Original Article

Mean Common or Mean Maximum Carotid Intima-Media Thickness as Primary Outcome in Lipid-Modifying Intervention Studies

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Aim: Carotid intima-media thickness (CIMT) measurements are used as a disease outcome in randomized controlled trials that assess the effects of lipid-modifying treatment. It is unclear whether common CIMT or mean maximum CIMT should be used as the primary outcome. We directly compared both measurements using aspects that are of great importance in deciding which is most favorable for use in clinical trials.

Methods: A literature search was performed (PUBMED, up to March 31, 2008). Fifteen trials with lipid-modifying treatment were identified that had information on both outcome measures. Common CIMT and mean maximum CIMT were compared on reproducibility, strength of relation with LDL and HDL cholesterol and congruency of their results (harm/neutral/beneficial) with data from event trials.

Results: Findings showed that the reported reproducibility was high for both measurements, although a direct comparison was not possible. The relationship between the achieved LDL-C and HDL-C levels with CIMT progression was modest and showed no difference in magnitude between CIMT measurements. CIMT progression rates differed across carotid segments with the highest progression rates observed in the bifurcation segment. Treatment effects differed across carotid segments without a clear preference pattern. Trials using mean maximum CIMT progression more often (12 out of 15 studies) paralleled the findings of event trials in contrast to the mean common CIMT (11 out of 15 studies), a difference not reaching statistical significance.

Conclusions: Based on the literature, with equal results for reproducibility (assumed), lipid relationship and congruency with event findings, but with treatment effects that differ across carotid segments that can not be predicted, the mean maximum CIMT as the primary outcome may be preferred in trials on the impact of lipid-modifying interventions. One advantage is that information on mean common CIMT can generally be obtained easily in protocols assessing mean maximum CIMT, but not the other way around.

Introduction

The change in carotid intima-media thickness (CIMT) over time has increasingly been used as an alternative outcome measure for cardiovascular events in studies that assess the effect of drugs to modify atherosclerotic vascular disease, especially lipid-modifying drugs. In measuring CIMT, there are several options to choose from with regard to the primary outcome parameter. In some trials, the primary outcome is the change in common CIMT progression, whereas in others the change in mean maximum CIMT progression is chosen. Mean common CIMT is generally based on CIMT measurements obtained from only the far or both the far and near walls of the common

Table 1. Search strategy for identification of articles

Search string (PubMed up to March 31, 2008)	# hits left
#1 (randomized AND (control OR controlled) AND (trial OR trials)) OR trial OR trials OR rct OR etiology OR intervention	6133182
#2 drug OR therapy OR treatment OR lipid OR lowering OR lipid-lowering OR statin OR statins	7889578
#3 (carotid AND (intima OR intimal) AND (media OR medial)) OR ((intima-media OR intimal-media) AND thickness) OR CIMT OR IMT AND (progression OR regression OR change) AND (mean OR common OR maximum)	1188
#1 and #2 and #3	561
English language only	533
Title/abstract/full text screening excluded • not a randomized trial involving statin treatment • no blinding of the treatment with respect to CIMT reading • not reporting both mean common CIMT measurement and mean maximum CIMT measurements	15

carotid artery segment on the left and right sides, 1 to 3 cm proximal to the carotid bifurcation. Suitable ultrasound images are usually stored once or multiple times. CIMT is generally measured off line from these stored images when the measurement is usually performed over a 10 mm artery segment for each image, and is expressed as the mean common CIMT in mm. The mean maximum CIMT is a summary measure that is computed as the mean of the single maximum CIMT measurements measured in 4 to 12 standard carotid artery walls (far or near wall of 2 to 3 distinct carotid segments: the common carotid segment (CCA), carotid bifurcation (BIF) and the internal carotid artery (ICA) segment) on both the left and right sides. Mean maximum CIMT ultrasound assessment generally also allows for acquiring the mean common CIMT as this approach was designed for an acquisition protocol.

