

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

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## KEYWORDS

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**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.<sup>1–7</sup>

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.<sup>8</sup> 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.*,<sup>9</sup> 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.<sup>10</sup> These findings do agree with data from autopsy studies performed around 1960,<sup>11-14</sup> 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.<sup>15-45</sup> 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.<sup>46</sup> 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.<sup>47</sup>

From Table 1, it can be 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.<sup>48-66</sup> 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 <sup>8</sup>	FP	37	CAD	CCA	CAG; $\geq 50\%$ 0,1,2,3,VD			0.44	+
2004	Tagawa <sup>15</sup>	FP	26/12	CAD	CCA					+
	Hallerstam <sup>16</sup>	FP	111	CAD	CCA	MFR			0.23	+
	Wagenknecht <sup>17</sup>	FP	438	Family with $\geq$ type II diabetics	CCA	CAC			0.36	+
	Kablak <sup>18</sup>	FP	558	Suspect CAD	CCA/BIF/ICA	CAG; $\geq 50\%$ 0,1,2,3,VD	Graded			+
2003	Paskierki <sup>103</sup>	FP	410		CCA	CAG; $\geq 50\%$	0.66 vs. 0.64			-
	Yildiz <sup>19</sup>	FP	79	Haemodialysis	Plaque	CAC			0.40	+
	Sonoda <sup>20</sup>	FP	23/21/15	CAD/HT/Con	CCA	MFR			0.51	+
	Takiuchi <sup>21</sup>	FP	149	24 NT/125 HT	CCA	MFR			0.46	+
	Alan <sup>22</sup>	FP	180+/53-	CAD/control	CCA	CAG				-
	Holaj <sup>23</sup>	FP	170	CAD	CCA	CAG				+
	Sakaguchi <sup>24</sup>	FP	270	CAD	CCA/BIF/ICA	CAG $\geq 50\%$	0.84 vs. 1.08	2.71/sd		+
	2002	Orem <sup>104</sup>	FP	86	CAD	CCA	CAG abnormal/normal	0.89 vs. 0.76		
Ishizu <sup>25</sup>		FP	90	CAD	Mean max	$\geq 75\%$	1.47 vs. 2.42	1.22/sd		+
Newman <sup>26</sup>		FP	414	General population	ICA/CCA	Calcifications		1.63/sd ICA 2.89/sd CCA	0.30 ICA 0.12 CCA	+
2001	Oei <sup>27</sup>	FP	2013	General population	CCA	Calcifications			0.17	+
	Furumoto <sup>28</sup>	FP	45	Suspect CAD	CCA	<50%; 50-90%; $\geq 90\%$	0.77/0.80/1.08		0.32	-
	Belhasen <sup>29</sup>	FP	152	Valve surgery	CCA	CAG; $\geq 70\%$	0.58 vs. 0.70		0.45	
	Claessens <sup>30</sup>	FP	366	CABG/PTCA	CCA	CAG; $\geq 90\%$ 0,1,2,3,VD	Graded			+
	Teragawa <sup>31</sup>	FP	81	Suspect CAD	CCA	CAG; $\geq 50\%$	0.79 vs. 1.09	5.2 (ns)		+
	Vasankari <sup>32</sup>	FP	62	Established CAD	CCA	CAG; $\geq 50\%$ 0,1,2,3,VD	Graded			+
2000	Kato <sup>33</sup>	FP	104	Angina	CCA	$\geq 50\%$	0.84 vs. 0.99	5.85		+
	Papamichael <sup>34</sup>	FP	165	CAD	CCA/FEM	CAG; $\geq 50\%$ 0,1,2,3,VD				(Carotid) - (Femoral) +
	Mack <sup>35</sup>	FP	133	CABG	CCA	CAG (lumen)			-0.04	-
	Balbarini <sup>36</sup>	FP	151	CAD	CCA/BIF/ICA	CAG			0.43	+
1999	Lekakis <sup>37</sup>	FP	224	CAD	CCA	CAG $\geq 50\%$ Gensini				+
	Davis <sup>38</sup>	FP	318	General population	CCA/BIF/ICA	CAC (yes/no)	0.77 vs. 0.82			+

