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Results From a Carotid Intima-Media Thickness Trial as a Decision Tool for Launching a Large-Scale Morbidity and Mortality Trial

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Background—Trials with carotid intima-media thickness (CIMT) as primary end point may improve the efficiency of the evaluation of new therapies targeting atherosclerosis considerably, and the results of CIMT trials may be used as a decision tool to help in the choice to launch or not to launch a large-scale morbidity and mortality (M&M) trial. We evaluated the literature to provide evidence to support or refute this proposition.

Methods and Results—PubMed Medline was systematically searched on May 1, 2012, for randomized double-blind controlled CIMT trials. The agreement between the results from CIMT and M&M trials was assessed, and positive and negative predictive values were calculated. Forty-eight CIMT trials were included. CIMT trials (n=20) on lipid-level modifying therapies are all, except one, in agreement with the M&M trial findings. For blood pressure-lowering trials (n=13), 3 were not congruent with the M&M trial. The positive and negative predictive value (95% confidence interval) of a CIMT trial to predict the outcome of a M&M trial are 96% (80–99%) and 83% (64–93%), respectively. The predictive values are higher for lipid-level modifying therapies than for other therapies.

Conclusions—A CIMT trial positioned before an M&M trial may considerably improve the efficiency of the evaluation of new drug therapies on atherosclerosis and cardiovascular disease risk. Hence, the results of a CIMT trial should be seen as a decision tool to support or refute the start of a large-scale M&M trial on drugs targeting atherosclerosis. **(*Circ Cardiovasc Imaging*. 2013;6:20-25.)**

Key Words: atherosclerosis ■ carotid intima-media thickness ■ epidemiology ■ noninvasive imaging ■ trials

Cardiovascular disease is still the leading cause of death worldwide and contributes considerably to morbidity.[1] The underlying cause of the majority of cardiovascular events is atherosclerosis, a chronic and progressive disease of the arterial system.[2] Research into the prevention of cardiovascular disease will become even more important given the aging population and global epidemics of diabetes and obesity, which are most pronounced in low- and middle-income countries.[3,4] The development of targeted new preventive therapies is one of the steps to control the cardiovascular epidemic. It is increasingly demanded that promising therapies are being evaluated in trials with cardiovascular morbidity and mortality (M&M) as a primary outcome. M&M trials, however, are costly, often multicenter studies with thousands of participants and a long follow-up. To improve the efficiency of the evaluation of new therapies and to get an indication of the effectiveness of new treatments before launching an M&M trial, there is great interest in valid alternative end points that can be used as a valid alternative or proxy for cardiovascular M&M. Alternative end points allow for the evaluation of novel preventive therapies in randomized controlled trials within a shorter timeframe, with fewer participants, at lower costs, and with sooner availability of trial results, when compared with an M&M trial. These studies may serve to direct or exclude subsequent large M&M trials. A measure of atherosclerosis is intuitively a suitable alternative end point for cardiovascular disease events, as atherosclerosis is the disease on the pathway between exposure to risk factors and the cause of the majority of cardiovascular events. Carotid intima-media thickness (CIMT), as measured using B-mode ultrasound, is a safe, inexpensive, reproducible, and noninvasive marker of atherosclerosis that has been used as alternative or surrogate end point for cardiovascular events in trials for almost 2 decades.[5] Figure 1 shows that M&M trials on lipid-level modifying therapies generally were conducted in thousands of participants with 5 years of follow-up, whereas CIMT trials have been performed in hundreds of participants who were followed for 24 to 36 months.[6] Yet, as evidence-based medicine eventually requires that new therapies are being evaluated using hard cardiovascular end points, an M&M trial

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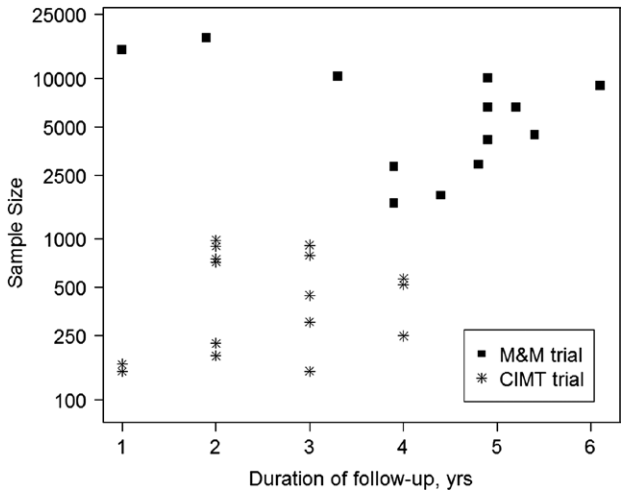

