

EDITORIAL COMMENT

Risk Factors for Development of Carotid Plaque Components*

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It is well established that rupture or erosion of atherosclerotic plaque is the primary cause of acute ischemic cardiovascular events, including both acute coronary syndrome and stroke or transient ischemic attack (1). There are several major determinants of plaque rupture or erosion: increased plaque volume; a large lipid-rich necrotic core (LRNC); presence of intra-plaque hemorrhage (IPH); dense clusters of intimal macrophages and increased inflammatory infiltration; and a thin or ruptured cap or an irregular surface (2,3). These determining plaque risk features can be directly and noninvasively assessed by using high-resolution carotid magnetic resonance imaging (MRI) (4-6).

In this issue of *JACC*, Borba et al. (7) present the results of a natural history study of change in 3 carotid plaque components (IPH, calcification, and LRNC) over 4 years and identify risk factors associated with the changes. The authors selected 198 surviving patients who had carotid wall thickness ≥ 2.5 mm (as assessed by using ultrasound) and who participated in the population-based Rotterdam Study. Among these patients with a mean age of 67.5 years, body mass index of 27.5 kg/m², and total cholesterol level of 5.52 mmol/l, 69% had hypertension, 18% had diabetes, 22% were current smokers, and 32% were treated with statins. Carotid MRI scans were performed at baseline and 4 years later to detect changes in plaque. The authors found that, over 4 years, 18.5%, 59.2%, and 39.6% of subjects developed IPH, calcification, and LRNC, respectively. Hypertension, including its severity and treatment, was significantly associated with new IPH or

calcification, and higher levels of cholesterol were associated with the development of LRNC.

These results (7) showed a high frequency of development of IPH, plaque calcification, and LRNC, and identified hypertension and higher levels of cholesterol as the risk factors for these new components. The results strongly support the importance of aggressive risk management to prevent atherosclerotic plaque progression and complication leading to ischemic events. The following additional topics of discussion hold great interest for future research.

IPH and Increased Adventitial Vasa Vasorum Neovascularization and Permeability Borba et al. (7) discussed the pathophysiology of IPH and increased blood pressure from the lumen to the plaque. Long-term hypertension can compromise endothelial function and cause arterial wall damage, leading to an increased density of fragile and leaky microvessels in the plaque. Microvessels, or neovasculature, can also develop from the adventitial vasa vasorum and enter the plaque. Several studies have suggested an association between vasa vasorum neovascularization and plaque instability (8-10). Dynamic contrast-enhanced (DCE) MRI using gadolinium agents can assess plaque perfusion arising from the adventitial vasa vasorum. Kinetic modeling of in vivo DCE-MRI can assess elevated vascularity (V_p = partial plasma volume) and vascular permeability (K^{trans}). Kerwin et al. (11) reported a correlation of 0.8 between V_p estimated by kinetic modeling of DCE-MRI and histological measurements of neovessel areas in subjects undergoing carotid endarterectomy. Sun et al. (12) showed that IPH (n = 15) was associated with a significantly higher value in adventitial K^{trans} (0.142 ± 0.042 min⁻¹ vs. 0.112 ± 0.029 min⁻¹; $p < 0.001$) than those without (n = 35) from 27 symptomatic patients. This association remained significant after adjusting for symptomatic status and degree of stenosis.

IPH is often found to co-exist with plaque rupture or ulceration and LRNC (13,14), and prospective natural history studies have shown that IPH is a determining factor for rapid plaque progression (15-17).

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A better understanding of the role that IPH plays in plaque rupture and progression is needed and should be the basis for future studies.

CHANGE IN CAROTID PLAQUE COMPONENTS WITH ANTIATHEROSCLEROSIS THERAPY

In addition to the relationship between higher levels of cholesterol and an increased likelihood of plaque containing LRNC seen in MESA (Multi-Ethnic Study of Atherosclerosis) (18), the current study (7) showed that higher levels of cholesterol were also associated with the development of new LRNC. Previous studies (19,20) have reported that plaque LRNC can be reduced with lipid treatment, lowering LDL-C levels with either statins or statin-based combination therapy. The CPC (Carotid Plaque Composition by MRI during Lipid Lowering) study (20) reported a 6.8% absolute reduction (52% relative reduction; 14.2% at baseline vs. 7.4% at 3 years; $p < 0.001$) in LRNC with 3 years of intensive lipid therapy to lower low-density lipoprotein cholesterol (LDL-C) levels to <70 mg/dl (on average). CPC also showed that LRNC can be partially depleted after 3 years in some, but not all, subjects undergoing intensive lipid therapy, reporting 11% fewer subjects had measurable LRNC (44% at baseline vs. 33% at 3 years; $p = 0.03$). The current study found that almost 40% of subjects developed new LRNC over 4 years despite 32% receiving statin therapy. Therefore, we raise 2 important, yet unanswered, questions: 1) does the persistent presence of LRNC predict residual cardiovascular risk under current intensive lipid therapy? And: 2) can novel LDL-C-lowering therapy with proprotein convertase subtilisin/kexin type 9 inhibition further reduce residual LRNC? Similarly, a recent study (21) that showed proprotein convertase subtilisin/kexin type 9 inhibition with evolocumab induced further regression of coronary atheroma volume is encouraging.

