Assessment of subclinical atherosclerosis by carotid intima media thickness: technical issues

Pierre-Jean Touboul¹, Diederick E Grobbee² and Hester den Ruijter²

Abstract
Carotid intima-media thickness assessed by ultrasonography of carotid arteries is a safe, non-expensive, feasible and accurate method for detecting early signs of atherosclerosis and carotid intima-media thickness and change in carotid intima-media thickness over time reflect cardiovascular disease risk. Technical aspects impact on the measurement, variability and interpretation of carotid intima-media thickness. These include device aspects, inter- and intra-sonographer variability and the ultrasound protocol used. The mean common carotid intima-media thickness and the mean maximum common carotid intima-media thickness are the most widely used carotid intima-media thickness measurements. Common carotid intima-media thickness values of around 0.5 mm are considered ‘normal’ in young adults. Values are higher in men than in women, in African–Americans than Caucasians and increase with age. Carotid intima-media thickness values at or above the 75th percentile of a reference population indicate increased cardiovascular risk. Guidelines differ in their recommendations for the use of carotid intima-media thickness measurements for risk assessment in primary prevention because evidence suggesting that it improves upon conventional risk scores is inconsistent. Carotid intima-media thickness is frequently used in clinical trials as a surrogate endpoint for cardiovascular events on the assumption that regression or slowed progression of carotid intima-media thickness, induced by cardiovascular risk interventions, reflects a reduction in cardiovascular events. However, further data are required to confirm this linear relationship. No international guidelines exist on the use of carotid intima-media thickness as a research tool. Quality control in acquisition, measurement and interpretation of carotid intima-media thickness are important considerations and the carotid intima-media thickness protocol used should be determined by the research question under investigation.

Keywords
Atherosclerosis, ultrasound, carotid artery, cardiovascular disease, imaging, surrogate endpoint

Introduction
Atherosclerotic vascular disease begins in childhood and develops over decades. Symptomatic cardiovascular disease (CVD) generally occurs when the atherosclerosis blocks blood flow causing ischaemia or when a thrombus forms on a plaque as a result of rupture or erosion. When a clinical event occurs, atherosclerotic disease is difficult to reverse.¹ Therefore, prevention of the development of atherosclerosis or of its progression has become an important goal in medicine in order to reduce death and morbidity from CVD. In 1986, Pignoli published the first paper on the relation between carotid intima-media histology and a double line pattern identified as the intima-media complex at the same site with ultrasound.² Since that time, ultrasonography of carotid arteries has become a frequently used method to detect early signs of atherosclerosis, i.e. increased...
thickness of the arterial wall or plaque occurrence. It is a safe, non-expensive, feasible and accurate method.

A thickened carotid intima-media thickness (CIMT) does not immediately lead to cardiovascular events, but reflects the degree of atherosclerosis elsewhere in the arterial system. When CIMT is measured at several time points within an individual, rate of change in CIMT can also be calculated. Both measures reflect CVD risk and can be used as a risk factor in a study or as an outcome measure. The first cohort studies reported relationships between cardiovascular risk factors and CIMT, after which the relationship between CIMT and events was established. Also, the rate of change in CIMT has been under investigation in trials and cohort studies.

Since the first description of CIMT as a marker for atherosclerosis, more than 3000 papers have been published on CIMT with very different methodological understanding and approaches. The technical aspects of CIMT measurements that should be considered before CIMT can be properly measured and interpreted are discussed below.

**Technical issues in CIMT ultrasound evaluation**

CIMT measurements are not the same. Each separate CIMT value has its own absolute value, reproducibility, obtainable completeness, rate of change over time and relationship with cardiovascular events. Variability in the absolute CIMT value can be attributed to various factors (Table 1). A main distinction is between variability due to the patients and the measurement of interest and variability resulting from the device, observer, measurement protocol, etc., all of which we would like to minimize as much as possible.

