Abstract—Carotid intima-media thickness (CIMT) measured by B-mode ultrasound is the most widely used noninvasive imaging method to assess atherosclerosis and cardiovascular risk. CIMT has been consistently associated with coronary artery disease and stroke; however, recent meta-analyses and systematic reviews suggest that its clinical usefulness may be limited because the addition of CIMT to traditional risk factors has not improved the risk prediction of cardiovascular events in the general population. Characterizing the carotid wall by MRI may have greater clinical utility compared with CIMT measurements by ultrasound. Unlike CIMT, MRI measurements of wall thickness include the adventitia and may be sensitive to adventitial thickening that results from vasa vasorum proliferation as a sign of early plaque development. MRI also has the ability to image the entire circumference of the carotid wall, including the outer wall of the carotid bulb where plaque forms in its earliest stage, and identify plaque components such as the lipid core, fibrous cap, and intraplaque hemorrhage that are closely related to plaque vulnerability and cardiovascular risk. Additional research is needed to assess the added prognostic value of MRI measurements of wall and plaque features in risk prediction beyond traditional risk factors. (Arterioscler Thromb Vasc Biol. 2014;34:00-00.)

Key Words: atherosclerosis □ carotid intima-media thickness □ coronary disease □ magnetic resonance imaging □ ultrasonography

Atherosclerosis is a systemic, chronic inflammatory disorder usually involving multiple vascular territories in the same patient, with carotid and coronary artery plaque known to be closely related.1–2 Both cross-sectional and longitudinal imaging studies have linked atherosclerotic plaque features between carotid and coronary arteries.3–10 Cross-sectional studies have shown associations between carotid intima-media thickness (CIMT) and the severity and extent of coronary atherosclerosis based on angiography.5–8 Furthermore, calcification and lipid-rich necrotic core identified in carotid plaque by MRI have been associated with stenosis and calcification on coronary angiography, and carotid intraplaque hemorrhage on MRI has been associated with partially calcified coronary plaques on angiography.3,4,9 In addition, CIMT and the presence of carotid artery plaque significantly predicted incident coronary artery calcium as well as the progression of coronary artery calcium in a prospective cohort study of 5445 participants from the Multi-Ethnic Study of Atherosclerosis (MESA).10

The superficial location, large size, and relative immobility of the carotid arteries make them especially amenable to noninvasive imaging, and thus characterization of atherosclerosis in the carotid arteries might offer valuable insight into the atherosclerosis status in other vascular beds. This is particularly important for assessing coronary artery atherosclerosis because coronary arteries are difficult to image in noninvasive studies. As a consequence, ultrasound imaging of the carotid arteries has become a popular clinical measurement, with carotid CIMT measured by B-mode ultrasound being the most widely used noninvasive imaging method to assess cardiovascular risk in primary prevention settings.11

This review summarizes the available epidemiological data examining the clinical usefulness of CIMT for risk prediction of coronary artery disease (CAD) and compares CIMT with other noninvasive modalities measuring carotid wall thickness and plaque such as MRI, 3-dimensional (3D) ultrasound, computed tomography (CT), and fluorodeoxyglucose positron emission tomography (FDG-PET).

CIMT by B-Mode Ultrasound and CAD CIMT has been consistently associated with CAD and stroke,12,13 but its clinical usefulness in adding predictive risk discrimination beyond traditional risk factors identified by the Framingham Risk Score has been questioned in recent systematic reviews and meta-analyses.12–14 A meta-analysis using
individual data from 14 population-based cohorts (45,828 participants) reported that for every 0.1-mm increase in the common CIMT, the hazard ratio of first-time myocardial infarction or stroke was 1.09 (1.07–1.12), with minor improvement in prediction when added to the Framingham Risk Score (0.002 increase in the C-statistic; net reclassification improvement, 0.8%). These results suggest that current evidence does not support routine use of CIMT in the general population to screen for cardiovascular disease because the added value is too small to result in health benefits. Of note, several recent studies have also explored other CIMT metrics (including CIMT progression, average of the maximal CIMT measured in different segments, and maximal CIMT of the internal carotid artery) and found significant associations with cardiovascular events. However, the clinical utility of these CIMT measurements beyond traditional risk factors is yet to be determined.

