European Heart Journal (2007) **28**, 398–406
doi:10.1093/eurheartj/ehl482

Review

Carotid intima-media thickness and coronary atherosclerosis: weak or strong relations?

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Received 14 July 2006; revised 2 January 2007; accepted 4 January 2007; online publish-ahead-of-print 2 February 2007

KEYWORDS
Carotid atherosclerosis;
Trials;
Surrogate endpoints;
Hypertension;
Statin

Aims Measurement of change in carotid intima-media thickness (CIMT) has been proposed as an alternative for the occurrence of cardiovascular (CV) events in the assessment of therapeutic interventions. Nevertheless, criticism has been voiced based on observations indicating a weak relation between CIMT and coronary atherosclerosis as well as on the virtual absence of data showing that progression of CIMT indeed predicts coronary artery disease (CAD) and stroke.
Methods and results We set out to review the evidence on these issues by performing a literature search on these topics. Of the 34 studies on the relation of CIMT with coronary atherosclerosis, as assessed by angiography ($n = 33$) or intravascular ultrasound ($n = 1$), 30 showed a modest positive relationship; the magnitude of which was similar to that found in autopsy studies. Of all studies on CIMT and future CV events ($n = 18$), 17 showed graded positive relationships. At present, only one study has provided evidence on the relation of change in CIMT and future CV events, showing an increased risk with CIMT progression. The paucity of data on progression and future CV risk is partly attributable to time windows required to complete these studies.
Conclusion The modest relation between CIMT and coronary atherosclerosis most likely reflects variability in atherosclerosis development between the vascular beds rather than limitations of CIMT measurements. Additional data on the relation between change in CIMT and future CV events is required and currently is in progress.

Introduction

Carotid intima-media thickness (CIMT) measurements have increasingly been used in observational and intervention studies. CIMT has been applied as an outcome variable in studies on the determinants of atherosclerosis, and it has been employed as an exposure variable in studies on the prognostic value of CIMT in order to predict coronary artery disease (CAD) and stroke. Change in CIMT over time as a marker for atherosclerosis progression and possibly change in cardiovascular risk, has predominantly served in intervention studies as a primary outcome variable aimed at assessing the effects of risk factor interventions. More recently, reports on the determinants of progression of CIMT have become available from observational studies. The current widespread application of CIMT measurements has been based on the validity, standardization, and reproducibility of the measurement, and the evidence that an increased CIMT can be regarded as a marker of atherosclerosis and of increased cardiovascular risk.[1–7]

Yet, criticism towards the value of these measurements can also be heard throughout the scientific community. Part of that comes from the observation that CIMT is a combined measure of the intimal and medial layer of the arterial wall, whereas the atherosclerotic process is restricted in particular in its early phase, to the intimal layer only. Furthermore, several reports point to the weak correlation between increased CIMT and coronary atherosclerosis and since the majority of the populations of the westernized societies die from CAD, these findings can be regarded as of great significance. Finally, the virtual absence of data showing that progression of CIMT predicts CAD and stroke further supports criticism of the research utility of CIMT measurements.

The current article attempts to provide an unbiased view, based on a literature search, towards these latter two aspects of criticism.

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Methods

Three literature searches were performed in the PubMed Medline (www.ncbi.nlm.nih.gov) database. The first search dealt with the relation of CIMT with coronary atherosclerosis using statements 'carotid intima-media thickness and coronary angiography; carotid intimal medial thickness and coronary angiography; carotid intima-media thickness and coronary atherosclerosis; carotid intimal medial thickness and coronary atherosclerosis; carotid atherosclerosis and coronary atherosclerosis'. This yielded 329 hits. The second search dealt with the relation of CIMT to risk of future events using statements 'carotid intima-media thickness and prediction; carotid intimal medial thickness and prediction; carotid intima-media thickness and cardiovascular events; carotid intimal medial thickness and cardiovascular events'. This gave 58 hits. The third search dealt with CIMT progression using statements 'carotid intima-media thickness progression; carotid intimal medial thickness progression'. This gave 284 hits.

