Unrecognized Myocardial Infarction in Relation to Risk of Dementia and Cerebral Small Vessel Disease

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Background and Purpose—Men, but not women, with unrecognized myocardial infarction (MI) have an increased risk of cardiac events and stroke compared with those without MI or with recognized MI. We investigated whether unrecognized MI is also a risk factor for dementia and cerebral small vessel disease (white matter lesions and brain infarction) in 2 population-based cohort studies.

Methods—In the Rotterdam Study, 6347 participants were classified at baseline (1990 to 1993) into those with recognized MI (subdivided into Q-wave and non-Q-wave MI), with unrecognized MI, and without MI based on electrocardiography and interview and were followed for incident dementia (n=613) until January 1, 2005. In the Rotterdam Scan Study, 436 nondemented persons were similarly classified based on electrocardiography and interview and underwent brain MRI for the assessment of white matter lesions and brain infarction.

Results—In men, unrecognized MI was associated with an increased risk of dementia (compared with men without MI hazard ratio, 2.14; 95% CI, 1.37 to 3.35) and with more white matter lesions and more often brain infarction on MRI. In women, no associations were found with unrecognized MI. Recognized MI was not associated with the risk of dementia in either sex. Men, but not women, with recognized MI had more often any brain infarction or asymptomatic brain infarction, especially if they had Q-wave MI. No consistent associations were found between recognized Q-wave or non-Q-wave MI and severity of white matter lesions. Additional adjustment for cardiovascular risk factors did not change the results.

Conclusions—Men with unrecognized MI have an increased risk of dementia and more cerebral small vessel disease. (Stroke. 2008;39:000-000.)

Key Words: brain infarction dementia small vessel disease unrecognized myocardial infarction white matter lesions

In the elderly, between 21% and 68% of all myocardial infarctions (MIs) that can be identified by electrocardiography (EKG) are asymptomatic or remain clinically unrecognized. Men with an unrecognized MI have an increased risk of clinical cardiac disease when compared with men without MI, and even when compared with men with recognized MI. For women, no such differences have been reported. In line with the findings regarding cardiac disease, we found that men, but not women, with unrecognized MI also have an increased risk of clinical stroke compared with persons without MI or recognized MI. However, most cerebrovascular disease in the elderly occurs subclinically as small vessel disease, which can be visualized with MRI as white matter lesions (WML) and asymptomatic (lacunar) brain infarcts. Cerebral small vessel disease may be clinically asymptomatic, but it is not innocuous, because it is related to an increased risk of clinical stroke, cognitive decline, and dementia. Whether unrecognized MI is related to cerebral small vessel disease is unknown.

Markers of vascular disease and vascular risk factors have been implicated in the etiology of dementia as well. Few studies investigated whether recognized MI was associated with an increased risk of dementia, and those that did reported inconsistent results. No study thus far investigated unrecognized MI in relation to risk of dementia.

We hypothesized that unrecognized MI might be an important risk factor for both cerebral small vessel disease and dementia. Therefore, we investigated the association of unrecognized MI with dementia in the Rotterdam Study and with cerebral small vessel disease in the Rotterdam Scan Study. Furthermore, given the unexplained yet consistent finding of an especially unfavorable prognosis of unrecognized MI, we hypothesized that unrecognized MI might be an important risk factor for both cerebral small vessel disease and dementia.
In 1995 to 1996, 563 participants from the Rotterdam Study, who were still nondemented and who were randomly selected by sex and 5-year age strata, participated in the Rotterdam Scan Study. In these participants, a separate interview, physical examination, and blood sampling was repeated in 1995 to 1996, and they also underwent a brain MRI scan. The MRI scan was acquired, at the most, 2 weeks after the repeat interview and examination. In 436 of these persons, we obtained a digitized EKG.

In both studies, interviews and examinations were held independently from spouses or other family members. Missing EKGs in both studies were random and due to technical problems or too few personnel to operate the apparatus. Both the Rotterdam Study and the Rotterdam Scan Study have been approved by the Medical Ethics Committee of the Erasmus Medical Center, The Netherlands.

