

Extensive or Restricted Ultrasound Protocols to Measure Carotid Intima-Media Thickness: Analysis of Completeness Rates and Impact on Observed Rates of Change Over Time

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Background: Ultrasound protocols to measure carotid intima-media thickness (CIMT) vary considerably with regard to carotid sites and angles that are assessed. Measurements from the carotid bifurcation and internal carotid artery are thought to be affected by large numbers of missing data. Actual published quantification of completeness rates and the relation with cardiovascular risk factors, however, is scarce. Also, it is currently unknown whether extensive ultrasound protocols including assessment of the carotid bifurcation and internal carotid artery add information in detecting rate of change in CIMT induced by drug therapy. These issues were addressed in this study using data from Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin (METEOR).

Methods: In METEOR, carotid ultrasound examinations were performed twice before randomization, once each at 6, 12, and 18 months after randomization, and twice after 24 months of study treatment. B-mode ultrasound images were obtained from the near and far walls of the left and right common carotid artery, bifurcation, and internal carotid artery at five predefined angles. Completeness of CIMT data was assessed by carotid site and by angle. A site was considered complete when any of the five angles was measured. The relation between completeness at baseline and cardiovascular risk factors was assessed using logistic regression analyses. Ultrasound protocols with a reduced number of carotid sites and angles were retrospectively constructed, and differences in the rate of change in maximum CIMT between ultrasound protocols were compared.

Results: At each visit, CIMT measurements from all 12 carotid sites were available for >94% of the participants. Incompleteness was the highest for near wall of the internal carotid artery and for the extreme angles (60° and 300°). Of 12 risk factors examined, higher body mass index was related to incompleteness. Ultrasound protocols with a reduced number of angles resulted in similar estimates for the differences in rate of change in maximum CIMT. However, reductions in the number of sites gave results in the same direction but with different magnitudes and larger standard errors.

Conclusions: High levels of complete data can be obtained with extensive ultrasound protocols that include measurement from the carotid bifurcation and internal carotid artery. A high body mass index contributes to incompleteness of CIMT measurements. Extensive ultrasound protocols are required to obtain the highest precision to observe a treatment effect and to fully cover the degree of atherosclerotic burden. (*J Am Soc Echocardiogr* 2012;25:91-100.)

Keywords: Carotid intima-media thickness, Ultrasound protocols, Completeness rates, Trial design

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Abbreviations

BMI = Body mass index
CIMT = Carotid intima-media thickness
METEOR = Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin
RADIANCE = Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor

Carotid intima-media thickness (CIMT) is commonly used in observational studies to examine determinants and consequences of atherosclerosis.¹⁻⁵ In addition, changes in CIMT over time are increasingly being used in clinical trials as an alternative end point for cardiovascular morbidity and mortality to study the efficacy of pharmacologic interventions.⁶ The main advantage of the use of CIMT as a primary outcome rather than hard end points, such as cardiovascu-

lar morbidity and mortality, is the reduction in costs due to a smaller sample size and shorter duration of follow-up. This may result in earlier detection of the presence or absence of effects of drug therapies on atherosclerotic progression.⁷

At present, little uniformity exists on ultrasound protocols across studies. Some studies have used extensive protocols, including measurements from the near and far walls of the common carotid artery, carotid bifurcation, and internal carotid artery at multiple angles of interrogation,⁸⁻¹¹ whereas others have restricted their protocols by measuring only the far wall of the common carotid artery.¹²⁻¹⁴ The thickest sites of the carotid artery are typically found in the internal carotid artery and in the carotid bifurcation. Difficulties in visualizing these sites in general, and near wall sites in particular, are thought to give rise to large amounts of missing data. One of the main arguments to restrict ultrasound protocols to measurements of the far wall of common carotid artery is that common CIMT data collection is nearly always complete in this segment.⁷ However, data on the completeness of CIMT measurements are often not reported, and if reported, only overall completeness rates are provided.^{10,15-17} Also, cross-sectional observed differences in absolute thickness across carotid segments do not necessarily result in a difference in observed rate of change over time. A thorough evaluation of whether observed rates of change in CIMT differ across ultrasound protocols that vary in the numbers of segments, sites, and angles assessed is lacking.

In contrast to the general view in the field, a recent analysis demonstrated that high levels of complete CIMT data could be obtained with extensive ultrasound protocols that also included measurements of the near wall of the carotid bifurcation and internal carotid artery.¹⁸ The investigators found that body mass index (BMI) and waist circumference were the main predictors of incomplete data.¹⁸

Because there is still no agreement on the optimal ultrasound protocol in terms of high completeness rates and the evidence on this issue is limited, we studied the completeness of CIMT data and its relation with cardiovascular risk factors using data from a randomized controlled trial that used an extensive ultrasound protocol. Because completeness alone should not be the main argument to use an extensive or a restricted ultrasound protocol, we subsequently studied the differences between extensive and restricted ultrasound protocols in relation to rate of change in CIMT.

The rationale, design, and main outcomes of this study have been described in detail elsewhere.^{10,19} Briefly, METEOR was a randomized, double-blind, placebo-controlled trial among 984 individuals at low risk for cardiovascular disease on the basis of 10-year Framingham risk of <10% but with modest increases in CIMT as evidenced by at least one maximum CIMT measurement ≥ 1.2 mm and no measurement ≥ 3.5 mm from two separate ultrasound examinations in any of the 12 carotid segments assessed (described below). The main objective of METEOR was to assess the impact of rosuvastatin 40 mg/day versus placebo on the rate of change in CIMT over 2 years of follow-up.

