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

Type of manuscript: *White Paper*

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ABBREVIATIONS

18F-FDG PET: fludeoxyglucose 18F - PET

ACAS: Asymptomatic Carotid Atherosclerosis Study

AHA: American Heart Association

CCA: Common Carotid Artery

CE: Contrast-enhancement

CEA: Carotid Endarterectomy

CT: Computed Tomography

CTA: Computed Tomography Angiography

CUBE: the GE name of their sequence and not an acronym

DCE-MRI: Dynamic Contrast Enhancement Magnetic Resonance Imaging

DIR: Double Inversion Recovery

DSA: Digital Subtraction Angiography

ECST: European Carotid Surgery Trial

FC: Fibrous Cap

FDA: Food and Drug Administration

FOV: Field-of-View

FSD: flow-sensitive dephasing

GBCA: gadolinium-based contrast agents

GRE: Gradient Echo

HU: Hounsfield Unit

IMT: Intima-media Thickness

ICA: Internal Carotid Artery

IPH: Intra-plaque Hemorrhage

IT: Inversion time

IVUS: Intra-vascular Ultrasound

keV: kiloelectronvolt

LRNC: Lipid-rich Necrotic Core

MPRAGE: Magnetization Prepared Rapid Acquisition Gradient Echo

MRA: Magnetic Resonance Angiography

MRI: Magnetic Resonance Imaging

MSDE: Motion-sensitized driven-equilibrium

NASCET: North American Symptomatic Carotid Endarterectomy Trial

PET: Positron Emission Tomography

PGLA: Polymer hydroxyl acidic core

QIR: Quadruple Inversion Recovery

SNAP: Simultaneous Non-contrast Angiography and intraPlaque Hemorrhage

SNR: Signal-to-Noise Ratio

SPACE: Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (Siemens)

TIA: Transitory Ischemic Attack

TOF: Time-of-Flight

US: Ultrasound

USPIO: Ultra-small Super-Paramagnetic Iron Oxide

VISTA: Volume ISotropic Turbo spin echo Acquisition (Philips)

ABSTRACT

Identification of carotid artery atherosclerosis is conventionally based on measurements of luminal stenosis and surface irregularities using in-vivo imaging techniques including ultrasound, CT and MR angiography, and digital subtraction angiography. However, histo-pathological studies demonstrate considerable differences between plaques with identical degrees of stenosis and indicate that certain plaque features are associated with increased risk for ischemic events. The ability to look beyond the lumen using highly developed vessel wall imaging methods to identify plaque vulnerable to disruption has prompted an active debate as to whether a paradigm shift is needed to move away from relying on measurements of luminal stenosis for gauging risk of ischemic injury. Further evaluation in randomized clinical trials will help to better define the exact role of plaque imaging in clinical decision-making. However, current carotid vessel wall imaging techniques can be informative. The goal of this paper is to present the perspective of the ASNR Vessel Wall Imaging Study Group as it relates to the current status of arterial wall imaging in carotid artery disease.

INTRODUCTION

The word "atherosclerosis" is derived from the two Greek words "athera" (mush) and "sclerosis" (hardening), indicating hardening of the vascular wall. This disease is highly prevalent in developed countries with carotid artery narrowing reported in up to 75% of men and 62% of women aged 65 years and older[1]. Stroke is the second most common cause of death worldwide[196] and approximately 18-25% of all strokes are due to carotid atherosclerotic disease[197].

Conventionally, identification of atherosclerosis affecting the carotid artery is based on measurements of the degree of luminal stenosis and surface irregularities[2,3] by ultrasound, catheter based angiography, and nowadays CTA or MRA[4,5]. However, histo-pathological studies initially performed on coronary arteries and subsequently on carotid arteries, demonstrate considerable differences between plaques with identical degrees of stenosis. These observations led to research indicating that certain plaque features are associated with increased risk for ischemic events[6,7,8]. The more recent introduction of fast multi-detector row Computed Tomography (CT) technology, high field MRI, and advanced ultrasound (US) systems has enabled accurate characterization of plaque features that relate to risk of ischemic injury[9,10,11,12]. The ability to look beyond the lumen using advanced wall imaging methods to identify "vulnerable plaque"[13,14] is spurring a paradigm shift away from simple measurement of percent luminal stenosis for gauging risk of ischemic injury. Currently, characterization of the vessel wall and atherosclerotic plaque are the focus of several ongoing research studies that are investigating the optimal approach to vulnerable plaque imaging[18,167,168].

Further evaluation in randomized clinical trials is needed to establish the exact role of plaque imaging in clinical decision-making. However, carotid vessel wall imaging techniques may be beneficial at present. For example, improved visualization of the location and extent of atherosclerotic plaque would assist in surgical planning prior to endarterectomy or carotid artery

stenting. Vessel wall imaging may also be helpful in borderline clinical cases. Identification of carotid plaque harboring a large lipid-rich necrotic core (LRNC) plaque with ulceration and intra-plaque hemorrhage (IPH) despite guideline based medical therapy in a patient with repeated strokes and 50% carotid stenosis may lead to consideration for carotid endarterectomy. In asymptomatic patients, vessel wall imaging with large LRNC may represent the phenotype of atherosclerotic disease amenable to more intensive lipid-lowering therapy[211]. Similarly, progressive vulnerable plaque features with increasing IPH in asymptomatic carotid stenosis may benefit from more intensive lipid-lowering therapy[122,212].

The goal of this paper is therefore to present the perspective of the ASNR Vessel Wall Imaging Study Group on the current status of arterial wall imaging in carotid artery disease.

CLINICAL BACKGROUND AND PHYSIOLOGY

For several years, digital subtraction angiography (DSA) remained the primary imaging method for studying carotid arteries for detecting stenosis secondary to atherosclerotic plaque[19,20]. The method provides optimal spatial resolution for defining the opacified lumen, the associated degree of luminal stenosis, and plaque-related luminal changes that include lumen irregularity and plaque ulcerations[21,22].

Carotid endarterectomy (CEA) trials were undertaken during the 1980s to the mid-1990s that quantified the benefit of CEA according to the degree of luminal stenosis[2,23,24,25,26]. These studies became the basis for considering degree of stenosis as the primary metric for stratifying subsequent stroke risk and selecting the optimal therapeutic approach (surgery vs. best medical management)[23]. In particular, three multi-center randomized studies, ECST (European Carotid Surgery Trial), NASCET (North American Symptomatic Carotid Endarterectomy Trial) and ACAS (Asymptomatic Carotid Atherosclerosis Study) evaluated cut-offs for degree of carotid stenosis as they relate to stroke risk reduction by CEA[24,25,26].

NASCET, ECST and ACAS used DSA to assess the percent reduction in luminal diameter of the artery. The methodology for carotid stenosis quantification is debated because NASCET and ECST used indirect ratio-percent methods[16]. Stenosis measurements with NASCET and ECST differ substantially: with the ECST method twice as many stenoses were classified as severe and less than a third of the number of stenoses as mild compared to the NASCET method [27]. Techniques that enable identification of both outer and inner walls of the artery might lead to more accurate assessment of risk. *Bartlett et al*[28] suggested use of this direct diameter based-measurement to overcome the limitations of the percent-based methods and the results they found suggest that this technique could be efficient.

The degree of luminal stenosis as a marker of atherosclerotic disease severity has been criticized because of observations that plaques producing only mild to moderate stenosis may still lead to acute cerebral infarction[15,17,29,30,31,32,64,148]. Histopathologic evaluation of these plaques showed that plaque erosion and disruption were common morphologic features found in symptomatic lesions, indicating that luminal narrowing was not the sole predictor of cerebrovascular events [29,30,31].

These studies introduced the following new concepts: (**1**) the degree of carotid stenosis is a weak indicator of the volume and extension of carotid plaque[33,34,35]; (**2**) a set of plaque features, identifiable by imaging are closely linked to the development of ischemic symptoms, and (3) these features can significantly increase the risk of stroke regardless of the degree of stenosis[36,37,38,39] Thanks to advancements in the imaging techniques to specifically target the vessel wall as opposed to the vessel lumen, considerable research effort is underway to identify those plaque-related parameters that, together with the degree of stenosis, can more accurately predict the presence of vulnerable plaque and the associated risk of ischemic events.