The choice of CIMT measurement as the primary outcome in trials of lipid-modifying drugs is generally based on personal preference and expert opinion. An evaluation of published data to support the use of either measure is lacking, but would facilitate evidence-based decisions. Arguments in favor of the common CIMT measurement over the mean maximum CIMT measurement generally include higher reproducibility, complete measurement assessment (very little missing data on common CIMT), an equally strong relation with future events, a stronger relation between progression rates and lipid levels, higher susceptibility to lipid-lowering treatment, and a more rapid ultrasound protocol[1, 2]. Support for mean maximum CIMT measurement over common CIMT measurement includes the view that reproduc-

ibility, measurement assessment, risk prediction, and lipid level relationships are similar to those of the common CIMT, but that the mean maximum CIMT assesses all aspects of carotid atherosclerosis[3]. This is of importance since carotid CIMT progresses differently over the carotid segments and it appears unpredictable at which segment lipid-modifying treatment might exert an effect[4]. In addition, when the mean maximum CIMT measurement is chosen, information on the mean common CIMT can also be collected so that both the mean maximum CIMT and the mean common CIMT can be used as outcome measurements.

We directly compared both measurements using aspects that are of great importance in deciding which is most favorable for use in clinical trials.

Methods

Identification of Articles

The library database PUB-MED (www.ncbi.nlm.nih.gov) was used to identify all published lipid-modifying randomized controlled trials that used CIMT as an outcome parameter (**Table 1**). The search was performed up to March 31, 2008. Two authors (SD, MLB) reviewed all articles. In addition, references in the retrieved articles were checked and added when the initial search did not include these trials. Studies were excluded when they did not involve a randomized trial, when blinding of the treatment with respect to CIMT reading was not established or when the report did not present progression rates for both mean common CIMT measurement and mean maximum CIMT measurements. Information retrieved from the articles included reproducibility measures; LDL and

HDL cholesterol levels at baseline and at end of study per treatment arm; segment-specific CIMT progression rates with corresponding standard errors; mean common CIMT progression rates with corresponding standard errors; mean maximum CIMT progression rates with corresponding standard errors; treatment effect and numbers of subjects in the control and intervention arms. In addition, we performed a search to identify trials with clinical events as an outcome for the lipid-lowering drugs used in the CIMT trials.

Data Analyses

First, results on reproducibility and differences in segment-specific CIMT progression rates are presented in a descriptive manner. Second, the relation between the achieved end of study HDL- and LDL-cholesterol levels and CIMT progression was examined using a weighted random effects regression model. Progression rates in each treatment arm of a trial were used. Studies were weighted by the inverse of the squared standard error of the progression rate in the treatment arm using a meta-regression statement in STATA (version 10), which also took the between-study arm variance into account (random effect model). The relation was estimated using the beta coefficient of the regression model with its corresponding 95% confidence interval (95%CI). When the confidence intervals between the estimated relation of LDL (or HDL) with common CIMT progression and with mean maximum CIMT progression did not overlap, statistical significance was assumed. Thirdly, the relation between mean common and mean maximum CIMT progression was assessed in a similar manner. Fourthly, to compare CIMT progression rates between segments, 95% CIs around the progression rates were estimated using data from the published reports. When the 95% CI did not overlap, progression rates were assumed to be statistically significant different. No adjustments were made for inflation of the Type I error due to multiple testing. Finally, to assess congruency we presented similarities and differences in the study outcome of the mean common CIMT and the mean maximum CIMT with the outcome of the event trials in a qualitative manner. For the proportion, we estimated 95% CI. As CIMT is a surrogate measure for atherosclerotic cardiovascular disease, results of CIMT trials should mirror event trials.

Results

Search Strategy

The literature search gave 563 hits. Restriction to the English language, and scanning through the title, abstract and, when needed, the main paper we identified 27 CIMT trials in which the effect of lipid lowering on CIMT progression was reported[5-31]. Of these, 14 provided information on both mean common CIMT and mean maximum CIMT. Through a reference check one additional trial was identified[32]. Ultimately, this resulted in 15 CIMT trials for analyses[5, 7-10, 12, 13, 15, 16, 18, 19, 21, 22, 30, 32].

For each drug used in the CIMT trials, the corresponding event trials were searched, resulting in 15 clinical event trials for lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, torcetrapib, rosuvastatin and ezetimibe, as presented in **Table 2**[33-49].