B-Mode Ultrasound Method

Ultrasound examinations were performed twice before randomization; once each at 6, 12, and 18 months after randomization; and then twice at the end of 24 months of study treatment. At each visit, ultrasound images were obtained from six well-defined arterial segments from both the left and right carotid artery (Figure 1), as detailed elsewhere.¹⁹ These segments were defined as the near and far walls of the common carotid artery extending from 10 to 20 mm proximal to the tip of the flow divider; the near and far walls of the carotid bifurcation as assessed from the tip of the flow divider, extending 10 mm proximal to the tip of the flow divider; and the near and far walls of the internal carotid artery as assessed in the 10 mm distal to the tip of the flow divider. There was no minimal acceptable length for a measurement, and a measurement was accepted as long as the reader had enough confidence to mark the CIMT. In METEOR, all images were measured in end-diastole at the top of the R wave of the electrocardiogram. The head of each participant was rotated 45° to the other side to better expose each carotid artery for interrogation. The Meijer carotid arc was used to image the artery at five prespecified angles in steps of 30° (from 60° to 180° on the right carotid artery and from 300° to 180° on the left carotid artery). This resulted in a maximum of 60 sets of CIMT measurements that could be provided at each examination.

The equipment used in METEOR for CIMT imaging was the Acuson Sequoia 512, Acuson Sequoia 256, and SONOLINE Antares (all Siemens Medical Solutions USA, Inc., Mountain View, CA) and the HDI 5000 (Phillips Medical Systems, Andover, MA). These devices all have electrocardiographic gating, and all used high-resolution linear-array probes around 7.5 MHz.

These systems were all approved by a quality control center, and the performance of these systems was monitored using phantoms. The real-time captured images were all stored on S-VHS videotape and were sent to one of two specialized ultrasound reading centers in Europe (University Medical Centre, Utrecht, The Netherlands) and the United States (Wake Forest University School of Medicine, Winston-Salem, NC) for CIMT measurement. All images were digitized and read at these two at reading centers.

All ultrasound scans were manually read with Image Pro software (Microsoft Corporation, Redmond, WA). Images were read by 16 readers who completed a uniform training program that ensured standardized settings across reading stations and core laboratories. Readers traced trailing edges on the near wall boundaries and leading edges on the far wall boundaries and were free to set as many anchors as needed to trace the interface, with straight lines connecting the anchor points. All images were read in a blinded batch fashion after each participant had finished. A batch consisted of all images collected from a single participant and was read by a single reader over an interval of a few days with visits arranged in random order to minimize

METHODS

Study Population

In this post hoc analysis, data from the Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin (METEOR) trial.

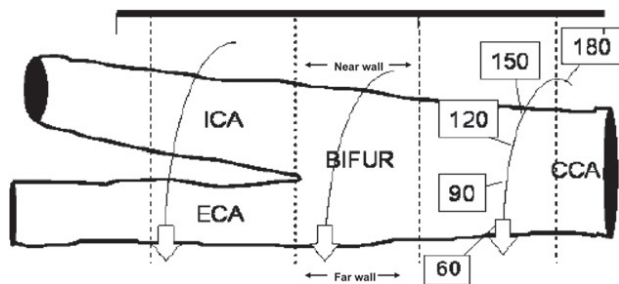


Figure 1 Graphical representation of circumferential assessment of the artery sites. *BIFUR*, Carotid bifurcation; *CCA*, common carotid artery; *ECA*, external carotid artery; *ICA*, internal carotid artery.

the impact of between-reader variability and temporal drift on estimates of change in CIMT within participants.

Laboratory Analyses

As previously described, blood samples were taken for analysis of serum lipids, lipoproteins, and C-reactive protein.¹⁰ The samples were sent immediately for analysis to one of two central standardized laboratories in Europe (Covance Central Laboratory Services, Geneva, Switzerland) and in the United States (Covance Central Laboratory Services, Indianapolis, IN). Baseline samples were used for the present analysis.

Variations in Ultrasound Protocols

We simulated eight different ultrasound protocols that may be considered once designing a CIMT trial by selectively excluding up to 83% of the specific carotid segments and carotid walls. The most extensive ultrasound protocol was the original METEOR protocol, which included assessment of the near and far walls of the left and right common carotid artery, carotid bifurcation, and internal carotid artery. In the most restricted ultrasound protocol, only measurements from the far wall of the left and right carotid artery were performed. Each of the eight ultrasound protocols was applied to settings in which five, three, or one circumferential carotid angle was measured. Angle-specific measurements in ultrasound protocols with assessment of five carotid angles were performed at 60°, 90°, 120°, 150°, and 180° on the right carotid artery and for the left carotid artery at 300°, 270°, 240°, 210°, and 180°. Ultrasound protocols with three circumferential CIMT measurements for each carotid site were performed at 90°, 120°, 150° for the right carotid artery and at 270°, 240°, and 210° for the left carotid artery. CIMT measurements were performed at 120° and 240° of the right and left carotid artery, respectively, in protocols in which only one carotid angle was evaluated for each carotid segment. The primary end point for this analysis was the annualized rate of change in the mean of the maximum CIMT measurements based on all scans performed during the 2-year study period from each of the 12 carotid artery sites. The maximum CIMT in each of the 12 sites is defined as the largest measurement derived from the assessed interrogation angles, each one 30° different from the adjacent angle (i.e., the number of CIMT values used for the model fit was maximally 12 for each visit, irrespective of the number of angles assessed). When a carotid plaque was present, it was included in this measurement.

