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Common Carotid Intima-Media Thickness and Risk of Acute Myocardial Infarction

The Role of Lumen Diameter

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Background—It has been argued that lumen diameter of the common carotid artery should be taken into account in analyses on common carotid intima-media thickness (CIMT) and cardiovascular risk. Yet, no published report has dealt with this issue in detail.

Methods—In the Rotterdam study baseline ultrasound images of the carotid arteries were made. During follow-up of 8.2 years, 656 new acute myocardial infarctions (AMI) occurred. Regression analysis was used to study myocardial infarction relation to right (or left) common CIMT with various adjustments for right-, or left-sided lumen diameter. Lumen adjustment was made by (1) a simple adjustment in a regression equation; (2) using the CIMT-to-lumen ratio; (3) using arterial mass, calculated as $(\{\pi\times[(\text{lumen}+\text{near wall CIMT}+\text{far wall CIMT})/2]^2\}-[\pi\times(\text{lumen}/2)^2])$.

Results—AMI disease risk increased per standard deviation increase in common CIMT (0.177 mm): hazard ratio (HR) 1.28 (95% CI, 1.19 to 1.37). When lumen diameter was taken into account the HR was 1.26 (95% CI, 1.18 to 1.35). The HR for the CIMT-to-lumen ratio was 1.18 (95% CI, 1.11 to 1.27) and for arterial mass 1.28 (95% CI, 1.19 to 1.37). Additional analyses indicated that the CIMT-to-lumen ratio at lower CIMT levels appears to reflect arterial remodelling rather than risk of cardiovascular disease.

Conclusion—We conclude that using the CIMT-to-lumen ratio yields the weakest associations. Other approaches for adjustment for common carotid lumen diameter do not affect the magnitude or precision of the association of common CIMT to risk of AMI. When the interest is in risk relations the preference goes to either CIMT or arterial mass measurement. **(*Stroke*. 2005;36:762-767.)**

Key Words: atherosclerosis ■ cardiovascular disease ■ risk assessment ■ risk factors

Common carotid intima-media thickness (CIMT) measurements have been used in observational studies[1,2] and trials[3] to study determinants of atherosclerosis and progression of atherosclerosis, and to evaluate atherosclerosis and progression of atherosclerosis as a risk factor for cardiovascular disease (CVD).[4–7] An increased common CIMT has consistently been related to cardiovascular risk factors.[1,2] Apart from those factors, increasing evidence has become available to indicate that common CIMT is related to changes in local shear stress and tensile stress and may be a direct function of lumen diameter.[8–11] It has been shown that arteries have the capacity to enlarge at early stages of atherosclerosis development to prevent luminal narrowing.[12] Through this remodelling process lumen diameter is preserved during atherosclerosis development. Indeed, carotid ultrasound studies indicated that as part of this arterial remodelling process, the increase in common CIMT parallels that of common carotid lumen diameter in cross-sectional analyses.[9,10] At a common CIMT of 1.0 to 1.1 mm,[11] or at a common CIMT of 1.2 mm or above,[8,13] however, lumen diameter appears to decrease. Thus, an increased common CIMT may reflect a nonatherosclerotic adaptive response to changes in shear stress and tensile stress and some have therefore proposed to account for this nonatherosclerotic thickening by taken lumen diameter into account in studies which evaluate the association between common CIMT and future CVD.[14] In general three approaches have been proposed, being the use of the common CIMT to lumen diameter ratio,[14] the use of arterial mass[15] and simple adjustment for lumen diameter in the analyses. In the published reports on common CIMT and risk of acute myocardial infarction (AMI), the issue of lumen diameter has not been addressed in detail.