More than 30 years ago, *Imparato et al*[6] found that there were certain plaque features, such as IPH, that were associated with an increased risk of plaque rupture and distal embolization. Since that time, roughly 1000 papers have been published on IPH as well as characterizing additional

features associated with plaque vulnerability, including the thickness of the fibrous cap, rupture of the cap, presence and size of the LRNC, and the presence of active plaque inflammation. Vulnerable plaques also tend to be characterized by an eccentric distribution, an irregular surface of the intimal layer, or superficial ulcerations with intimal exposure.

- Imaging Features of Plaques at Risk for Stroke

US can assess plaque composition based on echogenicity with classification systems proposed by *Geroulakos et al[53]* and *Bluth et al[54]*. The presence of echogenic/hypoechogenic elements are associated with the LRNC[55,56] whereas hyperechogenic regions or the presence of acoustic shadowing is indicative of calcification. US is sensitive in identifying calcification but when present, the ensuing acoustic shadowing limits visualization of tissues deep to the calcification[57].

CT has been used to type plaques based on Hounsfield attenuation. *De Weert et al[40,41]* categorized plaques as fatty for attenuation values < 60 HU, mixed for attenuation values between 60 HU and 130 HU, and calcified for attenuation values > 130 HU. By applying these thresholds, it is possible to identify those plaques with a LRNC from others with a prevalent expression of myofibroblasts, hemorrhage, or calcification[75]. Based on this analysis, calcified plaques were found to be 21 times less likely to be symptomatic than non-calcified plaques[45] whereas fatty plaques were clearly associated with an increased risk of rupture[39,46,].

MRI has the ability to distinguish plaque components such as the LRNC, fibrous tissue, and IPH with high accuracy[47,48,49,50,68,151]. The identification of calcified components can be more challenging than CT but MR typically offers good results[51,52].

- Luminal Morphology and Ulcerations

The morphology of the luminal surface of carotid plaques can be classified as smooth, irregular or ulcerated[58]. A **smooth surface** is identified as plain luminal morphology without any

sign of ulceration or irregularity. An **irregular surface** indicates the presence of small alterations of the luminal surface on the luminal profile of the plaque; this condition is considered a risk factor for embolism and is associated with an increased risk of TIA/stroke[49]. The third type of morphology is the **ulceration**. Plaque ulceration has been defined as "an intimal defect larger than 1 mm in width, exposing the necrotic core of the atheromatous plaque"[59]; however other authors suggested other (smaller) sizes[153,154,155]. The NASCET study demonstrated a significantly increased risk of cerebrovascular events in plaques with ulcerations[2].

- Intra-plaque hemorrhage

IPH is a common feature of atherosclerotic plaques and is considered one of the identifying features of vulnerable plaque[64]. A number of studies have found a statistically significant association between the presence of IPH and cerebrovascular events[65,192] and IPH has been implicated in plaque progression[231]. It is thought that the rupture of neovessels or plaque rupture itself causes IPH and some conditions such as inflammation, metabolic disease or diabetes may precipitate this event[67]. Recent literature also indicates a potential role of blood pressure[66,191].

Fissured Fibrous Cap and Lipid Rich Necrotic Core (LRNC)

The fibrous cap (FC), which separates LRNC from vessel lumen, is considered one of the most important features of the carotid artery vulnerable plaque model. The FC is a layer of fibrous connective tissue and contains macrophages and smooth muscle cells within a collagen-proteoglycan matrix associated with T-lymphocytes[78]. Vulnerable plaques are characterized by the presence of a thin FC covering a large LRNC containing macrophages and inflammatory cells. In both cross-sectional and longitudinal studies[38,122], the LRNC size was found to be a strong predictor of fibrous cap disruption. The fissuring or rupture of the FC exposes the LRNC to luminal blood activating the thromboembolic cascade. Therefore, LRNC and FC status are expected to be associated with risk of cerebrovascular events, as shown in single-center experience[170,192,193] The

intact thick FC is associated with a low risk of plaque rupture, a thin FC is associated with a mild risk, while a fissured FC is associated with a high risk of plaque rupture[81]. Additionally, percent LRNC area exceeding 40% of vessel wall area indicates a high risk for plaque rupture while percent luminal stenosis did not correlate with plaque rupture [122].

- Neovascularization and inflammation

Intraplaque neovascularization arises from newly formed microvessels that grow into the intima through breaks in the medial wall and are characterized by leaky capillaries with an endothelial lining that is immature, and imperfect due to the harsh atherosclerotic environment. Histopathological studies have demonstrated that neovessels can be found within carotid artery plaques, and the degree of neovascularity is associated with the "activity" of the plaque in terms of inflammation and increased risk of neovessel rupture and hemorrhage (IPH)[87,88]. Inflammation of unstable "vulnerable" atherosclerotic plaques was first identified in coronary artery lesions and subsequently demonstrated in carotid artery plaques[102,103].

The recruitment of inflammatory cells in atherosclerotic lesions is a constitutive phenomenon seen throughout the process of lesion initiation and plaque growth. In addition, inflammation appears to play a role in the process of plaque disruption[104]. Inflammatory cells are typically found in the plaque shoulder, in the cap, or both[103]. In many instances and particularly in advanced plaques with a complex architecture, inflammatory cells tend to accumulate focally within plaques[103,104].

Several types of inflammatory cells are detected in the carotid artery vulnerable plaque and some studies have found that the presence of macrophages is significantly associated with the risk of plaque rupture[105,106,107]; therefore, the identification of macrophages has become the target of imaging studies devoted to the detection of plaque inflammation[108,109,110,111,112].

- Plaque remodeling (positive vs negative)

The concept of plaque remodeling was initially described for atherosclerotic lesions in coronary arteries but is largely accepted for other vascular beds including the carotid arteries[117,118]. Carotid plaques can show either positive or negative remodeling or both. Positive remodeling is dilatation of the vessel wall in response to an increase in plaque volume with little or no compromise of the vessel lumen as the vessel initially attempts to maintain normal lumen diameter[119]. Negative remodeling is present when the vessel lumen diameter is decreased (stenosis).

- Plaque Volume

Recent studies have demonstrated that the volume of the carotid artery plaque could play a role in determining plaque "vulnerability" and risk of cardiovascular events[161]. Increasing plaque volume predicted cardiovascular events[163]. Some authors have hypothesized that the plaque volume may be a better indicator of the severity of atherosclerotic disease than the degree of stenosis[122]. Non-invasive in vivo assessment of atherosclerotic plaque volume and the relative contribution of different plaque components clearly have important clinical implications as they relate to risk assessment for ischemic events. In addition, it has been shown that higher LRNC volumes appear to be associated with the presence of plaque ulcerations, representing a significant risk factor for the development of cerebrovascular events[125]. Furthermore, plaque composition is known to change with increasing plaque volume. More specifically, there is an increase in the proportion of lipid and calcification with increasing plaque volume[125]. Plaque length, which relates more directly with plaque volume than degree of stenosis, has been shown to be an independent risk factor for peri-procedural complications and excess restenosis rate in a secondary data analysis of the CAVITAS Study[207].

- Summary concepts

It is clear that there are several plaque features of increased clinical risk supported by associations with endarterectomy specimen analyses. It is of utmost importance to test management strategies based on these MRI-defined features of risk before treatment guidelines can be established.. Currently there are several prospective trials intended to examine the value of prospective plaque imaging (ARIC, PARISK, CAPIAS, CARE-II, CAIN)[152,202,203,204,205,208]. In the meantime, it is possible that carotid plaque characterization may be of immediate clinical value today. Given that the presence of IPH, large LRNC, and/or thin-ruptured FC are associated with a higher risk of future cardiovascular events, the presence of these plaque features may warrant closer clinical follow-up and consideration for more intensive medical therapy. Despite attempts to encourage all physicians to manage atherosclerosis medically with current evidence-based guidelines, many patients are not receiving high intensity lipid lowering therapy even when indicated. Providing additional information based on carotid plaque MRI identification of IPH, large LRNC, and/or thin-ruptured FC may improve patient/physician compliance with current therapeutic guideline. If patients receiving standard-of-care medical therapy have repeated strokes ipsilateral to carotid plaque harboring "vulnerable" plaque features, they may warrant surgical intervention even if they do not meet the stenosis thresholds by NASCET criteria.