Statistical Analyses

Completeness rates were evaluated at the level of the carotid angle for the left and right carotid artery separately (five angles each), and

Table 1 Baseline characteristics of patients according to treatment allocation

Variable	Rosuvastatin (n = 702)	Placebo (n = 282)
Age (y)	57 ± 6.2	57 ± 6.0
Men	421 (60%)	167 (59%)
Caucasian	659 (94%)	268 (95%)
BMI (kg/m ²)	27.1 ± 4.0	27.5 ± 4.0
Smoking (during the previous month)	22 (3%)	16 (6%)
Family history of premature CHD*	65 (9%)	31 (11%)
Hypertension [†]	138 (20%)	58 (21%)
Total cholesterol (mg/dL)	229 ± 28.7	230 ± 27.7
LDL cholesterol (mg/dL) [‡]	155 ± 24.1	154 ± 24.2
HDL cholesterol (mg/dL) [‡]	50 ± 9.0	49 ± 9.2
Triglycerides (mg/dL)	126 ± 64.3	134 ± 67.8
CRP (mg/L)	1.40 (0.80–2.90)	1.60 (0.80–3.20)
Mean of the maximum of all 12 CIMT sites (mm)	1.15 ± 0.19	1.17 ± 0.20
Mean CIMT of the CCA [§] (mm)	0.76 ± 0.12	0.76 ± 0.12

CCA, Common carotid artery; CHD, coronary heart disease; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Data are expressed as mean ± SD, as number (percentage), or as median (interquartile range).

*Defined as CHD in a first-degree male relative aged < 55 years or in a first-degree female relative aged < 65 years.

[†]Blood pressure ≥ 140/90 mm Hg or taking antihypertensive medication.

[‡]To convert HDL and LDL cholesterol to millimoles per liter, multiply by 0.0259.

[§]Average of the mean CIMT of the four CCA sites: near and far walls of the right and left CCA.

carotid site (12 sites). Completeness of the angle-specific measurements is expressed as the average completeness on the six carotid sites that were examined on both the left and right carotid artery. Site-specific measurements were considered available when at least one CIMT measurement at any of the five angles was performed. This definition was used because in METEOR, the availability of at least one of five angle-specific measurements was required to have a site-specific CIMT value. All availability rates are presented as percentages. The numerator for completeness was the number of available CIMT measurements, and the denominator for completeness at a specific visit consisted of all those participants who indeed underwent carotid ultrasound examinations at that visit. Subgroup analyses were performed to examine differences in completeness for participants with BMIs ≥ 30 kg/m² and to study differences between European participants and participants from the United States.

Logistic regression analyses were used to study the relation between completeness of CIMT measurements at the site level at two baseline measurements and cardiovascular risk factors. Risk factors included were age, sex, BMI, alcohol use, family history of coronary heart disease (in a first-degree male relative aged < 55 years or in a first-degree female relative aged < 65 years), hypertension (blood pressure ≥ 140/90 mm Hg or taking antihypertensive medication), smoking during the previous month, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, C-reactive protein, and maximum CIMT. The levels of the risk factors were restricted to baseline measurements. Analyses were repeated with

