Left, Right, Near or Far Wall Common Carotid Intima-Media Thickness Measurements: Associations with Cardiovascular Disease and Lower Extremity Arterial Atherosclerosis

Michiel L. Bots,1,3 Paulus T. V. M. de Jong,2 Albert Hofman,1 and Diederick E. Grobbee1,3,*

1Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, The Netherlands; 2Department of Ophthalmology, University Hospital Dijkzigt, Rotterdam, The Netherlands; and 3Julius Center for Patient Oriented Research, Utrecht University, Utrecht, The Netherlands

ABSTRACT. We evaluated the differences in strength of the associations of prevalent cardiovascular disease and lower extremity arterial atherosclerosis to common carotid intima-media thickness, assessed by near wall measurements only, by far wall measurements only, and by the average of near and far wall measurements. The study was based on data from 1500 participants of the Rotterdam Study, a single-center-population-based prospective follow-up study among 7983 subjects, aged 55 years or over. Comparison of the strength of the associations of near wall intima-media thickness and of combined near and far wall intima-media thickness to cardiovascular disease and lower extremity arterial atherosclerosis revealed significantly stronger associations compared to observations observed for far wall intima-media thickness, in particular for stroke and lower extremity arterial disease. We conclude that near wall common carotid intima-media thickness measurement provides at least as good an indicator of atherosclerosis elsewhere and of cardiovascular risk as the far wall intima-media thickness measurement. J CLIN EPIDEMIOL 50;7:801–807, 1997. © 1997 Elsevier Science Inc.

KEY WORDS. Elderly, noninvasive, ultrasonography, wall thickness, methodology

INTRODUCTION

Several studies have used high resolution B-mode ultrasonography of the carotid arteries to study noninvasively the process of atherosclerosis [1–6]. The presence and extent of atherosclerosis is estimated through measurement of intima-media thickness. An ultrasound image of the common carotid artery shows a typical double-line pattern, which is similar in appearance for the near and far wall. On an ultrasound image the anatomical location of a biological structure is always defined by a leading edge, and the distance between two leading edges represents the thickness of a structure [7]. It has been shown that measurement of the far wall intima-media thickness is reflected by the distance between two leading edges (Fig. 1), whereas the near wall intima-media thickness measurement is reflected by the distance between two trailing edges [8]. In addition, studies in which ultrasound measurements of intima-media thickness were compared with histology showed that ultrasonic far wall intima-media thickness truly and accurately represents intima-media thickness as measured by histology [9–11]. In contrast, these studies have indicated that near wall intima-media thickness measurements may considerably underestimate the true intima-media thickness. Furthermore, the near wall measurement may be affected by the axial resolution and the gain settings of the ultrasound equipment. Based on these findings it has been argued that near wall measurements should not be used and that emphasis should be on far wall measurements [12].

The question is, however, whether it matters very much should near wall common carotid intima-media thickness measurements not accurately represent the true near wall intima-media thickness [13]. If the near wall intima-media thickness measurement systematically underestimates the true intima-media thickness the entire near wall intima-media thickness distribution will be shifted to a lower level. However, associations with cardiovascular disease, for example, should still remain valid. If, on the other hand, the underestimation of near wall intima-media thickness occurs at random, is independent of the true intima-media thickness and not associated with disease status, weakening of the magnitude of the associations under study may result.

In the present study, we set out to analyze the differences
in strength of the associations of prevalent cardiovascular disease, and presence of atherosclerosis of the arteries of the lower extremities to common carotid intima-media thickness, assessed by near wall measurements only, by far wall measurements only, and by the average of near and far wall measurements combined.

METHODS

Population

The Rotterdam Study is a single-center prospective follow-up study of a cohort of 7983 subjects, aged 55 years or over, living in the suburb of Ommoord in Rotterdam, The Netherlands [14]. The study has been approved by the Medical Ethics Committee of Erasmus University and written informed consent is obtained from all participants. The objective of the Rotterdam Study is to clarify determinants of chronic disabling diseases in an aging population. Incidence and risk factors of cardiovascular diseases, locomotor diseases, neurogeriatric diseases, and ophthalmologic diseases are studied. Baseline measurements were performed from March 1990 to June 1993. The overall participation rate of those invited for the study was 78%.

Carotid Arteries

Ultrasonography of both carotid arteries was performed with a 7.5-MHz linear array transducer using a Duplex scanner (ATL UltraMark IV). On a longitudinal two-dimensional ultrasound image of the carotid artery, the near and far wall of the carotid artery are displayed as two bright white lines separated by a hypo-echogenic space (Fig. 1) [15]. The distance between the leading edge of the first bright line on the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness of the far wall. 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 intima-media thickness [8].

