

Original Article

Completeness of Carotid Intima Media Thickness Measurements Depends on Body Composition: The RADIANCE 1 and 2 trials

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Aim: Ultrasound protocols to measure carotid intima media thickness (CIMT) differ considerably with regard to the inclusion of the number of carotid segments and angles used. Detailed information on the completeness of CIMT information is often lacking in published reports, and at most, overall percentages are presented. We therefore decided to study the completeness of CIMT measurements and its relation with vascular risk factors using data from two CIMT intervention studies: one among familial hypercholesterolemia (FH) patients, the Rating Atherosclerotic Disease change by Imaging With A New CETP Inhibitor (RADIANCE 1), and one among mixed dyslipidemia (MD) patients, the Rating Atherosclerotic Disease change by Imaging With A New CETP Inhibitor (RADIANCE 2).

Methods: We used baseline ultrasound scans from the RADIANCE 1 ($n=872$) and RADIANCE 2 ($n=752$) studies. CIMT images were recorded for 12 artery-wall combinations (near and far walls of the left and right common carotid artery (CCA), bifurcation (BIF) and internal carotid artery (ICA) segments) at 4 set angles, resulting in 48 possible measurements per patient. The presence or absence of CIMT measurements was assessed per artery-wall combination and per angle. The relation between completeness and patient characteristics was evaluated with logistic regression analysis.

Results: In 89% of the FH patients, information on CIMT could be obtained on all twelve carotid segments, and in 7.6%, eleven segments had CIMT information (nearly complete 96.6%). For MD patients this was 74.6% and 17.9%, respectively (nearly complete: 92.5%). Increased body mass index and increased waist circumference were significantly ($p=0.01$) related to less complete data in FH patients. For MD patients, relations were seen with increased waist circumference ($p<0.01$). Segment-specific data indicated that in FH patients, completeness was less for the near wall of the left (96%) and right internal carotid artery (94%) as compared to other segments (all $>98%$). In MD patients, completeness was lower for the near wall of both the right and left carotid arteries: 86.0% and 90.8%, respectively, as compared to other segments (all $>97%$).

Conclusions: With the current ultrasound protocols it is possible to obtain a very high level of completeness. Apart from the population studied, body mass index and waist circumference are important in achieving complete CIMT measurements.

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Key words; Atherosclerosis, Lipid lowering, Imaging, Methodology

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Introduction

Carotid intima-media thickness (CIMT) measurements have been used widely to evaluate cardiovascular disease (CVD) risk factors and CVD morbidity and mortality¹⁻³. Changes in CIMT over time are

being used to measure the efficacy of pharmacological interventions where CIMT is used as an alternative marker for atherosclerotic vascular disease risk⁴⁻¹⁴. At present, there is little agreement on ultrasound protocols to measure CIMT and they vary in measuring single or double walls (near and/or far wall), or single or multiple segments at set / pre specified angle(s) or unspecified free angle(s).

Completeness of CIMT information is often one of the arguments to restrict protocols to imaging the far wall of the common carotid artery only, or to imaging of the far wall of the other segments. Published data on the completeness of CIMT information stems from observational studies performed in the early nineties, when the yield of imaging of the bifurcation segment and internal carotid artery segment was limited¹⁵⁻¹⁹. Ultrasound protocols and imaging equipment have changed considerably, and ultrasound protocols for trials are generally more standardized than in earlier observational CIMT studies. Thus, these early estimates may not be applicable to the current situation. Furthermore, from the published information, in recent trials, aspects of the completeness of carotid segments and walls seem not to be available. If anything, generally, overall completeness information is presented^{7, 9, 11-14}. In addition, information on factors that reduce the completeness of CIMT measurement assessment has not been widely addressed in the literature; however, from experience, it is well known that carotid ultrasound imaging is more difficult in subjects with a short and thick neck.

In view of the lack of published information on these issues, we set out to study this using a large body of data obtained in two recently performed randomized controlled trials.

Methods

General

Data from the RADIANCE 1^{12, 18} and RADIANCE 2 trials were used^{11, 18}. The current analyses are based on participants that had at least one post-baseline CIMT measurement. These studies have been described in detail previously. In summary, RADIANCE 1 was a double-blind randomized placebo-controlled multi-center study in which 872 patients with heterozygous familial hypercholesterolemia (FH) were randomly assigned to receive either atorvastatin monotherapy or atorvastatin combined with 60 mg torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, for 2 years to study the effect on CIMT progression. RADIANCE 2 was a comparative study, a double-blind, placebo-controlled multi-center study

in which 752 participants with mixed dyslipidemia were randomly assigned to atorvastatin monotherapy or atorvastatin combined with 60 mg torcetrapib for 2 years to assess the effect of torcetrapib on the progression of atherosclerosis.

