Carotid Intima-media Thickness Measurements: Relations with Atherosclerosis, Risk of Cardiovascular Disease and Application in Randomized Controlled Trials

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and contributes considerably to morbidity.[1-3] The underlying cause is atherosclerosis.[4] The development of new preventive therapies is one of the steps to control the CVD epidemic. It is increasingly demanded that promising therapies be evaluated in trials using cardiovascular (CV) morbidity and mortality (M and M) as a primary outcome.[5] M and M trials, however, are very costly, often multicenter studies requiring thousands of participants, and with a long follow-up period. There is great interest in alternative endpoints that can be used as a valid alternative or proxy for CV M and M alternative endpoints (surrogate endpoints) allow for the evaluation of novel therapies in randomized controlled trials within a shorter timeframe, fewer participants, at lower costs, and with a shorter time to availability of trial results when compared to an M and M trial. These studies may show a direct effect on atherosclerosis progression and in the same time may serve to direct or exclude subsequent large M and M trials. A measure of atherosclerosis is intuitively a suitable alternative endpoint for CVD events as atherosclerosis is the disease between exposure to risk factors and the majority of CV events. Atherosclerosis can be noninvasively assessed from early to late stages of the disease process using different imaging techniques.[6-9]

B-mode ultrasound is one of those imaging techniques and has been used to obtain quantitative measurements of the carotid intima-media thickness (CIMT) and as such provides estimates for an individual on the absolute value (presence) and its change over time.[10,11] CIMT has been suggested to be an adequate alternative measurement for CV events (surrogate endpoint) in intervention studies.[10,11] Prentice and Boissel have proposed several criteria [Supplementary Table 1] for a surrogate endpoint that should have been met before it could be validly used.[12] We set out to review literature and provide evidence for the validity of CIMT measurements as an alternative measurement for atherosclerosis elsewhere in the arterial system and for CV events.

Validity, Concept and Reproducibility of the Measurement

Validity

In 1986, Italian investigators reported for the first time the results of an *in vitro* study which compared direct measurements of arterial wall thickness by gross and microscopic examination with B-mode real-time imaging of those same specimens.[13] Several studies followed. The overall conclusion was that CIMT measurements of the far wall closely relate to the true biological thickness of the vessel wall, whereas near wall CIMT measurements

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are an approximation of the true wall thickness.[14-18] Since then, the number of scientific publication has increased steadily [Figure 1] and CIMT is currently one of the most widely used noninvasive measures of atherosclerosis employed by clinicians and clinical investigators, both to quantify the extent of subclinical disease and to monitor change over time.

Acquisition of the images

Typically, the carotid artery is classified into three segments, each approximately 10 mm in length [Figure 2].[19] The most proximal segment, the 1 cm straight segment of the carotid artery immediately prior to the bifurcation, is the common carotid artery (CCA). Its distal boundary is identified by a divergence of the near and far walls as the artery begins to divide into its internal and external branches. This focal widening of the bifurcation extends over approximately 1 cm and is labeled the carotid bulb or bifurcation (CB). The distal margin is defined by the tip of the flow divider separating the diverging internal carotid artery (ICA) and external carotid artery. The final segment that is frequently examined is the proximal 1 cm of the ICA.

As indicated in Figure 3, CIMT has been assessed in a several ways, varying in side (left carotid artery, right carotid artery, or both), segment (common, bifurcation, and internal), wall (near wall and far wall on the image), and in angles (60, 90, 120, 150, 180, 210, 240, 270, and 300) by using an external arc for positioning (Meijer Carotid Arc^{R}).[20] Some studies measure CIMT only once and choose an image in which the interfaces are most clear (i.e., single optimal B-mode image).[21] Others searches for the point with the thickest CIMT (e.g., the highest burden of atherosclerosis).[22] Others choose from multiple optimal B-mode images,[23] or measure the CIMT from multiple images that were obtained from various standardized angles of interrogation [Figure 4]. The latter, using the Meijer Carotid Arc approach, allows for measurement at exactly the same location over time.[23] It is important to realize that each measurement approach has its own specific characteristics. Since atherosclerosis is asymmetrically distributed across the carotid artery, selectively measuring only one angle is likely to ignore the asymmetric nature of the disease.[24,25] Furthermore, each measurement approach has its own characteristics with respect to the assessment of atherosclerosis progression, as previously shown.[26] Finally, also measurement error or missing values tend to vary across the measurement approaches.[27,28]

