Pearls and Pitfalls of Carotid Artery Imaging Ultrasound, Computed Tomography Angiography, and MR Imaging

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Ultrasound, Computed Tomography Angiography, and MR Imaging

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KEYWORDS

• Carotid arteries • Vulnerable plaque • US • CTA • MRA

KEY POINTS

- Non-invasive plaque imaging modalities provide additional information beyond stenosis degree.
- Plaque vulnerability features can be detected with high diagnostic accuracy leveraging various imaging modality strengths.
- Radiologists and other clinicians need to become familiar with pearls and pitfalls of each of the plaque imaging modalities.

INTRODUCTION

Carotid atherosclerosis is a complex and multifactorial disease and a well-established risk factor for ischemic stroke (**Figs. 1** and **2**). The degree of carotid stenosis was considered the sole imaging criterion for stratifying carotid atherosclerosis severity based on prior randomized trials, namely the European Carotid Surgery Trial (ECST), the North American Symptomatic Carotid Endarterectomy Trial (NASCET), and the Asymptomatic Carotid Atherosclerosis Study.[1–3]

Several ex vivo studies reported significant differences in the risk of cardiovascular events given similar degree of luminal stenosis, focusing on "plaque vulnerability" based on plaque composition.[4–7] Vulnerable carotid plaques tend to progress rapidly and are highly associated with cardiovascular complications.[8]

Carotid plaque imaging can identify high-risk imaging markers of future cardiovascular events, directing patient stratification and management.[9,10] Recent years have seen imaging technique advancements, enabling reproducible multi-modality lesion detection and vulnerable feature characterization. Among them, ultrasound (US) represents a widely available imaging modality to evaluate not only the degree of carotid stenosis but also plaque echogenicity as an index of plaque vulnerability.[11,12] Computed tomography angiography (CTA) plays a crucial role in plaque evaluation enabling a more detailed description of plaque composition and morphology.[13–15] Finally, MR imaging is the most specific method for identifying histologically validated vulnerable plaque features, namely intraplaque hemorrhage (IPH), lipid-rich necrotic core (LRNC), and the thickness and integrity of the fibrous cap (FC). The ability to assess high-risk features may also be implemented by adding dedicated sequences to the standard MR imaging examination.[8,16]

In this review, we discuss the role of non-invasive imaging modalities in the landscape of carotid pathology, comparing their strengths, weaknesses, and potentialities.

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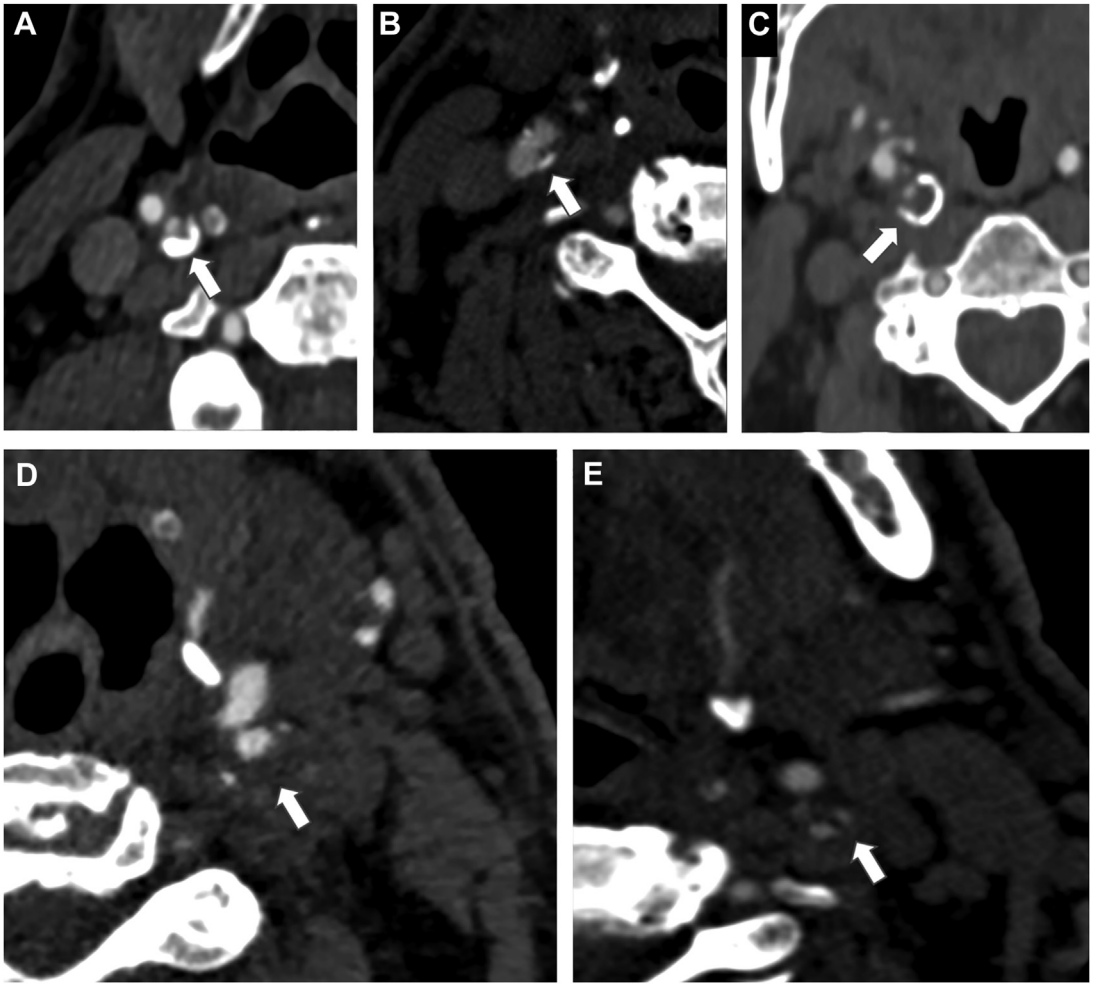

