Imaging and Diagnostic Testing

Are changes in carotid intima-media thickness related to risk of nonfatal myocardial infarction? A critical review and meta-regression analysis

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Background Carotid intima-media thickness (CIMT) is increasingly being used as a surrogate end point in randomized control trials (RCTs) of novel cardiovascular therapies. However, it remains unclear whether changes in CIMT that result from these therapies correlate with nonfatal myocardial infarction (MI).

Methods We performed a literature search of RCTs from 1990-2009 that used CIMT. Eligible RCTs (1) included quantitative and sequential assessments in CIMT at least 1 year apart and (2) reported nonfatal MI. Across RCTs, random-effects metaregression was employed to correlate differences in mean change in CIMT between treatment and control groups over time with the log odds ratios of developing nonfatal MI during follow-up.

Results Overall, we identified 28 RCTs with 15,598 patients. Differences in mean change in CIMT over time between treatment and control groups correlated with developing nonfatal MI during follow-up: for each 0.01 mm per year smaller rate of change in CIMT, the odds ratio for MI was 0.82 (95% CI, 0.69 to 0.96; $P = .018$). Results were similar in subgroups of RCTs with >1 year follow-up ($P = .018$) and those with at least 50 subjects in the treatment group ($P = .019$). However, there was no significant relationship between mean change in CIMT and nonfatal MI in RCTs evaluating statin therapy or those with high CIMTs at baseline ($P > .20$ in both instances).

Conclusions Less progression in CIMT over time is associated with a lower likelihood of nonfatal MI in selected RCTs; however, these findings were inconsistent at times, suggesting caution in using CIMT as a surrogate end point. (Am Heart J 2010;160:701-14.)

Background

Measuring surrogate end points of atherosclerosis is increasingly being used in randomized controlled trials (RCTs) of novel cardiovascular therapies.[1] Proponents argue that this approach avoids the substantial costs and lengthy follow-up required of traditional RCTs that are focused on "hard," but uncommon, clinical outcomes such as myocardial infarction (MI).[2] However, critics have pointed out that while they may be correlated with clinical outcomes, changes in surrogate end points over time that result from a particular therapy may not necessarily be predictive of future events.[3-5]

In recent years, assessment of carotid intima-media thickness (CIMT) has emerged as a simple and noninvasive technique for measuring atherosclerotic burden.[6] Unlike serum biomarkers that have been linked to the risk of atherosclerosis, CIMT has the theoretical advantage of directly visualizing a final consequence of the disease itself, namely atherosclerosis in the vessel wall.[7] Although the presence and extent of cross-sectional measurements of CIMT have been linked to a risk of subsequent cardiovascular events in several observational studies,[8-11] it remains unclear whether changes in CIMT over time also correlate with future clinical outcomes. Establishing this last issue is critical if CIMT is to be considered a useful surrogate end point in RCTs of cardiovascular therapies.

Accordingly, we performed a critical review of published RCTs that quantified changes in CIMT over time using B-mode carotid ultrasonography. We included any RCT that assessed the impact of a therapy on changes in CIMT on the occurrence of MI, irrespective of the particular therapy studied (e.g., statins).

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Methods

Literature search, data extraction, and study quality

A systematic review of the literature was conducted using the PubMed, MEDLINE and Current Contents databases, as well as the Cochrane Central Register of Controlled Trials from January 1990 to May 2009. We used a previously described search string[12,13] for identifying RCTs that was supplemented by the Medical Subject Headings *CIMT*, *carotid intima-media thickness*, *carotid ultrasonography*, *and B mode ultrasonography* to identify relevant articles. Two investigators (ZDG, JAV) reviewed the titles and abstracts of retrieved articles to identify potential RCTs for inclusion. Eligible RCTs had to include (1) randomized treatment and control groups, (2) quantitative and serial assessments of CIMT occurring at least 1 year apart, and (3) data on clinical outcomes including nonfatal MI in patients undergoing measurements of CIMT.

Information from eligible RCTs was abstracted independently by at least two reviewers using a standardized form. Abstracted data included (1) study size, (2) study population characteristics, (3) the type of drug being studied, (4) imaging protocols for assessing CIMT by carotid ultrasound, and (5) rates of nonfatal MI. For data on nonfatal MI, we accepted the definitions of events used by the authors, including broad categories of acute coronary syndromes. Although we did abstract data on death, we chose to focus our primary analysis on nonfatal MI given that patients who died during the follow-up period could not have undergone full serial assessments of CIMT. We examined the impact of including death in a sensitivity analysis. Data on stroke and coronary revascularization were abstracted but were either infrequently reported, or associated with low event rates in these populations; thus, these data are not formally reported.

We assessed the quality of RCTs by focusing on specific elements of study design (i.e., concealment of allocation during randomization, number of patients screened before enrollment, placebo use, extent of blinding, and follow-up). Any disagreements in abstracted data between reviewers were resolved by discussion. When multiple publications were available from the same study population, we extracted data with the longest reported follow-up.

We found CIMT to be measured using several different approaches across RCTs. All RCTs used B-mode ultrasound with multiple angles of the carotid typically used to determine the presence and location of arterial wall dimensions. Depending on the RCT, measurement of different segments was used in the calculation of CIMT, including left and right common carotid, bulb, bifurcation, and internal carotid arteries. In addition, the method for combining measurements from different segments into a summary measure of CIMT varied across RCTs. For this analysis, we reported the mean of mean values from multiple measurements of CIMT, when available; in other instances, the mean of maximum values was used.

Statistical analysis

For each RCT, net effects of a therapy on CIMT at the study level were calculated by subtracting the annualized mean change in CIMT over time in the treatment group from the annualized mean change in CIMT over time in the control group. Random-effects metaregression was used to determine whether changes in CIMT over time were linked to clinical outcomes.[14] We specifically evaluated the extent to which differences in mean changes in CIMT over time between treatment and control groups correlated with the log odds ratio of nonfatal MI.

