Incidence of recognized and unrecognized myocardial infarction in men and women aged 55 and older: the Rotterdam Study

Anneke de Torbal, Eric Boersma, Jan A. Kors, Gerard van Herpen, Jaap W. Deckers, Deirdre A.M. van der Kuip, Bruno H. Stricker, Albert Hofman, and Jacqueline C.M. Witteman*

Department of Epidemiology and Biostatistics, Erasmus MC, PO Box 1738, 3000 DR Rotterdam, The Netherlands

Received 12 April 2005; revised 31 October 2005; accepted 8 December 2005; online publish-ahead-of-print 14 February 2006

Aims Contemporary data on the incidence of unrecognized myocardial infarction (MI) among subjects aged 55 and older are limited.

Methods and results We studied the incidence of recognized and unrecognized MI in the Rotterdam Study, a population-based cohort of men and women aged 55 and older. The baseline examination was performed during 1990–93, with follow-up examinations during 1994–95, and 1997–2000. Baseline and follow-up 12-lead ECGs were analysed by the Modular ECG Analysis System. The 5148 participants who had no evidence of prevalent infarction were the subjects for analysis. Incident recognized infarction was defined as the occurrence of a fatal or non-fatal event coded as I21 according to the International Classification of Diseases, 10th edition. A repeat ECG was available in 4187 subjects. An unrecognized infarction was considered to have occurred if there was electrocardiographic evidence in the absence of a clinically recognized event. During a median follow-up of 6.4 years, 141 incident recognized infarctions occurred and the incidence rate of this event was 5.0 per 1000 person years. The incidence was higher in men (8.4) than in women (3.1). The incidence rate of unrecognized infarction was 3.8 per 1000 person years. Men (4.2) and women (3.6) had approximately similar incidence. Hence, the proportion of unrecognized infarction was lower in men (33%) than in women (54%). This difference in proportion of unrecognized infarctions was independent of age.

Conclusion A high proportion of incident MIs remains clinically unrecognized. As a history of MI is associated with an increased risk of repeat cardiovascular complications, our data suggest a need for periodical electrocardiographic screening to recognize (prevalent) infarctions and to install effective preventive treatment in those aged 55 and older.

KEYWORDS
Myocardial infarction; Electrocardiogram; Elderly; Incidence

Introduction

During the last decades, ischaemic heart disease mortality has considerably decreased in most countries belonging to the Western world.1,2 Changing coronary event rates is the major determinant of this decline, whereas improved coronary care and secondary prevention were responsible for decreased event rates.3,4 Despite these promising developments, ischaemic heart diseases will remain a major health issue during the decades ahead for several reasons. First, ischaemic heart diseases will persist to occur at early ages in individuals with a genetic predisposition and in those with an unfavourable clinical risk profile. Furthermore, survivors of an acute coronary syndrome constitute a population with chronic cardiac conditions and remain at increased risk of future fatal and non-fatal cardiac events. In addition, evidence exists that patients and doctors fail to adequately put effective preventive measures into practice.5 Last, but not the least, it should be realized that the Western world is ageing and heart diseases come with age. This latter observation has been the keynote behind the Rotterdam Study, a long-term prospective cohort study in men and women aged 55 and older,6 on which we report.

Myocardial infarction (MI) is the most dominant manifestation of ischaemic heart diseases. Although MI is usually associated with severe symptoms, several cohort studies have indicated that up to 44% of the events remain clinically unrecognized until routine and repeated imaging of the cardiac function is performed.7 These unrecognized or ‘silent’ MIs should not be considered minor events. In fact, it has been repeatedly demonstrated that patients with prevalent unrecognized MI have similar prognosis as those with prevalent recognized infarction.8–10

Contemporary data on the incidence of unrecognized MI among subjects aged 55 and older in the general population are limited. Most epidemiological studies were conducted before the 1990s, had an upper age limit, or enrolled patients with established coronary disease.11–20 In addition,
contradictory results have been reported, with some studies suggesting a steadily increasing incidence with age and others reporting a stabilizing or even decreasing incidence in individuals over the age of 70. These differences were probably confounded by gender differences between the studied cohorts. Against this background, we studied the incidence of recognized and unrecognized MI in the Rotterdam Study population. We were especially interested to learn to what extent the incidence of recognized and unrecognized MI increased with age, and if so, whether or not differences were apparent between men and women.