A recently published MRI study (22) reported an association between IPH and hypertension. The current study (7) also showed that antihypertension drug use and severity of hypertension were independently associated with new IPH. Indeed, future studies are needed to investigate whether lower blood pressure can prevent or reduce IPH. If verified, would different levels of blood pressure control offered by the different drug classes have a varying impact on the outcome?

The association of calcification as assessed by computed tomography (CT) scans and an increased risk for vascular events is mainly established in the coronary arteries. The Rotterdam Study group found a significant association between extracranial carotid calcification, detected by CT scans, and the presence

of cerebral infarcts on brain MRI (odds ratio [OR] for presence of cerebral infarcts per SD: 1.61 [1.15 to 2.25]; $p < 0.01$, adjusted for age, sex, and ultrasound carotid plaque scores [23]). However, this association has not been confirmed in carotid MRI studies.

MISSING LINK BETWEEN CHANGES IN CAROTID PLAQUE COMPONENTS AND FUTURE EVENTS

Previous studies (24-27) showed that plaque characteristics according to histological studies or MRI scans predict future systemic cardiovascular events, including coronary events. Hellings et al. (24) found that plaque composition according to histological study in 818 patients who underwent carotid endarterectomy was an independent predictor of future cardiovascular events. A meta-analysis of 9 MRI studies in 778 subjects (26) showed that subsequent stroke or transient ischemic attack was significantly and independently predicted by the presence of thin or ruptured cap (hazard ratio [HR]: 5.93; 95% confidence interval [CI]: 2.65 to 13.20), IPH (HR: 4.59; 95% CI: 2.91 to 7.24), and LRNC (HR: 3.00; 95% CI: 1.51 to 5.95). In the AIM-HIGH Carotid MRI Substudy cohort, we showed that thin or ruptured cap (HR: 4.3; $p = 0.003$) and a larger percent LRNC volume (HR: 1.57; $p = 0.002$) were predictive of systemic cardiovascular events that include 83% (15 of 18) of coronary events in patients with established vascular disease and a mean LDL-C level of 77 mg/dl and blood pressure of 128/75 mm Hg (27). Meanwhile, in this population, no clinical risk factors or lipids showed significant prediction of future events. In the current study, Borba et al. (7) also reported a high incidence of new IPH, calcification, and LRNC. However, it is unknown whether patients with new or persistent IPH or LRNC are truly at increased risk for future ischemic vascular events.

Future imaging studies evaluating the link between natural changes in plaque components or changes in response to a given therapy and subsequent cardiovascular events are warranted. Imaging with inclusion of clinical risk factors and biomarkers would further strengthen these studies. This link will help address an unmet clinical need in identifying those individuals who are at increased residual cardiovascular risk despite current intensive overall risk management and would potentially guide further therapy.

