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## Predictive Value of Noninvasive Measures of Atherosclerosis for Incident Myocardial Infarction The Rotterdam Study

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**Background**—Several noninvasive methods are available to investigate the severity of extracoronary atherosclerotic disease. No population-based study has yet examined whether differences exist between these measures with regard to their predictive value for myocardial infarction (MI) or whether a given measure of atherosclerosis has predictive value independently of the other measures.

**Methods and Results**—At the baseline (1990–1993) examination of the Rotterdam Study, a population-based cohort study among subjects age  $\geq 55$  years, carotid plaques and intima-media thickness (IMT) were measured by ultrasound, abdominal aortic atherosclerosis by x-ray, and lower-extremity atherosclerosis by computation of the ankle-arm index. In the present study, 6389 subjects were included; 258 cases of incident MI occurred before January 1, 2000. All 4 measures of atherosclerosis were good predictors of MI independently of traditional cardiovascular risk factors. Hazard ratios were equally high for carotid plaques (1.83 [1.27 to 2.62], severe versus no atherosclerosis), carotid IMT (1.95 [1.19 to 3.19]), and aortic atherosclerosis (1.94 [1.30 to 2.90]) and slightly lower for lower-extremity atherosclerosis (1.59 [1.05 to 2.39]), although differences were small. The hazard ratio for MI for subjects with severe atherosclerosis according to a composite atherosclerosis score was 2.77 (1.70 to 4.52) compared with subjects with no atherosclerosis. The predictive value of MI for a given measure of atherosclerosis was independent of the other atherosclerosis measures.

**Conclusions**—Noninvasive measures of extracoronary atherosclerosis are strong predictors of MI. The relatively crude measures directly assessing plaques in the carotid artery and abdominal aorta predict MI equally well as the more precisely measured carotid IMT. (*Circulation*. 2004;109:1089-1094.)

**Key Words:** atherosclerosis ■ coronary disease ■ epidemiology

Various noninvasive methods are available to detect the presence and severity of extracoronary atherosclerotic disease. Carotid atherosclerosis as shown on ultrasound, aortic atherosclerosis on abdominal x-ray, and lower-extremity atherosclerosis reflected by the ankle-arm index (AAI) are validated measures of atherosclerosis that are routinely used in population-based studies because they are relatively cheap, noninvasive, and easy to assess. They are strongly associated with the presence and amount of coronary calcification<sup>1</sup> and with traditional cardiovascular risk factors.<sup>2–4</sup>

Several studies have shown that these measures of atherosclerosis are good predictors of coronary heart disease (CHD).<sup>5–12</sup> However, differences between measures with regard to their predictive value for CHD may exist, because of either factors related to the site at which atherosclerosis was measured or factors associated with the measurement

method. No population-based study has yet compared the predictive value of several different measures of atherosclerosis or investigated whether the information provided by a given measure of atherosclerosis is independent of that provided by other atherosclerosis measures.

Within the Rotterdam Study, a population-based cohort study among men and women age 55 years and over, we prospectively investigated several noninvasive measures of extracoronary atherosclerosis and combinations of these measures in relation to the occurrence of myocardial infarction (MI).

### Methods

#### Population

The Rotterdam Study is a prospective population-based cohort study of 7983 men and women age  $\geq 55$  years. Its overall aim is to investigate the incidence and determinants of chronic disabling

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diseases. From 1990 to 1993, all inhabitants of a suburb of the city of Rotterdam age  $\geq 55$  years were invited to participate in the study. The overall response rate was 78%. A trained investigator visited all participants at home and collected information using a computerized questionnaire. The information obtained included current health status, medical history, drug use, and smoking behavior. In addition, during 2 visits to the research center, established cardiovascular risk factors were measured. The Medical Ethics Committee of the Erasmus University Medical Center approved the Rotterdam Study, and written informed consent was obtained from all participants. A more detailed description of the Rotterdam Study and the collection of data has been given elsewhere.<sup>13,14</sup>

### Study Population

Of the 7983 participants of the Rotterdam Study, 7393 had never experienced an MI or revascularization procedure before the baseline examination. For 6525 participants, the extent of atherosclerosis was assessed at at least 1 site of the vascular tree, and follow-up data on incident MI were available for 6442 of these participants. Subjects with missing data on more than 2 of the established cardiovascular risk factors were excluded ( $n=53$ ), resulting in a study population of 6389 participants.