Carotid Ultrasound Examinations

The ultrasound protocol for assessment of CIMT has been described in detail elsewhere^{11, 12, 20, 21}. In short, duplicate scans were made at baseline and at each patient's final visit, and single scans at visits at 6, 12, and 18 months, to give a maximum of seven scans for each patient. At each visit, sonographers acquired and recorded CIMT images of 12 artery-wall combinations of the near and far walls of the right and left carotid artery for the common, bifurcation, and internal carotid artery segments, at four predefined angles of 30° steps (90° to 180° on the right side and 270° to 180° on the left side) using the Meijers Carotid Arc[®]. This resulted in 48 possible measurements per patient. All imaging centers used the same imaging acquisition protocol and equipment (Sequoia 512 scanners equipped with 8L5 transducers; Siemens AG, Munich, Germany). Forty-eight 5-second image sequences (video clips) were saved in DICOM format (Digital Imaging in Communications in Medicine; National Electrical Manufacturers Association, Rosslyn, VA, USA). Imaging data were transferred directly from the study sites to the two reading centers (Vascular Imaging Center, University Medical Center, Utrecht, The Netherlands, and Wake Forest University Medical Center, Ultrasound Reading Center, Winston-Salem, NC, USA), where standardized equipment and protocols were used to process stored images. From every image sequence, readers selected one frame in end diastole for measurement of CIMT. Maximum thickness (and also mean of the common carotid artery) was measured semi-automatically with Artery Measurement System software (Chalmers University, Göteborg, Sweden)²⁰. A 'no measurement' could have resulted from two processes: (1) no imaging data had been stored for that specific angle and segment, or (2) the data provided were of insufficient quality to perform a CIMT measurement, as judged by the reader. Unfortunately, we were not able to distinguish between the two processes and additional information on whether a 'no measurement' was due to, for example, tortuous vessels, extreme acoustic shadowing, reverberations or artifacts was unfortunately not collected. Readers were unaware of the interventions assigned to patients, and of previous measurements. Quality assurance protocols have been described elsewhere¹⁸. In short, quality assurance processes included

Table 1. Baseline characteristics of the RADIANCE 1 and RADIANCE 2 study

	RADIANCE 1 <i>n</i> = 872	RADIANCE 2 <i>n</i> = 752
Age (years)	45 (12.5)	57 (8.2)
Male, <i>n</i> (%)	431 (49.4)	482 (64)
Mean maximum CIMT (mm)	1.14 (0.30)	1.31 (0.31)
Mean common CIMT (mm)	0.72 (0.15)	0.83 (0.15)
Systolic blood pressure (mm. Hg)	116 (11)	120 (11)
Diastolic blood pressure (mm. Hg)	73 (7)	74 (7)
HDL cholesterol (mg/dL)	52 (13)	47 (11)
LDL cholesterol (mg/dL)	139 (37)	100 (20)
Triglycerides (mg/dL)	113 (64)	183 (80)
Waist circumference (cm)	89 (12)	100 (13)
BMI (kg/m ²)	26.7 (4.4)	30.1 (4.4)
Hypertension *, <i>n</i> (%)	230 (26.4)	390 (52)
Diabetes mellitus (%)	22 (2.9)	191 (26)
Baseline glucose (mg/dL)	90.2 (17.8)	105 (28.5)

Values presented as the mean (standard deviation) or number (percentage); BMI=body mass index; CIMT=carotid intima-media thickness; *hypertension defined as systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm Hg or use of antihypertensive medication

the following: central training and certification of all sonographers and readers on each continent; annual international meetings of sonographers and readers to reinforce protocol and standardize implementation; and regular site visits and performance reviews. This included consensus among readers in deciding when a CIMT measurement could not be taken.

Statistical Methods

Completeness, defined as the presence of a CIMT measurement, was addressed in various ways since information on CIMT availability was present on an angle level (4 angles), wall level (near and far wall), carotid segment level (CCA, BIF, ICA), carotid side level (left, right) and overall ($2 \times 3 \times 2 = 12$ artery-wall combinations). Furthermore, when the study interest lies in the measurement of mean maximum CIMT, information of CIMT in the twelve segments should be available, and thus completeness of 12 artery-wall combinations was studied separately.