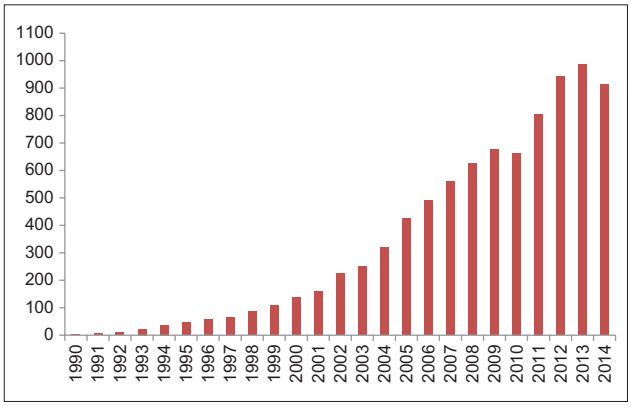

Figure 1: The number of publications (y-axis) using "carotid intima-media thickness (not animal)" in the title or abstract as assessed using PubMed database (http://www.ncbi.nlm.nih.gov/sites/entrez), by year of publication (x-axis), (December 16, 2014).

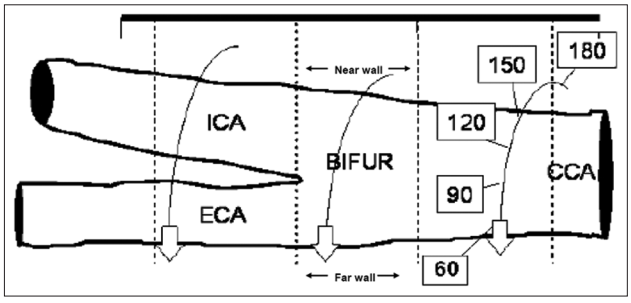

Figure 3: Graphical representation of the circumferential assessment of the artery sites. The angle values from 60 to 180 represent the standardized angles of interrogation. BIFUR: Carotid bifurcation; CCA: Common carotid artery; ECA: External carotid artery; ICA: Internal carotid artery.[29]

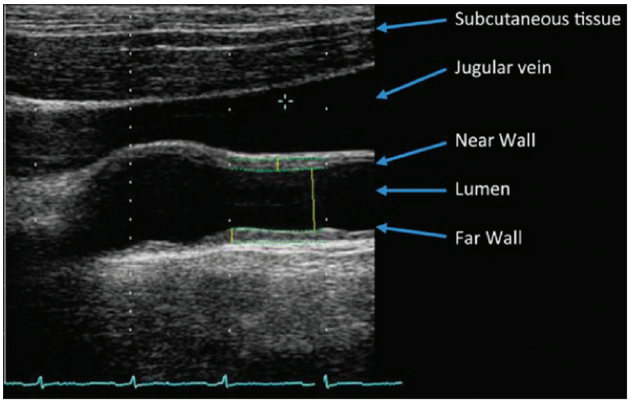

Figure 2: A typical B-mode ultrasound image from the carotid artery.[19]

