

EDITORIAL COMMENT

# From Plaque Burden to Plaque Composition

## Toward Personalized Risk Assessment\*



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**A**therosclerotic cardiovascular disease (ASCVD) imaging has the greatest promise for cardiovascular disease risk assessment in asymptomatic individuals. Studies have shown that various imaging modalities, such as coronary calcium scoring (CCS) and carotid intima media thickening (CIMT) measurement (1,2), improve risk stratification beyond traditional cardiovascular disease risk factors. Atherosclerosis as determined by these imaging modalities identifies the actual presence of disease, which represents a culmination of both traditional and nontraditional cardiovascular risk factors on the atherosclerotic disease process.

Imaging of atherosclerosis can be broadly categorized as imaging of the presence or burden of atherosclerosis (i.e., plaque burden), imaging of plaque morphology to identify plaques more likely to rupture and cause acute ASCVD, and imaging to

identify plaque activity (e.g., macrophage activity within plaques). Traditional atherosclerosis imaging modalities such as CCS and CIMT (with or without plaque assessment) measure plaque burden. Magnetic resonance imaging (MRI) offers high soft tissue contrast and therefore is increasingly being used to study plaque composition (e.g., presence of lipid-rich core or thin fibrous caps) (3). However, although high-risk plaques (i.e., plaques with large lipid-rich necrotic core or thin fibrous cap) are associated with a high risk of rupture at the individual plaque level, whether the presence of such high-risk features on these plaques predicts future ASCVD risk at the population level is not well known. Similarly, whether the association between measures of plaque morphology and future ASCVD risk is independent of the measures of plaque burden is not well known, as previous studies have shown that the presence of high-risk plaques (e.g., lipid-rich core on carotid MRI) is highly correlated with measures of plaque burden (e.g., carotid wall thickness) (3).

SEE PAGE 241

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In this context, the findings reported by Sun et al. (4) in this issue of *iJACC* are important and timely. Sun et al. (4) evaluated 232 subjects who were recruited in the MRI ancillary study from AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes Trial). AIM-HIGH was an event-driven trial of patients with clinically established atherosclerotic disease (i.e., secondary prevention). The 232 AIM-HIGH study participants enrolled in the MRI substudy underwent contrast-enhanced carotid MRI at 10 imaging sites with assessment of measures of plaque burden (e.g., carotid maximum wall thickness) and plaque morphology (lipid-rich core volumes, fibrous cap measurement, presence of plaque calcification or intraplaque hemorrhage [IPH]). Previously described definition of high-risk plaques, for example, American Heart Association (AHA) type VI

lesions (plaques with surface disruption, IPH, or mural thrombus) (5) or the Carotid Atherosclerosis Score type 4 (CAS-4) lesions (AHA type VI lesions as well as those with maximum percent lipid-rich necrotic core area >40%) (6) were also evaluated. Participants were followed for a median of 35.1 months for development of the AIM-HIGH primary endpoint of fatal and nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, and symptom-driven hospitalization. These events were adjudicated by the AIM-HIGH Clinical Events Committee. At median follow-up of 35.1 months, 18 subjects reached the AIM-HIGH primary endpoint, including myocardial infarction ( $n = 6$ ), ischemic stroke ( $n = 2$ ), hospitalization for acute coronary syndrome ( $n = 2$ ), symptom-driven coronary revascularization ( $n = 7$ ), and symptom-driven cerebrovascular revascularization ( $n = 1$ ). Results showed that plaque lipid content (hazard ratio [HR] per 1 SD increase in percent lipid-rich necrotic core volume: 1.57; 95% confidence interval [CI]: 1.22 to 2.01;  $p = 0.002$ ) and presence of thin/ruptured fibrous cap (HR: 4.31; 95% CI: 1.67 to 11.1;  $p = 0.003$ ) were associated with the AIM-HIGH primary endpoint. Plaque calcification content was not associated with the primary endpoint (HR per 1 SD increase in percent calcification volume: 0.66; 95% CI: 0.35 to 1.27;  $p = 0.2$ ). Presence of IPH was positively associated with the primary endpoint, although the results did not reach statistical significance (HR: 3.00; 95% CI: 0.99 to 9.13;  $p = 0.053$ ). There was no significant association between AHA type VI lesions (HR: 2.36; 95% CI: 0.77 to 7.71;  $p = 0.13$ ) or CAS-4 (HR: 2.79; 95% CI: 0.99 to 7.85;  $p = 0.051$ ) and the primary composite endpoint. Interestingly, none of the plaque burden measures were significantly associated with the primary composite endpoint, although there was a trend toward significant association between maximum wall thickness and the primary composite endpoint (HR per 1 SD increase: 1.43; 95% CI: 0.96 to 2.11;  $p = 0.08$ ). Finally, adjustment for Framingham risk score, maximum wall thickness, or AIM-HIGH treatment arm assignment did not significantly change the results.

