Imaging biomarkers of vulnerable carotid plaques for stroke risk prediction and their potential clinical implications

Luca Saba, Tobias Saam, H Rolf Jäger, Chun Yuan, Thomas S Hatsukami, David Saloner, Bruce A Wasserman, Leo H Bonati, Max Wintermark

Stroke represents a massive public health problem. Carotid atherosclerosis plays a fundamental part in the occurence of ischaemic stroke. European and US guidelines for prevention of stroke in patients with carotid plaques are based on quantification of the percentage reduction in luminal diameter due to the atherosclerotic process to select the best therapeutic approach. However, better strategies for prevention of stroke are needed because some subtypes of carotid plaques (eg, vulnerable plaques) can predict the occurrence of stroke independent of the degree of stenosis. Advances in imaging techniques have enabled routine characterisation and detection of the features of carotid plaque vulnerability. Intraplaque haemorrhage is accepted by neurologists and radiologists as one of the features of vulnerable plaques, but other characteristics—eg, plaque volume, neovascularisation, and inflammation—are promising as biomarkers of carotid plaque vulnerability. These biomarkers could change current management strategies based merely on the degree of stenosis.

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Department of Medical Sciences, University of Cagliari, Cagliari, Italy (Prof L Saba MD); **Department of Radiology, University Hospital Munich, Ludwig-Maximilians-University Munich, Munich, Germany** (T Saam MD); **Radiologisches Zentrum Rosenheim, Rosenheim, Germany** (T Saam); **Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation, University College London Institute of Neurology, London, UK** (H R Jäger MD); **Department of Radiology** (C Yuan PhD) **and Department of Surgery** (T S Hatsukami MD), **University of Washington, Seattle, WA, USA; Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA** (D Saloner MD); **The Russell H Morgan Department of Radiology and Radiological Sciences, The Johns Hopkins Hospital, Baltimore, MD, USA** (B A Wasserman MD); **Department of Neurology and Stroke Center, Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland** (L H Bonati MD); **and Department of Radiology, Neuroradiology Division, Stanford University, Stanford, CA, USA** (M Wintermark MD)

Correspondence to:
Prof Luca Saba, University of Cagliari—Azienda Ospedaliero Universitaria di Cagliari–polo di Monserrato, Cagliari 09128, Italy
lucasaba@tiscali.it

Introduction

Stroke represents a massive public health problem.[1] Approximately 18–25% of all ischaemic strokes are attributable to thromboembolism caused by carotid atherosclerotic disease.[1] European and US guidelines for prevention of stroke in patients with carotid plaques (atherosclerosis) are based on quantification of the degree of stenosis,[2,3] and this parameter serves for stratifying the severity of carotid artery atherosclerosis and, thus, for the choice of strategies to prevent the occurrence of stroke. However, developments in imaging techniques (eg, in ultrasound and CT) have enabled routine characterisation of carotid plaque features. A growing body of evidence suggests that some types of carotid plaques—so-called vulnerable plaques—are highly likely to cause ischaemic stroke and thrombotic complications, independent of the degree of stenosis.[4–6] Plaques that progress rapidly are also considered to be vulnerable.[7] Thus, the traditional idea of using the degree of luminal stenosis as the sole imaging marker for selection of the best therapeutic approach is challenged by evidence showing that carotid plaque composition has a role.[4–6] This paradigm shift represents an important element for research in primary prevention of ischaemic stroke and in secondary stroke prevention, because of the potential implications for management.

Guidelines from the American Society of Neuroradiology (ASNR)[8] and the European Society of Cardiology (ESC)[9] have highlighted the need for better diagnostic and therapeutic strategies. In 2018, the ASNR Vessel Wall Imaging Study Group published guidelines that focused on the implications and effects of technologies for carotid plaque imaging.[8] In the same year, the ESC recommended that carotid artery revascularisation should be considered for asymptomatic patients with a life expectancy longer than 5 years, moderate-to-severe (60–99%) carotid artery stenosis, and imaging features of plaque vulnerability (eg, intraplaque haemorrhage or lipid-rich necrotic core).[9] These guidelines reflect that the risk of stroke related to carotid plaques is attributable not only to the degree of stenosis but also to plaque composition.

In this Review, we discuss developments in imaging biomarkers for assessment of vulnerable carotid plaques, compare relative strengths and limitations of plaque imaging modalities, provide data for the predictive value of plaque imaging in patients with symptomatic and asymptomatic plaques (with and without stenosis), and discuss aspects of prevention and future research directions.

Features of vulnerability in carotid plaques

The aim of plaque imaging is to look beyond the lumen (and the degree of stenosis) and to identify those imaging biomarkers of vulnerable carotid plaques that are best suited for stroke risk prediction.[4,6] In the following sections, features linked to plaque vulnerability are presented based on most evidence (figure 1).

Intraplaque haemorrhage

Intraplaque haemorrhage is one of the key features of vulnerable carotid plaques[10] and contributes to enlargement of the lipid-rich necrotic core (LRNC) and rapid plaque progression.[11] In a meta-analysis of nine studies,[12] detection of carotid intraplaque haemorrhage by MRI was associated with increased risk for future ischaemic stroke in patients with symptomatic and asymptomatic carotid stenosis (hazard ratio [HR] 4·59, 95% CI 2·91–7·24). Intraplaque haemorrhage is also more prevalent in carotid arteries ipsilateral to embolic strokes of undetermined source,[13] even if other causes are also possible—eg, retrograde flow.[14] Intraplaque haemorrhages can also occur bilaterally, which could explain bilateral lesions detected by brain MRI that are due to carotid atherosclerosis rather than a cardioembolic source.[15]

Intraplaque haemorrhage is considered the strongest imaging parameter associated with the occurrence of stroke.[16] MRI is the best imaging technique for the detection of intraplaque haemorrhage because its appearance depends on the oxidative state of haemoglobin[17] and can be easily detected using common imaging sequences, such as T1-weighted fat-saturated turbo spin echo, inversion recovery turbo field echo, or inversion recovery fast