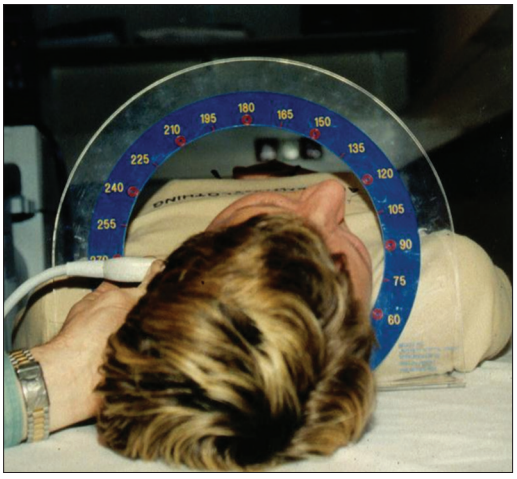

Figure 4: The Meijer Carotid Arc that allows for assessment of angles specific images.[23]

Actual measurement of the images

Ultrasound images in CIMT studies are typically acquired at the study site, stored digitally, and send to a reading laboratory for offline reading. At the core lab, typically quality control and quality assurance typically takes place first before the actual readings can start. These actual readings can be performed using several different edge detection methods (semi-automatic or manual).[29] Semi-automated edge detection is more often applied in settings where only the CCA is examined while manual edge detection is usually applied in settings where the carotid bifurcation and the ICA are also measured.[30]

The main difference between semi-automated edge detection and manual edge detection, however, is the actual manual drawing of the lines on the interfaces with manual edge detection. With semi-automatic edge detection, the reader still may adjust or modify the automatically drawn lines when the reader judges that the lines were incorrectly placed. A major advantage of semi-automated edge detection programs, besides being less resource intensive and time-consuming, may be the reduction in variability in CIMT readings as a result of reduction in the variability between readers and reduction of change in reading behavior over time (reader drift).[30] Many investigators have a clear view on this topic, mostly based on personal experience. Yet, there is little published evidence on this topic. Two recent studies indicated that manual and semi-automated edge detection of far wall common CIMT both result in high reproducibility, and largely show similar relations to CV risk factors, rates of change, and treatment effects.[30,31] Hence, choices between semi-automated and manual reading software for CIMT studies likely should be based on logistical and cost considerations rather than differences in expected data quality in populations with a low burden of atherosclerotic disease.

Reproducibility of the measurement for an individual

With reproducibility is meant that when an individual is measured today, the obtained value should be similar to that obtained tomorrow or next week. Between visit, reproducibility covers all sources that may affect the CIMT measurement: Position of the patient, image acquisition, reader variability, and within-patient variability in, for example, blood pressure or heart rate.

Although difficult to quantify, due to a wide variation in reporting of reproducibility results, it seems that the reproducibility of the CIMT measurements has improved considerably over the years.[32] Studies reporting on the intraclass correlation coefficient (ICC), showed that the ICC ranged from 0.60 to 0.75 in studies conducted during the late eighties.[33-37] whereas, more recent studies reported an ICC between 0.80 and 0.95.[38-40] Of note, it seems that in studies that started as an observational study the reproducibility was less than in studies focuses on measuring progression.[41,42]

A number of reports from randomized controlled trials recently addressed the reproducibility of CIMT measurements based on various ultrasound protocols.[28,43-46] In these trials, the ultrasound protocols were based on an assessment of both sides, all three segments, both walls and at least eight angles. With those data points, the interest was in providing the best balance between reproducibility, magnitude of CIMT change over time and its associated precision, and magnitude of effect of the intervention on CIMT change over time and its associated precision.

Relations with Established Cardiovascular Risk Factors

There is a wealth of evidence on the relation between unfavorable level of risk factors and increased CIMT. We made no attempt to refer to all the available publications on that issue. Most of the evidence comes from cross-sectional studies. Traditional risk factors such as ageing, male gender, elevated blood pressure, increased body mass index, high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, diabetes mellitus, and smoking have shown to be related to increased CIMT.[47-56] These relations also hold for individuals with an Asian ancestry.[57-63] In addition, increased CIMT has been associated with abnormalities in other organ systems such as the presence of white matter lesions in the brain,[64] left ventricular hypertrophy.[65-67] renal disease,[68] and endothelial dysfunction measured at the level of the brachial artery.[69]

