Carotid Intima-Media Thickness Measurements in Intervention Studies

Design Options, Progression Rates, and Sample Size Considerations: A Point of View

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Background—Carotid intima-media thickness (CIMT) measurements are currently widely used in randomized controlled trials (RCTs) to study the efficacy of interventions. In designing a RCT with CIMT as a primary outcome, several ultrasound options may be considered. We discuss the various options and provide a pooled estimate of CIMT progression. In addition, we quantify the effect of these choices on the sample size for a RCT.

Summary of Comment—To estimate the average CIMT progression rate, we performed a pooled analysis using CIMT progression rates of control groups from published RCTs. The pros and cons of the following ultrasound options are discussed: which arterial segments may be studied; whether near and far wall CIMT measurements should be performed; whether a single image (1 angle of interrogation) or multiple images (more angles of interrogation) should be used; whether a manual or an automated edge detection reading system should be used; and whether images should be read in a random fashion or in batches. The pooled analysis showed an annual rate of change in mean common CIMT of 0.0147 mm (95% CI, 0.0122 to 0.0173) and in mean maximum CIMT of 0.0176 mm (95% CI, 0.0149 to 0.0203).

Conclusions—Given the current evidence together with our experience with recently developed ultrasound protocols, we favor the use of mean maximum CIMT rather than mean common CIMT as the primary outcome measure in RCTs designed to evaluate the efficacy of pharmacological and nonpharmacological interventions in carotid artery atherosclerosis. (Stroke. 2003;34:2985-2994.)

Key Words: atherosclerosis ▪ carotid arteries ▪ intima-media thickness ▪ preventive medicine ▪ randomized controlled trials

Carotid intima-media thickness (CIMT) is widely used in observational studies to determine determinants and consequences of atherosclerosis.1–11 Several studies have shown that increased CIMT confers risk of future coronary heart disease and stroke,12–18 although some indicated no increased risk.19 In several studies CIMT was related to absolute risks of cardiovascular disease, as estimated by available risk functions.5,20,21 CIMT measurements are currently used in randomized controlled trials (RCTs) to evaluate the efficacy of interventions.11,22–52 In these trials, CIMT is used as an alternative end point (surrogate) for cardiovascular morbidity and mortality on the premise that change in CIMT reflects change in risk of cardiovascular disease. The main advantage of using CIMT in a trial as an outcome variable over morbidity and mortality is the considerable reduction in sample size and possibly in duration of follow-up.

When a randomized intervention study with CIMT as a primary outcome measure is designed, a number of features may have considerable effects on the conduct and size of the study. These include, in particular, the choice of the primary outcome CIMT measure (segments, near/far wall, angles of interrogation), reproducibility of CIMT measurement, expected CIMT progression rate, and expected effect of the intervention on the progression rate. At present, carotid ultrasound protocols differ considerably across studies. Some trials have reported change in mean common CIMT, others have reported change in overall mean maximum CIMT, ie, mean of the maximum thickness of 12 carotid segments, whereas others have reported progression rates for the common, bifurcation, and internal carotid artery separately. In some studies the CIMT outcome measurement was based on far wall measurements only, whereas in others near and far wall measurements were combined. Furthermore, from the published literature it is apparent that estimates of annual progression of CIMT tend to vary across trials, reflecting both differences in CIMT measures and differences in baseline risk between studies. The choice of which CIMT measurement is used...
as primary outcome may therefore have a considerable impact on the final sample size estimation.

We sought to discuss these ultrasound options and provide a pooled estimate of CIMT progression. In addition, we quantified the effect of these choices in terms of sample sizes needed for a RCT.