First, completeness was presented by angle and carotid segment separately. Next, the availability of one or more angle-specific CIMT measurements per carotid segment was presented. Subsequently, data were given for certain angle specific combinations by segment. Finally, the completeness of CIMT was presented by segments (complete was defined as CIMT available for all 12 artery-wall combinations).

The relation of completeness, i.e., CIMT available for all 12 segments, with several vascular risk fac-

tors, was studied using a logistic regression model. The outcome 'complete' was defined as CIMT available for all 12 segments. The odds ratio (OR) and its corresponding 95% confidence interval (95%CI) were estimated for several risk factors. An increased odds ratio (>1) should be interpreted as an increased risk of obtaining incomplete data. Results are presented for the two RADIANCE studies separately. Data were analyzed using SPSS version 14.0.

Results

Baseline characteristics of the study populations are given in **Table 1**. Participants in the RADIANCE 1 study were younger, had higher levels of LDL cholesterol, lower levels of triglycerides, lower waist circumference values and lower body mass index than participants in the RADIANCE 2 study (**Table 1**). There were more male participants and hypertension was less common in RADIANCE 2 than RADIANCE 1. Furthermore, CIMT was considerably higher in MD patients than FH patients.

Completeness per Segment

The availability of at least 1 CIMT measurement (out of the 4 (angles)) was 93.7% in the FH patient trial and 86.0% in the MD patient trial (**Fig. 1**). Segment-specific data indicated that, in FH patients, completeness was somewhat less for the near wall of the near and right internal artery (93.7%) than for