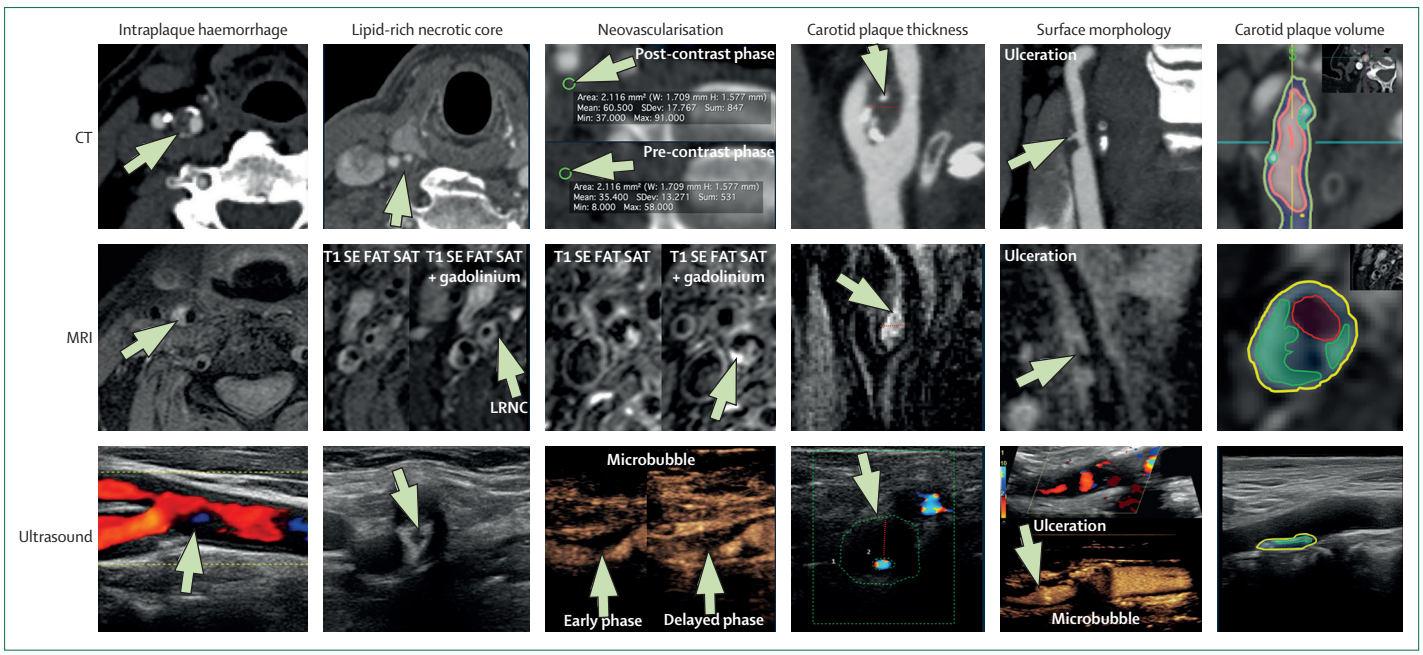

Figure 1: **Imaging features of plaque vulnerability**
Six features of carotid plaque vulnerability are shown in columns, and images were obtained by CT (upper row), MRI on a 3 Tesla scanner (middle row), and ultrasound (lower row). On ultrasound images, red colour indicates orthograde flow and blue colour shows retrograde flow. In the first column (intraplaque haemorrhage) and second column (LRNC), the arrow points to the feature detected. In the third column (neovascularisation), the arrows and green circles in the pre-contrast and post-contrast CT images (upper row) show how Hounsfield units increase after administration of contrast material. Similarly, in the MRI panel (middle row), after gadolinium contrast, the plaque (arrow) shows a significant increase in signal intensity because of enhancement of the plaque. The ultrasound images (lower row) show significant enhancement in the plaque (arrow) because of the presence of microbubble. Early phase is after 30 s and delayed phase is after 120 s. In the fourth column (carotid plaque thickness), the arrows indicate the plaque and the red dotted lines show the thickness of the plaque. The green dotted line in the ultrasound image represents the outer lumen of the plaque. In the fifth column (surface morphology), the arrows in all images show the ulcer. In the ultrasound images, the two panels show the difference in sensitivity using conventional B-mode colour Doppler and microbubble injection. In this case, the ulcer is visible only with the microbubble technique. The sixth column shows carotid plaque volume analysis and tissue segmentation. The red line shows the inner boundaries of the carotid plaque wall; the yellow line shows the outer boundary of the carotid plaque wall; the green colour represents the fatty component; the blue colour indicates the mixed component. IPH=intraplaque haemorrhage. LRNC=lipid-rich necrotic core. T1 SE FAT SAT=T1 spin-echo fat saturation MRI sequence.

spoiled gradient recalled acquisition in the steady state.[8] A prospective study of 38 patients with carotid artery disease using MRI for carotid plaque imaging[18] showed that detection of intraplaque haemorrhage could be achieved at lower spatial resolution using large field-of-view (FOV) neck coils, without the need for dedicated carotid small FOV surface coils (the sensitivity of neurovascular coils is 91%). MRI allows categorisation of intraplaque haemorrhage into fresh (type 1), recent (type 2), and old (type 3) subtypes, but no evidence is available to link the subtype of intraplaque haemorrhage with increased or reduced occurrence of future ischaemic strokes.[15]

Ultrasound and CT are less suitable methods for detection of intraplaque haemorrhage. Ultrasound has a low sensitivity and specificity for this particular parameter.[19] With CT, it is difficult to differentiate between fibrous, lipid, and intraplaque haemorrhage because of overlap in Hounsfield units,[20] which characterise radiation attenuation in different tissues.

Lipid-rich necrotic core and fibrous cap

Two further features of plaque vulnerability are associated with the LRNC and the fibrous cap. In carotid plaques, the LRNC is a heterogeneous tissue composed of cholesterol crystal, debris of apoptotic cells, and particles of calcium. The fibrous cap is a layer of fibrous connective tissue that separates the core of the plaque from the arterial lumen.

The LRNC is predictive of increased risk for stroke.[12] In a longitudinal MRI study of 120 asymptomatic individuals, carotid plaques with a maximum percentage of LRNC (%LRNC=LRNC area/wall−area) greater than 40% were more likely to develop rupture of the fibrous cap during 3-year follow-up compared with individuals with %LRNC less than 40%.[21] However, too few events were reported in this study to assess whether %LRNC was associated with stroke.

CT and MRI can both detect lipid components because of lipid–tissue attenuation properties and signal characteristics.[22–25] However, MRI is superior to CT for detection of the LRNC because this technique can distinguish between the LRNC and intraplaque haemorrhage whereas, with CT, these two features show attenuation values less than 60 Hounsfield units so they cannot be distinguished.[26] In a cross-sectional study of 1121 patients with asymptomatic carotid stenosis (50–99%),[27] the presence of hypoechogenic plaque areas on ultrasound was associated with the LRNC, in particular, echolucent areas near the plaque surface (so-called juxta-luminal black areas), which suggests ultrasound could provide

information about plaque composition. Currently, ultrasound cannot be considered reliable for detection of the LRNC because it is difficult to distinguish the LRNC from intraplaque haemorrhage because both features appear hypoechogenic.[27]

Alterations to the fibrous cap (thin or ruptured cap) are an important feature of plaque vulnerability.[12,28] MRI is the preferred technique to image this feature,[29,30] particularly with use of gadolinium-based contrast agents.[31,32]

Plaque inflammation and intraplaque neovascularisation

Another feature of plaque vulnerability is inflammation, which is often associated with angiogenesis and referred to as plaque activity.[33] In a cross-sectional study of 62 patients with atherosclerotic plaques,[34] an association between macrophage plaque infiltration, plaque rupture, and ischaemic symptoms was reported. Inflammatory cells accumulate in specific areas of the plaque, typically the shoulder or in the fibrous cap.[28,31] Imaging of inflammation is not routinely used in clinical practice—it is only used for research. In the past 5 years, several studies have shown the potential of PET to image and quantify plaque inflammation.[35–38] However, there is no consensus on the methodology for quantification of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake to image inflammation in patients with atherosclerosis.[39] Detection of intraplaque inflammation by MRI showed an association with histological markers of inflammation, suggesting that MRI could be a quantitative and non-invasive marker of plaque inflammation.[40] Further confirmatory studies are needed.