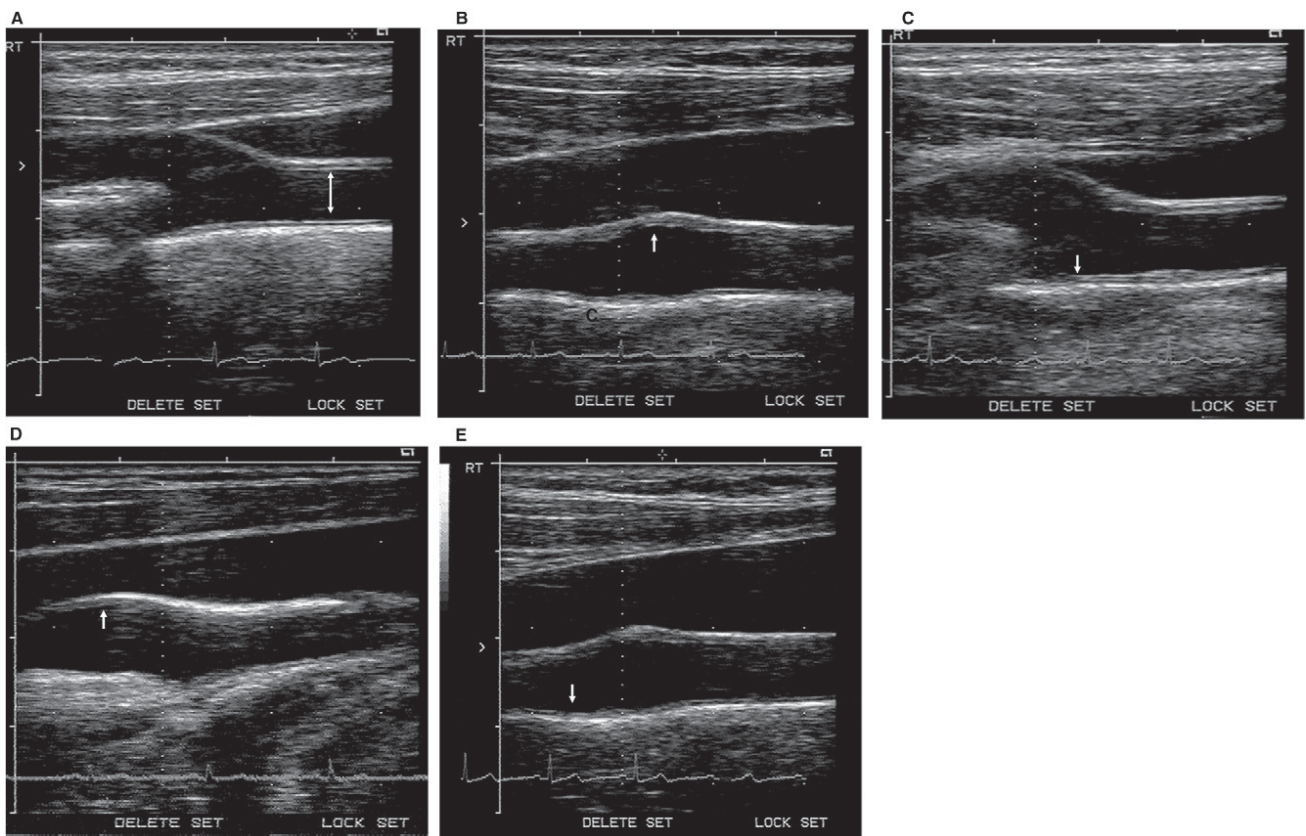


Figure 2 Longitudinal B-mode images of the carotid artery showing clear interfaces for measurement of CIMT multiple carotid segments. Arrows indicate the locations where CIMT measurements were performed. **(A)** Near and far walls of the common carotid artery. **(B)** Near wall of the carotid bifurcation. **(C)** Far wall of the carotid bifurcation. **(D)** Near wall of the internal carotid artery. **(E)** Far wall of the internal carotid artery.

adjustments for age, sex, and BMI, because these variables were considered to confound the univariate associations. Results of the adjusted and unadjusted analyses are presented as odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

The rate of change in CIMT in each of the ultrasound protocols considered was evaluated by a multilevel, repeated-measures, linear mixed-effects model using the lme4 package available in R statistical software.²⁰ This analysis was similar to the analysis performed in the original METEOR study.¹⁰ The levels used were defined by (1) the participant and (2) the carotid artery site within the participant. The repeated measure was time. The model was specified in terms of fixed effects for carotid artery site, age, sex, scan reader, ultrasound machine, treatment group, time, and the interaction between treatment group and time. Time as a continuous variable was the interval from the date of randomization to the date of CIMT measurement. Random effects within the model were intercept and slope for individual participants and for sites within participants.

RESULTS

The baseline characteristics of the study participants by treatment allocation are presented in Table 1. The mean age of the participants was 57 ± 6 years, the majority were men (60%), and the mean BMI was 27 ± 4.0 kg/m². Figures 2A to 2E provide example longitudinal B-mode images of the carotid artery showing clear interfaces for measurements of CIMT in the near and far walls of the common carotid artery, carotid bifurcation, and internal carotid artery.

Completeness at the Site Level

Table 2 shows the rates of completeness that were obtained on each of the 12 carotid sites. The percentage of CIMT measurements at the baseline examinations was 94% for the near wall of the right internal carotid artery and 96% for the near wall of the left internal carotid artery. Completeness on the other carotid artery sites, including the carotid bifurcation, was >99%.

The number of participants who withdrew from the study, who did not undergo ultrasound examinations and hence had no CIMT data, was nine (1%) for the 6-month visit, 52 (6%) for the 12-month visit, 110 (13%) for the 18-month visit, 133 (15%) for the first 24-month visit, and 160 (18%) for the second 24-month visit. Of those with ultrasound examinations after 2 years of follow-up, 95% of the near wall of the right internal carotid artery measurements and 97% of the near wall of the left internal carotid artery measurements were complete. Complete CIMT data on the other carotid sites was available in 99% of the subjects who underwent end-of-study ultrasound examinations.

Completeness rates for the near wall of the left and right internal carotid artery were lower than those of the far wall of the internal carotid artery. No major differences ($\leq 0.5\%$) were present between the near and far walls of the right or left common carotid artery or carotid bifurcation during all visits.

Analyzing participants from Europe and the United States separately showed a similar completeness rate of >99% for all carotid sites, except for the near wall of the internal carotid artery. Completeness for the near wall of the right internal carotid artery

Table 2 Percentages of available CIMT measurements by visit (rows) and carotid artery sites (columns)

Weeks after randomization	LCF	LCN	LBF	LBN	LIF	LIN	RCF	RCN	RBF	RBN	RIF	RIN
-4	>99.9	99.9	>99.9	99.7	99.7	96.2	>99.9	>99.9	99.8	99.9	99.1	93.9
-2	>99.9	99.9	99.8	99.4	99.4	96.2	99.9	99.9	99.9	>99.9	99.4	94.2
26	>99.9	99.9	99.8	99.7	99.5	96.7	99.9	99.9	>99.9	99.9	99.2	95.0
52	99.9	99.6	99.8	99.4	99.2	97.5	>99.9	>99.9	>99.9	99.9	99.5	94.8
78	99.9	99.9	99.9	99.2	98.8	96.0	>99.9	99.7	>99.9	99.9	99.2	95.0
104	>99.9	99.7	99.6	99.6	99.5	96.8	>99.9	99.9	>99.9	99.7	99.7	95.2
105	>99.9	99.7	99.9	99.4	98.9	97.2	>99.9	>99.9	99.9	99.9	99.3	95.8

LBF, Far wall of the left bifurcation; LBN, near wall of the left bifurcation; LCF, far wall of the left common carotid artery; LCN, near wall of the left common carotid artery; LIF, far wall of the left internal carotid artery; LIN, near wall of the left internal carotid artery; RBF, far wall of the right bifurcation; RBN, near wall of the right bifurcation; RCF, far wall of the right common carotid artery; RCN, near wall of the right common carotid artery; RIF, far wall of the right internal carotid artery; RIN, near wall of the right internal carotid artery.

