Journal Pre-proof

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PII: S0741-5214(24)00019-3

DOI: https://doi.org/10.1016/j.jvs.2024.01.004

Reference: YMVA 13438

To appear in: *Journal of Vascular Surgery*

Received Date: 13 December 2023

Revised Date: 30 December 2023

Accepted Date: 4 January 2024

Please cite this article as: Saba L, Cau R, Spinato G, Suri JS, Melis M, De Rubeis G, Antignani P, Gupta A, Carotid Stenosis and Cryptogenic Stroke: The Evidence from the Imaging-based Studies Carotid stenosis and Cryptogenic Stroke *Journal of Vascular Surgery* (2024), doi: https://doi.org/10.1016/j.jvs.2024.01.004.

Carotid Stenosis and Cryptogenic Stroke: The Evidence from the Imaging-based Studies

Carotid stenosis and Cryptogenic Stroke

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COI: The authors have no competing interests

Funding: This research received no external funding.

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 10172 in Acute Stroke Treatment (TOAST) criteria, a stroke is categorized as being caused by large artery atherosclerosis only when there is more than 50% luminal narrowing of the ipsilateral internal carotid artery. However, non-stenosing 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 non-stenosing 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 manuscripts 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 including Magnetic Resonance (MR), Computed Tomography (CT) and Ultrasound (US), facilitate more accurate detection of non-stenosing carotid artery plaque, allow to better stratify stroke risk leading to more tailored treatment strategy.

Conclusion: Early detection of non-stenosing 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.

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KEYWORDS: Cryptogenic stroke; Carotid imaging; CT; MRI; plaque vulnerability.

ABBREVIATIONS

CE: Contrast-enhancement

CEUS: Contrast Enhanced Ultrasound

CT: Computed Tomography

CTA: Computed Tomography Angiography

DCE-MRI: Dynamic Contrast Enhancement Magnetic Resonance Imaging

DECT: Dual Energy Computed Tomography

DSA: Digital Subtraction Angiography

DWI: Diffusion Weighted Imaging

FC: Fibrous Cap

IPH: Intra-plaque Haemorrhage

IPN: Intra-plaque Neovascularization

LRNC: Lipid-rich Necrotic Core

MRA: Magnetic Resonance Angiography

MR: Magnetic Resonance

MPT: Maximum Plaque Thickness

NASCET: North American Symptomatic Carotid Endarterectomy Trial

NM: Nuclear Medicine

PET: Positron Emission Tomography

TIA: Transient Ischemic Attack

US: Ultrasound

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

1.Introduction

Acute ischemic stroke poses a significant global burden, leading to substantial morbidity and mortality[1]. It contributes to about 5% of the world's disability-adjusted life years and is responsible for over 10% of global deaths[2]. In Europe and the USA, 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].

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 fully capture the underlying pathophysiology associated with cryptogenic stroke and the potential risk of embolic events.

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

2.Definitions and workup

Definitions

Ischemic stroke is an acute neurologic 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 due to congenital heart disease (e.g., patent foramen ovale), and acquired heart diseases (e.g., cardiomyopathy, endocarditis, atrial cardiopathy, valve disease); (2) vascular diseases (e.g., vasculitis, arterial dissection, non-stenosing carotid plaque, aortic arch atheroma); (3) thrombophilia; (4) occult malignancy[10].

Embolic Stroke of Undetermined Source (ESUS) represents a subtype of cryptogenic stroke. The term 'ESUS' is employed 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, while 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 due to etiologies other than embolism, such as unrecognized small vessel disease or even non-vascular causes. ESUS is not synonymous with

cryptogenic stroke, as cryptogenic stroke also includes patients with multiple potential etiologies, e.g., patients with atrial fibrillation and significant atherosclerotic plaque ipsilateral to the infarct, as well as patients with incomplete diagnostic work-up.

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 work-up

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 non-atherosclerotic 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 system

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% or more[16,17]. However, this

definition is arguably outdated as it is based on data and studies conducted over 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 between the 1980s and 1990s demonstrating the benefit of CEA in patients with moderate to severe stenosis (70% to 99%), namely: the European Carotid Surgery Trial (ECST), the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial (ACST-1)[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 (less than 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 (ESC) 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 re-shaping and re-discussing the types of cryptogenic stroke. In a recent paper by Kamel et al [26] was demonstrated that the inclusion of vulnerable plaques could reclassify the etiologies of up to 15% of cases. In addition, defining LAA stroke solely based on a 50% percent 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 (SPARKLE)[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].

3. 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,. In this study, the prevalence of carotid stenosis < 50% with high-risk features in the ipsilateral carotid was 32.5% (95% CI, 25.3-40.2) compared to 4.6% (95% CI, 0.1-13.1) in the contralateral carotid. The odds ratio of finding a plaque with high-risk features in the ipsilateral versus 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 to patients with cardioembolic or small vessel strokes.

Other publications have emphasized the association of non-stenosing carotid artery plaques in an unrecognized percentage of cryptogenic strokes[31,32]. For instance, a study conducted by Kopczak et al. 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% versus 12%, P = 0.0005). Complicated carotid artery plaques had a higher prevalence in cryptogenic stroke compared to cardioembolic/small vessel stroke (31% versus 15%, P = 0.02)[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 to cryptogenic stroke patients without a complicated plaque at presentation (HR5.6; 95%CI 1.43-21.83) with an incidence rate of TIA/stroke [3-year interval] of 10.92 vs 1.82 per 100 patient-years (P = 0.003)[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 1 summarized previous studies regarding non-invasive imaging features and attributable risk for symptom development.

3.1 The role of carotid artery imaging

Contemporary imaging modalities, including ultrasound, CT, and 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 neurologic 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 ultrasound 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 ultrasound can outline some sonomorphological characteristics associated with plaque vulnerability[37], including a large juxtaluminal hypoechogenic area[38], heterogeneous echotexture[39,40], and plaque echogenicity[41]. In addition, transcranial Doppler ultrasound 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 ultrasound is an independent predictors of future stroke risk[44].

Although carotid ultrasound is widely available, cost-effective, and radiation-free, CT 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.

3.2 Intra-plaque Hemorrhage

Intra-plaque 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=0.04)[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 cohort involving 560 patients with symptomatic carotid stenosis and 136 asymptomatic carotid stenosis patients 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 less than 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, US, MRI and CT, 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 European Carotid Surgery Trial (ECST) risk score (C-statistic increase from 0.67 to 0.75, P = 0.001)[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 (more than 6 weeks). The

likelihood of cerebrovascular events is at its highest with recent/acute IPH, however, it continues to be raised for over 18 months.

MRI is largely considered the most sensitive modality for IPH detection, since its appearance depends on the oxidative state of hemoglobin: in particular, strongly T1-weighted images with an inversion pre-pulse to suppress the signal of blood show IPH as a focus of hyperintense signal in the bulk of the plaque[47] **(Figure 1)**. CT is generally considered less sensitive because of a substantial overlap in the HU of fibrous, lipid and IPH components. US 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.

3.3 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 neurologic symptoms in up to 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 on 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] **(Figure 2)**. Contrast enhanced US and MRI are also accurate non-invasive imaging modalities to delineate intraluminal thrombus[54].

