Stroke remains a leading cause of morbidity and mortality. Treatment decisions are still based predominantly on studies correlating the risk reduction achieved from carotid endarterectomy (CEA) or carotid artery stenting (CAS) with the percentage of stenosis. While the benefit of CEA in recently symptomatic carotid artery stenosis > 70% has been demonstrated in multiple large randomized clinical trials, the role of surgical versus medical treatment in symptomatic patients with less significant carotid stenosis remains unclear. The benefit of CEA or CAS is even more controversial in patients with asymptomatic carotid stenosis. The Asymptomatic Carotid Atherosclerosis Study (ACAS) has reported a risk reduction following CEA in asymptomatic patients with stenosis greater than 50%–60%.

In this paper, the authors review the definition of high-risk plaque as developed by experienced researchers in atherosclerosis, including pathologists, clinicians, molecular biologists, and imaging scientists. Current concepts of vulnerable plaque are based on histological studies of coronary and carotid artery plaque as well as natural history studies and include the presence of a lipid-rich necrotic core with an overlying thin fibrous cap, plaque inflammation, fissured plaque, and intraplaque hemorrhage. The extension of these histologically identified high-risk carotid plaque features to human in vivo MRI is reviewed as well. The authors also assess the ability of in vivo MRI to depict these vulnerable carotid plaque features. Next, the ability of these MRI-demonstrated high-risk carotid plaque features to predict the risk of ipsilateral carotid thromboembolic events is reviewed and compared with the risk assessment provided by simple carotid artery stenosis measurements. Lastly, future directions of high-risk carotid plaque MRI are discussed, including the potential for increased clinical availability and more automated analysis of carotid plaque MRI. The ultimate goal of high-risk plaque imaging is to design and run future multicenter trials using carotid plaque MRI to guide individual patient selection and decisions about optimal atherosclerotic treatment strategies.

Correlating the American Heart Association Carotid Plaque Classification With Plaque MRI

Definition of Vulnerable Plaque

Histological studies have demonstrated that coronary artery plaques with a large lipid-rich necrotic core (LRNC) and an overlying thin fibrous cap (FC) are associated with sudden cardiac death. This finding has led to the concept of “vulnerable plaque.” Key features of the vulnerable plaque, including a large LRNC with a thin FC, active inflammation with activated macrophages, fissured plaques, and intraplaque hemorrhage.

Key Words

- carotid stenosis
- stroke
- carotid plaque
- MRI

Abbreviations used in this paper: ACAS = Asymptomatic Carotid Atherosclerosis Study; AHA = American Heart Association; CAS = carotid artery stenting; CE = contrast-enhanced; CEA = carotid endarterectomy; FC = fibrous cap; IPH = intraplaque hemorrhage; LRNC = lipid-rich necrotic core; MRA = MR angiography; SNR = signal-to-noise ratio; T1W = T1-weighted; T2W = T2-weighted; TIA = transient ischemic attack; TOF = time-of-flight.
plaque, superficial calcified nodules, and intraplaque hemorrhage (IPH), were defined in two consensus review articles published by a group of experienced researchers in atherosclerosis, including pathologists, clinicians, molecular biologists, and imaging scientists.\textsuperscript{15,16} The discussion of pathological definitions of vulnerable plaque was subsequently extended to MRI.\textsuperscript{22} The American Heart Association (AHA) has proposed a detailed classification scheme of atherosclerotic plaque (Fig. 1).\textsuperscript{28} This scheme has been modified for in vivo MRI to include the description of carotid plaques with LRNCs (AHA Type IV–V) as well as a more complex plaque with IPH, ruptured FC, and/or calcified protruding nodule (AHA Type VI).\textsuperscript{5}

**Lipid-Rich Necrotic Core With Thin FC**

Based on the histological studies of coronary artery plaque associated with sudden cardiac death, an LRNC has also been proposed to represent a phenotype of atherosclerotic disease with a high risk for future cardiovascular events.\textsuperscript{29} The most widely accepted hypothesis is that lipid-lowering therapy targets the plaque rupture risk features such as a large LRNC, thin FC, and high level of inflammatory infiltrates and activity. The lipid deple -tion theory suggests that plaque stability is improved and cardiovascular events are reduced with medical treatment such as statin therapy to deplete lipids and decrease the LRNC size.\textsuperscript{37} Multicontrast MRI of the carotid arteries has been validated with histology and shown to identify and quantify various carotid plaque components including the LRNC, FC, and IPH (Fig. 2).\textsuperscript{4,21} Contrast-enhanced (CE) T1-weighted (T1W) images improve differentiation of the LRNC from fibrous tissue.\textsuperscript{36} Further, multicontrast carotid plaque MRI has been shown to be capable of quantifying the LRNC volume in the clinical setting of a multicenter trial with low interscan variability.\textsuperscript{24}