CURRENT IMAGING STATE-OF-THE-ART

In this section of the paper we will summarize the imaging techniques that can be used in the imaging of the carotid artery wall.

- *US*

US is generally accepted as the standard imaging modality for first-line diagnosis of atherosclerosis of the carotid artery[126]. US has shown very good results in the identification and characterization of high-risk plaques in patients with atherosclerosis[127]. In particular, the use of micro-bubble contrast material facilitates assessment of vulnerable plaque features such as the

presence\absence of neovascularization[97,98]. The recently introduced volumetric US technology seems to add further value to this technique by improving the inter-observer concordance and increasing the spatial coverage[128]. Another US technique that could be used for carotid plaque characterization is intra-vascular US (IVUS). The advantage of IVUS is excellent spatial resolution which is possible given the short distance between the probe and the carotid plaque that permits the use of high frequency (up to 50 MHz) insonation without excessive attenuation.

US, however, suffers from some key limitations. In patients with short muscular necks, it may be very difficult to identify the carotid bifurcation[129]. In obese patients or in patients that have had radiotherapy, US assessment of the carotid arteries can be challenging. Another limitation of US is the evaluation of highly calcified plaques that create acoustic shadowing that can reduce visualization of the lesion[130]. Furthermore, US is less capable of detecting additional, more distally located ("tandem") stenoses than CTA or MRA. It is important to underline that IVUS is invasive and is only performed in selected cases that are largely treated with carotid artery stenting and thus no pathologic correlate is available. IVUS identification of the fibrous cap or visualization of friable plaque may correlate with increased risk of emboli. Moreover, the small cohorts of assessed IVUS patients, as well as the potential risk related to the procedure, need further analysis before it is included in the routine clinical work-up[158].

Luminal morphology and ulcerations: It has recently been shown that 3D US could be effective in the detection of ulceration in carotid artery plaques[164,165].

Intra-plaque hemorrhage: A few papers have assessed US performance in the detection of IPH and the results demonstrated low sensitivity and specificity[76,77].

Fibrous cap status: Some authors have explored the potential of conventional US to characterize FC but the results obtained were sub-optimal[198,199,200]. Recent papers[156,157] have suggested that intra-vascular ultrasonography (IVUS) can assess in detail plaque structure and FC but with associated procedural risk.

Neovascularization and inflammation: several recently published[95,96,97,98] contrast-enhanced ultrasound studies found that sonographic enhancement correlates with intraplaque neovascularization in carotid endarterectomy specimens. However, the reproducibility and utility of this modality for clinical care are not well established[99].

It is important to underline that US can also be used to assess those initial subtle wall alterations in the very early phases of atherosclerosis progression, for example, the intima-media thickness (IMT), that is considered a significant predictor of coronary and cerebrovascular events[131,132].

Recent studies assessed the reliability of US for assessing certain plaque features. Bar et al[189] assessed plaques in 30 patients. Inter-rater agreement values for the following plaque features were as follows: homogeneity 96% ($\kappa = 0.84$; $P < .001$), surface characteristics 90% ($\kappa = 0.77$; $P < .001$), and echogenicity 86% ($\kappa = 0.60$; $P < .001$). The correlation coefficient for plaque content and volume measurement agreement was 0.81 and measurements did not differ significantly (P=n.s.). In a paper published in 1999 by Hartmann[190] the kappa values and 95% confidence intervals for inter-rater reproducibility were 0.05 (-0.07 to 0.16) for plaque surface structure, 0.15 (0.02 to 0.28) for plaque heterogeneity, 0.18 (0.09 to 0.29) for plaque echogenicity, and 0.29 (0.19 to 0.39) for plaque calcification. The upper bounds of all of the confidence intervals were below the 0.40 level indicating very low reliability.

- CT

Modern CT scanners can provide exquisite, rapid high resolution imaging of the carotid artery lumen and the arterial wall. The introduction of multi-energy technology provided a tremendous boost to the development of CT techniques and constant advances in detector technology, in spatial and temporal resolution and release of advanced software for image reconstruction have helped to consolidate this technique as a reliable tool for the evaluation of

arterial pathology, with particular success in the detection and characterization of carotid atherosclerosis.

Because of its spatial resolution CT imaging seems to be a promising tool for the quantification of the volume of the carotid plaque as well as for the volume quantification of plaque sub-components (fatty – mixed – calcified) (**Figure 1**). Moreover, the introduction of multi-energy technology is opening new options in tissue characterization because the different tissue components show different attenuation levels with varying keV values[42].

Luminal morphology and ulcerations: CT offers very good results in detecting ulcerations when compared to histopathology (**Figure 2**), with performance significantly better than US[60,61], but the presence of a halo or edge blur may hinder detection of smaller ulcerations.

Intra-plaque hemorrhage: Detection of IPH using CT is challenging and conflicting results have been reported. While some authors have found that CT density is slightly higher in fatty plaques with IPH identified by MRI compared to plaques without IPH[201], others found no significant differences in HU of fatty plaques with and without IPH identified by MRI[202]. Other authors found a correlation between the presence of IPH and low HU value (< 30 HU)[74,75] which might be explained by the associated presence of LRNC. Recently, some authors suggested that the rim sign on CTA (soft tissue plaque with adventitial calcifications) as well as maximum soft plaque thickness could be predictive of carotid IPH[214].

Fibrous cap status: The assessment of the status of the FC using CT is complex because of the artifacts related to the edge-blur and halo effects, but authors suggest that CT can be used to assess the FC status, in particular to identify rupture[85,86]. Notably, it seems that the rupture of the FC correlates with the presence of post-contrast plaque enhancement in CTA analysis[36].

Neovascularization and inflammation: The degree of post-contrast plaque enhancement has been shown to be associated with the extent of neovascularization on CT[43]. The adventitial neovascularization has been assessed with both MR[159] and CT[91,92]. *Romero et al.* showed adventitial neovascularity on CTA to be significantly more common in symptomatic than in asymptomatic

patients with ≥70% stenosis[91] and for stenosis between 50% and 70%[92] and similar findings have been reported by MRI[159].

Plaque remodeling: CT studies have found that positive carotid remodeling was significantly greater in patients with cerebral ischemic symptoms than in asymptomatic patients and that the extent of expansive remodeling may indicate underlying atherosclerotic plaque vulnerability[120,121].

Plaque volume: CT can calculate the volume of the carotid artery plaque and determine the volume of the sub-components, according to HU threshold[123]. Further it has been shown in a CT/MRI comparison study that the best discriminating factor for predicting a complicated AHA type VI plaque is the thickness of the fatty plaque component with a receiver operating characteristic area under the curve of 0.89[202].

CT limitations: CT imaging has 3 main limitations: 1) the radiation dose delivered to patients, 2) the risk related to the administration of contrast material, and 3) the limited fatty tissue contrast. Diagnostic radiation exposure and the consequent potential radiation hazards represent a significant issue [133,134] particularly when longitudinal monitoring is required. The second limiting factor of CT is the potential anaphylactic reaction to contrast material[136,137] and contrast-induced nephropathy that is a common form of hospital-acquired acute renal failure[138,139]. A further limitation of CT is the limited published information concerning reliability of this technique and the prospective value of CT-based plaque features on stroke risk and / or stroke recurrence.

- MR

The use of high field strength (1.5 - 3 T) and dedicated surface radiofrequency coils improve the signal-to-noise ratio that allows for the evaluation of plaque components and investigation beyond the simple assessment of stenosis measurements. Multi-contrast carotid MRI (including T1-W, T2-W, and PD and TOF) can characterize plaque components (e.g., fibrous cap, LRNC, calcification, and intraplaque hemorrhage) without administration of contrast agents. Contrast-

enhanced MRI improves tissue characterization[48,49] and offers information on the presence of neovascularization (**Figure 3**, **Figure 4**).

Luminal morphology and ulcerations: MRI detects plaque ulcerations with sensitivity similar to CT[63] (**Figure 2**). *Etesami et al*[63] demonstrated that the use of contrast-enhanced MRA techniques improved the sensitivity for ulcerations by 37.5% compared to an unenhanced Time-of-Flight sequence.