Year	Author	FP	n	Population	CCA	CAD	CCA	CAG/Calcifications	Comparison	Mean max BIF/CCA	IMT	Significance
1998	Enderle <sup>39</sup>	FP	122	Suspected CAD	CCA	Suspected CAD	CCA	CAG; abnormal/normal; 0,1,2,3 VD	0.47 vs. 0.58 graded	0.32	0.32	+
1997	Arad <sup>40</sup>	FP	50	General population	Mean max	General population	Mean max	Calcifications	0.6 vs. 0.9	0.22-0.50	0.22-0.50	+
	Khoury <sup>41</sup>	FP	102	Suspect CAD	Mean max	Suspect CAD	Mean max	CAG; abnormal/normal		0.68/0.31	0.68/0.31	+
	Hulthe <sup>42</sup>	FP	32	CAD	BIF/CCA	CAD	BIF/CCA	CAG; 0,1,2,3 VD		0.37	0.37	+
	Visona <sup>43</sup>	FP	31	CAD	CCA	CAD	CCA	CAG abnormal/normal		0.26/0.23/0.29	0.26/0.23/0.29	+
	Adams <sup>44</sup>	FP	350	Suspect CAD	CCA	Suspect CAD	CCA	CAG; 0,1,2,3 VD				+
1994	Geroulakos <sup>45</sup>	FP	75	Suspect CAD	CCA	Suspect CAD	CCA	CAG; 0,1,2,3 VD	0.73;0.91;0.96;0.99	0.73;0.91;0.96;0.99	0.73;0.91;0.96;0.99	+
	Wofford <sup>105</sup>	FP	434	CAD patients	CCA	CAD patients	CCA	CAG; ≥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.<sup>66</sup>

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.<sup>67</sup>

### 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 (intra-class 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.<sup>68</sup> In contrast, blood pressure levels and HDL cholesterol were not related to progression of CIMT in this sample. Zureik *et al.*<sup>69</sup> 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.<sup>70</sup> 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.<sup>71</sup> 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.<sup>72</sup> 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.<sup>73</sup> 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.<sup>74</sup>

**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 <sup>48</sup>	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 <sup>49</sup>	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 <sup>50</sup>	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 <sup>51</sup>	CCA and ICA	MI and stroke	6.2	≥65 years (4476)	73	39	0.2 CCA	1.35 (1.25–1.45)
Bots <sup>52</sup>	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 <sup>61</sup>	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 <sup>62</sup>	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 <sup>63</sup>	CCA	Stroke	7	General population without previous MI or stroke (5163)	46–68		0.10	1.20 [1.08–1.33]
Murakami <sup>64</sup>	CCA	All-cause and vascular mortality	3.2	75 years (298)	75		0.30	CVD 2.35 [1.03–5.37]
Lorenz <sup>65</sup>	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] 1.4 (1.1–1.8)
Hodis <sup>53</sup>	CCA	Coronary death and non-fatal MI	8.8	CABG patients (146)	54	100	0.13	1.28 (0.59–2.78)
Held <sup>54</sup>	CCA, BIF ICA	Non-fatal MI and CV death	3.0	Angina pectoris (558)	60	67	1.02 vs. 0.81	3.17 (1.41–7.17)
Nishizawa <sup>55</sup>	Carotid artery, location not given	CV mortality	2.5	ESRD (438)	60	60	1.0–2.0 vs. 1.0	
Benedetto <sup>56</sup>	CCA	CV death	2.5	ESRD (138)	60	59	0.1	1.24 (1.06–1.44)
Kato <sup>57</sup>	CCA	CV mortality	~5	ESRD (219)	~58	66	0.1	1.41 (1.12–1.78)
Lacroix <sup>58</sup>	CCA	Worsening or recurrence of cardiac symptoms	0.9	PTCA patients (123)	62	22	≤0.7 vs. 0.7	No independent predictor
Folsom <sup>59</sup>	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 <sup>60</sup>	CCA, BIF, ICA	Angina pectoris and MI	3.1	DM type II (287)	62	43	1	4.9 (1.7–14.1)
Dijk <sup>66</sup>	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.<sup>75</sup> In addition, results from randomized controlled trials have consistently shown that lipid-lowering reduces progression of CIMT or sometimes induces regression.<sup>76–93</sup>

### 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.*<sup>94</sup> 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.<sup>95</sup> 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.<sup>96–99</sup> 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).<sup>46,100</sup> Recently, Espeland *et al.*<sup>101</sup> 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<sup>101</sup> and Prentice<sup>46</sup>

#### 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.<sup>101</sup> A similar analysis for blood pressure-lowering treatment was recently reported by Wang *et al.*<sup>102</sup>

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.