We set out to evaluate whether adjustment for lumen diameter in analyses of common CIMT to future AMI affects

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TABLE 1. General Characteristics of the Study Population (n=4721)

	Mean	SD
Women, %	61.5	
Age, y	70.0	8.9
Body mass index, kg/m^2	26.2	3.7
Current smoking, %	23.3	
Total cholesterol, mmol/L	6.64	1.22
HDL cholesterol, mmol/L	1.34	0.36
Total/HDL cholesterol ratio	5.24	1.60
Systolic pressure, mm Hg	139	22
Diastolic pressure, mm Hg	73.3	11.7
History of diabetes, %	10.6	
Glucose, mmol/L	6.9	2.7
Previous myocardial infarction, %	14.3	
Previous stroke, %	3.1	
Right mean far wall common CIMT, mm	0.77	0.21
Right mean near wall common CIMT, mm	0.83	0.21
Right mean common carotid lumen diameter, mm	6.54	0.85
Right mean common CIMT, mm	0.80	0.174
Right sided CIMT to lumen ratio	0.123	0.028
Right sided common carotid arterial mass, mm^2	18.65	5.67
Left mean far wall common CIMT, mm	0.78	0.22
Left mean near wall common CIMT, mm	0.81	0.19
Left mean common carotid lumen diameter, mm	6.35	0.81
Left mean common CIMT, mm	0.80	0.173
Left sided CIMT to lumen ratio	0.126	0.028
Left sided common carotid arterial mass, mm^2	18.07	5.40
New myocardial infarction, %	13.9	
Follow-up time, y	8.17	3.06

the magnitude and precision of estimates for common CIMT. Because the relation of common CIMT to lumen diameter reflects a local process data are presented for the left and right common carotid artery separately.

Methods

Population

The Rotterdam Study is a single center prospective follow-up study on disease and disability in the elderly in 7983 subjects, aged ≥55 years, living in the suburb of Ommoord in Rotterdam, The Netherlands, as detailed elsewhere.[16] Baseline data were collected from March 1990 to July 1993 in a home interview and 2 visits at the research center. The overall participation rate was 78%. The study has been approved by the Medical Ethics Committee of Erasmus University and written informed consent was obtained from all participants.

Common CIMT and Lumen Diameter Measurements

Following the ultrasound protocol, a careful search was performed for all interfaces of the near and far wall of the distal common carotid artery with a 7.5 MHz linear array transducer (ATL Ultra Mark IV). When an optimal longitudinal image was obtained, it was frozen on the R-wave of the electrocardiogram and stored on videotape. This procedure was repeated 3 times for both sides. The actual measurements of CIMT were performed off-line. From the videotape, the frozen images were digitized and displayed on the screen of a personal computer using additional dedicated software.[17] In short, with a cursor the interfaces of the distal common carotid artery were marked over a length of 10 mm. The beginning of the dilatation of the distal common carotid artery served as a reference point for the start of the measurement. The distance of the leading edge of the first bright line of the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the far wall common CIMT. For the near wall, the distance between the trailing edge of the first bright line to the trailing edge of the second bright line at the near wall provides the best estimate of the near wall common CIMT. The distance of the leading edge at the near wall (intima-lumen interface) and the lumen-intima interface at the far wall reflects the lumen diameter. The average of the CIMT and lumen diameter of each of the three frozen images was calculated. For each individual the common CIMT was determined as the average of near and far wall measurements of the right (or left) carotid artery and the lumen diameter was the average of the three right (or left) sided measurements. The readers of the ultrasound images from videotape were unaware of the case status of the subject. CIMT reproducibility has been published elsewhere.[18]

A common CIMT to lumen ratio was calculated by dividing the common CIMT by the lumen diameter. The common carotid arterial mass was calculated following the approach of Lemne et al: $(\{\pi\times[(\text{lumen}+\text{near wall CIMT}+\text{far wall CIMT})/2]^2\}-[\pi\times(\text{lumen}/2)^2])$.[15]

TABLE 2. Relation of Carotid Artery Parameters With Risk Myocardial Infarction

	Hazard Ratio	95% CI	Area Under ROC Curve	95% CI
Right-sided				
CIMT per SD	1.28	1.19–1.37	0.67	0.65–0.69
CIMT per SD adjusted lumen	1.26	1.18–1.35	0.67	0.65–0.69
CIMT/lumen ratio per SD	1.18	1.11–1.27	0.67	0.64–0.68
Carotid mass per SD	1.28	1.19–1.37	0.67	0.65–0.69
Left-sided				
CIMT per SD	1.24	1.16–1.33	0.66	0.64–0.68
CIMT per SD adjusted lumen	1.23	1.14–1.32	0.66	0.64–0.68
CIMT/lumen ratio per SD	1.16	1.08–1.24	0.66	0.64–0.68
Carotid mass per SD	1.25	1.16–1.34	0.66	0.64–0.68

Results obtained from a Cox proportional hazards model, adjusted for age and gender. The Area under ROC curve was estimated using a logistic regression model.