**Methods**

**Carotid Ultrasound Protocol**

To support some of our arguments by using quantitative examples, we used, apart from the published literature, baseline CIMT data, ie, measurements obtained during screening and randomization visits, from the Osteoporosis Prevention and Arterial Effects of Tibolone (OPAL) trial.53 Duplicate carotid ultrasound examinations of the common carotid artery, carotid bifurcation, and internal carotid artery were performed at baseline. The OPAL study involved 6 centers in the United States and 5 centers in Europe. Two core CIMT laboratories—1 in the United States (G.W.E., W.A.R.) and 1 in the Netherlands (M.L.B., D.E.G.)—are responsible for the OPAL CIMT readings. The OPAL ultrasound protocol comprised assessment in a standardized manner of longitudinal B-mode images of 12 carotid segments (near and far wall of left and right common carotid artery, carotid bifurcation, and internal carotid artery). Images were selected at the optimal angle of interrogation, an anatomic landmark, and also at 60, 90, 120, 150, and 180 degrees marked on the Meijer’s Arc (Figure 1) when the right side was scanned and at 300, 270, 240, 210, and 180 degrees when the left side was scanned. The entire ultrasound examination was recorded on S-VHS videotape. A complete OPAL scan yields 52 images on which CIMT will be measured.

**Estimates of Annual CIMT Progression Rates**

The library database PUBMED was used to identify randomized RCTs on progression of CIMT until January 2002. We used headings that were combinations of carotid intima-media thickness, carotid intimal-medial thickness, randomized controlled trials, trials, carotid atherosclerosis progression, and atherosclerosis progression. In addition, references in the retrieved articles were checked and added when the initial search did not include these trials. For the assessment of CIMT progression rates, studies were excluded when they were not placebo controlled or when change in CIMT over time was not reported, eg, when only the differences in CIMT progression between the treatment and placebo groups were reported and not the group-specific estimates.49 When a RCT had >1 report on CIMT progression rates, we included the report with the longest follow-up time or when the SE of the CIMT change estimate was not given.43

Information that was retrieved from the articles included author, year of publication, type of intervention, mean age, sex, presence of cardiovascular disease, LDL and HDL levels, systolic and diastolic blood pressure levels, smoking, diabetes, hypertension, and whether a qualifying lesion was needed for enrollment. Numbers of patients in the control and treated groups were recorded as well as annual segment-specific progression CIMT rates with SE and/or SD. When in the publication 2-year change or 4-year change in CIMT was reported, we used the 2-year CIMT estimate and divided the estimate by 2, whereby the SE was left unchanged.

**Statistical Approach**

The CIMT progression rates of the control groups in the RCTs were pooled by averaging the estimates weighed for the inverse variance \[1/(SE)^2\]. The study with largest size contributed most to the overall CIMT progression rate. In addition, separate progression rates were estimated for lipid intervention trials and for trials involving subjects with established coronary heart disease. An estimate of the SD of the pooled progression rate was obtained by using the median of the SDs reported in the trials.

For evaluating the effects of the various CIMT variables on the sample-size calculation for a trial, we used a pooled common CIMT progression rate of 0.0147 mm/y (0.044 mm/3 y) with the corresponding SD. For the mean maximum progression rates, we used an estimate of 0.0176 mm/y (0.053 mm/3 y). The sample sizes were calculated with the use of a 2-sided α and a 90% power for a period of 2 and 3 years. Dropouts were not taken into account.
Results

Primary Outcome Variable

Issues in the choice of the primary outcome variable relate to the following: (1) Which arterial segments should be examined (common, bifurcation, internal, combinations)? (2) Should CIMT measurements be performed on the near and far walls of the B-mode image? (3) Should we use 1 optimal (clearest) image or several images (Meijer’s Arc)?

Mean Common Versus Mean Maximum CIMT

Some trials used change in mean common CIMT as primary outcome, whereas others used change in overall mean maximum CIMT, ie, mean of the maximum thickness of 12 sites, as primary outcome (Tables 1 and 2). In general, the aim of a RCT with CIMT as an outcome is to measure the effect of the intervention in slowing down or reversing progression of atherosclerosis and reducing cardiovascular risk. The CIMT measure as such is used as a marker of change in atherosclerosis elsewhere in the arterial system and of change in cardiovascular risk. It is not the change in CIMT per se that leads to reduction of coronary heart disease or stroke incidence, and therefore one should choose the “best” marker reflecting atherosclerosis and/or cardiovascular risk.

One argument generally used to favor the use of common CIMT as primary outcome rather than mean maximum CIMT is the observation that common CIMT can be assessed in a more reproducible manner than mean maximum CIMT.11,55 Certainly, the earlier ultrasound protocols used in large population-based studies indicated that CIMT reproducibility was less for the bifurcation and internal carotid segments. 23 However, more recent studies indicated a much better and sometimes even equal reproducibility in mean maximum CIMT estimates compared with common CIMT.