Data on risk factors and change in CIMT or change in risk factors and change in CIMT is less readily available.[70-73] The Atherosclerosis Risk In Communities study in one of the earliest reports showed that baseline levels of established risk factors (such as diabetes, hypertension, LDL, and HDL cholesterol) were related to increased progression on CIMT.[70]

Relation with Atherosclerosis Elsewhere in the Arterial System

A variety of studies evaluated the relation between CIMT and presence of atherosclerotic abnormalities elsewhere in the arterial system. Relations were shown for the presence of atherosclerotic abnormalities in the carotid bifurcation and the ICA,[74-76] the abdominal aorta.[77] the arteries of the lower extremities,[78,79] and the coronary arteries.[80,81]

In a recent systematic review, most of the studies (29 out of 33) showed a graded positive relationship between CIMT and angiographically assessed coronary atherosclerosis with correlation coefficients in the order of 0.3–0.4.[82] Of importance, is to realize that these reported associations between carotid atherosclerosis and coronary atherosclerosis are of similar magnitude to those shown in autopsy studies.

Several studies looking at the relation between CIMT and coronary calcium showed similar kind of results.[83-85] In studies using intravascular ultrasound, generally significant positive relations are found between angiographic left

main coronary atherosclerosis and CIMT with correlation coefficients between 0.26 and 0.55.[86]

In summary, the relationship found between CIMT and coronary atherosclerosis in various studies support the notion that CIMT measurements are reflecting atherosclerosis elsewhere.

Carotid Intima-media Thickness and the Relation with Future Cardiovascular Events

Several large observational studies studied the relation of CIMT with future events.[87-89] In 2007, Lorenz *et al*. published a systematic review and meta-analysis of eight relevant general population-based studies that had reported on the ability of CIMT to predict future CV end points, including the three above, involving a total of 37,197 subjects followed for a mean of 5.5 years.[90] They reported that for an absolute CIMT difference of 0.1 mm, the future risk of myocardial infarction increases by 10–15%, and the stroke risk increases by 13–18%. There is a number of studies performed in participants with an Asian ancestry showing results consistent with those found in Caucasians.[91-95]

Currently, over 20 cohort studies that were performed among subjects with or without previous vascular disease, and with and without CVD risk factors, showed consistently that increased CIMT relates to increased CV risk, independently of established vascular risk factors.[96,97]

Lipid Lowering and Rate of Change in Carotid Intima-media Thickness

In Supplementary Table 2, an overview is provided of several trials that have been performed to evaluate the effects of therapeutic interventions on the rate of change in CIMT. In those trials, the rate of change in CIMT over time was the primary endpoint. The majority have evaluated the efficacy of lipid-level modifying therapies, primarily statins. These trials exemplify the ability to measure change over time in CIMT, which is a sensitive enough marker to detect differences across treatment arms.[98-142]

When the trials in which the efficacy of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) are compared to placebo are reviewed, all trials, except for one,[109] reported a statistically significant beneficial effect of statin therapy on rate of change in CIMT. In a meta-analysis of seven statin trials on different regimens, statin therapy was associated with a mean annual change in CIMT of −0.012 mm (95% confidence interval [*CI*]: −0.016 to −0.007).[143] Another meta-analysis of 11 statin trials showed that the difference in the rate of change in CIMT between statin therapy and placebo was −0.040 mm (95% *CI*: −0.052 to −0.028).[144] A systematic review by Huang *et al*. up to December 2011 identified 21 randomized controlled trials using different statins with a minimum follow-up of 6 months. This meta-analysis involving 6317 individuals showed that the pooled weighted mean difference in progression rate between statin therapy and placebo or usual care for the common CIMT was −0.029 mm (95% *CI*: −0.045, −0.013).[145] Feng *et al*. performed a systematic search of the regular databases and a Chinese database up to January 2013 to studies comparing Rosuvastatin with a placebo or other statins on CIMT.[146]