We constructed 2 × 2 tables of the rates of nonfatal MI between treatment and control groups in order to calculate odds ratios. In RCTs that evaluated multiple treatment groups (ie, >2 arms), we separately created tables that compared each treatment group in that study to the control group. When empty cells were present (because no clinical events occurred in either treatment and/or control groups), 0.5 was added to each cell in order to calculate odds ratios. We then logarithmically transformed odds ratios for the meta-regression analysis but reconverted them prior to reporting to improve interpretation.

Additional sensitivity and subgroup analyses were performed to evaluate the potential impact of key assumptions and study level factors on our overall results. These included an analysis of a combined end point of nonfatal MI and death as well as subgroup analyses that limited RCTs to those with: (1) at least 1 year of follow-up data and (2) at least 100 subjects in the treatment group. We also separately evaluated (1) RCTs of statin versus nonstatin therapy and (2) RCTs with baseline CIMT in the treatment group above and below the median for all the RCTs.

Finally, we performed a sensitivity analysis by sequentially eliminating each RCT, and assessed for the presence of publication bias by using the Begg and Mazumdar adjusted rank correlation test.[15] Weighted bubble plots were constructed to display fitted meta-regression lines for illustrative purposes. Stata Version 9 (StataCorp, LP, College Station, TX) was used for all analyses.

Results

The initial search returned 625 studies, of which 494 were initially excluded after title and abstract review. From these, we identified 28 RCTs with 32 randomized treatment and control groups that evaluated changes in CIMT over time and reported clinical outcomes of nonfatal MI. One study was excluded because outcomes were not reported specifically in the subgroup of patients undergoing CIMT, but rather for the entire study population[16]; another was excluded because it only reported outcomes for death.[17] The overall characteristics and results of the included studies are summarized in Tables I and II. The odds ratios for MI associated with these RCTs are displayed in Figure 1, sorted by smaller changes in CIMT over time in the treatment group relative to the control group.

A total of 15,598 subjects were randomized with 13,748 (85.9%) subjects having follow-up imaging with carotid ultrasound and CIMT measurements. The mean age of subjects in the RCTs was 54.7; 54.2% were men. The study populations varied considerably in their baseline risk for cardiovascular events with 6 studies specifically evaluating patients with established coronary artery disease or strong hereditary factors for atherosclerosis (eg, familial hypercholesterolemia).

Fifteen RCTs examined the effect of lipid-lowering agents on CIMT (with a lipid-lowering treatment at least one arm).[18-32] Specifically, five examined

Table I. Study characteristics

Study	Treated vs control	N*	Population	Follow-up†	Ultrasonography
Furberg et al[18] (ACAPS)§	Lovastatin vs placebo	919	LDL 130-159 mg/dL CIMT: 1 of 12 segments with maximum ≥1.5 mm in common or internal carotid arteries; ≥1.6 mm in bifurcation; all segments <3.5 mm	34 m (mean) 95% follow-up ultrasonography	10 MHz transducer 12 carotid artery segments
Salonen et al[19] (KAPS)	Pravastatin vs placebo	447	CAD LDL ≥155 mg/dL TC <290 mg/dL CIMT ≥1.3 mm	36 m 95% follow-up ultrasonography	10 MHz transducer 4 carotid arterial segments
Crouse et al[20] (PLAC-II)‖	Pravastatin vs placebo	151	Mean LDL ≥155 mg/dL CIMT ≥1.3 mm	36 m 100% follow-up ultrasonography	8 MHz transducer 12 carotid artery segments
Mercuri et al[21] (CAIUS)	Pravastatin vs placebo	305	Mean LDL 150-250 mg/dL; TG ≤ 109 No CAD ≥1 CIMT 1.3-3.5 mm	36 m 86% follow-up ultrasonography	8 MHz transducer 12 carotid artery segments
Borhani et al[33] (MIDAS)	Isradipine vs hydrochlorothiazide	883	DBP 95-115 mmHg CIMT 1.3-3.5 mm LDL 130-189	36 m 95% follow-up ultrasonography	8 MHz transducer 12 carotid artery segments
Zanchetti et al[34] (VHAS)¶	Verapamil vs chlorthalidone	498	Essential hypertension	48 m 92% follow-up ultrasonography	7.5-8 MHz transducer 6 carotid artery segments
Hodis, et al[22] (CLAS) follow-up	Colestipol-niacin vs placebo	188	Nonsmokers post-CABG	24 m 78% follow-up ultrasonography	7.5 MHz transducer 1 carotid artery segment
Hedblad et al[36] (BCAPS)#,‡	Metoprolol vs placebo	793	Plaque in right carotid artery No CAD	36 m 85% follow-up ultrasonography	7 MHz transducer 4 carotid artery segments
Smilde et al[23] (ASAP)**	Atorvastatin vs simvastatin	330	Heterozygous familial hypercholesterolemia	24 m 86% follow-up ultrasonography	10 MHz transducer 3 carotid artery segments
Hodis et al[44] (EPAT)	Micronized 17β-estradiol vs placebo	222	Postmenopausal women no CAD LDL ≥130 mg/dL	48 m 90% follow-up ultrasonography	7.5 MHz transducer 1 carotid artery segment
Hodis et al[43] (VEAPS)	alpha-tocopherol vs placebo	353	LDL > 130 mg/dL No CAD	72 m 94% follow-up ultrasonography	7.5 MHz transducer 1 carotid artery segment
Hoogerbrugge et al[35] (DAPHNE)††	Doxazosin vs hydrochlorothiazide	80	Essential hypertension Peripheral artery disease Mild hyperlipidemia	36 m 100% follow-up ultrasonography	7.0 MHz transducer 12 carotid artery segments
Taylor et al[24] (ARBITER)‡‡	Atorvastatin vs pravastatin	161	NCEP II criteria for lipid lowering therapy	12 m 86% follow-up ultrasonography	8 MHZ transducer 1 carotid artery segment
Zanchetti et al[37] (ELSA)§§	Lacidipine vs atenolol	2334	Hypertension (150-210/95-115 mmHg)	48 m 65% follow-up ultrasonography	8 MHz transducer 4 carotid artery segments