Molecular imaging is an innovative technique for detection of plaque inflammation. Several nanoparticles—eg, iron oxide, sodium fluoride, or polyethylene glycol molecules—have been investigated for molecular imaging of atherosclerosis in patients and animal models.[41–43] In particular, iron oxide contrast agents provide highly efficient iron labelling in macrophages for MRI-based detection in vivo and were reported as very promising for detection of plaque inflammation.[42] In a cross-sectional study of 23 patients with atherosclerotic plaques,[43] ^{18}F-sodium fluoride PET was used to distinguish between vulnerable and non-vulnerable carotid plaques. An earlier stage in the calcification process was shown using this technique, indicating that this method could be of value in early atherosclerotic development. However, molecular imaging is limited by the relatively long delay (2–24 h) needed between the time of contrast injection and post-contrast imaging,[41–43] making this type of imaging more complex compared with CT or MRI.

Another important feature of plaque vulnerability is intraplaque neovascularisation, which is associated with plaque activity in terms of increased risk for neovessel rupture, haemorrhage, and inflammation.[44] Inflammation and intraplaque neovascularisation might be also associated with stroke, but evidence is inconclusive.[44] In two cross-sectional studies of patients with symptomatic and asymptomatic atherosclerotic plaque,[45,46] plaque enhancement on contrast-enhanced ultrasound—a sonographic technique in which microbubble contrast agents filled with a perfluorinated gas are injected as intravascular tracers—was associated significantly with intraplaque neovascularisation. These findings were confirmed in a meta-analysis of 20 studies,[47] which concluded that contrast-enhanced ultrasound is a good technique to detect intraplaque neovascularisation. In another cross-sectional study of contrast-enhanced ultrasound in 41 patients with symptomatic atherosclerotic plaques,[48] a positive association was reported between microembolic signals (ie, small emboli that flow into the blood) and the presence of intraplaque neovascularisation in patients with symptomatic atherosclerotic carotid plaque.[48] CT can also be used to detect and quantify intraplaque neovascularisation because the amount of contrast enhancement on CT is associated with the extent of intraplaque neovascularisation.[49]

Detection of intraplaque neovascularisation by MRI showed a link between the degree of plaque enhancement and the degree of intraplaque neovascularisation.[50] Dynamic contrast enhancement perfusion MRI measures changes of signal intensity in tissues over time (usually up to 5–10 min) after bolus administration of gadolinium and permits quantification of plaque vascularity.[51] However, one of the main limitations of dynamic contrast enhancement perfusion MRI is that the vessel wall is difficult to image dynamically because of its small size and motion artifacts.[51]

Carotid plaque thickness

The thickness of the carotid artery plaque is quantifiable with ultrasound, CT, and MRI.[52,53] The maximum plaque thickness is a feature of plaque vulnerability because it is associated with the size and volume of the plaque. The Mannheim consensus defines plaques as having a thickness greater than 1·5 mm.[54] In a cross-sectional study of 1072 patients with cerebral ischaemic symptoms,[55] the maximum plaque thickness (quantified by MRI) was more strongly associated with cerebral ischaemic symptoms than was the degree of stenosis, showing that plaque size represents a parameter associated with the occurrence of stroke.

Surface morphology

The surface of carotid plaques can be categorised as smooth, irregular (surface fluctuates from 0·3 mm to 0·9 mm), or ulcerated (cavities measuring at least 1 mm).[56] Irregular morphology of the luminal surface—particularly the presence of ulceration—is considered a risk feature for stroke.[56] However, ulceration could be a marker of previous plaque rupture,[57] therefore, its predictive value is uncertain.

The carotid plaque surface can be assessed by ultrasound, CT, and MRI, with varying levels of diagnostic accuracy. Ultrasound is not considered the best technique

for detection of an irregular plaque surface or ulcerations because of acoustic shadowing of calcified components.[58,59] However, detection accuracy could be improved by use of contrast-enhanced ultrasound, because microbubbles facilitate differentiation between the intimal layer and blood flow.[60] In two cross-sectional studies of 237 patients using contrast CT[59] and 600 patients using contrast MRI,[61] diagnostic accuracy for detecting ulcers was superior to that with ultrasound (eg, CT sensitivity >90% *vs* ultrasound <40%).

Carotid plaque volume

Carotid plaque volume might be a useful identifying feature of carotid plaque vulnerability. Carotid artery plaque composition and volume changes were assessed restrospectively in two cohorts of patients,[62,63] and the volume of the carotid artery plaque was found to be associated with plaque vulnerability and stroke. Because of the good spatial resolution of CT, total carotid plaque volume and the volume of the subcomponents of the plaque (eg, fatty, mixed, calcified) can be calculated accurately, according to the attenuation values of the voxels.[64] In a prospective longitudinal study of 63 symptomatic patients with ipsilateral carotid atherosclerotic stenosis (30–69% stenosis) with follow-up of 55 months,[65] the annual progressive increase in carotid plaque volume, as assessed by MRI, was independently associated with recurrent ischaemic stroke. Similar to CT, MRI is highly useful for quantification of carotid plaque component volume.[66,67] Although the spatial resolution of MRI is lower than that of CT, soft tissue contrast with MRI is superior to CT. Findings of a meta-analysis of seven studies of three-dimensional ultrasound suggested good reproducibility for assessment of carotid plaque volume.[68]

Prevention of stroke

The effectiveness of carotid revascularisation for prevention of recurrent stroke in symptomatic patients (ie, who previously had a transient ischaemic attack or stroke) with moderate (50–69%) or severe (70–99%) carotid stenosis is well documented. However, in a longitudinal study of 853 patients who had previously had a stroke,[69] 44 (90%) of 49 people with moderate or severe stenosis who remained untreated did not have a recurrent stroke at 5 years.[69] Therefore, plaque imaging could identify patients who have stable plaques and in whom a carotid intervention might not be necessary. Moreover, plaque imaging could also help to identify symptomatic patients with mild (<50%) stenosis with vulnerable carotid plaques who are at high risk of recurrent stroke and who could benefit from carotid intervention.

Findings of a meta-analysis of five randomised controlled trials (3019 patients) published in 2017 showed a modest but significant benefit for carotid intervention in asymptomatic patients with severe carotid stenosis (pooled risk ratio for any periprocedural stroke, 1·84).[70] However, in a meta-analysis of 47 studies published in 2013,[71] the incidence of ipsilateral stroke in 26 cohorts of patients receiving medical treatment alone was 1·68% per year. It seems crucial to identify patients with asymptomatic carotid stenosis with stable and with unstable plaques and to select those patients who might benefit from a carotid intervention.

Prediction of recurrent stroke risk in patients with symptomatic carotid stenosis

Patients with symptomatic carotid stenosis commonly undergo carotid revascularisation to prevent recurrence of stroke.[9] The risk of stroke during the first 90 days after a transient ischaemic attack is 3·7–11·7%.[72,73] The presence of features of plaque vulnerability (eg, intraplaque haemorrhage, LRNC, status of the fibrous cap) can further increase the risk for occurrence of ischaemic stroke.