**Limitations of CIMT Measurements by B-Mode Ultrasound**

Several limitations of the CIMT measurements by B-mode ultrasound may explain its lack of added prognostic value to the Framingham Risk Score. CIMT is usually measured in the common carotid artery because of its easier accessibility and perpendicular location to the ultrasound beam, whereas carotid atherosclerosis predominantly occurs earliest downstream in the bulb (and often only in the bulb), which may not be as easily visible with B-mode ultrasound. Indeed, the presence of carotid plaque may be a stronger predictor of CAD than CIMT. A meta-analysis found that the presence of carotid plaque had a significantly higher diagnostic accuracy for the prediction of future myocardial infarction compared with CIMT. In this meta-analysis, CIMT measurement including plaque thickness in the bulb was a stronger predictor of cardiovascular events compared with CIMT in the common carotid artery, where it was less likely to develop plaque, whereas the presence of carotid plaque was more predictive than either CIMT phenotype.

In addition, B-mode ultrasound measurements of CIMT are usually based on far wall views of the carotid artery and are limited in measuring the entire circumference of the wall. Plaque formation in the carotid bifurcation, however, typically begins along the outer wall of the bulb because of predisposing hemodynamic factors and then progresses to involve the circumference of the bulb. Because of the typical orientation of the carotid bifurcation in the neck relative to the ultrasound transducer at the skin surface, the outer wall of the bulb may lie tangential to the ultrasound beam and, therefore, is not sensitively measured by B-mode ultrasound.

Finally, CIMT is a relatively simplistic measure of the carotid wall that fails to capture the complexity of plaque features. Components of carotid plaque, especially lipid-rich necrotic core, intraplaque hemorrhage, and thin fibrous cap, are closely related to plaque vulnerability and cardiovascular risk. However, B-mode ultrasound is restricted in its ability to define those plaque components.

**MRI Versus CIMT**

Recently, MRI has emerged as a superior noninvasive modality to characterize plaque features and image the arterial wall. Wall thickness measurements by MRI may have greater clinical utility compared with CIMT measurements by ultrasound. CIMT measurements include the sum of the intima and media, whereas MRI measurements can also include the adventitia. The adventitia is important for defining vascular inflammation because it is the source of vasa vasorum that proliferate into the arterial wall with intimal thickening and might be useful for detecting early plaque. Adventitial vasa vasorum may also provide insight into the progression of atherosclerosis to symptomatic disease. In a postmortem study of iliac, carotid, and renal arteries, patients with a history of cardiovascular events had a denser network of vasa vasorum in the adventitial layer compared with those without events, and adventitial thickening was present in arteries with negligible intimal thickening and normal arterial wall dimensions, suggesting that adventitial thickening can be an early sign of atherosclerosis. Another study of patients undergoing MRI for carotid plaque evaluation found that prominence of the adventitia seen on the MRI was associated with recent cerebrovascular ischemic events. Because wall thickness measurements by MRI include the adventitia, they may be sensitive to adventitial thickening that results from vasa vasorum proliferation as a sign of either early plaque development or later plaque instability.

In contrast to CIMT measurements by ultrasound, MRI has the ability to image the entire circumference of the wall and hence is able to detect early wall thickening that occurs along the outer wall of the carotid bulb where plaque forms in its earliest stage. In addition, MRI has the ability to accurately identify plaque components such as lipid core, fibrous cap, and intraplaque hemorrhage that are closely related to plaque vulnerability and cardiovascular risk.

Overall, there is good correlation between wall area, wall thickness, and plaque index measured by MRI and CIMT measurements obtained by ultrasound, but carotid MRI has higher reproducibility compared with ultrasound. Reader variability, rather than scan acquisition variability, seems to be the primary factor affecting the reliability of MRI measurements of carotid plaque characteristics, and reader error is mostly influenced by the size of the structure being measured relative to the spatial resolution of the scanner. With recent increases in field strength of MRI scanners.
used in clinical practice, one can achieve higher resolutions and expect further improvement in reliability estimates, as well as in our ability to detect early disease with small structural changes.44,45

Limitations of MRI

The clinical applicability of carotid MRI must be considered in light of several potential limitations of this imaging technique. Compared with carotid ultrasound, MRI is more expensive with a cost that can be >10× that of an ultrasound examination.46 Moreover, because of its high construction cost, MRI scanners tend to be less accessible compared with ultrasound systems. The high cost and limited availability of MRI may restrict its use as a first-line screening tool for asymptomatic atherosclerosis.47,48 Other relative limitations of carotid MRI include longer scan times and sensitivity to motion. Safety concerns also must be considered with MRI scanners that are not relevant to ultrasound, especially contraindications to exposure to the magnetic field. These include metallic foreign bodies in the orbit or near vital structures, cochlear implants, and pacemakers. Local heating with skin burns can occur from exposure to radiation.47 Nevertheless, 1 study reported that there was good agreement between carotid artery wall thickness measurements by multidetector-row CT angiography and CIMT measurements by ultrasound.53 Another study showed that carotid wall enhancement on CT angiography, indicating vasa vasorum neovascularization, was associated with previous stroke or transient ischemic attack.54 Because of its imaging limitations and risk related to radiation, carotid CT imaging is unlikely to play a major role as a screening tool for cardiovascular disease.

