Carotid Plaque-RADS, a novel stroke risk classification system Part 1: The rationale and proposed new image-based classification.

Running title: Carotid Plaque-RADS classification

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Abstract

Carotid artery atherosclerosis is highly prevalent in the general population and a well-established risk factor for acute ischemic stroke. Histopathological and imaging-based studies have identified plaque structure and composition as key determinants of either plaque vulnerability or stability. Although the morphological characteristics of vulnerable plaques are well recognized, there is a lack of consensus among radiologists in reporting plaque features and among treating physicians in interpreting such findings. Therefore, we propose a universal classification that can be used by both researchers and clinicians, namely, the “Plaque-Reporting And Data System (RADS)”. Plaque-RADS aims to provide a morphological determinant additionally to the currently sole quantitative descriptor "stenosis" and may help to specifically identify patients who might or might not benefit from best medical treatment alone and thus improve patient care.

The suggested Plaque-RADS classification is applied on a per-vessel basis in symptomatic and asymptomatic patients and represents the highest-grade carotid artery lesion detected by ultrasound, CTA or MRI. The score ranges from Plaque-RADS 1 for the complete absence of plaque to Plaque-

RADS 4 for a plaque complicated by intraplaque hemorrhage (IPH), rupture of the fibrous cap or intraluminal thrombus. Additional information, including the degree of plaque neovascularization, inflammation, plaque progression, positive remodeling, or calcification patterns may be provided as ancillary features.

Part 1 of this consensus document explains the rationale for the development of a new image-based classification of carotid atherosclerotic plaques, resulting in the introduction of the Plaque-RADS score. Part 2 of this consensus document discusses in detail the application of Plaque-RADS, the proposed modalities for each Plaque-RADS category and standardized reporting.

Key words: Carotid; atherosclerosis; imaging; stroke.

Condensed Abstract

The Plaque-RADS (Plaque-Reporting and Data System) score was created to standardize the reporting of carotid plaque characteristics, and to offer new aspects for the tailored management of individuals with asymptomatic and symptomatic atherosclerotic carotid lesions. Reduced variability in reporting facilitates communication between interpreting and referring clinicians, and generates robust data for auditing, data mining, quality improvement, research, and education. In addition to the degree of carotid stenosis Plaque-RADS may help to specifically identify patients who might or might not benefit from best medical treatment alone and thus improve patient care.

The Plaque-RADS classification is an intuitive nomenclature for several imaging modalities that reflects the severity of plaque instability and – if successfully implemented - could be an important tool to provide specific recommendations for the management of atherosclerotic carotid disease.

Bullet Points

- Carotid plaque structure and composition are critical determinants of plaque vulnerability.

- Plaque-RADS allows for a detailed, yet concise and uniform description of atherosclerotic lesions among ultrasound, CTA and MRI, with respect to the attributable cerebrovascular risk.
- The centerpiece of Plaque-RADS is a four-grade score (RADS 1-4) and a measurement of maximum wall thickness (MWT), which can be extended at will by sub-categories and ancillary features.
- Plaque-RADS has a high intra- and inter-observer reliability and can be easily implemented in routine clinical reporting.
- Standardized assessment of carotid plaque features could advance the management of carotid atherosclerotic disease.

Introduction and the purpose of this document

Recent research has brought to light specific morphologic carotid plaque features that associate with risk for atherosclerotic cardiovascular disease, including cerebrovascular, coronary, and peripheral arterial diseases [1,2,3]. In this regard, carotid imaging modalities have demonstrated their ability to characterize plaque features as predictors of future events, offering a significant contribution to risk stratification and clinical management of patients over carotid stenosis alone[4]. The 2017 European Society of Cardiology (ESC) clinical practice guidelines have recognized these developments and recommend to evaluate the presence of imaging characteristics that may indicate an increased risk of ipsilateral stroke additionally to the degree of carotid stenosis in asymptomatic individuals[5]. These include, amongst others, intraplaque hemorrhage (IPH) or lipid-rich necrotic core (LRNC) on magnetic resonance imaging (MRI) and large or echolucent plaques, and increased juxta-luminal black (hypoechoic) areas on carotid ultrasound[5]. Similarly, the European Society for Vascular Surgery (ESVS) clinical practice guidelines emphasize the importance of plaque vulnerability assessment[6]. Even though scoring systems for singular modalities have been suggested (e.g. AHA[7] for histology, modified AHA for MRI[8], Carotid plaque score for ultrasound[9], etc.), there is still no universal classification system for various imaging modalities that scores the severity of an atherosclerotic lesion based on plaque morphology and composition. The proposed Plaque-RADS score aims to create an intuitive, accurate, and standardized scoring system that can be used with various imaging modalities to provide risk estimates for first-time or recurrent large artery cerebrovascular events.

In Part I of this two-part consensus document, we therefore explain the rationale and scientific basis for the proposed “Plaque-Reporting And Data System (RADS)”. Part II of this consensus document discusses in detail the application of Plaque-RADS, the optimal modality for the recognition of each Plaque-RADS category and standardized reporting.

2. The increasing value of carotid plaque imaging

Most current guidelines on the management of carotid artery disease, consider the degree of carotid stenosis as the only validated parameter for treatment decision making[5,6,10]. This is primarily based on the results of a number of studies conducted from the 1980s to the 2000s that demonstrated the benefit of combined carotid endarterectomy (CEA) and best medical therapy in symptomatic and asymptomatic patients with carotid stenosis over best medical therapy alone[11–15]. However, as shown in meta-analyses by Abbott et al and Hadar et al, since the year 2000 the mean annual rate of ipsi- and contralateral cerebrovascular events has further decreased significantly with medical intervention alone in asymptomatic individuals with severe internal carotid artery (ICA) stenosis [16,17]. This effect has been mainly attributed to the introduction of antiplatelet agents and statins and results in fewer individuals likely to profit from additional CEA or stenting[17]. So especially in individuals with asymptomatic carotid stenosis >50% the identification of an unstable plaque may significantly improve patient selection and thus the number needed to treat for medical and/or surgical approaches and reduce the number of unnecessary invasive approaches[18–20].In patients with symptomatic carotid stenosis, who have a higher likelihood of high-risk plaques, CEA remains of proven benefit[11,12].

3. Why we need a Plaque-RADS classification system

As shown with previous scores, such as the Lung-RADS[21], BI-RADS[22], PI-RADS[23], LI-RADS[24], and CAD-RADS[25] score for lung, breast, prostate, liver, and coronary artery imaging, the use of a standardized reporting system improves communication and patient selection by reducing differences in terminology, harmonizing classification formats between different institutions, and facilitating the exchange of clear and systematic information between imaging and referring physicians and researchers.

To date there is no such system for a standardized classification of atherosclerotic carotid plaque. Instead, most clinical reports of CT-angiograms mention the degree of carotid stenosis, but despite their increasingly recognized value, specific plaque features are accounted for in only a minority of cases[26]. This lack of reporting, may be at least partly due to gaps in knowledge of high-risk plaque features and their associated risk and possible therapeutic consequences.

Consequently the introduction of a standardized classification system for carotid atherosclerotic plaque (Plaque-RADS)

1. will level the differences across the various institutions regarding the use of terminology and patient evaluation criteria, serving as a reference format in everyday clinical practice,
2. facilitates data mining and allow researchers across different institutions to collect information in a more homogenous and synergistic way; for example, in the course of time stratified prognostic data could be collected for each Plaque-RADS category and help clinicians design agreed-upon treatment flowcharts, and
3. draws attention to imaging findings representative of plaque morphology and composition beyond the mere degree of stenosis underscoring a paradigm shift.

4. The proposed Plaque-RADS reporting system

Plaque-RADS categories are based on specific imaging features of plaque composition and other characteristics. The score is applied on a per vessel basis and can be established by ultrasound, CTA, and MRI. **Figures 1 and 2** provide a flow-chart and schematic overview of the Plaque-RADS categories. Categories range from Plaque-RADS 1 (absence of atherosclerosis) to Plaque-RADS 4 (plaque with features of complicated plaque) and should represent the clinically most relevant finding per vessel. Further sub-specifications (a, b, c) can be provided for Plaque-RADS categories 3 and 4. Not all imaging modalities are equally well suited to identify the individual categories. The modality used to obtain the score should therefore always be provided.

In addition, the Plaque-RADS categories may be supplemented by “ancillary features” of carotid plaque vulnerability (see Part 2).

Table 1 summarizes the characteristic imaging features of the Plaque-RADS categories and the attributable risk of developing symptoms.

4.1 Plaque-RADS categories

Plaque-RADS 1

This category represents the normal vessel wall with no evidence of localized atherosclerotic plaque (Figure 3). Population-based cohort studies including the Rotterdam Study, the Tromsø Study, and the Multi-Ethnic Study of Atherosclerosis (MESA) study have shown that patients without carotid plaque are not at risk of atherosclerosis-related cardiovascular or cerebrovascular events[27–30]. Vessels of this category are consistent with AHA lesion-type I plaques.

Plaque-RADS 2

This category is defined by an eccentric plaque with a maximum wall thickness (MWT) <3 mm and the absence of complicated plaque features such as IPH, fibrous cap (FC) rupture, and intraluminal thrombus (Figure 4).

