Subclinical Atherosclerosis and Risk of Atrial Fibrillation

The Rotterdam Study

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Background: Myocardial infarction is an important risk factor for atrial fibrillation, but the role of subclinical atherosclerosis is unknown. This longitudinal study evaluates whether atherosclerosis affects the risk of atrial fibrillation in persons without overt coronary disease.

Methods: This investigation was part of the Rotterdam Study, a population-based cohort study among persons 55 years or older. Participants with atrial fibrillation at baseline, with a history of myocardial infarction, or with angina pectoris and those who had undergone cardiac operative procedures were excluded, leaving 4407 subjects for the analyses. Baseline intima-media thickness of the common carotid artery and the presence of carotid plaques were used as indices of generalized atherosclerosis. During a median follow-up of 7.5 years, 269 cases of incident atrial fibrillation were identified. Relative risks were calculated with 95% confidence intervals, adjusted for age and sex, using the Cox proportional hazards model. Additional adjustments were made for body mass index, hypertension, systolic blood pressure, serum cholesterol level, smoking, diabetes mellitus, left ventricular hypertrophy on the electrocardiogram, and the use of cardiac medication.

Results: The risk of atrial fibrillation was associated with carotid intima-media thickness (relative risk, 1.90; 95% confidence interval, 1.20-3.00, highest vs lowest quartile) and severity of carotid plaques (relative risk, 1.49; 95% confidence interval, 1.06-2.10, severe vs absence). Risk estimates were stronger in women than in men.

Conclusions: Atherosclerosis in participants without manifest atherosclerotic disease is an independent risk factor for atrial fibrillation. These results suggest that aggressive treatment of asymptomatic atherosclerosis may help to prevent atrial fibrillation.

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Myocardial infarction is a strong predictor of atrial fibrillation, especially in men. Myocardial damage, often in association with heart failure, contributes to the onset of atrial fibrillation in subjects with myocardial infarction. It is not known, however, whether the presence of coronary atherosclerosis without manifest myocardial infarction also causes atrial fibrillation. At a subclinical level, atherosclerotic vascular disease may cause some damage to myocardial tissue by gradually reducing the blood supply to the atrial tissues because of ischemia/infarction, causing premature apoptosis of myocytes, fibrous tissue replacement, and subsequent facilitation of reentry processes. The role of atherosclerosis in the development of atrial fibrillation is supported by results of studies in which atrial tissues were histologically investigated.

Results of studies that examined the relation between atrial fibrillation and cardiac manifestations of atherosclerosis, such as angina pectoris in the absence of a myocardial infarction and angiographically demonstrated narrowing of coronary arteries without overt damage to the heart, are conflicting. Studies dependent on coronary angiographic documentation of coronary artery disease are also limited by the selected nature of the population studied and, by the very nature of this measurement, cannot be feasibly or ethically applied to large-scale population surveys. A noninvasive index of atherosclerosis that uses ultrasonography, intima-media thickness, and plaques has been shown to be a good indicator of systemic atherosclerotic vascular disease, with a relation to the risk of stroke and myocardial infarction. To our knowledge, only 1 population-based study, the Cardiovascular Health Study, reported on the as-
association between atherosclerosis and risk of atrial fibrillation. In that study, no significant associations were found between 2 measures of generalized atherosclerosis (carotid intima-media thickness and the ankle-arm index) and risk of atrial fibrillation.6,7

In the present population-based analysis from the Rotterdam Study, we investigated the associations between intima-media thickness and plaques of the extracranial carotid arteries (as measured by ultrasonography) and risk of atrial fibrillation in asymptomatic persons during a median follow-up of 7.5 years.

METHODS

STUDY POPULATION

The Rotterdam Study is a population-based prospective cohort study aimed at assessing the occurrence and progression of and risk factors for chronic diseases in the elderly. Neurogeriatric, cardiovascular, locomotor, and ophthalmologic diseases are the main areas of interest.12 All residents of Ommoord, a suburb of Rotterdam, the Netherlands, who were 55 years or older were invited to participate. Of the 10 275 eligible individuals, 7983 (77.7%) responded. From 1990 to 1993, participants were interviewed at their homes and 7151 were examined at the research center to obtain baseline measurements, including a 10-second, 12-lead resting electrocardiogram (ECG). Those who did not visit the research center were in general dependent or lived in nursing homes. Participants were reexamined during 2 follow-up rounds. The first round of follow-up examinations was performed between July 1, 1993, and December 31, 1994. The second round of follow-up examinations started April 1, 1997, and ended December 31, 1999.