Reproducibility

For three trials[8, 13, 30], information on reproducibility could not be retrieved from the publication (**Table 2**). Reproducibility was expressed in various manners and for different processes (re-reading/repeated visits). Reproducibility information for both the mean common CIMT and mean maximum CIMT was reported in none of the papers. While the results generally showed excellent reproducibility for either measure, a direct comparison of reproducibility between mean common CIMT and mean maximum CIMT measurements could not be made from the presented data (**Table 3**).

Segment-Specific CIMT Progression and Treatment Effects

CIMT progresses differently over time in the common carotid segment, the carotid bifurcation and the internal carotid artery[4]. This is further exemplified by the results from the placebo arms in randomized controlled clinical trials (**Table 4**). In the placebo arms of the trials, absolute CIMT progression was generally higher for the carotid bifurcation than common carotid segment progression in six of the eight placebo controlled trials, which reached statistical significance in four of the trials (**Table 3**). In all eight placebo controlled trials the carotid bifurcation CIMT progression was lower in the intervention arm than in the placebo arm (**Table 3**), which reached statistical significance ($p < 0.05$) in four out of eight trials. The common CIMT progression estimates were lower in the intervention group in seven out of the eight trials, in which statistical significance was reached in five out eight trials. The internal CIMT progression estimates were lower in three out of five trials, and were statistically significant in two. The magnitude of segment-specific CIMT progression differed across trials, ranging from −0.021 to 0.046 mm/year in the common,

Table 2. Selected characteristics of randomized controlled trials of the effect of lipid-modifying drugs on changes in carotid intima-media thickness over time

Study	Intervention	Population	Follow-up, years	CIMT measurement
ACAPS[12]	Lovastatin 20-40 mg vs. placebo	919 asymptomatic patients and moderately elevated LDL-C	3	Near and far wall CCA, BIF, and ICA
ASAP[22]	Simvastatin 40 mg vs. atorvastatin 80 mg	325 patients with familial hypercholesterolemia	3	Far wall CCA, BIF, and ICA
BCAPS[13]	Fluvastatin 40 mg vs. placebo	793 asymptomatic patients	3	Far wall CCA and BIF
CAIUS[18]	Pravastatin 40 mg vs. placebo	305 asymptomatic patients and moderately elevated LDL-C	3	Near and far wall CCA, BIF, and ICA
CERDIA[5]	Simvastatin 20 mg vs. placebo	250 patients with diabetes type 2 and without CAD	4	Near and far wall CCA, BIF, and ICA
ENHANCE[16]	Simvastatin 80 mg + Ezetimibe 10 mg vs. Simvastatin 80mg	720 patients with heterozygous familial hypercholesterolemia	2	Far wall CCA, BIF, and ICA
HYRIM[32]	Fluvastatin 40 mg vs. placebo	568 drug-treated hypertensive men	4	Far wall CCA
INDIA[21]	Atorvastatin 10 mg vs. placebo	150 patients with CAD and normal LDL-C	1	CCA, BIF, and ICA
KAPS[19]	Pravastatin 40 mg vs. placebo	447 asymptomatic patients and elevated LDL-C	3	Far wall CCA and BIF
METEOR[9]	Rosuvastatin 40 mg vs. placebo	984 asymptomatic patients with elevated LDL-C	2	Near and far wall CCA, BIF, and ICA
PHYLLIS[30]	Pravastatin versus placebo	508 hypertensive, hypercholesterolemic patients with asymptomatic carotid atherosclerosis	2, 6	Near and far wall CCA, BIF
PLAC II[8]	Pravastatin 10-40 mg vs. Placebo	151 patients with CAD and elevated LDL-C	3	Near and far wall CCA, BIF, and ICA
RADIANCE 1[15]	Atorvastatin 56.5 mg + torcetrapib 60 mg vs. Atorvastatin 56.5 mg	904 patients with heterozygous familial hypercholesterolemia	2	Near and far wall of CCA, BIF, and ICA
RADIANCE 2[7]	Atorvastatin 13.5 mg + torcetrapib 60 mg vs. Atorvastatin 13.5 mg	752 patients with mixed dyslipidaemia	2	Near and far wall CCA, BIF, and ICA
REGRESS[10]	Pravastatin 40 mg vs. Placebo	225 men with CAD and normal to moderately elevated total cholesterol	2	Near and far wall CCA, BIF, ICA

Abbreviations: CIMT, carotid intima-media thickness; CI, confidence interval; CCA, common carotid artery; BIF, carotid bifurcation; ICA, internal carotid artery; MI, myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

from −0.022 to 0.090 mm/year in the bifurcation and from −0.035 to 0.044 mm/year in the internal carotid artery.