Plaques in this category may consist mainly of fibrous tissue, small lipid pools, a small LRNC, calcifications, or a combination of these tissue types.

These plaque features are hallmarks of relatively stable plaques although they are also potential precursors of more advanced lesions. The presence of these features results in an increase in wall thickness that has been shown to be associated with increased cerebrovascular and cardiovascular risk, but less than that associated with complicated plaque features[31]. In this regard, total plaque thickness, as determined by ultrasound, has been shown to improve the prediction of future

atherosclerotic cardiovascular events over and above that provided by traditional risk factors alone[32,33].

The risk of Plaque-RADS 2 lesions is higher than Plaque-RADS 1 lesions, but is still relatively low. This category contains plaques of AHA-lesion types III, IV/V (small), VII and VIII.

Although the assignment of a particular Plaque-RADS score depends primarily on qualitative plaque characteristics, it seems reasonable to introduce a dimensional threshold above which characteristics of vulnerable plaques are to be expected and various studies suggest that 3 mm is a suitable value for this purpose[34,35–37]. Accordingly, a MWT < 3 mm indicates wall thickening at which features of plaque instability are relatively rare.

More information on the rationale of this value will be discussed in Part 2.

Plaque-RADS 3

This category represents a carotid plaque with a MWT of ≥3 mm which may consist of a moderate to large LRNC, calcifications, healed ulcerations and fibrous tissue. Complicated plaque features, such as IPH, thrombus and plaque rupture are absent. Further subclassification may be undertaken with dedicated imaging. This category contains plaques of AHA-lesion types IV/V, VII, and VIII.

Plaque-RADS 3a

This subcategory represents a carotid plaque with a moderate to large LRNC, a thick FC, and a MWT of ≥3 mm in the absence of complicated plaque features (Figure 5).

Currently, data on the risk of LRNC is limited. Nonetheless a Meta-analysis by Gupta et al. showed an increased risk for future ipsilateral cerebrovascular events when LRNC is present with a HR of 3.00 (1.511 – 5.945; p = 0.002)[38]. Besides an increased downstream cerebrovascular risk the presence of a LRNC is also associated with an increase in cardiovascular risk. In a MRI sub-study of 1256 participants from the Atherosclerosis Risk in Communities (ARIC) Carotid Magnetic

Resonance Imaging study, the presence of LRNC was significantly associated with incident cardiovascular events[39].

Several other publications reported similar results[40–45], as summarized in **Table 2.**

Plaque-RADS 3b

This subcategory contains ≥3 mm carotid plaque with a moderate to large LRNC with thin and intact FC (Figure 6).

It must be emphasized that the capability of contemporary imaging to accurately assess thin FCs lacks evidence; in fact, most studies that attempted to quantitatively measure FCs are focused on thickness measurements of caps thicker than 1 mm[46,47]. The accuracy and precision of imaging techniques are sub-optimal for quantifying thin FC thickness and reliably distinguishing between thin and ruptured caps through direct visualization[48]. Promising results are emerging with photon counting CT in delineating thin FC[49,50].

Furthermore, non-invasive imaging modalities cannot characterize the fibrillar collagenous matrix of the FC, including collagen content, collagen fiber distribution, and the presence of degrading compounds.

Thus, for assigning a score 3b in the Plaque-RADS classification system, the thin FC may be either directly visualized (if the spatial resolution of the modality in use allows that) or inferred by the presence of a LRNC without visualization of a thick and intact FC. Most importantly, what distinguishes this class from higher-risk class 4 is the absence of complicated plaque features.

With regard to FC integrity, several studies have emphasized its determinant role in plaque stability[38,51]. A thick FC is associated with a low risk of plaque rupture, while the risk of rupture increases for a thin FC[38,51,52,45,53].

Plaque-RADS 3c

The defining feature of this category is plaque ulceration regardless of plaque thickness, in the absence of IPH, FC-disruption or intraluminal thrombus (Figure 7).

Histologically the term "ulceration" describes an intimal defect of at least 1 mm in width, with consequent exposure of the plaque's necrotic core to the vascular lumen[54].

From a pathogenic point of view, ulceration is associated with LRNCs and certain complicated plaque features, such as FC rupture and the presence of IPH[51,55]. However, several publications have monitored the natural history of carotid plaque ulcerations and demonstrated their capability to heal[56–60]. Even though studies are lacking, lesions of this category may be considered to carry a risk to re-rupture and to be surrogates for an increased cardiovascular risk.

Thus, for what pertains to the designation of score 3c in the Plaque-RADS classification system, the term ulceration must be intended as ulceration not associated with the presence of IPH (score 4a), visible FC disruption (score 4b) or intraluminal thrombus (score 4c); rather, the term ulceration in this context refers to a surface cavity most likely secondary to previous extrusion of atheromatous material in the context of a healed plaque rupture.

Plaque-RADS 4

Plaque-RADS score 4 is assigned in the presence of at least one of the following findings independent of plaque thickness: IPH, a ruptured FC or an intraluminal thrombus. When feasible, a further subclassification can be used, differentiating IPH, ruptured FC, and intraluminal thrombi into classes 4a, 4b, and 4c, respectively (**Figure 8**). Subclasses may provide important information in future studies to better understand statistical correlations between such specific entities and clinical events. This category contains plaques of AHA lesion type VI.

Plaque-RADS 4a

The defining feature of this category is IPH (Figure 9).

In the Carotid Plaque Imaging in Acute Stroke (CAPIAS) study, IPH was the most common feature of complicated plaques and present in 89% of all complicated plaques ipsilateral to acute ischemic

stroke[61]. In the recent prospective Plaque At RISK (PARISK) study of 244 patients with a recent symptomatic mild-to-moderate carotid stenosis during a mean follow-up period of 5.1 years the presence of IPH was associated with recurrent cerebrovascular events (HR 2.12, 95%CI 1.02-4.44)[62]. Along the same lines pooled individual patient data from 7 cohort studies of 560 patients with symptomatic and 136 patients with asymptomatic carotid stenosis found MRI-detected IPH in 51.6% of the symptomatic and 29.4% of the asymptomatic patients. Multivariate analysis identified IPH (HR 11.0, 95%CI 4.8-25.1) and severity of stenosis (HR 3.3, 95%CI 1.4-7.8) as independent predictors of recurrent ipsilateral stroke. Presence of IPH increased the risk for first-time stroke in asymptomatic patients with carotid stenosis by almost 8-fold (HR 7.9, 95%CI 1.3-47.6)[63]. Other meta-analyses yielded similar results[38,64].

Plaque-RADS 4b

The defining feature of this category is a ruptured FC, usually accompanied by juxtaluminal plaque hemorrhage[65](Figure 10).

Disruption of the FC, with the resultant exposure to thrombogenic subendothelial plaque constituents, can precipitate thromboembolic complications both in the carotid and coronary vascular bed[66]. It appears that plaque rupture represent a dynamic process of rupture, thrombus formation, healing, and remodeling of the plaque[67]. A meta-analysis of 363 carotid arteries from asymptomatic and symptomatic patients showed that a thin or ruptured FC (HR 5.93, 95%CI 2.65–13.29, P<0.01) is associated with future cerebrovascular events[38].

Plaque-RADS 4c

This category is characterized by carotid plaque with an intraluminal thrombus (Figure 11). Other features such as IPH or FC rupture may also be present.

Intraluminal carotid artery thrombi are associated with neurologic symptoms in up to 92% of cases[68], and a recognized predictor of stroke of carotid origin[31,69–71]. McNally et al. conducted a

retrospective cross-sectional study of 726 carotid-brain MRI examinations in patients undergoing stroke workup. After the exclusion of non-carotid-plaque stroke, occlusions, and near-occlusions the strongest predictor of carotid-source stroke was intraluminal thrombus (OR 103.6, 95%CI 8.64-710.8, P<0.001)[31].

Table 2 provides an overview of previous studies examining carotid plaque characteristics according to Plaque-RADS categories and attributable risk for symptom development.

Conclusion

Plaque-RADS is a standardized, cross-modality system for reporting carotid plaque composition and morphology. This structured system aims to provide an in-depth insight into carotid imaging markers of vulnerability, to better evaluate carotid artery disease and predict the risk of cerebrovascular events. The main purpose of Plaque-RADS is to create a standardized lexicon and structured reporting for carotid artery disease, and improve communication between those interpreting images, referring clinicians, and researchers by providing a clear and reproducible risk stratification of the patient.

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Tables

Table 1: Summary of Plaque-RADS categories based on imaging findings and the attributable risk of developing symptoms.

Plaque-RADS score		Attributable Risk of ipsilateral cerebrovascular events	Imaging Findings
1		Absent	Normal vessel wall
2		Low	Carotid wall thickness <3 mm
3		Moderate	Carotid wall thickness ≥ 3 mm or Healed Ulcerated plaque
	3a	Moderate	LRNC with intact thick FC (MWT ≥3 mm)
	3b	Moderate	LRNC with thin FC (MWT ≥3 mm)
	3c	Moderate	Healed Ulcerated plaque
4		High	Complicated plaque (irrespective of MWT)
	4a	High	IPH
	4b	High	Ruptured FC
	4c	High	Intraluminal thrombus
Ancillary features: Inflammation, Neovascularization, positive plaque remodeling, plaque progression, calcifications			
Modifiers: Limited diagnostic study (“L”), presence of a stent (“Stent”), previous carotid endarterectomy (“CEA”)			

FC = Fibrous Cap; IPH = Intraplaque Hemorrhage; LRNC = Lipid-Rich Necrotic Core;
MWT = Maximum Wall Thickness.