All abstracts were reviewed for appropriateness on the research issue by one of the authors (M.L.B.), and if so, the article was retrieved. Articles were considered appropriate if the quantitative information in the abstract on the relation between CIMT and a measure of coronary atherosclerosis, being based on a coronary angiogram, coronary calcium, or intravascular ultrasound. Furthermore, information should be available on the population studied. No restrictions were made to the manner by which the relation was quantified. In addition, the references of the articles were checked and the PubMed link 'related articles' was used to identify additional papers. From search 1, 33 articles were found in the main search, and one was identified through reference listing. For search 2, these numbers were 12 and 6, respectively. For search 3, these numbers were 1 and 0, respectively. All hits and articles were reviewed by one author only and this in theory might have biased the findings when, for example, for search 1 those papers with strong relations were selectively excluded. Yet, the inclusion criteria were wide, i.e. if quantitative information on the relationship was provided, the article was included. In addition, there is no direct benefit for the authors by doing so.

Results

CIMT and coronary atherosclerosis

Atherosclerosis is a systemic disease process and large sections of the arterial tree will suffer from atherosclerosis when exposed to elevated risk factor levels. However, it is well known that some parts, like the brachial artery, are almost always spared from atherosclerotic involvement, although studies show a positive correlation between CIMT and brachial IMT.[8] Also, the extent of atherosclerosis differs across vessels like the femoral arteries, the abdominal aorta, the coronary arteries, and the carotid arteries. This has been elegantly shown in a post-mortem study by Pasterkamp *et al.*,[9] who reported a five-fold difference in extent of atherosclerosis between the common carotid arteries and the coronary arteries, a three-fold difference between common carotid arteries and the femoral arteries, and a 1.5-fold difference between the coronary and femoral arteries.

To appreciate the comparisons between measurements of atherosclerosis obtained from various arterial beds, e.g. carotid arteries vs. coronary arteries, a search for a gold standard should be performed first. In this particular case the gold standard most likely constitutes post-mortem studies. These are however scarce. In a post-mortem study on 24 subjects, common CIMT measured by histopathology, was compared with atherosclerosis of the femoral artery. The correlation between mean distal common CIMT and relative plaque area in the femoral artery was 0.26, not statistically significant, yet this sample size was exceedingly small. Unfortunately, information on the comparison with coronary atherosclerosis was not provided.[10] These findings do agree with data from autopsy studies performed around 1960,[11–14] that also showed great variability and modest correlations between carotid and coronary arterial beds of around 0.3–0.5. Thus, if the autopsy studies are assumed to have no measurement error, the upper limit of what imaging studies may find in terms of correlation is 0.50. These results are indicative of the magnitude of correlations that are to be expected when comparing atherosclerosis measurements from two arterial beds.

Table 1 gives a summary of the findings reported in the studies relating CIMT to coronary atherosclerosis.[15–45] As is clear from the table, CIMT has been measured in several ways. CIMT can be measured in the common carotid artery (CCA), the carotid bifurcation (BIF), and the internal carotid artery (ICA). In addition to the three segments, CIMT can be measured at the near wall of the arterial segment (i.e. the ultrasound interface on the image closest to the transducer) or at the far wall of the arterial segment. Next to this, results of a measurement can be expressed as a mean thickness over a length (usually 10 mm in the CCA) or as a maximum thickness of that specific wall and segment. Finally, only one measurement may be used in the analyses (e.g. mean far wall CCA), or the segment and wall-specific measurements may be combined into one CIMT estimate (e.g. mean max CIMT, i.e. mean of all separate maximum measurements). At present, there is however, no consensus of which CIMT approach constitutes the 'best' CIMT measurement for atherosclerosis assessment, for vascular risk assessment, or for change over time in CIMT assessment.[46] From Table 1 it can be seen that in general, most of the studies (29 out of 33) showed a graded positive relationship, with correlation coefficients in the order of 0.3–0.4, although some report lower or higher correlation coefficients and some studies showed no relationship at all (*Table 1*). In addition, a study among 45 patients who underwent intravascular ultrasound and carotid B-mode ultrasound reported that the average maximum CIMT was significantly related with left main (LM) coronary atherosclerosis, as measured by both mean and maximal plaque areas. The correlation coefficients were 0.39 and 0.41, respectively.[47]

From *Table 1*, it can been seen that the sample size does not appear to impact the magnitude of the results. Both large and small studies show a range of correlation coefficients. Also, from the four studies in which no relation between CIMT and coronary atherosclerosis was reported, two were small and two were large. Publication bias therefore does not appear to be a major issue.