Results of two meta-analyses of nine[12] and eight[16] prospective studies have shown a strong link between the presence of intraplaque haemorrhage and the occurrence of future ischaemic stroke in patients with symptomatic carotid stenosis. Therefore, carotid revascularisation is warranted in patients with symptomatic carotid stenosis in whom intraplaque haemorrhage has been detected. Absence of intraplaque haemorrhage seems to be associated with a benign clinical course, even among patients with symptomatic moderate or severe carotid stenosis.[74]

Some carotid plaque features are associated with a low risk for recurrent stroke in patients with severe stenosis—eg, the heavily calcified plaque.[75] In a meta-analysis of 16 cross-sectional studies,[76] a significant negative relation was reported between calcified plaques and ipsilateral stroke (odds ratio [OR] 0·5, 95% CI 0·4–0·7). CT-based assessment of calcium content can be done semi-quantitatively using calcium scores[77] or quantitatively with direct volume analysis of plaque components.[8,78]

However, the effect of calcium in carotid artery plaques could be more complex than thought. In a cross-sectional study of 229 carotid plaques,[79] two types of calcium salts were identified in atheromatous plaques—hydroxyapatite and calcium oxalate. An association was noted between hydroxyapatite calcification and vulnerable carotid plaques, whereas calcium oxalate calcifications were mainly detected in non-vulnerable carotid plaques.[79] This finding could further increase the use of multi-energy CT scanners because of their potential to do spectral analysis and distinguish between hydroxyapatite and calcium oxalate calcifications.[80]

Prediction of primary stroke risk in patients with asymptomatic carotid stenosis

Prevention of primary stroke in asymptomatic patients with high-risk carotid plaques is challenging because of the risk of rupture independent of the degree of stenosis.[21,81] A prospective longitudinal study of 154 asymptomatic

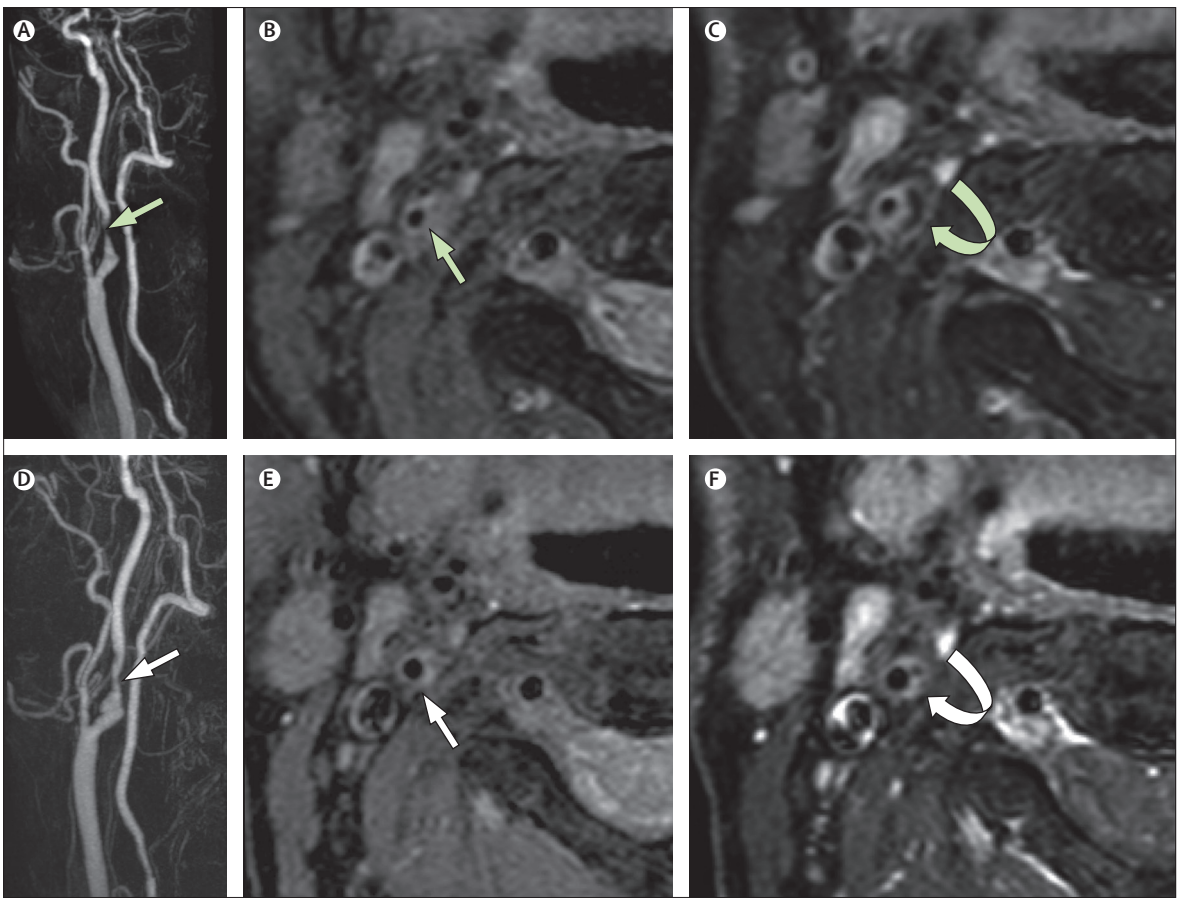

Figure 2: **Plaque reduction after statin treatment**
3 Tesla MRI studies of plaque regression (reduction of LRNC) in a 73-year-old male patient before (July, 2015) and after (July, 2017) statin treatment (atorvastatin 40 mg orally daily for 2 years). Contrast-enhanced magnetic resonance angiography shows a significant degree of stenosis in the right internal carotid artery (A; green arrow), with regression after 2 years (D; white arrow). Basal axial T1 turbo spin-echo with fat saturation shows a large plaque with intermediate signal intensity (B; green arrow). The axial T1 turbo spin-echo with fat saturation image acquired after 2 years shows decreased plaque size (E; white arrow). Basal axial T1 turbo spin-echo with fat saturation after gadolinium shows enhancement of the fibrous cap and adventitia with large LRNC (C; green curved arrow). The axial T1 turbo spin-echo with fat saturation image post gadolinium acquired after 2 years shows a pronounced decrease of enhancement and a reduction of the LRNC covered by an intact fibrous cap (F; white curved arrow). LRNC=lipid-rich necrotic core.

patients with moderate-to-severe (50–79%) carotid stenosis,[82] who were followed up by MRI for a mean period of 38·2 months, showed that carotid plaques with features of plaque vulnerability were associated with subsequent stroke. Risk of stroke was increased with a thin or ruptured fibrous cap, intraplaque haemorrhage, a larger maximum %LRNC, and a larger maximum plaque thickness.

In a longitudinal MRI cohort study of 1190 patients with asymptomatic carotid stenosis who were followed up for a mean of 53 months,[83] intraplaque haemorrhage was a risk factor for a subsequent stroke, with significantly lower event-free survival in patients with carotid artery plaques showing high signal intensity in T1-weighted images compared with patients with carotid plaques not showing high signal intensity on T1-weighted images. In another longitudinal MRI study,[84] 198 patients with carotid plaques were followed up for 4 years and an increase in prevalence of intraplaque haemorrhage with age and hypertension was reported, highlighting the importance of blood pressure lowering to prevent stroke.[85,86]

Thus, it is possible to detect imaging features—ie, intraplaque haemorrhage, a thin or ruptured fibrous cap, %LRNC, and larger maximum plaque thickness—with predictive value for stroke occurrence in patients who had not previously had a transient ischaemic attack. Incorporating the findings from these studies with emerging ideas of plaque regression (overall reduction in plaque volume)[87] and the results of lipid-lowering and anti-inflammatory treatment trials[88,89] could help build strategies combining imaging biomarkers during follow-up analysis to monitor drug effects.