Table 3 Percentages of available CIMT measurements over six carotid sites at the angle level for each ultrasound examination

Angle	Weeks after randomization						
	-4	-2	26	52	78	104	105
Left carotid artery							
180°	82.7	81.9	83.0	83.7	82.6	82.9	83.7
210°	88.3	88.7	88.8	89.9	89.4	89.1	89.8
240°	93.2	93.7	92.9	93.6	92.3	93.6	94.2
270°	87.6	88.3	87.6	88.3	87.6	86.4	86.5
300°	37.5	39.0	38.5	37.3	33.9	31.2	33.1
Right carotid artery							
180°	82.8	82.9	84.4	84.4	82.1	83.2	84.2
150°	89.1	88.7	89.7	89.3	89.7	90.5	89.4
120°	92.7	93.8	93.5	92.7	93.2	93.1	93.1
90°	90.0	90.3	91.3	82.7	89.8	89.2	90.7
60°	49.5	49.8	50.7	54.0	42.4	39.5	40.7

Availability results represent average availability for the near and far walls of the common carotid artery, carotid bifurcation, and internal carotid artery.

over time was on average 97% for European participants and 93% for participants from the United States. For the left internal carotid artery, 97% of the measurements were available for European participants, and 96% of the measurements were available for participants from the United States.

Availability of CIMT data in participants with BMIs ≥ 30 kg/m² was 90% for the near wall of the right internal carotid artery and 95% for the near wall of the left internal carotid artery. Completeness rates for all other carotid sites were similar to the analyses on all subjects.

Completeness at the Angle Level

The availability of CIMT measurements was the highest at 240° of the left carotid artery and at 120° of the right carotid artery (Table 3). At these angles, 93% of the CIMT measurements were available at baseline for both carotid arteries, with 94% available CIMT measurement at the end of follow-up for the left carotid artery and 93% for the right carotid artery. The lowest number of available measurements was found at the most extreme angles, which were 300° for the left ca-

Table 4 ORs (95% CIs) of the determinants of completeness of CIMT measurements

Variable	Unadjusted	Age and sex adjusted [†]	Age, sex, and BMI adjusted [§]
Age	0.98 (0.95–1.01)	1.00 (0.97–1.04)	0.98 (0.95–1.01)
Male gender	0.65 (0.45–0.94)	0.65 (0.42–1.00)	0.69 (0.47–1.01)
BMI	0.87 (0.84–0.91)	0.88 (0.84–0.92)	NA
Alcohol use	0.64 (0.44–0.93)	0.68 (0.46–0.99)	0.68 (0.46–1.01)
Family history of CHD*	1.42 (0.80–2.55)	1.30 (0.72–2.36)	1.29 (0.69–2.40)
Hypertension [†]	1.53 (0.99–2.36)	1.30 (0.72–2.36)	1.13 (0.71–1.81)
Smoking	1.66 (0.70–3.94)	1.37 (0.57–3.35)	1.89 (0.76–4.67)
LDL cholesterol	1.05 (0.78–1.41)	1.05 (0.78–1.41)	1.03 (0.76–1.41)
HDL cholesterol	1.28 (0.58–2.83)	1.71 (0.74–3.95)	1.05 (0.44–2.51)
Triglycerides	0.75 (0.60–0.94)	0.73 (0.58–0.91)	0.86 (0.67–1.10)
CRP	0.73 (0.55–0.98)	0.78 (0.58–1.06)	1.01 (0.70–1.45)
Maximum CIMT	0.86 (0.61–1.21)	0.87 (0.61–1.22)	0.86 (0.61–1.23)

CHD, Coronary heart disease; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Defined as CHD in a first-degree male relative aged < 55 years or in a first-degree female relative aged < 65 years.

[†]Blood pressure $\geq 140/90$ mm Hg or taking antihypertensive medication.

[‡]Age was adjusted for sex, and sex was adjusted for age.

[§]Age was adjusted for sex and BMI, and sex was adjusted for age and BMI.

rotid artery and 60° for the right carotid artery. At the beginning of the study, 38% of the CIMT measurements at 300° were available for the left carotid artery, and 50% of the measurements at 60° were available for the right carotid artery. Furthermore, completeness rates were generally lower in the left carotid artery than in the right carotid artery. The average completeness rates over all ultrasound examinations for the 180°, 210°, and 270° angles of the left carotid artery were 83%, 89%, and 87%, respectively. For the right carotid artery, the completeness rates for the 180°, 150°, and 90° angles were 83%, 89%, and 89%, respectively.

Determinants of Completeness

The completeness rate at baseline for carotid sites was highly right skewed. The majority of participants (84%) did have CIMT data for all sites at baseline. Three participants (0.3%) had no data at five sites,

Table 5 Annualized rate of change in mean maximum CIMT by treatment allocation with measurements from five, three, or one angle at a maximum of 12 carotid artery sites