(*continued on next page*)

Table I (*continued*)

Study	Treated vs control	N*	Population	Follow-up†	Ultrasonography
Taylor et al[25] (ARBITER 2)‖‖	Extended-release niacin + simvastatin vs simvastatin	167	Known CAD On statin therapy	12 m 89% follow-up ultrasonography	8 MHz transducer 1 carotid artery segment
Beishuizen et al[26]	Cerivastatin/simvastatin vs placebo	250	Type 2 diabetes mellitus No CAD	48 m 73% follow-up ultrasonography	7.5 MHz transducer 3 carotid artery segments
Katakami et al[41]¶¶	Metformin + glibenclamide vs glibenclamide	118	Type 2 diabetes mellitus	36 m 75% follow-up ultrasonography	7.5 MHz transducer 6 carotid artery segments
Katakami et al[41]¶¶	Gliclazide vs glibenclamide	109	Type 2 diabetes mellitus	36 m 82% follow-up ultrasonography	7.5 MHz transducer 6 carotid artery segments
Zanchetti et al[27] (PHYLLIS)	Fosinopril vs placebo	127	Hypertension Hypercholesterolemia Maximum CIMT 1.3-4.0 mm	31.2 m Follow-up NR	8 MHz transducer 8 carotid artery segments
Zanchetti et al[27] (PHYLLIS)	HCTZ + pravastatin vs placebo	126	Hypertension Hypercholesterolemia Maximum CIMT 1.3-4.0 mm	31.2 m Follow-up NR	8 MHz transducer 8 carotid artery segments
Zanchetti et al[27] (PHYLLIS)	Fosinopril + pravastatin vs placebo	128	Hypertension Hypercholesterolemia Maximum CIMT 1.3-4.0 mm	31.2 m Follow-up NR	8 MHz transducer 8 carotid artery segments
Zoungas et al[45] (ASFAST)	Folic acid vs placebo	315	Chronic renal failure (CrCl <25 mL/min)	36 m 100% follow-up ultrasonography	7.5 MHz transducer 1 carotid artery segment
Hodis et al[40] (TART)	Troglitazone vs placebo	299	Diabetes Fasting glucose 350 mg/dL Insulin monotherapy (≤150 units/day)	24 m 78% follow-up ultrasonography	7.5 MHz transducer 1 carotid artery segment
Mazzone et al[39] (CHICAGO)##	Pioglitazone vs glimepiride	462	Type 2 diabetes mellitus	18 m 78% follow-up ultrasonography	7.5 MHz transducer 1 carotid artery segment
Crouse et al[28] (METEOR)	Rosuvastatin vs placebo	984	LDL 120-190 mg/dL HDL ≤ 60 mg/dL TG ≤ 50 mg/dL CIMT 1.2-3.5 mm	24 m 90% follow-up ultrasonography	transducer MHz not specified 12 carotid artery segments
Kastelein et al[29] (RADIANCE 1)***	Torcetrapib + atorvastatin vs atorvastatin	904	Heterozygous familial hypercholesterolemia	24 m 94% follow-up ultrasonography	transducer MHz not specified 12 carotid artery segments
Bots et al[31] (RADIANCE 2)***	Torcetrapib + atorvastatin vs atorvastatin	752	Hyperlipidemia Hypertriglyceridemia	24 m 91% follow-up ultrasonography	transducer MHz not specified 12 carotid artery segments
Kastelein et al[30] (ENHANCE)‖‖	Simvastatin + ezetimibe vs simvastatin	720	Heterozygous familial hypercholesterolemia	24 m 89% follow-up ultrasonography	5-10 MHz transducer 6 carotid artery segments

Table I (*continued*)

Study	Treated vs control	N*	Population	Follow-up†	Ultrasonography
Howard et al[32] (SANDS)	Standard vs aggressive care	548	Type 2 diabetes mellitus LDL ≥100 mg/dL SBP ≥130 mmHg	36 m 91% follow-up ultrasonography	data NR
Meuwese et al[42] (CAPTIVATE)	Pactimibe vs standard care	892	Heterozygous familial hypercholesterolemia LDL >100 mg/dL TG <500 mg/dL Maximum CIMT 0.7-2.5 mm	15 m 80% follow-up ultrasonography	5-12 MHz transducer 3 carotid artery segments
Lonn et al[38] (STARR)	Ramipril vs placebo	1425	Plasma glucose 110-126 mg/dL Plasma glucose 140-200 mg/dL 2 h after oral glucose load No CV disease or diabetes	36 m 88% follow-up ultrasonography	≥7.5 MHz transducer 12 carotid artery segments
Lonn et al[38] (STARR)	Rosiglitazone vs placebo	1425	Plasma glucose 110-126 mg/dL Plasma glucose 140-200 mg/dL 2 h after oral glucose load No CV disease or diabetes	36 m 88% follow-up ultrasonography	≥7.5 MHz transducer 12 carotid artery segments

