

# The relationship between carotid intima–media thickness and global atherosclerosis

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## Summary

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**Background:** The aim of this study was to investigate the relationship between (i) carotid intima–media thickness (CIMT) at baseline as well as (ii) change in CIMT over 5 years ( $\Delta$ CIMT) and atherosclerotically induced luminal narrowing in non-coronary arterial territories assessed by whole-body magnetic resonance angiography (WBMRA).

**Methods and results:** In subgroups of the Prospective Investigation of Vasculature in Uppsala Seniors (PIVUS) study, US measurements of CIMT in the common carotid arteries were analysed at 70 and 75 years and  $\Delta$ CIMT was calculated ( $n = 272$ ). WBMRA, assessing arterial stenosis in five different territories by which also a total atherosclerotic score (TAS) was calculated, was performed at 70 years ( $n = 306$ ).

**Results:** Carotid intima–media thickness in the carotid artery at baseline was correlated with TAS ( $P = 0.0001$ ) when adjusted to a set of traditional risk factors for atherosclerosis, as well as to stenosis in two of the different investigated territories (aorta and lower leg,  $P = 0.013$  and  $P = 0.004$ ), but there was no significant correlation between  $\Delta$ CIMT and TAS ( $P = 0.41$ ).

**Conclusions:** In the present study, CIMT, but not  $\Delta$ CIMT over 5 years, in the carotid artery was related to overall stenoses in the body, as assessed by WBMRA. These findings support CIMT as a general marker for atherosclerosis.

## Introduction

Intima–media thickness in the carotid arteries (CIMT) measured by ultrasound (US) is a common tool in risk stratification for cardiovascular events due to atherosclerosis (Mancia *et al.*, 2007). The method is proven to predict the amount of plaques in the coronary arteries assessed by coronary angiography and coronary artery calcium scoring (CACS) (Davis *et al.*, 1999; Kablak-Ziembicka *et al.*, 2004). For assessing concomitant atherosclerotic changes in other vascular territories, such as the pelvic and leg arteries in the leg, ankle-brachial index (ABI) has been used to indicate atherosclerosis and CIMT has been found to relate to ABI as well (Bots *et al.*, 1994). An increase in CIMT has been associated with risk of cardiovascular disease (CVD), such as myocardial infarction, stroke and cardiac death (Chambless *et al.*, 1997; O'Leary *et al.*, 1999), although recent studies have implied that the correlation between CIMT and cardiovascular outcome might not be that strong after all (Griffin *et al.*, 2009; Lorenz *et al.*, 2010). Medical treatments with statins and  $\beta$ -blockers are recognized to slow down or bring CIMT progression to a halt (Hedblad

*et al.*, 2001; Crouse *et al.*, 2007) and in some cases even cause a regression of size (Riccioni *et al.*, 2008).

Whole-body magnetic resonance angiography (WBMRA) has been proven a useful research tool for visualizing the amount of stenoses and occlusions in the entire arterial tree, except for the intracranial and coronary arteries, at a single occasion (Hansen *et al.*, 2007). A total atherosclerotic score (TAS) has been introduced and shown to correlate with other scoring systems, such as the Framingham risk score (Hansen *et al.*, 2008), as well as cardiovascular outcome (Lundberg *et al.*, 2013). Using WBMRA, we have identified the degree of atherosclerosis in different vascular territories (carotid, aorta, renal, upper and lower leg) to relate to each other (Hansen *et al.*, 2007), emphasizing the global pattern of atherosclerosis.

A recent publication has revealed that CIMT correlates with cardiovascular outcome, whereas the progression of CIMT over time ( $\Delta$ CIMT) does not (Lorenz *et al.*, 2012). The primary aim of this study was to investigate whether a relationship exists between CIMT and atherosclerotically induced luminal narrowing overall and in different territories of the arterial tree as assessed by WBMRA. A secondary aim was to

also correlate changes in CIMT over 5 years with TAS, as the progression rate of CIMT has been suggested to correlate with outcome (Polak et al., 2011).