Fig. 1. Examples of different "high-risk" features of carotid plaque using CT. Panel *A–C* demonstrates different carotid plaque calcifications, in particular, heavy calcified plaque (*arrow* in *A*), microcalcification (*arrow* in *B*), and "positive rim" sign, defined as plaque with adventitial calcification (<2 mm thick) and internal soft plaque (>2 mm thickness) (*arrow* in *C*). CTA axial image (*D*) shows a hypodense plaque (HU value = 15) indicating the presence of LRNC (*arrow*). CTA axial image (*E*) demonstrates ulcerated stenosis in the postbulbous left internal carotid artery.

DEGREE OF STENOSIS

Currently, the degree of carotid stenosis was the key point considered in deciding management approaches, based on the NASCET and ECST trial results.[17,18] According to the current European Society of Cardiology (ESC) guidelines, US is the first-line examination.[19] The degree of carotid stenosis is estimated through different hemodynamic criteria on Doppler US, including peak systolic velocity, end-diastolic velocity, and carotid index allowing direct measurement of flow velocity,[19] with B-mode a supplementary method to evaluate carotid stenosis.[19]

The diagnostic accuracy of Duplex US demonstrated a sensitivity of 98% (95% CI, 97%–100%) and specificity of 88% (95% CI, 76%–100%) for detecting 50% to 70% stenosis and sensitivity of 90% (95% CI, 84%–94%) and specificity of 94% (95% CI, 88%–97%) for ≥70% stenosis.[20] US, despite its wide availability, ease, and low cost, is limited by intrinsic and extrinsic weaknesses. First, unfavorable patient anatomy (vessel tortuosity, short thick neck, high carotid bifurcation, external devices), calcified carotid plaque obscuring assessment, limited windows, and overestimation due to a contralateral carotid occlusion are limitations. Second, the US is operator-dependent and image quality often directly correlates to operator experience.[21]

The ESC guidelines recommend CTA and magnetic resonance angiography (MRA) as a complement to the US for carotid stenosis evaluation.[22,23]