## References

- Mancini GB. Carotid intima-media thickness as a measure of vascular target organ damage. *Curr Hypertens Rep* 2000;2:71-77.
- Bots ML, Grobbee DE. Intima media thickness as a surrogate marker for generalised atherosclerosis. *Cardiovasc Drugs Ther* 2002;16:341-351.
- de Groot E, Hovingh GK, Wiegman A, Duriez P, Smit AJ, Fruchart JC, Kastelein JJ. Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation* 2004;109(Suppl. 1):III33-III38.
- Amarenco P, Labreuche J, Lavalley P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* 2004;35:2902-2909.
- Poredos P. Intima-media thickness: indicator of cardiovascular risk and measure of the extent of atherosclerosis. *Vasc Med* 2004;9:46-54.
- Barth JD. Carotid intima media thickness and beyond. *Curr Drug Targets Cardiovasc Haematol Disord* 2004;4:129-145.
- Spence JD, Hegele RA. Non-invasive assessment of atherosclerosis risk. *Curr Drug Targets Cardiovasc Haematol Disord* 2004;4:125-128.
- Rohani M, Jogestrand T, Ekberg M, van der Linden J, Kallner G, Jussila R, Agewall S. Interrelation between the extent of atherosclerosis in the thoracic aorta, carotid intima-media thickness and the extent of coronary artery disease. *Atherosclerosis* 2005;179:311-316.
- Pasterkamp G, Schoneveld AH, van Wolferen W, Hillen B, Clarijs RJ, Haudenschild CC, Borst C. The impact of atherosclerotic arterial remodelling on percentage of luminal stenosis varies widely within the arterial system. A post-mortem study. *Arterioscler Thromb Vasc Biol* 1997;17:3057-3063.
- Pasterkamp G, Schoneveld AH, Hillen B, Banga JD, Haudenschild CC, Borst C. Is plaque formation in the common carotid artery representative for plaque formation and luminal stenosis in other atherosclerotic peripheral arteries? A post mortem study. *Atherosclerosis* 1998;137:205-210.
- Young W, Gofman JW, Tandy R, Malamud N, Waters ESG. The quantification of atherosclerosis. III. The extent of correlation of degrees of atherosclerosis within and between the coronary and cerebral vascular beds. *Am J Cardiol* 1960;6:300-308.
- Mitchell JRA. Relationship between arterial disease in different sites. A study of the aorta and coronary, carotid and iliac arteries. *Br Med J* 1962;5288:1293-1301.
- Holme I, Enger SC, Helgeland A, Hjermann I, Leren P, Lund-Larsen PG, Solberg LA, Strong JP. Risk factors and raised atherosclerotic lesions in coronary and cerebral arteries. Statistical analysis from the Oslo study. *Arteriosclerosis* 1981;1:250-256.
- Sternby NH. Atherosclerosis in a defined population. An autopsy survey in Malmo, Sweden. *Acta Pathol Microbiol Scand* 1968;(Suppl. 194):5-11.
- Tagawa T, Urabe Y, Kimura Y, Suzuki S, Ono H, Takeda K. Long-term treatment with probucol improves endothelial function in patients with coronary artery disease. *Hypertens Res* 2004;27:311-318.
- Hallerstam S, Larsson PT, Zuber E, Rosfors S. Carotid atherosclerosis is correlated with extent and severity of coronary artery disease evaluated by myocardial perfusion scintigraphy. *Angiology* 2004;55:281-288.
- Wagenknecht LE, Langefeld CD, Carr JJ, Riley W, Freedman BI, Moossavi S, Bowden DW. Race-specific relationships between coronary and carotid artery calcification and carotid intimal medial thickness. *Stroke* 2004;35:e97-e99.
- Kablak-Ziembicka A, Przewlocki T, Kostkiewicz M, Pieniazek P, Mura A, Podolec P, Tracz W. Relationship between carotid intima-media thickness, atherosclerosis risk factors and angiography findings in patients with coronary artery disease. *Acta Cardiol* 2002;57:40-41.
- Yildiz A, Tepe S, Oflaz H, Yazici H, Pusuroglu H, Besler M, Ark E, Erzenin F. Carotid atherosclerosis is a predictor of coronary calcification in chronic haemodialysis patients. *Nephrol Dial Transplant* 2004;19:885-891.
- Sonoda M, Yonekura K, Yokoyama I, Takenaka K, Nagai R, Aoyagi T. Common carotid intima-media thickness is correlated with myocardial flow reserve in patients with coronary artery disease: a useful non-invasive indicator of coronary atherosclerosis. *Int J Cardiol* 2004;93:131-136.