3.4 Rupture of 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 non-invasive 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 one year, showed that LRNC (HR 3.2, 95%CI 1.1-9.5, P=0.036), a thin and/or ruptured FC (HR 5.8, 95%CI 1.9-17.3, P=0.002), and IPH (HR 3.5, 95%CI 1.1-11.9, P=0.040) 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% versus 30–49% stenosis, 1.2, 95%CI 0.4-3.7, P=0.756)[60].

Also, a thin and /or ruptured fibrous cap is highly associated with a recent history of stroke or transient ischemic attack (TIA): in an MRI-based study, patients with ruptured fibrous cap were 23 times more likely to have had a recent stroke/TIA compared with patients with thick fibrous cap[61].

Another prospective longitudinal study published by Sadat et al. showed that FC disruption (HR 7.4, 95%CI 1.6-33.8, P=0.009) and IPH (HR 5.9, 95%CI 1.3-26.8, P=0.02) were risk factors for the development of subsequent cerebrovascular events during a median follow-up duration of 514 days[62].

3.5 Lipid Rich Necrotic Core

The lipid-rich necrotic core (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 CTA evidence of low attenuation plaque had a risk of ipsilateral cerebrovascular events by almost 3 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 greater than 40% wall area were prone to rupture of the FC in comparison with patients with a LRNC less than 40%[64]. A systematic review and meta-analysis published in 2013 showed that LRNC predicted stroke/TIA in asymptomatic subjects (HR 3.00, 95%CI 1.46- 22.5, P=0.012)[65]. MRI is considered the most sensitive modalities for LRNC evaluation due to its superior soft tissue contrast. Conversely, CT is generally considered less sensitive due to significant overlap in the Hounsfield unit of IPH and LRNC. Similarly, US is regarded less suitable for discriminate between hemorrhage and lipid components[55].**Figure 3**.

3.6 Plaque Morphology

In the years prior to 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 mm to 0.9 mm), or ulcerated (a term specifically designated for cavities measuring at least 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 and MRI appear to provide superior diagnostic accuracy in ulcer detection, significantly outperforming US (with a sensitivity rate exceeding 90% for CT, compared to less than 40% for US)[67]. The diagnostic accuracy provided by US can be enhanced using three-dimensional US improving plaque visualization[68,69].

3.7 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=0.0009) and females (HR 1.19,

95% CI 1.01-1.41, P=0.04) [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=0.015) was associated with the occurrence of major cardiovascular adverse events[69]. But 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 non-calcified component was present ipsilateral to stroke in 35% of patients (versus 15% of the contralateral)[70]. In the Chinese Atherosclerosis Risk Evaluation II Study performed on 1072 subjects, the MPT was more strongly associated with cerebral ischemic symptoms than the degree of stenosis[73].

Another well-known parameter of plaque vulnerability is the measurement of carotid plaque burden[72]. 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)[73].

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

3.8 Intraplaque neovascularization

Intraplaque neovascularization is characteristic of advanced atherosclerotic lesions[74–76] and it can be detected with contrast enhanced US, CT 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=0.004)[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=0.001) independent of the severity of carotid stenosis (HR 3.5, 95 % CI 1.4-8.6, P=0.007)[79]. This feature seems to be promising but further studies are necessary to confirm and adopt

it because currently the routine clinical practice has not adopted non-invasive imaging assessment of plaque inflammation and neovascularization.

3.9 Specific type of calcium configuration

While there's ongoing debate about the function of calcium in atherosclerosis, it's 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 are associated with the plaque vulnerability and sub-sequent risk of stroke[80]. In particular, it appears that some calcification patterns correlate with a higher 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 is regarded as the reference standard for detecting calcification within plaques **(Figure 4)**. However, it's worth noting that plaque calcification can also be identified with US, where it appears as a hyperechogenic area, and MRI, where it presents as a hypointense region on all contrast sequences. Nonetheless, it's important to acknowledge that the sensitivity and specificity of US and MRI for detecting calcification are generally lower compared to CT[55].

Table 2 summarized imaging features associated with the occurrence of cerebrovascular events and their preferred non-invasive imaging modalities.

3.10 Carotid Web

Carotid webs were first described in 1973 in a study of catheter angiograms at the Massachusetts General Hospital[85] and in the last 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].**Figure 5**. Carotid web represents between 9.4% and 37% of ischemic strokes that were initially misclassified as cryptogenic[88–90].

This condition seems to be more frequently associated to younger female subjects: Among the cases with webs in the study of Coutinho, 80% of patients were women, and the age range was 34 to 57 years[90]. In another paper by Zelada-Rios the prevalence of female patients was 60% with an age range from 37 to 43[91].

4. Future direction

4.1 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 developed an AI-based model for the classification of atherosclerotic plaque vulnerability on CT images using histological specimens as a ground truth[95]. 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 AHA histological definition (AUC of 0.97, 0.95, and 0.99,

respectively)[95]. Kamel et al. developed a machine-learning algorithm, using data from the Cornell Acute Stroke Academic Registry, to discriminate between cardioembolic and non-cardioembolic ESUS determining the proportion of patient with an occult cardioembolic source[98]. The AI-based model proposed was trained with demographic, clinical, echocardiographic, and laboratory data and achieved excellent accuracy in distinguish cardioembolic from non-cardioembolic cases (AUC of 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 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].

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

Recently, the Plaque-RADS (Reporting and Data System) 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].

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 intraplaque hemorrhage, a ruptured fibrous cap, and/or thrombus)[100].

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.

5. Conclusion

The pathophysiology of cryptogenic stroke is of increased importance as different therapeutic strategies are available. Non-stenosing 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.

References

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70(1):1-25. doi:10.1016/j.jacc.2017.04.052
2. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135(10):e146-e603. doi:10.1161/CIR.0000000000000485
3. GBD 2016 Neurology Collaborators Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. Published online 2019:459-480. doi:10.1016/S1474-4422(18)30499-X
4. Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL et al Demographic and Epidemiologic Drivers of Global Cardiovascular Mortality. *N Engl J Med*. 2015;372(14):1333-1341. doi:10.1056/NEJMoa1406656
5. Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. *Circ Res*. 2017;120(3):439-448. doi:10.1161/CIRCRESAHA.116.308413
6. Yaghi S, Bernstein RA, Passman R, Okin PM, Furie KL. Cryptogenic Stroke: Research and Practice. *Circ Res*. 2017;120(3):527-540. doi:10.1161/CIRCRESAHA.116.308447
7. Wardlaw J, Chappell F, Best J, Wartolowska K, Berry E. Non-invasive imaging compared with intra-arterial angiography in the diagnosis of symptomatic carotid stenosis: a meta-analysis. *Lancet*. 2006;367(9521):1503-1512. doi:10.1016/S0140-6736(06)68650-9