CABG, Coronary artery bypass grafting; *CAD*, coronary artery disease; *CrCl*, creatinine clearance; *CV*, cardiovascular; *DBP*, diastolic blood pressure; *HDL*, high density lipoprotein; *NCEP II*, National Cholesterol Education Program II; *NR*, not reported; *TC*, total cholesterol; *TG*, triglycerides.
* Number of patients randomized.
† Median follow-up unless specified.
§ Lovastatin and placebo arms evaluated for this analysis; warfarin arm excluded.
‖ Outcomes reported as deaths or "coronary events."
¶ Untreated population defined as those receiving chlorthalidone.
# Only metoprolol vs placebo group, fluvastatin arm excluded.
‡ Follow-up in metoprolol/placebo group.
** Untreated population defined as those receiving simvastatin.
†† Untreated population defined as those receiving hydrochlorothiazide.
‡‡ Untreated population defined as those receiving pravastatin.
§§ Untreated population defined as those receiving atenolol.
‖‖ Untreated population defined as those receiving simvastatin monotherapy.
¶¶ Untreated population defined as those receiving glibenclamide monotherapy.
Untreated population defined as those receiving glimepiride.
*** Untreated population defined as those receiving atorvastatin monotherapy.

pravastatin;[19-21,24,27] 4 examined atorvastatin[23,24,29,31]; 4 examined simvastatin (including 1 trial that initially examined cerivastatin but replaced it with simvastatin without unblinding[26])[23,25,26,30]; 1 examined rosuvastatin[28]; 1 examined lovastatin[18]; and 2 had an arm directly comparing different statins as monotherapy.[23,24] One trial did not explicitly specify which statins were used.[32] 7 trials evaluated antihypertensives,[27,33-38] and 4 trials evaluated anti-hyperglycemic agents.[38-41] The remainder of the trials examined other therapeutic interventions including pactimibe, estradiol, α-tocopherol, and folic acid.[42-45] Two studies compared a combination of atorvastatin plus torcetrapib to atorvastatin monotherapy[29,31]; 1 compared simvastatin plus ezetimibe to simvastatin monotherapy[30]; 1 compared simvastatin plus niacin to simvastatin monotherapy.[25] Of note, these latter 4 trials were considered to be "nonstatin" trials.

During metaregression analysis, we found a statistically significant association between mean changes in CIMT over time in the 32 treatment and control groups and the likelihood of developing nonfatal MI: for each 0.01 mm per year decreased change in CIMT, the odds ratio for MI was 0.82 (95% CI 0.69-0.96; P = .018; Figure 2). Results were similar when we restricted the analysis to RCTs with >1 year of follow-up data (28 treatment and control groups; odds ratio 0.78 per 0.01 mm smaller change in CIMT, 95% CI 0.64-0.96; P = .018), and with at least 50 subjects in the treatment group (29 treatment and control groups; odds ratio 0.81 per 0.01 mm smaller change in CIMT, 95% CI, 0.68-0.96; P = .019).

However, we found no significant association between change in CIMT and clinical outcomes in RCTs that evaluated statin therapy (10 treatment and control groups; odds ratio, 1.27 per 0.01 mm smaller change in CIMT; 95% CI 0.81-2.0, P = .23; Figure 3, *A*), but did find a significant association in those that evaluated nonstatin RCTs (22 treatment and control groups; odds ratio, 0.76 per 0.01 mm smaller change in CIMT; 95% CI 0.63-0.92,

Table II. CIMT data

Study	Baseline CIMT*		Treated	Control	*P*	Death		Fatal MI		Nonfatal MI		Stroke	
	T	NT				T	NT	T	NT	T	NT	T	NT
Furberg et al[18] (ACAPS)	1.33	1.32	(progression, mm/y) Mean max: –0.009 ± 0.003 Single max: –0.036 ± 0.011	(progression, mm/y) Mean maximum: 0.006 ± 0.003 Single maximum: 0.000 ± 0.011	 .001 .12	1	8	–	–	5	5	0	5
Salonen et al[19] (KAPS)	1.66	1.66	(progression, mm/y) CCA + bulb: 0.0168 ± 0.0035 Mean CCA: 0.0096 ± 0.0043 Bulb: 0.0279 ± 0.0045	(progression, mm/y) CCA + bulb: 0.0309 ± 0.0035 Mean CCA: 0.0285 ± 0.0043 Bulb: 0.0401 ± 0.0045	 .0046 .0019 .0563	3	4	0	2	3	6	2	4
Crouse et al[20] (PLAC-II)	1.32	1.32	(adjusted progression, mm/y) Aggregate: 0.0593 ± 0.0081 Mean CCA: 0.0295 ± 0.005	(adjusted, progression, mm/y) Aggregate: 0.0675 ± 0.0079 CCA: 0.0456 ± 0.0057	 .44 .03	3	5	–	–	4	10	–	–
Mercuri et al[21] (CAIUS)	1.06	1.04	(progression, mm/y) Mean max: –0.0043 ± 0.0028 First max: –0.045 ± 0.01	(progression, mm/y) Mean max: 0.0089 ± 0.0027 First max: –0.037 ± 0.012	 .0007 .5800	1	0	1	0	2	2	–	–
Borhani et al[33] (MIDAS)	1.17	1.17	(progression, mm) Mean max: 0.121 ± 0.008 Mean CCA: 0.064 ± 0.006 Mean bifurcation: 0.154 ± 0.014	(progression, mm) Mean max: 0.149 ± 0.008 Mean CCA: 0.061 ± 0.006 Mean bifurcation: 0.208 ± 0.014	 .02 .07 .01	8	9	–	–	6	5	6	3
Zanchetti et al[34] (VHAS)	0.857	0.896	(progression, mm/y) Mean maximum: 0.015 ± 0.071	(progression, mm/y) Mean maximum: 0.016 ± 0.067	 <.02	2	4	–	–	2	3	3	1
Hodis, et al[22] (CLAS) follow-up	0.66	0.66	(progression, mm/y) Mean CCA: –0.024 ± 0.031	(progression, mm/y) Mean CCA: 0.021 ± 0.021	 <.001	3	4	3	4	9	22	–	–