Figure 1. Sample size and duration of follow-up in morbidity and mortality trials and carotid intima-media thickness trials on lipid-level modifying therapies. Trial details are specified in reference 6.

seems inevitable before new therapies can be registered. Here, we put the proposition forward that the results of a CIMT trial should be seen as a decision tool to help in the choice to launch or not to launch a large-scale M&M trial, when the therapy targets atherosclerosis. Using the published literature, we provide the evidence to support or refute our proposition.

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Methods

PubMed Medline was systematically searched on May 1, 2012, for randomized double-blind controlled CIMT trials. Trials with a sample size larger than 50 participants, and with results from an M&M trial or meta-analyses on a comparable drug and in a similar population available in PubMed, were included. Study characteristics and results were extracted. The agreement between the results from CIMT and M&M trials was assessed based on probability values and the direction of the findings. The strength of the effect of a drug on CIMT and cardiovascular events or any other form of weighting the strength of the evidence about the consistency of CIMT and M&M studies was specifically not considered as many other factors, including differences in ultrasound protocol, study population, duration of follow-up, and drug dosage, could have affected this agreement rather than the effect of the therapy alone. Trial results were in agreement when the probability values on the efficacy of a therapy on CIMT change or event rates, respectively, were congruent. That is, a CIMT trial with a probability value ≤0.05, indicating a beneficial effect on CIMT change (ie, reduced progression or regression in CIMT), is in agreement with an M&M trial with a probability value ≤0.05 and reduction in event rates. A CIMT trial suggesting a neutral or negative effect on CIMT (ie, no difference in rates of change or increased progression) evidenced by a probability value >0.05 would be in agreement with an M&M trial showing no effect (ie, no difference in event rates), and a probability value greater than 0.05 or harm (ie, increased event risk) of a new therapy and a probability value smaller than 0.05. The positive and negative predicted values of a CIMT trial to predict the result of an M&M trial were subsequently calculated.

Importantly, we did not make an attempt to quantify the relation between the effect of a therapy on rate of CIMT change and its effect on cardiovascular events, as such an approach has been taken before and has many conceptual and methodological issues that severely bias the study findings.[7–9] Also, we did not deal with the prognostic value of a CIMT measurement, and do neither deal with the distinction between a surrogate and a prognostic marker, nor with the usefulness of CIMT as a surrogate of cardiovascular disease risk. Rather, we do address the value of the results of a CIMT trial in predicting the likelihood of success when an M&M trial is to be launched. So, the result of a CIMT trial is considered the test for launching or not launching a large-scale M&M trial.

Results

An overview of the 48 CIMT trials for which results from M&M trials also were available is given in the online-only Data Supplemental Table.

Table. CIMT Trial as Decision Tool for Launching a Large-Scale Morbidity and Mortality Trial, Overall and for Lipid-Level Modifying Therapies and Nonlipid-Level Modifying Therapies Separately

		M&M Trial		
		Positive	Neutral—Negative	
CIMT trial	Positive	True	False	PPV
		Positive	Positive	0.96
		23	1	(0.80; 0.99)
	Neutral—negative	False	True	NPV
		Negative	Negative	0.83
		4	20	(0.64; 0.93)
		Sensitivity	Specificity	
		0.85	0.95	
		(0.68; 0.94)	(0.77; 0.99)	
	PPV	NPV	Sensitivity	Specificity
Lipid-level modifying	1.00 (0.77; 1.00)	0.86 (0.49; 0.97)	0.93 (0.79; 0.99)	1.00 (0.61; 1.00)
Nonlipid-level modifying	0.91 (0.62; 0.98)	0.82 (0.59; 0.94)	0.77 (0.50; 0.92)	0.93 (0.70; 0.99)
Primary prevention	0.93 (0.70; 0.99)	0.67 (0.39; 0.86)	0.78 (0.55; 0.91)	0.89 (0.57; 0.98)
Secondary prevention	1.00 (0.72; 1.00)	0.91 (0.62; 0.98)	0.91 (0.62; 0.98)	1.00 (0.72; 1.00)

CIMT indicates carotid intima-media thickness; M&M, morbidity and mortality; NPV, negative predictive value; and PPV, positive predictive value.
Values between brackets are the 95% confidence intervals.

