH) in the right internal carotid artery of a 67-year-old man with an ipsilateral ischemic stroke. **(A-D)** Nonstenosing carotid atherosclerotic plaque with ulceration within the plaque (white arrow in **A** and **C**) and bright signal in T1-weighted images **(B)** indicative of IPH, in particular, early subacute as highlight in T2-weighted images **(C)**. *TOF*, time of flight.

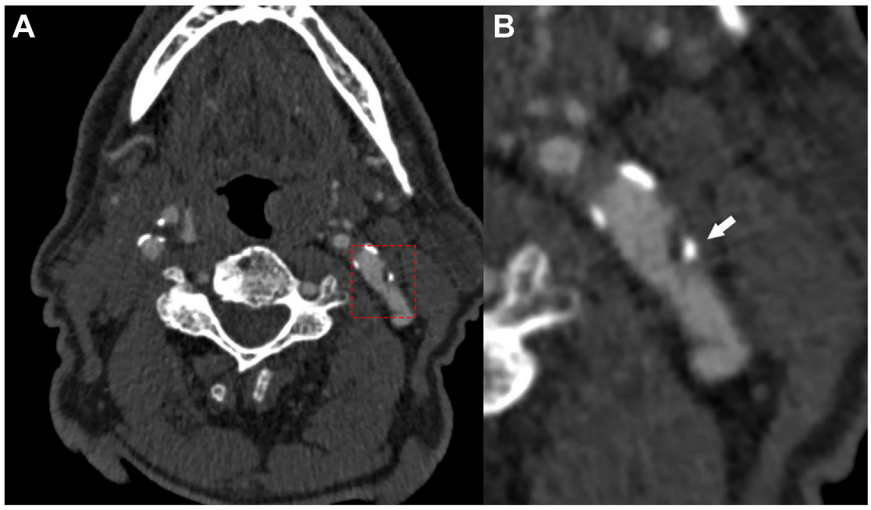

Fig 2. Intraluminal thrombus observed in the left carotid artery of an 82-year-old man with an ipsilateral ischemic stroke. Computed tomography (CT) scan shows an intraluminal filling defect in the left carotid artery indicative of a clot **(A** and **B)**.

Rupture of the fibrous cap. The fibrous cap (FC), a layer of fibrous connective tissue that separates the core of the plaque from the arterial lumen and its disruption, with the resultant exposure of thrombogenic subendothelial plaque constituents, can precipitate thromboembolic complications in the atherosclerotic carotid plaque. Currently, MRI is the most effective noninvasive imaging modalities for investigating the status of the FC.[55] Promising results are emerging with Photon Counting CT scanners in accurately delineating FC thickness.[56-59]

A longitudinal prospective study that investigated 126 patients with symptomatic carotid stenosis using MRI for a mean follow-up of 1 year showed that a lipid-rich necrotic core (LRNC) (HR, 3.2; 95% CI, 1.1-9.5; $P = .036$), a thin and/or ruptured FC (HR, 5.8; 95% CI, 1.9-17.3; $P = .002$), and IPH (HR, 3.5; 95% CI, 1.1-11.9; $P = .040$) were associated with recurrent cerebrovascular events. In addition, the authors reported that the degree of carotid stenosis was not associated with recurrent events (HR, for 50%-69% vs 30%-49% stenosis, 1.2; 95% CI, 0.4-3.7; $P = .756$).[60] Also, a thin and/or ruptured FC is highly associated with a recent history of stroke or TIA: in an MRI-based study, patients with ruptured FC were 23 times more likely to have had a recent stroke or TIA compared with patients with a thick FC.[61] Another prospective longitudinal study published by Sadat et al[62] showed that FC disruption (HR, 7.4; 95% CI, 1.6-33.8; $P = .009$) and IPH (HR, 5.9; 95% CI, 1.3-26.8; $P = .02$) were risk factors for the development of subsequent cerebrovascular events over a median follow-up duration of 514 days.