CIMT and future vascular events

In *Table 2*, a summary is given of the available studies on the role of CIMT in predicting future vascular events.[48–66] In general, studies among the general population showed a gradual graded increase in risk with increased CIMT. Studies carried out among populations with symptoms of cardiovascular disease showed positive relations, albeit the magnitude of the association differed across studies

Table 1 Characteristics of the studies into the relation of CIMT and coronary atherosclerosis assessed by imaging techniques in cross-sectional studies

Publication year	First author	Data	No. of patients	Type of patients	Type of CIMT	Coronary atherosclerosis	Findings			Conclusion (related yes/no)
							Mean difference in CIMT (mm)	OR	Correlation	
2005	Rohani[8]	FP	37	CAD	CCA	CAG; ≥50% 0,1,2,3,VD			0.44	+
2004	Tagawa[15]	FP	26/12	CAD	CCA					+
	Hallerstam[16]	FP	111	CAD	CCA	MFR			0.23	+
	Wagenknecht[17]	FP	438	Family with ≥type II diabetics	CCA	CAC			0.36	+
	Kablak[18]	FP	558	Suspect CAD	CCA/BIF/ICA	CAG; ≥50% 0,1,2,3,VD	Graded			+
	Paskierki[103]	FP	410		CCA	CAG; ≥50%	0.66 vs. 0.64			−
	Yildiz[19]	FP	79	Haemodialysis	Plaque	CAC			0.40	+
	Sonoda[20]	FP	23/21/15	CAD/HT/Con	CCA	MFR			0.51	+
2003	Takiuchi[21]	FP	149	24 NT/125 HT	CCA	MFR			0.46	+
	Alan[22]	FP	180+/53 −	CAD/control	CCA	CAG				−
	Holaj[23]	FP	170	CAD	CCA	CAG				+
	Sakaguchi[24]	FP	270	CAD	CCA/BIF/ICA	CAG ≥50%	0.84 vs. 1.08	2.71/sd		+
	Orem[104]	FP	86	CAD	CCA	CAG abnormal/normal	0.89 vs. 0.76			+
2002	Ishizu[25]	FP	90	CAD	Mean max	≥75%	1.47 vs. 2.42	1.22/sd		+
	Newman[26]	FP	414	General population	ICA/CCA	Calcifications		1.63/sd ICA 2.89/sd CCA	0.30 ICA 0.12 CCA	+
	Oei[27]	FP	2013	General population	CCA	Calcifications			0.17	+
	Furumoto[28]	FP	45	Suspect CAD	CCA	<50%; 50–90%; ≥90%	0.77/0.80/1.08		0.32	−
	Belhasen[29]	FP	152	Valve surgery	CCA	CAG; ≥70%	0.58 vs. 0.70		0.45	
	Claessens[30]	FP	366	CABG/PTCA	CCA	CAG; ≥90% 0,1,2,3,VD	Graded			+
2001	Teragawa[31]	FP	81	Suspect CAD	CCA	CAG; ≥50%	0.79 vs. 1.09	5.2 (ns)		+
	Vasankari[32]	FP	62	Established CAD	CCA	CAG; ≥50% 0,1,2,3,VD	Graded			+
	Kato[33]	FP	104	Angina	CCA	≥50%	0.84 vs. 0.99	5.85		+
2000	Papamichael[34]	FP	165	CAD	CCA/FEM	CAG; ≥50% 0,1,2,3,VD				(Carotid) − (Femoral) +
	Mack[35]	FP	133	CABG	CCA	CAG (lumen)			−0.04	−
	Balbarini[36]	FP	151	CAD	CCA/BIF/ICA	CAG			0.43	+
	Lekakis[37]	FP	224	CAD	CCA	CAG ≥50% Gensini				+
1999	Davis[38]	FP	318	General population	CCA/BIF/ICA	CAC (yes/no)	0.77 vs. 0.82			+

1998	Enderle[39]	FP	122	Suspected CAD	CCA	CAG; abnormal/normal; 0,1,2,3 VD	0.47 vs. 0.58 graded	0.32	+
	Arad[40]	FP	50	General population	Mean max	Calcifications		0.22–0.50	+
1997	Khoury[41]	FP	102	Suspect CAD	Mean max	CAG; abnormal/normal	0.6 vs. 0.9		+ +
	Hulthe[42]	FP	32	CAD	BIF/CCA	CAG; 0,1,2,3 VD		0.68/0.31	+ +
1996	Visona[43]	FP	31	CAD	CCA	CAG abnormal/normal		0.37	+ +
1995	Adams[44]	FP	350	Suspect CAD	CCA	CAG; 0,1,2,3 VD		0.26/0.23/0.29	+
1994	Geroulakos[45]	FP	75	Suspect CAD	CCA	CAG; 0,1,2,3 VD	0.73;0.91;0.96;0.99		+
1991	Wofford[105]	FP	434	CAD patients	CCA	CAG; $\geq$50% 0,1,2,3,VD	Graded		+