Methods

The Rotterdam Study

The Rotterdam Study is a prospective population-based cohort study of 7983 men and women aged 55 and older. Its overall aim is to investigate the incidence and determinants of chronic disabling diseases. From 1990 to 1993, all inhabitants of a suburb of the city of Rotterdam aged 55 and older 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 obtained information included current health status, medical history, drug use, and smoking behaviour. Additionally, during two visits to the research centre, established cardiovascular risk factors were measured. The Medical Ethics Committee of the Erasmus MC 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 have been given elsewhere.

Study population

A total of 7085 participants visited the Rotterdam Study research centre shortly after the enrolment interview. Living in a nursing home or limited mobility was the main reason for not visiting the research centre. A baseline 12-lead ECG was available in digital format for 6175 of them. These ECGs were analysed off-line using the automated Modular ECG Analysis System (MEANS). This system computes a representative averaged beat for each of the 12 leads, which signals are then used to automatically identify abnormal, pathological patterns. MEANS was developed at the Department of Medical Informatics of the Erasmus MC and has been extensively evaluated and validated in several clinical and pre-clinical settings. By using MEANS, 820 participants were identified with evidence of prevalent (recognized or unrecognized) MI. During the interview, data on history of cardiovascular diseases were collected, which were verified using medical records at the general practitioners’ (GPs) offices, which included hospital discharge letters. According to this information, there were another 207 participants with prevalent recognized MI. All subjects with evidence of prevalent MI were excluded, resulting in a study population of 5148 participants.

Definition of incident recognized MI

Clinical follow-up started at the baseline examination and for the present study lasted until 1 January 2000. Fatal and non-fatal cardiovascular events were reported by GPs in the research district with whom 85% of the participants of the Rotterdam Study were enlisted. Research physicians verified the information provided by using medical records from the GPs offices. All medical records of the participants under the care of GPs outside the study area were checked annually for possible events. Letters and, in the 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 GPs. Two research physicians independently coded all reported events according to the International Classification of Diseases, 10th edition (ICD-10). Codes on which the research physicians disagreed were discussed in order to reach consensus. A medical expert in cardiovascular disease (J.W.D.), whose judgement was considered final, reviewed all events. Incident recognized MI was defined as the occurrence of a fatal or non-fatal MI (ICD-10 code I21) that was recognized during clinical follow-up after the baseline examination.

Definition of incident unrecognized MI

Subjects were enrolled during 1990-93 and underwent their baseline examination in that period. Second and third rounds of examinations were scheduled during 1993-96 and 1997-99. All subjects who were still alive were invited to again visit the research centre. As the population was ageing (note that the median age of the study population at study entry was 67 years), a growing number of participants had died or became otherwise physically unable to visit the research centre. For 4187 participants, a repeat 12-lead ECG was derived during at least one of the follow-up rounds (2578 during both rounds, 1252 during the second round only, and 358 during the third round only), making them eligible for the analysis of incident unrecognized MI. These ECGs were analysed off-line using MEANS. A medical expert in electrocardiography (G.V.H.), whose judgement was considered final, reviewed all cases that were classified by MEANS as ‘possible’, ‘probable’, or ‘definite’ MI. An unrecognized MI was considered to have occurred if the expert confirmed that there was electrocardiographic evidence of MI in the absence of an incident clinically recognized MI since the baseline examination. The unrecognized MI was then thought to have occurred in the middle of the time interval between the baseline visit and the first follow-up visit or between the first and the second follow-up visits, as appropriate.

Data analysis

Continuous data are presented as median values and the corresponding 25th and 75th percentiles and discrete data are presented as numbers and percentages. Differences in baseline characteristics between subgroups were evaluated by Wilcoxon tests or Fisher’s exact tests, as appropriate. All tests were two-sided, and P < 0.05 was considered statistically significant.