**The patient and the ultrasonic device**

The CIMT measurement is obtained when the patient is in a supine position, with slight rotation of the neck to the contralateral side. Images are best obtained with linear/array transducers with high resolution probes with frequencies ≥7 MHz. Measurements are best acquired at the end of the diastole, because the systolic expansion of the lumen causes the CIMT to become thinner particularly in young subjects or in inflammatory disease. Grey scale imaging should be preferred to colour flow imaging as the latter is highly dependent on colour flow settings. Image resolution depends on settings (gain and depth) and frame rate. CIMT acquisition needs a depth setting between 35 and 45 mm, usually 40 mm. Gain settings should be adjusted to avoid over- or underexposure of the near and far walls. Time gain control may be important to adjust when the arterial lumen is filled of artefacts. Wall thickness depends on the anatomical location due to shear stress, which varies according to flow direction. At the bifurcation, the angle, the diameter of the bulb and the curvature of the origin of the internal carotid artery may induce arterial remodelling, which increases inter-individual variability of intima-media thickness (IMT) at these sites. Apart from device aspects, the absolute CIMT value depends heavily on patient characteristics, as recently reviewed by Peters and coworkers.

**Sonographer**

Key is the person who is responsible for the ultrasound examination. Currently, there is no standard for training and certification for sonographers and readers in Europe. A programme for training has been published; however, it has not been implemented in a systematic manner. At least, one should train the sonographers and readers to perform the measurement and interpret the findings. It is also recommended to obtain estimations of sonographers’ variability before

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<th>Table 1. Causes of variability in carotid intima-media thickness</th>
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<td><strong>Category</strong></td>
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CCA: common carotid artery; CBif: carotid bifurcation; ICA: internal carotid artery.
and repeatedly during the study. Groups that work with CIMT measurements should document their accuracy and reproducibility to ensure that it is similar to that reported in literature. Some devices are equipped with an online quality index that provides an index of success based on the quality of image acquisition, when used in real time.

**Acquisition of ultrasound images for CIMT measurements**

Ultrasound protocols to measure CIMT may vary in the selection of carotid segments, angles and walls of the carotid artery measured. Measurements can be done on the near wall and/or the far wall along the common carotid artery, the carotid bifurcation and/or the internal carotid artery at one or more angles of insonation (anterior, lateral and posterior). Some protocols measure only at the far wall of the common carotid segment using one image, whereas other protocols measure at the common carotid artery, the internal carotid artery and at the bifurcation. The near wall is more difficult to delimitate, particularly on posterior and anterior incidences. In vitro experiments show that the near wall CIMT best reflects the true thickness of the arterial wall, based on the properties of the ultrasound waves. The near wall represents at best an approximation of the true wall thickness. Furthermore, it is generally thought that near wall CIMT measurements are more difficult to obtain. Therefore, the consensus recommends that far wall acquisition can be acquired successfully in almost all patients. Yet, near wall measurements can be readily and easily measured on many occasions. Also, the near wall or the combination of near and far wall measures can be measured very reproducibly. In trials, the combination of near and far wall measures were superior to only far wall measurements. This is partly because random error is reduced when measures are averaged together. Thus, near wall measurements when combined with far wall data have shown to improve data quality and may provide valuable information when acquisition of both walls is optimal. The choice made to analyse both walls should, of course, also depend on the time invested for acquisition in relation to the scientific benefit.

The general thought is that, because of its accessibility, measurement of CIMT of the common carotid artery is more reproducible than that of the internal carotid artery or the bifurcation. Yet many studies have proven this concept to be wrong. CIMT measurement can be obtained from the internal carotid artery and the bifurcation in a very high percentage of subjects.