**Plaque Inflammation**

Observational studies on LRNC demonstrate that neo-angiogenesis is closely associated with plaque progression.\textsuperscript{32} Intimal neovascularization is predominantly thought to arise from the adventitia, where there are a plethora of preexisting vasa vasorum. The amount of adventitial neovascularity can be quantified using dynamic contrast-enhanced (DCE) MRI. Histological evaluation showed that adventitial K\textsuperscript{trans} calculated from DCE-MRI was significantly correlated with the amount of neovascularity and macrophages in the excised plaque, thus providing an in vivo marker of plaque inflammation, which has been described as a hallmark of the vulnerable plaque.\textsuperscript{11}

**Fissured Plaque**

Virmani et al. described the fissure plaque as a region of FC rupture where the juxtaluminal thrombus was in direct communication with the underlying LRNC.\textsuperscript{32} Using either noncontrast 3D time-of-flight (TOF) MR angiography (MRA) or a CE-T1W MRI series, multiple authors have demonstrated the ability of in vivo carotid plaque MRI to differentiate between a thick, intact FC and a thin or ruptured FC. Using 3D TOF MRA, Hatsukami et al. demonstrated a high level of agreement (89\%) between MRI and histological findings.\textsuperscript{9} Cai et al. used CE-T1W MRI series to optimally demonstrate the FC and showed moderate-to-good correlation between carotid MRI findings and the excised histological specimen for maximal thickness ($r = 0.78$, $p < 0.001$), length ($r = 0.73$, $p < 0.001$), and area ($r = 0.90$, $p < 0.001$) of the intact FC.\textsuperscript{4}

**Intraplaque Hemorrhage**

The cause of IPH is unclear. Some authors have suggested that hemorrhage into a plaque is related to rupture

![Different Types of Vulnerable Plaque](image-url)
Imaging of high-risk carotid plaques

**Better Risk Depiction by Carotid Plaque MRI Than Carotid Stenosis**

*Lipid-Rich Necrotic Core With a Thin FC as a Predictor of Risk*

Numerous studies have demonstrated the correlation between LRNC size and/or the presence of a thin or ruptured FC overlying the LRNC and recent symptoms as well as the subsequent development of new ipsilateral carotid thromboembolic symptoms, future carotid plaque destabilization with new FC rupture or new IPH, and progression in carotid plaque size. In a cross-sectional study of 97 consecutive patients with 50%–99% stenosis referred for carotid plaque MRI, there were significant associations between recent ipsilateral carotid stroke and/or transient ischemic attack (TIA) and the presence of an LRNC as well as the presence of a thin or ruptured FC. In that study, there was no correlation between carotid artery stenosis and symptoms (Figs. 3 and 4). In 2006, in a 3-year natural history study of 154 previously asymptomatic individuals with 50%–79% stenosis, Takaya et al. found that the presence of a thin or ruptured FC (HR 17.0, \( p \leq 0.001 \)) and larger maximum percentage of LRNC (HR for 10% increase 1.6, \( p = 0.004 \)) were predictors of the future development of neurological ischemia. A multivariate analysis of clinical and carotid plaque features in a study of 108 individuals with 50%–79% stenosis revealed that the size of the LRNC relative to plaque size was the strongest predictor of new FC rupture or ulceration after 3 years of follow-up. In a cross-sectional study of 334 patients from four imaging centers in the US and China, the LRNC size was the strongest predictor of other vulnerable plaque features such as IPH and FC rupture. Authors of that study proposed a 4-tier grading system for plaque burden that they termed the “Carotid Atherosclerosis Score” (CA score). Patients with a maximum wall thickness \( \leq 2 \) mm had a CA Score 1. Patients with a maximum wall thickness > 2 mm had a CA Score 2 if they demonstrated \(< 20\%\) maximum percentage area of LRNC, CA Score 3 if they had \(20\%–40\%\) maximum percentage area of LRNC, and a CA Score 4 if their maximum percentage area of LRNC was \(> 40\%\). The CA score was an accurate classifier of IPH (area under curve [AUC] = 0.91) and FC rupture (AUC = 0.93). The simple classification scheme could be easily applied clinically when reviewing carotid plaque sequences. Compared with MRA stenosis, the CA score was a stronger classifier of both IPH and FC.