Intra-plaque hemorrhage: MRI is considered the best imaging technique for the detection of IPH (**Figure 3, Figure 5**). Several studies have shown that the appearance of IPH depends on the oxidative state of the hemoglobin[69,70,71]. Because of the sensitivity of MRI in detecting IPH and the risk attributed to this feature, some authors suggest that MRI is the best modality for imaging carotid artery vulnerable plaque[10,64,68,72,73]. During the subacute and chronic phases, IPH appears bright on T1-weigthed imaging due to the relatively short T1 of methemoglobin. This phenomenon has been exploited using widely available sequences such as MP-RAGE, though other heavily T1-weighted techniques have been developed to satisfy this purpose such as MATCH and SNAP (**Figure 6, 7**). In MATCH, hyper-T1 contrast weighting is achieved by using inversion preparation and data acquisition at the background nulling point, and thus IPH can be exclusively visualized with a near dark background; on the other hand, background tissues can readily be visualized on other contrast weightings, thanks to the inherently co-registered multi-contrast acquisition[181,182] (**Figure 7**). IPH detection using 3D SNAP enables greater conspicuity of the lumen boundary compared to MP-RAGE[179] (**Figure 5, 6, 7**). SNAP provides the advantage of 3D isotropic resolution, as well as simultaneous bright-blood angiography to detect stenosis or ulceration that may be co-localized with IPH[230]. It is worth noting that it is not necessary to restrict carotid wall imaging to dedicated, small field-of-view (FOV) surface coils for IPH detection since this can be achieved at lower spatial resolution using large FOV neck coils[68,170,213] (**Figure 3**). In fact, IPH detection can be achieved on the mask sequence acquired as part of a routine contrast-enhanced MRA[68] (**Figure 3**).

Lipid-rich necrotic core: Initial research demonstrated that LRNC could be detected as a focal hypointense region on T2-W images[177,178] (**Figure 8**). Multiple studies have confirmed the improved detection of LRNC seen as a focal non-enhancing region on contrast-enhanced T1-W images within the carotid vessel wall[48,49]. Larger LRNC size correlates with future ipsilateral carotid symptoms. All validation of LRNC detection/quantification and predictive features has been based on multi-contrast carotid plaque MRI protocol using dedicated carotid coils. Recent work has suggested the ability to detect large LRNC using commercially available 3D T1-W sequences and large FOV neck coils. The Canadian Atherosclerosis Imaging Network (CAIN) has recently completed a prospective, multi-institution study using large FOV neck coils and commercial sequences from a variety of MR vendors to detect LRNC and IPH. When fully analyzed, CAIN may give us additional information about the ability of IPH and LRNC size detected with large FOV neck coils and commercial sequences to predict future ipsilateral events.

Fibrous cap status: MRI can assess fibrous cap status[49,82], as opposed to the other non-invasive imaging modalities such as CT and US[85]. A regular (thick) FC is characterized by the presence of a juxtaluminal band of low signal on time-of-flight (TOF) MR images and / or a hyperintense juxtaluminal region on contrast enhanced T1w images whereas a thin FC is present when this band of low signal on TOF or the hyperintense region on CE-T1w is not visible or when the juxtaluminal hyperintense region on CE-T1w MRI is interrupted. The fissured fibrous cap is characterized by two distinct features: 1) the absence of the juxtaluminal band of low signal and 2) the presence of a bright gray region adjacent to the lumen, corresponding to plaque hemorrhage and/or mural thrombus[83,84]. As shown by *Wasserman et al* and *Cai JM et al* [48,49,], contrast enhanced imaging could be useful for improving delineation of the cap compared to non-contrast (T2), and CE T1w imaging can be used to quantify the fibrous cap and the LRNC. Although resolving a thin fibrous cap defined by pathologic criteria would necessitate a higher field strength to overcome signal constraints, distinguishing thin/ruptured from thick fibrous cap thicknesses can be achieved at 1.5T (**Figure 8**)[90,232].

Consistent visualization of the FC requires dedicated carotid surface coils. *Yuan C et al*[84] and others have shown that the fissured FC has a statistically significant association with the presence of cerebrovascular symptoms[81] and is associated with a higher risk of ischemic symptoms in prospective studies[170,193].

Neovascularization and inflammation: There are new contrast agents using iron particles (ultrasmall super-paramagnetic iron oxide (USPIO) or P947)[149,150] that can evaluate plaque inflammation via uptake by phagocytic cells within the inflamed vessel wall. Small particle-based MRI contrast agents (iron oxide) can be used to evaluate the presence of plaque inflammation. These iron oxide particles enter atherosclerotic plaques with the agents accumulating in macrophages transformed from blood monocytes attracted by inflammatory mediators[108]. High-risk inflamed plaques contain a focal area of signal loss on MR images, due to iron oxide accumulation[109]. Iron nanoparticles (10–300 nm-sized) are also bound to antibodies, drugs, peptides, polysaccharides, and avidin–biotin cross-linked with polymers are used to assess endothelial function in animal models. Polymer hydroxyl acidic core (PGLA, PLA), dendrimers [polyamidoamine (PAMAM), diaminobutane (DAB)] have been described as suitable to functionalize the surface of superparamagnetic iron oxide[145] (15–60 nm SPIO) particles, allowing for ligand binding. Ligand-bound SPIO (anti-VCAM-1 and anti-E-selectin antibody conjugated SPIO) can cause dephasing and loss of T2* signal intensity due to susceptibility effects and are suitable for passive targeted imaging of inflammation in cardiovascular tissue[145]. In addition to iron oxide nanoparticle, various other nanoparticles are being used for molecular imaging of atherosclerosis in animal models e.g. liposome vesicles (50–70 nm) for US[141] / MRI[142], perfluorocarbon core emulsions (200–300 nm) for MRI, US, fluorescence, and nuclear imaging, CTI[143], HDL, and LDL micelles for MRI[144]. Other types of particles such as gold, carbon nanotube fullerenes (4 nm), quantum dots cadmium selenide spheres (2–10 nm) and metal-based agents are in the process of standardization and may be useful in fluorescent imaging[146]. Moreover, other

investigators have reported the possibility of viral capsid protein cages with gadolinium as potential nanospheres for drug encapsulation and imaging[147].

A recent MR study[93] showed that enhancement of carotid plaque after administration of gadolinium is associated with neovascularization (p < 0.001) (**Figure 4**). The correlation between the degree of plaque enhancement and the degree of neovascularization, which is itself linked to the degree of plaque inflammation, was also confirmed at histology in a recent study by *Millon et al*[94]. Investigations have shown that inflammatory cells are also present at the interface with the underlying necrotic core and in the plaque shoulder region[79,80]. From the imaging point of view, it is possible to distinguish two different types of neovascularization: 1) adventitial neovascularization and 2) intra-plaque neovascularization. The adventitial neovascularization has been assessed with MR[159]. Ectopic neovascularization in the intima and media is a hallmark of advanced atherosclerotic lesions but the adventitial layer is a fundamental target because it serves as the main source of ingrowth of new vessels. The degree of neovascularity measured using gadolinium perfusion methods correlated with adventitial perfusion as measured by its transfer constant[89] (**Figure 9**). *Wasserman et al.* categorized the circumferential enhancement (0, absent; 1, <50%; 2, ≥50%) on post-contrast MR by finding an association between grade of adventitial enhancement and cerebrovascular events. Plaque perfusion imaging using DCE-MRI has been shown to give reproducible physiological measurements of vasa vasorum[194,195]. However, protocol compliance may be more important for functional imaging such as DCE-MRI as compared to anatomic imaging.

Plaque volume: Recently published studies show the utility of MRI for this type of quantification [124,166]. In general, the reliability of MRI for plaque assessment has been very good. A study published by Wasserman in 2010[166] found that scan reliability for CCA lumen area was 0.94 whereas for ICA lumen area 0.89. In the assessment of the total wall volume the value was 0.79 but in the assessment of LRNC volume the value was very low (0.3). The authors found that overall

reliability is primarily related to reader variability rather than scan acquisition. The CV values for the plaque area or plaque volume are between 3-6%, as demonstrated by *Saam et al*[187,188].

Imaging studies have documented changes in atherosclerotic plaque volume and composition, and progression of subclinical lesions into rupture-prone plaques[215,216,217,218,219]. The ability to monitor these changes might contribute to our ability to estimate risk and assess pharmaceutical treatment efficacy[225]. For example, changes in plaque structure that correspond with a clinical event help to identify that plaque as a culprit lesion, which puts it at a higher risk for future stroke[15,200,226]. Several studies have reported using MRI for longitudinal analysis of carotid plaque variations[215,216,217] with fewer reports using CTA[218,219].