A second argument to use common CIMT rather than the mean maximum CIMT approach is that common CIMT data collection is nearly always complete, whereas measurements from the bifurcation and internal carotid segments have more missing values.23,24 Indeed, the latter segments have been shown to be more troublesome to assess. In particular, visualization of the near wall of the bifurcation and internal carotid artery appears to be problematic. However, with the OPAL ultrasound protocol, we have managed to obtain

<table>
<thead>
<tr>
<th>Publication Year</th>
<th>Acronym</th>
<th>Ref</th>
<th>Interventions</th>
<th>Subjects in Study</th>
<th>Age, y</th>
<th>Men, %</th>
<th>CHD, %</th>
<th>Qualifying Lesion</th>
<th>LDL, mmol/L</th>
<th>HDL, mmol/L</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
<th>Diabetes, %</th>
<th>Smoking, %</th>
<th>Hypertension, %</th>
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<td>22</td>
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<td>78</td>
<td>51</td>
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<td>0</td>
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<td>1.16</td>
<td></td>
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<td>1.20/1.53</td>
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<td>11.9</td>
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<td></td>
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<td></td>
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<td>CAUS</td>
<td>35</td>
<td>Pravastatin</td>
<td>305</td>
<td>55.3</td>
<td>53</td>
<td>0</td>
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<td>4.69</td>
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<td>0.94</td>
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<td>ROMEO</td>
<td>40</td>
<td>17-beta E2, CEE-N</td>
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<td>47.2</td>
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<td>3.90</td>
<td>1.5</td>
<td>115.9</td>
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<td>43</td>
<td>Ramipril</td>
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<td>61</td>
<td>82</td>
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<td>79</td>
<td>9</td>
<td>15</td>
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<td>49</td>
<td>17 beta e2</td>
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<td>1.74</td>
<td>144.6</td>
<td>85.1</td>
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<td>21.5</td>
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<td>Mean-max</td>
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<td>Fluvastatin/metoprolol</td>
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<td>46.2</td>
<td>3.5</td>
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<td>4.1</td>
<td>1.4</td>
<td>139.1</td>
<td>84.5</td>
<td>5</td>
<td>28.6</td>
<td>11.1</td>
<td>Mean fw cca</td>
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<td>ASAP</td>
<td>46</td>
<td>Atorvastatin vs simvastatin</td>
<td>325</td>
<td>48.5</td>
<td>26</td>
<td>No</td>
<td>8.1/8.2</td>
<td>1.06/1.24</td>
<td>130.5</td>
<td>79.1</td>
<td>1.8</td>
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<td>Mean fw cca, bif, ica</td>
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<tr>
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<td>SECURE</td>
<td>45</td>
<td>Ramipril</td>
<td>732</td>
<td>66.6</td>
<td>79</td>
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<td>No</td>
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<td>1.0</td>
<td>132</td>
<td>75</td>
<td>1.0</td>
<td>35</td>
<td>9</td>
<td>Mean-max</td>
</tr>
<tr>
<td>2005</td>
<td>PREVENT</td>
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<td>Amlodipine</td>
<td>825</td>
<td>79.9</td>
<td>100</td>
<td>No</td>
<td>3.64</td>
<td>1.20/1.42</td>
<td>128.8</td>
<td>78.8</td>
<td>26.7</td>
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<td>2006</td>
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<td>50</td>
<td>Nifedipine vs amio-skidate</td>
<td>439</td>
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<td>58</td>
<td>18</td>
<td>No</td>
<td>160</td>
<td>93</td>
<td>30</td>
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<tr>
<td>2007</td>
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<td>46</td>
<td>Amlodipine vs isonipril in FH patients</td>
<td>325</td>
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<td>59.4</td>
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<td>No</td>
<td>5.65</td>
<td>1.4</td>
<td>165</td>
<td>100</td>
<td>0</td>
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<td>100</td>
<td>Fw cca</td>
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TABLE 2. Estimates of Annual Rate of Change in CIMT (mm) Among Control Groups From Randomized Placebo-Controlled Trials