When an optimal longitudinal image was obtained following the Rotterdam Study scanning protocol [4], this image was frozen on the R-wave of the electrocardiogram and stored on video tape. This procedure was repeated three times for each left and right carotid artery. The actual measurements of intima-media thickness were performed offline. From the video tape, the frozen images were digitized and displayed on the screen of a personal computer using additional dedicated software. This procedure has been described in detail previously [8]. 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. This method permits the determination of mean value (average over 10 mm) for intima-media thickness. The average of the mean intima-media thickness of each of the three frozen images was calculated. For each individual the following common carotid intima-media thickness parameters were determined: left side near wall, left side far wall, left side average (combined near and far wall); right side near wall, right side far wall, right side average (combined near and far wall); combined near wall (average of left and right near wall), combined
far wall (average left and right side), and total (average of left and right side near wall and far wall).

Arteries of the Lower Extremities
The presence of atherosclerosis in the arteries of the lower extremities was evaluated by determination of the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm (ankle–arm index) as described elsewhere [16]. Systolic blood pressure was measured at the right upper arm in sitting position using a random-zero sphygmomanometer. The average of two measurements obtained at one occasion, separated by a count of the pulse rate, was used. The systolic blood pressure of the posterior tibial artery at both left and right side was measured using an 8-MHz continuous wave Doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK) and a random-zero sphygmomanometer. For each leg, a single measurement was taken with the subject in supine position. The lowest ankle–arm index in either leg was used in the analysis [17]. In agreement with the approach taken in other studies, [17–19] lower extremity arterial disease was considered present when the ankle–arm index was lower than 0.90 in at least one side.

Cardiovascular Disease and Risk Factors
In the Rotterdam Study, information on current health status and medical history was obtained using a computerized questionnaire. A history of myocardial infarction and stroke was obtained through direct questioning: “Did you ever suffer from a myocardial infarction diagnosed by a physician?” and “Did you ever suffer from a stroke, diagnosed by a physician,” respectively.

With respect to smoking, subjects were categorized in groups of current smokers, former smokers, and those who never smoked. Additionally, cigarette smoking was expressed in pack-years, calculated as the average daily number of cigarettes smoked divided by 20, times the reported number of years of smoking.

A non-fasting venous blood sample was taken, applying minimal stasis, using a 21-gauge Butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium). Serum 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.

Data Analysis
The present analysis was based on findings in a random sample of 1500 participants of the Rotterdam Study. No ultrasound scan was made in 34 subjects. Information on cardiovascular disease and lower extremity arterial disease was not available in 37 and 23 subjects, respectively. In 130 subjects data on intima-media thickness were not available: for the near wall left side (n = 46), near wall right side (n = 48), near wall both sides (n = 13), far wall left side (n = 16), far wall right side (n = 20), or far wall both sides (n = 3). In 16 subjects there was missing data for all measurements. Apart from age (72.0 years) and gender (70% women), there were no differences in cardiovascular risk factors between these 130 subjects and those with information on intima-media thickness. Complete data of all sides was available for 1276 subjects. In the present study no attempt was made to estimate intima-media thickness of a missing side using data from other sides for which a value was available.

The associations between different estimates of common carotid intima-media thickness, (i.e., intima-media thickness assessed by near wall measurements only, by far wall measurements only, and by the average of near and far wall measurements combined), and outcome (i.e., prevalent cardiovascular disease and lower extremity arterial atherosclerosis) were evaluated using multiple logistic regression. The odds ratios are expressed per increase of one standard deviation in intima-media thickness. Associations are presented with a 95% confidence interval (CI).

Relations between cardiovascular risk factors (i.e., systolic blood pressure, HDL cholesterol, and smoking [pack-years]) and several parameters of common carotid intima-media thickness were evaluated using linear regression analyses. Results are presented as means and standard errors (SE).

When the estimate of the near wall common carotid intima-media thickness or of the combined near and far wall intima-media thickness was equal or beyond the 95% CI of the association observed for far wall common carotid intima-media thickness, the findings for the near wall or combined near and far wall were considered to be significantly different from those observed for the far wall.

Additional analyses were performed for men and women separately and in two age categories (<75, ≥75 years). The magnitude of the associations was generally stronger for men than for women, and for young subjects compared to elderly subjects. However, the difference in magnitude between near wall, far wall, and combined near and far wall in each group was not significantly different from that observed for the overall findings. Therefore, overall findings are presented only, adjusted for age and gender.

RESULTS
Table 1 presents the selected general characteristics of the study participants. No significant differences in intima-media thickness were seen between left and right side and between near wall intima-media thickness and far wall intima-media thickness.