Fig. 1 describes the relation between mean common CIMT progression and mean maximum CIMT progression. The regression equation for the relation indicated that an increase in mean common CIMT progression was related to a significant 1.21 um [95% CI 0.86, 1.56] increase in mean maximum CIMT. The R squared for the model was 0.79.

Table 3. Parameters reported in the trials to indicate reproducibility of mean common and mean maximum CIMT measurement in randomized controlled trials on lipid-modifying drugs

Study name	Reproducibility parameters						
	Not reported	ICC	CoV	MAD	MD (SD) (mm)	Pearson R	Corr.Coef
ACAPS[12]		0.75*					
PLAC-II[8]	x						
KAPS[19]						CCA: 0.89 BIF: 0.79	
CAIUS[18]				0,07	0,007 (0.095)		0.85
REGRESS[10]		0.88					
BCAPS[13]	x						
ASAP[22]			<5%				
CERDIA[5]					0,004 (0,054)		
PHYLLIS[30]	x						
INDIA[21]			<1%				
HYRIM[32]			<6%				
RADIANCE 1[15]		0.90*					
RADIANCE 2[7]		0.92*					
METEOR[9]		0.93*		0,056			
ENHANCE[16]		0.92					

ICC: intra class correlation coefficient at baseline, CoV: coefficient of variance, MAD: mean absolute difference (mm) whereby the difference is absolutized, MD (SD) (mm): mean difference (standard deviation) in millimeters, Pearson R: Pearson's correlation coefficient, Corr.Coef (without indicating which correlation coefficient), CCA: common carotid artery, BIF: bifurcation of carotid artery. *ICC Intraclass correlation coefficients based on repeated visits

Achieved HDL and LDL Levels and CIMT Progression

The trials differed considerably in the studied population and in the methodology used to quantify CIMT. As both affect CIMT measurements and progression rates, two analyses were performed to study the strength of the relation between the achieved (end of trial) LDL cholesterol level and CIMT progression. One approach used all trial data, and another approach used only information from the six trials performed in asymptomatic populations and in a placebo-controlled study[8-10, 12, 18, 30]. Using all trials, the relationship between achieved LDL cholesterol and CIMT progression was modest: one mmol/L increase in achieved LDL was associated with 2.4 μm/year [95% CI -3.1, 7.9] increase in common CIMT progression and with a 3.6 μm/yr [-4.8, 12.0] increase in mean maximum CIMT progression. Using placebo-controlled trials, the relationship between the achieved LDL cholesterol and CIMT progression: 1 mmol/L increase in LDL was associated with 6.0 μm/year [95% CI -0.9, 13.0] increase in common CIMT progression and with a 6.8 μm/year [95% CI -4.9, 18.4] increase in mean maximum CIMT pro-

gression. As the 95% CI overlap, the differences in the strength of the relationship of LDL with progression did not differ between the two CIMT measurements.

For HDL per mmol/L increase, using all trials, the findings were -24 μm/year [95% CI -51, 3.0] increase in common CIMT progression and a -23 μm/year [-65, 19] increase in mean maximum CIMT progression. Using placebo-controlled trials, the findings were -18.6 μm/year [95% CI -48, 11] increase in common CIMT progression and a -17.4 μm/year [95% CI -66, 32] increase in mean maximum CIMT progression. As the 95% CI overlap, the differences in the strength of the relationship of HDL with progression did not differ between the two CIMT measurements.