<table>
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<tr>
<th>Publication Year</th>
<th>Acronym</th>
<th>Ref.</th>
<th>No. of Controls</th>
<th>CCA, mm</th>
<th>CCA SD</th>
<th>BIF, mm</th>
<th>BIF SD</th>
<th>Mean-Max, mm</th>
<th>Mean-Max SD</th>
<th>Comments</th>
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<td>1993</td>
<td>CLAS</td>
<td>22</td>
<td>39</td>
<td>0.02</td>
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<td>na</td>
<td>na</td>
<td>Mean fw cca</td>
<td></td>
<td></td>
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<tr>
<td>1994</td>
<td>ACAPS</td>
<td>24</td>
<td>230</td>
<td>ng</td>
<td>na</td>
<td>0.006</td>
<td>0.0455</td>
<td>Mean-max (12 segments)</td>
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<td>28</td>
<td>76</td>
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<td>0.0497</td>
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<td>0.1325</td>
<td>0.0675</td>
<td>0.0689</td>
<td>All segments given</td>
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<td>1995</td>
<td>REGRESS</td>
<td>29</td>
<td>127</td>
<td>-0.015</td>
<td>0.11</td>
<td>ng</td>
<td>ng</td>
<td>Mean fw cca</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>Phorea</td>
<td>49</td>
<td>93</td>
<td>ng</td>
<td>na</td>
<td>0.02</td>
<td>0.05</td>
<td>Mean-max 12 segments</td>
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<td>60</td>
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<tr>
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<td>60</td>
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<td>1995</td>
<td>KAPS</td>
<td>25</td>
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<td>0.0401</td>
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<td>45</td>
<td>227</td>
<td>ng</td>
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<td>Mean-max 12 segments</td>
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<td>42</td>
<td>408</td>
<td>0.0038</td>
<td>0.242</td>
<td>0.0177</td>
<td>0.4484</td>
<td>0.011</td>
<td>0.242</td>
<td>All segments given</td>
</tr>
</tbody>
</table>

Ref indicates reference; na, not assessed; ng, not given in the report; cca, common carotid artery; bif, carotid bifurcation; fw, far wall.

Reliable and reproducible CIMT information on the various segments of the carotid artery, without having a considerable proportion of missing data. Of the 864 OPAL participants, CIMT data were available in >99.5% of the screening and randomization visits (n = 1728) on all segments except the right bifurcation near wall (99.0%), left internal far wall (98.1%), right internal far wall (98.3%), left internal near wall (92.9%), and right internal near wall (88.6%). Overall, CIMT measurement data were available for all 12 carotid segments in 92.9%, and for 11 carotid segments in 98.1%, right internal near wall (98.3%), left internal far wall (98.3%), and for 9 carotid segments in 99.0%. CIMT data from <8 segments were observed in only 0.4% of the baseline scans. Similar observations have recently been made by others. The main underlying problem is that missing data may lead to bias in the CIMT progression rates. From the OPAL data, it is evident that only a small proportion of the information is missing. Furthermore, current statistical methods appear to be capable of overcoming the missing data issue (missing at random) by using maximum likelihood techniques, although, of course, complete data are preferable.

A third argument for using common CIMT rather than mean maximum CIMT is that common CIMT has shown to predict future cardiovascular events as well as mean maximum CIMT. Indeed, the relative risks related to an increase in CIMT did not differ significantly between segments, although one may wonder whether these studies were powered sufficiently to detect such a difference. Longitudinal findings from the Atherosclerosis Risk in Communities (ARIC) Study showed that the magnitude of the association of carotid bifurcation and internal CIMT measurements with incident coronary heart disease was weaker than for common CIMT. The differences, however, were not statistically significant.