In a longitudinal MRI study of 232 patients with atherosclerotic disease (median follow-up 35·1 months),[90,91] the amount of lipid in the carotid plaque and status of the fibrous cap were significantly associated not only with ischaemic stroke but also with systemic cardiovascular outcomes (fatal and non-fatal myocardial infarction,

	Validation studies (imaging method *vs* histopathology)	Reproducibility studies	Comments and limitations
Identification of plaque components (present *vs* absent)			
MRI	N >100; Cohen's kappa 0·52–0·95 for IPH, 0·73–0·98 for LRNC, 0·65–0·75 for calcification;[23] sensitivity 77–100% for IPH, 82–100% for LRNC,[23] specificity 74–100% for IPH, 65–100% for LRNC[23]	N>10; intra-reader, Cohen's kappa 0·82–0·90 for IPH, 0·69 for LRNC, 0·8 for calcification;[30] inter-reader, Cohen's kappa 0·62–0·75 for IPH, 0·58 for LRNC, 0·74 for calcification[23,30]	Best imaging method for detection of IPH and LRNC; good reproducibility; extensively validated
CT	N >10; excellent identification of calcification, debated for all other components	N>3; results and reproducibility vary wildly, small studies only	Best imaging method for detection of calcification; overlap of tissue densities for LRNC, IPH, and fibrous tissue
Ultrasound	N >10; overlap of echolucency between LRNC, fibrous tissue, and IPH[100]	N>10; no consistent data available, results vary wildly	Can distinguish between echolucent and echorich plaques but is unable to differentiate between the main plaque components (eg, IPH and LRNC)
Quantitative measurements: lumen and vessel wall			
MRI	N >10; Pearson's R 0·84 for wall, 0·81 for lumen area[22]	N >5; intra-reader, ICC 0·99 for lumen, ICC 0·98 for wall, CV 3·2–4·1% for lumen, CV 3·4–5·1% for wall;[32] inter-reader, ICC 0·98–0·99 for lumen, ICC 0·84–0·90 for wall, CV 5·3% for lumen, CV 7·9% for wall;[32] scan-rescan, ICC 0·99 for lumen, ICC 0·97 for wall, CV 4·3% for lumen, CV 5·8% for wall[67]	Highly accurate imaging method with excellent reproducibility; wall and lumen area measurements by MRI are ideally suited for cross-sectional and longitudinal studies; measurement errors can be used for power calculation for clinical trials[67]
CT	N >10; Pearson's R 0·85 for wall[24]	N >5: intrareader, CV 3% for lumen, CV 8% for wall;[24] inter-reader, CV 4% for lumen, CV 19% for wall[24]	Calcification can lead to overestimation of wall areas; variability of wall area measurements substantial because of difficulties to delineate the vessel wall from surrounding soft tissue with similar densities
Ultrasound	N >5; Pearson's R 0·76 for wall[53]	N >100; 2D measurements, ICC 0·65–0·9, CV 5–20%; data vary wildly;[96] 3D measurements, intra-reader, CV 2·8–6·0% for wall;[68] 3D measurements, inter-reader, CV 4·2–7·6% for wall[68]	Widely available, accurate, and reproducible imaging method for CIMT and plaque measurements; manual measurements are more observer-dependent than semiautomatic systems; 3D ultrasound can help to improve accuracy and reliability; calcification can lead to acoustic shadowing
Quantitative measurements: plaque components			
MRI	N >10; Pearson's R 0·75 for LRNC, 0·74 for calcification, 0·66 for IPH[22]	N >5: intra-reader, ICC 0·89–0·99 for LRNC,[22,32] ICC 0·9 for calcification,[22] ICC 0·74 for haemorrhage,[22] CV 8·7% for LRNC;[67] inter-reader, ICC 0·89–0·93 for LRNC,[22,32] ICC 0·9 for calcification,[22] ICC 0·74 (95% CI 0·45–0·89) for haemorrhage,[22] CV 17·6% for LRNC;[67] scan-rescan, ICC 0·99 for LRNC, ICC 0·95 for calcification, CV 11·1% for LRNC, CV 30·8% for calcification[67]	Optimum reproducibility for plaque components; contrast-enhanced T1 sequences improve delineation of LRNC; plaque component measurements by MRI are ideally suited for cross-sectional and longitudinal studies; measurement errors can be used for power calculation for clinical trials[67]
CT	N >5; Pearson's R 0·86 for calcification, 0·48 for LRNC; data for IPH not available	N >5: intrareader, CV 15% for LRNC, 8% for calcification; inter-reader, CV 40% for LRNC, 8% for calcification[24]	Only tissue component that can be reliably identified is calcification; accurate and reliable quantification of IPH and LRNC not feasible; automated segmentation might improve performance
Ultrasound	N >5; accurate quantification of plaque components not feasible	N >5; reliable quantification of plaque components not feasible	Not useful for quantification of LRNC, IPH, and calcification
Fibrous cap			
MRI	Identification of fibrous cap: N >5; Cohen's kappa 0·74–0·85 for intact *vs* ruptured fibrous cap;[23] quantification of fibrous cap: N >2; Pearson´s R 0·8 for area measurements[31]	N >5; intra-reader, Cohen's kappa 0·33–0·96;[29,30] inter-reader, Cohen´s kappa 0·26–0·78;[29,30] N>1; intrareader, ICC 0·72 for fibrous cap area;[31] inter-reader, ICC 0·78 for fibrous cap area[31]	MRI can identify and quantify the fibrous cap with good correlation to histopathology; contrast-enhanced T1-weighted sequences improves delineation of fibrous cap; reproducibility varies wildly; the best sequence to detect the fibrous cap is uncertain
CT	Identification and quantification of fibrous cap not feasible	Not applicable	The fibrous cap cannot be differentiated from soft plaque component
Ultrasound	N >5; sensitivity 73%, specificity 67%[101]	N >10; large variability, operator-dependent	Not the imaging modality of choice to assess the fibrous cap

(Table 1 continues on next page)

ischaemic stroke, and admission for acute coronary syndrome). Biomarkers of carotid plaque vulnerability could, therefore, be used as novel surrogate markers, not only for stroke but for systemic atherothrombotic risk.