SD indicates standard deviation

Cerebrovascular and Cardiovascular Risk Indicators

A history of AMI and stroke at baseline was assessed by the questions "Did you ever suffer from a AMI for which you were hospitalized?" and "Did you ever suffer from a stroke, diagnosed by a physician?". A subject's smoking status was classified as current, former and never smoker. At the research center height and weight were measured and body mass index (kg/m^2) was calculated. Sitting blood pressure was measured at the right upper arm with a random-zero sphygmomanometer. The average of 2 measurements obtained at 1 occasion, separated by a count of the pulse rate, was used in the present analysis. Hypertension was defined as a systolic blood pressure of $\geq$160 mm Hg, or a diastolic blood pressure of $\geq$95 mm Hg or, current use of antihypertensive drugs for the indication hypertension. Diabetes mellitus was considered present when subjects currently used oral blood glucose lowering drugs or insulin. Total cholesterol was determined using an automated enzymatic procedure. High-density lipoprotein (HDL) cholesterol was measured similarly, after precipitation of the non-HDL fraction with phosphotungstate-magnesium.

Follow-up procedures

Follow-up was from baseline to January 1, 2000.[19] Of all participants 2.6% were lost to follow-up. For these subjects, the follow-up time was computed until the last date of contact. Fatal and nonfatal cardiovascular events were reported by general practitioners (GP) in the research district, with whom 85% of the participants of the Rotterdam Study were enlisted. Research assistants verified all information by checking medical records at the GPs offices. Medical records of the participants under the care of GP outside the study area were checked annually for possible events. Letters and, in case of hospitalization, discharge reports from medical specialists were obtained. Vital status was regularly checked with municipal health authorities in Rotterdam. After notification, cause and circumstances of death were established by questionnaire from the GPs. Two research physicians independently coded all reported events according to the *International Classification of Diseases, 10th Edition* (ICD-10). Disagreements were discussed to reach consensus. Finally, a medical expert in CVD, whose judgment was considered final, reviewed all events. Incident AMI was defined as the occurrence of a fatal or nonfatal MI (ICD-10 code I21) after the baseline examination.

Ultrasonography of the carotid arteries was performed in 5965 of the 7983 subjects. Subjects who had their baseline Rotterdam Study examination at the end of 1992 and in 1993, ultrasonography could not always be performed because of the restricted availability of sonographers and among participants residing in home for the elderly a higher refusal rate was found. The present analysis is based on 4721 subjects of whom information on age, gender, right common CIMT and event status was known. The left side analyses was based on 4700 subjects. The mean duration of follow-up was 8.2 years.

Data Analysis

A Cox proportional hazard model was used. Analyses were performed using common CIMT with and without adjustment for lumen diameter, using the CIMT-to-lumen ratio and using arterial mass. Variables were examined both as continuous characteristic (per standard deviation increase) and in quartiles (3 dummys) based on the distribution among the controls. Analyses were initially adjusted for age and sex, and additionally for cardiovascular risk factors. Hazards ratios (HR) are presented with the 95% CI as measures of strength of the association.

Because the coefficients estimated by a logistic regression models were identical to those estimated by the Cox proportional hazards model, the area under the receiver operating curve (AUC) was estimated using the age and gender models from logistic regression analyses. The AUC is a measure of the ability for the CIMT measurement to correctly predict subjects that will or will not suffer from future cardiovascular disease.

To further elaborate on the CIMT-to-lumen ratio findings, we examined the relation of the parameters in strata of CIMT. The hypothesis was that when the CIMT-to-lumen ratio is considered an appropriate remodelling mechanism at CIMT values of $<$1.1. mm (or 1.2 mm), but a reflection inadequate remodelling at CIMT $>$1.1 mm, one would expect no relation between CIMT-to-lumen ratio at lower levels of CIMT, but a positive relation at values $>$1.1 mm with risk of AMI. Strata were based on arbitrary cut points of $<$0.70 mm (1379 subjects, 29 cases), 0.70 mm to 1.1. mm (3104/464) and $>=$1.1 mm (238/64).