Assessment of Myocardial Infarction on Electrocardiography
Assessment of MI was done as reported previously and similarly for both the Rotterdam Study and Rotterdam Scan Study. Participants were asked the following questions: “Did you ever experience a heart attack?” If so, “At what age?”, “Who made the diagnosis?”, and “Were you admitted to a hospital?” Afterward, a 12-lead EKG was recorded with an ACTA-ECG (Esaote, Florence, Italy) with a sampling frequency of 500 Hz. All EKGs were processed by the Modular EKG Analysis System (MEANS) to obtain EKG measurement and interpretation. MEANS determines common onsets and offsets for all 12 leads together on one representative averaged beat using template matching techniques. To determine MI, MEANS uses a comprehensive set of criteria that partly derive from the Minnesota codes. Pathological Q-waves are central in the diagnosis of MI using MEANS. The MEANS program has been extensively evaluated previously. Of persons with EKG evidence of MI but without self-report, information from general practitioners and cardiologists was collected to confirm that no clinically manifest MI had occurred. Additional information was also collected of persons with self-reported MI without EKG evidence of MI. This was done to distinguish persons who had a non-Q-wave MI or whose Q-wave had disappeared over time from persons who mistook other symptoms for MI.

Based on this procedure, we classified participants as follows. Recognized Q-wave MI included persons with self-reported MI confirmed by matching EKG characteristics. Recognized non-Q-wave MI included persons with self-reported MI confirmed only by clinical data. Unrecognized MI included all participants without documented or self-reported MI but with EKG characteristics matching an MI. All unrecognized MI were therefore non-Q-wave MI. The non-MI reference group consisted of all persons without indication of MI on EKG and no self-report or medical documentation of an MI.

Assessment of Incident Dementia
In the Rotterdam Study, the diagnosis of incident dementia was made following a 3-step protocol. At baseline (1990 to 1993) and during 3 follow-up visits (1993 to 1994, 1997 to 1999, 2002 to 2004), 2 brief tests of cognition (Mini-Mental State Examination and Geriatric Mental State schedule organic level) were used to screen all subjects. Screen-positives (Mini-Mental State Examination score <26 or Geriatric Mental State schedule organic level >0) underwent the Cambridge examination for mental disorders of the elderly. Persons who were suspected of having dementia were examined by a neuropsychologist if additional neuropsychological testing was required for diagnosis. When available, imaging data were used. In addition, the total cohort was continuously monitored for incident dementia through computerized linkage between the study database and digitalized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. The diagnosis of dementia and major subtypes of dementia was made in accordance with internationally accepted criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised), Alzheimer’s disease (National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer’s Disease and Related Disorders Association), and vascular dementia (National Institute of Neurological Diseases and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences) by a panel of a neurologist, neuropsychologist, and research physician. Follow-up was complete until January 1, 2005.

MRI Procedures
Within the Rotterdam Scan Study, cranial MRI scanning was performed in all participants with a 1.5-T scanner (VISION-MR; Siemens, Erlangen, Germany) using standard T1, T2, and proton-density weighted MR sequences. MRI acquisition parameters have been described.

We obtained continuous volumetric measures of WML (expressed as percentage of intracranial volume to correct for individual head size differences) using validated automated image analysis. We defined brain infarctions from MRI as focal hypointensities ≥3 mm or larger on T2-weighted images. Proton density scans were used to distinguish infarctions from dilated perivascular spaces. Hyperintensities in the white matter also had to have corresponding prominent hypointensities on T1-weighted images to distinguish them from WML. History of stroke and transient ischemic attack was assessed by self-report and by checking medical records independent from MRI data. We defined asymptomatic brain infarctions as evidence of one or more infarctions on MRI without a history of corresponding transient ischemic attack or stroke. Intrarater agreement for detection of infarcts was good (κ=0.80).

Assessment of Covariables
In both the Rotterdam Study and the Rotterdam Scan Study, physical examinations were performed using the same protocol, and computerized questionnaires were used to obtain information on present health status and medical history. Smoking status was verified during the interview. Sitting blood pressure was measured on the right upper arm using a random-zero sphygmomanometer. We used the average of 2 measurements measured on one occasion. Diabetes mellitus was defined as random or postload serum glucose level exceeding 11.1 mmol/L or the use of oral blood glucose-lowering drugs or insulin. Carotid intima media thickness was measured by longitudinal 2-dimensional ultrasound of the carotid artery. We calculated the mean common carotid artery intima media thickness as the mean of 4 locations: the near and far wall of both the right and left common carotid arteries. Atrial fibrillation was assessed on an EKG. Serum total cholesterol and high-density lipoprotein cholesterol were determined by means of an automated enzymatic procedure in nonfasting blood samples. Use of cardiovascular drugs was assessed by interview and pharmacy records. These drugs included nitrates, antihypertensives, statins, and antithrombotic agents, including aspirin. Genotyping of APOE was performed on coded DNA specimens without knowledge of the outcomes.