- Takiuchi S, Rakugi H, Fujii H, Kamide K, Horio T, Nakatani S, Kawano Y, Higaki J, Ogihara T. Carotid intima-media thickness is correlated with impairment of coronary flow reserve in hypertensive patients without coronary artery disease. *Hypertens Res* 2003;26:945-951.
- Alan S, Ulgen MS, Ozturk O, Alan B, Ozdemir L, Toprak N. Relation between coronary artery disease, risk factors and intima-media thickness of carotid artery, arterial distensibility, and stiffness index. *Angiology* 2003;54:261-267.
- Holaj R, Spacil J, Petrasek J, Malik J, Haas T, Aschermann M. Intima-media thickness of the common carotid artery is the significant predictor of angiographically proven coronary artery disease. *Can J Cardiol* 2003;19:670-676.
- Sakaguchi M, Kitagawa K, Nagai Y, Yamagami H, Kondo K, Matsushita K, Oku N, Hougaku H, Ohtsuki T, Masuyama T, Matsumoto M, Hori M. Equivalence of plaque score and intima-media thickness of carotid ultrasonography for predicting severe coronary artery lesion. *Ultrasound Med Biol* 2003;29:367-371.
- Ishizu T, Ishimitsu T, Kamiya H, Seo Y, Moriyama N, Obara K, Watanabe S, Yamaguchi I. The correlation of irregularities in carotid arterial intima-media thickness with coronary artery disease. *Heart Vessels* 2002;17:1-6.
- Newman AB, Naydeck BL, Sutton-Tyrrell K, Edmundowicz D, O'Leary D, Kronmal R, Burke GL, Kuller LH. Relationship between coronary artery calcification and other measures of subclinical cardiovascular disease in older adults. *Arterioscler Thromb Vasc Biol* 2002;22:1674-1679.
- Oei HH, Vliegenthart R, Hak AE, Iglesias del Sol A, Hofman A, Oudkerk M, Witteman JC. The association between coronary calcification assessed by electron beam computed tomography and measures of extracoronary atherosclerosis: the Rotterdam Coronary Calcification Study. *J Am Coll Cardiol* 2002;39:1745-1751.
- Furumoto T, Fujii S, Saito N, Mikami T, Kitabatake A. Relationships between brachial artery flow mediated dilation and carotid artery intima-media thickness in patients with suspected coronary artery disease. *Jpn Heart J* 2002;43:117-125.
- Belhassen L, Carville C, Pelle G, Monin JL, Teiger E, Duval-Moulin AM, Dupouy P, Dubois Rande JL, Gueret P. Evaluation of carotid artery and aortic intima-media thickness measurements for exclusion of significant coronary atherosclerosis in patients scheduled for heart valve surgery. *J Am Coll Cardiol* 2002;39:1139-1144.
- Claessens P, Claessens C, Claessens M, Claessens M, Claessens J. The 'CARFEM' vascular index as a predictor of coronary atherosclerosis. *Med Sci Monit* 2002;8:MT1-9.
- Teragawa H, Kato M, Kurokawa J, Yamagata T, Matsuura H, Chayama K. Usefulness of flow-mediated dilation of the brachial artery and/or the intima-media thickness of the carotid artery in predicting coronary narrowing in patients suspected of having coronary artery disease. *Am J Cardiol* 2001;88:1147-1151.
- Vasankari T, Ahotupa M, Toikka J, Mikkola J, Irjala K, Pasanen P, Neuvonen K, Raitakari O, Viikari J. Oxidized LDL and thickness of carotid intima-media are associated with coronary atherosclerosis in middle-aged men: lower levels of oxidized LDL with statin therapy. *Atherosclerosis* 2001;155:403-412.
- Kato J, Aihara A, Kikuya M, Matsubara M, Ohta M, Ohkubo T, Tsuji I, Sekino H, Meguro T, Imai Y. Risk factors and predictors of coronary arterial lesions in Japanese hypertensive patients. *Hypertens Res* 2001;24:3-11.
- Papamichael CM, Lekakis JP, Stamatiopoulos KS, Papaioannou TG, Alevizaki MK, Cimponeriu AT, Kanakakis JE, Papapanagiotou A, Kalofoutis AT, Stamatiopoulos SF. Ankle-brachial index as a predictor of the extent of coronary atherosclerosis and cardiovascular events in patients with coronary artery disease. *Am J Cardiol* 2000;86:615-618.
- Mack WJ, LaBree L, Liu C, Selzer RH, Hodis HN. Correlations between measures of atherosclerosis change using carotid ultrasonography and coronary angiography. *Atherosclerosis* 2000;150:371-379.
- Balbarini A, Buttitta F, Limbruno U, Petronio AS, Baglini R, Strata G, Mariotti R, Ciccone M, Mariani M. Usefulness of carotid intima-media

