Prevalence and Characteristics of Carotid Artery High-Risk Atherosclerotic Plaques in Chinese Patients With Cerebrovascular Symptoms: A Chinese Atherosclerosis Risk Evaluation II Study

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Background—Carotid atherosclerotic plaque rupture is an important source of ischemic stroke. However, the prevalence of high-risk plaque (HRP) defined as plaques with luminal surface disruption, a lipid-rich necrotic core occupying >40% of the wall, or intraplaque hemorrhage in Chinese population remains unclear. This study uses carotid magnetic resonance imaging (CMRI) to investigate HRP prevalence in carotid arteries of Chinese patients with cerebrovascular symptoms.

Methods and Results—Patients with cerebral ischemic symptoms in the anterior circulation within 2 weeks and carotid plaque determined by ultrasound were recruited and underwent CMRI. The HRP features were identified and compared between symptomatic and asymptomatic arteries. Receiver-operating-characteristic analysis was used to calculate area-under-the-curve (AUC) of stenosis and maximum wall thickness for discriminating presence of HRP. In 1047 recruited subjects, HRP detected by CMRI was nearly 1.5 times more prevalent than severe stenosis (≥50%) in this cohort (28% versus 19%, \(P<0.0001\)). Approximately two thirds of HRPs were found in arteries with <50% stenosis. The prevalence of HRP in symptomatic carotid arteries was significantly higher than that of the contralateral asymptomatic carotid arteries (23.0% versus 16.4%, \(P=0.001\)). Maximum wall thickness was found to be a stronger discriminator than stenosis for HRP (AUC: 0.93 versus 0.81, \(P<0.0001\)).

Conclusions—There are significantly more high-risk carotid plaques than carotid arteries with ≥50% stenosis in symptomatic Chinese patients. A substantial number of HRPs were found in arteries with lower grade stenosis and maximum wall thickness was a stronger indicator for HRP than luminal stenosis.

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Key Words: atherosclerosis • carotid artery • high-risk plaque • MRI • prevalence

Stroke is the leading cause of death in the Chinese population. As one of the primary contributors to stroke, large-artery atherosclerosis has been most commonly found in intracranial arteries in Chinese populations rather than extracranial carotid arteries, as in western countries. However, this evidence is based on arterial stenosis measurements and may not be representative of the key histological characteristics of high-risk plaques (HRPs), defined here as plaque with large lipid-rich necrotic core, intraplaque hemorrhage, or luminal surface disruption. Previous studies have shown that lipid-rich necrotic core, intraplaque hemorrhage, and thin/ruptured fibrous cap in

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An accompanying Appendix S1 is available at http://jaha.ahajournals.org/content/6/8/e005831/DC1/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

• In this multicenter study with recruitment of 1047 Chinese patients with recent cerebrovascular symptoms, we found that the high-risk plaque detected by carotid MRI (intraplaque hemorrhage, surface disruption or lipid-rich necrotic core >40%) was nearly 1.5 times more prevalent than severe stenosis (≥50%) in this cohort (28% versus 19%).

What Are the Clinical Implications?

• This study demonstrated that carotid magnetic resonance imaging helps accurately detecting high-risk plaques, particularly for patients with low grade stenosis, suggesting that incorporating carotid MRI in the clinical evaluation of cerebrovascular symptoms may be useful for optimizing treatment.

The goal of this study was to determine the prevalence of HRP in carotid arteries in Chinese patients with cerebral ischemic symptoms using standardized CMRI in a multicenter setting and characterize the relationship between HRP and luminal stenosis in this population.