Statistical Analysis
We tested differences in baseline demographic covariables between the 3 groups using Student t test for continuous variables and χ² test for dichotomous variables.
Table 1. Characteristics of the Study Population at Baseline of the Rotterdam Study

<table>
<thead>
<tr>
<th></th>
<th>No MI</th>
<th>Recognized MI*</th>
<th>Unrecognized MI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5578</td>
<td>424</td>
<td>345</td>
</tr>
<tr>
<td>Age, years</td>
<td>68.3 (8.5)</td>
<td>71.2 (8.2)‡</td>
<td>71.8 (8.8)‡</td>
</tr>
<tr>
<td>Women, %</td>
<td>61.4</td>
<td>30.0‡</td>
<td>53.9‡§</td>
</tr>
<tr>
<td>Presence APOE ε4 allele, %</td>
<td>25.3</td>
<td>25.1</td>
<td>21.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.3 (4.0)</td>
<td>26.4 (3.4)‡</td>
<td>27.0 (4.5)‡</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>22.9</td>
<td>20.3</td>
<td>28.1‡§</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>139.1 (22.3)</td>
<td>135.2 (22.0)‡</td>
<td>145.3 (20.6)‡§</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73.9 (11.4)</td>
<td>70.3 (11.3)‡</td>
<td>75.4 (11.9)‡§</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>6.6 (1.2)</td>
<td>6.6 (1.2)‡</td>
<td>6.6 (1.3)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
<td>1.4 (0.4)</td>
<td>1.1 (0.3)§</td>
<td>1.3 (0.3)§</td>
</tr>
<tr>
<td>Intima media thickness, mm</td>
<td>0.78 (0.15)</td>
<td>0.85 (0.18)†</td>
<td>0.83 (0.16)‡</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>9.0</td>
<td>17.0†</td>
<td>13.0§</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>2.1</td>
<td>3.4</td>
<td>6.1†</td>
</tr>
<tr>
<td>Use of cardiovascular drugs, %</td>
<td>33.0</td>
<td>83.0‡</td>
<td>39.0§</td>
</tr>
</tbody>
</table>

Values are percentages or means (SD).
*This group includes both persons with a Q-wave MI and a non-Q-wave MI.
†This group included only persons with Q-wave MI.
‡Significantly different (P<0.05) from persons without MI (age- and sex-adjusted, if applicable).
§Significantly different (P<0.05) from persons with recognized MI (age- and sex-adjusted, if applicable).

In the Rotterdam Study, we assessed the association of recognized Q-wave MI, recognized non-Q-wave MI, and unrecognized MI with risk of dementia and major subtypes of dementia with Cox proportional-hazard models adjusted for age and sex. Additionally, we adjusted for cardiovascular risk factors. Because previous reports suggested a difference in prognosis of unrecognized MI between men and women,5,7 we subsequently examined the association between MI and dementia in men and women separately and computed an interaction term between MI and sex. To assess whether the association between MI and dementia was mediated by stroke, we repeated the analyses excluding persons with prevalent stroke and censoring those with incident stroke at the time of stroke.

Results

Tables 1 and 2 show the characteristics of the study population. In the Rotterdam Study, 424 participants (297 in men) had a recognized MI, of whom 197 (130 in men) had a non-Q-wave MI. Of the 345 persons with unrecognized MI, 159 were men. In the Rotterdam Scan Study, 40 persons (32 in men) had a recognized MI, of whom 24 (19 in men) had a non-Q-wave MI. Twenty-two persons (6 in men) had an unrecognized MI. In both studies, there were no significant differences in baseline characteristics between persons with a recognized Q-wave MI and those with a recognized non-Q-wave MI. In both studies, persons with recognized Q-wave MI or non-Q-wave MI more often used cardiovascular drugs than those with unrecognized MI or without MI. Moreover, in the Rotterdam Study, persons with unrecognized MI had higher blood pressure and were more often smokers than persons without MI or with recognized Q-wave or non-Q-wave MI.

Incident Dementia

During 58712 person-years of follow-up in the Rotterdam Study, we identified 613 patients with dementia, of whom 479 were diagnosed with Alzheimer disease, 71 with vascular dementia, and 63 with dementia due to other causes. The incidence rate of dementia among persons without MI was 9.95 per 1000 person-years; among those with recognized Q-wave MI, this was 10.28 per 1000 person-years and among those with recognized non-Q-wave MI, 15.85 per 1000 person-years; finally, among persons with unrecognized MI, the incidence rate was 16.40 per 1000 person-years.