The relations between intima-media thickness and prevalent cardiovascular disease and lower extremity arterial disease are given in Table 2. Intima-media thickness was positively and significantly related to prevalent cardiovascular
TABLE 1. General characteristics of the participants in the present analysis of the Rotterdam Study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
<th>Women</th>
<th>Age (years)</th>
<th>Cardiovascular disease</th>
<th>Lower extremity arterial atherosclerosis</th>
<th>Common carotid intima-media thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1276</td>
<td>60.2%</td>
<td>69.4 (8.3)</td>
<td>Myocardial infarction</td>
<td>Ankle−arm index</td>
<td>Left side</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stroke</td>
<td>Lower extremity arterial disease</td>
<td>Near wall 0.79 (0.18)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Far wall 0.79 (0.21)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Right side</td>
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<td></td>
<td></td>
<td></td>
<td>Near wall 0.81 (0.21)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Far wall 0.78 (0.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Both sides combined</td>
<td>Near wall 0.80 (0.17)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Far wall 0.78 (0.18)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total 0.79 (0.15)</td>
<td></td>
</tr>
</tbody>
</table>

Values are percentages and means with standard deviation in parentheses.

Table 1 shows the general characteristics of the participants in the present analysis of the Rotterdam Study. The number of participants is 1276, with 60.2% being women and an average age of 69.4 years (SD 8.3). The study also looks at cardiovascular disease and lower extremity arterial atherosclerosis. No major differences in strength of the associations were seen between measurements at the left or right carotid artery (Table 2). With respect to differences in strength between associations for near wall only, far wall only and combined near and far wall, the associations were significantly stronger for near wall intima-media thickness and combined near and far wall compared to far wall intima-media thickness for stroke and lower extremity arterial disease. No differences in strength of the association were found for myocardial infarction. In general, the analyses based on the average of measurements at both sides provided the strongest associations with cardiovascular disease and lower extremity arterial atherosclerosis (Table 2).

Table 3 details the associations between cardiovascular risk factors and intima-media thickness. The magnitude of the associations did not significantly differ. However, the precision of the estimates of the associations under study increased when using intima-media thickness measurement that was based on combined near and far wall measurements. This was similar for systolic blood pressure, HDL cholesterol, and pack-years of smoking.

DISCUSSION

In the present study, associations between common carotid intima-media thickness and prevalent cardiovascular disease and lower extremity arterial atherosclerosis. No major differences in strength of the associations were seen between measurements at the left or right carotid artery (Table 2). With respect to differences in strength between associations for near wall only, far wall only and combined near and far wall, the associations were significantly stronger for near wall intima-media thickness and combined near and far wall compared to far wall intima-media thickness for stroke and lower extremity arterial disease. No differences in strength of the association were found for myocardial infarction. In general, the analyses based on the average of measurements at both sides provided the strongest associations with cardiovascular disease and lower extremity arterial atherosclerosis (Table 2).

Table 3 details the associations between cardiovascular risk factors and intima-media thickness. The magnitude of the associations did not significantly differ. However, the precision of the estimates of the associations under study increased when using intima-media thickness measurement that was based on combined near and far wall measurements. This was similar for systolic blood pressure, HDL cholesterol, and pack-years of smoking.

DISCUSSION

In the present study, associations between common carotid intima-media thickness and prevalent cardiovascular dis...
and presence of lower extremity arterial atherosclerosis were of similar magnitude when based on values obtained from either the left or the right carotid artery. The associations were significantly stronger when measurements were based on the near wall and when based on combined near and far wall compared to the far wall carotid artery, particularly for stroke and lower extremity arterial disease. The use of intima-media thickness defined as the average intima-media thickness obtained from both left and right carotid arteries further increased strength of the estimates of associations under study. Similar findings were observed for the magnitude of the associations between cardiovascular risk factors and common carotid intima-media thickness parameters. The precision of the associations increased when using an intima-media thickness measure that was based on the average of several measures.

Studies have indicated that ultrasonographic near wall intima-media thickness measurements relate to interfaces of the ultrasound image that bear no close relation with the true anatomical structures [7,8]. Furthermore, measurements performed at the near wall of the carotid artery have been reported to considerably underestimate the true intima-media thickness as compared to histology [9–11]. Therefore, some have argued that the near wall measurements should not be used [12]. Although the measurement of near wall common carotid intima-media thickness may systematically underestimate the true intima-media thickness, however, it appears to reflect the presence of atherosclerosis elsewhere in the arterial system as strongly as the far wall intima-media thickness measurement does. Furthermore, the association with prevalent cardiovascular disease is at least of the same magnitude as that found for far wall intima-media thickness measurements. Thus, our findings suggest that the near wall intima-media thickness of the common carotid artery provides at least as good an estimate of cardiovascular risk and of presence of atherosclerosis in arteries of the lower extremities as far wall measurements.

