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Prevalence of electrocardiographic unrecognized myocardial infarction and its association with mortality

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ABSTRACT

Background: Identifying unrecognized myocardial infarction (MI) is important for secondary prevention. The aim of this study is to determine the prevalence and correlates of unrecognized MI and the association with mortality in the general population.
Methods: All participants ≥18 years participating in the Lifelines population, a three-generation Cohort Study and Biobank, were included ($n = 152{,}180$). Participants with unrecognized MI were matched with controls without MI (1:2) based on age and gender. Unrecognized MI was defined when no history of MI was reported in combination with electrocardiographic (ECG) signs corresponding to MI. A history of MI was defined as a reported history of MI in combination with ECG signs and/or the use of antithrombotic medication.
Results: MI was present in 1881(1.2%) of participants and was unrecognized in 431 (22.9%) participants. Under the age of 50 years, percentages of unrecognized MI relative to the total amount of MI were 34% and 55% in men and women respectively. Compared to recognized MI, classical cardiovascular risk factors were less prevalent in participants with unrecognized MI. During a median follow- up time of 5, 4 and 4 years, 4.4%, 6.4% and 2.2% of participants with unrecognized MI, recognized MI and without MI died, respectively. In a multivariable logistic regression unrecognized MI was an independent predictor of death.
Conclusions: The prevalence of unrecognized MI is substantial and classical cardiovascular risk factors are less prevalent in participants with unrecognized MI. Nevertheless, unrecognized MI is associated with mortality. Risk stratification and early diagnosis is necessary to reduce the morbidity and mortality after MI.

1. Introduction

Coronary heart disease accounts for approximately one-third to one-half of the total cases of cardiovascular diseases (CVD) [1]. Earlier studies reported that 22% to 64% of the patients with coronary artery disease experience an unrecognized myocardial infarction (MI), with atypical or no symptoms of MI at all [2–5]. These patients do not receive secondary prevention and are at increased risk of clinical CVD compared to individuals without previous MI [6–9] and even compared to subjects in whom MI was recognized [10]. In addition, unrecognized MI has been associated with an increased risk for all-cause mortality in the Rotterdam study [11] and Atherosclerosis Risk in Community (ARIC) study [4]. The ARIC study presented an overview of (silent) MI, only in patients with the age between 45 and 64 years old [4]. The Rotterdam study observed an old population (>55 years of age) and dates back to the 1990s [11]. However, major changes in lifestyle, awareness and advances in diagnosis and treatment have since been made. We aimed to investigate the prevalence and correlates of unrecognized MI in the general adult population (≥18 years) and its association with mortality in the Lifelines Cohort study. The Lifelines Cohort study is a contemporary observational study including over 165,000 participants of the northern of the Netherlands and is designed to greater our understanding of healthy ageing in the 21st century.

2. Methods

2.1. Study design and subjects

Lifelines is a cohort and biobank that is open for all researchers. Information on application and data access procedure is summarized on www.Lifelines.net. The study design and rationale of Lifelines were previously described in detail [12–14]. Lifelines is a multidisciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological

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factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. Persons willing to participate received an informed consent form and a questionnaire and were invited to visit one of the twelve Lifelines Research sites. During the baseline visit the signed informed consent was taken in. Blood and 24 h urine samples of all participants were placed on 4 °C and transported to the Lifelines laboratory in Groningen. Drug use was collected in the questionnaire and categorized using the general Anatomical Therapeutic Chemical Classification System (ATC) codes. In addition, participants underwent physical examination. For the current study, all participants included were aged 18 years or above.