Table 2: overview of studies examining carotid plaque characteristics according to Plaque-RADS categories and attributable risk for symptom development.

Plaque-RADS Score	Authors	Type of study	Patient Population	Modalities	Variables	Patient Status	Outcome events	Risk of cerebrovascular events
2	Selwaness et al.[33]	Prospective	1731	MRI	Plaque thickness	Asymptomatic	Cardiovascular events	Males (OR 1.20, 95%CI 1.03-1.39) Females (OR 1.21, 95%CI 0.88-1.65).
2	Školoudík et al.[72]	Prospective	1391	US	Plaque thickness	Asymptomatic	Carotid plaque progression	Left side (OR 1.85, 95%CI 1.39-2.44) Right side (OR 1.37, 95%CI 1.07-1.77)
2	Nicolaides et al.[32]	Prospective	985	US	Plaque thickness	Asymptomatic	Cerebrovascular events	HR 1.25, 95%CI 0.66-2.36
2	Gupta et al.[36]	Retrospective	76	CT	Plaque thickness	Asymptomatic	Cerebrovascular events	OR 2.14, 95%CI 1.27-3.60
2	Takaya et al.[44]	Prospective	154	MRI	Plaque thickness	Asymptomatic	Cerebrovascular events	OR 1.6, 95%CI 1.1-2.3
2	McNally et al.[31]	Retrospective	726	MRI	Plaque thickness	Symptomatic	Previous cerebrovascular events	OR 1.24, 95%CI 0.98-1.45, P=0.020
3a	Gupta et al.[73]	Meta-analysis	7557	US	Hypoechoic plaques	Asymptomatic	Stroke	RR 2.31, 95 CI% 1.38-3.39
3a	Polak et al.[40]	Prospective	4886	US	Hypoechoic plaques	Asymptomatic	Stroke	OR 2.53, 95%CI 1.42- 4.53.
3a	Brunner et al.[39]	Prospective	1256	MRI	LRNC	Asymptomatic	Cardiovascular events	HR 2.39, 95%CI 1.61-3.54
3a	Baradaran et al.[41]	Meta-analysis	2624	CT	LRNC	Asymptomatic	Stroke	OR 2.92, 95%CI 1.41-6.04
3a	Mono et al.[42]	Retrospective	62	MRI	LRNC	Asymptomatic	Cerebrovascular events	HR 7.21, 95%CI 1.12-46.28
3a	Gupta et al.[38]	Meta-analysis	403	MRI	LRNC	Asymptomatic Symptomatic	Cerebrovascular events	OR 3, 95%CI 1.51-5.95
3a	Sun et al [45]	Prospective	214	MRI	LRNC	Asymptomatic	Cardiovascular events	HR 1.57, 95%CI 1.22-2.01

3a	Takaya et al.[44]	Prospective	154	MRI	LRNC	Asymptomatic	Cerebrovascular events	OR 4.4, 95%CI 0.6-33.7
3a	Kwee et al.[43]	Prospective	126	MRI	LRNC	Symptomatic	Recurrent cerebrovascular events	HR 3.20, 95%CI 1.078-9.504
3b/4b	Gupta et al.[38]	Meta-analysis	363	MRI	Thin/ruptured FC	Asymptomatic Symptomatic	Cerebrovascular events	OR 5.93, 95%CI 2.65-13.20
3b/4b	Sun et al[45]	Prospective	214	MRI	Thin/ruptured FC	Asymptomatic	Cardiovascular events	HR 4.31, 95%CI 1.67-11.2
3b/4b	Takaya et al.[44]	Prospective	154	MRI	Thin/ruptured FC	Asymptomatic	Cerebrovascular events	HR 17, 95%CI 2.2-132.0
3b/4b	Yuan et al[53]	Prospective	53	MRI	Thin/ruptured FC	Asymptomatic	Cerebrovascular events	Thin FC (OR 10, 95%CI 1-104) Ruptured FC (OR 23, 95%CI 3-210
3b/4b	Kwee et al [43.]	Prospective	126	MRI	Thin/ruptured FC	Symptomatic	Recurrent cerebrovascular events	HR 5.76, 95%CI 1.91-17.32
3c	Baradaran et al.[41]	Meta-analysis	NA (1801 carotid arteries)	CT	Plaque ulceration	Asymptomatic	Stroke	OR 2.2, 95%CI 1.4-3.4
3c	Brinjikji et al.[74]	Meta-analysis	NA (6707 carotid plaque)	US	Plaque ulceration	Asymptomatic	Stroke	OR 3.58, 95%CI 1.66-7.71
3c	Van Dam-Nolen et al.[75]	Prospective	244	TCD, US, CT, MRI	Plaque ulceration	Symptomatic	Recurrent cerebrovascular events	HR 1.38, 95%CI 0.60-3.20
4a	Van Den Bouwhuijsen et al.[30]	Prospective	329	CT, MRI	Calcification	Asymptomatic	IPH	OR 2.65, 95%CI 1.94- 3.64
4a	Gupta et al.[38]	Meta-analysis	678	MRI	IPH	Asymptomatic Symptomatic	Cerebrovascular events	OR 4.59, 95%CI 2.91-7.24
4a	Saam et al.[64]	Meta-analysis	689	MRI	IPH	Asymptomatic Symptomatic	Cerebrovascular events	HR 5.69, 95%CI 2.98-10.87
4a	Takaya et al.[44]	Prospective	154	MRI	IPH	Asymptomatic	Cerebrovascular events	HR 5.2, 95%CI 1.6-17.3
4a	Kurosaki et al.[76]	Retrospective	1190	MRI	IPH	Asymptomatic	Stroke	HR 4.2, 95%CI 2.48-4.71

4a	Schindler et al. [63]	Meta-analysis	696	MRI	IPH	Asymptomatic Symptomatic	Stroke Recurrent Stroke	HR 7.9, 95%CI 1.3-47.6 HR 10.2, 95%CI 4.6 -22.5
4a	Bos et al. [77]	Prospective	1349	MRI	IPH	Asymptomatic	Stroke Coronary artery disease	HR 2.18, 95%CI 1.18 - 4.05 HR 1.65, 95%CI 1.02 - 2.68
4a	Selwaness et al.[33]	Prospective	1731	MRI	IPH	Asymptomatic	Cardiovascular events	OR 2.39, 95%CI 1.32-4.35.
4a	Kwee et al. [43]	Prospective	126	MRI	IPH	Symptomatic	Recurrent cerebrovascular events	HR 3.54, 95%CI 1.058-11.856
4a	Sadat et al [78]	Prospective	61	MRI	IPH	Symptomatic	Recurrent cerebrovascular events	HR 5.85, 95%CI 1.27-26.77
4a	Van Der Toorn et al.[79]	Prospective	1349	MRI	IPH	Asymptomatic	Cerebrovascular events	Females (HR 3.37, 95%CI 1.81-6.25).
4a	Van Dam-Nolen et al.[75]	Prospective	244	TCD, US, CT, MRI	IPH	Symptomatic	Recurrent cerebrovascular events	HR 2.12, 95%CI 1.02-4.44
4a	Kopczak et al.[62]	Prospective	234	MRI	IPH	Symptomatic	Recurrent cerebrovascular events	HR 4.37, 95%CI 1.20-15.97
4a	McNally et al. [31]	Retrospective	726	MRI	IPH	Symptomatic	Previous cerebrovascular events	OR 25.2, 95%CI 10.1-57.0.
4b	Markus et al[71]	Prospective	467	TCD	Embolic Signal	Asymptomatic	Stroke	HR 5.57, 95%CI 1·61–19·32
4b	Sadat et al [78]	Prospective	61	MRI	Ruptured FC	Symptomatic	Recurrent cerebrovascular events	HR 7.39, 95%CI 1.61-33.82
4b	Kopczak et al.[62]	Prospective	234	MRI	Ruptured FC	Symptomatic	Recurrent cerebrovascular events	HR 4.91, 95%CI 1.31-18
4c	McNally et al. [31]	Retrospective	726	MRI	Intraluminal thrombi	Symptomatic	Previous cerebrovascular events	OR 103.6, 95%CI 8.64-710.8.
4c	Eesa et al.[69]	Retrospective	674	CT	Intraluminal thrombi	Symptomatic	Previous cerebrovascular events	OR 4.33, P=0.01

Figure legends

Figure 1: Step by step flowchart to classify carotid atherosclerotic plaques into the different Plaque-RADS categories.

Figure 2: Schematic representation of the different Plaque-RADS categories 1 to 4.

MWT = maximum wall thickness; LRNC = lipid-rich / necrotic core; FC = fibrous cap; IPH = intraplaque hemorrhage; CEA = Carotid endarterectomy

Figure 3: Plaque-RADS 1.