### Measures of Atherosclerosis

Each of the measures of atherosclerosis included in the present study was categorized into no, mild, moderate, and severe atherosclerosis. To be able to compare the associations of the different measures of atherosclerosis with incident MI, we aimed at categorizing the severity of atherosclerosis in such a way that especially the severe category included a comparable percentage of the population for all of the 4 measures.

### Carotid Atherosclerosis

By use of ultrasound, the common carotid artery, carotid bifurcation, and internal carotid artery were visualized over a length as large as possible and examined both left and right for the presence of plaques, which were defined as focal widenings relative to adjacent segments, with protrusion into the lumen, composed of calcified or noncalcified components. Those assessing the presence of plaques were blinded to all clinical information. Within the Rotterdam Study, a reproducibility study for plaques in the carotid artery on either side resulted in a  $\kappa$  of 0.67, indicating moderate agreement. A weighted plaque score ranging from 0 to 6 was computed by adding the number of sites at which a plaque was detected, divided by the total number of sites for which an ultrasonographic image was available and multiplied by 6 (the maximum number of sites).<sup>15</sup> Subjects for whom data on the presence of plaques were not available for at least 2 of the 6 sites that were examined were excluded. Subjects with a carotid plaque score of 0, 1, 2, and  $\geq 3$  points were considered to have no, mild, moderate, and severe carotid atherosclerosis, respectively.

The maximum common carotid intima-media thickness (IMT) was determined as the average of the maximum IMT of near- and far-wall measurements over a length of 1 cm, and the average of left and right maximum common carotid IMT was computed. In a reproducibility study, intraclass correlation coefficients between ultrasonographers, readers, and visits to the study center were 0.63, 0.88, and 0.74, respectively.<sup>16</sup> To indicate no, mild, moderate, and severe thickening of the carotid wall, we divided the IMT into quartiles based on the population distribution, using cutoff points of 0.88, 0.99, and 1.12 mm, respectively. Because of limited availability of ultrasonographers at the end of 1992 and in 1993, ultrasound data on carotid atherosclerosis are missing for part of the study population.

### Aortic Atherosclerosis

Aortic atherosclerosis was diagnosed by radiographic detection of calcified deposits in the abdominal aorta on a lateral abdominal film. In an autopsy study, radiographic assessment was shown to be highly specific, and in most cases visible calcification represented advanced intimal atherosclerosis.<sup>17</sup> A comparison study at our department among 56 subjects involving CT showed that abdominal calcifica-

tion could be detected radiographically in 32 subjects; in all but 1 of these subjects, calcification was located in the aorta on the corresponding CT images.<sup>3</sup> The extent of abdominal aortic atherosclerosis was scored according to the length of the involved area (with scores of 0 to 5 corresponding to 0,  $\leq 1$ , 1 to 2.5, 2.5 to 4.9, 5.0 to 9.9, and  $\geq 10.0$  cm, respectively). Subjects with an aortic atherosclerosis score of 0, 1, 2, and  $\geq 3$  points were considered to have no, mild, moderate, and severe aortic atherosclerosis, respectively.

### Lower-Extremity Atherosclerosis

We obtained the AAI as described before by computing the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm, a method that has been shown to provide reliable measurements of lower-extremity atherosclerosis.<sup>14,18</sup> The AAI is inversely related to the severity of lower-extremity atherosclerosis. For the analyses, we used the lowest value of 2 legs. Because arterial rigidity prevents arterial compression and will therefore lead to spurious high values of the AAI, an AAI  $>1.50$  was considered invalid. To indicate no, mild, moderate, and severe lower-extremity atherosclerosis, we divided the AAI into quartiles based on the population distribution, using cutoff points of 1.21, 1.10, and 0.97, respectively.

### Atherosclerosis Score

To compute a composite atherosclerosis score, we added 0, 1, 2, and 3 points to the score for a subject being in the no, mild, moderate, and severe category, respectively, for each of the 4 separate measures, thus creating a score ranging from 0 to 12 points. For subjects with complete data on 3 of the 4 measures of atherosclerosis, we computed a weighted atherosclerosis score by multiplying the score obtained for 3 measures by 4/3. The mean composite atherosclerosis score was 6.0 for men and 5.6 for women. To indicate no, mild, moderate, and severe atherosclerosis, we subsequently divided the composite score into quartiles based on the population distribution, using cutoff points of 4, 6, and 9, respectively.

Data on carotid plaques, carotid IMT, aortic atherosclerosis, lower-extremity atherosclerosis, and the composite atherosclerosis score were available for 5070, 5116, 5234, 5838, and 5197 subjects, respectively.