LRNC. The LRNC is a heterogeneous tissue formed by the death of lipid-laden macrophages, cholesterol crystal, smooth muscle foam cells, and the accumulation of plasma-derived lipids tethered by the intimal extracellular matrix macromolecules. LRNC plays a key role in the progression and vulnerability of atherosclerotic plaques. A meta-analysis of 16 studies published in 2017 showed that patients with CT angiography evidence of low

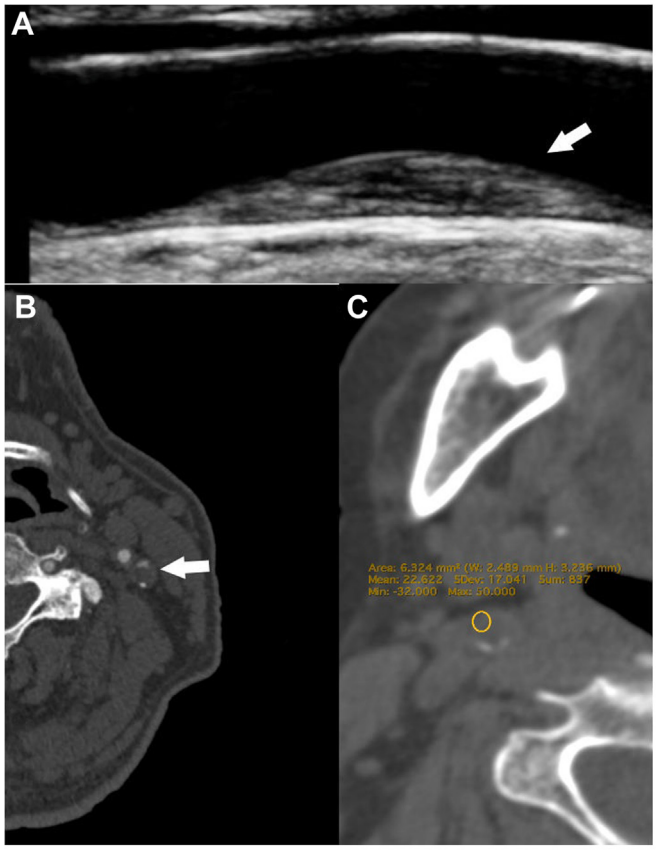

Fig 3. Examples of lipid rich necrotic core using ultrasound (US) examination **(A)** and computed tomography (CT) scan **(B, C)**. **(A)** Nonstenosing carotid plaque with a lipid-rich necrotic core (LRNC) and thick fibrous cap (FC) in the left common carotid artery of a 62-year-old woman with an ipsilateral ischemic stroke. **(B)** Low-attenuation, subocclusive plaque with a mean Hounsfield unit (HU) value of 43 HU in the left internal carotid artery resembling a LRNC, in a symptomatic 82-year-old man. **(C)** Low-attenuation, subocclusive plaque with a mean HU value of 22 HU in the right internal carotid artery of a 72-year-old man with an ipsilateral ischemic stroke. However, owing to the HU overlap between lipid and hemorrhage components, intraplaque hemorrhage (IPH) cannot be excluded.

attenuation plaque had a risk of ipsilateral cerebrovascular events by almost three times higher, regardless of the degree of stenosis.[63] A large LRNC size correlates with future ipsilateral cerebrovascular events as reported in a longitudinal MRI study of 120 asymptomatic patients with carotid plaque. The authors reported that patients with a LRNC of >40% wall area were prone to rupture of the FC in comparison with patients with a LRNC of <40%.[64] A systematic review and meta-analysis published in 2013 showed that LRNC predicted stroke or TIA in asymptomatic subjects (HR, 3.00; 95% CI, 1.46- 22.5; $P = .012$).[65] MRI is considered the most sensitive modality for LRNC evaluation owing to its superior soft tissue contrast. Conversely, CT scans are generally considered less sensitive owing to significant overlap in the Hounsfield unit of IPH and LRNC. Similarly, US examination is regarded less suitable for discriminate between hemorrhage and lipid components[55] (Fig 3).