Subjects were censored at the date of the (first) unrecognized MI, the date of the first recognized MI, the date of death, or the date on which they were last known to be alive, whichever date came first. The cumulative amount of person years was determined in strata according to the gender and the subject’s actual age: 55–59, 60–64, 65–69, 70–74, 75–80, and ≥80 years (note that we did not stratify subjects according to their age at study entry; a subject could contribute to more than one stratum because of his increasing age during follow-up). The age- and gender-specific incidence rate of (un)recognized MI was then determined, which was defined as the number of (un)recognized MIs during follow-up divided by the cumulative amount of person years. Incidence rates are presented as a number per 1000 person years and corresponding 95% confidence interval (CI). Linear regression analyses were applied to further evaluate the relation among age, gender, and the incidence of (un)recognized MI. Regression functions were fitted using the summative data that were observed in the specified strata, whereas data were weighted by the square root of the number of person years in each stratum.

Sudden death

Sudden death is usually defined as unexpected and non-traumatic death occurring instantaneously or within a few minutes of an event.
abrupt change in the clinical state of persons without prior conditions that would appear fatal. In participants who experience sudden death, incident MI cannot be diagnosed with sufficient certainty as per definition. As evidence exists that >90% of victims have previously known or unrecognized cardiac abnormality (although not necessarily coronary abnormality),27,28 we decided to also describe the incidence of sudden death in this report on incident MI. Events coded according to the ICD-10 system as I46 or R96 were classified as sudden death.

Results
Baseline characteristics of the study population are described in Table 1. There were significant differences between men and women in characteristics that have previously been associated with an increased incidence of MI, including age, a family history of MI, smoking behaviour, body weight, and blood cholesterol levels.29 No differences were observed in the baseline use of cardiovascular medication, including beta-blockers, serum lipid reducing agents, and angiotensin-converting enzyme (ACE)-inhibitors.

In the 5148 participants who were eligible for the analysis of incident recognized MI, 141 incident events occurred during a median follow-up of 6.4 (5.2, 6.6) years. The participants were responsible for a total of 28 121 person years. Hence, the incidence rate of recognized MI was 5.0 (95% CI 4.2–5.8) per 1000 person years. The incidence rate was higher in men (8.4 and 95% CI 6.6 –10.2) than in women (3.1 and 95% CI 2.3–3.9) and was also positively associated with age (Table 2). The higher MI incidence in men when compared with women was consistently observed in all age strata, but there was evidence of a differential relation between age and infarct incidence for men and women. In men, an age difference of 10 years was associated with a difference in incidence rate of 4.0 per 1000 person years, whereas a similar age difference in women was associated with a difference in incidence rate of only 1.5 per 1000 person years (Figure 1; P-value for the age × gender interaction is 0.08).

The higher incidence of recognized MI in men when compared with women was systematically observed in subgroups according to the selected baseline characteristics (Figure 2). It is worth noting that the incidence of recognized MI was higher in subjects using cardiovascular medication at baseline than in those not using such medication.

In the 4187 participants who were eligible for the analysis of incident unrecognized MI, MEANS found evidence of such events in 328 cases, of which 89 were confirmed after expert review. The participants were responsible for a total of 23 505 person years. Thus, the incidence rate of unrecognized MI was 3.8 (95% CI 3.0–4.6) per 1000 person years. The incidence rate was 4.2 (95% CI 2.8–5.5) in men and 3.6 (95% CI 2.6–4.5) in women. In men as well as in women, the incidence of unrecognized MI increased with age (Table 2). There was no evidence of a differential relation between the age and the incidence of unrecognized MI for men and women: an age difference of 10 years was associated with a difference in incidence rate of 2.1 per 1000 person years (Figure 1). Analyses of subgroups according to the selected baseline characteristics did not reveal any relevant divergent result.

Overall, 43% of incident MIs remained clinically unrecognized, but there was an important difference between men (33%) and women (54%). We found no association between the proportion of incident unrecognized MI and the age (Figure 3). The difference in the proportion of unrecognized MI between men and women was consistently observed in subgroups according to the baseline characteristics (Figure 4). A high relative frequency of incident unrecognized MI was observed in subjects who did not use cardiovascular medication at baseline.

Sudden death occurred in 32 subjects (12 men and 20 women) and 18 of these were classified as sudden cardiac death (eight men and 10 women). The incidence rate of sudden death was 1.2 (0.5–1.8) per 1000 person years in men and 1.1 (0.6–1.6) per 1000 person years in women.