8. Saba L, Saam T, Jäger HR, Yuan C, Hatsukami TS, Saloner D, et al. Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications. *Lancet Neurol*. 2019;4422(19):1-14. doi:10.1016/S1474-4422(19)30035-3
9. Saver JL. Cryptogenic Stroke. *N Engl J Med*. 2016;374(21):2065-2074. doi:10.1056/NEJMcp1503946
10. Mac Grory B, Flood SP, Apostolidou E, Yaghi S. Cryptogenic Stroke: Diagnostic Workup and Management. *Curr Treat Options Cardiovasc Med*. 2019;21(11):77. doi:10.1007/s11936-019-0786-4
11. Siegler JE. The Attributable Risk of Nonstenotic Cervical Carotid Plaque in Cryptogenic Embolic Stroke. *Stroke Vasc Interv Neurol*. 2023;3(4):e000727. doi:10.1161/SVIN.122.000727
12. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J. et al. Atrial Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370(26):2467-2477. doi:10.1056/NEJMoa1311376
13. Wachter R, Gröschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, et al. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF(RANDOMISED)): an open-label randomised controlled trial. *Lancet Neurol*. 2017;16(4):282-290. doi:10.1016/S1474-4422(17)30002-9
14. Saric M, Armour AC, Arnaout MS, Chaudhry FA, Grimm RA, Kronzon I, et al. Guidelines for the Use of Echocardiography in the Evaluation of a Cardiac Source of Embolism. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2016;29(1):1-42. doi:10.1016/j.echo.2015.09.011
15. Arachchillage DJ, Mackillop L, Chandratheva A, Motawani J, MacCallum P, Laffan M. Thrombophilia testing: A British Society for Haematology guideline. *Br J Haematol*. 2022;198(3):443-458. doi:10.1111/bjh.18239
16. Love BB, Bendixen BH. Classification of subtype of acute ischemic stroke definitions for use in a multicenter clinical trial. *Stroke*. 1993;24(1):35-41. doi:10.1161/01.STR.24.1.35
17. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (Updated ASCO Phenotyping). *Cerebrovasc Dis*. 2013;36(1):1-5. doi:10.1159/000352050
18. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke*. 1991;22(6):711-720. doi:10.1161/01.STR.22.6.711
19. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet (London, England)*. 1998;351(9113):1379-1387.
20. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA*. 1995;273(18):1421-1428.
21. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet (London, England)*. 2010;376(9746):1074-1084. doi:10.1016/S0140-6736(10)61197-X
22. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal,. *Eur Heart J*. 2018;39(9):763-816. doi:10.1093/eurheartj/ehx095
23. Johri AM, Nambi V, Naqvi TZ, Feinstein SB, Kim ESH, Park MM, et al. Recommendations for the Assessment of Carotid Arterial Plaque by Ultrasound for the Characterization of Atherosclerosis and Evaluation of Cardiovascular Risk: From the American Society of Echocardiography. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. 2020;33(8):917-933. doi:10.1016/j.echo.2020.04.021

24. Naylor R, Rantner B, Ancetti S, de Borst GJ, De Carlo M, Halliday A,et al. European society for vascular surgery (ESVS) 2023 Clinical practice guidelines on the management of atherosclerotic carotid and vertebral artery disease. *Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg*. Published online May 2022. doi:10.1016/j.ejvs.2022.04.011
25. Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, et al. Editor's Choice - Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg*. 2018;55(1):3-81. doi:10.1016/j.ejvs.2017.06.021
26. Kamel H, Navi BB, Merkler AE, Baradaran H, Díaz I, Parikh NS, et al. Reclassification of Ischemic Stroke Etiological Subtypes on the Basis of High-Risk Nonstenosing Carotid Plaque. *Stroke*. 2020;51(2):504-510. doi:10.1161/STROKEAHA.119.027970
27. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987;316(22):1371-1375. doi:10.1056/NEJM198705283162204
28. Bogiatzi C, Wannarong T, McLeod AI, Heisel M, Hackam D, Spence JD. SPARKLE (Subtypes of Ischaemic Stroke Classification System), incorporating measurement of carotid plaque burden: a new validated tool for the classification of ischemic stroke subtypes. *Neuroepidemiology*. 2014;42(4):243-251. doi:10.1159/000362417
29. Zhang H, Li Z, Dai Y, Guo E, Zhang C, Wang Y. Ischaemic stroke etiological classification system: the agreement analysis of CISS, SPARKLE and TOAST. *Stroke Vasc Neurol*. 2019;4(3):123-128. doi:10.1136/svn-2018-000226
30. Kamtchum-Tatuene J, Wilman A, Saqqur M, Shuaib A, Jickling GC. Carotid Plaque With High-Risk Features in Embolic Stroke of Undetermined Source. *Stroke*. 2020;51(1):311-314. doi:10.1161/STROKEAHA.119.027272
31. Freilinger TM, Schindler A, Schmidt C, Grimm J, Cyran C, Schwarz F, et al. Prevalence of nonstenosing, complicated atherosclerotic plaques in cryptogenic stroke. *JACC Cardiovasc Imaging*. 2012;5(4):397-405. doi:10.1016/j.jcmg.2012.01.012
32. Saam T, Hetterich H, Hoffmann V, Yuan C, Dichgans M, Poppert H,et al. Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging. *J Am Coll Cardiol*. 2013;62(12):1081-1091. doi:10.1016/j.jacc.2013.06.015
33. Kopczak A, Schindler A, Bayer-Karpinska A, Koch ML, Sepp D, Zeller J, et al. Complicated Carotid Artery Plaques as a Cause of Cryptogenic Stroke. *J Am Coll Cardiol*. 2020;76(19):2212-2222. doi:10.1016/j.jacc.2020.09.532
34. Kopczak A, Schindler A, Sepp D, Bayer-Karpinska A, Malik R, Koch ML et al. Complicated Carotid Artery Plaques and Risk of Recurrent Ischemic Stroke or TIA. *J Am Coll Cardiol*. 2022;79(22):2189-2199. doi:10.1016/j.jacc.2022.03.376
35. Cademartiri F, Balestrieri A, Cau R, Punzo B, Cavaliere C, Maffei E, et al. Insight from imaging on plaque vulnerability: similarities and differences between coronary and carotid arteries—implications for systemic therapies. *Cardiovasc Diagn Ther*. 2020;10(4):1150-1162. doi:10.21037/cdt-20-528
36. Saba L, Antignani PL, Gupta A, Cau R, Paraskevas KI, Poredos P, et al. International Union of Angiology (IUA) consensus paper on imaging strategies in atherosclerotic carotid artery imaging: From basic strategies to advanced approaches. *Atherosclerosis*. 2022;354:23-40. doi:https://doi.org/10.1016/j.atherosclerosis.2022.06.1014
37. Spanos K, Tzorbatzoglou I, Lazari P, Maras D, Giannoukas AD. Carotid artery plaque echomorphology and its association with histopathologic characteristics. *J Vasc Surg*. 2018;68(6):1772-1780. doi:10.1016/j.jvs.2018.01.068
38. Salem MK, Bown MJ, Sayers RD, West K, Moore D, Nicolaides A, et al. Identification of patients with a histologically unstable carotid plaque using ultrasonic plaque image analysis. *Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg*. 2014;48(2):118-125.