- thickness measurement and peripheral B-mode ultrasound scan in the clinical screening of patients with coronary artery disease. *Angiology* 2000;**51**:269–279.
37. Lekakis JP, Papamichael CM, Cimponeriu AT, Stamatelopoulou KS, Papaioannou TG, Kanakakis J, Alevizaki MK, Papapanagiotou A, Kalofoutis AT, Stamatelopoulou SF. Atherosclerotic changes of extracoronary arteries are associated with the extent of coronary atherosclerosis. *Am J Cardiol* 2000;**85**:949–952.
  38. Davis PH, Dawson JD, Mahoney LT, Lauer RM. Increased carotid intimal-medial thickness and coronary calcification are related in young and middle-aged adults. The Muscatine study. *Circulation* 1999;**100**:838–842.
  39. Enderle MD, Schroeder S, Ossen R, Meisner C, Baumbach A, Haering HU, Karsch KR, Pfohl M. Comparison of peripheral endothelial dysfunction and intimal media thickness in patients with suspected coronary artery disease. *Heart* 1998;**80**:349–354.
  40. Arad Y, Spadaro LA, Roth M, Scordo J, Goodman K, Sherman S, Ledo A, Lerner G, Guerci AD. Correlations between vascular calcification and atherosclerosis: a comparative electron beam CT study of the coronary and carotid arteries. *J Comput Assist Tomogr* 1998;**22**:207–211.
  41. Khoury Z, Schwartz R, Gottlieb S, Chenzbraun A, Stern S, Keren A. Relation of coronary artery disease to atherosclerotic disease in the aorta, carotid, and femoral arteries evaluated by ultrasound. *Am J Cardiol* 1997;**80**:1429–1433.
  42. Hulthe J, Wikstrand J, Emanuelsson H, Wiklund O, de Feyter PJ, Wendelhag I. Atherosclerotic changes in the carotid artery bulb as measured by B-mode ultrasound are associated with the extent of coronary atherosclerosis. *Stroke* 1997;**28**:1189–1194.
  43. Visona A, Pesavento R, Lusiani L, Bonanome A, Cernetti C, Rossi M, Maiolino P, Pagnan A. Intimal medial thickening of common carotid artery as indicator of coronary artery disease. *Angiology* 1996;**47**:61–66.
  44. Adams MR, Nakagomi A, Keech A, Robinson J, McCredie R, Bailey BP, Freedman SB, Celermajer DS. Carotid intima-media thickness is only weakly correlated with the extent and severity of coronary artery disease. *Circulation* 1995;**92**:2127–2134.
  45. Geroulakos G, O'Gorman DJ, Kalodiki E, Sheridan DJ, Nicolaides AN. The carotid intima-media thickness as a marker of the presence of severe symptomatic coronary artery disease. *Eur Heart J* 1994;**15**:781–785.
  46. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med* 1989;**8**:431–440.
  47. Ogata T, Yasaka M, Yamagishi M, Seguchi O, Nagatsuka K, Minematsu K. Atherosclerosis found on carotid ultrasonography is associated with atherosclerosis on coronary intravascular ultrasonography. *J Ultrasound Med* 2005;**24**:469–474.
  48. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb* 1991;**11**:1245–1249.
  49. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987–1993. *Am J Epidemiol* 1997;**146**:483–494.
  50. Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, Rosamond WD, Evans G. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol* 2000;**151**:478–487.
  51. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999;**340**:14–22.
  52. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* 1997;**96**:1432–1437.
  53. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 1998;**128**:262–269.
  54. Held C, Hjerdahl P, Eriksson SV, Bjorkander I, Forslund L, Rehnqvist N. Prognostic implications of intima-media thickness and plaques in the carotid and femoral arteries in patients with stable angina pectoris. *Eur Heart J* 2001;**22**:62–72.
  55. Nishizawa Y, Shoji T, Maekawa K, Nagasue K, Okuno S, Kim M, Emoto M, Ishimura E, Nakatani T, Miki T, Inaba M. Intima-media thickness of carotid artery predicts cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2003;**41**:S76–S79.
  56. Benedetto FA, Mallamaci F, Tripepi G, Zoccali C. Prognostic value of ultrasonographic measurement of carotid intima media thickness in dialysis patients. *J Am Soc Nephrol* 2001;**12**:2458–2464.
  57. Kato A, Takita T, Maruyama Y, Kumagai H, Hishida A. Impact of carotid atherosclerosis on long-term mortality in chronic hemodialysis patients. *Kidney Int* 2003;**64**:1472–1479.