US: Regular wall in the common carotid artery (CCA) and bifurcation. The vessel wall in ultrasound is homogenous and thin.

CT: Regular wall in the CCA and bifurcation on axial (a), coronal (b), and sagittal (c) reconstructions.

MRI: Regular wall of the CCA.

Histology: Normal vessel wall. High magnification of the boxed area shows tunica media and intima with mild intimal thickening which cannot be visualized with currently in vivo imaging modalities.

Figure 4: Plaque-RADS 2.

US: Eccentric wall thickening with speckled calcifications and acoustic shadowing (arrows). (a) Axial image; (b) Color Doppler image; (c) Longitudinal image.

CT: Diffuse carotid wall thickening with and without calcifications (f; open arrow).

MRI: Eccentric wall thickening and small calcification (arrow; hypointense in all weightings) of the right internal carotid artery.

Histology: Eccentric plaque with a wall thickness <3 mm. The magnification shows thickening of the intima.

Figure 5: Plaque-RADS 3a.

US: Large plaque of the carotid bifurcation with uniform isoechoic echogenicity on B-mode ultrasound imaging (arrowhead) consistent with LRNC and thick FC. a) longitudinal and b) transverse view; c) micro-flow imaging.

CT: Low-attenuating plaque with a mean HU value of 44 HU in the right internal carotid artery resembling a LRNC. The status of the FC cannot be assessed with CT.

MRI: Non-stenosing plaque of the left ICA. A large LRNC (arrowhead) appears isointense in TOF- images (, hypointense in the T1w post contrast images, and iso- to hyperintense in T1w pre-contrast, PDw, and T2w images. A thick and intact FC (arrow; hyperintense in T1w-CE and hypointense in TOF-imaging) separates the LRNC from the lumen.

Histology: Intimal thickening consistent with a thick FC over a LRNC (panel d and e). Panel f) shows a magnified view of a thick fibrous cap overlying the LRNC. Panel f) is reproduced from Frank et al [PMID: 17826632]

Figure 6: Plaque-RADS 3b.

US: Complex plaque with presence of JBAs in both the anterior and posterior component of the plaque with two discrete white areas (DWA) in the far wall component of the plaque consistent with a large LRNC or IPH at the origin of the left carotid bifurcation. Large sections of the plaque outline do not have a visible (i.e. thin) fibrous cap. a) and c) B-mode images; b) Color flow outlining the plaque. c) outlines the anterior and posterior plaque components.

MRI: Mildly stenosing plaque in the right ICA with a large LRNC (arrowheads; hypointense in contrast enhanced T1w). The FC is thin and not in its entity delineated (arrow in T1w-CE).

Histology: Thin fibrous cap (arrows in magnified image from g) overlying a large LRNC (g,h).

Figure 7: Plaque-RADS 3c.

US: Mixed hyper- and hypoechogenic plaque at the carotid bulb on B-mode ultrasound imaging with ulceration (*) on micro-flow imaging (a), and B-mode 3D-US with longitudinal (b), axial (c) and coronal view (d).

CT: Axial and sagittal views of an ulcerated plaque in the left ICA, visible as contrast outpouching (≥1 mm) into the plaque (arrows). High grade stenosis.

Histology: Ulcerated plaque. The arrow indicates the site of ulceration. Panel e is reproduced from Virmani et al [PMID: 18931283]

Figure 8: Complicated carotid plaque features in different imaging modalities. A fibrous cap rupture (white arrow) on US (a), an intraluminal thrombus (open arrow) on CT (c), and an intraplaque hemorrhage (arrowhead) on T1-weighted MRI imaging (e) with corresponding histological images (b, d, and f) from different subjects.

Figure 9: Plaque-RADS 4a.

MRI: Non-stenosing plaque of the right ICA. IPH Type I (arrowhead) resembled by hyperintense signal on T1w and TOF-images and isointense signal in PDw images. The FC cannot be delineated but no obvious plaque rupture is seen. IPH can be caused by "leaky" neovessels in a LRNC or by plaque rupture and is considered a hallmark of a high-risk lesion.

Histology: IPH in a LRNC. Panel e is reproduced from Kolodgie et al [PMID: 28818257].

Figure 10: Plaque-RADS 4b.

US: Ruptured plaque in the left carotid bulb. Calcified area on the anterior wall producing an acoustic shadow (white arrow in panel a). A free flap is visible in the lumen attached to the anterior wall on the left (white arrow in panel b). LRNC is not visible, presumably discharged, with color flow including flow reversal (blue area above the flap in panel b) between the flap and the near wall of the artery. This is a high-risk plaque.

MRI: Complex plaque in the left carotid bulb. Ulceration with rupture of the FC at the posterior end (solid arrow). The signal intensity of the ulcer is the same as that of the lumen. Large IPH in almost the entire plaque is seen as hyperintense on T1w, and TOF-images and isointense in PDw and T2w images (arrowhead) suggestive of fresh plaque hemorrhage. Speckled calcification appears as hypointense signal in all MRI sequences (open arrow). This is a high-risk plaque.

Histology: Ruptured fibrous cap (panel c and d). Magnification shows the area of fibrous cap rupture (red arrows) and adherent thrombus (asterisk, panel d)

Figure 11: Plaque-RADS IVc.

US: Severe stenosis in the proximal right carotid artery. DWA in the hypoechoic part of the plaque on the near wall without acoustic shadow indicates neovascularization (white arrow in panel b). Large JBA without a visible echogenic cap (open arrow in panel b) in the distal part of the stenotic area are compatible with intraluminal thrombus or LRNC indicating the need for further investigation with MRI. This is a high-risk plaque due to neovascularization, JBA, and severe stenosis. A) and b) B-mode image; c) Power Doppler image.

CT: Axial, sagittal, and coronal CT images demonstrating left carotid artery intraluminal thrombus and the "doughnut sign". The doughnut sign is seen as a filling defect surrounded by contrast (bold arrows).

MRI: Large thrombus (arrowhead) in the left carotid bulb, obstructing large parts of the origin of the ICA. The origin of the thrombus is most likely a rupture of the FC (not depicted). In TOF-imaging the thrombus causes a hypo-intense void of flow-signal.

Histology: Plaque rupture with intraluminal thrombus (arrow). Histological image is reproduced from Virmani et al [PMID: 18931283]

CT = Computed Tomography; DWA = Discrete white areas; FC = Fibrous Cap; FDG = F-18 Fluorodeoxyglucose; HU = Hounsfield Unit; IPH = Intraplaque Hemorrhage; JBA= Juxtaluminal black areas; LRNC = Lipid-Rich Necrotic Core; MRI = Magnetic Resonance imaging; NC = necrotic core; PET = Positron emission tomography; US = Ultrasound.
All histological images are stained with Movat pentachrome.

Carotid Plaque-RADS, a novel stroke risk classification system Part 2: Clinical application of Plaque-RADS classification.

Running title: Carotid plaque RADS classification

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Abstract

Carotid atherosclerosis is a crucial feature for evaluating the risk of cerebrovascular events. Identification and stratification of vulnerable plaque helps clinicians to choose the appropriate management and improves patient care. Although the morphological characteristics of vulnerable plaques are well recognized, there is a lack of consensus among radiologists in reporting plaque features and among treating physicians in interpreting such findings. Part 2 of this consensus document discusses in detail the clinical application of Plaque-Reporting and Data System (RADS), the proposed modalities per Plaque-RADS category, and standardized reporting.

Key words: Carotid; atherosclerosis; imaging; stroke.

Condensed Abstract

The Plaque-RADS score is designed to reduce variability among readers, enhance communication between interpreting and referring clinicians and scientists, and provide standardized terminology and structured reporting with the goal of increased accuracy in stroke risk stratification.

The Plaque-RADS classification is the first step towards an intuitive nomenclature that reflects the severity of carotid plaque instability and – if successfully implemented - could be an important tool to provide specific recommendations for managing carotid atherosclerotic disease.

Bullet Points

- There is a lack of consensus in reporting carotid artery atherosclerosis.
- A universal and complementary approach of non-invasive imaging advances plaque characterization.
- Standardized terminology and structured reporting across different imaging modalities may improve risk stratification of carotid plaques.

Introduction and purpose of this document

Non-invasive carotid imaging modalities have demonstrated their ability to characterize plaque features as predictors of future events in vivo, offering a significant contribution to risk stratification and patient management[1]. Translation of the present knowledge on plaque vulnerability into routine clinical practice requires a standardized reporting system. In this regard, the main motivation for developing the Plaque-Reporting And Data System (RADS) is to provide clinicians with an additional instrument to risk-stratify patients and to aid clinical management in carotid atherosclerosis.

Part 2 of this consensus document discusses in detail the optional provision of ancillary features, the report structure of Plaque-RADS, the reasoning for using a 3 mm cut-off for maximum wall thickness (MWT) measurements, the most suited imaging modalities per Plaque-RADS category, and standardized reporting.