MR limitations: An important limitation to contrast-enhanced MRI evaluation of plaque that has recently emerged is the potential for gadolinium toxicity, particularly when longitudinal monitoring is required. Recent studies have reported the accumulation of gadolinium in various tissues of patients without renal impairment, including in bone, brain, and kidneys[221,222,223], and in July 2015 the U.S. Food and Drug Administration (FDA) published a safety announcement that it is investigating the risk of brain deposits associated with the repeated use of gadolinium contrast agents in MRI[224], stating "*To reduce the potential for gadolinium accumulation, health care professionals should consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary. Health care professionals are also urged to reassess the necessity of repetitive GBCA MRIs in established treatment protocols*". This risk must now be weighed against the potential radiation hazard described earlier that limits longitudinal plaque monitoring by CT.

- Advanced algorithms to carotid artery plaque characterization

With the development of deep learning technology and plaque characterization algorithms applied to medical imaging, it is now possible to identify, classify and quantify target features from

imaging datasets such as total carotid artery plaque volume and plaque sub-components detection (calcium, IPH, lipid core)[227,228]. Deep learning technology has experienced rapid progress in health care over recent years with early reports of implementation in carotid imaging[229] raising the prospect of routine use in the clinical setting once validated.

- Functional – Molecular Imaging

"Molecular" imaging techniques have been gaining popularity. The objective of molecular imaging is to provide biological insight into the identification and classification of carotid artery plaques especially those at high risk. In atherosclerotic plaques, multiple and complex reactions take place at the molecular and cellular level, with various atherosclerosis-related biomarkers present at different stages of disease progression[140]. Conventional imaging with US, MR or CT cannot identify these components because of limited imaging contrast and therefore several methods have been proposed that use external contrast agents targeting these specific biomarkers.

A wide variety of studies have assessed the diagnostic potential of nuclear medicine techniques for imaging and quantifying plaque inflammation, such as by PET using the widely-available 18F-FDG or newer radiotracers such as ^{18}F-fluorocholine (**Figure 10**)[114,115,116] . Nuclear medicine tracer techniques have also shown efficacy in the identification of neovascularization[100,101].

Because vulnerable plaques are infiltrated by lymphocytes and macrophages with the latter cell population capable of taking up 18F-FDG from the interstitial spaces, 18F-FDG PET can be used to directly detect plaque inflammation in various anatomic locations[113]. In recent years, a number of studies have assessed the diagnostic potential of 18F-FDG PET to image and quantify plaque inflammation[114,115] as well as monitoring the reduction of plaque inflammation resulting from statin therapy[116]

RECOMMENDATIONS

Carotid MRI

Background: Results from recently published meta-analyses support the hypothesis that MRI detection of carotid IPH is associated with increased risk for future primary and recurrent ischemic neurological events[169,170,171]. Furthermore, absence of IPH portends a benign clinical course, even amongst patients with symptomatic 50-99% carotid stenosis[171]. Other plaque features associated with increased risk include identification of a large LRNC and a thin or ruptured fibrous cap[170].

Goals: (1) To provide general guidelines for carotid MR vessel wall imaging with recommended imaging sequences, spatial resolution and coverage. Guideline considerations are that the protocol can be applied broadly across a spectrum of clinical scanners and not require specialized software or research keys for implementation. (2) To recommend future areas for technical development and clinical expansion needs.

Essential Features for Identification with Carotid Plaque Imaging: Any MRI protocol for plaque imaging should be able to identify the following atherosclerotic plaque characteristics:

1. Stenosis and luminal surface condition (fibrous cap and ulceration).

2. Presence of intraplaque hemorrhage.

3. Presence of lipid rich necrotic core.

4. Plaque burden and distribution.

Minimum MRI Protocol Requirements for Identification of Essential Plaque Features (1.5T and 3T): Recommended *minimum* sequence requirements are

- Resolution: In-plane 0.6 mm, through-plane 2 mm.

- Longitudinal coverage: 3-4 cm centered on the carotid bifurcation.

- Effective blood suppression for plaque burden visualization sequence.

The protocol may include any combination of sequences that meet the minimum requirements set forth above. The sequences used can be either 2D or 3D or a combination provided

that they together meet the minimum sequence requirements above. Overall scan time can be adjusted based on field strength and availability of specialized hardware such as carotid phased array coils. 3T scanners are recommended for improved SNR.

Example Protocols: Four protocols are presented based on considerations for 2D and 3D imaging and the use of Gadolinium contrast agents (**Table 1-4**). If patients are able to undergo Gadolinium contrast injection, its use is recommended for the detection and quantification of LRNC and the delineation of the fibrous cap[48,172]. Use of large coverage 3D sequences can detect plaques extending beyond the 4 cm coverage centered on the bifurcation and are preferable. Carotid coils are recommended for use with all protocols, although large FOV neck coils can detect IPH. It is possible to add a 4 minute 3D MPRAGE sequence to routine clinical carotid MRA protocol. The protocol is similar to Table 1, but with 0.8 mm isotropic resolution using a large FOV neck coil instead of 0.6 mm using dedicated carotid surface coils. Focal regions of T1 hyperintensity within the carotid plaque that is 1.5x greater than the adjacent sternocleidomastoid muscle can be used to identify IPH.

MSDE[173]/FSD[174] flow suppression is required for 3D SPACE/CUBE/VISTA to ensure effective blood suppression to accurately identify plaque lumen boundaries. Good blood suppression post-contrast requires the use of MSDE or DIR/QIR[175] flow suppression. For DIR, the inversion time (TI) can be calculated based on estimated T1 values of blood at 5 minute intervals following contrast administration (0.1 mmol/kg) for 1.5T or 3T scanners[206]. We recommend a TI of 250 ms for 3T scanners for a TR triggered at 1RR interval, which generally produces adequate flow suppression beginning 5 minutes after injection despite variations in post-injection scan time and heart rate, which will affect the T1 blood values.

Discussion

Lumen: Quantifying luminal narrowing is a prerequisite, as stenosis severity is the cornerstone for treatment decisions in current clinical guidelines. Furthermore, detection of ulceration provides prognostic value. Use of TOF MRA for lumen assessment avoids the need for IV contrast, and may provide confirmatory evidence of intraplaque hemorrhage and, sometimes calcification. Addition or substitution with CE-MRA should be considered for those without contraindication for contrast administration. This would also provide an opportunity to perform post-contrast enhanced imaging of the vessel wall for direct identification of the LRNC and identification/confirmation of fibrous cap status and ulcerations.

IPH: MRI techniques are available for IPH detection across scanner platforms, and IPH's predictive value for ischemic events has been extensively evaluated, both with and without custom carotid coils. In a review performed by Gupta et al[170], studies were stratified by those utilizing multi-sequence, carotid coil-dependent protocols and those using a single sequence with standard large FOV neck coils for IPH detection. Using either technique, IPH was associated with significantly increased risk for TIA or stroke (HR (95% CI) 4.40 (2.10-9.23) and 5.04 (2.15-11.85), respectively). While IPH can be identified on T1w sequences such as T1w fast spin echo, T1w SPACE, TOF etc., a highly T1 weighted sequence such as MPRAGE can provide higher sensitivity and specificity for IPH detection[176].

Lipid-rich necrotic core: T2 weighted imaging can be used to detect the presence of LRNC[177,178]. Direct assessment of LRNC can also be done in patients undergoing contrast administration using a post-contrast T1w scan. CE-MRA followed by post-CE vessel wall imaging in patients without contraindication will improve detection and quantification of the LRNC and delineation of the fibrous cap[172].

Plaque burden and distribution: Knowledge of the location and distribution of plaque assists in pre-procedural planning. Time-efficient 3D large coverage black-blood MRI maybe better suited for this purpose.

