Unrecognized myocardial infarction and risk of atrial fibrillation: The Rotterdam Study

Bouwe P. Krijthe a,b, Maarten J.G. Leening a,c, Jan Heeringa a, Jan A. Kors e, Albert Hofman a, Oscar H. Franco a, Jacqueline C.M. Witteman a, Bruno H. Stricker a,b,d,e,f,*

a Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands
b Netherlands Consortium for Healthy Aging (NCHA), The Netherlands
c Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands
d Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands
e Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands
f Inspectorate of Health Care, the Hague, The Netherlands

ARTICLE INFO

Article history:
Received 22 June 2012
Received in revised form 16 November 2012
Accepted 24 December 2012
Available online 17 January 2013

Keywords:
Atrial fibrillation
ECG
Myocardial infarction
Epidemiology

ABSTRACT

Background: Persons with a clinically recognized myocardial infarction are at increased risk for atrial fibrillation. However, a large proportion of all myocardial infarctions remain clinically unrecognized. Whether subjects with electrocardiographic signs of an unrecognized myocardial infarction are also at an increased risk of developing atrial fibrillation is unknown. The objective of this study was to investigate whether unrecognized myocardial infarction was associated with an increased risk of atrial fibrillation in a prospective population-based cohort study.

Methods: The study is set within the prospective population-based Rotterdam Study. The study population comprised 2505 men and 3670 women without atrial fibrillation at baseline. Participants were classified based on electrocardiography, interview, and clinical data into those with recognized myocardial infarction, those with ECG based unrecognized myocardial infarction and those without myocardial infarction. Atrial fibrillation was ascertained from ECG assessments as well as medical records.

Results: During a mean follow-up of 11.7 years (SD 5.0), 329 men and 398 women developed atrial fibrillation. Unrecognized myocardial infarction was associated with a two-fold risk of developing atrial fibrillation in men (HR: 2.21, 95%CI:1.51 to 3.23) compared to men without a history of myocardial infarction, independent of age, and cardiovascular risk factors. In women, unrecognized myocardial infarction was not associated with atrial fibrillation (HR: 0.92, 95%CI:0.59 to 1.44).

Conclusion: The presence of an unrecognized myocardial infarction is associated with a twofold increased risk of atrial fibrillation in men, independent of known cardiovascular risk factors.

© 2013 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Atrial fibrillation is the most common sustained arrhythmia in the older population. Its prevalence and incidence increase with age [1–4]. Atrial fibrillation has significant impact on prognosis and quality of life. It is a major cause of morbidities such as dementia [5], stroke [6], and heart failure [7] and it is also associated with increased cardiovascular and overall mortality [8–10]. Persons with a history of myocardial infarction (MI) are at increased risk of atrial fibrillation [4,11]. However, it has previously been demonstrated that the overall detection of MIs is far from complete and that a large proportion of all MIs remains clinically unrecognized [12,13]. It was previously estimated that the proportion of unrecognized MIs from all MIs ranges from 21 to 33% in men and 26 to 54% in women [12–17]. Furthermore, in approximately 1 to 6% of the general elderly population electrocardiographic characteristics can be detected of an unrecognized MI [12,14,18]. Whether subjects with electrocardiographic signs of an unrecognized MI are also at an increased risk of developing atrial fibrillation is unknown.

Therefore, the objective of this study was to investigate whether unrecognized MI was associated with an increased risk of atrial fibrillation in a prospective population of community-dwelling elderly.

2. Methods

2.1. Study population

The current study was performed within the Rotterdam Study, a population-based prospective cohort study, designed to examine the onset of, and risk factors for disease in older adults, which started with a baseline visit between 1990 and 1993 [19]. All
participants aged 55 years and over in the Ommoord district of Rotterdam, The Netherlands were invited to participate (n = 10,275). Of them, 7983 (78%) participated in the study. At baseline, participants were interviewed at home and were examined at the research center, which included a 10 s, 12-lead resting electrocardiogram (ECG). From that visit onwards, participants were followed continuously and re-examined at three follow-up examination rounds (1993–1995, 1997–1999, and 2002–2004). Information on the presence and occurrence of disease at baseline and during follow-up is available by collaboration with the general practitioners in the study area. General practitioners in the Netherlands have a key position in the Dutch healthcare system. They register all diagnoses available from their own work and the work from physicians in the hospital and the out-patient clinic. The medical ethics committee of the Erasmus Medical Center, Rotterdam, approved the study, and all participants gave informed consent to participate in the study and to obtain information from treating physicians. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Myocardial infarction assessment