Plaque morphology. In the years before the advancement of technology that enabled detailed observation of carotid plaque structure, the surface morphology of the plaque was a key parameter of interest. The plaque surface can be characterized as smooth, irregular (where surface variation ranges from 0.3 to 0.9 mm), or ulcerated (a term specifically designated for cavities measuring ≥1 mm). Irregularities in the luminal surface, especially the occurrence of ulceration, are seen as potential stroke risk factors.[66] Evaluations of the surface of carotid plaques can be conducted through a range of imaging methods, but CT scans and MRI seem to provide superior diagnostic accuracy in ulcer detection, significantly outperforming US examination (with a sensitivity rate of >90% for CT, compared with <40% for US examination).[67] The diagnostic accuracy provided by US examination can be enhanced using three-dimensional US examination, improving plaque visualization.[68,69]

Plaque thickness and carotid plaque burden. Another feature of plaque vulnerability is the maximum plaque thickness. In 6584 asymptomatic individuals who participated in the Tromsø Study, maximum plaque thickness was associated with the occurrence of stroke both in males (HR, 1.23, 95% CI 1.10-1.38; $P = .0009$) and females (HR, 1.19, 95% CI 1.01-1.41; $P = .04$).[68] In a prospective longitudinal study of 6102 subjects with asymptomatic carotid stenosis, maximum plaque thickness (HR, 1.96; 95% CI, 0.91-4.25; $P = .015$) was associated with the occurrence of major cardiovascular adverse events.[69] However, the maximum plaque thickness seems to play a role also in patients with cryptogenic stroke: in a study performed on 85 patients with cryptogenic stroke, >3 mm plaque thickness of the noncalcified component was present ipsilateral to stroke in 35% of patients (vs 15% of the contralateral).[70,71] In the Chinese Atherosclerosis Risk Evaluation II Study performed on 1072 subjects, the maximum plaque thickness was more strongly associated with cerebral ischemic symptoms than the degree of stenosis.[72]

Another well-known parameter of plaque vulnerability is the measurement of carotid plaque burden.[73] In the PARISK study, the measurement of carotid plaque volume exhibited independent associations with recurrent ipsilateral cerebrovascular ischemic events (HR, 1.07 per 100 mL increase for plaque volume; 95% CI, 1.00-1.22).[72]

Plaque thickness and carotid plaque burden may be relatively easily assessed with US examination, CT scan, and MRI. In clinical practice, US examination is the preferred initial imaging modality for evaluating carotid plaque thickness owing to its widespread availability and feasibility.[55]

Intraplaque neovascularization. Intraplaque neovascularization is characteristic of advanced atherosclerotic lesions[74-76] and it can be detected with contrast-enhanced US examination, CT scans, and MRI.[77] A study performed in 2012 showed that neovascularization, was associated with cerebrovascular events (OR, 51.7; 95% CI, 3.40-469.80; $P = .004$)[78] and another prospective study performed on 155 symptomatic patients showed that intraplaque neovascularization is associated with recurrent cerebrovascular events (HR, 4.5, 95 % CI 1.9-10.90; $P = .001$), independent of the severity of carotid stenosis (HR, 3.5, 95 % CI 1.4-8.6; $P = .007$).[79] This feature seems to be promising, but further studies are necessary to confirm and adopt it because current routine clinical practice has not adopted noninvasive imaging assessment of plaque inflammation and neovascularization.