Finally, one should realize that a common CIMT measurement will take less time in image acquisition during the ultrasound examination and in the reading phase than a full assessment of all carotid segments, which is needed to estimate mean maximum CIMT. Although this affects mainly time constraints and budgetary constraints, it may serve as an argument to use common CIMT rather than mean maximum CIMT.
Near Wall Versus Near and Far Wall CIMT Measurements

Several studies in which the ultrasound measurements were compared with histology have indicated that the ultrasonographic far wall CIMT measurements reflect the true thickness. The CIMT measurement of the near wall of the carotid artery is at best an approximation of the true wall CIMT. Moreover, the precision of the estimate of the near wall CIMT depends on the gain setting. The near wall findings in the validation studies have led to intensive discussion of whether near wall intima-media measurements should be performed at all. At present, there are 2 strong and opposing views: (1) near wall measurements should not be used because they do not reflect the true thickness and therefore are invalid; and (2) near wall measurements are of value and should be used. The latter view recognizes and respects the view that the near wall measurement is only an approximation of its anatomic substrate, but there is substantial evidence to argue in favor of the use of near wall CIMT measurements to further improve overall precision of the estimates.

The reproducibility of near wall CIMT measurements is similar to that reported for far wall CIMT measurements. In addition, cross-sectional analyses of data from the Rotterdam Study have indicated that the association between near wall CIMT and prevalent cardiovascular disease is as strong and precise as the association found for the far wall. Combining information on near wall and far wall common CIMT into 1 IMT estimate (average of 4 sites) provided the strongest association with cardiovascular disease in this study. Similar results were obtained for the association with lower extremity arterial disease. Longitudinal results from the Rotterdam Study supported these cross-sectional findings: the association between near wall CIMT and stroke or myocardial infarction was as strong as that found for far wall CIMT. The combined near and far wall IMT showed the strongest association. Findings in 3 randomized, placebo-controlled intervention studies among subjects receiving placebo treatment indicated that the progression rate of near wall common CIMT was similar to that for far wall common CIMT. Importantly, combining information on both near and far walls yielded estimates of progression rates with higher precision, ie, smaller SEs. Finally, it has been shown that near wall CIMT measurement can be obtained in a considerable proportion of the participants with sufficient reproducibility. Therefore, measurement of near wall CIMT appears to yield valuable information and should not be discarded easily.

One should realize that in certain patient populations, ie, those with a very high prevalence of calcified plaques, near wall but also far wall CIMT measurements may be more difficult to obtain because of acoustic shadowing that complicates the ultrasound images and the visibility of the interfaces.

Optimal B-Mode Versus Multiple Images (Meijer’s Arc)

Current CIMT ultrasound protocols differ in that some use only a single optimal B-mode image, ie, an image in which the interfaces are most clear, some use only B-mode images showing the thickest CIMT, some use multiple optimal B-mode images, and some use B-mode images obtained from various angles of interrogation. Although associations of established risk factors with CIMT appear to be present in most studies, irrespective of the ultrasound protocol used, there has been no formal comparison of these approaches in terms of reproducibility, relation to risk factors, or future disease. This information is lacking because in 1 study only 1 ultrasound protocol is generally used. With the final OPAL data, we will be able to address these issues in a quantitative manner in the near future.

In general, the average of CIMT measurements obtained from several images, not necessarily from different angles, will tend to reduce measurement error and increase precision. This limits the ability to compare the approach of using several images obtained from the same angle with the multiple angle approach, as used in the OPAL study. In addition, it is well known that atherosclerosis tends to develop in an asymmetrical manner. When the interest is in assessment of atherosclerosis, standardized imaging from different angles most likely increases the likelihood of capturing more relevant information.

Design Options in Number of Ultrasound Examinations

In most of the currently published RCTs, follow-up scans were performed every 6 months after the randomization period. Some RCTs were designed with baseline and end-of-study scans only. In a number of recently finished trials, duplicate baseline and end-of-study ultrasound examinations were performed combined with ultrasound examinations at 6-month intervals. In general, the use of duplicate baseline and end-of-study assessments as well as assessment at regular intervals is assumed to increase precision. However, at present, quantification of the increase in precision of the CIMT outcome measurement with the use of the aforementioned options has not been done.

Compared with the use of only baseline and end-of-study assessments, a clear benefit of performing regular ultrasound examinations is that when participants drop out, relatively recent data are available on CIMT, and thus the data from these participants remain evaluable in the intention-to-treat analysis. Since dropout rates vary from 10% to 30% depending on the type of intervention, this should be considered. An alternative option, which may result in a considerably less loss of data, is to have ultrasound examinations performed on all participants who leave the study prematurely whenever possible. Another advantage of regular ultrasound examinations is that the skills of the sonographer remain up-to-date.