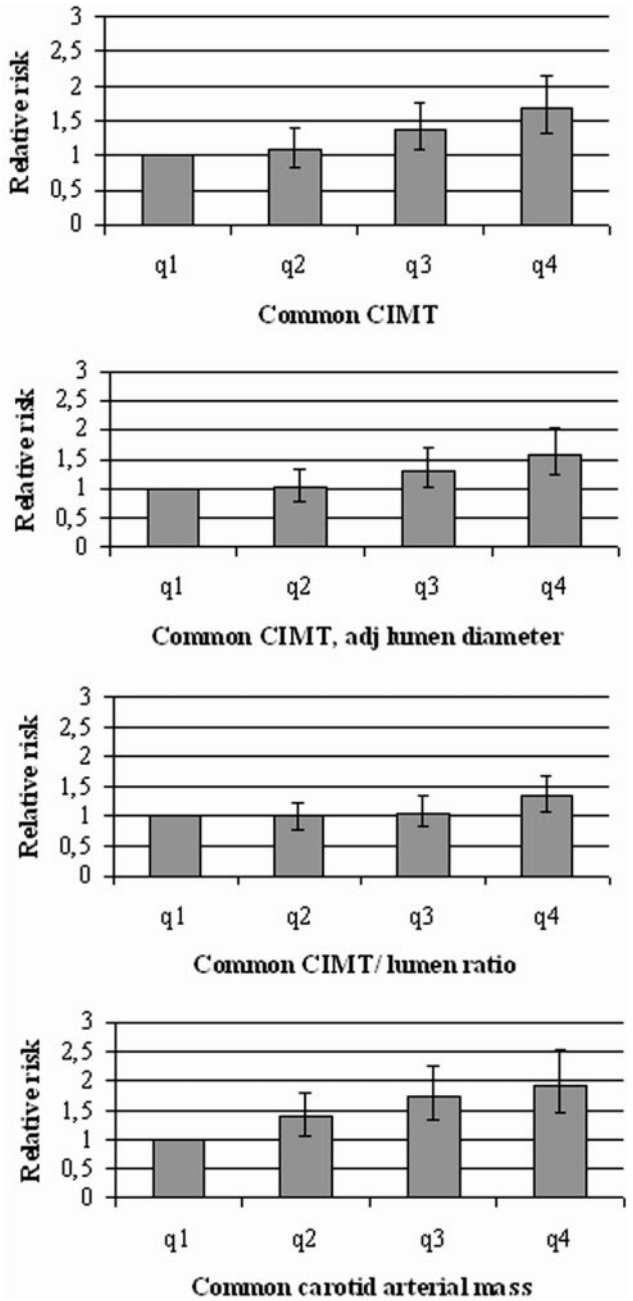

Figure 1. Risk of AMI by quartiles of the distribution of common CIMT, with and without adjustment for lumen diameter; of the CIMT/lumen ratio; of the arterial mass. Results are adjusted for age and sex. Cut points used were 0.681 to 0.777 to 0.885 mm for common CIMT; 0.106 to 0.119 to 0.136 for CIMT/lumen ratio; 14.63 to 17.65 to 21.52 for the arterial mass.