The medical ethics committee of the Erasmus University in Rotterdam approved the study, and all participants gave informed consent.

MEASUREMENTS OF ATRIAL FIBRILLATION AND ATHEROSCLEROSIS

Atrial fibrillation at baseline and during follow-up was ascertained using 3 methods, as described earlier.13 In short, at baseline and during the follow-up examinations, 10-second, 12-lead ECGs were recorded with an electrocardiograph (ACTA; Esaote, Florence, Italy), stored digitally, and analyzed by the modular ECG analysis system (MEANS).14-16 Additional information was obtained from the medical files of participating general practitioners, which included the results of their own work and those of physicians practicing in hospitals and outpatient clinics, and from a national registration of all hospital discharge diagnoses. All study participants were followed up from the date of entrance in the Rotterdam Study (1990-1993) to the date of the onset of atrial fibrillation, death, or loss to follow-up or to January 1, 2000, whichever came first. Follow-up by January 2000 was complete for 99.1% of the study population.

The common carotid artery, the bifurcation, and the internal carotid artery on both sides were visualized by means of ultrasonography using a 7.5-MHz transducer (ATL Ultramark IV; Advanced Technology Laboratories, Bethel, Wash). Common carotid intima-media thickness was measured for a 1-cm length that was proximal to the bulbus. The anterior and posterior walls in the left and right common carotid arteries were measured and averaged. The averages of the left and right side were added and divided by 2. If measurements at both sides were available. When the result of one side was absent owing to poor visualization, the result of the other side was used. A plaque was defined as a local broadening of the intima-media relative to the adjacent segments, with protrusion into the lumen composed of only calcified deposits or a combination of calcified and noncalcified material. The left and right common carotid arteries, left and right carotid bifurcation, and left and right internal carotid arteries were examined for the presence of plaques. A weighted plaque score was obtained by counting the sites where a plaque was visible and dividing this number by the total number of sites for which an ultrasonographic image was available. The result was multiplied by 6, the maximum number of sites. This score ranges from 0 to 6. Subjects were excluded from the analyses if visualization of more than 4 of the 6 sites had not been possible. All examinations were performed with the observer blinded to the clinical details of the participants.

MEASUREMENTS OF COVARIATES

Information on current health status, medical history, and smoking behavior was obtained using a computerized questionnaire. Participants were classified as current smokers, former smokers, or never smokers. The body mass index was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured twice at the right upper arm with a random-zero mercury sphygmomanometer in the sitting position. Systolic and diastolic blood pressures were calculated as the average of the 2 consecutive measurements. Hypertension was defined as a systolic blood pressure of 160 mm Hg or higher or a diastolic blood pressure of 100 mm Hg or higher or the use of blood-pressure-lowering drugs prescribed for hypertension. A history of myocardial infarction was defined as a self-reported myocardial infarction with hospital admission or the presence of a myocardial infarction on the ECG. A positive self-report of myocardial infarction was confirmed by reviewing the medical records of general practitioners and specialists. Angina pectoris was measured by the Rose questionnaire.17 Left ventricular hypertrophy was diagnosed using the MEANS program with an algorithm that takes into account QRS voltages, with an age-dependent correction and repolarization. Nonfasting blood samples were drawn by means of venipuncture. Serum total cholesterol levels were measured with an automated enzymatic method. Diabetes mellitus was defined as the use of antidiabetic medication or a random or postload serum glucose level of 220 mg/dL (≥11.1 mmol/L) or higher. Cases of incident myocardial infarction were ascertained as described previously.18

VITAL STATUS

Information on vital status was obtained on a regular basis from the Central Register of Population of the municipality of Rotterdam, from collaborating general practitioners, and by obtaining information during follow-up rounds. For those participants for whom information remained missing, the Central Registry of Genealogy of the Netherlands was consulted in The Hague. This national institute receives population registry records of inhabitants of the Netherlands who have died.

POPULATION FOR ANALYSIS

For the present study, an ECG was not available for analysis of atrial fibrillation in 343 participants who had visited the research center at baseline, mainly owing to logistic reasons. We additionally excluded 1666 participants belonging to at least 1 of the following categories: (1) participants with a history of myocardial infarction (typical, silent, or non-Q-wave) at baseline
RESULTS

The baseline characteristics of the study population are summarized in Table 1. During a median follow-up of 7.5 years, 269 new cases (6.1%) of atrial fibrillation were identified. Of those, 44 cases (16.4%) were identified by the ECG obtained at the research center only (n = 38) or were identified by ECG earlier than by the 2 other ascertainment methods (n = 6).