1. Ancillary features of plaque instability

The Plaque-RADS score incorporates the best-validated features of carotid plaque vulnerability described in the literature. However, other features of instability have been recently described and others will likely emerge. To be as comprehensive as possible, the Plaque-RADS score includes "Ancillary Features" (AnFe) that allow the provision of additional information in the characterization of a given plaque. Such diagnostic complementary information is often not routinely provided and large differences exist across institutions. Thus, AnFE do not determine the main Plaque-RADS score but rather serve as a complementary tool when available. The following list of frequently collected parameters of AnFe does not claim to be exhaustive.

Plaque inflammation and neovascularization

The inflammatory changes in the perivascular carotid fat tissue may be an additional indirect marker of plaque instability in the carotid arteries[2,3]. Promising results in the assessment of plaque inflammation are obtained using fluorodeoxyglucose positron emission tomography (18-FDG PET)[4,5,6,7] and dynamic contrast enhanced MRI[8] or MRI with ultra-small superparamagnetic iron oxide particles (USPIO)[9,10,11] (**Figure 1)**.

Another feature of plaque vulnerability is intraplaque neovascularization[12,13]. The appearance of plaque heterogeneity on US is often produced by the presence of discrete white areas (DWA) in hypoechoic plaques or hypoechoic areas in part of a plaque. Perfusion studies using microbubble agents have demonstrated that DWA consist of neovascularization[14] and it is associated with recurrent cerebrovascular events independent of the severity of carotid stenosis[15]. The importance of adventitial enhancement, as a marker of intraplaque neovascularization and an additional parameter of stroke risk stratification was also highlighted using CT and MRI[16,17]. However, routine clinical practice has not yet adopted non-invasive imaging assessment of plaque inflammation and neovascularization (**Figure 2**).

Positive carotid artery remodeling

Beyond the mere degree of carotid stenosis, positive carotid artery remodeling is a marker of vulnerability[13] and a parameter associated with cerebrovascular events[18,19]. Plaque remodeling can lead primarily to expansive plaque growth, which allows the normal lumen width to be maintained. In the further course, an increasing narrowing of the lumen may develop[18]. Nevertheless, various studies have shown that even in these low-grade stenosed vessels, large plaques with characteristics of vulnerability may already be present and associated with cerebrovascular symptoms[20] **(Figure 3)**.

Plaque burden

Several metrics of atherosclerotic plaque burden (i.e., plaque volume, total plaque area, and normalized wall index [NWI]) have been largely recognized[21]. Plaque area and plaque volume are highly reproducible measurements associated with plaque size[22] and cerebrovascular events[12,23]. However, while various atherosclerotic burden metrics exist, each one has its pros and cons making the selection of the most appropriate one difficult. For example, while total wall volume is a highly reproducible measure, it is dependent on the total longitudinal coverage of the vessel, individual artery size and the specific segment examined, making comparisons across different individuals and studies inconsistent. Conversely, the NWI (=wall area/total vessel area) offers a measure of plaque burden that accounts for inherent differences in wall area among vessels of differing diameters (common carotid, carotid bulb, and internal carotid artery). NWI is ≤0.4 in normal arteries and rises to 1.0 in occluded arteries[24,25]. NWI is a reliable metric of disease severity and plaque progression, an independent risk factor of cardiovascular events and positively correlates with the presence of complicated American Heart Association (AHA) type VI lesions[26–29].

Progression of stenosis

Another carotid plaque feature associated with cerebrovascular events is the progression of carotid artery stenosis[30,31]. A study conducted by Kakkos et al. recruiting 1121 patients with asymptomatic carotid stenosis of 50% to 99% demonstrated that stenosis progression was a risk factor for the development of subsequent cerebrovascular events[31]. The authors graded stenosis degree into six grades: 50% to 59%, 60% to 69%, 70% to 79%, 80% to 89%, 90% to 95%, and 96% to 99%, and defined progression of carotid artery stenosis severity as an increase in stenosis severity by at least one grade[31]. In the Plaque-RADS score, we chose to use the progression of total carotid artery stenosis rather than plaque volume or plaque area progression due to its simplicity, availability, and reproducible measurements across different imaging modalities.

Carotid plaque calcifications

The role of calcium in atherosclerosis remains controversial. However, it is generally agreed that size, shape, and position of calcification may all affect plaque development. Overall, it appears that some calcification patterns correlate with a higher degree of plaque instability. In particular, the positive rim sign strongly associates with plaque inflammation, leakage of the vasa vasorum, IPH, and cerebrovascular events[32,33]. The positive rim sign is defined as the presence of thin (<2 mm thick) adventitial calcifications with internal low attenuating plaque of ≥2 mm in maximum thickness[33].

Other patterns such as superficial nodular calcifications have been found to be associated with IPH and therefore may indicate an increased risk of cerebrovascular events[34,35] **(Figure 4)**. In some respect, such observations seem to be in line with similar findings in the coronary vasculature[13,36]. Virmani et al. described the superficial calcified nodule in coronary plaques as an entity associated with fibrous cap disruption and thrombi, to be differentiated from other fibrocalcific lesions which appeared to be the result of fibrotic changes and were usually associated with a stenotic lumen[36]. Promising results are emerging using 18F-sodium fluoride (18F-NaF) PET in identifying active formation of calcification that is associated with plaque vulnerability[37,38].

A detailed discussion of histology and diagnostic imaging aspect of the role of calcium in carotid atherosclerotic plaque is beyond the purpose of this paper but can be found in a recent review by Saba et al[39].

Table 1 summarizes previous studies regarding the role of the AnFe in carotid plaque classification.

2. Application of the Plaque-RADS classification system

As detailed in Part I, Plaque-RADS categories are assigned from classes 1 to 4, based on the identification of specific imaging features, essentially: Plaque-RADS 1 = normal vessel wall; Plaque-RADS 2 = eccentric wall thickening; Plaque-RADS 3 = MWT>3mm with possible lipid-rich necrotic core (LRNC) or presence of plaque ulceration independently of MWT; Plaque-RADS 4 = presence of complicated plaque features, such as intraplaque hemorrhage (IPH), fibrous cap (FC) rupture or intraluminal thrombus. With increasing Plaque-RADS category, the attributable cerebrovascular risk of a lesion increases. A separate Plaque-RADS score is assigned for each carotid artery. When using multiple modalities to determine the Plaque-RADS score, the highest score obtained should be used regardless of the imaging modality.

For the structured reporting of a Plaque-RADS score we recommend to use the following syntax, which will be further detailed in the following paragraphs:

Side of carotid: stenosis degree/ imaging modality Plaque-RADS score/ MWT/ Ancillary Features/ Modifiers.

Stenosis degree

It is important to stress that the Plaque-RADS score is not meant to replace the measurement of stenosis but rather integrate synergistically with it. Indeed, the independent association between the degree of carotid stenosis in both symptomatic[40,41] and asymptomatic patients[42,43,44] is well known. The degree of luminal stenosis should be reported using the North American Symptomatic Carotid Endarterectomy Trial (NASCET), as it is widely used and already harmonized across modalities.

Stenosis [%] = (Diameter of the normal distal ICA – Narrowest ICA Diameter in the stenotic segment) / Diameter of the normal distal ICA

Imaging modality

The imaging modality used to obtain the Plaque RADS score should be indicated. In the final evaluation, all modalities used should be listed, with the one leading to the highest score mentioned first. A detailed discussion of ideal imaging practice of the atherosclerotic plaque is beyond the purpose of this paper but can be found in the Consensus document by the ASNR Vessel Wall Imaging Study group[1].

Maximum wall thickness (MWT)

The MWT [mm] is derived via a linear measurement of the greatest thickness of the vessel wall as measured on axial images and includes the arterial vessel wall and both calcified and non-calcified components of the plaque.

Ancillary features

To accommodate the variety of other imaging vulnerability markers that have been well studied and validated in the scientific literature, and with an open mind for future advancements, we propose an optional sub-classifier of plaque RADS: AnFe. We suggested to report each individual AnFe in the final score.

Modifiers

Similar to coronary artery disease CAD-RADS[45], categories can be complemented by modifiers, including limited-diagnostic study ("L"), the presence of a stent ("Stent"), and previous carotid endarterectomy ("CEA").

The Modifier "L" can be applied if the study is not fully diagnostic, for example in case of motion artifact, blooming artifact on CT, or metal-induced artifact on CT or MRI.

Overestimation of restenosis using non-invasive imaging is a potential risk in stented carotid arteries. For this reason, the application of the Modifier "Stent" may be useful in clinical practice.

3. Why is MWT included in Plaque-RADS?

The likelihood of plaque-vulnerability increases with plaque size[46]. Since not every modality is suited to directly identify underlying features such as IPH, metrics of plaque burden may serve as surrogate parameters of these high-risk features. MWT can be obtained easily with high reproducibility with widely available imaging modalities and provides an immediate and straightforward appraisal of the dimensional entity of the lesio**n.** Its predictive power with regard to ASCVD events is similar to that of plaque volume[47]. To make the measurement more reproducible and the clinical application easier among the various imaging modalities, MWT includes both the calcified and the non-calcified components of the plaque and the vessel wall. The cut-off of 3 mm was chosen because previous studies have shown that plaques with a MWT below this value are very unlikely to have features of vulnerable or high-risk plaques[46,48,49]. Supporting these observations large (≥3 mm thick) but non-stenotic (<50%) plaques have been reported to be encountered more common ipsilateral than contralateral to cryptogenic stroke[49,50].Similarly, Jumah et al demonstrated that plaque thickness > 3 mm were more prevalent ipsilaterally to the stroke side in patients with embolic stroke of undetermined cause[49]. Hence a MWT of 3 mm comprises a reasonable threshold for the identification of a Plaque-RADS score III or higher.