Methods

Participants

The CARE-II (Carotid Atherosclerosis Risk Assessment) Study is a cross-sectional, observational, multicenter study (NCT02017756) conceived to assess carotid atherosclerotic plaque in Chinese patients with recent cerebral ischemic symptoms using standardized CMRI techniques. This study prospectively recruited patients 18 to 80 years of age with anterior circulation (carotid territory) cerebral hemispheric ischemic symptoms or amaurosis fugax including ischemic stroke and transient ischemia attack (TIA) in the prior 14 days and atherosclerotic plaque in at least one carotid artery as determined by B-mode ultrasound (intima-media thickness ≥1.5 mm). Ischemic stroke was diagnosed when patients had a compatible neurological deficit >24 hours after excluding intracerebral and subarachnoid hemorrhage and nonvascular causes using brain CT or MRI. TIA was defined as a neurological deficit attributed to focal brain ischemia with resolution within 24 hours of symptom onset. For simplicity, the arteries ipsilateral and contralateral to the ischemic symptoms were referred to as the symptomatic arteries and asymptomatic arteries, respectively, though the symptoms were not directly attributed to a carotid plaque. Exclusion criteria were as follows: (1) patients with evidence of cardioembolic stroke; (2) patients with hemorrhagic stroke; (3) history of radiation therapy in the neck; (4) claustrophobia; and (5) contraindication to magnetic resonance (MR) imaging examination.

Clinical characteristics from the time of the hospital visit for the recent ischemic symptoms were acquired from medical records. Demographic characteristics including age, sex, height and weight were recorded before MR examinations. History of hypertension (defined as a diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg), hyperlipidemia (defined as elevated concentrations of any or all of the lipids in the plasma, such as low density lipoprotein (LDL) >140 mg/dL, total cholesterol (TC) >200 mg/dL, or triglycerides (TG) >150 mg/dL), diabetes mellitus (fasting blood sugar level ≥126 mg/dL, 2-hour oral glucose tolerance test result ≥200 mg/dL, or hemoglobin A1c ≥6.5%), smoking (current or former), statin use, and coronary heart disease was collected. Coronary heart disease was defined as a condition and especially one caused by atherosclerosis that reduced the blood flow through the coronary arteries to the heart muscle and typically results in chest pain or heart damage. Lipid levels

symptomatic or asymptomatic carotid arteries with 30% to 99% stenosis were significantly associated with cerebrovascular events in European and North American populations. A similar correlation was found in few Chinese population-based studies. However, the prevalence of HRP in carotid arteries among Chinese with ischemic cerebrovascular events remains unclear.

Clinically, the risk of carotid atherosclerotic plaque is mainly evaluated by measuring arterial luminal stenosis though a substantial number of patients with <50% carotid stenosis still suffer from ischemic stroke. Some may be due to HRPs in other vascular beds including the intracranial arteries and aortic arch while some are due to a non-atherosclerotic etiology. However, there is evidence that some clinically cryptogenic strokes with <50% carotid stenosis may be due to HRP in the ipsilateral carotid artery, based on vessel wall MRI of German and American populations, indicating that atherosclerosis with <50% stenosis does not equate to risk free. Previous studies have shown that HRP features can be frequently observed not only in carotid arteries with severe stenosis but also in those with lower grade stenosis. The underestimation of patient risk by angiography suggests a substantial need for accurate detection of HRPs in carotid arteries with lower grade stenoses.

Carotid atherosclerotic plaque magnetic resonance imaging (CMRI) is capable of accurately characterizing plaque morphology, composition, and surface condition and has been extensively validated by histology. Carotid plaque features on CMRI have been found to strongly predict either first or recurrent stroke in patients with carotid 50% to 99% stenosis in multiple prospective single-center studies. However, there are limited reports of carotid HRPs in Chinese populations with a broad range of stenosis and a large sample size.
were tested during their hospital visit. Institutional review board approvals were obtained for the entire study and for each participating institution, and all study participants provided written informed consent.

**MR Imaging**

Participating radiologists and MR technologists from each imaging site were trained on image acquisition and quality evaluation. A CMRI protocol was implemented for carotid plaque imaging at all 13 participating centers. All CMRI was performed on 3.0T MR scanners with dedicated 8-channel phase array carotid coils. Imaging was centered on the carotid bifurcation of the index artery, defined as the artery ipsilateral to the ischemic symptoms, if known, or with the larger plaque. The imaging protocol and parameters for this study have been published.20