doi:10.1016/j.ejvs.2014.05.015
39. Brinjikji W, Rabinstein AA, Lanzino G, Murad MH, Williamson EE, DeMarco JK, et al. Ultrasound Characteristics of Symptomatic Carotid Plaques: A Systematic Review and Meta-Analysis. *Cerebrovasc Dis*. 2015;40(3-4):165-174. doi:10.1159/000437339
40. van Engelen A, Wannarong T, Parraga G, Niessen WJ, Fenster A, Spence JD, et al. Three-dimensional carotid ultrasound plaque texture predicts vascular events. *Stroke*. 2014;45(9):2695-2701. doi:10.1161/STROKEAHA.114.005752
41. Jashari F, Ibrahimi P, Bajraktari G, Grönlund C, Wester P, Henein MY. Carotid plaque echogenicity predicts cerebrovascular symptoms: a systematic review and meta-analysis. *Eur J Neurol*. 2016;23(7):1241-1247. doi:10.1111/ene.13017
42. Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. *Lancet Neurol*. 2010;9(7):663-671. doi:10.1016/S1474-4422(10)70120-4
43. Spence JD, Tamayo A, Lownie SP, Ng WP, Ferguson GG. Absence of microemboli on transcranial Doppler identifies low-risk patients with asymptomatic carotid stenosis. *Stroke*. 2005;36(11):2373-2378. doi:10.1161/01.STR.0000185922.49809.46
44. Markus HS, MacKinnon A. Asymptomatic embolization detected by Doppler ultrasound predicts stroke risk in symptomatic carotid artery stenosis. *Stroke*. 2005;36(5):971-975.
45. Kurosaki Y, Yoshida K, Fukuda H, Handa A, Chin M, Yamagata S. Asymptomatic Carotid T1-High-Intense Plaque as a Risk Factor for a Subsequent Cerebrovascular Ischemic Event. *Cerebrovasc Dis*. 2017;43(5-6):250-256. doi:10.1159/000455973
46. van Dam-Nolen DHK, Truijman MTB, van der Kolk AG, Liem MI, Schreuder FHBM, Boersma E,et al. Carotid Plaque Characteristics Predict Recurrent Ischemic Stroke and TIA. *JACC Cardiovasc Imaging*. 2022;0(0). doi:10.1016/j.jcmg.2022.04.003
47. McNally JS, Kim SE, Mendes J, Hadley JR, Sakata A, De Havenon AH, et al. Magnetic Resonance Imaging Detection of Intraplaque Hemorrhage. *Magn Reson Insights*. 2017;10:1-8. doi:10.1177/1178623X17694150
48. Mura M, Della Schiava N, Long A, Chirico EN, Pialoux V, Millon A. Carotid intraplaque haemorrhage: pathogenesis, histological classification, imaging methods and clinical value. *Ann Transl Med*. 2020;8(19):1273. doi:10.21037/atm-20-1974
49. Nicolaides AN, Kakkos SK, Kyriacou E, Griffin M, Sabetai M, Thomas DJ, et al. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *J Vasc Surg*. 2010;52(6):1485-1486. doi:10.1016/j.jvs.2010.07.021
50. Kakkos SK, Griffin MB, Nicolaides AN, Kyriacou E, Sabetai MM, Tegos T,et al. The size of juxtaluminal hypoechoic area in ultrasound images of asymptomatic carotid plaques predicts the occurrence of stroke. *J Vasc Surg*. 2013;57(3):608-609. doi:10.1016/j.jvs.2012.09.045
51. Bhatti AF, Leon LR Jr, Labropoulos N, Rubinas TL, Rodriguez H, Kalman PG, et al. Free-floating thrombus of the carotid artery: literature review and case reports. *J Vasc Surg*. 2007;45(1):199-205. doi:10.1016/j.jvs.2006.09.057
52. McNally JS, McLaughlin MS, Hinckley PJ, Treiman SM, Stoddard GJ, Parker DL, et al. Intraluminal thrombus, intraplaque hemorrhage, plaque thickness, and current smoking optimally predict carotid stroke. *Stroke*. 2015;46(1):84-90. doi:10.1161/STROKEAHA.114.006286
53. Eesa M, Hill MD, Al-Khathaami A, Al-Zawahmah M, Sharma P, Menon BK, et al. Role of CT Angiographic Plaque Morphologic Characteristics in Addition to Stenosis in Predicting the Symptomatic Side in Carotid Artery Disease. *Am J Neuroradiol*. 2010;31(7):1254 LP - 1260. doi:10.3174/ajnr.A2078
54. Menon BK, Singh J, Al-Khataami A, Demchuk AM, Goyal M. The donut sign on CT angiography: an indicator of reversible intraluminal carotid thrombus? *Neuroradiology*. 2010;52(11):1055-1056. doi:10.1007/s00234-010-0738-x

55. Cau R, Gupta A, Kooi ME, Saba L. Pearls and Pitfalls of Carotid Artery Imaging: Ultrasound, Computed Tomography Angiography, and MR Imaging. *Radiol Clin North Am*. 2023;61(3):405-413. doi:10.1016/j.rcl.2023.01.001
56. Dahal S, Raja AY, Searle E, Colgan FE, Crighton JS, Roake J, et al. Components of carotid atherosclerotic plaque in spectral photon-counting CT with histopathologic comparison. *Eur Radiol*. Published online 2022. doi:10.1007/s00330-022-09155-x
57. Cademartiri F, Meloni A, Pistoia L, Degiorgi G, Clemente A, De Gori C, et al Dual Source Photon-Counting Computed Tomography — Part II : Clinical Overview of Neurovascular Applications. Published online 2023.
58. Cademartiri F, Meloni A, Pistoia L, Degiorgi G, Clemente A, Gori C, et al. Dual-Source Photon-Counting Computed Tomography — Part I : Clinical Overview of Cardiac CT and Coronary CT Angiography Applications. Published online 2023.
59. Meloni A, Cademartiri F, Pistoia L, Degiorgi G, Clemente A, De Gori C, et al. Dual-Source Photon-Counting Computed Tomography — Part III : Clinical Overview of Vascular Applications beyond Cardiac and Neuro Imaging. Published online 2023.
60. Kwee RM, van Oostenbrugge RJ, Hofstra L, Teule GJ, van Engelshoven JM, Mess WH, et al. MRI of carotid atherosclerosis to identify TIA and stroke patients who are at risk of a recurrence. *J Magn Reson Imaging*. 2013;37(5):1189-1194. doi:10.1002/jmri.23918
61. Yuan C, Zhang SX, Polissar NL, Echelard D, Ortiz G, Davis JW, et al. Identification of Fibrous Cap Rupture With Magnetic Resonance Imaging Is Highly Associated With Recent Transient Ischemic Attack or Stroke. *Circulation*. 2002;105(2):181-185. doi:10.1161/hc0202.102121
62. Sadat U, Teng Z, Young VE, Walsh SR, Li ZY, Graves MJ, et al Association between Biomechanical Structural Stresses of Atherosclerotic Carotid Plaques and Subsequent Ischaemic Cerebrovascular Events – A Longitudinal in Vivo Magnetic Resonance Imaging-based Finite element Study. *Eur J Vasc Endovasc Surg*. 2010;40(4):485-491. doi:https://doi.org/10.1016/j.ejvs.2010.07.015
63. Baradaran H, Al-Dasuqi K, Knight-Greenfield A, Giambrone A, Delgado D, Ebani EJ,et al. Association between Carotid Plaque Features on CTA and Cerebrovascular Ischemia: A Systematic Review and Meta-Analysis. *Am J Neuroradiol*. Published online October 26, 2017. doi:10.3174/ajnr.A5436
64. Xu D, Hippe DS, Underhill HR, Oikawa-Wakayama M, Dong L, Yamada K, et al. Prediction of high-risk plaque development and plaque progression with the carotid atherosclerosis score. *JACC Cardiovasc Imaging*. 2014;7(4):366-373. doi:10.1016/j.jcmg.2013.09.022
65. Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke*. 2013;44(11):3071-3077. doi:10.1161/STROKEAHA.113.002551
66. Ferguson GG, Eliasziw M, Barr HWK, Clagett GP, Barnes RW, Wallace MC, et al. The North American Symptomatic Carotid Endarterectomy Trial : Surgical Results in 1415 Patients. *Stroke*. 2015;30:1751-1758. doi:10.1016/0370-2693(82)91293-X
67. Saba L, Caddeo G, Sanfilippo R, Montisci R, Mallarini G. CT and ultrasound in the study of ulcerated carotid plaque compared with surgical results: potentialities and advantages of multidetector row CT angiography. *AJNR Am J Neuroradiol*. 2007;28(6):1061-1066. doi:10.3174/ajnr.A0486
68. Kuk M, Wannarong T, Beletsky V, Parraga G, Fenster A, Spence JD. Volume of carotid artery ulceration as a predictor of cardiovascular events. *Stroke*. 2014;45(5):1437-1441. doi:10.1161/STROKEAHA.114.005163
69. Madani A, Beletsky V, Tamayo A, Munoz C, Spence JD. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound vs TCD microemboli. *Neurology*. 2011;77(8):744-750. doi:10.1212/WNL.0b013e31822b0090