Design Options in Offline Reading

In most of the RCTs, images were acquired in study centers, stored on videotape or digitally, and then shipped to 1 or 2 core laboratories for offline reading. The use of a core laboratory for offline reading seems important to keep measurement error minimal in the CIMT readings. In general, measurement error in CIMT measurements can be attributed to changes over time in ultrasound equipment performance, within-participant differences, within- and between-sonographer differences, and within- and between-reader differences. The latter 2 in particular are subject to modification. Several studies indicated that the variability in CIMT measurements due to sonographer is larger than that attribut-
able to the reading process, although the precise effect is difficult to separate since scanning and reading are very closely related. A recent analysis from the European Lacidipine Study on Atherosclerosis (ELSA) Study, a multicenter (23 sites, 50 sonographers, 9 readers) RCT, showed the highest intraclass correlation coefficient ($r=0.89$) when the sonographer and the reader were the same at both visits. Note that design options in offline readings deal primarily with limiting the measurement error in the CIMT measurement.

**Random Versus Batch Readings**

There are 2 reading approaches: random readings and batch readings. In the random reading approach, when the videotape or digitally stored images arrive at the core laboratory, a reader is randomly allocated to read that particular ultrasound examination. Batch reading implies that the same reader will read all scans of a certain participant. Both approaches have been applied in randomized trials. Batch readings were used in the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) and the INSIGHT studies, whereas random readings occurred in other trials. In theory, batch readings would tend to reduce measurement variability in the change over time CIMT estimates. However, a quantification of gain in precision between the random and batch reading approaches has not been performed because no trials have used both approaches simultaneously. Variability due to sonographer and possibly reading drift remains present in both approaches and therefore needs to be addressed. A slight drawback of batch readings compared with random readings may be that one has to wait for readings of the main study until a participant has completed the study. If batch reading is used, the core laboratory should still go through the performed ultrasound examination for quality assurance/quality control considerations.

In batch reading in particular, the issue of “blinding” the reader to the ultrasound scan sequence to prevent bias that might occur in the progression rates is a topic of discussion. However, our current view is that blinding of the reader regarding the sequence of the ultrasound scan is not needed. The disadvantage of removing all identifiable information from the images when starting the reading process is that such information is usually used to ensure that this particular image belongs to this participant at this visit. The lack of information may increase administrative errors. Furthermore, readers working in a core laboratory tend to read a large number of ultrasound examinations. Since most carotid ultrasound examinations look similar, the readers do not actively recall the thickness of an earlier scan that they might have read at a defined time. Additionally, when the outcome variable is based on averaged CIMT readings from various segments, recall is not an issue. However, at least the general rule that the reader is blinded to the assigned treatment should apply. This would ensure that any effects of possible recollection of CIMT values are randomly distributed across treatment groups.

**Manual Versus Automated Edge Detection**

In some trials automated edge detection programs have been used, whereas in others manual tracings of the ultrasound interfaces were used. A number of automated edge detection programs are available. Most of these automated edge detection programs have been applied for reading of the far wall of the common carotid artery, whereas the near wall was not considered. The approach of Liang and coworkers allows for near and far wall measurements of the common carotid artery and far wall measurements of the carotid bifurcation and internal carotid artery. The difference between automated edge detection and manual reading is the actual manual drawing of the lines on the interfaces. The variability related to site selection on the ultrasound image regarding the location of measurements and the area of the arterial segment that should be measured is similar in both approaches. The main potential advantage of automated edge detection programs is that they may reduce variability in CIMT readings as a result of reduction in the differences between readers and elimination of change in reading behavior over time (reader drift). The effect of automated edge detection on the extent of reduction in measurement variability depends on the contribution of sonographers and readers to the total variability. A number of studies have indicated that differences between sonographers have a relatively larger effect on the CIMT measurements than differences between readers. Indeed, reproducibility study results from a large, single-center, population-based study in which this technique was used were similar to those reported from other studies in which CIMT reading was performed manually. A formal quantification of the extent of reduction in measurement error with the use of either approach has not been done.

In general, when ultrasound images show clear interfaces (Figure 2), automated edge detection programs work very well, whereas when the interfaces on the ultrasound images are less clear (Figure 3), the automated edge detection program needs to be manually overridden, thereby eliminating the advantages of the use of automated edge detection.