Hedblad et al[36] (BCAPS)	0.920	0.89	(progression, mm/y) 36 m: Mean CCA: 0.022 ± 0.132	(progression, mm/y) 36 m: Mean CCA: 0.024 ± 0.132	 .897	4	7	–	–	3	5	1	7
Smilde et al[23] (ASAP)	0.93	0.92	(progression, mm) Mean overall: –0.031 ± 0.012 CCA: –0.041 ± 0.011	(progression, mm) Mean overall: 0.036 ± 0.011 CCA: –0.018 ± 0.010	 .0001 .07	1	2	–	–	1	2	0	1
Hodis et al[44] (EPAT)	0.752	0.776	(progression, mm/y) Right distal CCA: –0.0017	(progression, mm/y) Right distal CCA: 0.0036	 .046	0	1	0	1	1	1	1	0
Hodis et al[43] (VEAPS)	0.746	0.760	(progression, mm/y) Mean overall: 0.0040 ± 0.0007	(progression, mm/y) Mean overall: 0.0023 ± 0.0007	 .08	2	1	1	1	6	6	0	2
Hoogerbrugge et al[35] (DAPHNE)	1.05	1.08	(progression, mm) Mean CCA: –0.05 ± 0.14 Max CCA: –0.15 ± 0.16	(progression, mm) Mean CCA: –0.08 ± 0.12 Max CCA: –0.18 ± 0.20	 .82 .85	0	0	–	–	4	0	0	2
Taylor et al[24] (ARBITER)†	0.625	0.615	(progression, mm, 12 m) Mean distal CCA: –0.034 ± 0.021 Max distal CCA: –0.137 ± 0.68	(progression, mm, 12 m) Mean distal CCA: 0.025 ± 0.017 Max distal CCA: 0.002 ± 0.210	 .03 .08	0	0	–	–	3	2	0	1
Zanchetti et al[37] (ELSA)	1.162	1.159	(progression, mm/y) Mean overall: 0.013 ± 0.0028	(progression, mm/y) Mean overall: 0.0153 ± 0.0027	 .613	13	17	–	–	14	9	9	14
Taylor et al[25] (ARBITER 2)	0.893	0.868	(progression, mm) Mean overall: 0.014 ± 0.104	(progression, mm) Mean overall: 0.04 ± 0.100	 .08	1	2	–	–	2	2	0	1
Beishuizen et al[26]	0.759	0.757	(progression, mm) Aggregate carotid IMT: 0.003 ± 0.007 Mean CCA: 0.002 ± 0.007	(progression, mm) Aggregate carotid IMT: 0.006 ± 0.008 Mean CCA: –0.006 ± 0.009	 >.05 .48	3	4	–	–	0	4	–	–
Katakami et al[41] (Glibenclamide + metformin vs glibenclamide)	1.33	1.23	(progression, mm/y) Mean CCA: 0.003 ± 0.009 Max CCA: 0.041 ± 0.019	(progression, mm/y) Mean CCA: 0.064 ± 0.006 Max CCA: 0.114 ± 0.017	 <.0001 <.05	0	0	0	0	0	0	–	–

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Table II (*continued*)

Study	Baseline CIMT*		Treated	Control	*P*	Death		Fatal MI		Nonfatal MI		Stroke	
Katakami et al[41] (Gliclazide vs glibenclamide)	1.25	1.23	(progression, mm/y) Mean CCA: 0.032 ± 0.007 Max CCA: 0.044 ± 0.019	(progression, mm/y) Mean CCA: 0.064 ± 0.006 Max CCA: 0.114 ± 0.017	.043 <.05	0	0	0	0	0	0	–	–
Zanchetti et al[27] (PHYLLIS, HCTZ vs fosinopril)	1.22	1.22	(progression, mm) Mean CCA and bifurcation: –0.002 ± 0.004	(progression, mm) Mean CCA and bifurcation: 0.01 ± 0.004	.03	0	0	–	–	0	3	0	0
Zanchetti et al[27] (PHYLLIS, HCTZ vs HCTZ + pravastatin)	1.21	1.22	(progression, mm) Mean CCA and bifurcation: –0.002 ± 0.004	(progression, mm) Mean CCA and bifurcation: 0.01 ± 0.004	.03	0	0	–	–	0	3	0	0
Zanchetti et al[27] (PHYLLIS, HCTZ vs fosinopril + pravastatin)	1.20	1.22	(progression, mm) Mean CCA and bifurcation: –0.002 ± 0.004	(progression, mm) Mean CCA and bifurcation: 0.01 ± 0.004	.02	1	0	–	–	1	3	1	0
Zoungas et al[45] (ASFAST)	1.06	1.08	(progression, mm) Mean CCA: –0.002 ± 0.014	(progression, mm) Mean CCA: 0.03 ± 0.011	.82	21	24	–	–	23	19	8	18
Hodis et al[40] (TART)	0.809	0.821	(progression, mm/y) Mean CCA: 0.003 ± 0.0018	(progression, mm/y) Mean CCA: 0.0066 ± 0.0018	.17	0	0	–	–	4	3	2	3
Mazzone et al[39] (CHICAGO)	0.771	0.779	(progression, mm) Mean posterior CCA: –0.001 Max posterior CCA: 0.002	(progression, mm) Mean posterior CCA: 0.012 Max posterior CCA: 0.026	.02 .008	1	0	0	0	0	1	0	1
Crouse et al[28] (METEOR)	1.15	1.17	(progression, mm/y) Max 12 segment: –0.0014 ± 0.0014 Max CCA max: –0.0038 ± 0.0013 Mean CCA: 0.0004 ± 0.0007	(progression, mm/y) Max 12 segment: 0.0131 ± 0.0022 Max CCA: 0.0084 ± 0.0020 Mean CCA: 0.0088 ± 0.0012	<.001 <.001 <.001	1	0	–	–	3	0	–	–