After adjustments for age and sex, statistically significant associations were found between carotid intima-media thickness and carotid plaques and the risk of atrial fibrillation. The associations were stronger for the higher quartiles of intima-media thickness and increased severity of carotid plaques. After further adjustments for clinical features, the associations were somewhat attenuated but remained statistically significant (Table 2).

### Table 1. Baseline Characteristics of the Study Population by Sex: the Rotterdam Study, 1990-1999

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n = 1669 [37.9%])</th>
<th>Women (n = 2738 [62.1%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>67.1 ± 7.8</td>
<td>68.5 ± 8.8</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>25.6 ± 2.9</td>
<td>26.6 ± 4.0</td>
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<tr>
<td>Hypertension</td>
<td>26.4</td>
<td>36.4</td>
</tr>
<tr>
<td>Blood pressure, mean ± SD, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>138.9 ± 22.0</td>
<td>139.4 ± 22.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75.3 ± 11.7</td>
<td>73.2 ± 11.5</td>
</tr>
<tr>
<td>Cholesterol level, mean ± SD, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>243 ± 46</td>
<td>266 ± 46</td>
</tr>
<tr>
<td>HDL-C</td>
<td>48 ± 12</td>
<td>56 ± 14</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>30.7</td>
<td>19.7</td>
</tr>
<tr>
<td>Former</td>
<td>60.9</td>
<td>28.3</td>
</tr>
<tr>
<td>Never</td>
<td>8.5</td>
<td>52.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8.1</td>
<td>9.5</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>4.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Cardiac medication†</td>
<td>3.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Intima-media thickness, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.84 ± 0.15</td>
<td>0.80 ± 0.14</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>0.82 (0.73-0.92)</td>
<td>0.78 (0.70-0.88)</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>40.1</td>
<td>47.0</td>
</tr>
<tr>
<td>Mild</td>
<td>15.8</td>
<td>17.9</td>
</tr>
<tr>
<td>Moderate</td>
<td>17.4</td>
<td>16.3</td>
</tr>
<tr>
<td>Severe</td>
<td>26.8</td>
<td>18.7</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HDL-C, high-density lipoprotein cholesterol.

*SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259. Unless otherwise indicated, data are expressed as percentage of subjects. Percentages have been rounded and might not total 100.

†Indicates the use of digoxin, nitrates, or antiarrhythmic drugs.

### Table 2. Measures of Atherosclerosis and Risk of Atrial Fibrillation: the Rotterdam Study, 1990-1999

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Model 1* RR (95% CI)</th>
<th>Model 2† RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid intima-media thickness, quartile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>30/1056</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Second</td>
<td>42/1057</td>
<td>1.12 (0.70-1.79)</td>
</tr>
<tr>
<td>Third</td>
<td>86/1056</td>
<td>2.09 (1.36-3.20)</td>
</tr>
<tr>
<td>Fourth</td>
<td>98/1056</td>
<td>2.12 (1.36-3.29)</td>
</tr>
<tr>
<td>Carotid plaques</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>80/1860</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Mild</td>
<td>47/714</td>
<td>1.29 (0.90-1.86)</td>
</tr>
<tr>
<td>Moderate</td>
<td>46/701</td>
<td>1.23 (0.85-1.78)</td>
</tr>
<tr>
<td>Severe</td>
<td>77/913</td>
<td>1.51 (1.09-2.09)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

*Adjusted for age and sex.
†Adjusted for age, sex, body mass index, hypertension, systolic blood pressure, total serum cholesterol level, smoking, diabetes mellitus, left ventricular hypertrophy on the electrocardiogram, and cardiac medication (use of digoxin, nitrates, or antiarrhythmic drugs).
Separate results for men and women are presented in Table 3. In women, the associations between the atherosclerosis measures and risk of atrial fibrillation were positive and statistically significant and reflected a dose-response relationship. In men, however, the association between intima-media thickness and risk of atrial fibrillation increased with increasing quartiles of intima-media thickness, but this association was not statistically significant. No association was found between carotid plaques and risk of atrial fibrillation in men. When we repeated the analyses excluding those new atrial fibrillation cases that developed after an incident myocardial infarction (n = 13), the associations were not materially different (data not shown). The population-attributable risks associated with intima-media thickness and carotid plaques were 33% and 19%, respectively.

In this population-based study, we found that atherosclerosis was associated with new-onset atrial fibrillation in subjects without a history of coronary heart disease. The indices of atherosclerosis used in this study have been shown to be measures of generalized atherosclerosis. The results suggest that atherosclerosis may be a causal factor in the etiology of atrial fibrillation, even when no overt coronary heart disease is present.