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REFERENCES

1. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 2003;340:115-26.
2. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Cardiol* 2006;47 Suppl 8:C13-8.
3. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res* 2014;114:1852-66.
4. Cai JM, Hatsukami TS, Ferguson MS, Small R, Polissar NL, Yuan C. Classification of human carotid atherosclerotic lesions with in vivo multi-contrast magnetic resonance imaging. *Circulation* 2002;106:1368-73.
5. Takaya N, Cai J, Ferguson MS, et al. Intra- and interreader reproducibility of magnetic resonance imaging for quantifying the lipid-rich necrotic core is improved with gadolinium contrast enhancement. *J Magn Reson Imaging* 2006;24:203-10.
6. Cai J, Hatsukami TS, Ferguson MS, et al. In vivo quantitative measurement of intact fibrous cap and lipid rich necrotic core size in atherosclerotic carotid plaque: a comparison of high resolution contrast enhanced MRI and histology. *Circulation* 2005;112:3437-44.
7. Borba LP, Selwaness M, van der Lugt A, et al. Change in carotid plaque components: a 4-year follow-up study using serial magnetic resonance imaging. *J Am Coll Cardiol Img* 2017;10:XXX-XX.
8. Virmani R, Kolodgie FD, Burke AP, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. *Arterioscler Thromb Vasc Biol* 2005;25:2054-61.
9. Giannoni MF, Vicenzini E, Citone M, et al. Contrast carotid ultrasound for the detection of unstable plaques with neoangiogenesis: a pilot study. *Eur J Vasc Endovasc Surg* 2009;37:722-7.
10. Deyama J, Nakamura T, Takishima I, et al. Contrast-enhanced ultrasound imaging of carotid plaque neovascularization is useful for identifying high-risk patients with coronary artery disease. *Circ J* 2013;77:1499-507.
11. Kerwin WS, O'Brien KD, Ferguson MS, Polissar N, Hatsukami TS, Yuan C. Inflammation in carotid atherosclerotic plaque: a dynamic contrast-enhanced MR imaging study. *Radiology* 2006;241:459-68.
12. Sun J, Song Y, Chen H, et al. Adventitial perfusion and intraplaque hemorrhage: a dynamic contrast-enhanced MRI study in the carotid artery. *Stroke* 2013;44:1031-6.
13. U-King-Im JM, Fox AJ, Aviv RI, et al. Characterization of carotid plaque hemorrhage: a CT angiography and MR intraplaque hemorrhage study. *Stroke* 2010;41:1623-9.
14. van Dijk AC, Truijman MT, Hussain B, et al. Intraplaque hemorrhage and the plaque surface in carotid atherosclerosis: the Plaque At RISK Study (PARISK). *AJNR Am J Neuroradiol* 2015;36:2127-33.
15. Takaya N, Yuan C, Chu B, et al. Presence of intraplaque hemorrhage stimulates progression of carotid atherosclerotic plaques: a high-resolution magnetic resonance imaging study. *Circulation* 2005;111:2768-75.
16. Sun J, Underhill HR, Hippe DS, Xue Y, Yuan C, Hatsukami TS. Sustained acceleration in carotid atherosclerotic plaque progression with intraplaque hemorrhage: a long-term time course study. *J Am Coll Cardiol Img* 2012;5:798-804.
17. Sun J, Balu N, Hippe DS, et al. Subclinical carotid atherosclerosis: short-term natural history of lipid-rich necrotic core—a multicenter study with MR imaging. *Radiology* 2013;268:61-8.
18. Wasserman BA, Sharrett AR, Lai S, et al. Risk factor associations with the presence of a lipid core in carotid plaque of asymptomatic individuals using high-resolution MRI: the Multi-Ethnic Study of Atherosclerosis (MESA). *Stroke* 2008;39:329-35.
19. Underhill HR, Yuan C, Zhao XQ, et al. Effect of rosuvastatin therapy on carotid plaque morphology and composition in moderately hypercholesterolemic patients: a high-resolution magnetic resonance imaging trial. *Am Heart J* 2008. 0:1.e1-1.eB.
20. Zhao XQ, Dong L, Hatsukami T, et al. MR imaging of carotid plaque composition during lipid-lowering therapy a prospective assessment of effect and time course. *J Am Coll Cardiol Img* 2011;4:977-86.
21. Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV Randomized Clinical Trial. *JAMA* 2016;316:2373-84.
22. Sun J, Canton G, Balu N, et al. Blood pressure is a major modifiable risk factor implicated in pathogenesis of intraplaque hemorrhage: an in vivo magnetic resonance imaging study. *Arterioscler Thromb Vasc Biol* 2016;36:743-9.
23. Bos D, Ikram A, Elias-Smale SE, et al. Calcification in major vessel beds relates to vascular brain disease. *Arterioscler Thromb Vasc Biol* 2011;31:2331-7.
24. Hellings WE, Peeters W, Moll FL, et al. Composition of carotid atherosclerotic plaque is associated with cardiovascular outcome: a prognostic study. *Circulation* 2010;121:1941-50.
25. Saam T, Hetterich H, Hoffmann V, et al. Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging. *J Am Coll Cardiol* 2013;62:1081-91.
26. Gupta A, Baradaran H, Schweitzer AD, et al. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke* 2013;44:3071-7.
27. Sun J, Zhao XQ, Balu N, et al. Carotid plaque lipid content and fibrous cap status predict systemic CV outcomes: the MRI substudy in AIM-HIGH. *J Am Coll Cardiol Img* 2017;10:241-9.

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