Because atherosclerosis is an asymmetric disease, CIMT and its progression differs across the carotid segments. The carotid bifurcation and internal carotid artery, next to the common carotid artery, may carry additional information on atherosclerotic disease. In addition, the heterogeneity in the relationship between cardiovascular risk factors and CIMT measured at different carotid segments and walls is another argument in favour of a more extensive ultrasound protocol. Therefore, when one aims to fully describe the burden of atherosclerosis, restricting the ultrasound protocol to the far wall of the common carotid artery may have limitations. Plaque presence should always be associated with carotid examination. These lesions are more likely to be found at the bifurcations or at the origin of the internal carotid artery. Plaque presence overrides cardiovascular risk evaluation provided by increased IMT.

In 3364 individuals in whom the carotid artery was systematically examined using the same extensive ultrasound protocol, an asymmetric circumferential pattern in atherosclerosis was observed in both men and women, in young and old, in different race groups and across the four participating studies. The asymmetrical helix-like distribution of atherosclerosis in the carotid arteries expands the evidence by showing that the atherosclerotic configuration is similar across populations with different vascular risks and across gender, age and race. These findings show that the angle of insonation is an important determinant of the absolute value of maximum CIMT and this finding implies that future carotid ultrasound studies with maximum CIMT under investigation should include measurements from multiple carotid angles.

CIMT and carotid plaque are biologically and genetically distinct phenotypes of atherosclerosis. The definition of plaque may seem clear cut, yet between the observers, large differences exist in what people consider a plaque, even after training. An arbitrary definition of an atherosclerotic plaque is a focal thickening of the intima-media complex that is 50% thicker than the adjacent area, or as a focal thickening of over 1.5 mm. CIMT and plaque may reflect different aspects of the atherosclerotic process and are differentially related to risk factors and CVD. Studies that have separated increased CIMT and plaque have shown a greater risk for myocardial infarction with plaque. Moreover increased IMT predicts plaque occurrence in general populations.

**CIMT measurement**

The most common and basic CIMT measurements are the mean common CIMT and the mean maximum common CIMT. Mean common CIMT is the mean value of the elementary CIMT measurements that are performed over a 10 mm part of the far wall or both the
far and near wall of the common carotid artery. This can represent the mean of 100–150 values. Mean maximum CIMT is calculated as the mean of the single maximum CIMT measurements that are taken from different segments of the carotid artery and is the most often used for carotid atherosclerosis evaluation in clinical trials. When plaques are present in a segment, the maximal value is by definition at the maximum height of the plaque.

In most studies, CIMT is read from images using a reading programme where the reader can manually draw lines to quantify the IMT or use a semi-automated edge detection programme that automatically provides these lines in the region of interest. CIMT relations with risk factors and risk for future events are reported to be stronger for manual than for automated readings. However, automated reading was more strongly associated with future events in participants with a thinner common CIMT. These findings suggest that a manual approach might be preferred in populations with a high prevalence of atherosclerotic burden, whereas an automated approach might be favoured in settings with more easily detectable CIMT. In 43 healthy women, the reproducibility of automated and manual CIMT measurements of the common carotid artery, carotid bifurcation and internal carotid artery was studies that resulted in reliable CIMT readings across all carotid segments, although the measurement error was lower and repeatability of the measurements was higher for the automated technique. For the METEOR study, we recently showed that manual and semi-automated edge detection of lumen and wall interfaces for measurement of maximal far wall common CIMT both result in high reproducibility and largely show similar relations to cardiovascular risk factors, rates of change and treatment effects. It seems that choices between automated and manual reading software for CIMT studies should be based on logistical and cost considerations rather than differences in data quality. However, for studies including data acquisition evaluation by real time quality index, this evaluation is not yet available.

**Normal CIMT values**

What values of CIMT are ‘normal’ depends on the population and what is meant with CIMT. As previously explained, there is no need to measure IMT in the presence of plaques and there are no reference values for the bifurcation or the internal carotid IMT except for those obtained in the ARIC study, where definitions were less precise.