Table 3 shows that unrecognized MI was associated with a more than doubled risk of dementia, but only in men. In men, unrecognized MI was associated with an increased risk of...
both Alzheimer disease and vascular dementia; age-adjusted hazard ratios (95% CI) were 2.53 (1.49 to 4.30) for Alzheimer disease (126 cases) and 2.03 (0.71 to 5.80) for vascular dementia (37 cases). Recognized MI was not significantly associated with the risk of dementia (Table 3). The probability value of the interaction term between unrecognized MI and sex was \( \frac{0.01}{0.01} \), between recognized Q-wave MI and sex 0.42, and between recognized non-Q-wave MI and sex 0.28. Additional adjustment for cardiovascular risk factors did not change the estimates (Table 3). Excluding previous stroke cases and censoring incident stroke cases at the time of stroke did not attenuate the estimates either; if anything, the association became stronger; age-adjusted hazard ratio (95% CI) for dementia in men with unrecognized MI was 2.33 (1.38 to 3.95).

**MRI Outcomes**

In the Rotterdam Scan Study, we found that men with unrecognized MI had on average more WML than men without MI (Figure). Volume of WML did not differ between men with recognized Q-wave or non-Q-wave MI and men without MI. In contrast, women with unrecognized MI had an average WML load that was similar to that of women without MI. Women with a recognized Q-wave MI had on average more WML than women without MI. However, the interaction term between unrecognized MI and sex was significant \( (P=0.02) \), whereas the interaction term between recognized Q-wave MI and sex was not \( (P=0.7) \).

After adjustment for cardiovascular risk factors, the results were slightly attenuated, but the difference in volume of WML between men with unrecognized MI and without MI remained significant (fully adjusted difference in WML volume, 1.18%; 95% CI, 0.08 to 2.29).

Of the 374 persons without MI, 90 had a brain infarction on MRI (75 of these were asymptomatic). Among the 16 persons with recognized Q-wave MI, 10 had a brain infarction (7 asymptomatic). Among the 24 persons with recognized non-Q-wave MI, 10 had a brain infarction (8 asymptomatic). Finally, among the 22 persons with unrecognized MI, 10 had a brain infarction (9 asymptomatic). Men with a recognized MI were more likely to have any brain infarction or an asymptomatic brain infarction on their MRI scan than men without MI, especially if they had had a recognized Q-wave MI (OR, 6.98; 95% CI, 2.06 to 23.70; Table 4). Likewise, the prevalence of any brain infarctions was more than 7-fold increased in men with unrecognized MI (Table 4). Women with a recognized MI had a nonsignificantly increased prevalence of brain infarction on MRI, similarly for Q-wave and non-Q-wave MI. In contrast, unrecognized MI was not associated with the presence of brain infarction in women. The probability values of the interaction term between unrecognized MI and sex were 0.15 for any brain infarction and 0.25 for asymptomatic brain infarction. The corresponding probability values of the interaction term between recognized Q-wave MI and sex were not 0.08 (for persons without MI 0.08).

### Table 3. The Association Between MI and Dementia by Sex

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>HR (95% CI)*</td>
<td>HR (95% CI)†</td>
</tr>
<tr>
<td>No MI</td>
<td>524/5578</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Recognized MI</td>
<td>43/424</td>
<td>1.06 (0.78–1.46)</td>
<td>1.12 (0.77–1.64)</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>18/227</td>
<td>0.83 (0.52–1.33)</td>
<td>0.96 (0.56–2.13)</td>
</tr>
<tr>
<td>Non-Q-wave MI</td>
<td>25/197</td>
<td>1.34 (0.89–2.00)</td>
<td>1.30 (0.79–2.13)</td>
</tr>
<tr>
<td>Unrecognized MI</td>
<td>46/345</td>
<td>1.22 (0.90–1.65)</td>
<td>1.35 (0.95–1.92)</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex (if applicable).†Adjusted for age, sex, and additionally adjusted for presence of APOE ε4 allele, systolic blood pressure, diastolic blood pressure, body mass index, atrial fibrillation, diabetes mellitus, current smoking, intima media thickness, total cholesterol and high-density lipid cholesterol.

\( n \) indicates number of dementia cases; \( N \), total number of persons; HR, hazard ratio.
have looked at clinical stroke separately. In the er10,27,28 and to share similar (cardiovascular) risk factors.29
Indeed, both clinical and subclinical cerebrovascular disease have been shown to be closely associated with each other.

Table 4. The Association Between MI and Brain Infarction by Sex

<table>
<thead>
<tr>
<th>OR (95% CI) for Any Brain Infarction</th>
<th>OR (95% CI) for Asymptomatic Brain Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td><strong>Men</strong></td>
</tr>
<tr>
<td>No MI</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Recognized MI</td>
<td>3.57 (1.74–7.34)</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>6.39 (2.13–19.16)</td>
</tr>
<tr>
<td>Non-Q-wave MI</td>
<td>2.41 (0.97–5.99)</td>
</tr>
<tr>
<td>Unrecognized MI</td>
<td>2.36 (0.93–5.97)</td>
</tr>
</tbody>
</table>

Values are OR with 95% CIs adjusted for age and sex (if applicable).