## Material and methods

### Subjects

In the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study, approved by the Ethics Committee of the University of Uppsala, all inhabitants in the municipality of Uppsala, Sweden, were invited within 2 months of their 70th birthday to participate. Of 2025 subjects asked, 1016 (all Caucasians, 50.2% females) agreed and gave written informed consent. Within a month of their 75th birthday, 827 subjects from the original cohort accepted an invitation for re-examination; 52 had died; and 137 subjects declined the invitation. The time between the examinations was 5.13 (SD: 0.10) years.

Of the original 1016 subjects, a subpopulation of 306 consecutively chosen subjects underwent a WBMRA examination within 3–22 (mean: 16) months of enrolment; 305 were assessable. This subpopulation has previously been demonstrated to be representative of the total cohort (Hansen et al., 2007).

Of the 305 subjects with assessable WBMRA, 272 were examined by US regarding CIMT at both 70 and 75 years of age. The subjects' medications were also recorded at both time points.

### Evaluation of CIMT

The carotid arteries were assessed by external B-mode US imaging (Acuson XP128 with a 10-MHz linear transducer, Acuson Mountain View, CA, USA) by the same well-experienced technician at both examinations. The common carotid artery (CCA), the bulb and the internal carotid artery (ICA) were visualized, and the occurrence of plaque was recorded. A plaque was defined as local thickening of the intima–media by more than 50% compared to the surrounding CIMT. The CIMT was evaluated in the far wall in the CCA, 1–2 cm proximal to the bulb.

The images were digitalized and imported into an Artery Measurement Software (AMS) previously described (Liang et al., 2000) for dedicated analysis of CIMT and plaque size. A segment with good image quality (up to 10 mm) was chosen for IMT analysis from the CCA. The program automatically identifies the borders of the intima–media of the far wall and the inner diameter of the vessel and calculates CIMT and the diameter from around 100 discrete measurements through the 10-mm-long segment. This automated analysis could be manually corrected if not found appropriate at visual inspection. The given value for carotid artery CIMT is the mean value from both sides.

The mean length of the evaluated intima–media segments was 9.0 (SD 2.1) mm when subjects with a segment

recording <5 mm were excluded, leaving 946 subjects with valid recordings.

The measurements of CIMT were repeated in 30 random subjects giving a coefficient of variation in carotid artery CIMT of 7.2%.

### Magnetic resonance angiography

Imaging was performed on a 1.5-Tesla MRI system (Gyrosan Intera, Philips Medical Systems, Best, the Netherlands) with a 30 mT m<sup>-1</sup> gradient system, using the standard quadrature body coil. The whole body was scanned in the supine position using a 3D RF-spoiled T1-weighted gradient echo sequence before and after the injection of 40 ml Gd-DTPA-BMA (Omniscan™, GE Healthcare, Oslo, Norway) at a rate of 0.6 ml s<sup>-1</sup>. The acquired slice thickness was 4 mm with a resolution of 1.76 × 1.76 mm. Imaging did not include the coronary or intracranial arteries.

The arterial tree was categorized into five territories: (i) the carotids including internal carotid artery and common carotid artery; (ii) the aorta including both the thoracic and abdominal part; (iii) the renal arteries; (iv) the pelvic/upper legs including common iliac artery, external iliac artery, common femoral artery, superficial femoral artery and popliteal artery; and (v) the lower legs including tibio-peroneal trunk, anterior tibial artery, peroneal artery and posterior tibial artery.

In order to obtain a comparable graded number, reflecting the atherosclerosis in each territory, an atherosclerotic score (AS) was calculated for each territory. A normal vessel segment received null points, <50% stenosis was given one point, and 50% reduction or more of the vessel diameter including occlusions was given two points. The points for the vessel segments in a territory were summarized. That sum was then divided with the maximum sum that would be achieved if all included segments had a more than 50% stenosis or occlusion. The quotient was then multiplied by 100. Hence, each territory could obtain a maximum AS of 100.