![Fig. 2. Comparison of high-resolution MR angiography (MRA), multicontrast 3-T in vivo carotid plaque MRI, and ex vivo histological evaluation of CEA specimen. A: There is 82% carotid stenosis on the 500-µm resolution contrast-enhanced (CE) carotid MRA. B: These examples of T1-weighted (T1W), T2-weighted (T2W), 3D time-of-flight (TOF) MRA, and CE-T1W plaque images obtained at the level of the carotid artery stenosis shown in panel A demonstrate how the 3-T in vivo carotid plaque MRI identifies the LRNC (light gray outline) and loose matrix (dark gray outline) through the right carotid artery plaque. C: The region of the LRNC is dark (chevron) on these T2W images, while the area of loose matrix (arrow) is bright. D: The percent areas of plaque that were characterized as LRNC (light gray outline) and loose matrix (dark gray outline) on the histological slide is similar to that measured on the in vivo 3-T MR images.](image-url)
rupture. Authors of that study proposed that the CA score would complement carotid artery stenosis in classifying the severity of atherosclerotic disease. Subsequently, the CA score was prospectively evaluated using an independent cohort of 73 asymptomatic subjects who underwent serial carotid MRI over a 3-year period. Applied prospectively, the CA score was associated with new FC rupture and greater lesion growth. Carotid stenosis was not significantly associated with any end point (presented at the 2013 Radiological Society of North America Annual Meeting, Chicago, IL). The original AHA plaque classification and these subsequent in vivo carotid plaque MRI trials suggest that the LRNC may be a useful phenotype of atherosclerotic disease that may predict future plaque destabilization and thromboembolic events.

Multiple drug trials have shown the ability of in vivo MRI to evaluate the effectiveness of statin treatment to decrease the size of an LRNC. Corti et al. first demonstrated the ability of in vivo carotid plaque MRI to depict a response to statin therapy in a cohort of 21 asymptomatic hypercholesterolemic patients monitored over a 2-year period. Although specific identification of plaque components was not pursued in that study, it is likely that most if not all of the patients had an LRNC given their severity of hypercholesterolemia and their statin-naïve status at the beginning of the study. In a subsequent study of 33 patients randomized to receive low- or high-dose rosuvastatin, only patients with an LRNC at the beginning of the study demonstrated a decrease in overall carotid plaque volume and LRNC with the statin therapy.

In one of the first prospective tests of the lipid depletion theory, Zhao et al. enrolled 33 patients with an LRNC who were treated with intensive lipid-lowering therapy. After 3 years of lipid therapy, these 33 subjects had a significant reduction in plaque lipid content. For the first time, an understanding of the time course was provided, with statistically significant plaque lipid depletion observed after 1 year of treatment and continuing into the 2nd year. The LRNC size reduction preceded the plaque regression, consistent with the lipid depletion therapy. It is interesting to note that the results of this study provide a possible biological explanation for the clinical benefit in placebo-controlled drug trial studies in which the reduction in cardiovascular events in actively treated subjects begins at 1–2 years. This study also demonstrated a reduction in the plaque area within each patient only at the levels at which an LRNC existed at baseline. Carotid intima-media thickness specifically excludes regions of carotid plaque and may not be able to demonstrate changes related to drug therapy.

Taken as a whole, there is ample peer-reviewed literature to suggest that the presence of an LRNC repre-

**Fig. 3.** Coronally acquired MR angiogram and transverse images of a complicated plaque of the left carotid artery in a 75-year-old man with right-sided weakness. A: Maximum intensity projection of CE-MRA demonstrates a 55% smooth stenosis at the left internal carotid artery. The horizontal line indicates the level of the transverse carotid plaque images shown in B. B: Disrupted dark band (arrow) on the TOF angiogram and discontinuation of the high-intensity band on CE-T1W image indicate a thin FC. High intensity on TOF and precontrast T1W images indicates regions of hemorrhage (arrowheads). The low-intensity area on the CE-T1W image indicates an LRNC area occupying 31% of the wall area (chevron). Notice that the hemorrhage seen on TOF and T1W images almost completely fills the LRNC as seen on the CE-T1W image. Symptomatic plaques tend to have plaques with a hemorrhagic LRNC and a thin or ruptured FC. Reprinted with permission from Demarco JK et al: MR carotid plaque imaging and contrast-enhanced MR angiography identifies lesions associated with recent ipsilateral thromboembolic symptoms: an in vivo study at 3T. AJNR Am J Neuroradiol 31:1395–1402, 2010. © by American Society of Neuroradiology.
Imaging of high-risk carotid plaques

sent a phenotype of atherosclerotic disease with a high risk for future cardiovascular events, that in vivo MRI is capable of identifying and quantifying the size of an LRNC, that the presence and size of an LRNC provide reasonable selection criteria to identify patients suitable for additional intensive lipid-lowering therapy, and that in vivo MRI provides a reproducible technique to measure the effectiveness of lipid-lowering therapies. Thus, carotid plaque MRI detection and/or quantification of an LRNC, as compared with simple carotid stenosis measurements, may provide improved risk stratification with better patient selection for additional treatment as well as a mechanism for evaluating the effectiveness of the additional treatment.