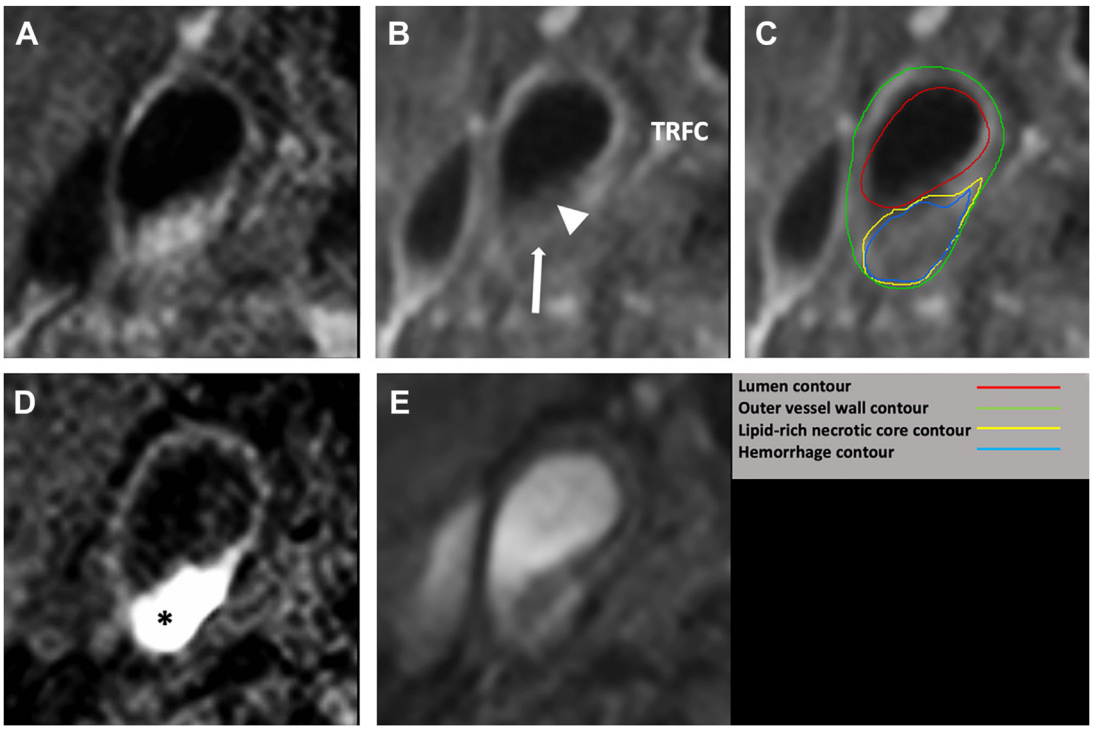

Fig. 2. Multi-sequence carotid MR imaging at the same cross-sectional level. The following MR images are acquired in the transverse plane: (*A*) pre-contrast T1-weighted (T1w) quadruple inversion recovery (QIR) turbo spin echo (TSE), (*B*) pre-contrast and (*C*) post-contrast T1w QIR TSE, (*D*) T1w inversion recovery (IR) turbo field echo (TFE), and (*E*) time of flight (TOF). LRNC was identified as an intraplaque region that does not show contrast enhancement (*arrow*). A hyperintense signal in the bulk of the plaque can be clearly observed in the IR-TFE image, indicating the presence of intraplaque hemorrhage (*asterisk*). The fibrous cap was scored as thin or ruptured (TRFC) because there was no signal enhancement in the region between the LRNC and the lumen (*arrowhead*).

CT demonstrates excellent diagnostic accuracy with sensitivity and specificity of 95% and 98% for the detection of >70% stenosis, respectively. Conversely, CT is limited by heavy calcified plaque.[21] Finally, contrast-enhanced (CE)-MRA represents the most sensitive tool for carotid stenosis.[24]

CAROTID PLAQUE

High-risk carotid plaque features, including IPH, thinning or rupture of FC, maximum wall thickness or plaque volume, plaque morphology, LRNC, plaque inflammation, plaque neovascularization, and calcifications may be investigated by different non-invasive modalities with lesser or greater capacity to provide insight into plaque composition and morphology. In the following section, features related to plaque vulnerability are presented with a particular focus on the pearls and pitfalls of the various modalities.

Maximum Wall Thickness

Maximum wall thickness is the maximum thickness of the plaque,[25] and correlates with plaque volume, a feature of plaque vulnerability. Plaque thickness is relatively easily assessed by US, CTA, or MRA.[8] In daily clinical practice, US, due to its availability and feasibility, is the first-line modality to assess carotid plaque thickness.[26,27] A prospective cohort study of 43 patients from the ORION trial with 16% to 79% carotid stenosis who underwent carotid MRA and US demonstrated significant inter-modality plaque thickness measurement agreement (Pearson correlation coefficient $r = 0.93$; $P < 0.001$).[28] However, when US imaging is limited,[29] CTA or MRA can appropriately evaluate plaque characteristics.[16]

The carotid plaque area and volume are highly reproducible parameters associated with plaque size.[30,31] In the Plaque At RISK (PARISK) study, carotid plaque volume and area were independently associated with recurrent ipsilateral cerebrovascular ischemic events (HR: 1.07 per 100 mL increase for plaque volume; 95% CI 1.00–1.22).[31] Plaque area and volume are more accurate than plaque thickness in measuring plaque progression/regression because plaque grows in all directions.[32]

Plaque Surface Morphology and Ulcerations

The luminal surface of carotid plaque can be categorized as smooth (regular luminal morphology), irregular (small luminal alteration from 0.3 to 0.9 mm), and ulcerated (intimal defect causing an extension of the lumen into the plaque measuring at least 1 mm).[13,16] The plaque surface can be evaluated using US, CTA, and MRA, with variable diagnostic accuracy.[8,10] US is specifically suboptimal compared with CTA or MRA unless ultrasound-enhancing agents are used.[16]

Carotid contrast-enhanced ultrasound (CEUS) can enhance image quality, improving luminal and plaque anatomy evaluation including plaque surface irregularities and ulcerations.[25] Widespread utilization of CEUS for plaque imaging, however, is off-label and is not addressed in the most recent American Society of Echocardiography guidelines.[33] 3D US methods have also shown promise in the assessment of carotid plaque irregularities.[34,35] The main strength of 3D quantification of carotid plaque is its multiplanar capacity, enabling a comprehensive assessment of plaque morphology, geometry, and surface irregularities.[25]