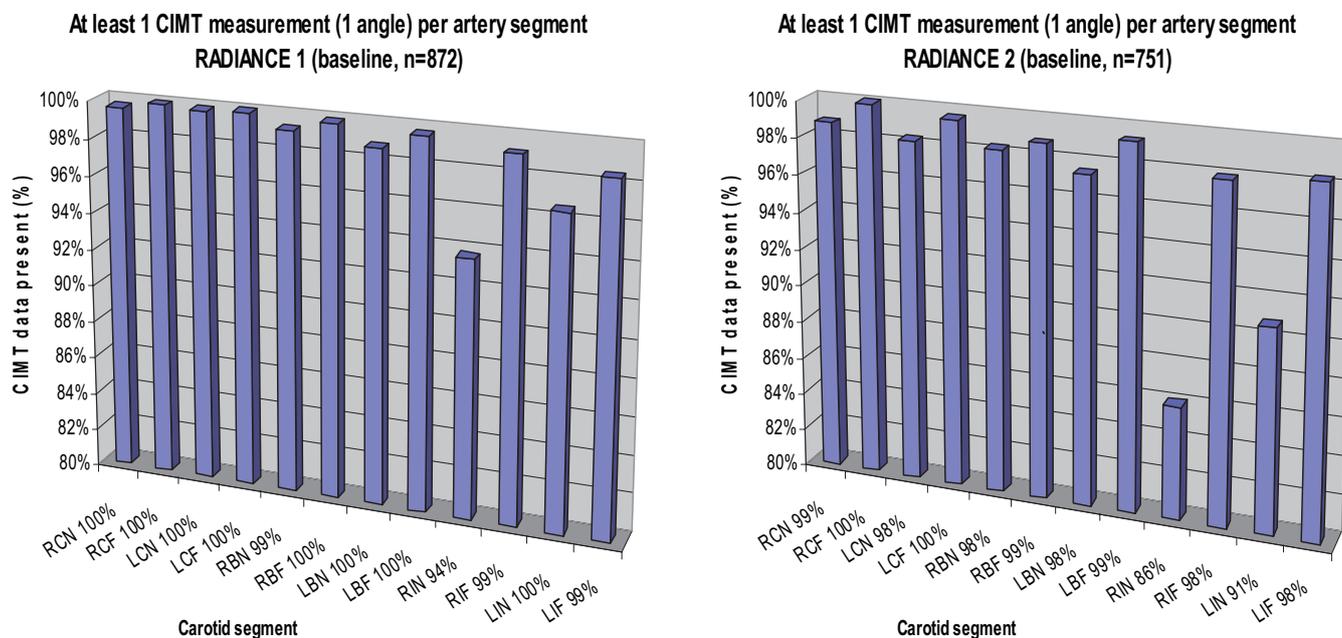


Fig. 1. Availability of CIMT measurements per standard artery segment

Availability is defined as at least one CIMT measurement at any one of the four angles / measurements of each one of twelve standard artery segments. RCN: near wall of the right common carotid artery; RCF: far wall of the right common carotid artery; LCN: near wall of the left common carotid artery; LCF: far wall of the left common carotid artery; RBN: near wall of the right bifurcation; RBF: far wall of the right bifurcation; LBN: near wall of the left bifurcation; LBF: far wall of the left bifurcation; RIN: near wall of the right internal carotid artery; RIF: far wall of the right internal carotid artery; LIN: near wall of the left internal carotid artery; LIF: far wall of the left internal carotid artery)

other segments (all >98%). In MD patients, completeness was lower for the near wall of both the right and left carotid artery: 86.0% and 90.8%, respectively than for other segments (all >97%).

When completeness was defined as the availability of all four angle CIMT measurements, percentages were still considerably high in FH patients (**Fig. 2, left**). Completeness percentages in general were higher for far wall than near wall measurements. Also, the completeness percentages declined when going from the common carotid segment to the bifurcation segment to the internal carotid segment. A similar pattern was seen for completeness rates among MD patients, although rates were lower than in FH patients (**Fig. 2, right**). Obtaining CIMT information from the near walls of the internal carotid segments proved to be most difficult.

CIMT Measurements per Segment, Wall and Angle

Table 2 provides information on the percentage of participants with CIMT measurements divided by segment, wall and angle for both studies. Completeness was higher in FH patients than in MD patients for nearly all combinations. The near wall of the inter-

nal carotid artery on both the left and right sides had the lowest completeness in both studies. Measurements of the 120°/240° and 150°/210° angles were most complete.

In studies focusing on the assessment of mean maximum CIMT for each participant, i.e., taking the average of the maximum CIMT measurement of each of the 12 segments, information on completeness (having at least one CIMT measurement per segment) is important. At least 89.0% of FH patients had one CIMT measurements at 12 segments. In addition, 96.6% had at least one CIMT measurement in 11 segments. For MD patients these percentages were 74.6% and 92.7%, respectively.

Determinants of Completeness

An increased waist circumference and increased body mass index in FH patients were related to a statistically significant increased risk of incompleteness (i.e., CIMT measurement in less than 12 segments): OR (95%CI) 1.28 (1.07; 1.54) and 1.92 (1.21; 3.05) respectively. Age, lipid levels, blood pressure and CIMT at baseline showed no relation with completeness (**Table 3**). In the MD population, an increased