70. Mathiesen EB, Johnsen SH, Wilsgaard T, Bønaa KH, Løchen ML, Njølstad I. Carotid Plaque Area and Intima-Media Thickness in Prediction of First-Ever Ischemic Stroke. *Stroke*. 2011;42(4):972-978. doi:10.1161/STROKEAHA.110.589754
71. Sillesen H, Sartori S, Sandholt B, Baber U, Mehran R, Fuster V. Carotid plaque thickness and carotid plaque burden predict future cardiovascular events in asymptomatic adult Americans. *Eur Hear journal Cardiovasc Imaging*. 2018;19(9):1042-1050. doi:10.1093/ehjci/jex239
72. Coutinho JM, Derkatch S, Potvin AR, Tomlinson G, Kiehl TR, Silver FL, et al. Nonstenotic carotid plaque on CT angiography in patients with cryptogenic stroke. *Neurology*. 2016;87(7):665-672. doi:10.1212/WNL.0000000000002978
73. Zhao X, Hippe DS, Li R, Canton GM, Sui B, Song Y, et al. Prevalence and Characteristics of Carotid Artery High-Risk Atherosclerotic Plaques in Chinese Patients With Cerebrovascular Symptoms: A Chinese Atherosclerosis Risk Evaluation II Study. *J Am Heart Assoc*. 2017;6(8):e005831. doi:10.1161/JAHA.117.005831
74. Spence JD. Measurement of carotid plaque burden. *Curr Opin Lipidol*. 2020;31(5):291-298. doi:10.1097/MOL.0000000000000706
75. van Dam-Nolen DHK, Truijman MTB, van der Kolk AG, Liem MI, Schreuder FHBM, Boersma E,et al. Carotid Plaque Characteristics Predict Recurrent Ischemic Stroke and TIA: The PARISK (Plaque At RISK) Study. *JACC Cardiovasc Imaging*. 2022;15(10):1715-1726. doi:https://doi.org/10.1016/j.jcmg.2022.04.003
76. Saba L, Lanzino G, Lucatelli P, Lavra F, Sanfilippo R, Montisci R, et al. Carotid Plaque CTA Analysis in Symptomatic Subjects with Bilateral Intraparenchymal Hemorrhage: A Preliminary Analysis. *AJNR Am J Neuroradiol*. 2019;40(9):1538-1545. doi:10.3174/ajnr.A6160
77. Baradaran H, Gupta A. Carotid vessel wall imaging on CTA. *Am J Neuroradiol*. 2020;41(3):380-386. doi:10.3174/AJNR.A6403
78. Saba L, Anzidei M, Marincola BC, Piga M, Raz E, Bassareo PP,et al. Imaging of the carotid artery vulnerable plaque. *Cardiovasc Intervent Radiol*. 2014;37(3):572-585. doi:10.1007/s00270-013-0711-2
79. Saba L, Lai ML, Montisci R, Tamponi E, Sanfilippo R, Faa G,, et al. Association between carotid plaque enhancement shown by multidetector CT angiography and histologically validated microvessel density. *Eur Radiol*. 2012;22(10). doi:10.1007/s00330-012-2467-5
80. Qiao Y, Etesami M, Astor BC, Zeiler SR, Trout 3rd HH, Wasserman BA. Carotid plaque neovascularization and hemorrhage detected by MR imaging are associated with recent cerebrovascular ischemic events. *AJNR Am J Neuroradiol*. 2012;33(4):755-760. doi:10.3174/ajnr.A2863
81. Song Y, Dang Y, Wang J, Cai H, Feng J, Zhang H, et al. Carotid Intraplaque Neovascularization Predicts Ischemic Stroke Recurrence in Patients with Carotid Atherosclerosis. *Gerontology*. 2021;67(2):144-151. doi:10.1159/000511360
82. Saba L, Nardi V, Cau R, Gupta A, Kamel H, Suri JS, et al.Carotid Artery Plaque Calcifications: Lessons from Histopathology to Diagnostic Imaging. *Stroke*. 2022;53(1):290-297. doi:10.1161/STROKEAHA.121.035692
83. Van den Bouwhuijsen QJ, Bos D, Ikram MA, Hofman A, Krestin GP, Franco OH, et al.. Coexistence of calcification, intraplaque hemorrhage and lipid core within the asymptomatic atherosclerotic carotid plaque: The Rotterdam study. *Cerebrovasc Dis*. 2015;39(5-6):319-324. doi:10.1159/000381138
84. Eisenmenger LB, Aldred BW, Kim SE, Stoddard GJ, de Havenon A, Treiman GS, et al. Prediction of carotid intraplaque hemorrhage using adventitial calcification and plaque thickness on CTA. *Am J Neuroradiol*. 2016;37(8):1496-1503. doi:10.3174/ajnr.A4765
85. Benson JC, Nardi V, Madhavan AA, Bois MC, Saba L, Savastano L,et al. Reassessing the Carotid Artery Plaque "Rim Sign" on CTA: A New Analysis with Histopathologic