Specific type of calcium configuration. Although there is ongoing debate about the function of calcium in atherosclerosis, it is broadly accepted that factors like the size, shape, and location of calcifications can influence the progression of plaque formation and some recent papers have showed that, in some cases, these factors are associated with plaque vulnerability and subsequent risk of stroke.[80] In particular, it seems that some calcification patterns correlate with a greater degree of plaque instability. In particular, the positive rim sign strongly associates with plaque inflammation, leakage of the vasa vasorum and IPH formation. A prospective cohort study of 329 patients from the population-based Rotterdam Study with asymptomatic carotid plaque reported that a higher calcification load was associated with the presence of IPH (OR, 2.65; 95% CI, 1.94-3.64).[81] In particular the positive rim sign (defined as the presence of thin, <2-mm-thick, adventitial calcifications) seems to be associated with the presence of IPH.[82,83] Recently, Saba et al showed that a positive rim sign had a higher prevalence of cerebrovascular events in comparison to other types of carotid calcifications.[84] CT scan is regarded as the reference standard for detecting calcification within plaques (Fig 4). However, it is worth noting that plaque calcification can also be identified with US examination, where it appears as a hyperechogenic area, and MRI, where it presents as a hypointense region on all contrast sequences. Nonetheless, it is important to acknowledge that the sensitivity and specificity of US examination and MRI for detecting calcification are generally lower compared with CT scans.[55] Table II summarizes imaging features associated with the occurrence of cerebrovascular events and their preferred noninvasive imaging modalities.

Carotid web. Carotid webs were first described in 1973 in a study of catheter angiograms at the Massachusetts General Hospital[85] and in mor recent years these have been considered an underappreciated risk factor for stroke. Carotid web identifies a shelf-shaped filling defect arising from the posterolateral wall of the carotid bulb,[86] because its protrusion into the lumen of the carotid artery, it can altered blood flow and lead to blood stasis, resulting in thrombus formation and subsequent ischemic stroke[87](Fig 5). Carotid web represents between 9.4% and 37.0% of ischemic strokes that were initially misclassified as cryptogenic.[88-91] This condition seems to be more frequently associated to younger female subjects: among the cases with webs in the study of Coutinho et al,[90] 80% of patients were women, and the age range was 34 to 57 years. In another paper by Zelada-Rios et al,[93] the prevalence of female patients was 60% with an age range from 37 to 43 years.

FUTURE DIRECTIONS

Artificial intelligence in cryptogenic stroke. The field of artificial intelligence (AI) in cardiovascular imaging has experienced substantial expansion in recent years and offers exciting prospects for revolutionizing clinical practice.[92,93] AI, with its subset, namely, machine learning and deep learning, has the potential not only to help in assessing carotid plaques with their features of vulnerability, but also in the early detection of the mechanisms underlying acute ischemic stroke.[94] Buckler et al[95] developed an AI-based model for the classification of atherosclerotic plaque vulnerability on CT images using histological specimens as a ground truth. The overall cohort enrolled consisted of 53 patients with carotid atherosclerosis randomly assigned to the derivation cohort (n = 30) and to the validation cohort (n = 23). The proposed convolutional neural network model demonstrated strong agreement with pathological classification (kappa, 0.82) and high accuracy for identification of unstable plaque, stable plaque, and minimal disease according to the modified American Heart Association histological definition (area under the curve, 0.97, 0.95, and 0.99, respectively).[95-97] Kamel et al[98] developed a machine-learning algorithm, using data from the Cornell Acute Stroke Academic Registry, to discriminate between cardioembolic and noncardioembolic ESUS determining the proportion of patient with an occult cardioembolic source. The AI-based model proposed was trained with demographic, clinical, echocardiographic, and laboratory data and achieved excellent accuracy in distinguish cardioembolic from noncardioembolic cases (area under the curve, 0.85). Then, the authors applied the final model to an independent set of 580 ESUS cases, reporting that 44% (95% credibility interval, 39%-49%) resulted from cardiac embolism and the predicted probability of occult cardiac embolism was associated with the diagnosis of atrial fibrillation (OR, per 10% increase, 1.27 [95% CI, 1.03-1.57]; c-statistic, 0.68 [95% CI, 0.58-0.78]).[98] In