### Follow-Up Procedures

Follow-up started at the baseline examination and for the present study lasted until January 1, 2000. Of all participants in the present study, 168 (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 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 general practitioners' offices. All medical records of the participants under the care of general practitioners outside the study area were checked annually for possible events. Letters and, in case of hospitalization, discharge reports from medical specialists were obtained. With respect to the vital status of participants, information was also obtained regularly from the municipal health authorities in Rotterdam. After notification, cause and circumstances of death were established by questionnaire from the general practitioners. Two research physicians independently coded all reported events according to the International Classification of Diseases, 10th edition (ICD-10).<sup>19</sup> Codes on which the research physicians disagreed were discussed to reach consensus. Finally, a medical expert in cardiovascular disease, whose judgment was considered final, reviewed all events. Incident MI was defined as the occurrence of a fatal or nonfatal MI (ICD-10 code I21) after the baseline examination.

### Statistical Analyses

For subjects with missing data on clinical characteristics measured on a continuous scale, we imputed the population mean ( $n=308$  with missing data on at most 2 characteristics). For subjects with missing data on smoking habits ( $n=128$ ) or diabetes mellitus ( $n=30$ ), we made use of a missing variable indicator. Proportional hazards

**TABLE 1. Baseline Characteristics of the Study Population**

Characteristic	All Subjects (n=6389)
Age, y	69.3±9.2
Gender, % women	61.9
Current smokers, %	21.5
Body mass index, kg/m <sup>2</sup>	26.3±3.7
Total cholesterol, mmol/L	6.6±1.2
HDL cholesterol, mmol/L	1.4±0.4
Systolic blood pressure, mm Hg	139.6±22.3
Diastolic blood pressure, mm Hg	73.9±11.6
Diabetes mellitus, %	10.1
Cholesterol-lowering medication, %	1.6
Blood pressure-lowering medication, %	29.4
Aspirin, %	8.7
Carotid plaques, %*	57.8
Intima-media thickness, mm	1.02±0.21
Aortic atherosclerosis, %†	65.3
Ankle-arm index‡	1.05±0.23
Composite atherosclerosis score§	5.8±3.3

Data are mean±SD for continuous variables and percentages for dichotomous variables.

\*As indicated by a carotid plaque score >0.

†As indicated by an aortic atherosclerosis score >0.

‡Lowest of left and right leg.

§With a range of 0 to 12 points.

regression analysis was used to evaluate the predictive value for MI of categories of the individual measures of atherosclerosis and of the composite atherosclerosis score, taking only age and gender into account (model 1), or also smoking habits, body mass index, total and HDL cholesterol, systolic and diastolic blood pressure, presence

of diabetes mellitus, and use of aspirin, blood pressure-lowering, and cholesterol-lowering medication (model 2). Subsequently, to investigate whether a given measure of atherosclerosis predicts MI independently of the other measures, we included each possible combination of 2 measures of atherosclerosis in the fully adjusted model. Finally, for each combination of 2 measures of atherosclerosis, we divided the population into 9 groups based on the 9 possible combinations of no, mild/moderate (as 1 category), and severe atherosclerosis as categorized per measure. To compute hazard ratios for MI, we used the group with subjects who were for both measures in the category of no atherosclerosis as the referent group. All analyses were performed using SPSS 9.0 for Windows.

## Results

Baseline characteristics of the total study population are shown in Table 1. The distribution of no, mild, moderate, and severe carotid plaques was 42.2%, 15.3%, 18.4%, and 24.0%, respectively. For aortic atherosclerosis, these numbers were 34.7%, 9.6%, 26.5%, and 29.2%.

During follow-up, incident MI occurred in 258 subjects (4.0%; 143 men and 115 women). Tables 2 and 3 show that all measures of atherosclerosis were strongly predictive of incident MI, even after adjustment for a wide range of cardiovascular risk factors and medication use (model 2). When analyzed as continuous variables, the multivariate hazard ratios for MI associated with 1 SD increase in carotid IMT and 1 SD decrease in the AAI were 1.28 (1.14 to 1.44) and 1.20 (1.05 to 1.39), respectively, in a fully adjusted model (model 2). Of the 4 individual measures, the hazard ratios were equally high for carotid plaques (1.83 [1.27 to 2.62] for the severe category, model 2), carotid IMT (1.95 [1.19 to 3.19]), and aortic atherosclerosis (1.94 [1.30 to 2.90]). Hazard ratios were slightly lower for lower-extremity atherosclerosis (1.59 [1.05 to 2.39]), although differences were very small. The multivariately adjusted hazard ratios for peripheral arte-