Congruency between Results for Mean Common and Mean Maximum CIMT from CIMT Trials and Results from Event Trials

The outcomes of the CIMT trials for mean common CIMT, mean maximum CIMT, and the congruency with results from event trials are presented in Table 4. The results of event trials indicated that treatment with lovastatin, pravastatin, fluvastatin, atorvas-

Table 4. Carotid intima-media thickness progression (mm/year) per carotid segment in randomized controlled trials on the effect of lipid-modifying treatment

Study name	Intervention	CCA [95% CI]			BIF [95% CI]			ICA [95% CI]		
KAPS[19]	Pravastatin 40 mg	0,010†	0,002	0,018	0,028†	0,019	0,037	NR		
	Placebo	0,029†	0,021	0,037	0,040†	0,031	0,049	NR		
PLAC-II[8]	Pravastatin 40 mg	0,030†	0,019	0,041	0,090	0,060	0,120	0,044	0,015	0,073
	Placebo	0,046†	0,035	0,057	0,104	0,074	0,134	0,043	0,014	0,072
CAIUS[18]	Pravastatin 40 mg	−0,003†	−0,008	0,002	−0,013†	−0,021	−0,005	NR		
	Placebo	0,008†	0,003	0,013	0,004†	−0,004	0,012			
REGRESS[10]	Pravastatin 40 mg	−0,005	−0,044	0,034	0,030	−0,048	0,108	−0,030	−0,108	0,048
	Placebo	0,010	−0,029	0,049	0,045	−0,033	0,123	−0,035	−0,133	0,063
ASAP[22]	Atorvastatin 80 mg	−0,021	−0,043	0,001	−0,011†	−0,050	0,028	−0,016	−0,065	0,033
	Simvastatin 40 mg	−0,009	−0,011	−0,007	0,031†	−0,004	0,066	0,044	−0,040	0,128
BCAPS[13]	Fluvastatin 40 mg	0,004	−0,007	0,015	0,057	0,018	0,096	NR		
	Placebo	0,012	−0,003	0,027	0,079	0,033	0,125	NR		
CERDIA[5]	Simvastatin 20 mg	0,002	−0,009	0,013	−0,017	−0,032	−0,002	0,005	−0,025	0,035
	Placebo	−0,006	−0,018	0,006	−0,010	−0,027	0,007	0,031	−0,009	0,071
INDIA[21]	Atorvastatin 10 mg	−0,008†	−0,015	−0,001	−0,022†	−0,038	−0,006	−0,009†	−0,017	−0,001
	Placebo	0,011†	−0,002	0,024	0,013†	−0,003	0,029	0,007†	−0,001	0,015
METEOR[9]	Rosuvastatin 40 mg	−0,004†	−0,006	−0,001	−0,004†	−0,007	−0,001	0,004†	−0,001	0,009
	Placebo	0,008†	0,004	0,012	0,017†	0,007	0,027	0,015†	0,006	0,023
RADIANCE 2[7]	Atorvastatin 13.5 mg* & torcetrapib 60 mg	0,013	0,009	0,017	0,028	0,013	0,044	0,025	0,011	0,039
	Atorvastatin 13.5 mg*	0,008	0,004	0,012	0,033	0,017	0,049	0,036	0,022	0,049
ENHANCE[16]	Simvastatin 80 mg & Ezetimibe 10 mg	0,001	−0,007	0,009	0,007	−0,006	0,021	0,005	−0,008	0,018
	Simvastatin 80 mg	0,001	−0,007	0,010	0,003	−0,011	0,017	0,000	−0,013	0,012