Time of flight-MRA (TOF-MRA) is limited in ulceration detection due to signal dephasing and saturation in focal areas of complex flow such as an ulcer crater.[36] It can also overestimate the degree of stenosis.[27] Contrast-enhanced (CE) MRA can overcome these limitations because it is not dependent on blood flow. Etesami et al. reported that 37.5% of ulcerated plaques detected with CE-MRA images were not visualized with TOF-MRA.[37] In addition, CE-MRA can identify ulcerations in calcified plaque.[27]

CT is the reference standard non-invasive imaging modality to evaluate plaque ulcerations. A cross-sectional study of 237 patients reported a higher sensitivity and specificity for CT in comparison with the US (sensitivity of 93.75% vs 37.5% and specificity of 98.59% vs 91.3%, respectively)[38] in comparison to surgical specimens for ulcerated plaque. The primary limitation of CT for carotid plaque assessment is beam hardening from extensive calcification. This limitation can be overcome with dual-source CT, which uses low- and high-peak kilovoltage acquisitions allowing the removal of calcified plaque components from the lumen, permitting a more accurate assessment of plaque and lumen.[27,39]

Plaque Composition

Carotid plaque consists of several components and the proportion of subcomponents can correlate with future ischemic events.[16,40] The characterization of different tissue types, including carotid plaque, was initially qualitatively evaluated using US via grayscale values according to echogenicity and heterogeneity; however, this information can be augmented with quantitative analyses, specifically grayscale median (GSM).[25] GSM is the median gray value of the US pixel and has been evaluated in the Imaging in Carotid Angioplasty and Risk of Stroke study, an international multicenter registry that investigated the relationship between the GSM of carotid plaque and the risk of stroke during carotid artery stenting.[41] The Italian survey on CArdiac RehabilitatiOn and Secondary prevention after cardiac revascularization (ICARIOS) study reported that the rate of cerebrovascular events was higher in patients with GSM<25 in comparison to patients with GSM>25.[41] Histological studies also reported an association between less calcification, unstable plaque, a large lipid core, a thin FC, and increased inflammation and neovascularization histologically and low GSM US values.[30,42,43]

Carotid atherosclerotic plaque component differentiation using CT is based on Hounsfield unit (HU) densities. Carotid plaques are classified as fatty (<60 HU), mixed (60–130 HU), and calcified (>130 HU) on CT.[44] Dual-energy CT (DECT) facilitates better tissue characterization, with higher spatial resolution, lower contrast agent utilization, lower radiation dose, and reduced artifacts.[45] In addition, the introduction of spectral CT with photon counting brings the promise of improved plaque characterization through the generation of contrast agent concentration and photon attenuation maps.[46] Histological validation and longitudinal studies are warranted to evaluate the impact and predictive value of spectral photon counting CT on carotid plaque vulnerability for stroke assessment. Specifically, using data from randomized prospective trials (eg, Comparison of Spectral Photon Counting CT with Dual-Energy CT and MR Imaging for Plaque and Lumen Carotid Arteries Evaluation (CAPL) [NCT04466787]) may contribute to better understanding the role of spectral photon counting CT.

Different plaque components can be identified using high-resolution, multiparametric MRA, including pre- and post-contrast high-resolution 2D or 3D T1-weighted, magnetization-prepared rapid gradient-echo (MPRAGE), T2-weighted, and TOF-MRA sequences. Fat suppression and blood suppression are valuable for optimal lesion contrast from surrounding tissues, and to avoid artifacts that may mimic pathological lesions.[47,48]

LRNC consists of heterogeneous collections of cholesterol crystals and cellular debris. MR imaging is the gold standard for LRNC visualization

due to superior soft tissue contrast.[8,10] LRNC presents as a focal hypointense area on T2-weight images and is best appreciated on CE-MRA as a focal non-enhancing area.[8]

LRNC can be also visualized using CT due to lipid attenuation properties with HU values < 60. A histological study by Walker and colleagues[49] reported a trend toward lower attenuation measurements with increased intraplaque lipid, but with a high standard deviation of HU values. These results highlighted an important limitation to the application of CT for the characterization of LRNC, namely the significant overlap of HU values between LRNC, fibrous tissue, and IPH.[49] Another potential limitation of intraplaque lipid assessment on CT is obscuration from heavily calcified plaque.[6] De Weert and colleagues[50] reported that LRNC can be detected with good correlation with the histological specimen ($R^2 = 0.77$) only in mildly calcified plaques.

US can detect LRNC as a hypoechogenic area, also known as a juxta-luminal black area. Plaques with juxtaluminal LRNC on histology demonstrated significantly lower GSM values, reflecting a hypoechoic region at the plaque surface ($P = 0.009$).[51] Nonetheless, US is not useful for discriminating between IPH and LRNC, thus limiting US value in carotid plaque characterization.[8,13]

FC is a connective tissue layer that divides the plaque from the lumen. FC ulceration and/or rupture exposes the LRNC to platelets and coagulation factors leading to a thromboembolic cascade.