Confirmation. *AJNR Am J Neuroradiol*. 2022;43(3):429-434. doi:10.3174/ajnr.A7443
86. Saba L, Chen H, Cau R, Rubeis GD, Zhu G, Pisu F, et al. Impact Analysis of Different CT Configurations of Carotid Artery Plaque Calcifications on Cerebrovascular Events. *AJNR Am J Neuroradiol*. 2022;43(2):272-279. doi:10.3174/ajnr.A7401
87. Momose KJ, New PFJ. Non atheromatous stenosis and occlusion of the internal carotid artery and its main branches. *AmerJRoentgenol*. 1973;118(3):550-566. doi:10.2214/ajr.118.3.550
88. Kim SJ, Allen JW, Bouslama M, Nahab F, Frankel MR, Nogueira RG, et al. Carotid Webs in Cryptogenic Ischemic Strokes: A Matched Case-Control Study. *J Stroke Cerebrovasc Dis*. 2019;28(12). doi:10.1016/j.jstrokecerebrovasdis.2019.104402
89. Compagne KCJ, Dilba K, Postema EJ, van Es ACGM, Emmer BJ, Majoie CBLM, et al. Flow patterns in carotid webs: a patient-based computational fluid dynamics study. *Am J Neuroradiol*. 2019;40(4):703-708.
90. Zhang AJ, Dhruv P, Choi P, Bakker C, Koffel J, Anderson D, et al. A systematic literature review of patients with Carotid web and acute ischemic stroke. *Stroke*. 2018;49(12):2872-2876. doi:10.1161/STROKEAHA.118.021907
91. Sajedi PI, Gonzalez JN, Cronin CA, Kouo T, Steven A, Zhuo J, et al. Carotid bulb webs as a cause of "cryptogenic" ischemic stroke. *Am J Neuroradiol*. 2017;38(7):1399-1404. doi:10.3174/ajnr.A5208
92. Coutinho JM, Derkatch S, Potvin AR, Tomlinson G, Casaubon LK, Silver FL, et al. Carotid artery web and ischemic stroke. *Neurology*. 2017;88(1):65-69. doi:10.1212/WNL.0000000000003464
93. Zelada-Ríos L, Barrientos-Imán D, Simbrón-Ribbeck L, Argomedo CA, Ramírez-Quiñones J, Rosa PC, et al. Importance of multiplanar reformation angiographic images for the detection of carotid web: A case series. *Brain Circ*. 2023;9(1):44. doi:10.4103/bc.bc_75_22
94. Cau R, Flanders A, Mannelli L, Politi C, Faa G, Suri JS, et al Artificial Intelligence in Computed Tomography Plaque Characterization: A Review. *Eur J Radiol*. Published online 2021:109767. doi:https://doi.org/10.1016/j.ejrad.2021.109767
95. Cau R, Pisu F, Muscogiuri G, Mannelli L, Suri JS, Saba L. Applications of artificial intelligence-based models in vulnerable carotid plaque. *Vessel Plus*. 2023;7:20. doi:10.20517/2574-1209.2023.78
96. Miceli G, Basso MG, Rizzo G, Pintus C, Cocciola E, Pennacchio AR, et al. Artificial Intelligence in Acute Ischemic Stroke Subtypes ording to Toast Classification: A Comprehensive Narrative Review. *Biomedicines*. 2023;11(4). doi:10.3390/biomedicines11041138
97. Buckler AJ, Gotto AM Jr, Rajeev A, Nicolaou A, Sakamoto A, St Pierre S, et al. Atherosclerosis risk classification with computed tomography angiography: A radiologic-pathologic validation study. *Atherosclerosis*. 2023;366:42-48. doi:https://doi.org/10.1016/j.atherosclerosis.2022.11.013
98. Kamel H, Navi BB, Parikh NS, Merkler AE, Okin PM, Devereux RB,et al. Machine Learning Prediction of Stroke Mechanism in Embolic Strokes of Undetermined Source. *Stroke*. 2020;51(9):e203-e210. doi:10.1161/STROKEAHA.120.029305
99. Kigka VI, Sakellarios AI, Mantzaris MD, Tsakanikas VD, Potsika VT, Palombo D, et al. A Machine Learning Model for the Identification of High risk Carotid Atherosclerotic Plaques. In: *2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*. ; 2021:2266-2269. doi:10.1109/EMBC46164.2021.9630654
100. Lal BK, Kashyap VS, Patel JB, Gupta A, Chrencik MT, King AH, et al. Novel Application of Artificial Intelligence Algorithms to Develop a Predictive Model for Major Adverse Neurologic Events in Patients With Carotid Atherosclerosis. *J Vasc Surg*. 2020;72(1):e176-e177. doi:10.1016/j.jvs.2020.04.306
101. Saba L, Agarwal N, Cau R, Gerosa C, Sanfilippo R, Porcu M, et al Review of imaging

biomarkers for the vulnerable carotid plaque. *JVS Vasc Sci*. Published online 2021. doi:https://doi.org/10.1016/j.jvssci.2021.03.001

102. Saba L, Cau R, Murgia A, Nicolaides AN, Wintermark M, Castillo M, et al. Carotid Plaque-RADS, a novel stroke risk classification system. *JACC Cardiovasc Imaging*. Published online September 2023. doi:10.1016/j.jcmg.2023.09.005

Tables

Table 1: overview of studies examining non-invasive 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=0.01
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 greater than 40% wall area were prone to rupture of the FC in comparison with patients with a LRNC less than 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 = 0.01
Coutinho et al 44	Retrospective	62	CTA	Carotid WEB	OR = 8.0, 95% confidence interval = 1.2-67, p = 0.032
Mathiesen et al48	Retrospective	6584	US	MPT	(95% CI, 1.09-1.38; P=0.0009) in men and 1.19 (95% CI, 1.01-1.41; P=0.04) in women
Sillesen et al 49	Prospective	5808	US	MPT	After adjusting for risk factors, hazard ratios 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 = 0.015] for primary MACE and 3.13 (95% CI 1.80-5.51, P < 0.001) for secondary MACE.
Coutinho et al 50	Retrospective	85	CTA	MPT	>3 mm plaque thickness of the non-calcified component was present ipsilateral to stroke in 35% of patients (versus 15% of the contralateral) , p = 0.01
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 versus 0.81, P<0.0001).

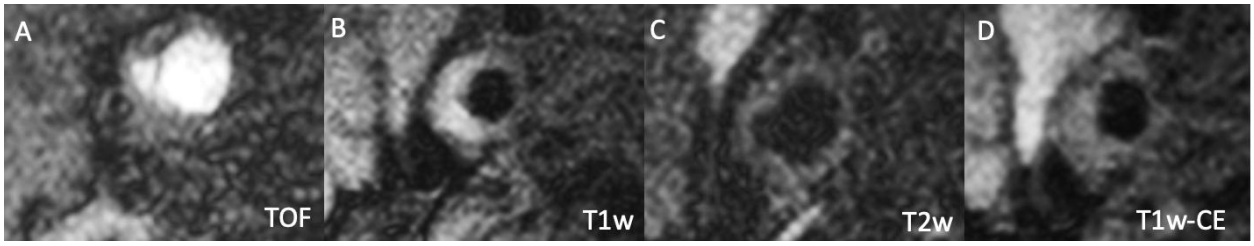
Qiao et al.56	Retrospective	47	MRI	Intraplaque neovascularization	neovascularization, associated with cerebrovascular events (OR 51.7; 95%CI 3.40-469.80, P=0.004) after controlling for age, sex, cardiovascular risk factors, wall thickness, and stenosis
Song et al.57	Prospective	155	US	Intraplaque neovascularization	Intraplaque neovascularization is associated with recurrent cerebrovascular events (HR 4.5, 95 % CI 1.9-10.90, P=0.001) independent of the severity of carotid stenosis (HR 3.5, 95 % CI 1.4-8.6, P=0.007)