Lipid-Level Modifying Therapy

The majority of CIMT trials (42%) have evaluated the efficacy of lipid-level modifying therapies, primarily statins, on the rate of change in CIMT. Statin therapy substantially reduces low-density lipoprotein cholesterol levels, targets atherosclerosis as shown by favorable alterations in the rate of CIMT change under statin therapy, and also causes a marked reduction in cardiovascular event rates.[10–12] The results of the CIMT trials are all, except one, in agreement with the M&M trial findings. Despite substantial risk reductions achieved by statin therapy, significant residual cardiovascular disease risk among statin users remains. This has lead to studies using lipid-modifying agents other than statins, such as torcetrapib, ezetimibe, niacin, fibrates, and acyl–coenzyme A:cholesterol acyltransferase (ACAT) inhibitors. The results from these CIMT trials are in agreement with the M&M trials, as they did neither significantly alter the rate of CIMT change (ie, no change in rate of CIMT change over time) between treatment arms nor did the M&M trial show improvement in cardiovascular outcomes. In fact, some of these therapies caused harm because of unforeseen off-target effects. Very recently, dal-OUTCOME, the M&M trial on dalcetrapib, has stopped because of a lack of clinically meaningful efficacy, which is in agreement with the diverse effects on different measures of atherosclerosis found in dal-VESSEL and dal-PLAQUE.[13,14] Retrospectively, the neutral or negative results from these CIMT studies were in agreement with the M&M trials and indicate that the CIMT trial could have served as a decision tool to discontinue or to refrain from launching these M&M trials.

Blood Pressure-Lowering Therapy

Hypertension is an important risk factor of cardiovascular disease and lowering blood pressure levels certainly plays an important role in the prevention of cardiovascular events. There has been a large number of blood pressure-lowering trials that used either rate of change in CIMT or cardiovascular events as primary outcome. Not all trials with CIMT as primary outcome are congruent with the M&M trials (online-only Data Supplemental Table). Out of the 13 blood pressure-lowering trials, 3 were not congruent with the M&M trial. Specifically, there was no agreement among the results from the CIMT trials, the M&M trial for the angiotensin-converting enzyme inhibitor (ramipril versus placebo), and 1 trial with angiotensin II blocker (losartan versus atenolol).[15–17] The 10 other CIMT trials using other blood pressure-lowering agents were congruent with the M&M trials.

Blood Glucose-Lowering Drugs

There are 4 trials that have evaluated the effects of glucose-lowering therapy on rate of change in CIMT and also on cardiovascular event risk (online-only Data Supplemental Table). The results from the CIMT trials were all congruent with the M&M trials.

Other Pharmacological Interventions

Several CIMT studies have been performed using several agents, of which antiatherosclerotic properties were assumed and were also evaluated in M&M trial. These trials used antioxidants, hormone replacement therapy, and antiobesity therapy (online-only Data Supplemental Table). With 1 exception, all CIMT trial results showed neutral results and were in agreement with the results from the M&M trials (ie, no beneficial effect of the intervention).

Positive and Negative Predictive Value of a CIMT Trial

Based on the trials from the online-only Data Supplemental Table together, the positive and negative predictive value (95% confidence interval) associated with the CIMT trial results as decision tool to launch or not to launch an M&M trial are 96% (80–99%) and 83% (64–93%), respectively. The predictive values are higher for lipid-level modifying therapies and in secondary prevention, than for other therapies and primary prevention, respectively (Table).

Discussion

CIMT is a valid surrogate end point for cardiovascular events in trials. We specifically did not aim to review the evidence for the use of CIMT as surrogate end point in trials, as this involves a different approach and has been done before.[5] In this study, we have evaluated whether the results of a CIMT trial can be used as a decision tool to help in the choice to launch or not to launch a large-scale M&M trial. The published literature suggests that the results of a CIMT trial could be viewed as a decision tool to help in the choice to launch or not to launch a large-scale M&M trial, when the therapy targets atherosclerosis. Although these results support our proposition, some caution is needed. In approximately 10% of the trials listed in the online-only Data Supplemental Table (5/48), there was no agreement between the CIMT and M&M trials. In 4 cases, an M&M trial would not have been launched based on the results from a CIMT trial, although the M&M trial did show a significant reduction in cardiovascular M&M.