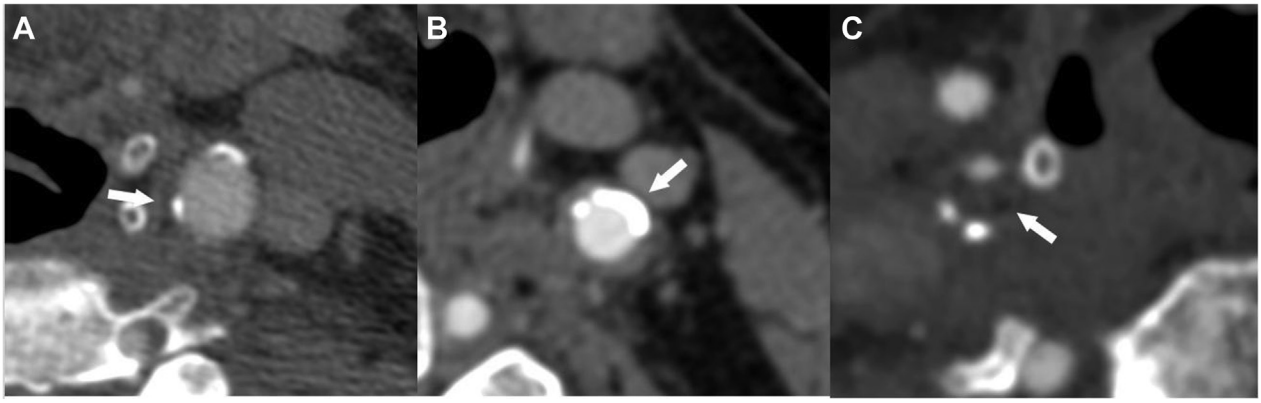

Fig 4. Examples of different types of carotid calcifications as demonstrated on computed tomography (CT) scan. **(A)** Carotid plaque with superficial calcifications (white arrow). **(B)** Carotid plaque with bulky calcification (white arrow). **(C)** Carotid plaque with positive rim sign (white arrow).

Table II. Overview of imaging features associated with the occurrence of cerebrovascular events and their preferred noninvasive imaging modalities

Carotid imaging features	Noninvasive imaging of choice	Key imaging characteristics
IPH	MRI	Hyperintense region area within the plaque, with or without association to the carotid lumen on T1-weighted and TOF sequences. T2w sequence allows to further characterize IPH as early subacute (iso-/hypointense) and late subacute (hyperintense)
Intraluminal thrombus	CT	Intraluminal filling defect surrounded by the contrast agent.
Rupture of FC	MRI	Disrupted hypointense band on T1-weighted contrast-enhanced imaging with an irregular luminal surface on all images
Lipid rich necrotic core	MRI	Hypointense region on T2-weighted sequences without enhancing region in the bulk of the plaque on T1-weighted contrast-enhanced imaging.
Carotid web	CT	Shelf-shaped, linear, thin filling defect located along the posterolateral wall of the carotid bulb
Plaque ulcerations	CT	Contrast material that extends from the vascular lumen into the plaque, typically covering a distance of ≥1 mm
Plaque thickness	US, CT, MRI	All imaging modalities suitable. US represents first-line imaging modality owing to its availability and feasibility
Intraplaque neovascularization	Routine clinical practice has not yet adopted noninvasive imaging assessment of plaque neovascularization	Contrast-enhanced US represent the most validate noninvasive imaging modalities, showing intraplaque neovascularization as the presence of microbubbles within the plaque.
Calcifications	CT	High-attenuation plaque, usually >130 HU

CT, Computed tomography; *FC*, fibrous cap; *HU*, Hounsfield unit; *IPH*, intraplaque hemorrhage; *MRI*, magnetic resonance imaging; *US*, ultrasound.

addition, AI can merge a large amount of imaging data with clinical characteristics and demographic data, representing a new horizon in ischemic stroke assessment.[98-100]

The introduction of a novel stroke risk classification system: The Plaque-RADS. Given the ever-growing number of publications emphasizing the significance of atherosclerotic plaque composition and morphology in