**Image Interpretation**

Vessel wall images of bilateral carotid arteries were interpreted by trained reviewers with >3 years’ experience in cardiovascular plaque imaging using custom-designed software (CASCADE; University of Washington, Seattle, USA). Each axial image was reviewed by 2 reviewers with consensus. Reviewers were blinded to all clinical information. The lumen and wall boundaries were outlined manually, from which lumen area, wall area, total vessel area, and maximum wall thickness at each axial location was extracted (Figure 1) using the CASCADE software. The presence/absence and areas of calcification, lipid-rich necrotic core, intraplaque hemorrhage and surface disruption were identified and measured using published criteria.9 Briefly, intraplaque hemorrhage was defined as a hyperintense region within the plaque on time-of-flight (TOF), T1-weighted (T1W), particularly magnetization-prepared rapid gradient-echo (MP-RAGE) images. Lipid-rich necrotic core was determined when there was a region appearing isointense on TOF and T1W images and hypointense on T2W images within the plaque. Disrupted luminal surface was identified when there was deficit in fibrous cap or discontinuous surface of the plaque. Large lipid-rich necrotic core was defined as lipid-rich necrotic core occupied more than 40% percent of wall area at axial image. Volumes were calculated from axial area measurements by summing and multiplying by the slice thickness. Percent wall volume (%wall volume=100×wall volume/total vessel volume), component volumes and component % volumes (100×component volume/wall volume) were computed. The maximum percentage of the vessel wall occupied by each plaque component was calculated from the measured areas. The HRP was defined as a lesion with intraplaque hemorrhage, large lipid-rich necrotic core or disrupted luminal surface were identified.5 Three-dimensional TOF MR angiographic images are reconstructed by maximum intensity projection to measure the luminal stenosis of carotid arteries using the NASCET algorithm.21 The luminal stenosis was divided into 0%, 1% to 29%, 30% to 49%, and ≥50% categories. Stenosis and plaque component review were performed separately.

**Statistical Analysis**

Continuous variables are presented as mean±standard deviation (SD) and categorical variables are presented as count (percentage). The prevalence of HRP features among the subset of confirmed symptomatic arteries was compared

### Table 1. Clinical Characteristics of Study Population

| Variable             | No. (%) or Mean±SD |
|----------------------|---------------------|
| Sex, male            | 711 (67.9)          |
| Age, y               | 62±11               |
| Body mass index, kg/m² | 24.3±3.1           |
| On statin therapy    | 386 (36.9)          |
| Medical history      |                     |
| Hypertension         | 751 (71.7)          |
| Hyperlipidemia       | 554 (52.9)          |
| Diabetes mellitus    | 313 (29.9)          |
| Smoking              | 531 (50.7)          |
| Coronary heart disease | 165 (15.8)      |
| Lipids, mg/dL        |                     |
| Total-C              | 177±44              |
| LDL-C                | 112±38              |
| HDL-C                | 44±15               |
| Triglycerides        | 154±94              |
with the contralateral asymptomatic artery using the sign test. Per-artery stenosis measurements were correlated with other plaque features and plaque burden measurements using logistic and linear regression. All regression models were adjusted for age, sex and imaging site. Receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC) were used to assess the performance of luminal stenosis and plaque burden measurements for discriminating between arteries with and without HRP. All statistical calculations were conducted with the statistical computing language R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria). Throughout, two-sided tests were used with statistical significance defined as \( P<0.05 \).

### Results

A total of 1072 eligible subjects completed carotid MR imaging from January 2012 to June 2015. Of the corresponding 2144 arteries examined, 114 were excluded due to the following reasons: (1) insufficient image quality \((n=50)\); (2) inadequate imaging coverage \((n=40)\); (3) total occlusion \((n=23)\); and (4) arterial dissection \((n=1)\). After exclusions 1047 subjects and 2030 arteries were available for analysis. Of these \(68\%\) male and mean age \(62\pm11\) years, \(72\%\) had hypertension, \(30\%\) had diabetes mellitus, \(53\%\) had hyperlipidemia, and \(51\%\) had a history of smoking. Clinical characteristics of this study population are detailed in Table 1.