Future improvements and needs for MRI

Technical developments in the following areas are urgently needed:

a. Improved spatial resolution both in-plane and through-plane to better characterize finer structures such as fibrous caps.

b. More effective blood flow suppression for large spatial coverage imaging acquisition and pre- and post-contrast administration.

c. Dedicated carotid coils that are integrated with head and neck coils for extensive coverage.

d. Improved techniques for identifying the lipid rich necrotic core, especially without the need for contrast application.

e. More effective methods to deal with motion.

f. A streamlined imaging protocol that is able to identify multiple imaging targets in one or two imaging sequences.

g. Effective image processing tools for efficient quantitative identification of imaging targets

h. Development of training programs for MR specialists on image acquisition and for radiologists on vessel wall image interpretation.

i. Ultimately – a guideline that clearly calls for the need of carotid plaque imaging and one simple protocol that can meet all the needs.

Currently, there are many new techniques being developed for carotid plaque imaging. 3D-SNAP provides non-contrast enhanced MRA and simultaneous IPH detection[179]. 3D-SHINE provides information about the state of IPH in addition to IPH detection[180]. IPH can also be identified on a pre-contrast mask of CE-MRA if available[68]. MATCH provides comprehensive information regarding plaque composition in a single sequence[182]. 3D-MERGE[183] and 3D-DASH[184] provide large coverage blood suppression for plaque burden measurements. Diffusion-weighted imaging can detect LRNC without the use of contrast media[209]. Self-gating has been

used to reject data acquired during swallowing motion[210]. T1 insensitive blood suppression techniques such as Quadruple Inversion Recovery[175] provide good blood suppression for post-contrast imaging. However, these supplementary techniques require specialized equipment (3T, custom-carotid coils, custom sequences) and more intensive interpreter training.

Carotid CT

Background: Currently no meta-analysis or prospective trials have suggested that some specific CT features are associated with an increased risk for future primary and recurrent ischemic neurological events, even if there are several prospective trials on their way or have been published that examine the value of plaque imaging prospectively (PARISK, CAPIAS, CARE-II)[202,203,204] However, cross-sectional studies have found that some CT characteristics (HU attenuation – presence of neovascularization) are associated with increased risk of cerebrovascular events[39,186].

Goals: (1) To provide general guidelines for carotid CT vessel wall imaging with recommended desirable imaging techniques, tissue contrast, spatial resolution and coverage. Guideline considerations are that the protocol can be applied broadly across a spectrum of clinical CT scanners and not require specialized software or research keys for implementation. (2) To recommend future areas for technical development and clinical expansion needs.

Essential Features for Identification with Carotid Plaque Imaging: Any CT protocol for plaque imaging should be able to identify the following atherosclerotic plaque characteristics:

1. Stenosis and luminal surface condition (plaque morphology and ulceration).

2. Type of plaque (fatty versus mixed versus calcified)

3. Presence of plaque enhancement

4. Plaque burden and distribution.

Minimum CT Protocol Requirements for Identification of Essential Plaque Features:

Recommended *minimum* parameter requirements are

- Resolution: isotropic voxel with 1 mm resolution

- Longitudinal coverage: from aortic arch to intra-cranial vessel

- CT generation: third with at least 16-dectetor-row

Example Protocols: Four protocols are presented (**Table 5-8**). No CT study of carotid arteries must be performed without the administration of contrast material. The use of biphasic approach (un-enhanced scan followed by contrast scan) allows the assessment of the carotid plaque neovascularization. This is becoming more important but is not considered currently necessary. In order to reduce the radiation dose delivered to the patients the z-length of the basal scan should cover only the carotid artery plaque bifurcation (4 cm coverage centered on the bifurcation). Dual energy CT technique[43] allows virtual un-enhanced image in order to assess plaque enhancement without the need of a biphasic approach.

Discussion

Lumen: Quantifying luminal narrowing is a prerequisite. In order to correctly assess the degree of stenosis, by avoiding the halo or edge blur the correct window settings should be used[185]. At the current level of technology, the status of the FC cannot be adequately explored by CT.

Type of Plaque: According to the HU attenuation the carotid plaque can be categorized as fatty (< 60 HU), mixed (between 60 HU and 130 HU) and calcified (> 130 HU). By applying these thresholds, it is possible to identify those plaques with a LRNC from others. Applying the HU classification, however, creates 2 problems that have recently come to light: (**1**) the HU value of the plaque is dependent on the level of energy applied, as demonstrated by *Saba et al* by using multi-energy systems[42], (**2**) the carotid artery plaques may show contrast enhancement (by comparing the attenuation values of the basal and post-contrast scans) suggesting that the attenuation value of the plaque obtained after administration of contrast material represents two different parameters: the

type of the plaque and the degree of neovascularization of the tissue[43,44]. This is not a problem if pre and post contrast scans or dual energy is applied (capable of distinguishing plaque from contrast enhancement) but this is not usually done clinically secondary to an increase in x-ray dose

Carotid plaque enhancement. Assessment of plaque enhancement is limited in the case of single phase CTA, and multiphase CTA is rarely performed outside of research studies due to radiation concerns. An un-enhanced axial CT obtained over 4 cm centered on the carotid bifurcation, followed by a CTA would theoretically be ideal in assessing plaque enhancement but carries less radiation penalty. Alternatively, some authors have employed dual energy techniques with use of the virtual non -enhanced image in order to assess plaque enhancement with less radiation dose[43].

Plaque burden and distribution: Knowledge of the location and distribution of plaque assists in pre-procedural planning. Moreover, CT can calculate the volume of the carotid artery plaque and determine the volume of the sub-components, according to HU threshold[123].

Future improvements and needs for CT

Technical developments in the following areas are urgently needed:

a. Improved contrast resolution for greater discrimination of tissue types in plaque

b. Improved techniques, such as multi-energy applications for identifying the lipid rich necrotic core, especially without the need for contrast application

c. Evidence based guidelines that invoke the need for carotid plaque imaging preferably using one simple universal protocol that can meet all needs.

Currently, most of the research on carotid artery CT is focusing on methods (1) that reduce the radiation dose delivered to the patients, and (2) improve carotid artery plaque characterization using multi-energy tools that promise more accurate detection of plaque components.

CONCLUSION

In the last 20 years there has been a paradigm shift in the imaging of atherosclerotic carotid artery, from the assessment of the degree of luminal stenosis to the characterization of plaque. Several features have been identified which are potentially associated with plaque rupture and imaging has been used to identify these features in vivo.

Researchers and clinicians now have several imaging modalities that allow in-depth exploration of carotid artery plaque and its components. Sonography should be considered as a first-line exam, at least for screening, whereas CT and MR improve identification of several plaque features associated with vulnerability.

Also promising are nuclear medicine and molecular imaging techniques that can further explore assessment of plaque vulnerability especially inflammation, but these approaches are still investigational and not part of the main diagnostic algorithm of carotid atherosclerosis. In the future larger prospective longitudinal studies investigating these technological advances may fully exploit the clinical potential of vessel wall imaging.

ACKNOWLEDGMENT

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TABLES

Table 1

3D Non-contrast Protocol				
Name	**3D TOF**	**3D MP-RAGE**	**3D T1w SPACE/CUBE/VISTA**	**3D T2w SPACE/CUBE/VISTA**
Plaque Feature	Stenosis, Ulceration, Calcification	Intraplaque Hemorrhage	Plaque burden and distribution	LRNC
Sequence[a]	FFE/SPGR	IR-TFE/SPGR	TSE/FSE	TSE/FSE
Image mode	3D	3D	3D	3D
Scan plane	Axial	Coronal	Coronal	Coronal
TR, msec	24	15	1000	2500
TE, msec	4.6	Min	30	250
FOV, cm	16x16	16x16	16x16	16x16
Resolution, mm^2	0.6x0.6	0.6x0.6	0.6x0.6	0.6x0.6
Slice thickness, mm	1[b]	0.6	0.6	0.6
Blood suppression	Saturation – veins	None	MSDE/FSD[c]	MSDE/FSD[c]
Special parameters	Flip angle 20°	Flip angle 15°; TI=500 ms Turbo factor = 30, IRTR=800ms	Echo train: variable VFA T1	Echo train: variable VFA T2
Fat suppression	No	Yes (Water Excitation)	Yes	Yes

[a] Siemens/Philips/GE acronyms.
[b] Interpolated resolution
[c] MSDE: Motion-sensitized driven equilibrium, FSD: Flow sensitized dephasing
*Pulse gating not required for any sequence