  58. Lacroix P, Aboyans V, Espaliat E, Cornu E, Virot P, Laskar M. Carotid intima-media thickness as predictor of secondary events after coronary angioplasty. *Int Angiol* 2003;**22**:279–283.
  59. Folsom AR, Chambless LE, Duncan BB, Gilbert AC, Pankow JS. Prediction of coronary heart disease in middle-aged adults with diabetes. *Diabetes Care* 2003;**26**:2777–2784.
  60. Yamasaki Y, Kodama M, Nishizawa H, Sakamoto K, Matsuhisa M, Kajimoto Y, Kosugi K, Shimizu Y, Kawamori R, Hori M. Carotid intima-media thickness in Japanese type 2 diabetic subjects: predictors of progression and relationship with incident coronary heart disease. *Diabetes Care* 2000;**23**:1310–1311.
  61. Kitamura A, Iso H, Imano H, Ohira T, Okada T, Sato S, Kiyama M, Tanigawa T, Yamagishi K, Shimamoto T. Carotid intima-media thickness and plaque characteristics as a risk factor for stroke in Japanese elderly men. *Stroke* 2004;**35**:2788–2794.
  62. Rosvall M, Janzon L, Berglund G, Engstrom G, Hedblad B. Incident coronary events and case fatality in relation to common carotid intima-media thickness. *J Intern Med* 2005;**257**:430–437.
  63. Rosvall M, Janzon L, Berglund G, Engstrom G, Hedblad B. Incidence of stroke is related to carotid IMT even in the absence of plaque. *Atherosclerosis* 2005;**179**:325–331.
  64. Murakami S, Otsuka K, Hotta N, Yamanaka G, Kubo Y, Matsuoka O, Yamana K, Shinagawa M, Nunoda S, Nishimura Y, Shibata K, Takasugi E, Nishinaga M, Ishine M, Wada T, Okumiya K, Matsubayashi K, Yano S, Ichihara K, Cornelissen G, Halberg F. Common carotid intima-media thickness is predictive of all-cause and cardiovascular mortality in elderly community-dwelling people: Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study. *Biomed Pharmacother* 2005;**59**(Suppl. 1):S49–S53.
  65. Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). *Stroke* 2006;**37**:87–92.
  66. Dijk JM, van der Graaf Y, Bots ML, Grobbee DE, Algra A. Carotid intima-media thickness and the risk of new vascular events in patients with manifest atherosclerotic disease: the SMART study. *Eur Heart J* 2006;**27**:1971–1978.
  67. Simon A, Levenson J. May subclinical arterial disease help to better detect and treat high-risk asymptomatic individuals? *J Hypertens* 2005;**23**:1939–1945.
  68. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: a population-based ultrasonography study. *Atherosclerosis* 1990;**81**:33–40.
  69. Zureik M, Touboul PJ, Bonithon-Kopp C, Courbon D, Berr C, Leroux C, Ducimetiere P. Cross-sectional and 4-year longitudinal associations between brachial pulse pressure and common carotid intima-media thickness in a general population. The EVA study. *Stroke* 1999;**30**:550–555.
  70. Espinola-Klein C, Rupprecht HJ, Blankenberg S, Bickel C, Kopp H, Victor A, Hafner G, Prellwitz W, Schlumberger W, Meyer J. Impact of infectious burden on progression of carotid atherosclerosis. *Stroke* 2002;**33**:2581–2586.
  71. Chambless LE, Folsom AR, Davis V, Sharrett R, Heiss G, Sorlie P, Szklo M, Howard G, Evans GW. Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities Study, 1987–1998. *Am J Epidemiol* 2002;**155**:38–47.
  72. Yanez ND III, Kronmal RA, Shemanski LR, Psaty BM. Cardiovascular Health Study. A regression model for longitudinal change in the presence of measurement error. *Ann Epidemiol* 2002;**12**:34–38.
  73. van der Meer IM, Iglesias del Sol A, Hak AE, Bots ML, Hofman A, Witteman JC. Risk factors for progression of atherosclerosis measured at multiple sites in the arterial tree: the Rotterdam Study. *Stroke* 2003;**34**:2374–2379.
  74. Mackinnon AD, Jerrard-Dunne P, Sitzer M, Buehler A, von Kegler S, Markus HS. Rates and determinants of site-specific progression of carotid artery intima-media thickness: the carotid atherosclerosis progression study. *Stroke* 2004;**35**:2150–2154.
  75. Thomas JD, Adams DB, Devries S, Ehler D, Greenberg N, Garcia M, Ginzton L, Gorcsan J, Katz AS, Keller A, Khandheria B, Powers KB, Roszel C, Rubenson DS, Soble J Digital Echocardiography Committee of