Data were from published reports. When segment-specific estimates could not be retrieved, trials were excluded (ACAPS, RADIANCE 1, PHYLLIS, HYRIM). CCA: common carotid artery segment, BIF: bifurcation segment, ICA: internal carotid artery segment, NR: not reported in the paper or not assessed in the study; * Mean titrated daily dose used in the trial. † difference between interventions statistically significant ($p < 0.05$)
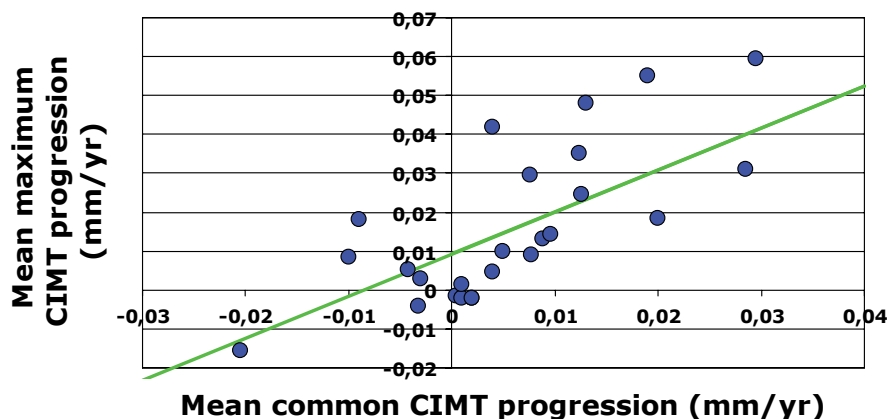
Fig. 1. Relation of common CIMT progression with mean maximum CIMT progression based on results from the BEISHUIZEN Study, RADIANCE 2, PLAC-II, METEOR, ACAPS, BCAPS, RADIANCE 1, CAUIS and KAPS Study. Results based on a weighted random effects regression model.

Table 5. Congruency of outcome of CIMT trials with outcome of event trials

		CIMT-trials		Event-trial	Congruency CIMT trial and event trial		
Study name	Intervention/control	Trial outcome*		Trial outcome	No difference	Favors[†] mean common	Favors[†] mean max
		Mean common CIMT	Mean Maximum CIMT				
ACAPS[12]	Lovastatin/placebo	Neutral	Benefit	Benefit[39]			X
PLAC-II[8]	Pravastatin/placebo	Benefit	Neutral	Benefit[33, 47]		X	
KAPS[19]	Pravastatin/placebo	Benefit	Benefit	Benefit[46]	X		
CAIUS[18]	Pravastatin/placebo	Benefit	Benefit	Benefit[46]	X		
REGRESS[10]	Pravastatin/placebo	Neutral	Benefit	Benefit[33, 47]			X
PHYLLIS[30]	Pravastatin/placebo	Neutral	Benefit	Benefit[46]			X
BCAPS[13]	Fluvastatin/placebo	Benefit	Neutral	Benefit[40, 41]		X	
HYRIM[32]	Fluvastatin/lifestyle	Benefit	Benefit	Benefit[34, 40, 41, 44]	X		
METEOR[9]	Rosuvastatin/placebo	Benefit	Benefit	Benefit[48]	X		
ASAP[22]	Atorvastatin/simvastatin	Neutral	Benefit	Benefit[37, 43]			X
CERDIA[5]	Simvastatin/placebo	Neutral	Neutral	Benefit[37]	X		
INDIA[21]	Atorvastatin/placebo	Benefit	Benefit	Benefit[38, 45]	X		
RADIANCE 1[15]	Torcetrapib + Atorvastatin/Atorvastatin	Harm	Neutral	Harm[35]		X	
RADIANCE 2[7]	Torcetrapib + Atorvastatin/Atorvastatin	Neutral	Neutral	Harm[35]	X		
ENHANCE[16]	Ezetimibe + Simvastatin/Simvastatin	Neutral	Neutral	Neutral[49]	X		

Implications of the results of lipid-modifying randomized controlled trials on CIMT progression are presented by type of primary outcome. Trials are only included that provide information on both common and mean maximum CIMT change. *Trial outcome defined as: Neutral: no significant difference in CIMT progression between the intervention group compared to the control group = reject new treatment; Benefit: significant reduction in CIMT progression in the intervention group compared to the control group = accept new treatment; Harm: significant increase in CIMT progression in the intervention group compared to the control group = reject new treatment. [†]favor: defined as an outcome measure that confirms the primary research question.

tatin, simvastatin and rosuvastatin has beneficial effects on events[33, 34, 36-41, 43-48] (**Table 5**). The results of torcetrapib event trials were classified as harmful (harm), as the event trial showed increased risk of mortality and morbidity[35]. For ezetimibe, the only available evidence on event risk comes from the SEAS

trial of subjects with aortic stenosis. The results showed a neutral effect on the reduction of event with ezetimibe as compared to placebo in subjects treated with 80 mg simvastatin[49].