Identifying high-risk plaque features in patients with non-stenotic plaques

Although substenotic plaques in coronary arteries are a well-recognised cause of myocardial infarction,[92] the

	Validation studies (imaging method *vs* histopathology)	Reproducibility studies	Comments and limitations
(Continued from previous page)			
Ulceration			
MRA	N >10; sensitivity 80%; specificity 82%[23]	Good reliability	Good for ulcer detection; contrast-enhanced MRA superior to non-contrast-enhanced MRA
CTA	N >10; Cohen's kappa 0·86 for ulcer detection[25]	Good reliability	Excellent for ulcer detection; superior to contrast-enhanced MRA because of better spatial resolution
Ultrasound	N >10; sensitivity 33–75%; specificity 33–92%[101]	N >10; large variability; operator-dependent	Ultrasound is not the imaging method of choice for ulcer detection; detection can be improved with contrast-enhanced ultrasound and 3D methods
Plaque inflammation and neovascularisation			
DCE-MRI	N >10; Pearson's R 0·75 for k-trans *vs* macrophage content, 0·68 for v(p) *vs* neovasculature[40]	N >3; no sufficient data; reported reproducibility varies wildly; dependent on pharmacokinetic model and on type of contrast agent	Quantification of inflammation and neovessel density feasible; no consensus on best technique; results are not comparable across centres; only for research studies
CT	N <3; Pearson´s R 0·53 for carotid plaque enhancement *vs* microvessel density[49]	N <3; no significant difference between observers[49]	Requires precontrast and post-contrast scan (increased radiation); only for research
Contrast-enhanced ultrasound	N >10; Pearson's R* 0·88 for neovascularisation, 0·78 for inflammation[46]	N=5; no reliable and consistent data available	Use of microbubbles allows detection and quantification of neovascularisation and inflammation; no clear consensus on assessment; method operator-dependent
^{18}F-FDG PET and CT	N >10; Pearson's R 0·70 for FDG uptake *vs* macrophage content, 0·85 for FDG uptake (mean tissue to background ratio) *vs* CD68 as marker of inflammation[38]	N >10; intra-reader, ICC 0·93–0·98;[37] inter-reader, ICC 0·71–0·92;[37] N >1; scan-rescan, ICC 0·79–0·92[37]	Best imaging method for accurate and reliable detection of plaque inflammation; main disadvantage is the high radiation dose; has the same limitation for other plaque components as CT alone

Studies were selected on the basis of impact factor of the publishing journal, number of citations, date of publication (older papers or landmark papers were preferred), and type of statistical methods (papers with similar statistical methods were preferred to facilitate comparison of results). N=number of studies. IPH=intraplaque haemorrhage. LRNC=lipid-rich necrotic core. ICC=intraclass correlation coefficient. CV=coefficient of variation (measurement error). 2D=two dimensional. 3D=three dimensional. CIMT=carotid intima-media thickness. MRA=magnetic resonance angiography. CTA=computed tomography angiography. DCE-MRI=dynamic contrast-enhanced magnetic resonance imaging. k-trans=transfer constant. v(p)=fractional plasma volume. FDG=fluorodeoxyglucose. *R^2 values were used in the original report.

Table 1: **Validation and reproducibility studies for identification or quantification of plaque components and lumen and wall area measurements**

role of substenotic plaques in carotid arteries as a cause of stroke requires further research. Growing evidence suggests that stroke could be caused by the presence of vulnerable carotid plaques, even in the absence of moderate or severe stenosis (>50%).[6,55,81,93] The role of plaque features (eg, intraplaque haemorrhage, %LRNC) in this population of patients is supported by data from only a few small studies, but the future occurrence of ischaemic events with presence of plaque is definitely possible. Secondary analyses of ongoing prospective trials (eg, CREST [NCT02089217], ECST-2 [ISRCTN97744893], and ACAS-2 [ISRCTN21144362]) assessing the effect of carotid plaque components versus stroke occurrence in patients with substenotic carotid arteries could help to confirm or exclude other parameters.

Mild stenosis (<50%) associated with plaque vulnerability is linked to the idea of positive plaque remodelling.[94] This condition occurs when progression of a carotid plaque leads to outward expansion of the outer wall boundary, due to the increase in plaque volume, while preserving the dimension of the lumen.[94] Thus, features of plaque vulnerability seen in plaques with mild stenosis,[55] and in some cases in the absence of any detectable stenosis, could be accounted for by positive remodelling of the plaque. Under this scenario, a plaque with relatively small luminal stenosis can be disproportionately advanced based on its composition because of outward growth. Carotid plaque thickness and normalised wall index might be a better indicator of the severity of atherosclerotic disease than the degree of stenosis,[95] but this hypothesis needs to be tested in randomised controlled trials. If a patient has a stroke ipsilateral to a vulnerable carotid plaque, they might warrant carotid revascularisation (or intensive medical treatment) even if stenosis thresholds defined by NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria are not met.[56]

Longitudinal assessment of atherosclerotic plaques

A longitudinal study has shown that progression of the carotid artery plaque—particularly, expansion of intraplaque haemorrhage volume—is associated with increased occurrence of stroke.[84] Intima-media thickness[96] and plaque progression[97] measured by ultrasound have also been shown to increase stroke risk in patients with asymptomatic carotid stenosis. However, although atherosclerosis has generally been considered a chronic and irreversible disease process, a meta-analysis of seven studies[87] showed that atherosclerosis can regress with

	Type of study	Study population	Variable analysed	Outcome event	Patients			
					All	Symptomatic	Asymptomatic	By degree of stenosis
MRI	Meta-analysis[16]	n=689 symptomatic and asymptomatic patients with mild (30–50%), moderate (50–70%), and severe (70–99%) carotid stenosis	IPH	TIA, amaurosis fugax, stroke	Event rate: 17·7% per year for IPH-positive *vs* 2·4% per year for IPH-negative (HR 5·7, 95% CI 3·0–10·9)	n=431; HR 11·7 (95% CI 5·2–26·5)	n=258; HR 3·5 (95% CI 2·6–4·7)	Not available
MRI	Meta-analysis[12]	n=363 symptomatic and asymptomatic patients with 0–99% (no, mild, moderate, and severe) stenosis	Thin or ruptured fibrous cap	TIA, stroke	HR 5·9 (95% CI 2·7–13·2)	Not available	Not available	Not available
MRI	Meta-analysis[12]	n=403 symptomatic and asymptomatic patients with 0–99% (no, mild, moderate, and severe) stenosis	Lipid-rich necrotic core	TIA, stroke	HR 3·0 (95% CI 1·5–6·0)	Not available	Not available	Not available
Ultrasound	Meta-analysis[103]	n=7557 patients with 0–99% (no, mild, moderate, and severe) asymptomatic carotid stenosis	Plaque echolucency	Stroke	Not applicable	Not available	HR 2·3 (95% CI 1·6–3·3)	n=2095; >50% (moderate stenosis), HR 2·6 (95% CI 1·5–4·6)
Ultrasound	Meta-analysis[104]	n=499 symptomatic and n=7937 asymptomatic patients	Plaque echolucency	TIA, stroke	Not applicable	n=499; RR 3·0 (95% CI 1·9–4·8)	n=7937; RR 2·7 (95% CI 1·9–4·0)	Data for asymptomatic patients only: mild-to-severe stenosis, RR 2·3 (95% CI 1·3–4·0); moderate-to-severe stenosis, RR 2·6 (95% CI 1·3–5·2); severe stenosis, RR 4·7 (95% CI 2·0–12·0)
Ultrasound	Meta-analysis[52]	n=45 828 asymptomatic patients from population-based studies	IMT	Stroke, myocardial infarction	Not applicable	Not available	HR 1·09 (95% CI 1·07–1·12) per 0·1 mm increase in IMT of the carotid artery	..