Kastelein et al[29] (RADIANCE 1)	0.71	0.72	(progression, mm/y) Max 12 segment: 0.0047 ± 0.0028 Max CCA: 0.0040 ± 0.0025 Mean CCA: 0.0038 ± 0.0013	(progression, mm/y) Max 12 segment: 0.0053 ± 0.0028 Max CCA: −0.0042 ± 0.0025 Mean CCA: −0.0014 ± 0.0013	.87 .02 .005	0	1	–	–	3	0	1	1
Bots et al[31] (RADIANCE 2)	0.83	0.83	(progression, mm/y) Max 12 segment: 0.025 ± 0.005 Max CCA: 0.022 ± 0.004 Mean CCA: 0.013 ± 0.002	(progression, mm/y) Max 12 segment: 0.030 ± 0.005 Max CCA: 0.020 ± 0.004 Mean CCA: 0.008 ± 0.002	.46 .65 .06	1	1	–	–	2	0	1	0
Kastelein et al[30] (ENHANCE)	0.69	0.70	(progression, mm) 6 segment mean: 0.0111 ± 0.0038 CCA: 0.0019 ± 0.0044	(progression, mm) 6 segment mean: 0.0058 ± 0.0037 CCA: 0.0024 ± 0.0043	.29 .93	1	1	–	–	3	2	1	1
Howard et al[32] (SANDS)	0.808	0.797	(progression, mm) Mean CIMT: −0.012 ± 0.0077	(progression, mm) Mean CIMT: 0.038 ± 0.011	<.001	3	5	–	–	4	2	1	3
Meuwese et al[42] (CAPTIVATE)	0.785	0.775	(progression, mm) Mean CIMT: 0.019 ± 0.0047 Max CIMT: 0.017 ± 0.0067	(progression, mm) Mean CIMT: 0.005 ± 0.0041 Max CIMT: 0.013 ± 0.0059	.04 .64	3	1	–	–	10	3	1	0
Lonn et al[38] (STARR, ramipril vs placebo)	0.75	0.76	(annualized progression, mm/y) Aggregate max CIMT: 0.0083 ± 0.0011	(annualized progression, mm/y) Aggregate max CIMT: 0.0069 ± 0.0011	.37	6	7	–	–	2	2	0	2
Lonn et al[38] (STARR, rosiglitazone vs placebo)	0.75	0.76	(annualized progression, mm/y) Aggregate max CIMT: 0.0063 ± 0.0011	(annualized progression, mm/y) Aggregate max CIMT: 0.0090 ± 0.0011	.08	4	9	–	–	3	1	1	1

CCA, Common carotid artery; *HCTZ*, hydrochlorothiazide; *max*, maximum; *NT*, not treated; *T*, treated; –, not reported.
*Value in millimeters.
† After the conclusion of ARBITER 2, 130 participants were followed up for an additional 12 months during open-label therapy with extended-release niacin. In this later trial, the ARBITER 3 study, regression of CIMT was apparent during ongoing niacin therapy such that, among all the participants, the mean CIMT was significantly reduced (–0.4 ± 0.14 mm, *P*=.008) at the end of 24 months.

P = .008; Figure 3, *B*). Similarly, we found a significant association between change in CIMT and clinical outcomes in subjects with low CIMTs at baseline (17 treatment and control groups; odds ratio 0.81 per 0.01 mm smaller change in CIMT; 95% CI 0.67-0.98 P = .029 while those with high CIMTs at baseline did not (15 treatment and control groups; odds ratio 0.86 per 0.01 mm smaller change in CIMT, 95% CI 0.52-1.41 P = .52.

When we examined the relationship between mean changes in CIMT and the combined end point of MI and death, we found that there were similar associations in general to those described above (32 treatment and control groups; odds ratio 0.84, 95% CI 0.72-0.97; P = .021). Finally, we found no statistical evidence for publication bias using the Begg and Mazumdar adjusted rank correlation test (P = .83; Figure 4).

Discussion

Among RCTs evaluating a wide range of cardiovascular therapies, our analyses found a statistically significant relationship between mean changes in CIMT over time in treatment and control groups and the risk of developing nonfatal MI. However, these findings were not consistent across some subgroup and in sensitivity analyses. In particular, we found no relationship between changes in CIMT over time and nonfatal MI in RCTs that evaluated statin therapy and in patients with high CIMTs at baseline.

Prior work has postulated that CIMT may be a valid surrogate end point for coronary atherosclerosis,[46] drug efficacy,[7,47] and clinical outcomes such as MI, but these studies have primarily relied on measurements of CIMT at baseline.[10,48] Although our analysis is generally supportive of these conclusions, we noted some inconsistencies that raise concerns about the universal applicability of CIMT as a surrogate end point in RCTs. Furthermore, these findings emphasize the need to better identify potential limitations that may be associated with its use, such as the type of drug being evaluated. For example, our findings were particularly strong among RCTs that evaluated antihypertensives[49] and nonconventional lipid-lowering agents (eg, pactimibe)—the latter being a group that has not been previously evaluated by any systematic review.