**TABLE 2. Hazard Ratios for Incident Myocardial Infarction Associated With Carotid Measures of Atherosclerosis**

	Severity of Atherosclerosis			
	No	Mild	Moderate	Severe
Carotid plaques				
Model 1	1.0	1.33 (0.84–2.09)	1.49 (0.99–2.24)	2.45 (1.72–3.47)
Model 2	1.0	1.19 (0.75–1.88)	1.28 (0.85–1.94)	1.83 (1.27–2.62)
+ Carotid intima-media thickness	1.0	1.19 (0.75–1.89)	1.24 (0.81–1.88)	1.74 (1.19–2.56)
+ Aortic atherosclerosis	1.0	1.18 (0.74–1.88)	1.06 (0.68–1.65)	1.49 (1.01–2.21)
+ Lower-extremity atherosclerosis	1.0	1.20 (0.76–1.92)	1.22 (0.80–1.88)	1.82 (1.25–2.65)
Carotid intima-media thickness				
Model 1	1.0	1.68 (1.03–2.75)	2.05 (1.26–3.32)	2.91 (1.80–4.70)
Model 2	1.0	1.56 (0.95–2.54)	1.63 (1.00–2.65)	1.95 (1.19–3.19)
+ Carotid plaques	1.0	1.56 (0.94–2.57)	1.49 (0.90–2.46)	1.70 (1.01–2.85)
+ Aortic atherosclerosis	1.0	1.53 (0.92–2.57)	1.52 (0.91–2.55)	1.79 (1.06–3.01)
+ Lower-extremity atherosclerosis	1.0	1.64 (1.00–2.70)	1.59 (0.96–2.64)	1.94 (1.17–3.23)

The no, mild, moderate, and severe categories included 2140, 778, 935, and 1217 subjects for carotid plaques and 1277, 1279, 1287, and 1273 subjects for carotid intima-media thickness. All hazard rate ratios were adjusted for age and gender (model 1), and subsequently (model 2) for smoking habits, body mass index, total and HDL cholesterol, systolic and diastolic blood pressure, presence of diabetes mellitus, and use of aspirin, blood pressure-lowering, and cholesterol-lowering medication. Model 2 was additionally adjusted for severity of atherosclerosis as indicated by the various atherosclerosis measures, added to the model individually.

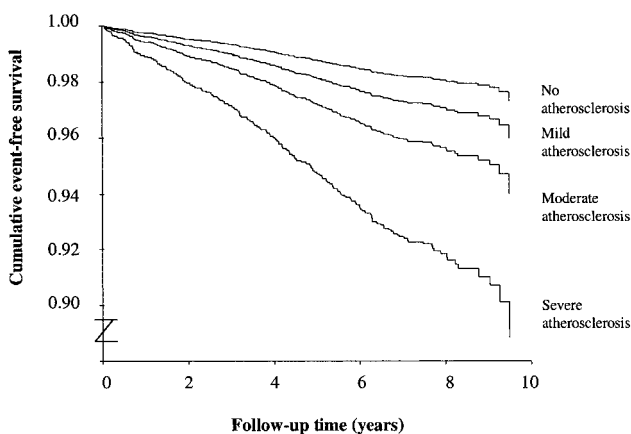
**TABLE 3. Hazard Ratios for Incident Myocardial Infarction Associated With Aortic and Lower-Extremity Atherosclerosis and With the Composite Atherosclerosis Score**

	Severity of Atherosclerosis			
	No	Mild	Moderate	Severe
<b>Aortic atherosclerosis</b>				
Model 1	1.0	1.16 (0.62–2.17)	2.13 (1.43–3.18)	2.56 (1.73–3.78)
Model 2	1.0	1.06 (0.56–1.98)	1.81 (1.21–2.70)	1.94 (1.30–2.90)
+ Carotid plaques	1.0	0.92 (0.45–1.87)	1.84 (1.20–2.83)	1.64 (1.05–2.57)
+ Carotid intima-media thickness	1.0	1.02 (0.52–2.03)	1.84 (1.20–2.83)	1.80 (1.16–2.78)
+ Lower-extremity atherosclerosis	1.0	0.85 (0.42–1.72)	1.83 (1.21–2.76)	1.93 (1.27–2.91)
<b>Lower-extremity atherosclerosis</b>				
Model 1	1.0	1.25 (0.82–1.89)	1.89 (1.28–2.78)	2.19 (1.48–3.23)
Model 2	1.0	1.12 (0.74–1.70)	1.55 (1.04–2.31)	1.59 (1.05–2.39)
+ Carotid plaques	1.0	1.20 (0.75–1.91)	1.61 (1.03–2.53)	1.54 (0.97–2.45)
+ Carotid intima-media thickness	1.0	1.20 (0.76–1.90)	1.62 (1.04–2.53)	1.59 (1.01–2.50)
+ Aortic atherosclerosis	1.0	1.02 (0.65–1.59)	1.39 (0.90–2.14)	1.51 (0.97–2.34)
<b>Composite atherosclerosis score</b>				
Model 1	1.0	1.52 (0.92–2.51)	2.28 (1.43–3.62)	4.35 (2.75–6.86)
Model 2	1.0	1.28 (0.77–2.12)	1.71 (1.06–2.76)	2.77 (1.70–4.52)