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### Table 2. Carotid Atherosclerotic Plaque Characteristics on MR Imaging

| Variables                        | Level of Analysis | Subjects (N=1047) | Known Symptomatic Arteries* (N=584) |
|----------------------------------|-------------------|-------------------|-------------------------------------|
| High-risk plaque†                |                   | 292 (27.9)        | 134 (22.9)                          |
| Individual high-risk features    |                   |                   |                                     |
| Disrupted luminal surface        |                   | 113 (10.8)        | 50 (8.6)                            |
| Intraplaque hemorrhage           |                   | 201 (19.2)        | 87 (14.9)                           |
| %lipid-rich necrotic core >40%   |                   | 202 (19.3)        | 97 (16.6)                           |
| Luminal stenosis‡                |                   |                   |                                     |
| ≥50%                             |                   | 184 (18.9)        | 91 (16.6)                           |
| 30% to 49%                       |                   | 82 (8.4)          | 30 (5.5)                            |
| 1% to 29%                        |                   | 225 (23.1)        | 99 (18.1)                           |
| 0%                               |                   | 481 (49.5)        | 327 (59.8)                          |
| Plaque burden                    |                   |                   |                                     |
| Maximum wall thickness, mm       |                   | 3.3±1.8           | 2.9±1.7                             |
| Maximum %wall area, %            |                   | 58.6±16.3         | 55.6±16.3                           |
| %wall volume, %                  |                   | 41.0±8.5          | 41.9±9.7                            |
| LRNC                             |                   | 785 (75.0)        | 376 (64.4)                          |
| Presence                         |                   | 175.2±265.8       | 132.2±201.5                         |
| % Volume§, %                     |                   | 16.6±11.0         | 17.7±12.7                           |
| Calcification                     |                   | 548 (52.3)        | 241 (41.3)                          |
| Presence                         |                   | 52.8±84.4         | 35.8±48.2                           |
| % Volume§, %                     |                   | 6.7±4.1           | 7.0±4.5                             |

Values are no (%) or mean±SD. MR indicates magnetic resonance.

*All subjects were symptomatic, but the side of symptoms was only confirmed in 584 arteries (see Figure 1).

†Plaque with any of disrupted luminal surface, intraplaque hemorrhage and %lipid-rich necrotic core >40%.

‡Available for 972 subjects and 547 known symptomatic arteries.

§Only including subjects/arteries with corresponding component present.
Characteristics of Carotid Atherosclerotic Diseases

The prevalence of HRP among the 1047 subjects was 28% (Table 2). The prevalence of the individual high-risk features disrupted luminal surface, intraplaque hemorrhage and %lipid-rich necrotic core \(\geq 40\%\) were 11%, 19%, and 19%, respectively. Of the 972 subjects with luminal stenosis measurements available, the prevalence of stenosis \(\geq 50\%\) was only 19%, \(\approx 30\%\) lower than the prevalence of HRP (\(P<0.001\)). Plaque burden (maximum wall thickness, maximum %wall area and %wall volume) and other plaque features are further summarized in Table 2.

Of the 1047 subjects included in the statistical analysis, 605 had a confirmed side of symptoms (see flow chart in Figure 2). From these subjects, there were 584 arteries ipsilateral to the confirmed side of symptoms (referred to as symptomatic arteries) available for analysis. The prevalence of HRP among these symptomatic arteries was 23%. The prevalence of stenosis \(\geq 50\%\) was 27% lower than that of HRP, at 17% of the 547 with luminal stenosis measurements available, similar to the results based on all 1047 subjects (Table 2).

Comparison Between Symptomatic and Asymptomatic Carotid Arteries

Of the 584 known symptomatic arteries there were 566 with a paired contralateral asymptomatic artery that could be used for comparison. The prevalence of HRP in these 566 symptomatic carotid arteries was significantly higher than that of the contralateral asymptomatic carotid arteries (23.0% versus 16.4%, \(P=0.001\)), as was the prevalence of stenosis \(\geq 50\%\) (16.6% versus 9.6%, \(P=0.0002\)). The symptomatic carotid arteries also had a higher prevalence of disrupted luminal surface (8.1% versus 5.3%, \(P=0.052\)), intraplaque hemorrhage (14.7% versus 10.9%, \(P=0.029\)), and %lipid-rich necrotic core \(\geq 40\%\) (16.6% versus 9.9%, \(P=0.0002\)) compared with the contralateral asymptomatic carotid arteries.