ECGs were processed by the Modular ECG Analysis System (MEANS) to obtain ECG measurement and interpretation [20–22]. To determine MI, MEANS uses an extensive set of criteria that is partially derived from the Minnesota code [23]. Subsequently, two research physicians blinded to other clinical information validated the ECGs selected by MEANS. A cardiologist, who specialized in ECG methodology, ascertained the final diagnosis of MI. The diagnosis of MI using MEANS is mainly driven by pathological Q waves and auxiliary criteria, such as QR ratio and R-wave progression. ST-T changes were not considered as criteria for MI by MEANS, but were taken into account by the cardiologist validating and ascertaining the diagnosis of MI based on the ECG. Assessment of recognized MI status was done by verification of the medical records after either self-reported MI or ECG abnormalities indicative of prior MI, as reported previously for the Rotterdam Study [24]. We classified participants at baseline as follows: a history of ‘recognized MI’ included people with self-reported MI and/or ECG characteristics matching an MI, confirmed by clinical data. A history of ‘unrecognized MI’ included all participants without documented or self-reported MI, but with ECG characteristics matching an MI. All other participants were classified as having ‘no MI’.

2.3. Atrial fibrillation assessment

Prevalent and incident atrial fibrillation was ascertained using three methods [1]. At baseline and at each follow-up examination an ECG was recorded, stored digitally, and analyzed by MEANS [20–22]. Notably, MEANS is characterized by a high sensitivity (96.6%) and a high specificity (99.5%) in coding arrhythmias [20]. Additionally, information was obtained from the treating general practitioners, which included their own results as well as results from medical specialists practicing in hospitals and out-patient clinics. Finally, information was obtained from a nationwide medical registry of all hospital discharge diagnoses. To verify the diagnosis of atrial fibrillation, all ECGs with a diagnosis of atrial fibrillation, atrial flutter, or any other rhythm disorder were coded independently by two research physicians who were blinded to the MEANS diagnosis. The judgment of a cardiologist was taken as decisive in those cases in which disagreement persisted between the coding physicians. We did not distinguish between paroxysmal atrial fibrillation and atrial flutter when we identified cases because both conditions are very similar with respect to risk factors and consequences [25,26]. Also, we did not discriminate between paroxysmal atrial fibrillation and chronic atrial fibrillation. The date of incident atrial fibrillation was defined as the date of the first occurrence of symptoms with subsequent ECG verification. In a minority of the cases, when atrial fibrillation had been diagnosed at the research center only and when further information was available on a more precise date of onset, we defined the date of onset as the midpoint of the time interval between examination at which atrial fibrillation was detected and the previous examination at the research center.

2.4. Vital status

Information on vital status of each participant was obtained on a weekly basis from the Central Population Register of the municipality of Rotterdam, from collaborating general practitioners, and by collecting information during follow-up examination rounds. If no information could be obtained from these sources, the Central Registry of Genealogy of the Netherlands was consulted. This national institute receives population registry records of all inhabitants of the Netherlands who have died.

2.5. Covariable assessment

Age at baseline was included in all analyses. Body mass index (BMI) was calculated by dividing weight in kilograms by height in squared meters (kg/m²). Blood pressure was measured twice at the right upper arm with a random zero Hg sphygmomanometer in the sitting position. Systolic and diastolic blood pressures were calculated as the average of the two consecutive measurements. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol levels were measured with an automated enzymatic method. Data on medication use were obtained during the home interview by copying the labels of all the medication used. Information on smoking status was also acquired from the home interview. Heart failure was assessed using a validated score based on the definition of heart failure by the European Society of Cardiology [27,28]. Prevalent chronic obstructive pulmonary disease (COPD) was obtained from the medical records, and defined as the diagnosis of COPD by a medical specialist [29]. Prevalent diabetes mellitus was defined as the use of anti-diabetic medication or a pre- or post-load serum glucose level of >11.0 mmol/L.