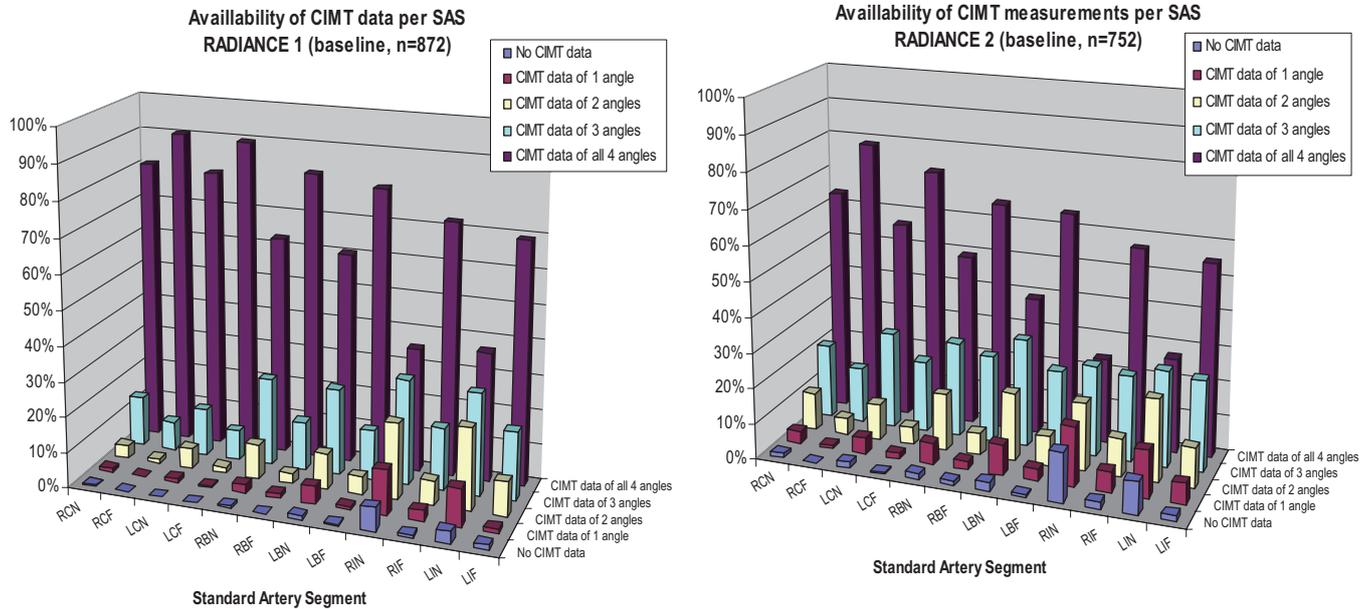


Fig. 2. Availability of CIMT measurements per standard artery segment.

CIMT measurements of 0 (= none) / 1 / 2 / 3 / 4 (all 4 angles) available. RCN: near wall of the right common carotid artery; RCF: far wall of the right common carotid artery; LCN: near wall of the left common carotid artery; LCF: far wall of the left common carotid artery; RBN: near wall of the right bifurcation; RBF: far wall of the right bifurcation; LBN: near wall of the left bifurcation; LBF: far wall of the left bifurcation; RIN: near wall of the right internal carotid artery; RIF: far wall of the right internal carotid artery; LIN: near wall of the left internal carotid artery; LIF: far wall of the left internal carotid artery)

Table 2. Percentage of CIMT measurements presented by wall, segment and angle in RADIANCE 1 (872 scans) and RADIANCE 2 (752 scans) at baseline

	RADIANCE 1				RADIANCE 2				
	90°	120°	150°	180°	90°	120°	150°	180°	
RCN	92,7%	96,0%	95,8%	89,4%	RCN	84,6%	90,9%	88,5%	78,4%
RCF	95,3%	98,2%	98,5%	96,8%	RCF	90,3%	94,9%	96,0%	90,9%
RBN	90,8%	90,6%	85,8%	78,4%	RBN	76,0%	89,3%	87,1%	79,4%
RBF	90,6%	95,8%	96,4%	93,5%	RBF	83,0%	94,1%	95,3%	90,7%
RIN	71,4%	75,0%	64,0%	59,4%	RIN	80,7%	83,9%	79,0%	72,2%
RIF	84,3%	92,2%	91,5%	88,4%	RIF	82,0%	90,0%	91,1%	87,4%
	270°	240°	210°	180°		270°	240°	210°	180°
LCN	92,1%	96,4%	94,4%	88,9%	LCN	69,8%	81,1%	75,8%	68,3%
LCF	94,0%	98,5%	98,2%	96,3%	LCF	77,9%	89,3%	91,3%	88,5%
LBN	84,1%	90,0%	82,7%	79,5%	LBN	62,6%	62,1%	56,5%	48,7%
LBF	89,0%	94,4%	95,4%	92,9%	LBF	75,2%	82,3%	87,9%	82,6%
LIN	80,4%	75,6%	65,0%	60,9%	LIN	66,2%	73,5%	58,6%	51,1%
LIF	80,8%	89,9%	92,1%	88,8%	LIF	71,0%	83,8%	87,6%	84,6%

The right carotid artery is scanned at 90°, 120°, 150° and 180°; the left artery scanned at equivalent angles 270°, 240°, 210° and 180°. RCN: near wall of the right common carotid artery; RCF: far wall of the right common carotid artery; LCN: near wall of the left common carotid artery; LCF: far wall of the left common carotid artery; RBN: near wall of the right bifurcation; RBF: far wall of the right bifurcation; LBN: near wall of the left bifurcation; LBF: far wall of the left bifurcation; RIN: near wall of the right internal carotid artery; RIF: far wall of the right internal carotid artery; LIN: near wall of the left internal carotid artery; LIF: far wall of the left internal carotid artery)

Table 3. Relation between vascular risk factors with incompleteness of CIMT measurements. Incompleteness defined as less than all CIMT measurement in 12 segments