FP, full paper; ABS, abstract only; CAG, coronary angiogram; VD, vessel diseased; MFR, myocardial flow reserve; CAC, coronary calcifications; Mean max, mean of segment specific maximum IMT measurements; FEM, femoral IMT; graded, severity of coronary atherosclerosis shows a graded relation with increasing IMT; NT, normotensive; HT, hypertensive.

owing to differences in units of measurement of CIMT. Data from the SMART study indicated that these positive associations also hold for patients with symptomatic coronary heart disease, for patients with cerebrovascular disease, and for patients with peripheral vascular disease.[66]

In most of the studies on the relation of CIMT and future events, the magnitude of the relations attenuated considerably when vascular risk factors were accounted for in the analyses. The relationships were thus partly mediated by risk factors, which further supports the notion that CIMT is a measurement in which long-term exposure to elevated risk factors is reflected. This notion has recently been detailed.[67]

Determinants of change over time in CIMT

Data on determinants of change over time in CIMT comes from observational studies and from randomized controlled trials. CIMT measurements performed in observational studies initiated around 1990 were not *a priori* set up for assessment of change over time. As a result, reproducibility of the CIMT measurement is much lower than in trials (intraclass correlation of repeated measurement of CIMT of 0.59–0.75 in observational studies and $>$0.90 in trials), and measurement error higher; thus the reported associations likely underestimate the true relationships. One of the earliest reports from Salonen and co-workers with data on 100 subjects, indicated that increasing age, LDL cholesterol, pack-years of smoking showed the strongest relationships with 2-year progression of CIMT.[68] In contrast, blood pressure levels and HDL cholesterol were not related to progression of CIMT in this sample. Zureik *et al*.[69] reported on the relations of pulse pressure and 4-year change in common CIMT among 957 healthy 59–71-year-old French men and women in the Étude du Vieillissement Artériel (EVA) study. The AtheroGene Study among 502 subjects with suspected CAD indicated that age, male gender, and current smoking were determinants of common CIMT progression over a period of 2.5 years.[70] The Atherosclerosis Risk in Communities study among 12 644 middle aged and women, reported diabetes, current smoking, HDL cholesterol (in white men), and pulse pressure to be positively related to increased progression of CIMT from 1987 to 1998.[71] In addition, increase in baseline from 1987 to 1998 in LDL cholesterol, triglycerides, and onset of hypertension and diabetes were positively related to increased progression. In contrast, results from the Cardiovascular Heath Study among 65-year-old men and women revealed no relations between established risk factors and 3-year progression of CIMT.[72] Data from the Rotterdam study among 3409 men and women aged 55 years or over, with second measurement after 6.5 years, indicated that moderate to severe progression of common CIMT was related to age, body mass index, male gender, current smoking, systolic blood pressure, and hypertension. Lipid levels, however, were not related to increased progression of common CIMT.[73] Recent information from the Carotid Atherosclerosis Progression Study among 3383 men and women, with a second CIMT measurement after 3 years, showed that age, male gender, hypertension, diabetes, and smoking related to increased progression of internal CIMT, whereas no relation was found for common CIMT.[74]

Table 2 Summary of prospective studies examining the relationship between CIMT and vascular events