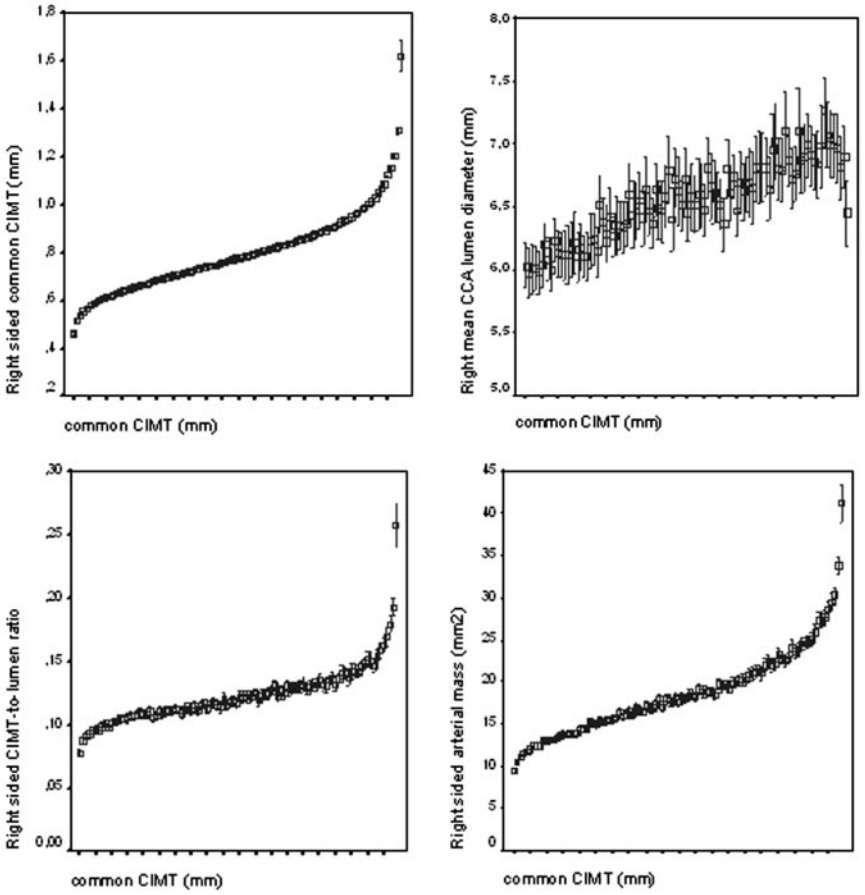

Figure 2. Relations of common CIMT (top left), lumen diameter (top right), CIMT-to-lumen ratio (bottom left) and common carotid arterial mass (bottom right) with increasing common CIMT (in equal groups of ≈50 subjects). Y-axis are means with 2 times the standard error.

Results

General characteristics of the study population are described in table 1. Table 2 indicates that the direction of relationships with future events do not differ across the chosen models. There was an increase in risk of AMI with an increase in common CIMT, with and without adjusted for lumen diameter, and with an increase in arterial mass. The CIMT-to-lumen ration showed the weakest relation (Figure 1). Additional adjustment for cardiovascular risk factors, notably hypertension, HDL cholesterol, diabetes mellitus, current smoking, body mass index, previous cardiovascular disease attenuated the associations. The fully adjusted HR per 1 SD increase for right-sided common CIMT was 1.17 (95% CI, 1.08 to 1.27), with adjustment for lumen diameter 1.16 (95% CI, 1.07 to 1.26), for CIMT to lumen ratio 1.09 (95% CI, 1.01 to 1.18) and for carotid mass 1.19 (95% CI, 1.09 to 1.29). Although the magnitude of the associations differed between measures, the 95% CIs overlapped. Moreover, the areas under the receiver operating curve for the age and gender adjusted models were identical for all models. Identical findings were found for the left side (Table 2).

Right-sided lumen diameter was related to risk of AMI, independent of common CIMT (age- and sex-adjusted HR per standard deviation increase of 1.15 [95% CI, 1.06 to 1.24]). With further adjustment for cardiovascular risk factors the HR was 1.11 [95% CI 1.02 to 1.21].

The relation of common CIMT, lumen diameter, the CIMT-to-lumen ratio and arterial mass with increasing common CIMT appear to show that arterial mass gradually increased with increasing common CIMT (Figure 2). The same holds for lumen diameter, yet with a decline at high levels. In contrast, the CIMT-to-lumen ratio increased much less steep across a wide range of common CIMT values and only rapidly at high levels of common CIMT. The stratified analyses indicated that relations between CIMT or arterial mass with AMI risk were positive and statistically significant in all strata (Table 3). However, for the CIMT to lumen ratio, a positive finding was only found in the highest CIMT strata (Table 3).

Discussion

The present study provides evidence that adjustment for common carotid lumen diameter in analyses evaluating common CIMT as a predictor of AMI does not severely affect the magnitude and precision of the results when using a simple adjustment or calculation of the carotid mass. Using the CIMT-to-lumen ratio gave the weakest relation, although 95% CIs of the various parameters overlapped. The magnitude of the associations was attenuated when all cardiovascular risk factors were taken into account.