Discussion
The incidence rate of MI in men and women aged 55 and over amounted approximately 9 per 1000 person years. On average, four of these events remained clinically

### Table 1 Baseline characteristics of the study population stratified by gender

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>1920</td>
<td>3228</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>66.1 (61.0, 72.6)</td>
<td>68.4 (61.8, 75.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of MI</td>
<td>34.1</td>
<td>37.4</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4.7</td>
<td>5.9</td>
<td>0.07</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>30.3</td>
<td>41.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current</td>
<td>29.9</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>61.5</td>
<td>28.2</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>8.6</td>
<td>53.4</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.5 (23.8, 27.5)</td>
<td>26.2 (23.9, 29.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137 (123, 152)</td>
<td>138 (123, 154)</td>
<td>0.2</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.21 (1.04, 1.44)</td>
<td>1.46 (1.22, 1.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.5 (4.9, 6.1)</td>
<td>6.0 (5.4, 6.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of beta-blockers</td>
<td>24.5</td>
<td>22.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Use of serum lipid reducing agents</td>
<td>15.6</td>
<td>13.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Use of ACE-inhibitors</td>
<td>17.9</td>
<td>15.2</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Additionally, one sudden death occurred per 1000 person years. The incidence of recognized MI and the incidence of unrecognized MI increased with age. The incidence of recognized MI was higher in men than in women, but the incidence of unrecognized MI was approximately similar.

With a relative frequency of 43%, unrecognized MI represented a significant portion of all incident MIs. Previous epidemiological studies reported values ranging from 4 to 44%. Differences in baseline characteristics between the investigated cohorts, especially in age, gender, cardiovascular risk factors, prior history of cardiovascular diseases, and the use of cardiovascular medication, may explain these findings. Indeed, we found an important difference in the proportion of unrecognized MI between subjects who used beta-blockers, serum lipid reducing agents, or ACE-inhibitors at their baseline visit and those who did not. Although the reason for baseline medication use was not registered, it seems reasonable to speculate that subjects using such cardiovascular medication are at elevated risk of cardiovascular complications, at least in the opinion of the prescribing physician, and that they are aware of this risk. Persons who are aware of their increased risk might be more likely to recognize and report symptoms suggestive of MI than those who are unaware.

We excluded subjects with clinical or electrocardiographic evidence of prevalent MI, mainly because it is virtually impossible to separate between prevalent and incident unrecognized MI in these individuals by using MEANS. In the same train of thought, this may have resulted in a high incidence of unrecognized MI relative to other investigations. For example, in the HERS study, 17% of the participants had pathological Q-waves on the baseline ECG, whereas only a 4% relative frequency of unrecognized incident MI was reported. In contrast, the incidence of unrecognized MI might still have been underestimated in our study. As the diagnosis was solely based on the electrocardiographic findings, MIs which did not result in lasting ECG abnormalities were missed logically. It has been suggested that 10–25% of patients who survived an infarction may have a normal post-MI ECG or a normalized ECG during long-term follow-up.

The observed high incidence of unrecognized MI relative to other investigations might further be explained by differences in the applied methodology. Most investigations used the Minnesota codes to analyse and classify ECGs, which were assigned visually from paper records, and it is known that these codes have modest sensitivity to diagnose MI in the general population. The computerized MEANS, which we applied, has not been used for the diagnosis of incident MI in earlier studies. Consequently, head-to-head comparisons with other systems are lacking. Still, in a previous study of our group, we demonstrated that MEANS has satisfying sensitivity to diagnose prevalent MI. As an
increasing sensitivity is usually coupled with decreasing specificity, an analysis of ECGs by computerized systems only will not be sufficient in epidemiological studies. In our study, the ECG analysis by MEANS was followed by a visual inspection of cases that were initially labelled as incident MI. Indeed, 73% of these cases were not confirmed (note that we also reviewed cases that were classified as ‘possible’ MI, whereas in earlier studies, only cases labelled as ‘probable’ or ‘definite’ MI were considered).24

In each of the distinguished age categories, men had a higher incidence of recognized MI than women and a similar incidence of unrecognized MI. Thus, we found evidence that MIs are less often recognized in women than in men, irrespective of characteristics that have previously been associated with an increased incidence of MI. This observation is in agreement with other available data, including the Framingham and Cardiovascular Health studies,12,18 but in contrast to the recent Reykjavik study.16,17 In the latter study, however, the data search for men was dependent on the baseline disease status, whereas for women it was not. This might have resulted in a higher proportion of MIs among women being classified as clinically recognized.