Sites measured (n)	Rate of change in CIMT (SE) (mm/y)		
	Rosuvastatin	Placebo	Rosuvastatin vs placebo
Five angles			
CCA, BIF, and ICA, NFW (60)	-0.0014 (0.0014)	0.0131 (0.0022)	-0.0145 (0.0026)
CCA, NFW (20)	-0.0038 (0.0013)	0.0084 (0.0021)	-0.0122 (0.0025)
CCA and BIF, NFW (40)	-0.0039 (0.0015)	0.0126 (0.0024)	-0.0166 (0.0028)
CCA and ICA, NFW (40)	0.0000 (0.0014)	0.0112 (0.0023)	-0.0112 (0.0027)
CCA, FW (10)	-0.0056 (0.0017)	0.0045 (0.0027)	-0.0101 (0.0032)
CCA and BIF, FW (20)	-0.0045 (0.0021)	0.0112 (0.0033)	-0.0157 (0.0040)
CCA and ICA, FW (20)	0.0012 (0.0019)	0.0092 (0.0030)	-0.0081 (0.0036)
CCA, BIF, and ICA, FW (30)	-0.0004 (0.0019)	0.0119 (0.0030)	-0.0123 (0.0036)
Three angles			
CCA, BIF, and ICA, NFW (60)	-0.0008 (0.0014)	0.0139 (0.0022)	-0.0147 (0.0026)
CCA, NFW (20)	-0.0029 (0.0013)	0.0099 (0.0020)	-0.0128 (0.0023)
CCA and BIF, NFW (40)	-0.0029 (0.0015)	0.0133 (0.0024)	-0.0162 (0.0028)
CCA and ICA, NFW (40)	0.0002 (0.0014)	0.0126 (0.0022)	-0.0124 (0.0026)
CCA, FW (10)	-0.0053 (0.0017)	0.0046 (0.0026)	-0.0099 (0.0031)
CCA and BIF, FW (20)	-0.0040 (0.0021)	0.0103 (0.0033)	-0.0143 (0.0039)
CCA and ICA, FW (20)	0.0006 (0.0018)	0.0092 (0.0028)	-0.0087 (0.0033)
CCA, BIF, and ICA, FW (30)	-0.0005 (0.0018)	0.0114 (0.0029)	-0.0119 (0.0034)
One angle			
CCA, BIF, and ICA, NFW (60)	-0.0026 (0.0013)	0.0147 (0.0021)	-0.0173 (0.0024)
CCA, NFW (20)	-0.0014 (0.0014)	0.0109 (0.0022)	-0.0122 (0.0026)
CCA and BIF, NFW (40)	-0.0038 (0.0015)	0.0132 (0.0024)	-0.0170 (0.0028)
CCA and ICA, NFW (40)	-0.0006 (0.0014)	0.0143 (0.0022)	-0.0149 (0.0026)
CCA, FW (10)	-0.0045 (0.0018)	0.0068 (0.0029)	-0.0113 (0.0034)
CCA and BIF, FW (20)	-0.0048 (0.0020)	0.0119 (0.0032)	-0.0167 (0.0038)
CCA and ICA, FW (20)	-0.0009 (0.0019)	0.0116 (0.0030)	-0.0125 (0.0035)
CCA, BIF, and ICA, FW (30)	-0.0022 (0.0017)	0.0135 (0.0027)	-0.0158 (0.0032)

BIF, Carotid bifurcation; CCA, common carotid artery; FW, far wall; ICA, internal carotid artery; NFW, near and far walls.

three (0.3%) had no data at four sites, eight (0.9%) had no data at three sites, 38 (4%) had no data at two sites, and 82 (9%) had no data at one site.

Table 4 shows the determinants of arterial-site completeness at the prerandomization visits. Univariate analyses showed that male sex, higher BMI, alcohol use, higher levels of triglycerides, and higher C-reactive protein levels were associated with a lower number of available CIMT measurements. When adjusted for age and sex, a higher BMI (OR, 0.88; 95% CI, 0.84–0.92), alcohol use (OR, 0.68; 95% CI, 0.46–0.99), and a higher level of triglycerides (OR, 0.73; 95% CI, 0.58–0.91) remained associated with a lower number of CIMT measurements. When adjusted for age, sex, and BMI, the association between the number of sites with CIMT measurements and alcohol use and triglyceride level, respectively, were substantially attenuated, with 95% CIs that included 1.

Rate of Change in CIMT Across Ultrasound Protocols

The annualized rates of change in CIMT for each of the eight ultrasound protocols considered in which five angles were measured are shown in Table 5. Findings on rate of change in maximum CIMT between treatment groups were largely in the same direction across the ultrasound protocols (i.e., nonsignificant regression in the rosuvastatin group and significant progression in the placebo group) and with statistically significant differences between treatment groups (Table 5).

However, protocols in which both the near and far walls were assessed consistently had the smallest standard errors, indicating the highest precision, compared with ultrasound protocols in which only the far walls were assessed. In addition, the magnitudes of the treatment effects differed across the ultrasound protocols depending on which carotid segments were assessed. The detected rates of change were the largest in protocols that included the carotid bifurcation, whereas rates of change in CIMT were smallest in protocols that included only the common carotid artery.

Figure 3 shows the difference between rosuvastatin and placebo in rate of change in CIMT across the eight ultrasound protocols in which the number of angles assessed differed from five to three or one angle. The direction, magnitude, and precision of these rates of change were similar within ultrasound protocols that assessed the same carotid segments but measured five, three, or one angle.

DISCUSSION

The present study demonstrates that high levels of complete CIMT data were obtained using an extensive ultrasound protocol that includes measurements from the near wall of the carotid bifurcation and internal carotid artery. Rates of change in CIMT differed in magnitude, but not in direction, when limited ultrasound protocols were