MWT was chosen as an additional metric marker of carotid stenosis because, especially in low-grade stenosing atherosclerotic plaques, the cerebrovascular risk would be underestimated if only the degree of stenosis was used.

4. Which imaging modality should be used?

We believe that plaque risk stratification should not be restricted to a single imaging modality. In fact, current imaging techniques complement each other in their ability to detect specific plaque features and together allow a more detailed description. **Table 2** summarizes key plaque features across different imaging modalities.

In clinical practice, the choice of modality will depend on the technology available and the intrinsic pros and cons of each specific modality[51,52,53]. Therefore, we consider it appropriate that together with the assignment of a plaque to a given Plaque-RADS category, practitioners should indicate the specific modality used. Whenever a "first-choice" technique could not be employed, further examination to confirm the findings should be considered.

Tables 3 and 4 summarize the modalities of choice for determining Plaque-RADS category and the detection of ancillary findings, respectively.

A detailed discussion of technological and imaging aspects of the atherosclerotic plaque is beyond the purpose of this paper but can be found in the Consensus document by the ASNR Vessel Wall Imaging Study group[1].

Plaque-RADS 1

US can depict the arterial wall and plaques allowing for the evaluation of intima-media thickness (IMT), wall- and plaque thickness, and plaque area. The presence of an atherosclerotic plaque and abnormal luminal narrowing can thus be easily ruled out using US. Several large studies indicate US of the carotid bifurcations as a valid non-invasive tool to assess subclinical atherosclerosis[54,55]. Although MRI and CT are not the primary imaging modality to rule out carotid atherosclerosis, they can – if available – be used for this purpose.

Plaque-RADS 2

Wall thickening may be satisfactorily quantified via US[56,57]. For example, Underhill et al. found a good correlation between automated measurements of the mean wall thickness performed by MRI and IMT measurements by B-mode US (ρ= 0.93, P<0.001)[58]. We suggest to use US for the identification of a Plaque-RADS 2 score if there are no large calcifications with heavy acoustic shadowing or physical limitations to the sonographic evaluation of the body segment. In any other circumstance, CT or MRI should be favored**.**

Plaque-RADS 3

US can identify large LRNCs as hypoechoic plaques. Some authors demonstrated a good degree of agreement between US and histology in measuring FC thickness values[59]. A thick intact FC, hallmark of a score 3a, appears as a hyperechogenic structure.

US can also identify LRNCs with a thin FC as so-called juxta-luminal black areas (JBA), which translates into a Plaque-RADS score 3b. Histological studies have demonstrated that a JBA is associated with a LRNC located close to the lumen on histology[60], macroscopic plaque ulceration[61], a large lipid core, and a thin FC. However, US cannot distinguish large LRNCs from IPH, and JBAs may also represent plaque rupture (score 4b) or intraluminal thrombus (score 4c). Therefore, the identification of a hypoechoic plaque without a visible hyperechoic FC or a JBA found on US should alert the clinician to consider further investigation of plaques with MWT ≥ 3 mm with a modality capable to define the potential presence of IPH and/or plaque rupture (ideally MRI), which would then result in an upgrade to Plaque-RADS score 4.

Lipid components of LRNCs can be effectively detected by CT. However, despite few exceptions[62] it is broadly agreed that due to Hounsfield Units (HU) overlap this modality also has limitations in the capability to discriminate the presence of IPH[63,64]. CT is considered unable to detect FC thickness and/or FC integrity[53].

MRI generally performs better in the characterization of LRNCs both for its capability to rule out the presence of IPH and to depict the presence of a thin FC, the latter preferably detected with the use of gadolinium-based contrast agents[22,65].

In summary, for identifying a Plaque-RADS 3 score, we suggest the use of US, CT, or MRI, even though only MRI can reliably rule out the presence of IPH. Currently, there is growing potential for advanced CT techniques, such as spectral and photon-counting CT, to discriminate plaque subcomponents, which may render this modality suitable for this task in the near future[62].

The delineation of carotid plaque surface can be performed with virtually all imaging modalities including US, contrast-enhanced US (CEUS), CT angiography (CTA), MRI, and the traditional reference method of digital subtraction angiography.

Several studies show that US can effectively depict plaque ulcerations (score 3c). With CTA as reference standard Rafailidis et al. reported that Contrast-enhanced ultrasound (CEUS) outperformed color Doppler imaging in identifying carotid ulceration in terms of sensitivity (94.1 *vs* 41.2%), specificity (97.95 *vs* 97.95%), positive (94.1 *vs* 87.5%), and negative predictive values (97.95 *vs* 82.8%)[66].

On CTA, ulceration appears as contrast material that extends beyond the vascular lumen within the plaque for at least 1 mm[67]. Several CT-based studies have shown good agreement with Digital subtraction angiography (DSA) for the detection of ulcerated plaques[68]. MRI has also been used successfully for the diagnosis of ulcerated carotid plaques with a good inter-observer agreement[69].

Plaque-RADS 4

MRI is widely considered the most sensitive modality for IPH detection. In particular, strongly T1-weighted images with an inversion pre-pulse to suppress the signal of blood show IPH as a focus of hyperintense signal in the bulk of the plaque[70]. CT is generally considered less sensitive because of substantial overlap in the HU of fibrous, lipid, and IPH components. US is generally considered

unsuitable,[71] although the latest results from recent studies cited in this document suggest otherwise with experienced operators[12,72].

Currently, MRI is considered the reference standard for the evaluation of the FC. Using MRI, the ruptured FC is identified by the absence of the juxtaluminal hypointense band on time of flight (TOF)-images typical of intact FC; an additional hyperintense region adjacent to the lumen corresponds to plaque hemorrhage or mural thrombus[73]. Hatsukami et al. found a high level of agreement between in vivo MRI and histological findings on the thickness and sites of potential rupture of the FC in advanced atherosclerotic disease[74]. On the other hand, numerical simulations of carotid MRI showed that for fibrous caps smaller than approximately 200 μm the fibrous cap thickness measurement becomes more inaccurate[75].

Another important point to discuss is related to the size of IPH / LRNC that demonstrated an association with ipsilateral acute ischemic stroke[76]. The calculation of the size / volume of IPH and LRNC is time-consuming, has a relatively high intra- and interobserver variability and requires custom-designed software, which is currently only available in specialized centers. In order to keep the Plaque-RADS score as simple as possible, we advise against using quantitative measurements of these plaque features in the current Plaque-RADS score.

A JBA on US could be either a 3b (large LRNC with a thin fibrous cap) or 4c (intraluminal thrombus). Because ultrasound can rarely distinguish between the two (except if the thrombus is on top of a calcified plaque), the presence of a JBA is an indication for considering referral for MRI[77].

CT is generally not considered a reliable modality in the evaluation of the FC, mostly due to artifacts related to edge-blur and halo effects and an inability to differentiate the FC from the surrounding tissues[73]. However, some authors suggest that the ruptured FC correlates with the presence of plaque enhancement in CT angiography analysis[78].

With regards to the presence of intraluminal thrombi, several publications indicate that US is a sensitive modality, which may demonstrate a floating thrombus dynamically changing its position

over time[79]. CTA and MRA are also accurate, showing thrombi as a filling defect within the lumen surrounded by contrast material, the so-called "doughnut sign"[80]. Transcranial Doppler ultrasound (TCD) can be used to detect microembolic signal that appears as unidirectional high intensity increase, short duration, and random occurrence signals during the cardiac cycle, and are accompanied a "whistling" sound. The presence of embolic signal on TCD independently predicts of ipsilateral future stroke risk[81] and may help to initiate further imaging work-up to diagnose a plaque with a high Plaque-RADS score.

5. Reporting the Plaque-RADS score

The Plaque-RADS classification syntax requires that each reported item is separated by the slash sign (/) in the following order:

-side of carotid: stenosis degree/ imaging modality Plaque-RADS score/ MWT/ Ancillary Features / Modifiers

Thus, using an example, a plaque in a symptomatic patient with ipsilateral 50% stenosis with IPH with positive remodeling would be classified as:

- Right carotid: 50%/***MRI Plaque-RADS 4a***/ 5mm/ Positive Remodeling.

It is important to emphasize that AnFE do not determine the main Plaque-RADS score. Therefore, the assessment of the AnFe is not mandatory in the Plaque-RADS score but rather serve as a complementary tool when available, also for research purpose.