- the American Society of Echocardiography. Guidelines and recommendations for digital echocardiography. *J Am Soc Echocardiogr* 2005;18:287-297.
76. Blankenhorn DH, Selzer RH, Crawford DW, Barth JD, Liu CR, Liu CH, Mack WJ, Alaupovic P. Beneficial effects of colestipol-niacin therapy on the common carotid artery. Two- and four-year reduction of intima-media thickness measured by ultrasound. *Circulation* 1993;88:20-28.
  77. Mack WJ, Selzer RH, Hodis HN, Erickson JK, Liu CR, Liu CH, Crawford DW, Blankenhorn DH. One-year reduction and longitudinal analysis of carotid intima-media thickness associated with colestipol/niacin therapy. *Stroke* 1993;24:1779-1783.
  78. Furberg CD, Adams HP Jr, Applegate WB, Byington RP, Espeland MA, Hartwell T, Hunninghake DB, Lefkowitz DS, Probstfield J, Riley WA. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation* 1994;90:1679-1687.
  79. Salonen R, Nyyssonen K, Porkkala E, Rummukainen J, Belder R, Park JS, Salonen JT. Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circulation* 1995;92:1758-1764.
  80. Crouse JR III, Byington RP, Bond MG, Espeland MA, Craven TE, Sprinkle JW, McGovern ME, Furberg CD. Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *Am J Cardiol* 1995;75:455-459.
  81. de Groot E, Jukema JW, van Boven AJ, Reiber JH, Zwinderman AH, Lie KI, Akerstaff RA, Brusche AV. Effect of pravastatin on progression and regression of coronary atherosclerosis and vessel wall changes in carotid and femoral arteries: a report from the Regression Growth Evaluation Statin Study. *Am J Cardiol* 1995;76:40C-46C.
  82. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu C, Liu C, Alaupovic P, Kwong-Fu H, Azen SP. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized controlled clinical trial. *Ann Intern Med* 1996;124:548-556.
  83. Mercuri M, Bond MG, Sirtori CR, Veglia F, Crepaldi G, Feruglio FS, Descovich G, Ricci G, Rubba P, Mancini M, Gallus G, Bianchi G, D'Alo G, Ventura A. Pravastatin reduces carotid intima-media thickness progression in an asymptomatic hypercholesterolemic mediterranean population: the Carotid Atherosclerosis Italian Ultrasound Study. *Am J Med* 1996;101:627-634.
  84. MacMahon S, Sharpe N, Gamble G, Hart H, Scott J, Simes J, White H. Effects of lowering average of below-average cholesterol levels on the progression of carotid atherosclerosis: results of the LIPID Atherosclerosis Substudy. LIPID Trial Research Group. *Circulation* 1998;97:1784-1790.
  85. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001;357:577-581.
  86. Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation* 2001;103:1721-1726.
  87. Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* 2002;106:2055-2060.
  88. Beishuizen ED, van de Ree MA, Jukema JW, Tamsma JT, van der Vijver JC, Meinders AE, Putter H, Huisman MV. Two-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. *Diabetes Care* 2004;27:2887-2892.
  89. Sawayama Y, Shimizu C, Maeda N, Tatsukawa M, Kinukawa N, Koyanagi S, Kashiwagi S, Hayashi J. Effects of probucol and pravastatin on common carotid atherosclerosis in patients with asymptomatic hypercholesterolemia. Fukuoka Atherosclerosis Trial (FAST). *J Am Coll Cardiol* 2002;39:610-616.