Table 2

3D Contrast Protocol			
Name	**3D TOF**	**3D MP-RAGE**	**Pre-contrast and post-contrast** [**] **3D T1w SPACE/CUBE/VISTA**
Plaque Feature	Stenosis, Ulceration, Calcification	Intraplaque Hemorrhage	Plaque burden and distribution, LRNC
Sequence[a]	FFE/SPGR	IR-TFE/SPGR	TSE/FSE
Image mode	3D	3D	3D
Scan plane	Axial	Coronal	Coronal
TR, msec	24	15	1000
TE, msec	4.6	Min	30
FOV, cm	16x16	16x16	16x16
Resolution, mm^2	0.6x0.6	0.6x0.6	0.6x0.6
Slice thickness, mm	1[b]	0.6	0.6
Blood suppression	Saturation – veins	None	MSDE/FSD[c]
Special parameters	Flip angle 20°	Flip angle 15°; TI=500 ms Turbo factor = 30, IRTR=800ms	Echo train: variable VFA T1
Fat suppression	No	Yes (Water Excitation)	Yes

[a] Siemens/Philips/GE acronyms.
[b] Interpolated resolution
[c] MSDE: Motion-sensitized driven equilibrium, FSD: Flow sensitized dephasing
*Pulse gating not required for any sequence
**Clinical CE-MRA per institutional protocol can be used before post-contrast sequence

Table 3

2D Non-contrast Protocol						
Name	TOF MRA Localizer	Oblique T1W Localizer	T1W	T2W	3D-TOF	MPRAGE
Plaque feature	Localize Artery	Localize Bifurcation	Plaque burden and distribution	LRNC	Stenosis, Ulceration, Calcification	Intraplaque hemorrhage
Sequence[a]	FFE/SPGR	TSE/FSE	TSE/FSE	TSE/FSE	FFE/SPGR	IR-TFE/IR-FSPGR
Image mode	2D	2D	2D	2D	3D	3D
Scan plane	Axial	Oblique	Axial	Axial	Axial	Axial
TR, msec	25	2000	800	4800	24	13
TE, msec	4	8	10	50	Min	Min
FOV, cm	16x12	16x16	16x16	16x16	16x16	16x16
Resolution, mm^2	0.63x0.83	0.63x0.63	0.63x0.63	0.63x0.63	0.63x0.63	0.63x0.63
Slice thickness, mm	2	2	2	2	2/-1	2/-1
# of slices	32	6	16	16	40	40
Blood suppression[b]	None	DIR	DIR	DIR	None	None
Special parameters	Flip angle 40°	Echo train 14; 3 slices/TR	Echo train 10;	Echo train 12; 8 slices/TR	Flip angle 20°	Flip angle 15°, Turbo factor 30, TI 500ms, IRTR=800ms
Fat suppression	No	Yes	Yes	Yes	No	Water excitation

[a] Siemens/Philips/GE acronyms.
[b]DIR: Double inversion recovery
*Pulse gating not required for any sequence

Table 4

2D Contrast Protocol					
Name	TOF MRA Localizer	Oblique T1W Localizer	Pre-contrast and Post-contrast** T1W	3D-TOF	MPRAGE
Plaque feature	Localize Artery	Localize Bifurcation	Plaque burden and distribution, LRNC	Stenosis, Ulceration, Calcification	Intraplaque hemorrhage
Sequence[a]	FFE/SPGR	TSE/FSE	TSE/FSE	FFE/SPGR	IR-TFE/IR-FSPGR
Image mode	2D	2D	2D	3D	3D
Scan plane	Axial	Oblique	Axial	Axial	Axial
TR, msec	25	2000	800	24	13
TE, msec	4	8	10	Min	Min
FOV, cm	16x12	16x16	16x16	16x16	16x16
Resolution, mm^2	0.63x0.83	0.63x0.63	0.63x0.63	0.63x0.63	0.63x0.63
Slice thickness, mm	2	2	2	2/-1	2/-1
# of slices	32	6	16	40	40
Blood suppression[b]	Saturation - veins	MSDE	QIR***	Saturation - veins	No
Special parameters	Flip angle 40°	Echo train 14; 3 slices/TR	Echo train 10;	Flip angle 20°	Flip angle 15°, Turbo factor 30, TI 500ms, IRTR=800ms
Fat suppression	No	Yes	Yes	No	Water excitation

[a] Siemens/Philips/GE acronyms.
[b]MSDE: Motion-sensitized driven equilibrium, QIR: Quadruple inversion recovery
*Pulse gating not required for any sequence
**Clinical CE-MRA per institutional protocol can be used before post-contrast sequence
***Double inversion recovery (DIR) can be used but blood suppression may be incomplete and inversion time (TI) is variable dependent on patient and contrast bolus

Table 5 : Toshiba Aquilion Vision

-	Scanogram (AP – Lat)	Basal Scan (optional)	Contrast Scan
Coverage	Sternum to mid head	Mid neck in order to cover the bifurcation	From aortic arch to mid head
Scan Mode	Scanogram	Helical	Helical
Start time	NA		Bolus Tracking[a]
Range	500 (mm)	8 cm	Variable
Collimation	NA	0.5 x 80	0.5 x 80
Pitch	NA	1	1
kV	120	120	120
mA	50-200[b]	350	350
Rotation time	NA	0.275 second	0.275 second
Direction	NA	Caudio – Cranial[c]	Caudio – Cranial[c]
Slice thickness	NA	1 mm	1 mm
Slice interval	NA	0.5 mm	0.5 mm
FOV	wide	20 cm	20 cm
Filter	NA	Sharp (FL03)	Sharp (FL03)
CTDI(mGy)	-	15	15
DLP(mGy.cm)	-	0.6	0.6
Amount of CM	-	-	40-50 mL[d]
IDR	-	-	1.4 – 1.5 gI/sec
Concentration*	-	-	370 mgI/mL
Flow rate*	-	-	4 mL/sec

[a] – Position of bolus tracking : aortich arch – threshold 100 HU
[b] – 50 mA in AP and 200 in Lat
[c] – it is possible also cranio-caudal
[d] – variable according to the concentration
* – concentration x flow rate = IDR. The parameter to be considered is IDR

Table 6 : SIEMENS SOMATOM SENSATION 64

-	Scanogram (AP – Lat)	Basal Scan (optional)	Contrast Scan
Coverage	Sternum to mid head	Mid neck in order to cover the bifurcation	From aortic arch to mid head
Scan Mode	Scanogram	Helical	Helical
Start time	NA		Bolus Tracking[a]
Range	500 (mm)	8 cm	Variable
Collimation	NA	0.6 x 64	0.6 x 64
Pitch	NA	0.55	0.55
kV	120	120	120
mA	50-200[b]	350	350
Rotation time	NA	0.28 second	0.28 second
Direction	NA	Cranio – Caudal[c]	Cranio – Caudal[c]
Slice thickness	NA	1 mm	1 mm
Slice interval	NA	0.5 mm	0.5 mm
FOV	wide	20 cm	20 cm
Filter	NA	Sharp (B30f)	Sharp (B30f)
CTDI(mGy)	-	18	18
DLP(mGy.cm)	-	0.65	0.65
Amount of CM	-	-	40-50 mL[d]
IDR	-	-	1.4 – 1.5 gI/sec
Concentration*	-	-	370 mgI/mL
Flow rate*	-	-	4 mL/sec

[a] – Position of bolus tracking : aortich arch – threshold 100 HU
[b] – 50 mA in AP and 200 in Lat
[c] – it is possible also caudo-cranial with optimal results
[d] – variable according to the concentration
* – concentration x flow rate = IDR. The parameter to be considered is IDR

Table 7 : Philips ICT

-	Scanogram (AP – Lat)	Basal Scan (optional)	Contrast Scan
Coverage	Sternum to mid head	Mid neck in order to cover the bifurcation	From aortic arch to mid head
Scan Mode	Scanogram	Helical	Helical
Start time	NA		Bolus Tracking[a]
Range	500 (mm)	8 cm	Variable
Collimation	NA	0.625 x 128	0.625 x 128
Pitch	NA	0.933	0.933
kV	120	120	120
mA	50-200[b]	350	350
Rotation time	NA	0.5 second	0.5 second
Direction	NA	Cranio – Caudal[c]	Cranio – Caudal[c]
Slice thickness	NA	1 mm	1 mm
Slice interval	NA	0.5 mm	0.5 mm
FOV	wide	20 cm	20 cm
Filter	NA	Sharp (B)	Sharp (B)
CTDI(mGy)	-	15	16
DLP(mGy.cm)	-	0.6	0.6
Amount of CM	-	-	40-50 mL[d]
IDR	-	-	1.4 – 1.5 gI/sec
Concentration*	-	-	370 mgI/mL
Flow rate*	-	-	4 mL/sec