A global total atherosclerosis score was defined as the sum of the five territories, which meant that the maximum TAS was 500 points. Aneurysms and vessel segments that could not be evaluated were excluded from the calculations.

### Statistics

Difference between the groups regarding sex was analysed using ANOVA. For CIMT, mean values are used as the spread was normally distributed, whereas for TAS median values are used as the spread was skewed. Relationships between TAS and CIMT (or ΔCIMT) were evaluated by Tobit (censored) regression analysis, because one-third of the TAS observations were zero. The first set of models were adjusted for sex only (same age in all subjects), while the second set of models were adjusted for multiple risk factors (antihypertensive medication, systolic blood pressure, statins and LDL cholesterol – at the ages of 70 and 75 years). Differences between the groups

regarding TAS, as well as differences between numbers of plaques, were evaluated using Kruskal–Wallis test. Two-tailed significance values were given with  $P < 0.05$  regarded as significant.

## Results

The descriptive statistics regarding subject characteristics, including medication, are presented in Table 1.

Mean CIMT in the cohort was  $0.90 \pm 0.17$  mm with no significant difference between sexes (males:  $0.92 \pm 0.17$  mm and females:  $0.89 \pm 0.16$  mm). Lumen diameter of the CCA for the cohort was  $6.25 \pm 0.71$  mm, with a significant ( $P < 0.0001$ ) difference between sexes (males:  $6.47 \pm 0.76$  mm and females:  $6.01 \pm 0.58$  mm). The TAS median was 12.5 points (0–50 points between the 25 and 75th percentile).

Carotid intima–media thickness was significantly correlated with TAS (beta = 0.61,  $P = 0.0001$  adjusted for sex and beta = 0.358,  $P = 0.0221$  adjusted for multiple factors). When divided into the five territories, CIMT was significantly correlated with AS in the aorta when adjusted for sex, and in the lower legs when adjusted for both sex and multiple factors, but not for the other territories (see Table 2).

The change in CIMT ( $\Delta$ CIMT) over 5 years ( $0.057 \pm 0.12$  mm) did not correlate significantly with TAS, either in the whole body ( $P = 0.41$ ) or in the separate territories.

Total atherosclerotic score increased with the number of carotid arteries affected by plaque ( $P < 0.0001$ ) when the subjects were divided into groups according to the number of carotid arteries affected by plaque at US (Table 3). AS

increased significantly in the carotid arteries ( $P < 0.0001$ ) and in the upper leg territory ( $P = 0.0033$ ), but not in the aorta ( $P = 0.058$ ), renal arteries ( $P = 0.84$ ) or the lower legs ( $P = 0.11$ ) when AS was related to the number of carotid arteries with plaque at US.

There was no correlation between the change in number of plaque in the carotid arteries at US over 5 years and CIMT or  $\Delta$ CIMT over the same period of time (age: 70–75).

## Discussion

In the present study, CIMT of the carotid arteries was related to a global measure of stenoses in the major parts of the arterial tree, as expressed by TAS, confirming CIMT as an indicator of general atherosclerosis. The relationship remained significant also after adjustment for traditional risk factors.

Previous studies have revealed CIMT to be related to the degree of atherosclerosis in the coronary arteries (Lekakis et al., 2000), but no previous study has compared CIMT with the degree of atherosclerosis in other parts of the arterial tree. In a study comparing CIMT with ABI as an indicator for atherosclerotic vessel wall abnormalities of the arteries of the lower extremity, it was found that an increase in CIMT was related to a decrease in ABI (Bots et al., 1994). However, recently ABI has been established to underestimate the prevalence of significant stenoses and occlusions in the leg (Wikstrom et al., 2008).