At this point, it should be emphasized that cardiovascular events cannot be prevented by inhibiting atherosclerosis progression alone. That is, new medical therapies may not necessarily affect atherosclerosis and CIMT, but can reduce cardiovascular M&M through other important mechanisms underlying cardiovascular events, such as thrombosis or inflammation. Hence, the mechanism (ie, atherosclerosis or not) through which the intervention is assumed to affect cardiovascular risk is of key importance in the decision to start a CIMT trial. Failure to do this may create the unwarranted situation where a drug that has no effect on CIMT will not enter the market, even though it could have potential benefits on cardiovascular M&M. Aspirin, for example, significantly reduces cardiovascular event rates by inhibiting platelet aggregation and is widely used in the prevention of cardiovascular events.[18] The beneficial effect of aspirin, however, is unlikely to be demonstrated in a CIMT trial, as atherosclerosis is not the targeted disease mechanism. Hence, CIMT trials on drugs not affecting atherosclerosis progression are likely to give false-positive or false-negative results and should be discouraged. Figure 2 further stresses this point and provides a conceptual framework of the conditions to be verified before launching a CIMT trial as decision tool for the start of an M&M trial. Agreement between the results of a CIMT trial and a M&M trial is most likely to be expected when the evaluated drug therapy prevents cardiovascular events by targeting a risk

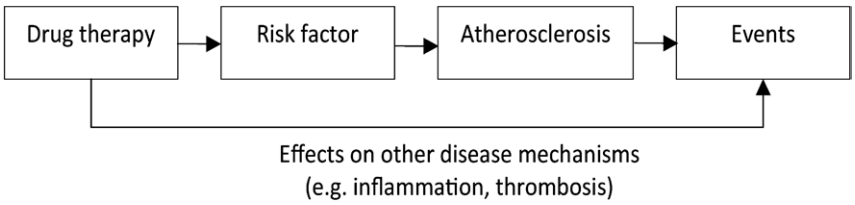

Figure 2. Conceptual framework of the conditions to be verified before launching a carotid intima-media thickness (CIMT) trial as decision tool for the start of an morbidity and mortality (M&M) trial.

factor that plays a role in the development of atherosclerosis, and has no adverse effects on other disease mechanisms that are known to contribute to the occurrence of cardiovascular events.

The predictive values shown in the Table are very supportive for the use of the results of a CIMT trial to predict the outcome of a large and long-term M&M trial. Yet, the results of this study should also be interpreted with caution for some reasons. First, underestimation of the predictive values may have occurred because of differences between CIMT and M&M trials in terms of study population and control arm (placebo or active comparison) causing random misclassification, rather than because of differences in the efficacy of the treatment on atherosclerosis and events rates.

Second, partial verification bias may have occurred as the reference test (ie, the M&M trial) may have been more likely to be performed in a selection of the drugs (ie, the drugs that already showed positive results in the CIMT trial). Indeed, there is a number of drugs for which negative or neutral CIMT trials have not (yet) been followed by an M&M trial.[19,20] This bias may have underestimated the negative predictive value of a CIMT trial, as it may be more likely that an M&M trial is not performed when a neutral or negative rather than a positive effect is expected. Also, there may be publication bias because of the difficulty of publishing negative or neutral findings. This may work in 2 directions. First, the results from the CIMT trial were neutral or negative, which lead to not publishing the results if there was an M&M trial showing beneficial results already. Second, the CIMT study was beneficial and published, followed by a large M&M study that is neutral/negative and not published. Although the clinical trial registry may have resolved the issue of publication bias to some extent, it may still play a role in here. However, we have no quantitative data on these issues, so it is hard to estimate, if present, the extent of the bias that may potentially have occurred.

Third, the potential value of the result of a CIMT trial as decision tool to launch an M&M trial is also determined by the amount of currently available evidence. Evidence may be more solid for lipid-level modifying therapies and antihypertensive therapies, which constitute 69% of our results (33/48) and for which the agreement with M&M trials was assessed using meta-analyses of large-scale M&M trials. In contrast, the level of agreement between CIMT trials and M&M trials for glucose-lowering therapies, antioxidants, hormone replacement therapy, and antiobesity therapies was based on less evidence, some on only single studies (online-only Data Supplemental Table).