  90. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Buller HR, Sijbrands EJ, Kastelein JJ. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004;292:331-337.
  91. Zanchetti A, Crepaldi G, Bond MG, Gallus G, Veglia F, Mancia G, Ventura A, Baggio G, Sampieri L, Rubba P, Sperti G, Magni A, PHYLLIS Investigators. Different effects of antihypertensive regimens based on fosinopril or hydrochlorothiazide with or without lipid lowering by pravastatin on progression of asymptomatic carotid atherosclerosis: principal results of PHYLLIS—a randomized double-blind trial. *Stroke* 2004;35:2807-2812.
  92. Anderssen SA, Hjelstuen AK, Hjermann I, Bjerkan K, Holme I. Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives. *Atherosclerosis* 2005;178:387-397.
  93. Asselbergs FW, van Roon AM, Hillege HL, de Jong PE, Gans RO, Smit AJ, van Gilst WH, PREVEND IT Investigators. Effects of fosinopril and pravastatin on carotid intima-media thickness in subjects with increased albuminuria. *Stroke* 2005;36:649-653.
  94. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 1998;128:262-269.
  95. Baldassarre R, Paoletti R, for the IMPROVE study group. The IMPROVE study: carotid intima-media thickness and IMT-progression as predictors of vascular events in high risk European population. (Abstract). XV International Symposium on Drugs Affecting Lipid Metabolism. Venice, 24-25 October 2004.
  96. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* 1986;74:1399-1406.
  97. Gamble G, Beaumont B, Smith H, Zorn J, Sanders G, Merrilees M, MacMahon S, Sharpe N. B-mode ultrasound images of the carotid artery wall: correlation of ultrasound with histological measurements. *Atherosclerosis* 1993;102:163-173.
  98. Gussenhoven EJ, Essed CE, Lancee CT, Mastik F, Fritman P, van Egmond FC, Reiber J, Bosch H, van Urk H, Roelandt J. Arterial wall characteristics determined by intravascular ultrasound imaging: an *in vitro* study. *J Am Coll Cardiol* 1989;14:947-952.
  99. Wendelhag I, Gustavsson T, Suurkula M, Berglund G, Wikstrand J. Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system. *Clin Physiol* 1991;11:565-577.
  100. Boissel JP, Collet JP, Moleur P, Haugh M. Surrogate endpoints: a basis for a rational approach. *Eur J Clin Pharmacol* 1992;43:235-244.
  101. Espeland MA, O'leary DH, Terry JG, Morgan T, Evans G, Mudra H. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. *Curr Control Trials Cardiovasc Med* 2005;6:3.
  102. Wang JG, Staessen JA, Li Y, Van Bortel LM, Nawrot T, Fagard R, Messerli FH, Safar M. Carotid intima-media thickness and antihypertensive treatment: a meta-analysis of randomized controlled trials. *Stroke* 2006;37:1933-1940.
  103. Pasierski T, Sosnowski C, Szulczyk A, Leszczynski L, Rewicki M. The role of ultrasonography of the peripheral arteries in diagnosing coronary artery disease. *Pol Arch Med Wewn* 2004;111:21-25.
  104. Orem C, Durmus I, Kilinc K, Baykan M, Gokce M, Orem A, Topbas M. Plasma fibronectin level and its association with coronary artery disease and carotid intima-media thickness. *Coron Artery Dis* 2003;14:219-224.
  105. Wofford JL, Kahl FR, Howard GR, McKinney WM, Toole JF, Crouse JR III. Relation of extent of extracranial carotid artery atherosclerosis as measured by B-mode ultrasound to the extent of coronary atherosclerosis. *Arterioscler Thromb* 1991;11:1786-1794.