The statin trials indicate that statin therapy inhibits atherosclerotic disease at the subclinical stage and provide evidence that CIMT measurements are able to show the beneficial effects of statins. A point of interest and importance is that the effect of statins on rate of change in CIMT appeared to be different across different carotid walls and segments, which calls for assessment of information from different carotid segments in trials.[26]

Rate of Change in Carotid Intima-media Thickness and Future Cardiovascular Events

Investigators have argued that data should become available that assesses whether a change in CIMT relates to change in risk of CV events. In particular in the clinical trial world, such an observation is regarded as a final part of the evidence chain to support the CIMT measurement for use in trials.[147] Yet, studies to demonstrate that are difficult to conduct as they first need to show the impact of an intervention on rate of change in CIMT and next have sufficient sample size and follow-up time after this demonstration to assess the ability of measured CIMT change to account for subsequent changes in CVD risk. Importantly, most trials with excellent CIMT data on the rate of change in CIMT did not follow participants for the occurrence of events after the trial was finished. Moreover, these CIMT trials were not designed (too small sample size) for evaluation of vascular events. And thus data on change in CIMT induced by lipid-level modifying or blood pressure lowering therapies and change risk for CV events is very limited.

The only published paper is the Cholesterol Lowering Atherosclerosis Study (CLAS) trial.[148] The 2-year CLAS trial demonstrated that colestipol-niacin therapy reduced rate of change in CIMT. The trial cohort subsequently was surveyed over an average of 8.8 years after the conclusion of CLAS to evaluate the posttrial incidence of coronary events. The trial showed statistically significant favorable results: That is, a lower rate of change in common CIMT over time was related to a lower risk of an event. Those with an annual common CIMT progression rate of 0.034 mm/year had a 2.9-fold higher CVD risk compared to those with a common CIMT progression rate of 0.011 mm or less. The risk for those with progression rates between 0.011 and 0.017 mm was increased 1.8-fold, and the risk for those with progression rates between 0.018 and 0.033 mm was increased 2.3-fold. In addition to this paper, Espeland *et al*. performed a meta-analysis showing that across the trials, statin therapy was associated with an average decrease of CIMT progression of 0.012 mm/year (95% *CI*, −0.016 to −0.007).[143] Using the same studies, they

performed a meta-analysis which yielded a risk reduction of 52% for CVD events. In this approach, the authors linked the CIMT benefit to the reduction of events.

In addition, the PROG-IMT initiative recently published their findings on the rate of change in CIMT and future events.[41] PROG-IMT was based on a change in CIMT found in observational studies, so natural history in common CIMT rather than the pharmaceutically induced rate of change. No relation between the rate of change in common CIMT and risk of CV events was detected. The reproducibility between the first and the second CIMT measurement was surprisingly low (correlation coefficient <0.10). The IMPROVE study, a recent observational initiative performed in 7 centers in 5 European countries enrolled 3482 subjects, (median 64 years; 47.8% men) with 3 or more vascular risk factors, and was designed to assess CIMT progression.[42] An increase in mean common CIMT of 0.058 mm was related to an increased risk of CV events of 11% (95% *CI*: 8%, 34%). The CIMT estimate based on the fastest change in any segment showed a progression rate of 0.27 mm/year. An increase of one standard deviation, that is, 0.26, was related to an increase in risk of 26% (95% *CI*: 8%, 44%).[42] In a cohort of 342 Japanese patients with type 2 diabetes mellitus without history of CV events whose CIMT was assessed more than twice by ultrasonography were recruited and followed up for CV events, Okayama *et al*. showed that the change in CIMT was significantly associated with CV events, with a hazard ratio of 2.24 (95% *CI*, 1.25–4.03, using the median of CIMT change of 0.011,14 mm/year as cut point.[149]