Fourth, a dichotomous criterion for assessing agreement based on statistical significance of the trial result was used and the different strengths of evidence about the consistency of the results of a CIMT trial and the results of an M&M trial was not explicitly weighted. Yet, other factors than statistical significance alone, like the direction and magnitude of the effect of a therapy on rate of CIMT change, also play a role in the decision on whether or not to launch an M&M trial. Statistical significance of a study is, of course, highly correlated with the statistical power of a study, and differences in statistical power across studies may thus artificially have affected our findings. However, one may assume that CIMT trials, as part of good clinical practice, are powered and designed a priori in such a way that, if present, the potential effect of the evaluated therapy could be found. Also, we a priori excluded studies with a sample size smaller than 50 participants, to reduce the chance of disagreement because of a major effect of small studies with reduced statistical power. As such, we consider it unlikely that differences in statistical power across CIMT studies had a major impact on our findings. Additionally, although weighing studies according to the strength of the agreement between the results of the CIMT trial and M&M trials may be warranted, quantifying these weights according to, for example, the signal-to- noise ratio in the CIMT trial seems impossible, as such approach is likely to introduce imbalance in weighting because of material differences in CIMT ultrasound protocols across CIMT studies in terms of measurement sites (ie, different angles, segments, walls, and sites), end point definition (mean CIMT or maximum CIMT), and reading methods.[21] These differences in ultrasound protocol all result in different effect sizes and precision estimates, regardless of the efficacy of the treatment and the expected agreement with the M&M trial. Hence, we chose to use an unweighted approach, as we feel that there is no valid method to account for any potential difference in the strength of evidence about the consistency of the CIMT and M&M trial results.

Finally, although we focused on the results of a CIMT trial as decision tool to launch an M&M trial, it may well be that other marker of cardiovascular risk also perform well. Yet, the performance of the results of trials on other noninvasive imaging or circulatory markers of cardiovascular risk, such as coronary arterial calcification or C-reactive protein, as decision tools to launch an M&M trial for definite efficacy assessment needs to be established in further studies.

Notwithstanding these potential limitations, the published literature clearly supports that the final result of a CIMT trial is useful as a decision tool to predict the presence or absence of an effect of drug therapies targeting atherosclerosis on cardiovascular events. As such, we propose that the result of a CIMT trial should be seen as a decision tool to help in the choice to launch or not to launch a large-scale M&M trial, when the therapy targets atherosclerosis (Figure 3). Evidence

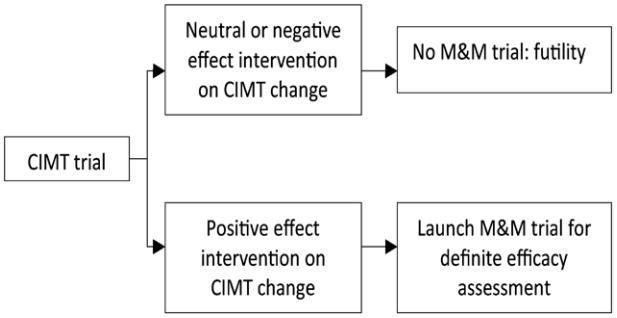

Figure 3. Position of carotid intima-media thickness (CIMT) as decisive tool in the evaluation of new drug therapies.

for choosing the most optimal methods for assessment of CIMT in trials has recently been published and could serve as a guidance for the design of future CIMT trials.[22–37]

In conclusion, a CIMT trial positioned before an M&M trial may considerably improve the efficiency of the evaluation of new drug therapies on atherosclerosis and cardiovascular disease risk. Hence, the result of a CIMT trial should be seen as a decision tool to support or refute the start of a large-scale M&M trial on drugs targeting atherosclerosis.

Disclosures

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CLINICAL PERSPECTIVE

New and promising therapies developed to prevent cardiovascular diseases are typically evaluated in trials with cardiovascular morbidity and mortality (M&M) as a primary outcome. M&M trials, however, are very costly studies, often with thousands of participants and a long follow-up. To improve the efficiency of the evaluation of new therapies, trials with carotid intima-media thickness (CIMT) as primary end point are conducted that typically include several hundred of individuals and have a shorter duration of follow-up. In this review, we assessed whether the results of a CIMT trial can be used as a decision tool to help in the choice to launch or not to launch a large-scale M&M trial. There was congruency between the results of a CIMT trial and M&M trial in 43 of the 48 comparisons. Agreement between the results of a CIMT trial and an M&M trial was primarily found when the evaluated drug therapy prevents cardiovascular events by targeting a risk factor that plays a role in the development of atherosclerosis and has no adverse effects on other disease mechanisms that are known to contribute to the occurrence of cardiovascular events. If these conditions are met, a CIMT trial positioned before an M&M trial may considerably improve the efficiency of the evaluation of new drug therapies on atherosclerosis and cardiovascular disease risk. Hence, the results of a CIMT trial should be seen as a decision tool to support or refute the start of a large-scale M&M trial on drugs targeting atherosclerosis.