Discussion
We found that men, but not women, with unrecognized MI had an increased risk of dementia, more WML, and more often any brain infarction or an asymptomatic brain infarction compared with those without MI, even when known cardiovascular risk factors were accounted for. Recognized MI, both Q-wave and non-Q-wave, was not associated with the risk of dementia in either sex. Men, but not women, with recognized MI more often had any brain infarction or an asymptomatic brain infarction on MRI, especially if they had a Q-wave MI. No consistent associations were found between recognized Q-wave or non-Q-wave MI and severity of WML.

The strengths of our studies include the population-based setting, the large number of participants, and the virtually complete follow-up for dementia. Moreover, we focused on clinical and subclinical manifestations of both cardiac and cerebrovascular disease. A limitation is the cross-sectional study design of the Rotterdam Scan Study, which might limit our interpretation of the data with respect to the temporal relationship between MI and MRI parameters. Another possible limitation could be that MI on EKG was diagnosed using the MEANS computer program, which might have led to misclassification. However, this program has been extensively validated and diagnoses correlate well with diagnoses made by an experienced cardiologist. Also, any misclassification is likely to be nondifferential because MEANS diagnoses were made independent from clinical diagnosis of dementia and assessment of MRI outcomes.

Most studies reporting on the prognosis of unrecognized MI did not investigate neurological outcomes but focused on cardiac events. Only the Rotterdam Study and the Framingham study have looked at clinical stroke separately. In the present study, we focused on dementia and cerebral small vessel disease.

Our observation regarding the association between unrecognized MI and subclinical cerebral small vessel disease is in line with our previous report with respect to clinical stroke. Indeed, both clinical and subclinical cerebrovascular disease have been shown to be closely associated with each other and to share similar (cardiovascular) risk factors. In turn, our finding that persons with unrecognized MI have an increased risk of dementia fits well with previous studies reporting that markers of vascular disease and vascular risk factors are involved in the pathogenesis of dementia, presumably by leading to subclinical cerebral small vessel disease. Moreover, we found that the increased risk was confined to men and not women. This is in accordance with studies that showed an increased risk of cardiovascular morbidity and clinical stroke in men with unrecognized MI but not in women. An explanation for this difference between men and women might be the higher background prevalence of cerebrovascular disease in men compared with women. Another possibility is that misclassification of MI on EKG may occur more often in women. EKG abnormalities that can be mistaken for MI are not caused by coronary disease are more often seen in women than in men, possibly caused by difficulties in correctly placing the electrodes due to breast tissue. Because of this possible nondifferential misclassification of our determinant, dilution of the effect might have occurred and therefore the true effect may have been missed in women in our data set. Such misclassification might also explain the higher prevalence of unrecognized MI among women than men. Finally, to rule out the possibility that sex differences occurred by chance, other studies should seek to replicate our findings.

In contrast to our findings in persons with unrecognized MI, we did not find consistent associations of recognized MI, either Q-wave or non-Q-wave with dementia, WML, or brain infarction, for either sex. We only found statistically significant associations for recognized Q-wave MI with any brain infarction or an asymptomatic brain infarction in men and with WML in women. This is in line with published data on differences between unrecognized and recognized MI with respect to prognosis for cardiovascular morbidity. A possible explanation for this difference is that inherent lack of preventive treatment and specific lifestyle advice contributed to a poorer prognosis after unrecognized MI. Support for this comes from the observation that in both the Rotterdam Study and the Rotterdam Scan Study, the proportions of cardiovascular drug users were higher among persons with a recognized than with an unrecognized MI. Still, adjusting for cardiovascular risk factors did not change the associations. This may indicate that unrecognized MI gives a better indication of the cardiovascular damage that has accumulated over time than cardiovascular risk factors measured only once at baseline.
In conclusion, our study shows that presence of unrecognized MI is associated with an increased risk of dementia and a higher prevalence of cerebral small vessel disease in men, but not in women. Given the large proportion of MI that remains unrecognized in the general elderly population, our data suggest that screening men for unrecognized MI using EKG might identify those at an increased risk of various adverse outcomes. These persons could then benefit from subsequent installment of preventive therapy. However, before such screening is initiated, our results first need to be replicated in other population-based studies.

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Disclosures
None.

References
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