Recently, two meta-analyses were published trying to address this issue using aggregated data from published reports.[150,151] The two meta-analyses have been criticized because of flaws in the design and analyses.[152,153] Flaws include the misuse of the concept of atherosclerosis, pooling of trials carried out with treatments having heterogeneous efficacy and among patients, who had very different risk profiles; pooling of measurements from a wide variety of methodologies that shared a common name, "CIMT;" lack of power for detecting relationships using meta-regression techniques, and lastly, the ecologic fallacy. Hence, the conclusions of these two meta-analyses should not be considered appropriate.[153]

At present, direct quantitative evidence to translate the reduction in CIMT progression rates in a reduction in clinical outcome is modestly available.[148] Yet, the lack of such information does not invalidate the CIMT measurement for use in trials on atherosclerosis regression and reduction of CV risk.

Criteria of Prentice and Boissel to Support Surrogacy

Prentice and Boissel have proposed several criteria [Supplementary Table 1] for a surrogate marker that should have been met before it could be validly used. In the previous paragraphs, we have addressed in detail the criteria by Prentice (P1, P2 and P3 from the Supplementary Table 1). The criteria P4 is more difficult to address since it mandates studies in which data on the intervention, on the CIMT change and on clinical events are all present in one study. This type of data is only present from meta-analyses as performed by Espeland *et al*.[143] They showed a pooled estimate between statin use and CV events of 0.48 (0.30, 0.78). When in the analyses they adjusted for the rate of change in CIMT, the pooled estimate was attenuated to 0.64 and no longer statistically significant ($P = 0.13$). This suggests that changes in CIMT may account for some, but not all, of the effect of statins on CV events.

With respect to the evidence fitting the Boissel criteria:

- B1: Efficiency. CIMT measurements are relatively easy to obtain using noninvasive means and are can be obtained in nearly every individual. It is clear that M and M trials on lipid-level modifying therapies generally were conducted in thousands of participants with 5 years of follow-up, whereas CIMT trials have been performed in hundreds of participants who were followed for 24–36 months.[26]
- B2: Linkage. There is abundant evidence from several observational studies to suggest that increased CIMT is related to an increased risk of CV events.[41,96] The linkage between pharmaceutical induced rate of change in CIMT and future CV events has not been firmly established
- B3: Congruency. The congruency argument is important and has a number of aspects that should be addressed. First, individuals with and without vascular disease should exhibit differences in CIMT, which has been clearly demonstrated.[29] Moreover, evidence from randomized controlled trials suggests that CIMT change over time are larger in individual with CVD as compared to those without. The pooled annual common CIMT progression rate observed in the control arm of trials in patients with coronary heart disease was 0.0170 mm (SD 0.06 [median]). The reported estimate for the annual mean maximum CIMT progression rate was 0.0258 mm (SD 0.068 [median]).[154] The second aspect is that anticipated clinical benefits should be deducible from the observed changes in the surrogate marker in the trials. As indicated under B2: Linkage, this type of evidence is not readily available yet. The third aspect deals with the notion that the surrogate should produce parallel estimates of risk and benefit as endpoints. This has been made likely by Espeland *et al*.[143] Recently, the approach by Espeland has been substantiated and extended by a systematic review in which the agreement between the results from CIMT and M and M trials was assessed, and positive and negative predictive values were calculated.[155] Forty-eight CIMT trials were included. CIMT trials ($n = 20$) on lipid-level modifying therapies were all, except one, in agreement with the M and M trial findings. These results demonstrate a strong congruency between results from a CIMT trial and an M and M trial using the same compound.

The Best Approach for Carotid Intima-media Thickness Trials

Based on the experience in previous large-scale trials there is a number of aspects that one may consider in designing a multicenter randomized controlled trial with CIMT as primary outcome parameter.[29]

How to choose the best carotid intima-media thickness measurement: Side, segments, walls, and angles?