Supplemental Material

Results from a carotid intima-media thickness trial as a decision tool for launching a large scale morbidity and mortality trial

Supplementary Table. Characteristics and results of CIMT trials on different drug therapies and agreement with results from morbidity and mortality trials											
Study	**Comparison**	**Condition**	**N**	**Fu, yrs**	**CIMT sites**	**Outcome**	**Treatment change**	**Control change**	**p-value**	**Endpoint M&M trial***	**Agreement**
Lipid-level modifying therapy											
Primary prevention											
ACAPS[1]	Lovastatin 20–40mg vs. placebo	Asymptomatic, moderately elevated LDL-C	919	3	Nfw CCA, BIF, and ICA	Mnmx, mm	-0.0090	0.0060	0.001	CHD and stroke[2]	Yes
ASAP[3]	Atorvastatin 80 mg vs. Simvastatin 40mg	FH	325	2	Nfw CCA and BIF, fw ICA	Mn, mm	-0.0310	0.0360	<0.001	CHD and stroke[4]	Yes
BCAPS[5]	Fluvastatin 40 mg vs. placebo	Asymptomatic	793	3	Fw CCA and BIF	Mn, mm	0.0110	0.0360	0.002	CHD and stroke[2]	Yes
CAIUS[6]	Pravastatin 40 mg vs. placebo	Asymptomatic, moderately elevated LDL-C	305	3	Nfw CCA, BIF, and ICA	Mnmx, mm/y	-0.0043	0.0089	0.001	CHD and stroke[2]	Yes
CERDIA[7]	Simvastatin 20mg vs. placebo	DM2, no CAD	250	4	Nfw CCA, BIF, and ICA	Mn, mm	0.0020	-0.0060	0.480	CHD and stroke[2]	No
HYRIM[8]	Fluvastatin 40mg vs. placebo	Treated hypertension	568	4	Fw CCA	Mxmn, mm	0.0490	0.0760	0.030	CHD and stroke[2]	Yes
KAPS[9]	Pravastatin 40 mg vs. placebo	Asymptomatic, elevated LDL-C	447	3	Fw CCA and BIF	Mnmx, mm/y	0.0168	0.0309	0.005	CHD and stroke[2]	Yes
METEOR[10]	Rosuvastatin 40mg vs. placebo	Asymptomatic, elevated LDL-C	984	2	Nfw CCA, BIF, and ICA	Mnmx, mm/y	-0.0014	0.0131	<0.001	CHD and stroke[2]	Yes
Secondary prevention											
ARBITER[11]	Atorvastatin 80 mg vs. Pravastatin 40 mg	Meeting NCEP II criteria for lipid-lowering therapy	161	1	Fw CCA	Mn, mm	-0.0340	0.0250	0.030	CVD[12]	Yes
INDIA[13]	Atorvastatin 10mg vs. placebo	CAD, normal LDL-C	150	1	CCA, BIF, and ICA	Mnmn, mm	-0.0130	0.0090	0.001	CHD and stroke[2]	Yes
LIPID[14]	Pravastatin 40mg vs. placebo	CAD, moderately elevated TC	522	4	Fw CCA	Mn, mm	-0.0140	0.0480	<0.001	CHD and stroke[2]	Yes
MARS[15]	Lovastatin 80mg vs. placebo	CAD, moderately elevated TC	188	2	Fw CCA	Mn, mm/y	-0.0280	0.0150	<0.001	CHD and stroke[2]	Yes
PLAC II[16]	Pravastatin 10-40mg vs. placebo	CAD, elevated LDL-C	151	3	Nfw CCA, BIF, and	Mnmx, mm/y	0.0593	0.0675	0.001	CHD and stroke[2]	Yes