Currently, MRA is the best non-invasive imaging modality to investigate FC status. On MRA, a normal FC appears as a juxtaluminal band of low signal on TOF-MRA.[52] The absence of the dark juxtaluminal band or presence of focal juxtaluminal hyperintensity is indicative of "vulnerable plaque".[8,52] Contrast agents can help discriminate between FC and LRNC. The contrast increases the signal intensity of fibrous tissue in comparison with LRNC and, therefore, contrast-enhanced MR imaging has good reproducibility of FC status assessment.[53,54]

On US, FC appears as an echogenic structure with stronger echoes compared to plaque and blood.[55] The evaluation of FC status and thickness has a 73% sensitivity and 67% specificity using stratified GSM parameters.[51] Conversely, CT is not suitable for FC assessment due to edge-blur and halo effect artifacts.[13] Some studies, however, suggest that fissured FC can be detected using CT. Saba and colleagues[56] demonstrated that plaques with histologically confirmed fissured FC showed higher enhancement on CT compared to non-fissured plaques.

IPH is considered one of the most important features associated with plaque instability. MR imaging is the best modality for the detection of IPH, due to its ability to characterize the hemoglobin oxidative state.[13,57] Several studies suggested the use of fat-suppressed T1-weighted sequences in clinical practice to identify IPH. This sequence, thanks to an inversion pulse for blood suppression, identifies IPH as a focal intraplaque hyperintense signal with intensity >150% of that of adjacent muscles.[4,8]

A number of recent studies have suggested that CT can also detect IPH,[36,58,59] including studies that showed a good correlation between IPH detected by CT and the corresponding histologic section ($\kappa = 0.712$; $P = 0.102$),[60] with limitations in smaller plaques and heavily calcified plaques.[60] The sensitivity and specificity of CT to detect IPH was 100% and 64%, respectively.[61,62]

Plaque inflammation and neovascularization: Plaque inflammation, another vulnerable plaque feature, remains predominantly investigative. MRA using ultrasmall superparamagnetic iron oxide nanoparticles as a surrogate marker of macrophage accumulation and activity has shown promising results.[63,64] Alternatively, fluorodeoxyglucose positron emission tomography (18-FDG PET) can identify areas of inflammation.[65] Another indirect approach to assess plaque inflammation is to evaluate the perivascular adipose tissue for stranding using CTA.[66]

Plaque imaging can also detect plaque neovascularization using US, CTA, or MRA.[13] In particular, dynamic contrast-enhanced (DCE)-MRA is well-suited to evaluate intraplaque neovessels.[13,67] CEUS can also be used to detect plaque neovascularization, defined as the movement of microbubbles from the adventitia to the plaque core.[68,69] A meta-analysis including 20 studies demonstrated the association between plaque enhancement on CEUS and intraplaque neo-vessels.[70] Finally, some studies suggested that the amount of plaque enhancement on CTA is associated with the extent of intraplaque neovascularization.[56,71]

Calcifications: Controversial results have emerged regarding the role of calcium in atherosclerosis and its relationship with plaque vulnerability.[14] The size and location of carotid calcifications are related to the variable risk of cerebrovascular events. Studies have suggested that microcalcifications were significantly associated with unstable plaques,[72,73] whereas large calcifications are protective.[14]

Recently, Saba and colleagues[73] investigated the relationship between calcium configuration and the prevalence of cerebrovascular events

using CT, highlighting the potential role of calcium in plaque vulnerability. CTA is considered the reference standard in the detection of calcification. Nevertheless, plaque calcification can be detected with US (as a hyperechogenic area) and MR imaging (as a hypointense region on all contrast sequences) with lower sensitivity and specificity compared to CTA.[55]

GENERAL TECHNIQUE LIMITATIONS

Beyond the limitations of each modality in identifying high-risk plaque, it is necessary to know the general technique limitations. In particular, the US application is limited by the operator's skill, composition (calcifications), anatomy, and a limited anatomic window.[21]

The CTA disadvantages include ionizing radiation exposure and adverse reactions to iodinated contrast media. Another CTA limitation is limited differentiation of the outer carotid wall in the absence of the surrounding adipose tissue.[57]

The limitations of MR imaging include its long acquisition time, the need for specialized hardware (carotid coils) for high-resolution images to detect FC status, the complexity of interpretation, and limited access.[74] If only IPH is scored on carotid MR imaging, a short MR image examination with a standard neurovascular coil is sufficient and image interpretation is straightforward.

SUMMARY

Various non-invasive plaque imaging modalities can provide detailed information on the carotid plaque with supplementary and complementary roles in identifying high-risk features. Further evidence is necessary to incorporate each of these imaging modalities with their advantages and limitations into a standardized diagnostic flowchart with the purpose to offer a significant contribution to risk stratification and patient management.