2.6. Population for analysis

The study population comprised 7983 persons. Persons who did not visit the research center at baseline and therefore did not have an ECG recorded were excluded (n = 894). Also those with missing baseline ECG data, due to technical problems or lack of qualified personnel, were excluded (n = 536). Furthermore 378 participants with prevalent atrial fibrillation at baseline were excluded from the analyses. This resulted in a population for analyses of 6175 participants. All participants were followed from their baseline ECG assessment in the Rotterdam Study (1990–1993) until the date of diagnosis of atrial fibrillation, the date of death, loss to follow up, or end of the study period (January 1st, 2008).

2.7. Statistical analyses

Because of the large difference in prevalence of atrial fibrillation between men and women, all analyses were stratified by sex. Participants were categorized as those having unrecognized MI on baseline ECG, those with clinically recognized MI at baseline, and as those without a history of MI. Baseline characteristics of all participants were compared according to these categories. We then assessed the association of recognized and unrecognized MI with atrial fibrillation, using Cox proportional hazards regression analyses. First, we adjusted only for age. Age-adjusted hazard curves are presented comparing the cumulative incidence of atrial fibrillation between the MI categories. Second, we additionally adjusted for the following cardiovascular risk factors at baseline: systolic and diastolic blood pressure, use of blood pressure lowering medication, BMI, total and HDL cholesterol, smoking status, diabetes mellitus, COPD, and heart failure. Finally, we adjusted for incident heart failure during follow-up (time-dependent). Approximately 5% of the participants had missing values for one or more covariates. These missing values were handled using the expectation maximization algorithm. All measures of association are presented with 95% CIs. Data were analyzed using the SPSS PASW statistical package, version 17.0 (IBM corporation).

3. Results

3.1. Baseline characteristics

Baseline characteristics of the study population are described in Table 1. The population included 2505 men of whom 142 were classified with an unrecognized MI and 270 with a recognized MI. Of the 3670 women, 193 were classified with an unrecognized MI and 112 with a recognized MI. Compared to those without a history of MI, participants with an unrecognized MI were older, had higher systolic and diastolic blood pressure, were more likely to smoke and to have heart failure independent of age. Men with unrecognized MI were also more likely to have diabetes than men without MI. Compared to participants with a recognized MI, participants with an unrecognized MI had a higher systolic blood pressure, were less likely to use blood-pressure lowering medication and were less likely to have been diagnosed with heart failure. Additionally, men with unrecognized MI were more likely to smoke than those with a recognized MI. During a mean follow-up of 11.7 years (SD 5.0), 727 participants, of whom 329 men, developed atrial fibrillation, and 2,301 died. During follow-up, 638 participants developed heart failure.

3.2. Unrecognized MI and risk of atrial fibrillation

Fig. 1 displays the age-adjusted hazard curves for developing atrial fibrillation for men and women separately, based on the presence of recognized and unrecognized MI. Compared to men without MI, men with unrecognized MI had a higher risk of atrial fibrillation (age-adjusted HR of atrial fibrillation: 2.36 (95% CI: 1.62 to 3.43) (Table 2). The age-adjusted HR of atrial fibrillation in men with recognized MI was 1.70 (95% CI: 1.26 to 2.31). Additional adjustment for the other covariables slightly attenuated the estimate to 2.21 (95% CI: 1.51 to 3.23). For unrecognized MI and remained unchanged for recognized MI. Finally, adjustment for heart failure during follow-up lowered the associations to 2.03 (95% CI: 1.38 to 2.97) for unrecognized MI and 1.48 (95% CI: 1.07 to 2.05) for recognized MI.
In women, unrecognized MI was not associated with atrial fibrillation. Adjusted for age, the HR was 0.99 (95%CI: 0.64 to 1.54), and additional adjustment for the other risk factors only slightly changed this estimate (HR: 0.92, 95%CI: 0.59 to 1.44). Recognized MI was significantly associated with atrial fibrillation in women, when adjusted for age (HR: 1.64, 95%CI: 1.02 to 2.65). However, after adjustment for other risk factors this association was no longer statistically significant (HR: 1.36, 95%CI: 0.82 to 2.26).