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REGRESS[17]	Pravastatin 40mg vs. placebo	CAD, normal to moderately elevated TC	225	2	Nfw CCA	Mn, mm	-0.0500	0.0000	0.009	CHD and stroke[2]	Yes
ARBITER 2[18]	Simvastatin + Niacin 1000mg vs. Simvastatin	CAD, low HDL-C	167	1	Fw CCA	Mn, mm	0.0140	0.0400	0.080	CVD[19]	Yes
FIELD[20]	Fenofibrate 200mg vs. placebo	DM2	170	5	Nfw CCA, BIF, and ICA	Mnmn, mm	0.0540	0.0690	0.987	CVD[20,21]	Yes
ENHANCE[22]	Simvastatin 80mg + Ezetimibe 10mg vs. Simvastatin 80mg	FH	720	2	Fw CCA, BIF, and ICA	Mn, mm	0.0111	0.0058	0.290	CVD[23]	Yes
RADIANCE 1[24]	Atorvastatin 56.5 mg + torcetrapib 60mg vs. Atorvastatin 56.5mg	FH	904	2	Nfw of CCA, BIF, and ICA	Mnmx, mm/y	0.0047	0.0053	0.870	CVD[25]	Yes
RADIANCE 2[26]	Atorvastatin 13.5 mg + torcetrapib 60mg vs. Atorvastatin 13.5mg	Mixed dyslipidaemia	752	2	Nfw CCA, BIF, and ICA	Mnmx, mm/y	0.0250	0.0300	0.460	CVD[25]	Yes
CAPTIVATE[27]	Pactimibe 100mg vs. placebo	FH	892	2	Nfw CCA, BIF, and ICA	Mnmx, mm/y	0.0170	0.0130	0.640	CVD[27]	Yes
Antihypertensive therapy											
Primary prevention											
PHYLLIS[28]	Fosinopril 20mg vs. hydrochlorothiazide 25mg	Hypertension and hypercholesterolemia	508	2.6	Nfw CCA and BIF	Mnmx, mm	-0.0020	0.0100	0.010	CVD[29]	Yes
STARR[30]	Ramipril 15mg vs. placebo	Impaired glucose tolerance and/or impaired fasting glucose	1425	3	Nfw CCA, BIF, and ICA	Mnmx, mm/y	0.0083	0.0069	0.37	CVD[29]	No
BCAPS[5]	Metoprolol 25mg vs. placebo	Asymptomatic	794	3	Fw CCA and BIF	Mn, mm	0.1540	0.2270	0.014	All-cause mortality[31]	Yes
ELVA[32]	Metoprolol 100mg vs. placebo	Primary hypercholesterolemia	129	3	Fw CCA and BIF	Mn	-0.06	0.0300	0.0110	All-cause mortality[31]	Yes
ELSA[33]	Lacidipine 4mg vs. atenolol 50mg	Hypertension	2334	4	Fw CCA and BIF	Mnmx, mm	0.0087	0.0145	<0.001	CVD[29]	Yes
INSIGHT-IMT[34]	Nifedipine 30 mg or Amiloride 2.5 mg and hydrochlorothiazide 25	Hypertension	439	4	Fw CCA	Mn, mm	-0.0007	0.0077	0.003	CVD[29]	Yes

	mg										
MIDAS[35]	Isradipine 2.5-5mg vs. hydrochlorothiazide 12.5-25mg	Hypertension	883	3	Nfw CCA, BIF, and ICA	Mnmx, mm	0.1210	0.1490	0.680	CVD[35]	Yes
Stanton et al.[36]	Amlodipine 5-10mg vs. Lisinopril 5-20mg	Hypertension	69	1	Fw CCA	Mn, mm	-0.0480	-0.0270	0.044	CVD[29]	Yes
DAPHNE[37]	Doxazosin 1-16mg vs. diuretic hydrochlorothiazide 12.5-100mg	Hypertension	80	3	Nfw CCA, BIF, and ICA	Mnmx, mm	-0.1500	-0.1800	0.850	CVD[38]	Yes
LAARS[39]	Losartan 50mg vs. Atenolol 50mg	Hypertension	280	2	Fw CCA	Mean CCA	-0.038	-0.0370	NS	CVD[40]	No
Secondary prevention											
SECURE[41]	Ramipril 10mg vs. Placebo	Vascular disease or DM	732	4.5	Nfw CCA, BIF, and ICA	Mnmx, mm/y	0.0137	0.0217	0.033	CVD[42, 41]	Yes
PART-2[43]	Ramipril 5-10 mg vs. Placebo	CAD	617	4	Fw CCA	Mn, mm	0.0300	0.0200	0.58	CVD[29]	No
PREVENT[44]	Amlodipine 5-10mg vs. placebo	CAD	377	3	Nfw of CCA, BIF, and ICA	Mnmx, mm/y	-0.0126	0.0330	0.007	CVD[29]	Yes
Antioxidants											
Primary prevention											
VEAPS[45]	Vitamin E vs. Placebo	Asymptomatic	332	3	Fw CCA	Mn, mm/y	0.0040	0.0023	0.08	CVD[46]	Yes
MAVET[47]	Vitamin E vs. Placebo	Smoking	409	4	Nfw CCA, fw BIF and ICA	Mn, mm	0.0035	-0.0005	0.20	CVD[46]	Yes
FACIT[48]	Folic acid 800 ug vs. placebo	Asymptomatic	819	3	Nfw CCA	Mn, mm/y	0.0019	0.0013	0.59	CVD[49]	Yes
BVAIT[50]	Folic acid 5 mg + vitamin B12 0.4 mg + vitamin B6 50 mg vs. placebo	Asymptomatic	506	3.1	Fw CCA	Mn, mm	0.0022	0.0029	0.31	CVD[49]	Yes
Secondary prevention											
SECURE[41]	Vitamin E vs. Placebo	Vascular disease or DM	732	4.5	Nfw CCA, BIF, and ICA	Mnmx, mm/y	0.0180	0.0174	NS	CVD[46]	Yes
ASFAST[51]	Folic acid 15mg vs. placebo	Chronic renal failure	315	3.6	Fw CCA	Mnmx, mm	-0.0200	0.0300	0.43	CVD[49]	Yes
Hormone replacement therapy											