In eight CIMT trials, the results showed a similar direction for both CIMT and event outcome measurements, while in seven CIMT trials, congruency with event trials depended on the choice of the primary outcome measure. In four trials[10, 12, 22, 30], expected effects were found for the mean maximum CIMT but not for the common CIMT for mean, whereas in three trials[8, 13, 15] an effect was found for the common CIMT and not for the mean maximum CIMT. Thus, when relying on the mean maximum CIMT only, three trials would have been falsely negative (no effect on CIMT, clear clinical events effect). When relying on common CIMT only, four studies were falsely negative; however, there was no statistical significant difference between the congruency percentage for the common CIMT (73% [95% CI 51, 96]) and that for the mean maximum CIMT (87% [95% CI 69, 100]).

Discussion

Our review indicated that the mean common CIMT and mean maximum CIMT measurements showed equal results for reproducibility, lipid relations and congruency with event findings. The main difference between the two measurements is that treatment effects differ across carotid segments and that the treatment effects do not appear to be predictable.

Some issues in this review need to be considered. Firstly, in the published reports, information on reproducibility of mean common and mean maximum CIMT was not given separately. Furthermore, the parameters reflecting reproducibility presented in the reports varied so much (**Table 2**) that a direct formal comparison of the reproducibility of both measures was not possible. This observation calls for standardization in the assessment and the reporting of reproducibility data in CIMT trials. The most important estimate of reproducibility seems to be based on two CIMT assessments that were separated in time (preferable days or weeks), since this approach captures the variability in a CIMT measurement due to the combination of acquisition, sonographers, readers, and participants. Parameters to describe reproducibility are detailed elsewhere[50, 51]. Another aspect is that interest should lie in reporting the reproducibility of CIMT progression estimates; however, this has never been done. As a direct comparison of the reproducibility of common CIMT and mean maximum CIMT measurements is impossible by looking across studies, data

on this issue are only available using studies in which the CIMT protocols were quite elaborate and collected information to estimate both CIMT parameters. As far as we know, there is only one report which compares reproducibility parameters for the common and mean maximum CIMT separately[52]. In that study of healthy postmenopausal women, the between-visit reproducibility of both CIMT measurements, based on assessments of at least three different angles of interrogation, including near and far wall measurements, was excellent for both CIMT measurements[52]. The Intraclass correlation coefficient for the common CIMT was between 0.87 and 0.88 and for mean maximum CIMT was between 0.81 and 0.84[52]. Although data from other trials are currently being analyzed taking a similar approach[7, 9, 15], at present the published data are very limited. Secondly, in our comparison we did not address the probability of having missing CIMT data in areas of the carotid tree and how that may affect main trial outcomes. Although most trials report overall completeness information, segment-specific data on completeness is usually lacking. Information from the Muscatine study indicated that complete CIMT could be obtained for the common segment in 99%, for the bifurcation in 93% and for the internal in 88%[53]. We know of only one trial in which analysis addressed missing values in a sensitivity analytic approach, concluding that the lack of CIMT data did not impact the main findings in that trial[9]. Thirdly, we acknowledge that in this review we restricted ourselves to the comparison of two methods of measuring CIMT, the mean common CIMT and the mean maximum CIMT. In other trials, combinations of CIMT measurements (common and bifurcation only, CIMT measurements in areas free of plaque) have been used; however, this restriction does not invalidate the findings, but may restrict the generalizability of our findings. Fourthly, we restricted ourselves to trials into the effect of lipid-modifying agents, and did not extend our analyses to trials into the effect of blood pressure-lowering agents or glucose-modifying agents on CIMT progression; thus, our findings may not be extrapolated to these intervention studies. In addition, we did not address the desirability of using CIMT measurements versus other measurements to quantify atherosclerosis non-invasively, such as the measurement of plaque, plaque characteristics, or volume measurements, in intervention studies as this has been described elsewhere in great detail[54-57]. Our analysis is therefore meant for those that have decided to measure CIMT as the primary outcome in trials, but are still discussing which CIMT measurement is most desirable. Finally, for the

comparison between the two CIMT measurementss we restricted ourselves to trials including both CIMT measurements; therefore, several trials that measured common CIMT progression only were not mentioned here in detail. The results of four of these studies were congruent with results from events trials[6, 14, 24, 25] but in one study were not[17].