Unadjusted	RADIANCE 1			RADIANCE 2		
	OR	95% ci	<i>p</i> -value	OR	95% ci	<i>p</i> -value
Age (years)	1,08	(0,91;1,28)	0,38	0,97	(0,80;1,19)	0,79
Systolic blood pressure (mm. Hg)	0,97	(0,79;1,19)	0,75	1,08	(0,93;1,26)	0,31
Diastolic blood pressure (mm. Hg)	1,05	(0,76;1,44)	0,77	1,16	(0,91;1,48)	0,22
HDL-cholesterol (mg/dL)	0,94	(0,80;1,11)	0,46	0,87	(0,74;1,02)	0,09
LDL-cholesterol (mg/dL)	1,00	(0,95;1,06)	0,95	0,98	(0,90;1,06)	0,57
Triglycerides (mg/dL)	1,02	(0,99;1,05)	0,23	1,02	(0,94;1,11)	0,60
Waist circumference (cm)	1,28	(1,07;1,54)	0,01	1,12	(0,98;1,28)	0,09
Body mass index (kg/m ²)	1,92	(1,21;3,05)	0,01	2,04	(1,40;2,98)	0,00
Glucose level (per 10 mg/DL)	1,02	(0,90;1,14)	0,80	1,07	(1,02;1,13)	0,01
History of diabetes mellitus	1,31	(0,38;4,5)	0,67	1,47	(1,02;2,12)	0,04
Mean common CIMT (mm)	1,34	(0,61;2,94)	0,47	0,61	(0,21;1,71)	0,34
Mean maximum CIMT (mm)	0,94	(0,46;1,90)	0,86	0,51	(0,25;1,05)	0,07

OR: odds ratio; 95%CI: 95% confidence interval. Odds ratios represent the odds on completeness of measurements (complete = CIMT measurements at all 12 artery segment - wall combinations) with an increase of 10 units of the risk factor, except for mean common and mean maximum CIMT

body mass index was related to an increased risk of incompleteness with an OR (95%CI) 2.04 (1.40; 2.98). Waist circumference showed the same trend; however, this did not reach statistical significance (Table 3). Indicators of glucose intolerance (diabetes and glucose) were significantly related to lack of completeness; however, in an analyses in which BMI was taken into account, the glucose intolerance relations lost statistical significance. *P* value for diabetes mellitus in adjusted models was 0.15 and 0.06 for glucose levels, indicating that the relations with glucose intolerance is mainly due to body mass index.

Change Over Time in Completeness

To check whether there was change in completeness over time, we repeated these analyses for both studies for the duplicate end of study ultrasound scans (results not shown). The results were comparable with a slight improvement for completeness in all angles and artery-wall combination, most probably due to the increasing experience of sonographers and readers who performed the ultrasound scans. Again, the near wall of the internal carotid artery and the extreme angle 180° had the lowest level of completeness.

Discussion

The present study provides empirical data on the completeness of CIMT using current ultrasound protocols. We show that the completeness of CIMT measurements is very high, and is related to segments of

the carotid artery, the wall and the angles at which they are examined. Furthermore, increased body mass index and waist circumference affects the ability to obtain CIMT measurements. Finally, the characteristics of the study population also appear to be an influence.

There are some methodological issues that need to be considered. In the current analyses we recorded the presence of CIMT measurement without further studying the CIMT values for correctness. Some CIMT measurements might have been incorrect and thus should have been removed from the dataset and thus our completeness rates may be overestimated. However, because of the high standard of the core laboratory in which the measurements were performed, with periodic quality assessments of intra- and inter-reader reproducibility, we consider that a material effect of inaccurate measurements on our findings is unlikely. Furthermore, these were the CIMT measurement on which the original literature^{11, 12)} was based.

Comparison of our findings with other studies is difficult, since the literature generally only presents overall completeness rates, which to some extent are unclear as to what determines the numerator and denominator. Overall reported completeness rates included 88% in the ENHANCE-study¹³⁾ and 88.6% in the OPAL study²¹⁾. Specified completeness measures were provided in the observational Muscatine study among young and middle-aged adults²²⁾ with percentages of complete CIMT measurements at the common carotid artery (near wall: 98.9%; far wall:

99.7%), the carotid bifurcation (near wall: 92.7%; far wall: 92.8%) and the internal carotid artery (near wall: 74.0%; far wall: 88.0%). Our overall estimates in FH and MD subjects compare favorably with those results.

In the RADIANCE studies, sonographers and readers were trained and certified before the study. Furthermore, continuous quality control measures were taken¹⁸. Our longitudinal findings suggest that the experience of sonographers and readers minimally affects the improved measurement availability of segments and angles, and thus point towards patient characteristics as the main source of completeness.