Intraplaque Hemorrhage as a Predictor of Risk

During IPH, there is extravasation of lipid-rich membranes of the red blood cells plus deposition of iron into the carotid plaque. Both are proinflammatory processes resulting in carotid plaque destabilization. A recent prospective longitudinal MRI investigation of 31 patients showed that carotid plaque IPH was associated with accelerated plaque progression in a period of 18 months. The presence of IPH is also associated with future additional carotid plaque IPH, suggesting that IPH is an important transition point from stable to unstable carotid plaque morphology. Previous histological studies have had a very limited ability to illustrate this transition because they provide a single time point in the evolution of carotid plaque atherosclerosis. Noninvasive carotid plaque MRI gives us the ability to better understand both the evolution of carotid plaque disease and our ability to alter the natural history of atherosclerosis.

Intraplaque hemorrhage at baseline alone or in combination with other plaque features has been correlated with the subsequent development of new ipsilateral carotid thromboembolic symptoms and a progression in carotid plaque size. During a mean follow-up of 38.2 months in 154 patients with asymptomatic moderate carotid artery stenosis, 12 carotid cerebrovascular events occurred. Both the presence and size of IPH correlated with a new ipsilateral carotid stroke or TIA. In a longitudinal study of 98 patients with asymptomatic moderate carotid artery stenosis, slightly more than one-third of the patients demonstrated IPH, but all 6 future ipsilateral carotid events occurred in these patients. Altaf et al. enrolled 64 recently symptomatic patients who demonstrated 30%–69% carotid stenosis in a prospective trial of carotid plaque MRI. On the initial carotid plaque MRI study of the 64 recently symptomatic carotid arteries, 39 (61%) demonstrated IPH. After a mean follow-up of 28 months, 14 new ipsilateral carotid events occurred. Thirteen of the 14 events occurred in arteries with IPH on the initial carotid plaque MRI study.

In a meta-analysis of 8 longitudinal studies of IPH detected on in vivo MRI, including the 3 articles cited in the

![Fig. 4. Transverse carotid plaque images and coronally acquired CE-MR angiogram of the left carotid artery in an asymptomatic 61-year-old woman. A: Maximum-intensity projection of the CE-MRA demonstrates 74% stenosis at the left internal carotid artery. The horizontal line indicates the level of the transverse carotid plaque images shown in B. B: Transverse image of a TOF angiogram demonstrates a smooth luminal surface and a dark juxtaluminal band indicating an intact thick FC. The thick FC is easier to appreciate as a high-intensity band (arrows) on the CE-T1W and T2W images. An isointense area on TOF and T1W images, an isointense to low-intensity area on the T2W image, and a low-intensity area on the CE-T1W image indicate an LRNC without hemorrhage occupying 29% of the wall area (arrowheads). Notice that the LRNC is easiest to appreciate on the CE-T1W image. Asymptomatic plaques tend to have a smaller LRNC without hemorrhage as well as a thick FC. Reprinted with permission from Demarco JK et al: MR carotid plaque imaging and contrast-enhanced MR angiography identifies lesions associated with recent ipsilateral thromboembolic symptoms: an in vivo study at 3T. AJNR Am J Neuroradiol 31:1395–1402, 2010. © by American Society of Neuroradiology.](image-url)
above paragraph, Saam et al. demonstrated that despite a large degree of detected heterogeneity in the published studies, the presence of IPH on MRI is associated with an approximately 5.6-fold higher risk for cerebrovascular events as compared with the risk in subjects without IPH. The authors concluded that homogenization of future studies is warranted to allow sufficient assessment of the level of evidence for future intervention trials.

**Sex Differences in Carotid Plaque Components as a Predictor of Risk**

In 131 patients with asymptomatic carotid stenosis > 50% on duplex ultrasonography, men had higher-risk plaque features than women after controlling for potential confounders (Figs. 5 and 6). Specifically, men tend to have a higher incidence of LRNC and thin or ruptured FC as well as larger LRNCs and IPHs compared with women. The higher prevalence of these potential vulnerable plaque features in men as compared with women may be one reason that CEA was shown to be more effective for women than in men. Additional studies have shown that these sex differences in high-risk carotid plaque sequences exist even in patients with asymptomatic carotid stenosis < 50%. Thus, sex-based management may be important in patients with asymptomatic carotid atherosclerosis across all stages of carotid stenosis.