4. Discussion

4.1. Main findings

Our results indicate that unrecognized MI in men is associated with a more than two-fold increased risk of developing atrial fibrillation, compared to men without a history of MI. This association was independent of cardiovascular risk factor. In women, unrecognized MI was not associated with an increased risk of atrial fibrillation.

---

**Table 1**

Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No MI</td>
<td>Recognized MI</td>
</tr>
<tr>
<td>N</td>
<td>2093</td>
<td>270</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.2 (7.9)</td>
<td>68.8 (9.0)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>139 (22)</td>
<td>135 (20)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75 (11)</td>
<td>72 (10)</td>
</tr>
<tr>
<td>Blood pressure lowering drugs</td>
<td>445 (213)</td>
<td>185 (68.5)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.3 (1.2)</td>
<td>6.5 (1.2)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>1.2 (0.3)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 (2.9)</td>
<td>26.1 (3.1)</td>
</tr>
</tbody>
</table>

All values are means (standard deviations) or absolute numbers (%).

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; HDL, high-density lipoprotein; MI, myocardial infarction; N, number at risk.

* p-value < 0.05, compared with no MI.

**Table 2**

Hazard rates on the association of unrecognized MI with atrial fibrillation, stratified on sex.

<table>
<thead>
<tr>
<th></th>
<th>Model 1a</th>
<th>Model 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (CI)</td>
<td>HR (CI)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No MI</td>
<td>2093</td>
<td>248 (11.8)</td>
</tr>
<tr>
<td>Recognized MI</td>
<td>270</td>
<td>50 (18.5)</td>
</tr>
<tr>
<td>Unrecognized MI</td>
<td>142</td>
<td>31 (21.8)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No MI</td>
<td>3365</td>
<td>359 (10.7)</td>
</tr>
<tr>
<td>Recognized MI</td>
<td>112</td>
<td>18 (16.1)</td>
</tr>
<tr>
<td>Unrecognized MI</td>
<td>193</td>
<td>21 (10.9)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, Hazard rate ratio; MI, myocardial infarction; N, number at risk; n, number of atrial fibrillation events (% of N).

* Adjusted for age.

**Fig. 1.** Age-adjusted hazard curves for the risk of atrial fibrillation for men and women, separately.
4.2. Comparison with the literature

Unrecognized MI has previously been associated with an increased risk of cardiovascular and total mortality comparable to recognized MI [13,15–17]. Furthermore, unrecognized MI is reported to be associated with increased risks of morbidity, such as recurrent coronary heart disease [30,31], stroke [31], and heart failure [31]. These results were later replicated within the Rotterdam Study for stroke, [32] heart failure [33] and also dementia [34]. Like our current results, these studies showed that unrecognized MI was a strong risk factor for disease in men, but not in women.

Benjamin et al., previously showed that the association of recognized MI with atrial fibrillation was different for men and women [4]. They found that clinically recognized MI was significantly associated with atrial fibrillation in men, independent of cardiovascular risk factors. In women however, recognized MI was associated with atrial fibrillation after adjustment for age, but this association was no longer statistically significant after adjustment for other cardiovascular risk factors. Our results show a similar difference in prognosis between men and women for both recognized and unrecognized MI.