The explanation of the observed high relative frequency of unrecognized MI in women is not straightforward, and most likely multiple factors play a role. It has been described that men and women experience chest pain in different ways.30 In a recent study in patients presenting with unstable angina, women reported more intensive pain than men, but less often reported typical chest pain and less often related their pain to heart disease.31 In another study in patients with non-traumatic chest pain, women were more likely to describe their pain in affective terms.32 This negative interpretative perception of (chest) pain may hold women back from reporting suggestive symptoms, while physicians may be in doubt whether or not to consider heart disease as the source of complaints. It should be noticed in this respect that women and their doctors have traditionally worried about mortality from breast and gynaecological malignancies, rather than heart diseases.30 In contrast, evidence exists that women who present with chest pain more often suffer from atypical, non-cardiac symptoms than men.13

Limitations
A substantial number of subjects were excluded from this study because they did not have a baseline or follow-up ECG. In general, the exclusion of patients based on missing data can seriously alter the study population and...
introduce selection bias. In this particular case, subjects with missing ECGs were considerably older than those in whom ECGs were available (median baseline age: 75 vs. 66 years). As the incidence of recognized as well as unrecognized MI increased with age, their exclusion might have resulted in an underestimation of the factual incidence.

Our study was conducted in the 1990s. During this decade, several cardioprotective agents became widely available, including ACE-inhibitors, beta-blockers (these agents also have blood pressure lowering effects), and statins. Also diabetes mellitus emerged as a risk factor of cardiovascular disease, and strict blood glucose control in diabetics is nowadays recommended. As per design, the number of data items to be collected in the Rotterdam Study was limited; only two follow-up visits were scheduled, 3 years apart. Thus, changes in clinical risk profile or medication use over time have not been monitored in detail. Consequently, it remains unknown to what extent these developments that occurred after the baseline examination have influenced the incidence of recognized and unrecognized MI in specific subgroups of the Rotterdam Study population.

We did not have detailed information on the prevalence of left or right bundle branch block in our study population. This is a potential limitation, as it is well known that the prevalence of a bundle branch block complicates the MI diagnosis. However, it should be emphasized that the diagnosis of recognized MI was not only based on the admission ECG, but also on the clinical observations during hospitalization, results of laboratory testing (CK-MB elevations), non-invasive cardiac imaging, and coronary angiography. Hence, it is unlikely that clinically sound MIs have been missed because of the presence of a bundle branch block. As far as the diagnosis of unrecognized MI is concerned, MEANS automatically excludes ECGs with QRS...
morbidity compatible with bundle branch block. We realize that this might have resulted in a (slight) underestimation of the incidence of unrecognized MI.

As far as the diagnosis of MI is concerned, it has been argued that the Q-wave never lies.35 Indeed, electrocardiographic criteria to diagnose ‘Q-wave’ MIs have high specificity. However, the sensitivity of the ECG to diagnose unrecognized non-Q-wave MIs is limited, especially in the case of apical necrosis.36 Still, all available studies that have been conducted so far relied on the ECG to diagnose unrecognized MI. Therefore, it has been argued that many of these events were probably never detected.15 One might speculate that the application of other diagnostic tools, including echocardiography, thallium perfusion imaging, and radionuclide angiography, may reveal a higher proportion of unrecognized MIs.

Conclusion

The incidence rate of MI amounted 12 per 1000 person years in men and 7 per 1000 person years in women aged 55 and older, whereas approximately one-third (men) to half (women) of these events remained clinically unrecognized. The incidence of MI increased with age, but the relative frequency of unrecognized MI did not. Because patients with a history of MI are at increased risk of repeat cardiovascular complications, our data suggest a need for periodical electrocardiographic screening to recognize (prevalent) infarctions in subjects above the age of 55 years and to install effective preventive treatment.

Conflict of interest: none declared.

References