Guidelines on how to measure CIMT have been published.[156,157] Nevertheless, there are still no accepted standards on the most optimal ultrasound protocol for either single nor repeated CIMT assessments. Hence, choices on the CIMT ultrasound protocol to be used are generally based on experience and expert opinion rather than on solid evidence from methodological studies. Even though some methodological issues are being addressed, there are many outstanding topics that need to be further evaluated. The debate is about simple protocols versus extensive protocols. Important to realize is the setting for which a protocol is used.[20] For protocols used in randomized controlled trials, emphasis is on assessment of the rate of change. A number of reports have provided evidence on the best balance between reproducibility, completeness of the data, magnitude of CIMT change over time and its associated precision, and magnitude of effect of intervention on CIMT change over time, and its associated precision.[27,28,44-46] Trials evaluating the effect of lipid lowering on CIMT progression have shown that CIMT measurements of both the near and far wall measurements are superior to trials only having only far wall measurements. With respect the use of angle specific measurement, analyses from studies indicated that extensive ultrasound protocols including near and far wall measurements from two or more angles provide a better balance between high reproducibility, large progression rates, and large and precise intervention effects when compared to single angle protocols from the far wall alone. This may especially be beneficial in settings where sample sizes and effect sizes are small. With respect to segments (common versus all three segments), there are trials showing a beneficial response to an intervention on the rate of change in CIMT measured using a single angle far wall common CIMT measurement.[26] The issue is that it remains unknown whether trials showing an effect on the CCA alone would have found a similar or improved effect if an extensive protocol has been used. There are trials that failed to show an intervention effect on the common CIMT, whereas a beneficial effect was found on the aggregate CIMT measure and on clinical events. These findings underscore our viewpoint that an ideal ultrasound protocol does not exist and that the choice for an ultrasound protocol always should depend on a well-considered evaluation of the expected rates of change and associated precision at the different carotid segments. However, as it remains impossible to predict at which carotid segment drug therapies will have their effect,[26,158] extensive protocols may be preferred.

Although studies with extensive ultrasound protocols may be considered the most precise and most comprehensive studies, there are disadvantages in terms of cost and logistics as well. Extensive ultrasound protocols take more time for acquisition and quantification. Moreover, extensive ultrasound protocols require more extensive training of sonographers than ultrasound protocols measuring the CCA alone. While the current evidence indicates that extensive ultrasound protocols do provide the highest quality data in intervention studies, the choice of the ultrasound protocol should always be based on the specific questions that one wants to address and the resources available. It should be noted that a less extensive protocol with careful quality control is always preferable to a more extensive protocol with inadequate quality control.

Missing data when having an extensive ultrasound protocol?

We showed that high levels of complete data can be obtained with extensive ultrasound protocols that include measurement from the carotid bifurcation and ICA.[44,45,158] For example, in the METEOR study, the percentage of CIMT measurements at the baseline examinations was 94% for the near wall of the right ICA, and 96% for the near wall of the left ICA. Completeness on the other carotid artery sites, including the carotid bifurcation, was >99%. A high body mass index contributes to the incompleteness of CIMT measurements.[158]

Sample size consideration for a trial

Sample size calculations for l trials generally use expected changes between groups, and variances obtained from literature. However, this approach neglects the impact of differences in trial design. Designs with a shorter duration of follow-up increased within-individual variance and required larger sample sizes to detect the same treatment effect.[159,160] In addition, reducing the number of scans at the end of the study from two to one increased and reducing the number of baseline scans from two to one further increased the required sample size.[160]

What to do with implausible biological values?

Implausible CIMT values may refer to an observation within an individual that is far from the values observed in the remainder of the individuals. These implausible values are observed at a single time point and reflect extreme values of an individual relative to other individuals. However, in longitudinal datasets, implausible values may also occur within an individual with repeated measurements, that is, one of the repeated measurements is temporally far distant from the previous and/or subsequent measurements. No established cut-off values or rigid mathematical definition exists of what constitutes a biologically implausible value either between or within individuals. Hence, determining whether or not an observation is biologically implausible has subjective components. There are two options to deal with biologically implausible values. The first is to accept that they are a genuine part of the outcome of the study, and the second is to delete these values from the dataset. It is currently unclear to what extent implausible values affect the

assessment of treatment effects. In METEOR, the percentage of biologically implausible CIMT values ranged from 0.6% to 9.7%, depending on the definition used. Across all definitions, removal of biologically implausible CIMT values marginally reduced standard errors and did not change the primary outcome. Given the relative subjectivity involved in defining biologically implausible CIMT values, removal of data should be discouraged in situations in which there is no immediate concern about the plausibility of the data.[161]

Imputation needed or not?