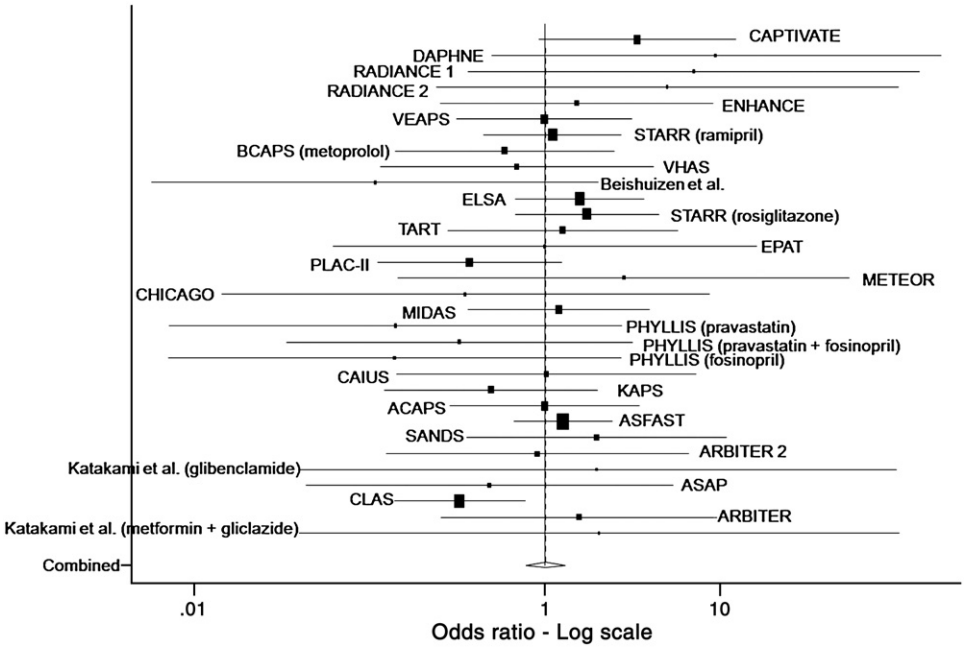
Our findings, however, were less consistent for statin therapy, which was rather surprising and counterintuitive. Prior studies have suggested that statin therapy reduces CIMT and the unparalleled cardiovascular benefits of statin therapy have been repeatedly demonstrated in landmark clinical trials. In fact, Espeland et al[47] systematically addressed the issue of whether CIMT was a valid surrogate end point in RCTs of statin therapy and came to a different conclusion. Inconsistencies between that study's findings and ours likely result from different methodological approaches. For example, Espeland et al arrived at their conclusion by noting that the addition of change in CIMT as a covariate in regression models raised the summary odds ratio of developing a cardiovascular event on statin therapy in their meta-analysis from 0.48 to 0.64. Although this technically made the summary odds ratio non-significant, the fact that it remained much <1 suggested that the clinical benefits of statin therapy likely work by mechanisms other than their effect on CIMT. In addition, Espeland et al included fewer RCTs overall and only included those that directly compared statin therapy to placebo; 2 RCTs included in our analysis compared two different statin therapies head-to-head.[23,24]

Furthermore, we believe that there are potential mechanistic reasons why the clinical benefit of statin therapy in RCTs may be independent of their effect on CIMT. First, there is the widely discussed possibility that the efficacy of these drugs is primarily related to "nontraditional" pathways that are not associated with changes in atherosclerotic plaque progression but, rather, to their effects on vascular remodeling, inflammation, and plaque composition. All of these latter pleiotropic effects may be more relevant for preventing clinical outcomes like nonfatal MI.[50-52]

Another possible explanation is that statin therapy was largely evaluated in RCTs with patients who had high CIMTs at baseline. This finding is relevant since we also found a strong association between changes in CIMT and clinical outcomes in RCTs enrolling patients with low CIMTs at baseline, but less so in RCTs where patients had higher CIMTs at baseline. Our findings here suggest that changes in CIMT over time that occur during the incipient stages of disease may be more predictive of future events than changes that occur in patients with more extensive atherosclerosis at baseline. As the burden of atherosclerosis increases, it could be that changes in CIMT in response to therapy may lose its value as a surrogate end point.

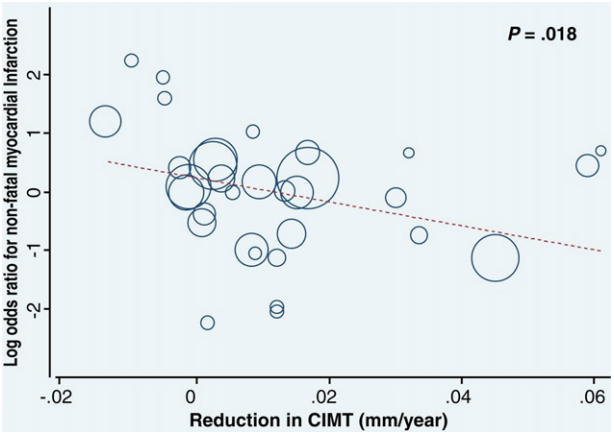
It also is important to note that even when a therapy leads to improvements in atherosclerotic burden within the carotid artery, clinical outcomes may still worsen due to potential harm at other vascular and non-vascular sites. For example, it has been postulated that the cholesteryl ester transfer protein, torcetrapib, failed to show benefit in clinical outcomes due to its adverse effects on blood pressure and electrolyte levels that were associated with activation of the renin-angiotensin-aldosterone system.[53] A second example is the recently published ARBITER 6-HALTS trial that examined the effects of ezetimibe or niacin in conjunction with statin therapy on the progression of CIMT.[54] The trial was terminated prematurely given that an interim analysis showed that niacin was superior to ezetimibe in reducing CIMT. However, an unexpected finding was that significant reductions in low-density lipoprotein (LDL) due to ezetimibe were

Figure 1



Log-odds ratio for myocardial infarction associated with treatment for all 32 treatment and control groups in the 28 randomized controlled trials, sorted by the smallest to largest difference in CIMT between treatment and control groups.