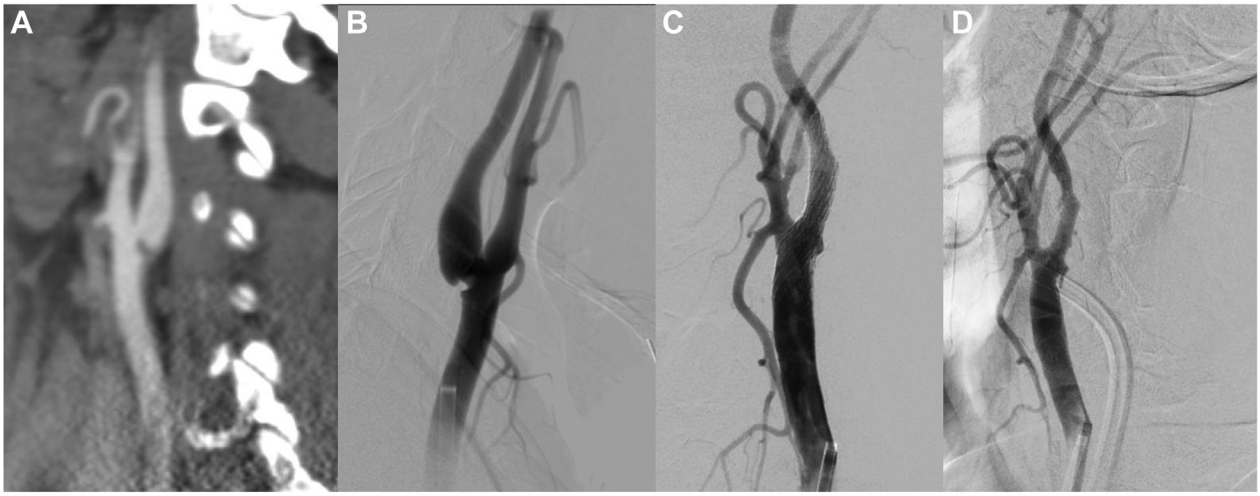

Fig 5. Example of a carotid web on computed tomography (CT) scan and digital subtraction angiography before and after stent placement. **(A)** Right internal carotid web near the bifurcation on CT scan coronal views. **(B)** Carotid web at the bifurcation with a filling defect and turbulent flow on the anteroposterior digital subtraction angiography view. **(C** and **D)** Right carotid artery after stent placement in anteroposterior **(C)** and lateral **(D)** views.

determining stroke risk,[33,99] the implementation of a standardized, universal, and cross-modality reporting system undeniably benefits clinical practice.

Recently, the Plaque Reporting and Data System (Plaque-RADS) classification has been introduced with the aim of establishing a consistent lexicon and structured reporting system for carotid atherosclerosis diseases, enhancing communication between radiologists, referring clinicians, and researchers by providing a transparent and reproducible method for personalized patient risk stratification.[100-102] The Plaque-RADS provides a morphological and compositional plaque assessment additionally to the currently sole quantitative descriptor "stenosis, ranging from Plaque-RADS 1 (indicating the complete absence of carotid plaque) to Plaque-RADS 4 (indicating complicated plaque with features such as IPH, a ruptured FC, and/or thrombus).[100-102]

The application of a scoring system that take into account plaque morphology and composition, in addition to the degree of carotid stenosis, may offer a deeper understanding of ischemic stroke etiologies. Furthermore, it has the potential to reclassify certain cryptogenic strokes based on imaging features related plaque vulnerability. Future multicenter trials are necessary to assess the utility of the Plaque-RADS score in cases of cryptogenic stroke and its ability to reclassify stroke etiologies.

CONCLUSIONS

The pathophysiology of cryptogenic stroke is of increased importance as different therapeutic strategies are available. Nonstenosing carotid artery plaques with vulnerability features are an increasingly widely recognized component of cerebrovascular risk. Advanced imaging techniques could significantly enhance the diagnosis of cryptogenic stroke. Further studies are needed to corroborate these findings and recommends the incorporation of such cutting-edge imaging methodologies into routine diagnostic protocols to enhance stroke management and prevention.

AUTHOR CONTRIBUTIONS

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Writing the article: LS, RC, GS, GR
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DISCLOSURES

None.

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