Other Noninvasive Imaging Modalities

Recent advances in ultrasound technology have led to 3D techniques that have the ability to directly measure total plaque volume and vessel wall volume and are more sensitive to plaque changes compared with CIMT.49,50 Together with morphological B-mode ultrasound, 3D ultrasound may be a more cost-effective plaque measurement and cardiovascular risk screening tool compared with MRI. Compared with MRI, however, 3D ultrasound is limited in its ability for soft tissue characterization and cannot distinguish lipid-rich necrotic core from intraplaque hemorrhage.51 Calcification is another major barrier for 3D ultrasound because large calcified plaques can cause acoustic shadowing and obscure the structure behind the surface of calcification.51,52

CT is not a preferred modality for measuring carotid wall or plaque because of limitations associated with dense calcification, poor contrast between lipid and fibrotic components, and exposure to radiation.55 Nevertheless, 1 study reported that there was good agreement between carotid artery wall thickness measurements by multidetector-row CT angiography and CIMT measurements by ultrasound.53 Another study showed that carotid wall enhancement on CT angiography, indicating vasa vasorum neovascularization, was associated with previous stroke or transient ischemic attack.54 Because of its imaging limitations and risk related to radiation, carotid CT imaging is unlikely to play a major role as a screening tool for cardiovascular disease.

18F-FDG-PET is another noninvasive imaging modality for assessing plaque vulnerability, particularly plaque inflammation. FDG is taken up by macrophages and can be imaged with PET to identify areas of inflammation and vulnerability to rupture.55 Some key limitations of FDG-PET include the low specificity of FDG uptake and its poor resolution compared with MRI or CT.56 To compensate for this, PET has been coupled with MRI or CT in PET/MRI or PET/CT scanners, which combine both modalities and can tie together detailed anatomic information of MRI or CT scanning along with the functional information of PET scanning. The clinical role of FDG-PET in predicting cardiovascular disease is still under active investigation. A study of 40 patients undergoing carotid FDG-PET imaging found higher FDG uptake in those with a history of CAD.57 In 101 patients with stable cancer who underwent whole-body 18F-FDG-PET/CT scans, high arterial wall FDG uptake was associated with recent cardiovascular events occurring <6 months before or after PET.57 Another study of 932 patients with cancer showed that increased arterial wall FDG uptake was predictive of incident vascular event (defined as ischemic stroke, myocardial infarction, or revascularization).58 Functional imaging of atherosclerotic plaque to
identify vulnerable features is an evolving field and can also be done by other techniques. For example, molecular imaging agents have been designed for MRI, including functionalized nanoparticles that bind to fibrin50 and receptor-mediated agents that target neovascularity.60 The description of these techniques is beyond the scope of this review.

Economic Considerations

It has been estimated that ≈30 million Americans ≥50 years of age may need screening for asymptomatic atherosclerosis.46 Compared with ultrasound, the high cost of MRI and other nonultrasound-based imaging techniques limits their use as first-line screening tools for asymptomatic atherosclerosis. These more advanced imaging techniques may better serve as a second step in multimodality screening, in which patients are first screened with a low-cost imaging technique such as ultrasound, and those with abnormal findings will receive an additional scan using advanced imaging techniques to provide more specific characterization of plaque features and improved risk stratification.47 However, to our knowledge, there are no data evaluating the economic impact of the use of advanced imaging modalities for atherosclerosis screening thus far. Additional research is necessary to determine the cost-effectiveness of alternative imaging strategies, especially for asymptomatic individuals.

Conclusions

In summary, there is a modest association between CIMT assessed by B-mode ultrasound and CAD, but the addition of CIMT to traditional risk factors does not improve risk prediction in the general population. MRI may be a superior non-invasive modality to measure carotid wall thickness and to characterize plaque composition for this purpose. Additional research in population-based studies is needed to better assess the added prognostic value of MRI measurements of wall and plaque features in risk prediction beyond traditional risk factors.

Sources of Funding

This research was supported by contract R01HL105930 from the National Heart, Lung, and Blood Institute (to B.R. Wasserman).

Disclosures

None.

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Is Carotid Intima-Media Thickness as Predictive as Other Noninvasive Techniques for the Detection of Coronary Artery Disease?
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Arterioscler Thromb Vasc Biol. published online April 24, 2014;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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