CLINICS CARE POINTS

- Carotid artery atherosclerosis is associated with an increased risk of cardiovascular events.
- IPH, thinning or rupture of FC, maximum wall thickness or plaque volume, plaque morphology, LRNC, plaque inflammation, plaque neovascularization, and calcifications are markers of plaque vulnerability and predictors of future events.
- Non-invasive plaque imaging techniques complement each other in their ability to identify features of plaque instability.

REFERENCES

1. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. Stroke 1991;22(6):711–20.
2. 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):1379–87.
3. Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke 2009; 40(10):e573–83.
4. Saba L, Brinjikji W, Spence JD, et al. Roadmap consensus on carotid artery plaque imaging and impact on therapy strategies and guidelines: an international, multispecialty, expert review and position statement. AJNR Am J Neuroradiol 2021;42(9): 1566–75.
5. Saba L, Sanfilippo R, Sannia S, et al. Association between carotid artery plaque volume, composition, and ulceration: a retrospective assessment with MDCT. AJR Am J Roentgenol 2012;199(1):151–6.
6. Zhu G, Hom J, Li Y, et al. Carotid plaque imaging and the risk of atherosclerotic cardiovascular disease. Cardiovasc Diagn Ther 2020;10(4):1048–67.
7. Schindler A, Schinner R, Altaf N, et al. Prediction of stroke risk by detection of hemorrhage in carotid plaques: meta-analysis of individual patient data. JACC Cardiovasc Imaging 2020;13(2 Pt 1):395–406.
8. Saba L, Moody AR, Saam T, et al. Vessel wall–imaging biomarkers of carotid plaque vulnerability in stroke prevention trials. JACC Cardiovasc Imaging 2020;13(11):2445–56.
9. Singh N, Marko M, Ospel JM, et al. The risk of stroke and TIA in nonstenotic carotid plaques: a systematic review and meta-analysis. AJNR Am J Neuroradiol 2020;41(8):1453–9.
10. Saba L, Yuan C, Hatsukami TS, et al. Carotid Artery Wall Imaging: Perspective and Guidelines from the ASNR Vessel Wall Imaging Study Group and Expert Consensus Recommendations of the American Society of Neuroradiology. Am J Neuroradiol 2018; 39(2). https://doi.org/10.3174/ajnr.A5488.
11. Picano E, Paterni M. Ultrasound tissue characterization of vulnerable atherosclerotic plaque. Int J Mol Sci 2015;16(5):10121–33.
12. Jashari F, Ibrahimi P, Bajraktari G, et al. Carotid plaque echogenicity predicts cerebrovascular symptoms: a systematic review and meta-analysis. Eur J Neurol 2016;23(7):1241–7.