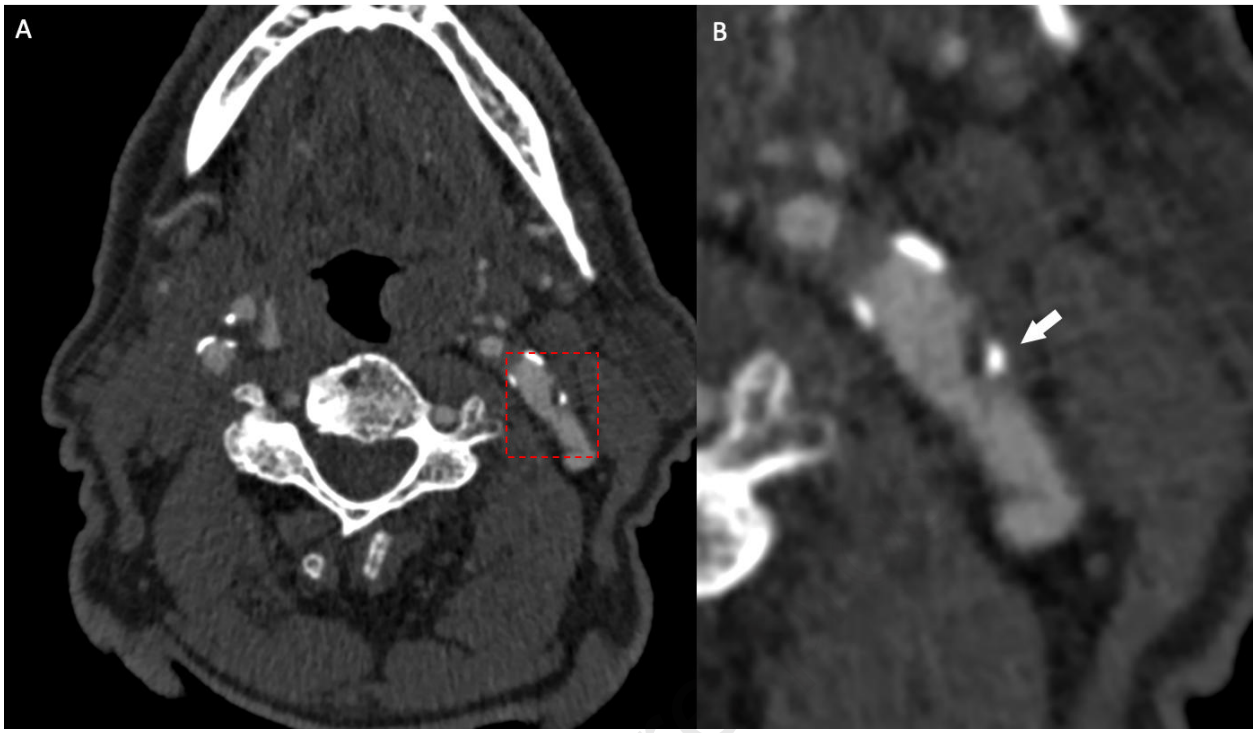
Table 2: Overview of imaging features associated with the occurrence of cerebrovascular events and their preferred non-invasive imaging modalities.

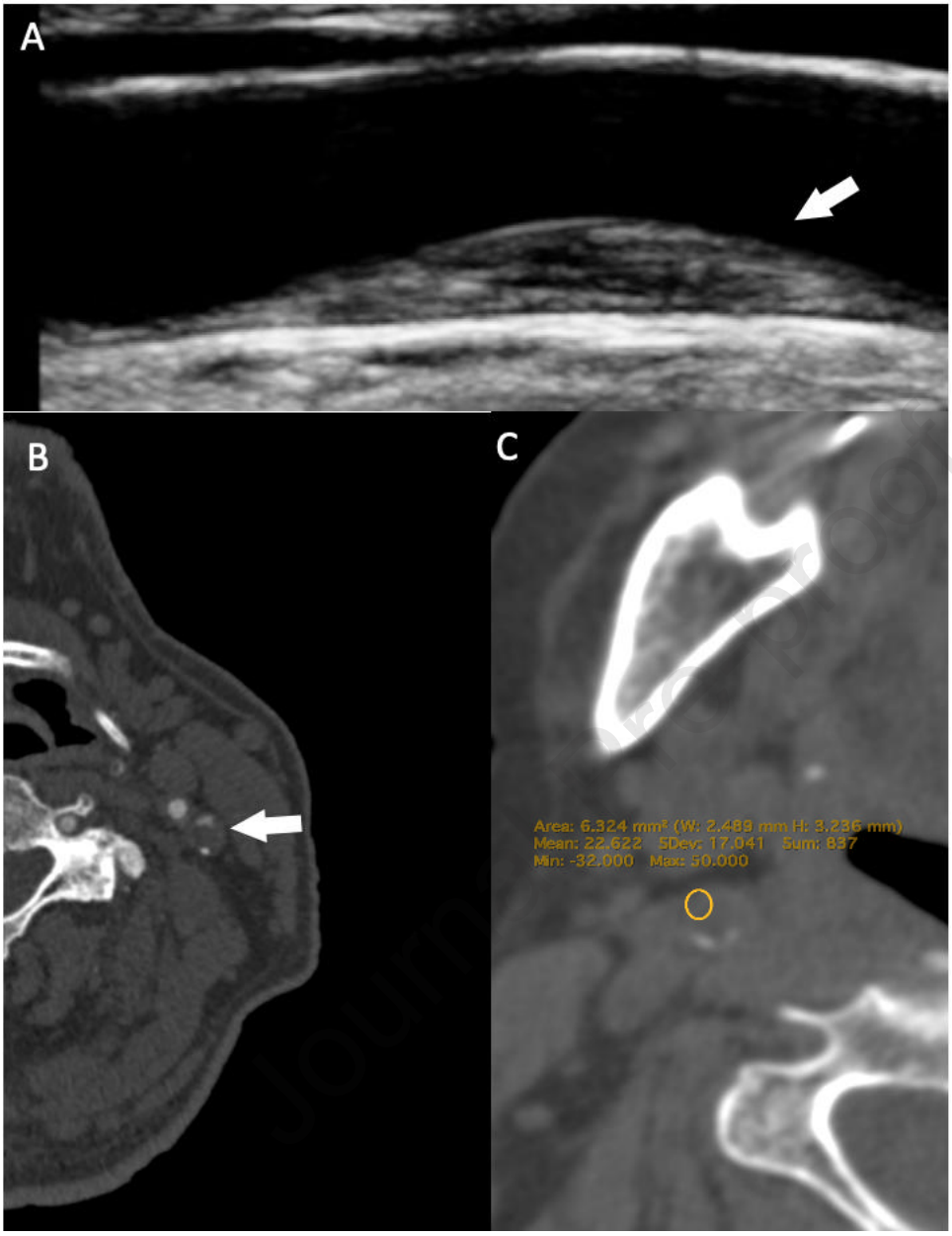
Carotid imaging features	**Non-invasive imaging of choice**	**Key imaging characteristics**
Intraplaque hemorrhage	**MRI**	Hyperintese region area within the plaque, with or without association to the carotid lumen on T1w and TOF sequences. T2w sequence allows to further characterize IPH as early subacute (iso-/hypointense) and late sub-acute (hyperintense)