Completeness was lower in the mixed dyslipidemia population than the familial hypercholesterolemia population, which may be attributed to several aspects. First, the MD population was clearly more overweight, which is related to more incompleteness through either a physical limitation (short, thicker neck), which makes image acquisition more difficult, or through the fact that the ultrasound appearance of the CIMT in the near and far walls in these subjects is more difficult to distinguish because of surrounding tissues. Secondly, the MD population had a more extensive atherosclerosis burden, as indicated by thicker common and mean maximum CIMT. It is well appreciated that arterial walls are more difficult to visualize in the presence of acoustic shadowing, and thus a CIMT measurement is more difficult to perform. Finally, the way atherosclerosis develops in FH patients may be different than in MD patients; the former giving rise to more circular homogenous development, whereas the latter more heterogenous and plaque like²³.

In contrast to general opinion (i.e., high lack of completeness for bifurcation and internal segments), our findings indicate that high levels of completeness can be obtained for most artery-wall combinations of the carotid artery if multiple measurements are performed per artery-wall combination (multiple angles). The question that has not been addressed is whether lack of completeness affects the estimated CIMT progression rates and affects the direction and magnitude of the treatment effect. Presently, several statistical models exist that can be applied to datasets with missing data, e.g. multilevel linear mixed-effects model^{7, 24-26}. In this statistical approach, regression lines are fitted using restricted maximum likelihood methods to site-specific CIMT values rather than to means over carotid sites to deal with missing data. The reason for this is that some carotid artery sites are consistently more difficult to visualize than others, giving rise to missing data, depending on the site. These

models, using all available CIMT measurement points at all visits, provide progression estimates that are less biased by lack for completeness. Another approach to deal with missing data is imputation²⁷⁻²⁹. To the best of our knowledge, the consequence of imputation on CIMT progression estimates and treatment effects has not been quantified, although in one study⁷ the application of imputation was described briefly, not affecting the main results. Finally, an approach to limit lack of completeness, is to restrict the ultrasound protocol to segments, walls and angle that show high completeness levels; however, studies into the effect of such choices on reproducibility, CIMT progression estimates and the ability to detect treatment effects are very limited³⁰, have only been published in abstract form at conferences³¹, and stem from our group. Generally, these analyses indicate that multi-angle protocols perform 'better' in terms of reproducibility (higher), progression rates (more precise) and treatment effect (larger and more precise).

In conclusion, with the advanced ultrasound technology available today it is possible to obtain a high level of completeness in CIMT trials. Apart from the type of population studied, body mass index and waist circumference are important in achieving complete CIMT measurements.

Trial Registration

RADIANCE 1 ClinicalTrials.gov number, NCT00136981

RADIANCE 2 ClinicalTrials.gov number, NCT00134264

Conflicts of Interest

Dr Dogan and Dr van Duivenvoorden report no conflict of interest.

Dr Kastelein reports receiving consulting fees and lecture fees from Pfizer.

Dr. Shear reports being an employee of Pfizer at the time of the conduct of the study.

Dr. Grobbee reports receiving consulting fees, lecture fees and grant support from Pfizer, AstraZeneca, Servier, Organon, Merck, and Unilever.

Dr Evans has received honoraria, consulting fees, and grant support for professional input on CIMT issues from Astra-Zeneca, Organon, and Pfizer.

Dr. Visseren has received research grants from Merck and the Netherlands Organisation for Health Research and Development.

Dr. Bots has received consulting fees, lecture fees and grant support from Pfizer, AstraZeneca, Servier, Organon, Merck, and Unilever.

No other potential conflicts of interest relevant to this article were reported.

APPENDIX

Core Laboratories

CIMT Laboratory Europe (C van Everdingen, A Geerts, M Geurtsen, M Djuanda, A Kuin, F Leus, R Meijer, D Mooiweer-Bogaardt, K Nijssen, H Noordzij, L Romkes, B Sies; E Stooker, F Verhey, B van der Vlist, L van der Vlist, E Wineke, H Wisse) and at the CIMT Core Laboratory United States (M Barr, K Bettermann, S Burton, A Conner-Day, B Ettenger, J Griffin, C Halverson, B Holley, L Hoots, J Fleshman, M Lauffer, L Passmore, C Sharpe, M Wilder, P Miller, T Vitek, G Wolgast).

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