In line with the recent publication in the Lancet by Lorenz et al. (2012), the change in CIMT over 5 years did not correlate with either overall atherosclerosis or stenoses in separate territories. This is probably due to the baseline CIMT representing the accumulated vascular disease at the age of 70 years, whereas  $\Delta$ CIMT merely corresponds to the last 5 years' influence of a slowly progressing disease. Statins and  $\beta$ -blockers have been shown to halt the thickening of the intima–media complex (Hedblad et al., 2001; Crouse et al., 2007). In this study, there was an increase in statins use from 13 to 26% and in  $\beta$ -blocker medication from 19 to 28% in 5-year study time; the relative small absolute increase in these medications renders it unlikely that this explains the lack of correlation between  $\Delta$ CIMT and TAS. In addition, it is also well known that ultrasound evaluation of CIMT is associated with user-dependent reproducibility errors yielding in an uncertainty to detect small changes.

The number of carotid arteries with plaque at US was also correlated with TAS, but not with the AS for the separate territories that make up TAS. One reason for the lack of correlation between plaques in the carotid (US-assessed) and WBMRA-assessed arteries elsewhere could probably be an effect of the vascular remodelling phenomenon described by Glagov 1987 (Glagov et al., 1987). A compensatory enlargement of the area inside the internal elastic lamina is found early in plaque formation. For the renal arteries, it has been reported in a autopsy study that only 2% of the plaque formation was at the expense of the luminal area and the remaining

**Table 1** Characteristics of the study population.

Variable	Age 70 (303–306 observations)	Age 75 (269–298 observations)	Units
	Mean $\pm$ SD	Mean $\pm$ SD	
SBP	148.97 $\pm$ 22.27	148.03 $\pm$ 19.28	mmHg
DBP	78.22 $\pm$ 9.98	75.74 $\pm$ 9.94	mmHg
Fasting blood glucose	5.34 $\pm$ 1.58	5.38 $\pm$ 1.47	mmol l <sup>-1</sup>
Anti-HT med	33	50	%
MI	7	8	%
Stroke	4	10	%
Diabetes	11	13	%
$\beta$ -Blockers	19	28	%
Statins	13	26	%
Smoker	8	5	%
Total cholesterol	5.37 $\pm$ 0.96	5.39 $\pm$ 1.09	mmol l <sup>-1</sup>
HDL cholesterol	1.48 $\pm$ 0.37	1.41 $\pm$ 0.40	mmol l <sup>-1</sup>
Serum triglycerides	1.31 $\pm$ 0.63	1.38 $\pm$ 0.63	mmol l <sup>-1</sup>
BMI	26.87 $\pm$ 4.06	26.54 $\pm$ 4.08	kg m <sup>-2</sup>

SBP, systolic blood pressure; DBP, diastolic blood pressure; Anti-HT med, antihypertensive medication; MI, myocardial infarction; HDL, high-density lipoprotein; BMI, body mass index.

**Table 2** Total atherosclerotic score (TAS) for the whole body and AS for separate arterial territories and their correlation with CIMT and  $\Delta$ CIMT over 5 years.

	TAS/AS vs. IMT and $\Delta$ IMT					
	Adjusted for sex			Adjusted for multiple factors		
	Beta	95% CI	P-value	Beta	95% CI	P-value
CIMT						
Whole body (TAS)	0.61	0.317 to 0.903	0.0001	0.358	0.053 to 0.663	0.0221
Carotids (AS)	0.19	-0.03 to 0.42	0.098	0.14	-0.08 to 0.37	0.22
Aorta (AS)	0.36	0.08 to 0.64	0.013	0.28	-0.1 to 0.56	0.058
Renals (AS)	0.37	-0.31 to 1.06	0.288	0.2	-0.49 to 0.89	0.567
Upper legs (AS)	0.21	0.04 to 0.38	0.17	0.18	0.01 to 0.36	0.42
Lower legs (AS)	0.31	0.1 to 0.52	0.004	0.25	0.04 to 0.47	0.019
$\Delta$ CIMT						
Whole body (TAS)	-0.342	-0.765 to 0.081	0.1144	-0.168	-0.566 to 0.231	0.41
Carotids (AS)	-0.14	-0.48 to 0.2	0.423	-0.18	-0.51 to 0.15	0.297
Aorta (AS)	0.01	-0.04 to 0.43	0.949	0.08	-0.33 to 0.49	0.703
Renals (AS)	0.16	-0.79 to 1.11	0.74	0.06	-0.86 to 0.98	0.894
Upper legs (AS)	-0.23	-0.49 to 0.03	0.86	-0.18	-0.44 to 0.08	0.175
Lower legs (AS)	-0.31	-0.63 to 0	0.51	-0.24	-0.55 to 0.07	0.13