[a] – Position of bolus tracking : aortich arch – threshold 100 HU
[b] – 50 mA in AP and 200 in Lat
[c] – it is possible also caudo-cranial with optimal results
[d] – variable according to the concentration
* – concentration x flow rate = IDR. The parameter to be considered is IDR

Table 8 : GE Lightspeed VCT

-	Scanogram (AP – Lat)	Basal Scan (optional)	Contrast Scan
Coverage	Sternum to mid head	Mid neck in order to cover the bifurcation	From aortic arch to mid head
Scan Mode	Scanogram	Helical	Helical
Start time	NA		Bolus Tracking[a]
Range	500 (mm)	8 cm	Variable
Collimation	NA	0.625 x 64	0.625 x 64
Pitch	NA	0.984	0.984
kV	120	120	120
mA	50-200[b]	350	350
Rotation time	NA	0.5 second	0.5 second
Direction	NA	Cranio – Caudal[c]	Cranio – Caudal[c]
Slice thickness	NA	1 mm	1 mm
Slice interval	NA	0.625 mm	0.625 mm
FOV	wide	20 cm	20 cm
Filter	NA	Sharp (B)	Sharp (B)
CTDI(mGy)	-	15	16
DLP(mGy.cm)	-	0.6	0.6
Amount of CM	-	-	40-50 mL[d]
IDR	-	-	1.4 – 1.5 gI/sec
Concentration*	-	-	370 mgI/mL
Flow rate*	-	-	4 mL/sec

[a] – Position of bolus tracking : aortich arch – threshold 100 HU
[b] – 50 mA in AP and 200 in Lat
[c] – it is possible also caudo-cranial with optimal results
[d] – variable according to the concentration
* – concentration x flow rate = IDR. The parameter to be considered is IDR

FIGURE LEGENDS

FIGURE 1: Plaque volume analysis in a 75 year-old man with a TIA. In the Volume Rendered image the carotid is traced (a) and in the Curved-Planar-Reconstructed post-processed image (*CTA module – Aquarius iNtuition Editition ver 4.4.12.138.2907 – TeraRecon, Foster City, CA – USA*) (b) the plaque is identified based on the green contours (white arrows). The volume analysis with automated boundary detection and tissue segmentation is shown in panels c, d and e (corresponding to the three arrows, proximal to distal) with contours delineating the lumen (red contour), outer wall (blue contour), and shading of calcium (blue), mixed tissue (green), and lipid component (red).

FIGURE 2: Ulcerated carotid artery plaques detected with CT and MR. In the first case the CTA of a 74 year-old man with a TIA demonstrates an ulcerated carotid artery plaque (white arrows) in the left internal carotid artery (white arrow) in the MIP (a) and axial source image (b). In the second case a MRI analysis of a 63 year-old man with a TIA shows a tiny ulceration (white arrows) in the right internal carotid artery is visible in the axial (a) and in the para-coronal plane (b)

FIGURE 3: Carotid atherosclerotic plaque MRI and specimen from a 73 year-old man with stenosis of the carotid bulb measuring 69% by NASCET criteria demonstrated on a contrast-enhanced MRA (A). The precontrast (mask) image from the contrast-enhanced MRA demonstrates bright signal indicative of intraplaque hemorrhage, specifically subacute blood, or methemaglobin (B, arrow). Subacute blood is also identified as bright signal on the precontrast T1W black blood image (C, arrow). A rim of hemosiderin is identified as hypointense signal on the post-contrast black blood image (D) and a hemosiderin sensitive sequence (E), and confirmed on endarterectomy specimen (F, G). The fibrous cap is also delineated (green arrow, D and F). Black blood imaging was achieved using 2-dimensional cardiac-gated double inversion recovery turbo spin echo.

FIGURE 4: Carotid atherosclerotic plaque MRI and specimen from a 76 year-old woman with transient ischemic attacks ipsilateral to carotid bulb stenosis measuring 47% by NASCET criteria demonstrated on a contrast-enhanced MRA (A). Narrowing is caused by the plaque characterized by 2-dimensional cardiac-gated double inversion recovery black blood MRI (B). Regional enhancement (green arrow) within the lipid core (yellow arrow) suggests focal inflammation with neovascularity as confirmed on the endarterectomy specimen (C, green circle). Contrast-enhancement is also useful for delineating the fibrous cap (B, C - orange arrowheads). Calcification is identified as areas of hypointensity (B, C – red arrows and circle).

FIGURE 5: Smooth left internal carotid artery stenosis with intraplaque hemorrhage. All images were acquired with a 16 Channel Neurovascular Coil at 3 T. The contrast-enhaced MRA (CEMRA) demonstrates a smooth, non-ulcerated stenosis in the bulbous and post bulbous part of the left internal carotid artery (white open arrow) (a) . Oblique reformat of a coronally acquired magnetization prepared rapid gradient echo (MPRAGE) shows extensive intraplaque haemorrhage (IPH) which appears hyperintense (white arrow). The IPH is hyperintense on the non-enhanced T1 FAT SAT spine echo (SE) image (c), and isointense on the gadolinium enhanced T1 FAT SAT SE image (d). On the TOF MRA source data the IPH appears also hyperintense but to a lesser degree than the intraluminal flow signal (e).

FIGURE 6: Matched cross-sectional images of a carotid plaque with high signal intensity (white arrows) consistent with the presence of intraplaque hemorrhage on MP-RAGE (a) and SNAP MRI (b). Note the greater conspicuity of the carotid lumen (L) on SNAP compared to the MPRAGE image. There is a penetrating ulcer (indicated by the asterisk) that is more easily detected on SNAP compared to the TOF MRA image (c).

FIGURE 7: In a 68-year-old male patient, co-existent plaque components, fresh intraplaque hemorrhage (arrows) and superficila calcifications (arrowheads), are detected by MATCH (first row) and the conventional multi-contrast protocol (second row). Compared to T1W TSE and TOF, MATCH provides more conspicuous depiction of intraplque hemorrhage on the hyper T1W image and calcification on the gray blood image. Notice that the calcification is also visible on the MATCH T2W image but not on the T2W TSE image.

FIGURE 8) Contrast Enhanced MRA of the extracranial carotid bifurcation indicating the level of 2D FSE images obtained with 1.5 T. b) T1-weighted double inversion recovery black blood FSE image showing an eccentric plaque (arrow) in the internal carotid artery, and c) T2-weighted double inversion recovery black blood FSE image at the same level showing a crescentic, hypointense signal from the necrotic core which is seprated by higher intensity fibrous cap from the flow lumen.

FIGURE 9: K^{trans} map of a patient with carotid plaque. Maps were generated using pharmacokinetic modeling of dynamic contrast-enhanced MR images. The parametric map is overlaid on anatomic MR image, and voxel K^{trans} values (Patlak model) are color coded. The necrotic core exhibits low K^{trans} values at the center of plaque, while the highly vascularized adventitia at the outer rim exhibits high K^{trans} values. There is another region of higher K^{trans} values near the inner rim of the plaque.

FIGURE 10: ^{18}F-fluorocholine positron emission tomography-computed tomography (^{18}F-FCH PET-CT) image of a symptomatic (arrow) and contralateral asymptomatic (arrow head) carotid plaque of a patient who experienced right-sided stroke. **A**, Diagnostic contrast-enhanced CT shows a significant stenosis in the right internal carotid artery because of a calcified plaque, whereas a non-calcified atherosclerotic plaque can be seen on the contralateral internal carotid artery. **B**, CT,

inset on the symptomatic plaque. **D**, CT, inset on the asymptomatic plaque. **D**, The fused PET-CT image denotes a focal area of high ^{18}F-FCH uptake in the right symptomatic carotid plaque, whereas there is no visible ^{18}F-FCH uptake in the left asymptomatic carotid plaque. **E**, fused PET-CT, inset on the symptomatic plaque. **F**, fused PET-CT, inset on the asymptomatic plaque.