Some aspects of the present study should be addressed first. In the present analyses current medication was not taken into account as such. Lipid lowering and blood pressure lowering drugs have shown to reduce CIMT progression, without affecting lumen diameter.[1,3] Yet, this has no major impact on our findings, because current lipid and blood

TABLE 3. Relation of Carotid Artery Parameters With Risk of Myocardial Infarction by Common CIMT

	Common CIMT, mm		
	<0.70	0.70–1.09	≥1.10
CIMT per SD	1.25 (1.01–1.55)	1.16 (1.06–1.27)	1.39 (1.14–1.69)
CIMT/lumen ratio per SD	0.90 (0.74–1.08)	1.02 (0.93–1.12)	1.45 (1.17–1.80)
Carotid mass per SD	1.33 (1.12–1.58)	1.20 (1.09–1.32)	1.23 (1.00–1.53)

Results obtained from a Cox proportional hazards model, adjusted for age and gender and given as hazard ratios per strata specific standard deviations with 95% confidence limits.

pressure levels were controlled for taking most of the potential confounding effect away. Also, the proportion statin use at baseline in 1990 was very low. Furthermore, adjustment for antihypertensive and lipid lowering medication does not appear to considerably affect the magnitude of relations under study, when also blood pressure and lipids have been controlled for.[20] Our results pertain to common CIMT only and it has been shown that the internal carotid artery may be more restricted in her capacity to enlarge with the development of atherosclerosis compared with what is found for the common carotid segment.[21]

An increased common CIMT may reflect a nonatherosclerotic adaptive response,[11,22] and therefore to account for this nonatherosclerotic thickening lumen diameter should be taken into account in order to come up with an atherosclerotic marker. Also, studies showed that risk factor relations were more pronounced with carotid mass as compared with common CIMT.[23] Our analyses suggest that adjustment for lumen diameter, except using the CIMT-to-lumen ratio, does not severely affect the magnitude and precision of the estimates of the association of CIMT to CVD. Our findings comply with the GENIC study in which common CIMT was an risk factor for ischemic stroke, independent of lumen diameter.[24] The CIMT-to-lumen ratio at lower common CIMT levels, however, appears to reflect a remodelling process rather than an atherosclerotic marker, and was related to AMI risk. Therefore, when the interest is in risk relation the preference goes to either CIMT or arterial mass measurement.

Our finding does not necessarily indicate that lumen diameter measurements should not be performed in CIMT studies. From the shear stress and tensile stress proposed mechanisms it may be deducted that changes in shear stress lead to lumen diameter changes, which then are followed by nonatherosclerotic adaptive changes in common CIMT in order to keep tensile stress as constant as can be.[25] It therefore may be of importance in studies that evaluate change over time in common CIMT to try to quantify changes in lumen diameter during the study.[3,25] Furthermore, several studies have indicated that the balance between lumen diameter and common CIMT may reflect remodelling processes which may have merit to be studied separately from CIMT.[22,26–28] For example, remodelling of the carotid artery was disturbed in subjects with glucose intolerance compared with healthy subjects,[27] or differed between treated hypertensives and normotensives or untreated hypertensives.[20] Also, certain patterns of CIMT, and CIMT-to-lumen ratios combined with carotid mass estimates that may reflect various stages of vascular hypertrophy, which predict future cardiovascular events, independently from CIMT.[28]

A relatively novel finding in the present study is the graded positive association of lumen diameter with AMI. This may appear counterintuitive: a larger lumen, a greater risk? In the Rotterdam Study, measurements were done in end-diastole. Therefore, a larger lumen in diastole might reflect a lesser intrinsic vessel elasticity and thus a stiffer vessel, which might explain the positive association.

In conclusion, the CIMT-to-lumen ratio yields the weakest associations with future risk of AMI. Other approaches for adjustment for common carotid lumen diameter do not affect the magnitude of the association of common CIMT to risk of AMI. When the interest is in risk relations the preference goes to either CIMT or arterial mass measurement.

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