Figure 2



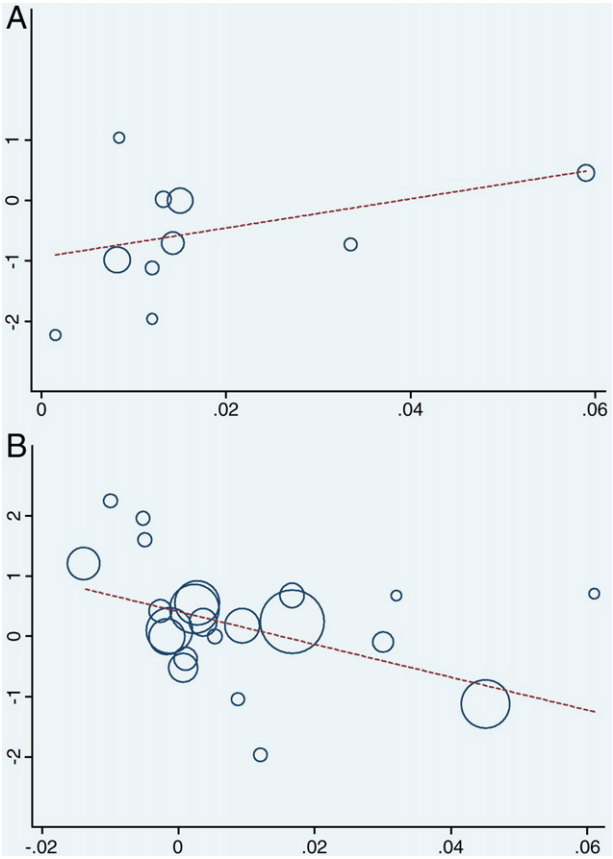
Log odds ratio of nonfatal myocardial infarction by changes in CIMT across all 32 treatment and control groups.

associated with an *increase* in CIMT. Both examples raise caution about the use of surrogate end points in cardiovascular trials.

There are several limitations in our analysis, which are in large part due to marked degree of heterogeneity within the trials included in the regression analysis. First, we discovered that CIMT is measured and reported in many different ways, including the use of the mean of the maximum CIMTs versus the mean of the mean values. This variability in reporting may have limited our ability to detect significant findings in many of the subgroup and sensitivity analyses despite the large number of trials we had identified. Second, our analysis centers on how the change in CIMT parallels the beneficial effects of interventions targeted at reducing "hard" cardiovascular outcomes. The short-term follow-up of many of these trials may have mitigated our ability to assess many of these outcomes which are typically apparent for many agents only after longer follow-up. Third, the age distribution of patients was not uniform, and older individuals tend to have larger CIMTs at baseline—this may have affected the finding of the tight association between changes in CIMT and patients with low CIMTs at baseline, but less so in patients with higher CIMTs at baseline. Finally, there may be carotid segment-specific responses of the targeted interventions, and the results from single-level protocols (which analyze one carotid artery segment) may differ from multilevel protocols (analyzing several segments).

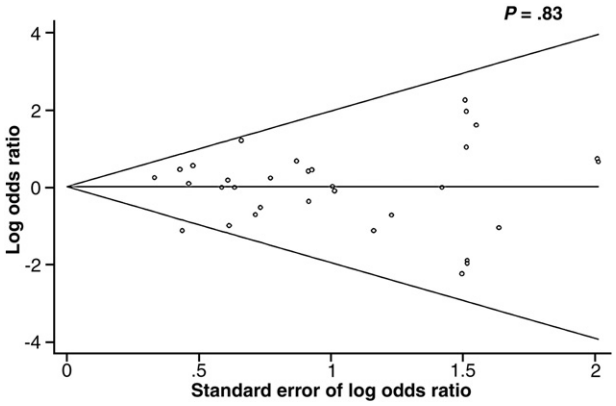
There are also limitations inherent to metaregression analysis. Although meta-regression is appropriate in directly evaluating study level factors, there are serious

Figure 3



A, Log odds ratio of nonfatal myocardial infarction by changes in CIMT across 10 treatment and control groups in randomized controlled trials specifically evaluating statin therapy. **B**, Log odds ratio of nonfatal myocardial infarction by changes in CIMT across 22 treatment and control groups in randomized controlled trials specifically evaluating nonstatin therapy.

Figure 4



Funnel plot of all studies with pseudo 95% confidence limits, comparing log odds ratio of developing nonfatal myocardial infarction with its standard error. The absence of asymmetry suggests that there was no publication bias.

limitations when factors vary at the patient level due to the potential for ecological bias.[55] Lack of individual data also limited our ability to evaluate the timing of nonfatal MIs in relation to changes in CIMT. Because both events could have occurred during follow-up, we were unable to directly link changes in CIMT over time to subsequent outcomes. To perform this type of analysis would have required RCTs to report additional follow-up for clinical outcomes after the last assessment of CIMT; these data were not available in the literature.

In addition, the associations derived from meta-regression analysis are observational, and thus weaker than the relationships derived from randomized comparisons. Therefore, our results should be recognized as hypothesis-generating and should be interpreted in that context. Finally, the sample size of the meta-regression is limited by the number of studies that are available. Although we included a fair number of studies in this analysis, this number diminished rapidly during subgroup and other exploratory analyses.[55]

Finally, we evaluated changes in CIMT in RCTs that used B-mode carotid ultrasonography, a well-validated but imperfect imaging modality for assessing carotid atherosclerosis. Newer non-invasive techniques such as magnetic resonance imaging have attractive properties that may improve the assessment of atheroma burden in this vascular territory.[7] Recent investigations in carotid magnetic resonance imaging have already begun to be used as a means of evaluating the changes associated with cardiovascular therapies.[56-60] Its use may lead to more accurate quantification of atherosclerotic burden and improve the correlation of changes in CIMT with clinical outcomes.

In conclusion, we found in a critical review and meta-regression analysis that slower progression in CIMT, as measured by B-mode carotid ultrasonography, was associated with lower risk of nonfatal MI. However, these findings were observed primarily in RCTs of non-statin therapies and patients with low CIMTs at baseline. Although the use of CIMT holds potential value as a surrogate end point for RCTs, caution will need to be exercised in interpreting studies that rely exclusively on CIMT, particularly for studies that evaluate statin therapy and those that enroll patients with high CIMTs at baseline.

Disclosures

The authors have no financial disclosures or conflicts of interest.

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