**Future Directions**

*Increased Clinical Availability of in Vivo Carotid Plaque MRI*

An improved quality of carotid plaque MRI along with a decreased imaging time is one direction for future work. A novel 4- to 5-minute 3D-based MRI technique called “3D SNAP,” which provides simultaneous noncontrast MR angiography with the ability to detect IPH, has been proposed. Recent work on 3D carotid plaque sequences has also demonstrated an ability to improve resolution with the good signal-to-noise ratio (SNR) that is inherent with 3D imaging. A combination of three 4-minute carotid plaque sequences (3D SNAP and 3D T1W pre- and postcontrast) may provide all the information necessary to fully characterize an LRNC, FC, and IPH. If this hypothesis is proven, then rapid multicontrast carotid plaque imaging could be added to routine clinical carotid MRA.

Improved carotid plaque coils are also being evaluated. First-generation 4-channel carotid coils have provided high SNR images of the midneck with approximately 10–12 cm of coverage in the superoinferior direction. Second-generation carotid coils utilize a higher coil density (6–8 coils) to improve overall SNR and increase coverage in the superoinferior direction to 16–18 cm. These coils are approved by the FDA and clinically available today for most MR vendors. Third-generation coils with tight integration of improved carotid coils into a larger neurovascular coil capable of imaging from the aortic arch through the circle of Willis as well as the brain are being developed. Combined with new rapid 3D carotid plaque sequences, rapid 30-minute arch and carotid MRA with dedicated carotid plaque imaging or a 45-minute brain/MRA/carotid plaque protocol would be possible. These new capabilities would greatly expand the routine clinical availability of carotid plaque imaging by providing access to plaque imaging within current scan times of carotid MRA.

Rapid automated carotid plaque analysis would greatly aid the clinician with the interpretation of multicontrast carotid plaque sequences. Validation of automated carotid plaque analysis utilizing predominantly 2D MR sequences has been completed. Future work will extend the automated carotid plaque analysis to include all 3D MR sequences.

*Future Multicenter Trials Using in Vivo Carotid Plaque MRI to Guide Treatment Decisions*

By far, the most important future direction is to test the hypothesis that vulnerable plaque imaging, as opposed to simple carotid stenosis measurements, can guide therapy and improve patient outcome. It is possible that vulnerable carotid plaque imaging may help guide both medical therapy and surgical intervention. As proposed above, patients with large LRNCs identified by carotid plaque MRI may be a subgroup with asymptomatic carotid atherosclerosis that may benefit the most from aggressive medical therapy. Additional clinical trials randomizing patients with LRNCs to standard and aggressive medical therapy are being proposed. Initial trials will...
likely use a decrease in the LRNC size as a surrogate marker for improved atherosclerotic treatment, although larger multicenter trials with enough patients to test for a statistically significant improvement in hard end points, such as stroke and TIA, will be needed to fully test the hypothesis. Improved availability of clinical MRI to detect vulnerable carotid plaque will greatly facilitate these studies. Likewise, vulnerable plaque imaging in patients with recently symptomatic carotid artery stenosis may better stratify risk and identify additional patients who would benefit from surgical intervention (CEA or CAS) and are currently not being offered these procedures. It is likely that the presence, size, location, and/or type of IPH can identify patients with mild-to-moderate carotid artery stenosis who are at an increased risk of ipsilateral stroke and/or TIA and who may benefit from surgical intervention. Future large multicenter trials will clarify the risk of future ipsilateral events in patients with recent stroke and/or TIA and form the basis for designing follow-up surgical trials.

Conclusions

A cornerstone of stroke prevention has been the identification of risk factors. While great strides have been made with the treatment of hypertension and hyperlipidemia, future reductions in stroke may require the identification of individual risk factors. In this paper we have reviewed current concepts of vulnerable plaque and demonstrated the ability of in vivo MRI to depict these vulnerable carotid plaque features. Multiple single-center studies have shown the ability of MRI-defined carotid plaque features to predict future events better than simple carotid artery stenosis measurements. Ongoing and proposed multicenter trials across North America and Europe will test the feasibility of vulnerable plaque imaging to accurately predict the risk of new thromboembolic symptoms. Future interventional and drug trials using vulnerable plaque imaging to guide individual patient selection and treatment are now being proposed.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: DeMarco.

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