Generally, CIMT is perceived as common carotid IMT, yet this needs to be clearly stated. Common CIMT values are reported to be higher in men than in women. Also, African–American people have higher values than Caucasians. In general, normal values for the common CIMT are thought to be around 0.5 mm in young adults to 1.2 mm or thicker in the elderly. Also, values depend on age, gender, risk factor prevalence, echogenicity, segment, measurement algorithm and ultrasound device. In its 2008 consensus statement, the American Society of Echocardiography suggested that CIMT values at or above the 75th percentile of a reference population indicate increased cardiovascular risk. Currently, several initiatives have been launched to combine existing cohorts worldwide to come up with some estimates of normal values where adjustments for equipment and reader algorithms can be taken into account.

**CIMT and cardiovascular risk prediction**

Currently, cardiovascular risk prediction in asymptomatic individuals is based on the level of cardiovascular risk factors incorporated in scoring equations. Several scores are available, with the Framingham risk score among the most widely used. However, more than 40% incident events remain unexplained by these scores. Measurement of CIMT has been proposed to be added to cardiovascular risk factors to improve individual risk assessment. So far, individual studies reported on the added value of CIMT measurements in cardiovascular risk prediction, but the evidence is not consistent across studies. This may be attributed to differences in CIMT measurement, in distribution of age and gender, in number of events, in cut-off values for risk categories and in endpoint definition. Therefore, the guidelines differ in their recommendations to use CIMT measurements in primary prevention and also as to whom should be considered, ranging from measurement in all individuals to measurement in only those at intermediate risk. The recently published Appropriate Use Criteria states that indications for CIMT measurements were largely within the detection of coronary heart disease risk among intermediate risk patients, metabolic syndrome and older patients. Ongoing studies may provide guidance on this topic.

**CIMT in clinical trials**

CIMT is often used in clinical trials as a surrogate endpoint for CVD events with the idea that regression or slowed progression of CIMT, induced by cardiovascular drugs, reflects a reduction in cardiovascular events. The continuous nature of CIMT makes it logical to assume that this linear relation indeed exists. However, evidence that changes in CIMT one-on-one reflect changes in cardiovascular event risk is inconsistent. One recent meta-analysis on this topic using aggregate data pooled from literature showed that changes in
CIMT did not reflect a reduction in events. A second recent meta-analysis using a similar approach and using the same data showed that slowed progression in CIMT over time is associated with a lower likelihood of non-fatal myocardial infarction in selected trials but that these findings were inconsistent at times, suggesting caution in using CIMT as a surrogate end point. Yet both studies should be interpreted with caution, as both may suffer from considerable flaws, as reviewed in detail elsewhere. Besides ecological fallacy, flaws may include heterogeneity in treatment efficacy, patient population and methodologies of measuring CIMT, in addition to a lack of power. What is needed is an individual participant data analysis in order to overcome the flaws of these earlier meta-analyses using aggregated data.

Current technical recommendations for CIMT measurement and recommended protocols

In spite of the tremendous increase in the use of CIMT in cardiovascular research, there are no international guidelines on how the technique should be applied as a research tool. Two consensus reports have touched upon this topic, the first was the Mannheim consensus organized in 2004 and updated in 2006 and 2010. The second was published in 2008 and came from the American Society of Echocardiography. Both recommend CIMT to be measured preferably in the far wall. Key is, of course, that the final choice for a certain protocol should be entirely driven by the research question to be answered and not primarily by a consensus protocol. One recently published protocol using trained sonographers can be utilized in answering many research questions. The protocol includes information from the common, bulb and internal carotid segments and a separate measure of focal plaque. The protocol was feasible and reproducible when strict quality control was ensured. The choice for an ultrasound protocol should depend on the research question with a well-considered balance between time and costs on the one hand and data quality and the value of additional information obtained using extensive protocols on the other.

Summary

When CIMT measurements are used for cardiovascular research purposes or in clinical practice, strict attention needs to be paid to quality control in acquisition, measurement and interpretation. The final choice for a CIMT protocol depends on the purpose of the measurement, the research question at hand and the balance between costs, data quality and the value of additional information.

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Conflict of Interest

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References