4.3. Possible mechanisms

Several mechanisms may explain the association of MI with atrial fibrillation. Possibly atrial dysfunction or atrial stretching in response to infarction plays a role. This can lead to increased atrial pressures and a restrictive filling pattern, which has previously been related to development of atrial fibrillation [35]. Moreover, in reaction to atrial stretching catecholamines are produced, which have previously been associated with atrial fibrillation [36]. Also it has been suggested that atrial fibrillation follows secondary to left ventricular dysfunction and hemodynamic disturbances after MI [37,38]. Finally, ischaemia might create both atrial fibrillation triggers as well as a substrate for atrial fibrillation maintenance [39]. It is unclear why the association of MI with atrial fibrillation is different between men and women. In our study, recognized MI was associated with AF in men and women after adjustment for age. In women this association did not remain statistically significant after adjustment for cardiovascular risk factors. It might be possible this can be explained by a lack of power. However it has also been suggested that in response to acute coronary ischemia women are relatively protected from apoplosis and experience less adverse cardiac remodeling than men [40]. It remains to be elucidated to what extent this contributes to the development of atrial fibrillation.

While for recognized MI the risk estimate was lower in women than in men, the most obvious difference between men and women was seen for unrecognized MI. It has been suggested that the pathophysiology of unrecognized MI is similar to those that go clinically recognized [18]. This suggests that the most likely explanation for the absence of the association of unrecognized MI with atrial fibrillation in women is a misclassification of this condition. Murabito et al. suggested that ECG abnormalities not caused by coronary artery disease but resulting from misplacement of ECG electrodes due to difficulties with lead placement owing to breast tissue, can be mistaken for MI [41]. Nevertheless, the reason behind the currently identified gender differences remains unexplained and deserve further evaluation.

Finally, our results suggest that the risk of atrial fibrillation is somewhat higher for those with unrecognized MI than for those with recognized MI. We also found that those with an unrecognized MI had higher systolic and diastolic blood pressure, were less likely to use antihypertensive drugs, and were more likely to smoke, compared to those with recognized MI. It is possible that lifestyle changes and treatment following the diagnosis of MI, lower the risk of atrial fibrillation and thereby explain why recognized MI is associated with a lower risk of atrial fibrillation than unrecognized MI.

4.4. Strengths and limitations

Strengths of this study are the population-based design, with a long-term follow-up of 11.7 years. We were able to use data from a large population that included 6175 participants of whom 335 had ECG characteristics matching an unrecognized MI at baseline and 692 who developed atrial fibrillation during follow-up. Also, at baseline we did not inform participants or their treating physicians about the finding of an unrecognized MI on their ECG. The decision reflected the perception at that time that an unrecognized MI was less severe than a recognized MI, and was motivated by a lack of evidence that treatment could effectively reduce the risk of subsequent cardiovascular disease [32]. Our results therefore adequately assess the natural history of unrecognized MI with atrial fibrillation in the general population. Since the fourth research visit in 2002 we started to report findings of unrecognized MI to the participants and treating doctors.

By combining multiple sources of data on the occurrence of atrial fibrillation we limited the chance of misclassification. It is possible that the classification of unrecognized MI includes some misclassification, for instance in the case of non-Q-wave MIs or Q-waves that have disappeared over time. Finally, because we were unsure of the exact date of the occurrence of the unrecognized MI, we used the date of the ECG as the date of unrecognized MI diagnosis. This restricts our findings to the long-term risk of atrial fibrillation. Finally we were not able to adjust our analyses for valvular disease or thyroid function which are known risk factors of atrial fibrillation.

5. Conclusion

Unrecognized MI as identified by ECG is associated with a more than twice increased risk of atrial fibrillation in men, compared to those without an MI. Atrial fibrillation is an important health problem. Subjects with unrecognized MI are not treated for the disease, while detection of the MI followed by lifestyle changes and appropriate treatment may lower the risk of atrial fibrillation.

Acknowledgments

The authors thank all the participants and staff of the Rotterdam Study, as well as the general practitioners and pharmacists of the Ommoord district for help with data collection and validation.

Funding

The Rotterdam Study is supported by the Erasmus Medical Center and Erasmus University Rotterdam; The Netherlands Organization for Scientific Research (NWO); The Netherlands Organization for Health Research and Development (ZonMW); the Research Institute for Diseases in the Elderly (RIDE); The Netherlands Heart Foundation; the Ministry of Education, Culture and Science; the Ministry of Health Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. This study was further supported by a grant from NWO/ZonMW (91876619).

Conflict of interest

The authors declare that there are no financial competing interests associated with this study.

References