Finally, it is fundamental to consider the appropriateness of the modality used for each Plaque-RADS score. Whenever practitioners find that the study could not definitively exclude the possibility of a relevant score upgrade, further investigation should be considered. By means of example, the identification of a Plaque-RADS score 3a on CT may require further investigation on MRI to rule out the presence of IPH (which would upgrade to score 4a). Rather than adding a classification category

dedicated to the imaging modality, we suggest that "Consider MRI examination" is reported in the score and further information is provided in the impressions; in this case plaque in an asymptomatic patient with 70% carotid stenosis and a MWT of 5 mm, a positive rim sign and positive remodeling would read as:

- Left carotid: 70%/***CT Plaque-RADS 3a***/MWT=5mm/ Positive rim sign AND Positive Remodeling/Consider MRI examination

Inter-observer agreement

The inter-observer agreement was assessed based on Cohen κ test to investigate the reproducibility of Plaque-RADS categories (0.00 = poor, 0.00–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, and 0.81–1.00 = almost perfect)[82]. The study included evaluation of 100 vessels on US, 100 vessels on CT, and 100 vessels on MRI.

There was excellent inter-observer agreement on US, CT, and MRI images (kappa = 0.804, $p < 0.001$; kappa = 0.868, $p < 0.001$; and kappa = 0.876, $p < 0.001$; respectively). Additionally, the overall inter-reader agreement among the readers across different modalities was excellent (kappa = 0.856, $p < 0.001$). The results are presented in **Table 5**.

To evaluate the inter-observer agreement of Plaque-RADS system, the study involved US,CT, and MRI specialists blinded to the clinical status.

Strengths and Limitations

The strength of the plaque RADS score is its unified reporting system that considers multiple features of plaque vulnerability beyond mere stenosis severity. It incorporates current research findings and can be applied across multiple imaging modalities. In this way, carotid plaques can be classified reliably according to their cerebrovascular risk, regardless of the imaging technique used. By establishing a simple four-grade plaque vulnerability score it creates a common language

between sonographers, CT and MRI specialists and the treating clinicians and research scientists. Recent guidelines on carotid artery atherosclerosis have emphasized the need for additional imaging techniques looking beyond the degree of luminal stenosis to assess plaque vulnerability. Plaque-RADS fills this gap. It is easy to assess and therefore suitable for routine clinical use. Moreover, it has the potential to be applied in future clinical trials on carotid atherosclerosis. However, the plaque RADS score still needs to be validated in larger cohorts.

Future direction: Artificial intelligence and Computational fluid dynamics.

Artificial intelligence (AI) in cardiovascular imaging is a rapidly evolving field and is poised to make a major impact on clinical practice [83]. The application of AI, more specifically Machine Learning (ML) and Deep Learning, can help in evaluating carotid plaques with their vulnerable features to better decide whether invasive procedures and treatment are necessary. AI models have been developed to simplify plaque characterization and predict histological plaque composition[85,86]. In addition, AI can combine a large volume of imaging data with clinical parameters, representing a new frontier in carotid plaque risk assessment[87]. AI-based models could facilitate the application of the Plaque-RADS score in clinical practice, leading to reduced diagnostic time and automatic classification of plaque risk.

A growing interest is emerging on computational fluid dynamics (CFD) to simulate blood flow inside the carotid arteries. Indeed, hemodynamic conditions affect both the development, progression, and plaque complications[88]. In this scenario, CFD can investigate the local hemodynamics and thrombotic environment in carotid atherosclerotic disease[89–91].

Conclusion

Plaque-RADS is a standardized and reliable system of reporting carotid plaque composition and morphology via different imaging modalities, such as US, CT, and MRI. A standardized lexicon and

structured reporting aim to enhance communication between radiologists, referring clinicians, and scientists. Future follow-up studies to test the ability of Plaque-RADS to predict clinical outcomes in large cohorts will be necessary to gauge its utility and ability to add value to other biomarkers of risk for cerebrovascular events. Ultimately, testing the effectiveness of therapies allocated based on Plaque-RADS are needed to spur the broad adoption of this instrument.

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Figure legends

Figure 1: Ancillary Findings-Inflammation: PET-MRI: Carotid magnetic resonance vessel wall imaging demonstrating plaque with a ruptured FC (open arrow) and underlying hyperintensity on T1w and TOF-imaging consistent with IPH (bold arrows). PET and fused images show high FDG-accumulation in the corresponding area consistent with inflammation.

Figure 2: Ancillary Findings-Neovascularization: ROI measurements in the non-calcified proportion of an asymptomatic plaque before (a) and after (b) contrast material administration indicate a significant increase in plaque density consistent with the presence of intraplaque neovascularization (from 20 HU to 31 HU). Representative histological images show an area with microvessels. Histological images are stained with H&E.

Figure 3: Ancillary Findings-Remodeling: Example of eccentric (panel c) and concentric (panel d) internal carotid artery plaques evidenced by CT. Representative histological images show positive remodeling of the common carotid artery. The distal section shows greater plaque burden with positive remodeling with intraplaque hemorrhage as compared to the proximal section. Histological images are stained with Movat pentachrome.

Figure 4: Ancillary Findings-Calcification: Different types of calcifications evidenced in CT.

In the panel a, a positive rim sign (white arrowhead), defined as carotid plaque with adventitial calcification (<2 mm thick) and internal soft plaque (≥ 2 mm thick) is demonstrated.

The panel b shows superficial nodule calcifications protruding into internal soft plaque (white arrowhead). Representative histological images show carotid plaque with different types of calcifications. Panel c and d shows micro and punctate calcification. Panel e shows fragmented calcification. Panel f is the site of carotid bifurcation showing areas of nodular calcification high-lighted in g within the intima with a thick fibrous cap (absence of thrombosis). The boxed area from

h is shown at high power note nodules of calcification with an overlying thrombus. Images f,g, and h are reproduced from Kolodgie et al [PMID: 28818257].

Histological images of f,g, and h are stained with Movat pentachrome and the rest of H&E.

Tables

Table 1: Overview of previous studies regarding the role of the Ancillary features in carotid plaque classification

Authors	**Type of study**	**Modalities**	**Ancillary features**	**Patient Population**	**Patients Status**	**Results**
Saba et al.[2]	Retrospective	CT	Plaque inflammation	100	Asymptomatic Symptomatic	Perivascular fat density demonstrated a statistically significant positive correlation with contrast plaque enhancement on CT (ρ value = 0.6582, P=0.001). This correlation was stronger for symptomatic patients than for asymptomatic patients (ρ value = 0.7052, P=0.001 *vs* ρ value = 0.4092, P=0.001),
Baradaran et al.[3]	Retrospective	CT	Plaque inflammation	92	Asymptomatic Symptomatic	Symptomatic patients had higher mean pericarotid fat density compared with asymptomatic patients (−66.2±19.2 *vs* −77.1±20.4, P=0.009)
Tang et al.[9]	Retrospective	MRI	Plaque inflammation	20	Asymptomatic	The mean signal difference between asymptomatic patients with coronary artery disease and truly asymptomatic patients was 24.9% (95% CI 16.7% to 33.0%; P<0.001).
Kooi et al.[10]	Prospective	MRI	Plaque inflammation	11	Asymptomatic	USPIOs accumulate predominantly in macrophages in ruptured and rupture-prone human atherosclerotic lesions
Kelly et al.[5]	Prospective	18-FDG-PET	Plaque inflammation	109	Symptomatic	The derived risk score (SCAIL), including stenosis and plaque inflammation, was associated with recurrent stroke (adjusted HR 2.4; 95%CI 1.2–4.5, P=0.01)
Camps-Renom et al.[6]	Prospective	18-FDG-PET	Plaque inflammation	135	Symptomatic	The risk of stroke recurrence increased progressively according to the SCAIL score (P=0.04) in subgroups with uncertain benefit from revascularization in endarterectomy trials.
McCabe et al.[7]	Prospective	18-FDG-PET	Plaque inflammation	181	Symptomatic	The SCAIL score which incorporates a measure of stenosis severity and 18FDG uptake predicted 5-year ipsilateral stroke (adjusted HR 2.73 per 1-point increase, 95% CI 1.52–4.90, p = 0.001).