To our knowledge, the Cardiovascular Health Study is the only population-based study that previously investigated associations between measures of atherosclerosis and atrial fibrillation. In that study, carotid intima-media thickness and the ankle-arm index were not associated with incident atrial fibrillation. The reason for the discrepancy with our findings is not clear. There are, however, important differences in populations, ascertainment methods, and analyses between the 2 studies. For example, the Cardiovascular Health Study included self-reported cases of atrial fibrillation, and the proportion of those who had a history of a myocardial infarction in the Cardiovascular Health Study was lower than that in the Rotterdam Study (9.2% vs 13.2%), despite the older mean age of the Cardiovascular Health Study population. The older age of the Cardiovascular Health Study population is notable, because one could speculate that atherosclerosis may be a causal factor in the etiology of atrial fibrillation, even when no overt coronary heart disease is present.

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Associations of carotid intima-media thickness and risk of atrial fibrillation were weaker in men than in women, and the association between carotid plaques and atrial fibrillation was absent in men. We are unable to fully explain these differences between the sexes, but one possibility is that men with a high degree of atherosclerosis have died of cardiovascular disease before entering our study or before the development of atrial fibrillation.

Reliable associations strongly depend on accurate incidence figures. Population-based incidence figures of atrial fibrillation, however, are rare. Our incidence rates are comparable to those reported by the Framingham Study. The incidence figures of the Cardiovascular Health Study, however, are twice as high and probably reflect the older age of that cohort and other ascertainment methods. We could hypothesize that atherosclerosis, gradually or abruptly, reduces the blood supply to the sinus node and the atrial tissues that affect the gradual spreading of the electrical impulse over the atria and a normal conduction of the atria. This reduced flow may cause fibrosis and microscopic scarring of the atrial wall, resulting in areas with reduced conduction or even blocked conduction. Areas in the atria with decreased conduction velocity have been shown to favor reentry mechanisms, which can result in the development of atrial fibrillation.

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example, in a study of subjects with longstanding atrial fibrillation, nodal artery stenosis was present without distinct lesions of the sinus node or the internodal tracts, suggesting that diminished blood flow may play a role in the origin of atrial fibrillation in these cases. In another large pathological study, approximately 16% of subjects with longstanding atrial fibrillation had moderate to severe coronary artery disease without any histological evidence of infarction. Finally, it has been postulated that the sinus node artery plays an essential role in the synchronization of the numerous sites of automaticity within the sinus node. Dysfunction or rigidity of the sinus node artery could thus lead to a state of decreased rhythmic stability.

Our study is limited by the assumption that measures of noncoronary atherosclerosis are markers of the extent of coronary atherosclerosis. However, a previous investigation from our group found that the measures of noncoronary atherosclerosis, including carotid intima-media thickness and carotid plaques, were strongly associated with coronary calcification, as measured by electron beam computed tomography. Not all participants in the Rotterdam Study who completed the baseline examinations had an ultrasonographic examination, owing to a restricted availability of ultrasonographers at the end of 1992 and in 1993. Therefore, missing data on the ultrasonographic examinations were random and not based on the disease status of the participants. We did not distinguish between atrial fibrillation (paroxysmal or permanent) and atrial flutter when identifying cases, but these arrhythmias have the same risk factors and the same consequences.

Moreover, periods of atrial fibrillation in paroxysmal atrial fibrillation are much more common than is generally perceived by patients or their physicians and, over time, a high proportion of paroxysmal atrial fibrillation changes into chronic atrial fibrillation.

In aging populations, as is the case in Western Europe, atrial fibrillation will become progressively more important as its prevalence increases sharply with age. Atrial fibrillation is associated with considerable morbidity and mortality, increasing numbers of hospital admissions, and rising costs. Our findings suggest that the effect of atherosclerosis on the development of atrial fibrillation may be larger than is commonly thought. The results indicate that the management of atherosclerotic vascular disease and its risk factors in the general population and the aggressive treatment of participants with higher levels of atherosclerosis may contribute to a decrease in the incidence of atrial fibrillation, thereby lowering the disease burden and costs. The population-attributable risks for intima-media thickness of 33% and for carotid plaques of 19% suggest that successful preventive treatment of atherosclerosis may result in a considerable reduction of atrial fibrillation cases in the community.

In conclusion, in this prospective, population-based study, we found that measures of generalized atherosclerosis predict the onset of atrial fibrillation in persons without obvious coronary heart disease. The findings suggest that aggressive management of atherosclerotic vascular disease, including in asymptomatic subjects, may help to prevent atrial fibrillation.

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