No meta-analyses were available for CT, PET and CT, or contrast-enhanced ultrasound. Meta-analyses were selected on the basis of impact factor of the publishing journal, number of patients, and number of citations. IPH=intraplaque haemorrhage. TIA=transient ischaemic attack. HR=hazard ratio. RR=relative risk. IMT=intima-media thickness.

***Table 2*: Prediction of future cerebrovascular events in symptomatic and asymptomatic patients with carotid stenosis**

high-dose lipid-lowering therapy (figure 2). In the longitudinal Rotterdam study of 1740 patients who underwent carotid MRI,[98] high-dose statins beneficially affected the composition of carotid atherosclerosis by shifting the composition from vulnerable carotid plaque with a lipid core to a more stable calcified plaque. Another meta-analysis of nine studies[99] provided evidence for an interaction between changes in levels of cholesterol and C-reactive protein, an increase in carotid plaque echogenicity, and benefits of statins on atherosclerotic plaque regression.

The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial of 10 061 patients[88] showed that anti-inflammatory treatment targeting the interleukin-1β innate immunity pathway significantly lowered the incidence of cardiovascular events compared with placebo. These results indicate that intensive medical treatment (eg, with lipid-lowering or anti-inflammatory agents) could drive plaque reversion and conversion to a stable phenotype.

Conclusion and future directions

Several imaging techniques can be used to investigate carotid artery plaques and features of vulnerability, and the information offered by these methods is—in some cases—complementary (table 1). Because of its wide availability and low cost, ultrasound is primarily used to assess a plaque's echogenicity, with good sensitivity in the detection and characterisation of vulnerable carotid plaques;[100,102–104] however, the accuracy of ultrasound compared with CT and MRI is suboptimum.[105] Furthermore, the scarcity of consistent interobserver and intraobserver agreement and a poor signal-to-noise ratio limit the use of this technique.[102] Moreover, the operator-dependent nature of ultrasound (more than other imaging techniques) renders longitudinal monitoring difficult.[102]

CT can be used to assess the burden (volume) of atherosclerotic plaques and detect ulcerations,[8] providing good detail for morphological analysis and for calcium identification.[8] The limitations of CT are mainly related

	Minimum technical requirement	Optimum technical requirement
Identification of carotid plaque components		
MRI	1·5 Tesla scanner; resolution: in-plane 0·6 mm, through-plane 2 mm; effective blood suppression for carotid plaque burden visualisation sequence	3 Tesla scanner with dedicated carotid coils; resolution: in-plane 0·6 mm, through-plane 2 mm; effective blood suppression for carotid plaque burden visualisation sequence
CT	16 multidetector row CT	≥64 multidetector row CT
Ultrasound	High-frequency linear transducer (>7 MHz)	High-frequency linear transducer (>7 MHz)
Quantitative measurements: lumen, vessel wall, and plaque components		
MRI	1·5 Tesla scanner; resolution: in-plane 0·6 mm, through-plane 2 mm; effective blood suppression for carotid plaque burden visualisation sequence; turbo spin echo; fast spin echo	3 Tesla scanner with dedicated carotid coils; resolution: in-plane 0·6 mm, through-plane 2 mm; effective blood suppression for carotid plaque burden visualisation sequence; motion-sensitised driven equilibrium; flow-sensitised dephasing
CT	16 multidetector-row scanner	64 multidetector-row scanner
Ultrasound	High-frequency linear transducer (>7 MHz)	High-frequency linear transducer (>7 MHz)
Intraplaque haemorrhage		
MRI	1·5 Tesla scanner; inversion recovery fast spoiled gradient recalled acquisition in the steady state; inversion recovery turbo field echo or inversion recovery fast spoiled	3 Tesla scanner with dedicated carotid coils; inversion recovery fast spoiled gradient recalled acquisition in the steady state; inversion recovery turbo field echo or inversion recovery fast spoiled
CT	16 multidetector-row scanner	64 multidetector-row scanner
Ultrasound	High-frequency linear transducer (>7 MHz)	High-frequency linear transducer (>7 MHz)
Fibrous cap and ulcer		
MRI	1·5 Tesla scanner; fast-field echo; spoiled gradient echo	3 Tesla scanner with dedicated carotid coils; fast-field echo; spoiled gradient echo
CT	16 multidetector-row scanner	64 multidetector-row scanner
Ultrasound	High-frequency linear transducer (>7 MHz)	High-frequency linear transducer (>7 MHz)
Plaque inflammation and neovascularisation		
MRI	1·5 Tesla scanner; turbo spin echo; fast spin echo	3 Tesla scanner with dedicated carotid coils; turbo spin echo; fast spin echo; dynamic contrast enhancement
CT	16 multidetector-row scanner	64 multidetector-row scanner
Ultrasound	High-frequency linear transducer (>7 MHz) and microbubble injection	High-frequency linear transducer (>7 MHz) and microbubble injection
Calcium		
MRI	1·5 Tesla scanner; fast-field echo; spoiled gradient echo	3 Tesla scanner with dedicated carotid coils; fast-field echo; spoiled gradient echo
CT	16 multidetector-row scanner	Multienergy spectral imaging (tissue decomposition for identification of different types of calcium)
Ultrasound	High-frequency linear transducer (>7 MHz)	High-frequency linear transducer (>7 MHz)

Table 3: **Minimum and optimum technical requirements for carotid plaque imaging**

to the radiation dose delivered to patients and the potential side-effects of contrast materials (eg, contrast-induced renal failure, hypotension, and bronchospasm). Moreover, with CT it is difficult to reliably differentiate between soft plaque components because of an overlap in Hounsfield units, and this technique cannot identify the fibrous cap and overestimates the stenosis grade because of calcium deposits.[106]

MRI is currently the most suitable imaging technique to characterise features of plaque vulnerability (table 2). Among features that can be detected, intraplaque haemorrhage has a strong association with the occurrence of future stroke.[68,69] We support the notion of adding a sequence that can detect intraplaque haemorrhage in the vessel wall to the standard MRI examination of the brain, which only adds 4–6 min scan time and can be done using standard clinical coils, making clinical translation of this feature feasible and achievable.[107] Drawbacks of MRI are the relatively longer overall study time and sensitivity of image quality to motion effects.[101]

It is important to underline that new developments in imaging techniques (eg, contrast-enhanced ultrasound for plaque neovascularisation, CT for detection of intraplaque haemorrhage, neurovascular coils for MRI plaque imaging, dynamic contrast enhancement perfusion MRI for plaque vascularity, and ^{18}F-FDG uptake for plaque inflammation)[39,44,49] cannot be considered yet as mainstream techniques for plaque imaging or as state-of-the-art techniques. The suggestion that these techniques can be used already in clinical practice is premature because it is unclear whether they can improve treatment strategies and, ultimately, their effects on outcomes have not been thoroughly investigated. Moreover, it is also important to remember that there are some technical requirements for optimum plaque imaging (table 3).[8]

Evidence indicates that making treatment decisions based on plaque features could be beneficial in terms of cost-effectiveness. Cost-effectiveness analysis aims to