CIMT was significantly correlated with TAS when adjusted for sex as well as multiple factors. When divided into the five territories, CIMT was only significantly correlated with AS in the aorta (adjusted for sex) and in the lower legs (adjusted for both sex and multiple factors).  $\Delta$ CIMT over 5 years did not correlate significantly with TAS.

TAS, total atherosclerotic score; AS, atherosclerotic score; CIMT, carotid intima-media thickness;  $\Delta$ CIMT, change in CIMT over 5 years (from age 70–75), multiple factors, antihypertensive medication at age 70 and 75; systolic blood pressure at age 70 and 75; statins at age 70 and 75; and LDL cholesterol at age 70 and 75.

**Table 3** Mean total atherosclerotic score (TAS) in groups with different number of carotid arteries with plaque.

Number of carotid arteries with plaque	Mean TAS	Count
0	111.3	100
1	147.4	98
2	178.2	90

TAS, total atherosclerotic score.

A significant difference in mean TAS ( $P < 0.0001$ , Kruskal–Wallis test) was observed between the groups.

98% was compensated by arterial enlargement (Pasterkamp et al., 1997). The same study revealed a similar luminal enlargement in the coronary and carotid arteries, whereas the arteries in the lower extremities were more prone to luminal stenosis early in plaque formation. This implicates that only a fraction of the plaque mass would be visible on a lumenography such as WBMRA with the major part invisible, and can explain why CIMT in our study also related to the degree of stenosis in the aorta and the lower legs, but not the other substations, when evaluated by WBMRA.

A limitation of the study was the homogeneity of the sample to 70-year-old Caucasians. Caution should therefore be made to draw conclusions to other ethnic and age groups.

The PIVUS study had a moderate participation rate. However, an analysis of non-participants showed the present sample to be fairly representative of the total population regarding most cardiovascular disorders and drug intake (Lind et al.,

2005). The mean time between the US examination and the WBMRA was 16 months, and some changes during that time span in the atherosclerotic status cannot be excluded even though atherosclerosis is a slowly progressing disease (Joakimsen et al., 1999). Luminal narrowing can occur for reasons other than atherosclerosis, for example arteritis, but in this elderly population, it is most likely that the vast majority of luminal narrowing would be caused by atherosclerosis.

Dedicated peripheral MRA is well validated towards golden standard, digital subtraction angiography (DSA) (Burbelko et al., 2012). As discussed in a previous study (Hansen et al., 2007), WBMRA has a lower spatial resolution than dedicated MRA; that is the price for increasing the anatomical coverage. WBMRA of the lower extremities has been compared to DSA with good sensitivity and specificity (Herborn et al., 2004), and other vascular territories examined using WBMRA have also been compared with DSA with good results (Hansen et al., 2006).

In conclusion, CIMT at age 70, but not  $\Delta$ CIMT over 5 years (70–75 years), in the common carotid artery was related to stenoses throughout the arterial tree, as assessed by WBMRA. These findings support CIMT as a general marker for atherosclerosis.

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## Conflict of interest

Lars Johansson is employed by AstraZeneca, R&D Mölndal, Sweden. Lars Lind has been employed by AstraZeneca, R&D

Mölndal, Sweden, and has received financial support from AstraZeneca for the PIVUS study.

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