Association Between Carotid HRPs and Luminal Stenosis

HRP was found in 23% of known symptomatic arteries, but the frequency of HRP varied by degree of stenosis (\(P<0.0001\), Figure 3). The prevalence of HRP ranged from 6.4% (21/327) in arteries with no detectable stenosis, to 29.3% (29/99) in arteries with 1% to 29% stenosis, up to 53.3% (16/30) and 56.0% (51/91) in arteries with 30% to 49% and \(\geq 50\%\) stenosis, respectively. Of note, 56% of all HRPs detected were found in arteries with \(< 50\%\) stenosis (66 HRPs with stenosis <50% out of 117 HRPs with stenosis measurements available). Figures 4 and 5 show examples of HRPs without luminal stenosis.

Indicators for Carotid HRPs

From ROC analysis, the AUC of luminal stenosis was 0.81 (95% CI: 0.76–0.84) for discriminating between arteries with and without HRP. The other measurements of plaque burden

Figure 3. Prevalence of high-risk features by degree of luminal stenosis in known symptomatic arteries. High-risk plaque is a composite of disrupted luminal surface, intraplaque hemorrhage or %lipid-rich necrotic core \(\geq 40\%\).
each had a significantly higher AUC than luminal stenosis (AUC: 0.81 versus 0.91–0.93, P<0.0001 for all comparisons), with maximum wall thickness having the largest at 0.93 (95% CI: 0.91–0.95) (Figure 6). The prevalence of HRP for different ranges of maximum wall thickness is shown in Figure 7. The difference in AUC (ΔAUC) between maximum wall thickness and stenosis was 0.12 (95% CI: 0.08–0.16, P<0.0001) after adjusting for age, sex and imaging site. When stenosis and maximum wall thickness were combined in a single model using logistic regression for predicting presence of HRP, there was no significant improvement in AUC compared to that from maximum wall thickness alone (ΔAUC=0.002, 95% CI: −0.001–0.006, P=0.16, adjusted for age, sex and imaging site).

Discussion
To the best of our knowledge, this study is one of the first to investigate the characteristics of carotid HRPs and stenosis in a multicenter setting using a consistent MR plaque imaging technique. Our study showed, in this study sample, plaques with high-risk features were nearly 50% more prevalent than those of plaques with ≥50% stenosis, and most of these HRPs were found in arteries with <50% stenosis. In addition, we found that symptomatic arteries had more HRP features than the contralateral asymptomatic arteries, though the contralateral arteries in these symptomatic patients had HRP in approximately one sixth of cases. In discriminating the presence of HRP, maximum wall thickness was found to be a stronger indicator than luminal stenosis. These findings call for attention to a clinically under-recognized at-risk population: those with HRPs but mild-to-moderate levels of stenosis.

In this study, 19% of subjects had plaques with ≥50% stenosis, which is similar to previous reports of Chinese populations. In the CICAS (Chinese Intracranial Atherosclerosis) Study, severe atherosclerotic lesions (>50% stenosis) in extracranial carotid arteries were found in 14% of ischemic stroke patients. Similar prevalences were found in Taiwanese (HRP prevalence: 13%) and Hong Kong (HRP prevalence: 18%) Chinese populations. The higher prevalence of carotid HRP (28%) observed in the present study compared with the prevalence of severe stenosis (19%), and the finding that
many HRPs were found in arteries with <50% stenosis suggest that vessel wall imaging may be more useful for stratifying risk than luminal imaging. A similar result was seen in a US population as reported by Saam et al. There are also prospective studies which have found that vessel wall measurements are more strongly correlated with presence of HRP or cerebrovascular outcomes than luminal stenosis, though in cohorts with high grade stenosis. One such study was reported by Xu et al, which found that the carotid atherosclerosis score (CAS)—defined by wall thickness and lipid-rich necrotic core size by carotid MRI—was more predictive of plaque growth and incident disrupted luminal surface than luminal stenosis. Another study by Nicolaides et al found that ultrasound-based measurements of plaque significantly improved risk stratification for subsequent cerebrovascular or retinal ischemic events compared with a risk model based on stenosis and clinical risk factors alone.