Missing endpoint data are a common and severe problem in clinical trials in which the endpoint is repeatedly measured over time. Missing data may lead to bias in the point estimates or may affect precision. Several techniques have been described to deal with the impact of missing data. Multiple imputation (MI) has shown to be the preferred method for incomplete data situations where information on determinants or outcomes is missing. We empirically showed that MI of missing endpoint data prior to linear effects model analyses does not increase precision in the estimated rate of change in the endpoint.[162] Hence, MI had no added value in this setting, and standard LME modeling remains the method of choice.

Batch reading or not?

In CIMT trials, carotid ultrasound scans are collected in central core laboratories (specialized vascular imaging centers) where CIMT is measured in a later stage. Typically, there are two approaches to read CIMT from images: Random continuous readings (nonbatch) and batch readings.[154] In the nonbatch approach, CIMT measurements are performed continuously over the course of the study, by randomly allocating a reader to a scan that is received at the core laboratory. In batch reading, one reader reads all the scans of a certain participant in a short time period after collection of the last scan. A logistic advantage of nonbatch reading is efficiency and short lag time between data availability and completion of the trial. A disadvantage of nonbatch reading, however, may be the temporal component. In studies that last several years between the first CIMT measurements and the last CIMT measurements, theoretically a drift may occur in the estimates of the rate of change, due to change over time in measuring habits of reading personnel of the core laboratory. Drift may affect rates of change in theory. Drift should not affect treatment effects, as readers are blinded for assignment of the intervention, and thus potential drift is likely to affect both treatment arms and thereby the estimated difference between the treatment arms should remain equal. In batch reading, all images of one individual are collected at the end of the trial and CIMT is quantified from all images in a short time window by one "reader." Empirical data on this issue is, however, scarce.[132]

Summary

Advances in the field of carotid ultrasound have been incremental, resulting in a steady decrease in measurement variability. Improvements in edge detection algorithms point toward increasing automation of CIMT measurements. The major advantage of CIMT is that it is completely noninvasive and can be repeated as often as required. It provides a continuous measure since all subjects have a measurable carotid wall. It is also relatively inexpensive to perform, and the technology is widely available. A graded relation between raising LDL cholesterol and increased CIMT is apparent. Increased CIMT has been shown consistently to relate the atherosclerotic abnormalities elsewhere in the arterial system. Moreover, increased CIMT predicts future vascular events in both populations from Caucasian ancestry and those from Asian ancestry. Furthermore, lipid-lowering therapy has been shown to affect CIMT progression within 12–18 months in properly designed trials with results congruent with clinical events trials. In conclusion, when one wants to evaluate the effect of a pharmaceutical intervention that is to be expected to beneficially affect atherosclerosis progression and to reduce CV event risk, the use of CIMT measurements over time is a valid, suitable, and evidence-based choice.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

Dr. Bots previously received study grants for studies on carotid intima-media thickness and/or honoraria for professional input regarding issues on carotid intima-media thickness from Astra-Zeneca, Icelandic Heart Foundation, Organon, Pfizer, Dutch Foundation, Netherlands Organisation for Health Research and Development, Servier and Unilever. Dr. Bots runs the Vascular Imaging Center, a core laboratory for the quantification of noninvasively assessed atherosclerosis in observational and intervention studies. Mr. Evans has received honoraria, consulting fees and grant support for professional input on CIMT issues from Astra-Zeneca, Organon, and Pfizer.

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