First author	CIMT measurement	Clinical events associated with CIMT	FU (years)	Type of patient and (*n*)	Age at entry (years)	Male (%)	Unit of CIMT measurement (mm)	Adjusted RR (95% CI)
Salonen[48]	CCA and BIF	Fatal and non-fatal MI	0.08–2.5	General population (1288)	42–60	100	0.1	1.11 (1.06–1.16)
Chambless[49]	CCA, BIF, ICA	MI and coronary death	5.2	General population (12 841)	45–64	43	0.19 CCA	M: 1.32 (1.13–1.54) F: 1.92 (1.66–2.22)
Chambless[50]	CCA, BIF, ICA	Non-fatal and fatal stroke	7.2	General population (14 214)	45–64	45	0.18 CCA	M: 1.52 (1.28–1.80) F: 1.72 (1.49–1.99)
O'Leary[51]	CCA and ICA	MI and stroke	6.2	≥65 years (4476)	73	39	0.2 CCA	1.35 (1.25–1.45)
Bots[52]	CCA	MI and stroke	2.7	≥55 years (7983)	∼71	∼64	0.16	Stroke 1.41 (1.25–1.82) MI 1.43 (1.16–1.78)
Kitamura[61]	CCA and ICA combined	Stroke	4.5	General population without previous MI or stroke (1289)	60–74	100	Lowest vs. highest quartile	5.2 [1.8–14.6]
Rosvall[62]	CCA	MI or cardiac death	7	General population without previous MI or stroke (5163)	46–68		0.10	1.23 [1.14–1.33]
Rosvall[63]	CCA	Stroke	7	General population without previous MI or stroke (5163)	46–68		0.10	1.20 [1.08–1.33]
Murakami[64]	CCA	All-cause and vascular mortality	3.2	75 years (298)	75		0.30	CVD 2.35 [1.03–5.37]
Lorenz[65]	CCA, BIF, ICA	MI and stroke	4.2	19–90 years (5052)	19–90		0.16	MI: CCA: 1.16 [1.05–1.27] MI: ICA: 1.06 [0.96–1.17] Stroke: CCA: 1.11 [0.97–1.28] Stroke: ICA: 1.10 [0.96–1.26] Both: CCA: 1.17 [1.08–1.26] Both: ICA: 1.09 [1.01–1.18]
Hodis[53]	CCA	Coronary death and non-fatal MI	8.8	CABG patients (146)	54	100	0.13	1.4 (1.1–1.8)
Held[54]	CCA, BIF ICA	Non-fatal MI and CV death	3.0	Angina pectoris (558)	60	67	1.02 vs. 0.81	1.28 (0.59–2.78)
Nishizawa[55]	Carotid artery, location not given	CV mortality	2.5	ESRD (438)	60	60	1.0–2.0 vs. 1.0	3.17 (1.41–7.17)
Benedetto[56]	CCA	CV death	2.5	ESRD (138)	60	59	0.1	1.24 (1.06–1.44)
Kato[57]	CCA	CV mortality	∼5	ESRD (219)	∼58	66	0.1	1.41 (1.12–1.78)
Lacroix[58]	CCA	Worsening or recurrence of cardiac symptoms	0.9	PTCA patients (123)	62	22	≤0.7 vs. 0.7	No independent predictor
Folsom[59]	CCA, BIF, ICA	MI, coronary revascularization, and CHD death	10.2	DM (1500)	45–64	43	1	M: 2.3 (not given) F: 4.7 (not given)
Yamasaki[60]	CCA, BIF, ICA	Angina pectoris and MI	3.1	DM type II (287)	62	43	1	4.9 (1.7–14.1)
Dijk[66]	CCA	Coronary ischaemic events	2.8	CHD, stroke, and PAD patients	60	75	0.32	1.16 (1.01–1.34)

ESRD, end-stage renal disease; CHD, coronary heart disease; PAD, peripheral arterial disease; DM, diabetes mellitus; M, males; F, females; follow-up and age at entry are given as mean, median, or range.

Where observational studies usually have only two CIMT measurements over time and were not performed with an *a priori* objective to measure change over time in CIMT, such measurements in intervention studies are usually done more often (annual, or every 6 months) and therefore progression estimates are based on slope estimation from several points rather than from points at baseline and end of study only. Trials investigating the effect of blood pressure lowering treatment on CIMT progression have indeed shown that blood pressure lowering results in reduced progression.[75] In addition, results from randomized controlled trials have consistently shown that lipid-lowering reduces progression of CIMT or sometimes induces regression.[76–93]

Change over time in CIMT and risk of future events

Although many randomized controlled trials have been used (change in CIMT) as primary outcome, and thus provide excellent estimates of progression of CIMT over time, the participants of these trials are usually not followed for the occurrence of events after the trial has finished and thus data on change in CIMT and future risk is very limited. To the best of our knowledge, only one study has provided information on the relation of change in CIMT and the risk of future events. In a population of 146 men with coronary artery disease, aged 40–59 years with a follow-up of 8.8 years, Hodis *et al.*[94] showed that a 0.03 mm/year increase in common CIMT was related to a 2.2-fold increased risk of coronary events.