Intraluminal thrombus	CT	Intraluminal filling defect surronded by the contrast agent.
Rupture of Fibrous cap	MRI	Disrupted hypointense band on T1w-CE with an irregular luminal surface on all images
Lipid rich necrotic core	MRI	Hypointense region on T2w sequences without enhancing region in the bulk of the plaque on T1w-CE .
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 at least 1 mm
Plaque thickness	US, CT, MRI	All imaging modalities suitable. US represents first-line imaging modality due to its availability and feasibility
Intraplaque neovascularization	Routine clinical practice has not yet adopted non-invasive	Contrast-enhanced US represent the most validate non-invasive imaging

	imaging assessment of plaque neovascularization (CEUS)	modalities, showing intraplaque neovascularization as the presence of microbubbles within the plaque.
Calcifications	CT	High-attenuation Plaque, usually > 130 HU



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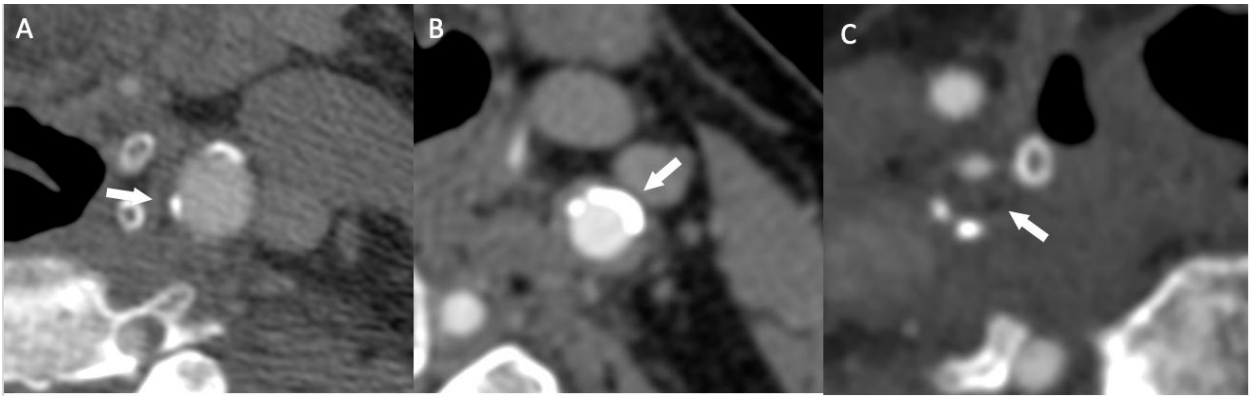

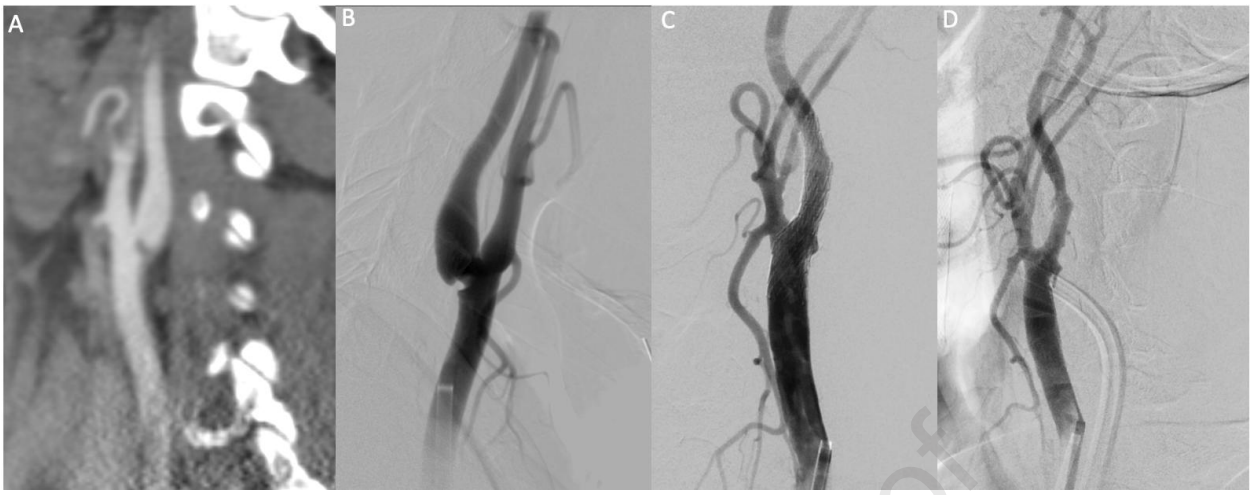

Figure legends

Figure 1: Example of IPH in the right internal carotid artery of a 67-years man with an ipsilateral ischemic stroke.

Panel A-D demonstrate non stenosing carotid atherosclerotic plaque with ulceration within the plaque (white arrow in panel A and panel C) and bright signal in T1w images (panel B) indicative of intraplaque hemorrhage, in particular, early subacute as highlight in T2w images (panel C).

Figure 2: Intraluminal thrombus observed in the left carotid artery of an 82 years old man with an ipsilateral ischemic stroke. CT shows an intraluminal filling defect in the left carotid artery indicative of a clot (panel A and B)

Figure 3: Examples of lipid rich necrotic core using US (panel A) and CT (Panel B-C). Panel A shows a non-stenosing carotid plaque with LRNC and thick fibrous cap in the left common carotid artery of a 62-years old woman with an ipsilateral ischemic stroke. Panel B demonstrates a low-attenuation, sub-occlusive plaque with a mean HU value of 43 HU in the left internal carotid artery resembling a LRNC, in a symtomatic 82-years old man. Panel C illustrates a low-attenuation, sub-occlusive plaque with a mean HU value of 22 HU in the right internal carotid artery of a 72-years old man with an ipsilateral ischemic stroke. However, due to the HU overlap between lipid and hemorrhage components, intraplaque hemorrhage cannot be excluded.

Figure 4: Examples of different types of carotid calcifications as demonstrated on CT.

Panel A demonstrates a carotid plaque with superficial calcifications (white arrow).

Panel B shows a carotid plaque with bulky calcification (white arrow)

Panel C displays a carotid plaque with positive rim sign (white arrow)

Figure 5: Example of a carotid web on CT and digital subtraction angiography before and after stent placement. Panel A shows the right internal carotid web near the bifurcation on CT coronal views. Panel B demonstrates the carotid web at the bifurcation with a filling defect and turbulent flow on the anteroposterior digital subtraction angiography view. Panels C and D exhibit the right carotid artery after stent placement in anteroposterior (C) and lateral (D) views

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