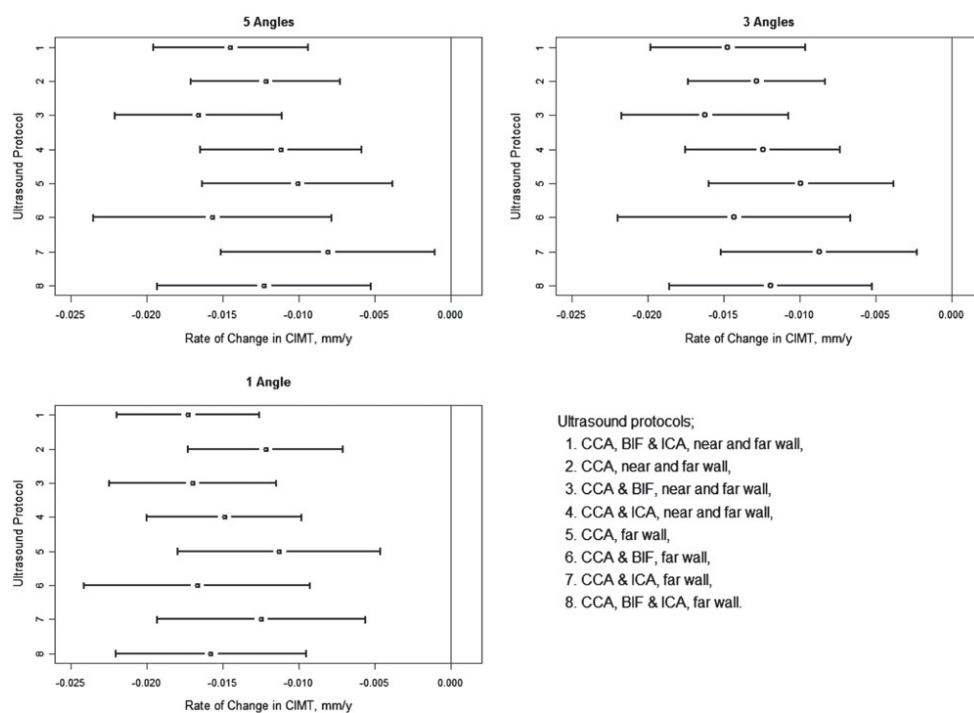


Figure 3 Difference between rosuvastatin and placebo in rate of change in maximum CIMT across ultrasound protocols and 95% CIs. *BIF*, Carotid bifurcation; *CCA*, common carotid artery; *ICA*, internal carotid artery.

used. Also, extensive ultrasound protocols were more precise to observe treatment effects than restricted protocol approaches. Hence, our completeness findings challenge the general view that measurements from the near wall of the carotid bifurcation and internal carotid artery are difficult to achieve and are a major source of missing data. Moreover, our data show that ultrasound protocols including near and far wall assessments at multiple carotid segments provide a broad range of data on the status and the progression of atherosclerosis, which become incomplete and less precise when restricted ultrasound protocols are used. Although the METEOR results were robust for limitations in the ultrasound protocol, restrictions in the ultrasound procedure may become critical and important in settings in which intervention effects or sample sizes are smaller and a treatment effect could not be observed at all.

Completeness Rates in Previous Studies

Data to support the difficulties with measurement of the carotid bifurcation and internal carotid artery are very limited, and this view is based largely on results from studies conducted a decade ago.^{15,21-23} For example, measurements of the carotid bifurcation and internal carotid artery were available in only 83% and 56% of the individuals in the Rotterdam Study, respectively, whereas measurements of the common carotid artery could be obtained in 97% of the individuals.²³ Completeness rates from more recent studies support the use of more extensive protocols, including measurements from the carotid bifurcation and internal carotid artery, because these studies showed a marked improvement in data availability with completeness rates of $\geq 84\%$ for all carotid sites.^{9,16,18}

The completeness rates presented here are similar to completeness rates in the Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor (RADIANCE) trials.¹⁸ The RADIANCE trials were performed in participants with mixed dyslipidemia and familial

hypercholesterolemia, whereas the METEOR results presented here come from a low-risk population. Therefore, the presence and extent of carotid atherosclerosis may seem to be different across these populations and may influence completeness rates. However, showing that completeness can be obtained in a variety of populations with a different level of local atherosclerosis adds to the generalizability of the feasibility of obtaining high completeness rates with extensive ultrasound protocols.

Determinants of Incomplete Data

Increased BMI was associated with a higher probability for missing CIMT measurements. Such an observation is generally recalled by sonographers and is consistent with the findings in RADIANCE 1 and 2.¹⁸ The mixed dyslipidemia population in RADIANCE 2 was more overweight than the METEOR and familial hypercholesterolemia population in RADIANCE 1.¹⁸ This difference in BMI may have caused the lower completeness rate of near wall measurements of the internal carotid artery in patients with mixed dyslipidemia (86%). Image acquisition may be more difficult in overweight subjects because of greater difficulties in distinguishing near and far wall boundaries on an ultrasound image or because of physical limitations associated with a shorter or thicker neck. The mixed dyslipidemia population may also have more atherosclerotic plaque burden, which could make the arterial walls more difficult to visualize because of increased reflectance from surrounding tissues. Although we found an association between BMI and data availability in the present study, no association between baseline thickness of the CIMT and data completeness was found. This implies that although increased BMI is related to missingness, the missingness could not be explained by the actual thickness of the CIMT. Hence, it is unlikely that a thicker CIMT, reflecting atherosclerotic disease, has been missed in participants with high BMIs.

Extensive or Restricted Ultrasound Protocols

A recent consensus statement from the American Society of Echocardiography recommended restricting CIMT ultrasound protocols to measurement of the far wall common carotid artery alone, supplemented by carotid plaque assessment in the common carotid artery, carotid bifurcation, and internal carotid artery.²⁴ Although our findings could be used to support assessment of the near wall and the carotid bifurcation and internal carotid artery, these measurements are currently not recommended in the American Society of Echocardiography statement. In addition, the usefulness of CIMT measurements from circumferential angles of insonation and the number of ultrasound examinations over time are additional issues that are relevant for the choice of extensive or restricted ultrasound protocols.