Another of the reasons for the paucity of this type of data is the time window required to perform baseline and follow-up measurements, and subsequently have cardiovascular events to occur. To illustrate this point, manuscripts on the relation of baseline CIMT and future CV events from large observational studies took between 5 and 12 years to be published. Given that recent papers from such studies on determinants of progression have just been published, it is obvious that it may take some time before a sufficient number of events have been collected to allow estimation of relationships with sufficient precision. However, such data is urgently needed. Apart from the existing cohorts that will provide evidence on this issue, the IMPROVE study among 3600 subjects at high risk of vascular disease recruited from seven European countries has been initiated specifically to study determinants of progression of CIMT.[95] Baseline data will be collected and after 15 months a second CIMT measurement will be taken. Event follow-up will continue up to 3 years. Results on progression are expected at the end of 2007.

Discussion

In the present article, we have tried to address the limitations in the assessment of (change in) CIMT as a suitable alternative for CV events in studies on the effects of vascular risk factors. Part of the criticism has come from observations indicating a weak relation between CIMT and coronary atherosclerosis. In fact the majority of the published reports revealed relationships between coronary atherosclerosis and CIMT in the expected direction. Furthermore, the associations are of a similar magnitude to that shown in autopsy studies. Thus, a modest relation between CIMT and coronary atherosclerosis most likely reflects variability in atherosclerosis development between the vascular beds rather than limitations in CIMT measurements.

A second limitation dealt with the virtual absence of data showing that progression of CIMT predicts coronary heart disease and stroke. The limited data on this issue may to some extent be attributable to the time windows required for these studies in their generation of results. Moreover, since the earlier observational studies using CIMT measurement have more measurement error when compared with more recent studies, they need larger sample sizes and a larger number of events to provide precise and stable estimates of CIMT progression. Therefore, this lack of information remains to be addressed.

A third critique deals with the observation that CIMT is a combined measure of the intimal and medial layer of the vessel wall, and that the atherosclerotic process is restricted in particular in its early phase to the intimal layer only. Indeed, studies comparing far wall B-mode ultrasound with histology showed that the combined intima and media is measured.[96–99] Nevertheless, the relations between measured CIMT and measured coronary atherosclerosis appear to be of the same magnitude as those seen in autopsy studies.

For a measurement to be suitable as an alternative for CV events in intervention studies, criteria have been proposed (*Table 3*).[46,100] Recently, Espeland *et al.*[101] applied these two sets of criteria to evaluate whether change in CIMT might be suitable as an alternative for CV events in seven lipid-lowering trials. In the article, Espeland showed that lipid-lowering therapy already affects progression of CIMT before a reduction in events can be established, using a smaller number of subjects and a shorter time frame when compared with an event trial. Furthermore, evidence was

Table 3 Criteria for surrogacy proposed by Boissel[101] and Prentice[46]

Clinical criteria for surrogacy (Boissel)
B1: Efficiency
Relatively easy to measure, preferably non-invasively
Trials should be smaller and of shorter duration
Changes in surrogate should precede clinical endpoints so that progression may be assessed more quickly
B2: Linkage
Quantitative and qualitative relation between surrogate and event
B3: Congruency
Surrogate should produce parallel estimates of risk and benefit.
Changes in events should be deductible from observed changes in surrogate
Statistical criteria for surrogacy (Prentice)
P1: The intervention should affect the distribution of the endpoint
P2: The intervention should affect the distribution of the surrogate
P3: The distribution of the endpoint should dependent on surrogate
P4: The surrogate should fully account for the impact of the intervention on the endpoint

provided that change in CIMT progression due to lipid-lowering therapy, in part, explained the reduction in vascular events.[101] A similar analysis for blood pressure-lowering treatment was recently reported by Wang *et al.*[102]

In conclusion, at present, multiple lines of evidence are supportive of assessment of change in CIMT as an alternative for cardiovascular events to study effects of interventions. A modest relation between CIMT and coronary atherosclerosis most likely reflects variability in atherosclerosis development between the vascular beds rather than a poor CIMT measurement. Additional data on the relation between change in CIMT and future CV events is urgently required and currently is in progress.

Conflict of interest: none declared.

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