Primary prevention											
EPAT[52]	Estradiol 1mg vs. placebo	Asymptomatic, postmenopausal	222	2	Fw CCA	Mn, mm	-0.0017	0.0036	0.046	CHD[53]	No
OPAL[54]	Tibolone 2.5 mg vs. CEE/MPA (0.625 + 2.5 mg vs. placebo	Asymptomatic, postmenopausal	866	3	Nfw CCA, BIF, and ICA	Mn	0.0077/0.0074	0.0035	0.03/0.04	CHD[53]	Yes
Colacurci[55]	Raloxifene 60mg vs. placebo	Asymptomatic and postmenopausal	155	1.5	Nfw CCA, fw BIF and ICA	Mn, mm	0.0112	0.0857	0.0040	CVD[56]	Yes
Secondary prevention											
HERS[57]	CEE/MPA 0.625 + 2.5 mg vs. placebo	Postmenopausal with CHD	362	4	Nfw CCA and BIF	Mnmx	0.026	0.031	0.4400	CHD[58]	Yes
Glucose-lowering therapy											
Primary prevention											
STARR[30]	Rosiglitazone 8mg vs. placebo	Impaired glucose tolerance and/or impaired fasting glucose	1425	3	Nfw CCA, BIF, and ICA	Mnmx, mm/y	0.0063	0.0090	0.0800	CVD[59]	Yes
Secondary prevention											
CHICAGO[60]	Pioglitazone hydrochloride 15-45 mg vs. glimepiride 1-4 mg	DM2	462	1.5	Fw CCA	Mn, mm	-0.0010	0.0120	0.020	CVD[61]	Yes
Langenfeld[62]	Pioglitazone 45mg vs. glimepiride	DM2	179	0.5	Nfw CCA	Mn	-0.033	-0.0020	0.01	CVD[61]	Yes
RAS[63]	Rosiglitazone 4-8mg vs. placebo	DM2 or insulin resistance syndrome	555	1	Fw CCA and BIF	Mn,mm	0.0490	0.0600	0.310	CVD[59]	Yes
Anti-obesity therapy											
Primary prevention											
AUDITOR[64]	Rimonabant 20mg vs. placebo	Abdominal obesity and metabolic syndrome	661	2.5	Fw CCA, BIF, and ICA	Mn, mm/y	0.005	0.007	0.45	CVD[65]	Yes

Abbreviations: BIF, carotid bifurcation; CAD, coronary artery disease; CCA, common carotid artery; CHD, coronary heart disease; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; DM2, diabetes mellitus type 2; ICA, internal carotid artery; FU, follow-up; FH, familial hypercholesterolemia; Fw, far wall; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Nfw, near and far wall; M&M, morbidity and mortality; Mnmx, mean of the maximal segment-specific CIMT measurement; Mnmn, mean of the mean segment-specific CIMT measurement; Mn, mean CIMT measurement; TC, total cholesterol

* the numbers in this column refer to the number of the M&M trial in the reference list

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