When comparing the strength of the relationship between LDL cholesterol achieved and CIMT progression, it is less strong than that in trials on coronary atherosclerosis progression assessed by IVUS or quantitative coronary angiography (QCA)[58, 59] This is mainly a consequence of the differences in study populations and approaches to quantify CIMT between CIMT trials as compared to populations and quantification of total atherosclerotic volume between IVUS and QCA trials. Where quantification of coronary atherosclerosis progression was performed among subjects indicated for coronary angiography, the populations in CIMT studies were asymptomatic low-risk subjects, diabetics, subjects with familial hypercholesterolemia and patients with previous vascular disease. In IVUS and QCA studies, quantification of coronary atherosclerosis progression was more standardized across core laboratories and the currently published IVUS results presented largely come from one core laboratory, whereas that of CIMT measurements does not. Various approaches have been used to quantify CIMT and various core laboratories have been used. The actual value of CIMT depends on the ultrasound equipment used in the studies, the acquisition of the images (near, far wall, single angle, multiple angles), and the offline measurement approach of the CIMT (manual tracings, trailing edges and leading edges, automated edge detection programmes) and the potential presence or absence of reader drift in a trial[3] These differences in approaches to quantify CIMT do not affect the difference in CIMT progression between treatment arms in one trial, but do hamper studies into the relationship of achieved lipid levels and CIMT progression using treatment arm data from various trials.

In this era, in which imaging of atherosclerosis becomes increasingly important in studying the efficacy of new anti-atherosclerotic treatments, the choice of the endpoints is crucial and several lines of evidence support the use of CIMT measurements. Increased CIMT is related to coronary atherosclerosis in a manner expected from pathology studies[60], and increased CIMT predicts the occurrence of future events[61]. In addition, it is important for trials that use CIMT progression as a surrogate marker for vascular events that the findings in the trial parallel the results of event tri-

als. The studies included in this review were lipid-modifying trials using a statin versus placebo or versus another less potent statin. Had the 15 trials used the common CIMT measurement only as primary outcome, in four trials a different, and potentially 'wrong', conclusion would have been reached. In contrast, had the trials used mean maximum CIMT measurements as the primary outcome, 3 trials would have led to a different conclusion; however, the difference between two CIMT measurements was not statistically significant. In mean maximum CIMT trials, however, information on mean common CIMT is generally also collected and would have been available as a secondary outcome.

What is apparent from **Table 4** is that CIMT progresses differently in different segments of the arterial tree; this was documented earlier[3, 4, 62]. Also, risk factors seem to differ in how they affect segment CIMT progression[4, 62]. Furthermore, the effect of lipid lowering on CIMT progression differs across carotid segments, without a clear pattern; it seems unpredictable at which segment the agent will show its strongest effect. As CIMT progression is a diffuse process involving all carotid artery sites, pooling CIMT measurements across arterial segments and walls often yields the most efficient analyses[4].

In a randomized controlled trial using the change in CIMT as the outcome, a primary endpoint must be selected. Apart from the data presented here, budgetary aspects may also to some extent be important in the choice for of primary endpoint. A mean maximum CIMT measurement ultrasound protocol is more laborious, with more time needed for offline CIMT reading than for the common CIMT measurement, thereby making the mean maximum approach more costly than the mean common approach. Data comparing information in terms of the expected benefit and costs are not available.

In conclusion, based on the literature, with equal results for reproducibility (assumed), lipid relations and congruency with event findings, but with treatment effects that differ across carotid segments and that can not be predicted, the mean maximum CIMT as the primary outcome may be preferred in trials on the impact of lipid-modifying interventions. An advantage is that information on mean common CIMT can generally be obtained easily in protocols assessing mean maximum CIMT, but not the other way around.

Conflicts of Interests

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