Carotid Intima-media Thickness and/or Carotid Plaque: What is Relevant?

Carotid intima-media thickness (CIMT) is often used as a risk predictor for cardiovascular complications in epidemiological studies. It has also served as a surrogate marker in the testing of novel anti-atherosclerotic pharmaceutical compounds, where halting CIMT growth (or regression) is interpreted as a positive beneficial effect. Finally, in some primary prevention studies, CIMT is used to evaluate individual risks for future cardiovascular complications. However, recently published data are now questioning the relevance of CIMT in individual patient management.

CIMT measurement was introduced as a research tool three decades ago and was based on the principle that atherosclerosis begins with a gradual accumulation of lipid in the arterial wall resulting in universal or localized thickening. Including the arterial media within the measurement was actually a technical matter, because ultrasound was not able (at that time) to discriminate between intima and media, rather than wrongly assuming that the atherosclerotic process affected the media as well. This is an important point, as both the intima and the media may thicken for different reasons: intima because of accumulation of lipids (atherosclerosis) and media because of hypertrophy of smooth muscle cells (hypertension/remodelling).

Historically, CIMT was measured on the anterior and posterior walls at three anatomical locations: the distal common carotid artery (CCA), the proximal internal carotid artery (ICA), and the external carotid artery (ECA). The six CIMT values from each carotid artery were then combined and averaged into a single CIMT value, thereby reflecting the atherosclerotic burden of both carotid arteries in the patient. In later revisions to practice, the number of measurement sites was reduced and current guidelines recommend only imaging the posterior wall of the distal 10 mm of the CCA.

The rationale underpinning this change in practice was that the best resolution/sharpest images were obtained when scanning the vessel wall at a 90 degree angle (between the direction of the emitted ultrasound waves and the reflecting anatomical structure). Even though the carotid bulb and ICA are more prone towards developing atherosclerosis, an estimation of IMT in these regions would be less accurate because of the branching angle of the ICA from the CCA, which runs more or less parallel to the skin surface in the majority of people. A single CCA CIMT measurement method was found to be reasonably reproducible, giving robust data for large populations of patients. The average variability for repeated measurements was 0.06–0.20 mm ± 0.08–0.26 mm, with the largest variability being found (not surprisingly) in earlier studies.2,5

Considering that CIMT values between 0.5 and 0.8 mm are considered to be within the normal range, individual variability can turn out to be quite considerable. CIMT has been reported as the maximum CIMT (at any point within the 10 mm CCA segment) and the mean CIMT. The latter measurement is recommended as being the more robust. Automated edge detection software improves reproducibility and, more recently, greater focus has been directed towards achieving a clear discrimination between CIMT assessment and atherosclerotic plaque.6

In epidemiological studies, CIMT measurement was evaluated to see whether it could better predict cardiovascular and/or cerebrovascular outcomes than traditional risk factors, such as those identified in the Framingham Study: sex, age, smoking, blood pressure, LDL and HDL cholesterol, and diabetes. By adding in a measurement of CIMT, it has been possible to achieve incremental prediction over the Framingham Risk Score (FRS) alone for groups of people. Generally, the group with the lowest IMT experience fewer late cardiovascular events (death, myocardial infarction, stroke, new angina, etc.) compared with those with the highest IMT quartiles/percentiles.3,5,7–9 However, the predictive value for an individual person seems limited — if it exists at all.

In the Cardiovascular Risk Prediction Study (CAPS), the group with the highest CIMT did have a slightly higher risk of cardiovascular complications than those with the lowest CIMT. However, risk assessment for the individual participant was unaltered by CIMT measurement — even after 10 years of follow-up.10 Similarly, other studies have found little if any incremental value of measuring CIMT; most often expressed as a net reclassification of risk assessment by traditional risk factors.11,12 For instance, comparing different methods for risk assessment in the Multi Ethnic Study of Atherosclerosis (MESA) study, the coronary calcium score (CACS), the ankle brachial index (ABI), CRP, and family history were all independent risk predictors; however, CIMT was not.12 Similarly, the High-Risk Plaque Study, which included 6,100 asymptomatic Americans with an average age of 69 years, found that CIMT had no predictive value over FRS, whereas the coronary artery calcium score (CACS) and carotid plaque burden (a measure of the amount of carotid plaque, as assessed by several cross-sectional images), were highly predictive of the development of late atherosclerotic complications.13–15 In fact, the mere presence of plaque in the carotid artery has, for a long time, been known to be much more predictive of an adverse cardiovascular outcome than that of the thickest CIMT group.3,7,11