13. Saba L, Agarwal N, Cau R, et al. Review of imaging biomarkers for the vulnerable carotid plaque. JVS Vasc Sci 2021. https://doi.org/10.1016/j.jvssci.2021.03.001.
14. Saba L, Nardi V, Cau R, et al. Carotid artery plaque calcifications: lessons from histopathology to diagnostic imaging. Stroke 2022;53(1):290–7.
15. Cademartiri F, Balestrieri A, Cau R, 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):1150–62.
16. Saba L, Saam T, Jäger HR, et al. Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications. Lancet Neurol 2019;4422(19):1–14.
17. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273(18):1421–8.
18. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998;339(20):1415–25.
19. Messas E, Goudot G, Halliday A, et al. Management of carotid stenosis for primary and secondary prevention of stroke: state-of-the-art 2020: a critical review. Eur Heart J Suppl 2020;22(Suppl M):M35–42.
20. Jahromi AS, Cinà CS, Liu Y, et al. Sensitivity and specificity of color duplex ultrasound measurement in the estimation of internal carotid artery stenosis: a systematic review and meta-analysis. J Vasc Surg 2005;41(6):962–72.
21. Adla T, Adlova R. Multimodality imaging of carotid stenosis. Int J Angiol 2015;24(3):179–84.
22. Aboyans V, Ricco J-B, Bartelink M-LEL, 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.
23. Prokop M, Waaijer A, Kreuzer S. CT angiography ofthe carotid arteries. JBR-BTR 2004;87(1):23–9.
24. Yang CW, Carr JC, Futterer SF, et al. Contrast-enhanced MR angiography of the carotid and vertebrobasilar circulations. AJNR Am J Neuroradiol 2005;26(8):2095–101.
25. Johri AM, Nambi V, Naqvi TZ, 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 2020;33(8):917–33.
26. Landry A, Spence JD, Fenster A. Measurement of carotid plaque volume by 3-dimensional ultrasound. Stroke 2004;35(4):864–9.
27. Zhao X, Hippe DS, Li R, 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.
28. Underhill HR, Kerwin WS, Hatsukami TS, et al. Automated measurement of mean wall thickness in the common carotid artery by MRI: a comparison to intima-media thickness by B-mode ultrasound. J Magn Reson Imaging 2006;24(2):379–87.
29. Yuan J, Usman A, Das T, et al. Imaging carotid atherosclerosis plaque ulceration: comparison of advanced imaging modalities and recent developments. AJNR Am J Neuroradiol 2017;38(4):664–71.
30. Mitchell CC, Stein JH, Cook TD, et al. Histopathologic validation of grayscale carotid plaque characteristics related to plaque vulnerability. Ultrasound Med Biol 2017;43(1):129–37.
31. van D-ND HK, TM TB, van der KA G, et al. Carotid plaque characteristics predict recurrent ischemic stroke and TIA. JACC Cardiovasc Imaging 2022;0(0). https://doi.org/10.1016/j.jcmg.2022.04.003.
32. Spence JD. Carotid plaque measurement is superior to IMT Invited editorial comment on: carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis-Yoichi Inaba, M.D., Jennifer A. Chen M.D. Atherosclerosis 2012;220(1):34–5.
33. Porter TR, Mulvagh SL, Abdelmoneim SS, et al. Clinical applications of ultrasonic enhancing agents in echocardiography: 2018 american society of echocardiography guidelines update. J Am Soc Echocardiogr 2018;31(3):241–74.
34. Rafailidis V, Sidhu PS. Vascular ultrasound, the potential of integration of multiparametric ultrasound into routine clinical practice. Ultrasound 2018;26(3):136–44.
35. Rafailidis V, Huang DY, Yusuf GT, et al. General principles and overview of vascular contrast-enhanced ultrasonography. Ultrason (Seoul, Korea) 2020;39(1):22–42.
36. Saba L, Saam T, Jäger HR, et al. Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications. Lancet Neurol 2019;18(6):559–72.
37. Etesami M, Hoi Y, Steinman DA, et al. Comparison of carotid plaque ulcer detection using contrast-enhanced and time-of-flight MRA techniques. AJNR Am J Neuroradiol 2013;34(1):177–84.
38. Saba L, Caddeo G, Sanfilippo R, et al. 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):1061–6.
39. Vlahos I, Chung R, Nair A, et al. Dual-energy CT: vascular applications. AJR Am J Roentgenol 2012; 199(5 Suppl):S87–97.
40. Cau R, Flanders A, Mannelli L, et al. Artificial intelligence in computed tomography plaque characterization: a review. Eur J Radiol 2021;109767. https://doi.org/10.1016/j.ejrad.2021.109767.
41. Biasi GM, Froio A, Diethrich EB, et al. Carotid plaque echolucency increases the risk of stroke in carotid stenting. Circulation 2004;110(6):756–62.
42. Salem MK, Bown MJ, Sayers RD, et al. Identification of patients with a histologically unstable carotid plaque using ultrasonic plaque image analysis. Eur J Vasc Endovasc Surg 2014;48(2):118–25.
43. Spanos K, Tzorbatzoglou I, Lazari P, et al. Carotid artery plaque echomorphology and its association with histopathologic characteristics. J Vasc Surg 2018;68(6):1772–80.
44. Saba L, Anzidei M, Marincola BC, et al. Imaging of the carotid artery vulnerable plaque. Cardiovasc Intervent Radiol 2014;37(3):572–85.
45. Opincariu D, Benedek T, Chitu M, et al. From CT to artificial intelligence for complex assessment of plaque-associated risk. Int J Cardiovasc Imaging 2020;(50). https://doi.org/10.1007/s10554-020-01926-1.
46. Boussel L, Coulon P, Thran A, et al. Photon counting spectral CT component analysis of coronary artery atherosclerotic plaque samples. Br J Radiol 2014; 87(1040):20130798.
47. Kassem M, Florea A, Mottaghy FM, et al. Magnetic resonance imaging of carotid plaques: current status and clinical perspectives. Ann Transl Med 2020;8(19):1266.
48. Mazzacane F, Mazzoleni V, Scola E, et al. Vessel wall magnetic resonance imaging in cerebrovascular diseases. Diagnostics 2022;12(2):1–20.
49. Walker LJ, Ismail A, McMeekin W, et al. Computed tomography angiography for the evaluation of carotid atherosclerotic plaque. Stroke 2002;33(4): 977–81.
50. de Weert TT, Ouhlous M, Meijering E, et al. In vivo characterization and quantification of atherosclerotic carotid plaque components with multidetector computed tomography and histopathological correlation. Arterioscler Thromb Vasc Biol 2006;26(10): 2366–72.
51. Sztajzel R, Momjian S, Momjian-Mayor I, et al. Stratified Gray-Scale Median Analysis and Color Mapping of the Carotid Plaque. Stroke 2005;36(4):741–5.
52. Yuan C, Zhang S, Polissar NL, 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): 181–5.
53. Dong L, Kerwin WS, Ferguson MS, et al. Cardiovascular magnetic resonance in carotid atherosclerotic disease. J Cardiovasc Magn Reson 2009;11(1):53.
54. Kwee RM, van Engelshoven JMA, Mess WH, et al. Reproducibility of fibrous cap status assessment of carotid artery plaques by contrast-enhanced MRI. Stroke 2009;40(9):3017–21.
55. Huibers A, De Borst GJ, Wan S, et al. Non-invasive carotid artery imaging to identify the vulnerable plaque: current status and future goals. Eur J Vasc Endovasc Surg 2015;50(5):563–72.
56. Saba L, Tamponi E, Raz E, et al. Correlation between fissured fibrous cap and contrast enhancement: preliminary results with the use of CTA and histologic validation. AJNR Am J Neuroradiol 2014;35(4): 754–9.
57. Murgia A, Erta M, Suri JS, et al. CT imaging features of carotid artery plaque vulnerability. Ann Transl Med 2020;8(19):1261.
58. Saba L, Lanzino G, Lucatelli P, et al. Carotid Plaque CTA Analysis in Symptomatic Subjects with Bilateral Intraparenchymal Hemorrhage: A Preliminary Analysis. AJNR Am J Neuroradiol 2019;40(9):1538–45.
59. Saba L, Francone M, Bassareo PP, et al. CT Attenuation Analysis of Carotid Intraplaque Hemorrhage. AJNR Am J Neuroradiol 2018;39(1):131–7.
60. Wintermark M, Jawadi SS, Rapp JH, et al. High-resolution CT imaging of carotid artery atherosclerotic plaques. AJNR Am J Neuroradiol 2008;29(5): 875–82.
61. Ajduk M, Pavić L, Bulimbasić S, et al. Multidetector-row computed tomography in evaluation of atherosclerotic carotid plaques complicated with intraplaque hemorrhage. Ann Vasc Surg 2009; 23(2):186–93.
62. Ajduk M, Bulimbasić S, Pavić L, et al. Comparison of multidetector-row computed tomography and duplex Doppler ultrasonography in detecting atherosclerotic carotid plaques complicated with intraplaque hemorrhage. Coll Antropol 2013;37(1): 213–9.
63. Andelovic K, Winter P, Jakob PM, et al. Evaluation of Plaque Characteristics and Inflammation Using Magnetic Resonance Imaging. Biomedicines 2021; 9(2). https://doi.org/10.3390/biomedicines9020185.
64. Kooi ME, Cappendijk VC, Cleutjens KBJM, et al. Accumulation of Ultrasmall Superparamagnetic Particles of Iron Oxide in Human Atherosclerotic Plaques Can Be Detected by In Vivo Magnetic Resonance Imaging. Circulation 2003;107(19): 2453–8.
65. Poredos P, Gregoric ID, Jezovnik MK. Inflammation of carotid plaques and risk of cerebrovascular events. Ann Transl Med 2020;8(19):1281.
66. Baradaran H, Myneni PK, Patel P, et al. Association between carotid artery perivascular fat density and