Recently, Furberg and coworkers used baseline data collected from three trials to show that there were no differences between intima-media thickness measurements of left carotid artery compared to those obtained from the right carotid artery [20]. Furthermore, progression rate of near wall common carotid intima-media thickness was similar to that for far wall common carotid intima-media thickness. Inclusion of near wall measurements in the estimates of progression reduced the variability of progression considerably, leading to increased precision. In the present study common carotid intima-media thickness was studied as a determinant (exposure) of an outcome. In general, measurement imprecision of the exposure independent of the outcome (random) will tend to reduce the magnitude of an observed association between a determinant and outcome [21,22].

The present study demonstrates that combined near wall and far wall intima-media thickness of the common carotid artery provides the strongest associations with prevalent cardiovascular disease and with presence of atherosclerosis elsewhere in the arterial system. Thus, the use of the combination of intima-media thickness measurements at several locations probably leads to improved precision of the assessment of the atherosclerosis status; that is, it reduces the extent of misclassification of a subject.

In the analyses with cardiovascular risk factors, intima-media thickness was used as an outcome instead of exposure. When measurement error of the outcome is not associated with the risk factor, it is assumed that misclassification occurs equally among cases and controls (nondifferential misclassification) [23]. This imprecision will not lead to attenuation of the linear regression coefficient. Only the precision of the estimate will be reduced [21]. Our findings in Table 3 show that the use of combined near and far wall measurements lead to estimates of similar magnitude but of increased precision (i.e., smaller standard errors). This supports the notion that the atherosclerosis status of subjects is better classified by the use of intima-media thickness information from several sources, such as near and far wall.

In practical terms, our findings indicate that in studies in which intima-media thickness is compared between subjects with and without the exposure of interest, the sample size needed to perform such a study is considerably reduced when based on the combined near and far wall intima-media thickness (Table 4). The beneficial effect of also measuring near wall intima-media thickness may then outweigh some disadvantages such as a slight increase of time spent on the ultrasonography and on the analysis.

The issue whether intima-media thickness measurements of the common carotid in itself reflect local atherosclerosis or not, is still subject of debate. It is conceivable that increased common carotid intima-media thickness does not represent atherosclerosis, but merely reflects an adaptive response of the vessel wall to changes in shear stress, tensile stress, and blood flow [24]. Atherosclerosis is viewed as a disorder which is restricted to the intima layer of the arterial vessel wall and ultrasound imaging cannot discriminate between the intima and the media layers of vessel wall [25]. However, it may be questioned whether it matters very much should common carotid intima-media thickness not represent local atherosclerosis [13]. Increased common carotid intima-media thickness may be of use as a “marker,” an indicator of atherosclerosis elsewhere [26,27], in the arte-

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**Table 4. Number of subjects needed to detect a 0.04-mm difference in common carotid intima-media thickness between exposed and unexposed subjects**

<table>
<thead>
<tr>
<th>Number of subjects</th>
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<tbody>
<tr>
<td>Both sides (left and right)</td>
</tr>
<tr>
<td>Near wall</td>
</tr>
<tr>
<td>Far wall</td>
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</table>

*Power calculation for comparisons of means between exposed and unexposed subjects with an α = 0.05, two sided; β = 0.90; standard deviation as in Table 1.*
rial system and of increased cardiovascular risk [28]. Our findings indicate that this may apply at least equally well to near wall and far wall intima-media thickness measurements.

Some limitations of the present results should be acknowledged. First, the Rotterdam Study is a single-center study in which external factors, such as gain settings that may affect the near wall measurements, may be easier to keep constant over the study period than in multicenter studies. Unfortunately, similar analyses from multicenter studies have to our knowledge not yet been published and are clearly of interest. Second, it should be noted that in our experience near wall intima-media thickness measurements of at least one or both sides could not be obtained from the images in 8.9% of the subjects. For far wall measurements, data on either left, right, or both sides were missing in 3.1% of the study population. This indicates some more difficulty with visualization of the near wall interfaces. In analyses indicators of presence or absence of near wall measurements may be added to the regression model, or a near wall estimate may be used based on the measurement of the side that is available, or a model may be used to impute missing values.

In conclusion, the near wall common carotid intima-media thickness measurement provides at least as good an indicator of atherosclerosis elsewhere and of cardiovascular risk as the far wall intima-media thickness measurement. The average of both near and far wall measurements results in the strongest associations.

The contribution to the data collection of the general practitioners of the suburb of Ommoord, the field workers, ultrasound technicians, computer assistants, laboratory technicians is gratefully acknowledged.

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References