See legend to Table 2. The no, mild, moderate, and severe categories included 1818, 502, 1388, and 1526 subjects for aortic atherosclerosis; 1415, 1471, 1448, and 1504 subjects for lower-extremity atherosclerosis; and 1499, 1151, 1349, and 1198 subjects for the composite atherosclerosis score.

rial disease as defined by an AAI  $<0.9$  or  $<0.8$  were 1.11 (0.81 to 1.54) and 1.12 (0.76 to 1.64), respectively.

Hazard ratios were highest for the composite atherosclerosis score (Table 3). In subgroup analyses stratified by gender, the multivariately adjusted risk estimates for the mild, moderate, and severe categories of the composite atherosclerosis score compared with no atherosclerosis were 1.30 (0.71 to 2.38), 1.14 (0.62 to 2.10), and 2.24 (1.22 to 4.11), respectively, for men and 1.15 (0.46 to 2.89), 2.98 (1.35 to 6.59), and 3.80 (1.64 to 8.79), respectively, for women. For each of the 4 separate measures of atherosclerosis, hazard ratios also tended to be higher for women than for men, especially in the severe categories (data not shown). The survival curves for different categories of the composite atherosclerosis score are shown in Figure 1.



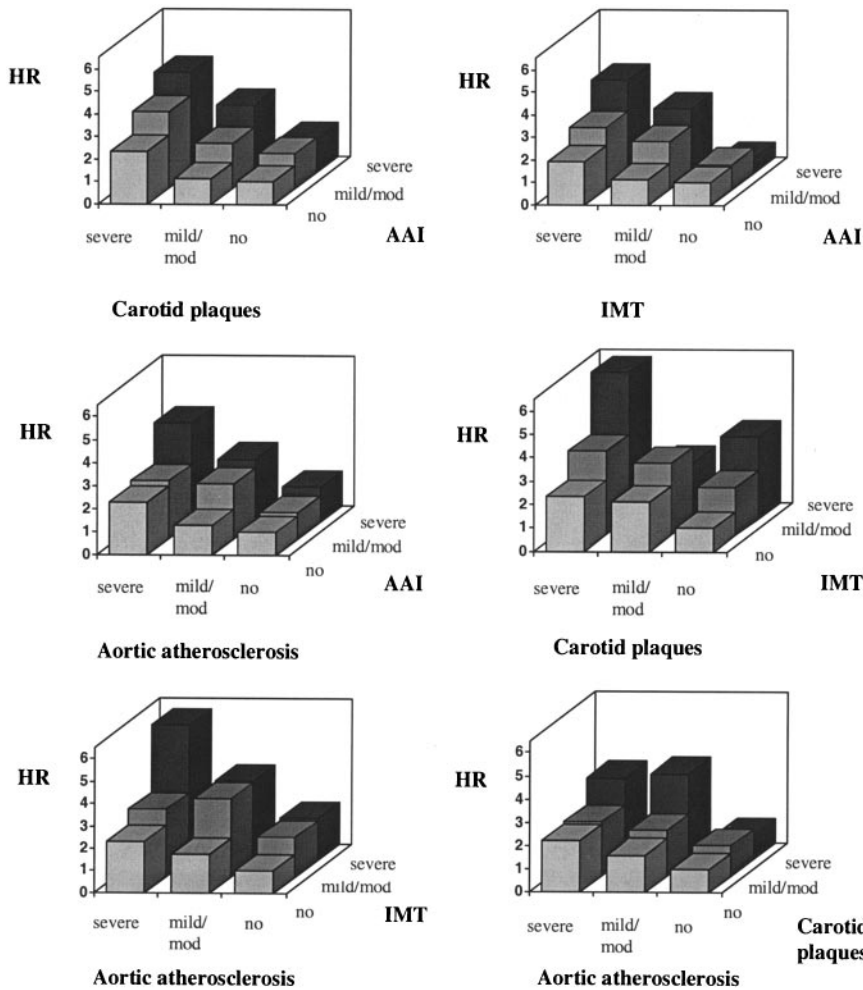
**Figure 1.** Survival curves for no, mild, moderate, and severe atherosclerosis as indicated by the composite atherosclerosis score. Analyses were adjusted for age and gender.