cerebrovascular ischemic events. J Am Heart Assoc 2018;7(24):e010383.
67. van Hoof RHM, Heeneman S, Wildberger JE, et al. Dynamic contrast-enhanced MRI to study atherosclerotic plaque microvasculature. Curr Atheroscler Rep 2016;18(6):33.
68. Coli S, Magnoni M, Sangiorgi G, et al. Contrast-enhanced ultrasound imaging of intraplaque neovascularization in carotid arteries: correlation with histology and plaque echogenicity. J Am Coll Cardiol 2008;52(3):223–30.
69. Hoogi A, Adam D, Hoffman A, et al. Carotid plaque vulnerability: quantification of neovascularization on contrast-enhanced ultrasound with histopathologic correlation. AJR Am J Roentgenol 2011;196(2):431–6.
70. Huang R, Abdelmoneim SS, Ball CA, et al. Detection of carotid atherosclerotic plaque neovascularization using contrast enhanced ultrasound: a systematic review and meta-analysis of diagnostic accuracy studies. J Am Soc Echocardiogr 2016;29(6):491–502.
71. Saba L, Lai ML, Montisci R, et al. Association between carotid plaque enhancement shown by multidetector CT angiography and histologically validated microvessel density. Eur Radiol 2012;22(10):2237–45.
72. Montanaro M, Scimeca M, Anemona L, et al. The paradox effect of calcification in carotid atherosclerosis: microcalcification is correlated with plaque instability. Int J Mol Sci 2021;22(1). https://doi.org/10.3390/ijms22010395.
73. Saba L, Chen H, Cau R, et al. Impact analysis of different CT configurations of carotid artery plaque calcifications on cerebrovascular events. AJNR Am J Neuroradiol 2022;43(2):272–9.
74. Cau R, Bassareo PP, Mannelli L, et al. Imaging in COVID-19-related myocardial injury. Int J Cardiovasc Imaging 2020. https://doi.org/10.1007/s10554-020-02089-9.