	Imaging methods used	Study design	Primary endpoint	Participants enrolled (n)	Completion year*	Recruitment status
PARISK (Plaque at Risk; NCT01208025)	MRI	Prospective cohort	The main objective is to show whether imaging characteristics assessed at baseline can predict clinical events in patients with 30–69% (moderate) symptomatic carotid stenosis	244	2017	Completed
CAPIAS (CArotid Plaque Imaging in Acute Stroke; NCT01284933)	MRI	Prospective cohort	To determine the frequency, characteristics, and outcomes of vulnerable carotid artery plaques ipsilateral to an acute ischaemic stroke or transient ischaemic attack in the territory of the internal carotid artery	300	2019	Recruiting
CAIN (MRI Characterization of Carotid Plaque and Prediction of End-organ and Clinical Outcomes; NCT01440296)	MRI	Prospective cohort	To accurately characterise carotid plaque morphology in non-surgical patients with mild-to-moderate (50–70%) carotid disease and assessment of ischaemic brain disease	500	2018	Recruiting
SCAPIS (Swedish CArdioPulmonary bioImage Study; NCT0304920)	Ultrasound, CT, MRI	Prospective cohort	To use advanced imaging methods to examine atherosclerosis in the coronary and carotid arteries together with information obtained by proteomics, metabolomics, or genomics technologies to improve risk prediction for cardiovascular disease	30 000	2018	Recruiting
SRSP (Smart Risk Stroke Prediction by MRI; NCT00860184)	MRI	Prospective cohort	To determine whether the magnetic resonance SmartRisk module is effective at stratifying risk of a carotid-related cerebrovascular event in patients with asymptomatic 50–79% (moderate) carotid stenosis	300	2018	Recruiting
ROTTERDAM Scan Study	MRI	Prospective cohort	To determine how carotid plaque components and which cardiovascular risk factors are associated with the development of cerebrovascular events	3392	Not specified	Recruiting
ACTRIS (Endarterectomy combined with OMT *vs* OMT alone in patients with asymptomatic severe atherosclerotic carotid artery stenosis at higher-than-average risk of ipsilateral stroke; NCT02841098)	MRI	Randomised controlled trial	To determine whether carotid surgery combined with OMT improves long-term survival free of ipsilateral stroke in patients with asymptomatic carotid stenosis at higher-than-average risk of ipsilateral stroke when compared with OMT alone	700	2024	Not yet recruiting
ECST-2 (European Carotid Surgery Trial 2; ISRCTN97744893)	MRI	Randomised controlled trial	To determine whether in patients with carotid stenosis with low and intermediate risk for stroke, OMT alone is as effective in the long-term prevention of cerebral infarction and myocardial infarction as is revascularisation and OMT combined	200	2022	Not yet recruiting

OMT=optimised medical treatment. *Completion year estimated for studies still recruiting.

Table 4: **Ongoing imaging studies examining the effect of carotid plaque components and morphology on cardiovascular and cerebrovascular risk in symptomatic and asymptomatic patients**

identify the best approach, including economic impact and balancing the advantages with respect to risk prevention and related direct costs. In a model-analysis study,[108] two competing stroke prevention strategies were compared: first, a medical strategy comprising intensive medical treatment-based management; second, an imaging-based strategy in which the subset of patients with asymptomatic carotid artery stenosis with intraplaque haemorrhage on MRI would undergo immediate carotid endarterectomy in addition to ongoing intensive medical therapy. MRI of intraplaque haemorrhage was shown to be a cost-effective method to identify patients with asymptomatic carotid artery stenosis who are most likely to benefit from carotid endarterectomy,[108] with subsequent effects on life expectancy (12·95 years *vs* 12·65 years) and economics (US$13 699 *vs* $15 297).

Some future challenges need to be clarified. A key point is to show the link between biomarkers of plaque vulnerability and their role in clinical decision making. Several prospective studies have been published either with preliminary results or showing rationale and design, including MESA,[109] ARIC,[110] SCAPIS,[111] CAPIAS,[112] PARISK,[113] CAIN,[114] Rotterdam Scan Study,[115] CARE-II,[116] and HeCES2.[117] These studies aim to assess the value of plaque imaging for stroke risk stratification by showing that identification of vulnerable carotid plaques with MRI helps predict ischaemic stroke and improves reclassification of baseline cardiovascular risk. Several ongoing randomised clinical trials (SmartRisk [NCT00860184], CREST-2 [NCT02240862], and ACST-2 [ISRCTN21144362]) are also assessing the value of plaque imaging in stroke risk stratification and outcome. Ongoing randomised trials comparing best medical treatment alone with carotid revascularisation either select patients (eg, ACTRIS [NCT02841098]) or measure the benefit of revascularisation (eg, ECST-2 [ISRCTN97744893]) based on carotid plaque MRI or other extended imaging (table 4).

Another challenge is to define—among the many different features of plaque vulnerability—those that are best suited to identify the optimum treatment for each

Search strategy and selection criteria

We searched PubMed for reports published between Jan 1, 2013, and Dec 31, 2018. Search terms included "carotid", "plaque", "imaging", "inflammation", "CT", "CTA", "MR", "MRA", "US", "CEUS", "PET", and "molecular imaging". Further, we reviewed the reference lists of retrieved reports to identify additional articles. We did not restrict our search by language. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review, and preference was given to the inclusion of randomised controlled trials, longitudinal studies, meta-analyses, and studies with adequate methodology. Moreover, published practice guidelines and their reference lists were reviewed.

individual patient and that help to obtain an optimised risk model, which goes beyond the degree of stenosis and that incorporates morphology and composition of atherosclerotic plaques. Artificial intelligence could have a fundamental role; advances in this area of research have opened up avenues for creating novel modelling and predictive methods for clinical use. The explosion in imaging data is creating a path for such approaches because of the huge amount of information included in CT and MRI datasets. Deep learning might provide the ability to identify patterns of imaging information and improve risk stratification[118] with automated detection of those quantitative biomarkers, by automatically creating a model-of-risk incorporating all imaging features from different techniques using a multitechnique or features approach.[119]

Finally, further evaluation in randomised clinical trials is needed to establish the exact role of vulnerable carotid plaque biomarkers in clinical decision making for the prevention of ischaemic stroke. While awaiting the results of such trials, carotid plaque imaging could be already beneficial now because the presence of some detectable features is associated with a higher risk of future strokes and might warrant closer clinical follow-up and consideration for more intensive medical treatment or—in selected patients—even revascularisation.

Contributors

LS, TS, and HRJ contributed to the literature search, figure preparation, and writing of the Review. CY, TSH, DS, BAW, LHB, and MW contributed to the literature search and writing of the Review.

Declaration of interests

TSH reports grants from Philips Healthcare, outside of the submitted work. LHB reports grants from the Swiss National Science Foundation, the University of Basel, and the Swiss Heart Foundation, during the conduct of the study; personal fees and non-financial support from Amgen and Bayer, outside of the submitted work; grants from AstraZeneca, outside of the submitted work; and personal fees from Bristol-Myers Squibb and Claret Medical, outside of the submitted work. MW reports fees (equities) from MoreHealth (second opinion service), Magnetic Insight (imaging technique for rodents, technique not mentioned in the Review), and Icometrix (multiple sclerosis focus), outside of the submitted work. LS, TS, HRJ, CY, DS, and BAW declare no competing interests.

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