**Progression Estimates of CIMT**

Table 1 shows the general characteristics of the current published RCTs that use CIMT progression as an outcome.
Study populations vary considerably across trials, mostly because of the intervention studied, i.e., lipid-lowering regimens, estrogen-progestin therapy, and blood pressure–lowering regimens. In Table 2, rates of change in common CIMT and mean maximum CIMT as observed in the control groups of these trials are given with corresponding SD. From the table it is evident that rates of change in CIMT differ considerably across studies, even within groups using the same type of population. The overall weighed rate of change in mean common CIMT based on data from 13 studies was 0.0147 mm/y (95% CI, 0.0122 to 0.0173), with a median SD of 0.053. For the rate of change in mean maximum CIMT based on data from 7 studies, the estimate was 0.0176 mm/y (95% CI, 0.0149 to 0.0203), with a median SD of 0.050.

For subjects with previous coronary heart disease, estimates were 0.0170 mm/y (95% CI, 0.0114 to 0.0227) for mean common CIMT and 0.0258 mm/y (95% CI, 0.0209 to 0.0307) for mean maximum CIMT, on the basis of data from 6 and 3 studies, respectively. On the basis of data from 9 lipid-lowering trials, the common CIMT estimate was 0.0147 mm/y (95% CI, 0.0115 to 0.0179). The mean maximum CIMT estimate was 0.0159 mm/y (95% CI, 0.0125 to 0.0192) on the basis of data from 4 trials.

**Sample Size Considerations**

From Table 2, it is clear that rates of change in CIMT differ considerably across studies and populations. The sample size consideration depends heavily on the magnitude of the rate of change in CIMT, its precision, and the assumed effectiveness of the intervention. Table 3 provides sample size calculations based on the pooled CIMT rates, assuming different effects, with a 2-sided α and a power of 90% and no dropouts. The number of patients needed in each arm of a parallel RCT varies for the common CIMT from 762 (2 years, 30% effect) to 30 (3 years, 100% effect). Similarly, for the mean maximum CIMT, the number of patients ranges from 468 to 19.

### Discussion

Over the past years, a large number of trials have been performed in which CIMT was used as an alternative end point for cardiovascular morbidity and mortality to study the efficacy of certain interventions. The main advantage of using CIMT as an end point in a trial over morbidity and mortality as end points is the considerable reduction in sample size and possibly shorter duration of follow-up. We addressed a number of topics important in the design and conduct of such an intervention study. In addition, we provided an estimate of CIMT change over time based on pooling of data from the published literature.

One of the premises of a CIMT trial is that the CIMT reflects atherosclerosis and cardiovascular risk. Atherosclerosis is viewed as a disorder that is restricted primarily, in its early stages, to the intimal layer of the arterial vessel wall, and ultrasound imaging cannot discriminate between the intimal layer and the medial layer of the vessel wall. Thus, an increased common CIMT may reflect either increased intimal thickening, increased thickening of the medial layer, or a combination of both. Some studies have reported an association between left ventricular mass and increased common CIMT.74–76 These results may suggest that the process underlying increased CIMT may to some extent be hypertrophy of the medial layer. Additionally, some have suggested that CIMT is a result of adaptive thickening in response to changes in transmural pressure, shear stress, and lumen diameter.77,78 This theory would call for additionally measur-

<table>
<thead>
<tr>
<th>CIMT Outcome</th>
<th>Intervention Duration</th>
<th>Estimated Change in mm (SD)</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean common</td>
<td>2 y</td>
<td>0.0294 mm (0.053)</td>
<td>762</td>
<td>424</td>
<td>273</td>
<td>191</td>
<td>139</td>
<td>107</td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>3 y</td>
<td>0.0441 mm (0.053)</td>
<td>339</td>
<td>191</td>
<td>122</td>
<td>85</td>
<td>62</td>
<td>48</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>Mean-max</td>
<td>2 y</td>
<td>0.0352 mm (0.050)</td>
<td>468</td>
<td>264</td>
<td>170</td>
<td>118</td>
<td>87</td>
<td>66</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>3 y</td>
<td>0.0528 mm (0.050)</td>
<td>210</td>
<td>118</td>
<td>75</td>
<td>52</td>
<td>38</td>
<td>30</td>
<td>23</td>
<td>19</td>
</tr>
</tbody>
</table>