The value of performing near wall CIMT measurements has been debated for many years, because near wall CIMT measurements are an approximation of the true wall thickness.²⁵⁻²⁷ Recent studies have demonstrated that ultrasound protocols assessing both the near and far walls provide the best balance between high reproducibility, large progression rates, and large and precise intervention effects.^{18,28,29} Our findings are in agreement with these studies and suggest that combining near and far wall measurements improve data quality and may add valuable information.

Measurements of the carotid bifurcation and internal carotid artery are also not recommended by the American Society of Echocardiography consensus statement, given the expected difficulties with visualization of these arterial segments.²⁵ We showed that CIMT measurements from the internal carotid artery and carotid bifurcation are nearly always complete and that exclusion of these segments may not fully describe the burden of atherosclerosis and the effect of treatment on changes in this burden. This finding is supported by studies showing that progression rates and that the effects of treatment differ across the carotid segments.^{10,11,30,31}

The usefulness of CIMT measurements from different circumferential carotid angles has not been extensively studied. A recent study showed that atherosclerosis is asymmetrically distributed across carotid angles within an arterial segment.³² Hence, the angle of insonation is an important determinant of the absolute value of maximum CIMT and supports the future use of CIMT measurements from multiple carotid angles. However, we found minor differences in observed treatment effect and its precision with the inclusion of five, three, or one circumferential carotid angle. This may indicate that the rates of change in CIMT are similar across angles of interrogation, even though the absolute values differ per angle.

Besides restrictions in the number of CIMT measurements, the number of ultrasound examinations over time could also be a mean to restrict an ultrasound protocol in longitudinal studies. We recently showed that study designs with a reduced number of ultrasound examinations over time did minimally affect the direction and magnitude of treatment effects on the rate of change in CIMT.³³ However, a reduced number of exams substantially increased standard errors of rates of change, suggesting that larger sample sizes would be required to have the same level of statistical power.

Implications

Our study supports the use of extensive ultrasound protocols. However, costs and time investments are clearly higher once choosing an extensive CIMT protocol with assessment of the near and far walls of multiple carotid segments at several angles of insonation. For example, a full METEOR scan took approximately 45 min, whereas a restricted ultrasound protocol with evaluation of the far

wall of the common carotid artery at one angle may be performed within 20 min. Nevertheless, high reproducibility, complete data, and assessment of all aspects of carotid atherosclerosis are key reasons to measure CIMT repeatedly across multiple segments and carotid angles. However, the choice of ultrasound protocol and ultrasound equipment should depend on a well-considered balance between time and costs on one hand and data quality and the value of additional information obtained using extensive protocols on the other.³⁴ Foremost, as studies of the rate of change in CIMT over time have different issues to address than studies of determinants of CIMT or CIMT as a predictor of risk, the main driving force for ultrasound protocols is of course in relation to the research question at hand.

Future Directions

The present study showed that high levels of complete data could be obtained using extensive ultrasound protocols. A recent study demonstrated the feasibility of the use of an extensive ultrasound protocol in a screening program for subclinical atherosclerosis.³⁵ However, data that directly compare the risk stratification abilities of a far wall common CIMT measurement versus one that uses information from multiple carotid segments are not yet available. These data are important given the growing interest in the use of measures of subclinical atherosclerosis to improve risk stratification for cardiovascular disease events.³⁶⁻³⁸

Limitations

The availability of CIMT measurements in the present study was examined without further inspection of the correctness of these values. Inclusion of incorrect values could affect the associations found between incompleteness and risk factors. However, the analyses herein were performed on the same data set as was used for the original METEOR publication.¹⁰ The high quality of the ultrasound equipment in the imaging centers and the core laboratories and the training and continuous quality control used, which resulted in high interreader and intrareader reproducibility, allow us to assume that a substantial effect of incorrect measurements on these results is not likely. Also, the present study was based on analyses of existing data collected during the METEOR trial, which was not primarily designed to address the questions of the current study. Although a prospective study design may have been preferred, we consider it unlikely that the retrospective design used here would have affected the completeness rates. Finally, 1.5% of the screened individuals were not included in METEOR, because of the inability to determine whether at least one CIMT measurement was ≥ 1.2 and < 3.5 mm at two screening examinations. The reasons for ineligibility to determine this criterion were anatomic deviations, including nonvisualized tip of the flow divider, deep vessels, or tortuous vessels. Hence, our results apply only to low-risk individuals in whom visualization of the carotid artery is possible.

CONCLUSIONS

Extensive ultrasound protocols that include examination of the near walls of the carotid bifurcation and internal carotid artery from multiple angles of interrogation are feasible and can provide high levels of complete CIMT data. Although completeness is high, relatively more CIMT measurements are missing with increasing BMI. Extensive ultrasound protocols are required to obtain the highest precision to observe a treatment effect and to describe the asymmetric nature of atherosclerotic burden in its full range.

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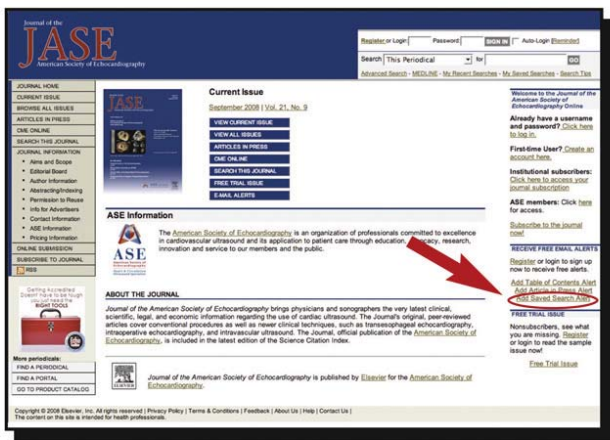
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