Tang et al.[11]	Prospective	USPIO-MRI	Plaque inflammations	47	Asymptomatic	lipid-lowering therapy demonstrated significant change in USPIO-enhanced MRI-defined inflammation.
Nicolaides et al.[12]	Prospective	US	Intraplaque neovascularization	1121	Asymptomatic	The presence of DWA, as a marker of neovascularization, is associated with cerebrovascular event (HR 1.68, 95 % CI 0.92-3.06)
Song et al.[15]	Prospective	US	Intraplaque neovascularization	155	Asymptomatic	Intraplaque neovascularization is associated with recurrent cerebrovascular events (HR 4.5, 95 % CI 1.9-10.90, P=0.001) independent of the severity of carotid stenosis (HR 3.5, 95 % CI 1.4-8.6, P=0.007)
Romero et al.[16]	Retrospective	CT	Intraplaque neovascularization	75	Asymptomatic Symptomatic	Carotid wall enhancement was statistically more likely present in symptomatic patients. (OR 3.63; 95% CI 1.32-9.93, P=0.01)
Qiao et al.[17]	Retrospective	MRI	Intraplaque neovascularization	47	Symptomatic	Adventitial enhancement, as a marker of neovascularization, was associated with cerebrovascular events (OR 51.7; 95%CI 3.40-469.80, P=0.004) after controlling for age, sex, cardiovascular risk factors, wall thickness, and stenosis
Miura et al.[18]	Retrospective	CT, MRI	Positive plaque remodeling	28	Asymptomatic Symptomatic	Patients with positive plaque remodeling in carotid arteries demonstrated a higher prevalence of stroke in comparison with patients with negative remodeling (P<0.05)
Nicolaides et al.[21]	Prospective	US	Plaque burden	985	Asymptomatic	The logistic regression model demonstrated that the addition of individual ultrasonographic measurements to the model increased discrimination for the prediction of atherosclerotic cardiovascular events with an AUC of 0.747 (0.706-0.788), 0.742 (0.699-0.784), and 0.751 (0.710-0.793) for IMT, total plaque area, and total plaque thickness, respectively
Sillesen et al.[47]	Prospective	US	Plaque burden	5808	Asymptomatic	After adjusting for risk factors, hazard ratios for maximum plaque thickness and carotid plaque volume with primary major ASCVD events as an end point were 1.96 [95% CI 0.91-4.25, P = 0.015] for primary MACE and 3.13 (95% CI 1.80-5.51, P < 0.001) for secondary MACE.
Saam et al.[26]	Retrospective	MRI	Plaque burden	175	Asymptomatic	NWI is positively correlated with the presence of complicated AHA type VI lesions (ρ value = 0.57, P<0.001) hemorrhage (ρ value = 0.56, P<0.001) and fibrous cap rupture (ρ value = 0.374 P<0.001)

Saam et al.[27]	Prospective	MRI	Plaque burden	74	Asymptomatic	NWI is a reliable metric of the rate of wall progression and disease severity (4.2% per year; P=0.001)
Lu et al.[28]	Retrospective	MRI	Plaque burden	272	Symptomatic	Patients with ischemic stroke had a significantly greater maximum NWI in comparison with those with TIA (OR 1.56; 95%CI 1.02–2.38, P= 0.038)
Jia et al.[29]	Prospective	MRI	Plaque burden	228	Symptomatic	NWI was an independent risk factor of stroke (OR 3.472, 95%CI 2.943-4.096, P=0.011) with an AUC of 0.798 (95%CI 0.660–0.937)
Shah et al.[30]	Retrospective	US	Plaque progression	864	Asymptomatic	Progression of severity of carotid stenosis is an independent predictors of TIA and stroke
Kakkos et al.[31]	Prospective	US	Plaque progression	1121	Asymptomatic	Plaque progression was a risk factor for the development of subsequent stroke (RR 1.92, 95%CI 1.14-3.25)
Van den Bouwhuijsen et al.[92]	Prospective	MRI	Calcification	329	Asymptomatic	Higher calcification load was associated with the presence of IPH (OR 2.65; 95%CI 1.94-3.64)
Yang et al.[35]	Prospective	CT	Calcification	154	Symptomatic	Superficial (OR 3.4; 95%CI 1.1–10.8, P= 0.001) and multiple calcifications (OR 3.9; 95%CI 1.4–10.9, P= 0.009) were associated with IPH
Eisenmenger et al.[93]	Retrospective	CT	Calcification	96	Asymptomatic	Positive rim sign (OR 11.9; 95%CI 4.4–32, P<0.001) was associated with IPH
Benson et al.[32]	Retrospective	CT	Calcification	77	Asymptomatic	Positive rim sign was associated with a higher proportion of hemorrhage within a plaque (P=0.049).
Saba et al.[33]	Retrospective	CT	Calcification	790	Asymptomatic Symptomatic	Patients with a positive rim sign had a higher prevalence of cerebrovascular events in comparison to other types of carotid calcifications
Hop et al[37]	Retrospective	^{18}F-NaF	Calcification	23	Asymptomatic Symptomatic	^{18}F-NaF uptake was present in regions without evidence of calcification on CT scan. Regions of CT calcification had low 18F-NaF uptake.

AHA= American Heart Association; ASCVD = Atherosclerotic Cardiovascular Disease; AUC = Area under the curve; CI = confidence interval; CT = Computed Tomography; DWA = Discrete white areas; FC = Fibrous Cap; 18-FDG-PET = F-18 Fluorodeoxyglucose Positron emission tomography; HR = hazard ratio; IPH = Intraplaque Hemorrhage; IMT = Intima-media thickness; LRNC = Lipid-Rich Necrotic Core; MACE = Major adverse cardiovascular event; MRI = Magnetic Resonance imaging; NWI = normalized wall index; OR = odds ratio; US = Ultrasound; USPIO = Ultrasmall Superparamagnetic Iron Oxide;

Table 2**:** summarizes key plaque features across different imaging modalities.

Plaque-RADS Key Components	**Key Imaging Characteristics**		
	US	CTA	MR
Calcification	Hyperechogenic region with acoustic shadowing	High-attenuation Plaque, usually > 130 HU	An
LRNC	Lesion with more than 75% of its area being hypoechoic, or the plaque with gray scale median less than 30 with a visible echogenic fibrous cap. Presence of JBA, defined as the plaque area with GSM lower than 25 after image normalization. *CAVE: JBA could be either 3 or 4 Plaque-RADS categories.*	Low-attenuation Plaque, usually < 60 HU *CAVE: HU-overlap with IPH and fibrous tissue*	T1v of t T1v pre
Fibrous cap	Hyperechogenic structure between lumen and bulk of plaque	Currently not suited to assess.	T1v TO bet pla
Plaque ulceration	B-mode: Cavity in the plaque surface, irrespective of size, with a lower surface echogenicity than that of the adjacent plaque surface. CEUS: interruption of the plaque-lumen borders for at least 1 × 1 mm.	Contrast material that extends beyond the vascular lumen into the plaque, usually for at least 1 mm.	An into flow bes
IPH	Currently unsuitable to distinguish large LRNCs with a thin FC from IPH.	Low attenuation plaque, usually < 25 HU *CAVE: HU-overlap with lipid and fibrous tissue*	T1v are ass T2v /hy hyp
Intraluminal thrombus	B-mode: Cannot distinguish large LRNCs with a thin FC from intraluminal thrombus. CEUS: Hypoechoic filling defect with microbubbles delineating circumferentially the thrombus	Filling defect within the lumen, which is completely surrounded by the contrast agent for more than one axial source image	MR MR T1v T1v enh
Modalities of choice			

* [Intensities in reference to sternocleid muscle or the normal vessel wall]

CE = Contrast Enhanced; CEUS = Contrast Enhanced Ultrasound; CT = Computed Tomography; FC = Fibrous Cap; IPH = Intraplaque Hemorrhage; HU = Hounsfield Unit; LRNC = Lipid-Rich Necrotic Core; MRI = Magnetic Resonance imaging; MRA = Magnetic Resonance

Angiography; TOF = Time-of-Flight; US = Ultrasound.

Table 3: summary of the modalities of choice in Plaque-RADS category.

Plaque-RADS Score		Physical description	Modality of choice	Comments
I		Normal vessel wall	US, CT, MRI	US represents first-line imaging modality for the screening of asymptomatic patients.
II		MWT < 3mm AND absence of complicated plaque features	US, CT, MRI	US may be considered suitable in the absence of strong acoustic shadowing or other physical barrier.
III		MWT > 3mm OR ulcerated plaque independently of MWT		
	IIIa	LRNC with intact thick FC	MRI, CT, US	MRI outperforms both US and CT in the evaluation of the FC
	IIIb	LRNC with intact thin FC	MRI, CT, US	
	IIIc	Ulcerated plaque	MRI, CT, US	All imaging modalities suitable
IV		Complicated plaque		
	IVa	IPH	MRI, (CT), (US)	MRI is modality of choice for IPH detection. US and CT only useful in few selected cases.
	IVb	Ruptured FC	MRI, (CT), (US)	
	IVc	Intraluminal thrombi	MRI, CT, US	

CT=Computed Tomography; FC= Fibrous Cap; IPH = Intraplaque Hemorrhage; LRNC = Lipid-Rich Necrotic Core; MWT = Maximum wall thickness; MRI =Magnetic Resonance Imaging; US=Ultrasound;

Table 4: summary of the modalities of choice in the detection of ancillary findings

Ancillary features	Modality of choice
Plaque inflammation	18-FDG PET (MRI USPIO)
Plaque neovascularization	MRI CEUS CT* (US)
Progression of stenosis	US CT MRI

Positive plaque remodeling	US CT MRI
Plaque burden	US CT MRI
Type of calcification	CT** (MRI) (US)

* Contrast plaque enhancement difference from basal to CTA
** Method of choice for calcium classification.

CT=Computed Tomography; DCE = Dynamic Contrast Enhanced; 18-FDG PET =Fluorodeoxyglucose Positron Emission Tomography; MRI=Magnetic Resonance Imaging; US=Ultrasound; USPIO=Ultrasmall Superparamagnetic Iron Oxide.

Table 5: Interobserver agreement of Plaque-RADS categories

Plaque-RADS modalities	**Cohen's Kappa**	
	Kappa	P-value
Ultrasound	0.804	< 0.001
Computed Tomography	0.868	< 0.001
Magnetic Resonance Imaging	0.876	< 0.001