Based on a 2-sided alpha of 0.05, a power of 90%, and no dropouts.
ing lumen diameter in a RCT. When the focus in studies is the process of carotid atherosclerosis per se, one should circumferentially evaluate the entire carotid artery. Examination of only the common carotid artery would not suffice. In view of these notions, one should realize that the CIMT measure as such is used as a marker of change in atherosclerosis elsewhere in the arterial system and of change in cardiovascular risk. It is not the change in CIMT per se that leads to prevention of coronary heart disease or stroke, and therefore one should choose the marker that best reflects atherosclerosis and/or cardiovascular risk. In addition, numerous population-based and hospital-based studies have shown graded relations between elevated levels of risk factors and increased CIMT. Moreover, increased CIMT has been related to atherosclerosis in abdominal aorta,\textsuperscript{79} atherosclerosis in arteries of the lower extremities,\textsuperscript{80–82} and coronary calcium assessed by electron beam CT.\textsuperscript{83–85} Studies of the association between CIMT and coronary atherosclerosis, as assessed by coronary angiography, show generally modest positive associations.\textsuperscript{5,29,86–94} Data on the relation of change in CIMT and risk of future events are limited at present.\textsuperscript{14}

Atherosclerosis can be viewed as a gradual process from thickening to plaques. This review focused on CIMT and not on assessment of carotid plaques. This is because change in CIMT is established as a valid end point in RCTs investigating efficacy of interventions. In addition, the definition of plaques is difficult and varies considerably across studies. Plaques have been defined on the basis of visual inspection, an arbitrary level of CIMT, or presence of acoustic shadowing. RCTs investigating change in plaques are limited. It should be noted that when mean maximum CIMT measurement is used as outcome, generally the thickness measurements that are taken at sites of a plaque are included in that mean maximum estimate.

We attempted to address in a balanced manner several important issues in the design phase of a RCT with CIMT as the primary or secondary outcome. Since the atherosclerotic process is a focal abnormality, we believe that circumferential scanning of all segments of the carotid artery with the use of Meijer’s Arc provides a better estimate of the extent and severity of carotid atherosclerosis in an individual. Several studies showed that mean maximum CIMT measurements can be obtained in practically all subjects in a reliable and reproducible manner. Therefore, we propose to use mean maximum CIMT as a primary CIMT outcome measurement in RCTs, with segment-specific CIMT measurements as secondary outcomes. We acknowledge that such an approach may require more time for image acquisition during the ultrasound examination and in the reading phase compared with common CIMT measurements. This will mainly affect time constraints and budgetary constraints. Our point of view is based on the interpretation of published material and on the experience of the authors. We are well aware that other views, also based on interpretation of the literature and personal experiences, are present that certainly deserve merit. The present article is meant to stimulate further discussion on this issue, with possibly the ultimate goal of standardization in the near future.

In general, the use of a core laboratory for offline reading seems important to minimize measurement error in CIMT readings. To our knowledge, the studies published thus far have had CIMT readings performed at 1 core laboratory in 1 location in 1 country. In the OPAL study, 2 core laboratories are operating, 1 in the United States and 1 in Europe, using uniform reading equipment, certification procedures, and reading protocols. There is intense contact between the reading centers. As such, the 2 core laboratories can be viewed as 1 large reading center with 2 locations. A slight negative factor is that between-reading center reproducibility studies need to be planned before the start of the trial as an additional quality assurance/quality control aspect. The benefits of this approach are that each reading center is responsible for continent-specific training, certifications, and quality assurance/quality control aspects as well as readings.

In conclusion, weighing the pros and cons given the current evidence in the literature, together with our experience with recently developed ultrasound protocols, we favor the use of mean maximum CIMT over mean common CIMT as the primary outcome in RCTs that are designed to evaluate the efficacy of pharmacological and nonpharmacological interventions.

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Carotid Intima-Media Thickness Measurements in Intervention Studies: Design Options, Progression Rates, and Sample Size Considerations: A Point of View
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