In this study, symptomatic arteries were more likely to have HRP features than asymptomatic arteries, which was expected based on prior studies which associated these features with subsequent cerebrovascular events. However, we also found that nearly one sixth of asymptomatic arteries had HRPs. Histology-based studies have also documented intraplaque hemorrhage in 41% to 53.2% of asymptomatic plaques after endarterectomy. An autopsy study reported that 35.8% of asymptomatic carotid plaques had intraplaque hemorrhage. Most plaques in these histologic studies had >50% stenosis, which may in part explain why intraplaque hemorrhage was more common than in the present study. Nonetheless, the relatively common occurrence of HRP features, as defined in this article, in asymptomatic carotid arteries suggest that further investigation in a longitudinal study is needed to develop predictive models that incorporate clinical, hemodynamic, plaque structural and quantitative compositional features.

In the present study, maximum wall thickness was found to be a stronger discriminator for HRP than luminal stenosis based on ROC analysis. This is consistent with some prior smaller studies which found that wall thickness tended to be more strongly associated with individual HRP features such as intraplaque hemorrhage and disrupted luminal surface than stenosis. One possible explanation for why wall thickness can correlated better with the state of the plaque than luminal stenosis is positive remodeling of the plaque. Positive remodeling is when progression of an atherosclerotic plaque leads to outward expansion of the outer wall boundary while preserving the dimension of the lumen to maintain. Under this scenario, a plaque with relatively little luminal stenosis.
can be disproportionately advanced based on its composition due to this outward growth. Thus, assessing wall thickness may be a more sensitive strategy for screening for HRPs. Ultrasound may be used as an alternative non-invasive carotid imaging modality for this purpose, as Underhill et al previously demonstrated excellent agreement between wall thickness measured by MR vessel wall imaging and intima-media thickness by ultrasound.

This study has several limitations. First, this is a hospital-based cohort and may not be representative of the entire population. Clinical risk factors were collected retrospectively from medical records, limiting our ability to characterize the treatment patients were receiving before the time of their acute, qualifying event, and whether current standards for optimal medical treatment were being met for each patient. While all recruited patients experienced recent cerebrovascular symptoms and thus represents a high-risk population, not all had confirmed diagnosis of ischemic stroke or transient ischemia attack in the anterior circulation by a neurologist. Furthermore, those with anterior lacunar infarcts, which may be due to small vessel disease rather than large artery atherosclerosis, and those with co-existing intracranial artery or aortic disease were not excluded. These factors may have attenuated the observed relationship between HRP in the extracranial carotid artery and side of symptoms. Second, in this study, carotid vessel wall imaging was performed with a 2D multicontrast imaging protocol which has 32 mm of longitudinal coverage centered on the carotid bifurcation. The limited longitudinal coverage of this technique may not capture atherosclerotic lesions occurring in more distal segments of the internal carotid artery or more proximal segments of common carotid arteries. Recently, 3D MR vessel wall imaging techniques with large coverage have been proposed for plaque assessment in carotid arteries. These
3D imaging techniques allow comprehensive evaluation of atherosclerotic disease in extracranial carotid arteries. Third, the measurement of luminal stenosis was based on angiographic images derived from the three dimensional time-of-flight imaging sequence. The gold standard for measuring carotid artery stenosis is digital subtraction angiography (DSA). MRA may overestimate carotid artery stenosis compared with DSA.\textsuperscript{33} It has been shown that CT angiography has the best agreement with DSA in measuring carotid stenosis compared with MR angiography and ultrasound.\textsuperscript{34} Fourth, this study only measured plaque characteristics in one vascular bed (the extracranial carotid artery). Previous studies have shown that the combination of plaque burden in carotid and femoral arteries can improve the stratification of cardiovascular disease risk.\textsuperscript{35,36} And fifth, this is a cross-sectional study, lacking data on the role of HRP features and their progression\textsuperscript{37}. Future prospective, multicenter studies investigating the clinical relevance of carotid HRP features across a wider range of stenosis and the clinical significance of progression in plaque structural and compositional features are warranted.

Conclusions

There are significantly more high-risk carotid plaques than carotid arteries with $\geq$50% stenosis in symptomatic Chinese patients. A substantial number of HRPs were found in arteries with lower grade stenosis and maximum wall thickness was a stronger indicator for HRP than luminal stenosis. While the clinical implications of these findings in terms of optimal treatment and outcomes need to be determined through longitudinal studies, these findings call for further development and evaluation of diagnostic tools beyond angiography capable of identifying HRPs, such as MR vessel wall imaging.

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Disclosures

None.

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