When we simultaneously included 2 measures of atherosclerosis in the model, the hazard ratios for these measures were not meaningfully different from those obtained from fully adjusted models in which only 1 atherosclerosis measure was included, indicating independence of effect (Tables 2 and 3). Figure 2 clearly shows that for combinations of measures of atherosclerosis, categorization according to an extra measure of atherosclerosis adds prognostic information with regard to the occurrence of MI to categorization according to a single atherosclerosis measure.

## Discussion

The results of the present study show that measures of atherosclerosis assessing the severity of carotid plaques, carotid IMT, aortic atherosclerosis, or lower-extremity atherosclerosis are all strong predictors of incident MI. Although differences were small, risk estimates for lower-extremity atherosclerosis were slightly weaker than those for measures of carotid or aortic atherosclerosis.

Carotid atherosclerosis as shown on ultrasound, aortic atherosclerosis on abdominal x-ray, and lower-extremity atherosclerosis reflected by the AAI are all strongly associated with the presence and amount of coronary calcification,<sup>1</sup> traditional cardiovascular risk factors,<sup>2–4</sup> and the incidence of CHD.<sup>5–12,20</sup> Compared with carotid IMT and the AAI, the presence and severity of carotid plaques or aortic atherosclerosis are less frequently studied in relation to cardiovascular disease. Importantly, the present study shows that the hazard ratios for MI for these measures, which are based on the relatively crude but direct assessment of the presence of atherosclerotic plaques, were as high as those for carotid IMT, a measure that requires very precise measurements.



**Figure 2.** Hazard ratios (HR) for MI for combinations of measures of atherosclerosis. mod indicates moderate. AAI reflects lower-extremity atherosclerosis. Analyses were adjusted for age and gender.

The predictive value for MI of each of the individual measures of atherosclerosis was independent of a wide variety of traditional cardiovascular risk factors and of medication use. For purposes of MI risk stratification, the measurement of extracoronary atherosclerotic disease as an indication of the presence of unknown or unmeasured cardiovascular risk factors, such as genetic predisposition or inflammation,<sup>21,22</sup> may therefore be a meaningful addition to the measurement of traditional cardiovascular risk factors. Although the measurement of carotid IMT is unlikely to be of use as a screening tool in the general population,<sup>23</sup> measurement of the AAI has been suggested to be useful in persons  $\geq 50$  years old or persons at high risk.<sup>24</sup> However, the hazard ratios for MI associated with lower-extremity atherosclerosis were slightly lower in the present study than those associated with the other measures of atherosclerosis, which may be explained by the fact that the AAI is an indirect measure of lower-extremity atherosclerosis, which may also be influenced by hemodynamic factors and vascular stiffness. Future research, which should also include a measure of coronary calcium, is needed to establish the clinical value of the various measures of atherosclerosis either in the general population or in populations at high risk of MI.

The Rotterdam Study comprises a large and well-defined study population. A great strength of the present study is that

severity of atherosclerosis was measured at multiple sites in the arterial tree, making it possible to compare multiple measures of atherosclerosis with regard to their predictive value for MI within one study population. Nevertheless, several methodological aspects of this study need to be considered. Not all participants had complete data on all 4 of the measures of atherosclerosis presented in the study. Although we cannot exclude the possibility that health-related issues have also played a role, missing data are predominantly because of logistic reasons and are unlikely to have affected our results. Furthermore, it would be interesting to see how the hazard ratios for MI associated with measures of extracoronary atherosclerosis as reported in the present study relate to those associated with coronary atherosclerosis. To date, no prospective population-based data have yet been published on coronary atherosclerosis and incident MI.

In conclusion, noninvasive measures of extracoronary atherosclerosis are strong predictors of MI. The relatively crude measures directly assessing plaques in the carotid artery and abdominal aorta predict MI equally well as the more precisely measured carotid IMT.

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