There are limitations of the current analyses that are important to discuss. The study included 18 events, of which only 10 were “hard ASCVD events” with revascularization-driven events ( $n = 8$ ) constituting a large proportion. The study only included secondary prevention patients in the AIM-HIGH trial; therefore, the results likely are not generalizable to primary prevention populations in which treatment pattern and use of cardiovascular preventive pharmacotherapy (some of which could alter plaque

morphology) are different. Given the small number of events, analyses pertaining to whether markers of high-risk plaques predict risk beyond markers of plaque burden (e.g., improvement in risk discrimination [e.g., C index] and risk reclassification) could not be performed.

Despite these limitations, the results provide proof of concept and improve our understanding of vascular biology. These results also have implications for risk assessment and treatment. The results indicate that in patients with established atherosclerosis, carotid MRI with identification of high-risk plaques could be a valuable tool to identify patients who might be at high risk for recurrent events. These results also identify that imaging of high-risk plaques could potentially be used as a surrogate marker either to assess the efficacy of investigational cardiovascular disease risk reduction therapies before expensive outcomes trials are conducted or to enrich cardiovascular disease outcomes trials with patients who have a high likelihood of recurrent ASCVD events, thereby potentially decreasing the number of patients needed or the follow-up duration required for these outcomes trials. These results also highlight the fact that atherosclerosis is a systemic disease, and, therefore, atherosclerosis in one bed (e.g., carotid) could predict adverse cardiovascular outcomes in another bed (e.g., coronary arterial bed).

These results strengthen a growing body of evidence that measures of atherosclerosis as measured by carotid MRI are associated with increased ASCVD risk. For example, in a previous retrospective study, patients with prior major adverse cardiovascular or cerebrovascular events had significantly higher measures of plaque burden (wall thickness, wall area, and normalized wall index) in the carotid artery and thoracic aorta as measured by MRI of carotid arteries and thoracic aorta, respectively (7). In the MESA (Multi-Ethnic Study of Atherosclerosis), MRI-assessed carotid remodeling index (wall area divided by the sum of wall area and lumen area, which is a measure of plaque burden independent of the vessel size) and lipid-rich core presence were associated with an increased future risk of ASCVD events (8). For traditional risk factors, the C statistic for event prediction was 0.696. For the model incorporating MRI remodeling index and lipid core, the C statistic was 0.734. Net reclassification improvement for event prediction using models that incorporated MRI remodeling index and lipid core presence was 7.4% and 15.8% for participants with and those without cardiovascular events, respectively ( $p = 0.02$ ).

Taken together, these results indicate that assessment of measures of plaque morphology and high-risk plaques by MRI does aid in identification of patients at increased risk for adverse cardiovascular events in primary and secondary prevention settings. These findings may be immediately applicable to designing more “personalized” clinical trials that identify very high-risk individuals, thus allowing for smaller trials to test novel therapies. However, before MRI can be used as a routine imaging modality for ASCVD risk estimation, more data are needed as to how do the MRI measures of plaque composition and morphology change with therapy and whether these

changes are associated with future ASCVD events. Finally, given the cost of MRI and the time needed for image acquisition on individual patients, there is a great need for comparative efficacy studies evaluating various imaging modalities (CCS, CIMT, MRI) in terms of their relative efficacy and cost-effectiveness in identifying patient at higher risk for ASCVD events.

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