According to Peters,16 the value of adding CIMT to the FRS (expressed as the Net Reclassification Improvement), varied considerably from zero to 12% and was less consistent and of a smaller magnitude compared with carotid plaque presence and CACS. Similarly, den Ruijter concluded
that although the addition of CIMT measurement to FRS was associated with a small improvement in the 10-year risk prediction for first-time MI or stroke, this improvement in risk prediction was unlikely to be of clinical importance. For these reasons, the latest primary prevention recommendations from the American College of Cardiology/American Heart Association advises against using CIMT measurement for predicting individual cardiovascular risk prediction on the basis that it is not useful and could be potentially harmful. Finally, serial CIMT measurements (in order to follow IMT progression with time) have been removed from contemporary recommendations by European and American expert groups. In addition, the “PROG-IMT collaborative project”, based on 16 studies including 37,000 people/patients, advised that serial CIMT measurements were not useful for predicting future cardiovascular events.

So, given that atherosclerosis involves arterial wall thickening, why is it that CIMT measurement does not reliably predict cardiovascular outcomes when the simple presence of a carotid plaque is such a powerful predictor? There are at least three explanations: (i) considering the beam width of focused ultrasound (1–2 mm) and the CCA diameter, the resulting IMT measurement will only represent a small part of the CCA vessel wall circumference. Atherosclerosis does not develop as a uniform, circumferential thickening of the vessel wall and does not consistently localize to the anterior or posterior wall regions. Accordingly, assessment of CIMT will be greatly influenced by which part of the arterial circumference is being imaged; (ii) the atherosclerotic process predominantly affects the intima and, thus, the inclusion of media thickness measurements could confound meaningful interpretation; (iii) uniform thickening of the arterial wall will not predispose towards a higher risk of acute thrombosis as would rupture of the fibrous cap within a vulnerable plaque.

So, is there any role for CIMT measurement? For assessment of CIMT in younger persons at increased risk of cardiovascular disease, a thick IMT will indicate true thickening, provided measurement is performed using an insonation angle of 90 degrees and ensuring capture through the centre of the artery. However, a thin or “normal” IMT could simply be the result of scanning an area without thickening or plaque, therefore being misleading, and serial measurements are not helpful because of inter-scan variability. For vascular surgeons, therefore, IMT measurement probably has no clinical value.

Is ultrasound scanning of the carotid artery for assessment of carotid plaques of any use in cardiovascular risk prediction? The increased risk of atherosclerotic complications in patients with carotid stenosis has been recognized for decades and, in 2003, carotid stenoses (including asymptomatic lesions) were classified as being a “coronary risk equivalent”. This implies a similar long-term risk to patients with clinical coronary disease and appropriate secondary prevention strategies should be implemented. Even though the risk of ipsilateral stroke is declining, cardiovascular risk (in general) remains increased in patients with asymptomatic carotid stenosis. The mere presence of a carotid plaque is a much stronger predictor of cardiovascular complications, compared with CIMT and other more conventional risk factors for atherosclerosis. A carotid plaque (defined as a local protrusion of at least 0.5 mm, a 50% local thickening of IMT or a CIMT >1.5 mm) is associated with a doubling of the risk of late cardiovascular events. Furthermore, different ways of quantifying plaque size, that is measuring plaque area from two-dimensional B-mode images, suggests that the greater the plaque size, the greater the risk of late cardiovascular events. More recently, quantification of plaque size from both carotids has been found to be as predictive of major cardiovascular events as the coronary calcium score, the current golden standard for risk prediction. Four studies, including more than 29,000 people, uniformly shows that the addition of ultrasound imaging for carotid plaque to FRS results in significant reclassification. With all the recent advances of ultrasound over CT, the use of carotid ultrasound to identify those in need of primary prevention may result in much more effective treatment.

It is now accepted that the use of atherosclerosis risk factors for predicting cardiovascular risk is not accurate. More important seems to be that the individual patient’s susceptibility towards developing atherosclerosis may reflect whether the patient can resist these risk factors or not. Unfortunately, there is no test for “atherosclerosis susceptibility”. It was long hoped that genetic testing would become the solution; however, this has remained disappointing. Instead, imaging the carotid arteries reveals who is actually developing atherosclerotic disease and, because of the slow nature of the plaque build-up, the time window for therapeutic intervention is substantial. The most important piece of missing information, however, is the trial that will show whether a screened population fares any better than an unscreened. Unfortunately, such a trial will probably fail because those in the control group will likely get treated at some stage or seek screening themselves.

In conclusion, evidence supporting a role for CIMT measurement in individual patients is poor. However, assessment of carotid arteries for the presence and volume of plaque seems very much more promising for directing enhanced primary prevention strategies to those who really need it.

REFERENCES


22 Naylor AR, Gaines PA, Rothwell PM. Who benefits most from intervention for asymptomatic carotid stenosis: patients or professionals? *Eur J Vasc Endovasc Surg* 2009;37:625–32.


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