2.2. Definition (unrecognized) MI

During the baseline visit a 12-lead electrocardiogram (ECG) was made. All ECGs were initially automatically evaluated by the WelchAllyn CardioPerfect (version 1.6.2.1105) software. When automatic evaluation of the ECG was classified as abnormal (possible MI), the ECG was reviewed by an interventional cardiologist based on: any Q wave in leads V2–V3 ≥ 0.02 s or QS complex in leads V2 and V3. Q wave ≥0.03 s and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF or V4–V6 in any two leads of a contiguous lead grouping (I, aVL; V–V6; II, III, aVF). R wave ≥0.04 s in V1–V2 and R/S ≥ 1 with a concordant positive T wave in absence of conduction defect [15]. After recognition of the unrecognized MI, the general practitioner of the participant was informed. Unrecognized MI was defined when participants did not report a medical history of MI in the questionnaire (collected during the baseline visit of the LifeLines Cohort study) in combination with ECG signs corresponding to MI. A history of MI was defined as participants reporting a history of MI in the questionnaire in combination with ECG signs of MI and/or the use of antithrombotic medication. When there was no evidence of an infarction on ECG, participants were classified as controls. After this, a matched control group was made based on age and gender (1:2).

2.3. Other definitions

Conduction disorder included left or right bundle branch block, left anterior or posterior fascicular block or intraventricular conduction delay. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥90 mm Hg or use of blood pressure–lowering drugs. Hypercholesterolemia was defined as total cholesterol ≥193 mg/dL (5.0 mmol/L) and self-reported myocardial infarction, a total cholesterol ≥251 mg/dL (6.5 mmol/L) or use of cholesterol-lowering medications. Diabetes mellitus was considered to be present if diabetes mellitus was self-reported or fasting (8–14 h) glucose value was ≥126 mg/dL (7.0 mmol/L) or a random or postload glucose value was ≥200 mg/dL (11.1 mmol/L) or if a participant used anti-diabetic medication. Kidney disease was defined as estimated Glomerular Filtration Rate (eGFR) ≥60 mL/min/1.73 m^2 with 24 h albumin >30 or eGFR <60 mL/min/1.73 m^2. Smoking included current and former smokers and was obtained from a questionnaire. Family CVD was defined as the presence of CVD in first degree relatives acquired before the age of 65, obtained from a questionnaire. A medical history of chest pain, coronary artery bypass surgery or percutaneous coronary intervention was assumed as present if participants reported chest pain in questionnaire. Self-reported heart failure was validated with medication use or the implantation of a cardiac device. Excessive alcohol use was defined as more than fourteen alcoholic units per week for males and >7 alcoholic units per week for females. CHADSVASC score was generated with a history of *C*ongestive heart failure, *H*ypertension, *A*ge ≥ 75 years, *D*iabetes Mellitus, prior *S*troke or thromboembolism, *V*ascular disease, *A*ge between 65 and 74 years and *Sex Category* [16]. The definition for atrial fibrillation consisted of self-reported atrial fibrillation with the use of vitamin K antagonist or other oral anticoagulants or the presence of atrial fibrillation on ECG with the use of anticoagulants or a CHADVASC < 2. Framingham risk score was generated with age, total cholesterol, smoking, HDL-cholesterol and systolic blood pressure [17]. Drug use was collected in the questionnaire and categorized using the general Anatomical Therapeutic Chemical Classification System codes. Information about mortality was obtained from the municipal personal records database.

2.4. Statistical analyses

Patients with unrecognized MI were randomly matched with two controls using the *ccmatch* command in Stata based on age in years at baseline and gender. Dichotomous variables are presented as percentages, and continuous variables as mean with standard deviation (SD). Continuous variables not normally distributed were presented as medians with their interquartile ranges (IQRs). The Chi-square test was used to compare frequencies of events in participants with unrecognized MI and recognized MI or participants with unrecognized MI and without MI. Continuous variables not normally distributed and differences in continuous variables between participants with unrecognized MI and recognized MI or participants with unrecognized MI and without MI were tested by two-sample Wilcoxon rank-sum (Mann-Whitney) test.

Downwards-stepwise multivariable conditional logistic regression analyses were performed to determine correlates of baseline variables and unrecognized MI (cutoff for entry 0.10; and removal 0.05). To validate the model, forward-stepwise multivariable conditional logistic regression was performed as well (cutoff for entry and removal set at a significance level of 0.05). This analysis takes the matched structure of the data into account. Medication and biomarkers in the blood were not included in regression analyses because of the correlation with cardiovascular risk factors and diseases. Univariate conditional regression analysis was reported with *p*-value and when significant, concomitant odds ratios (OR), and confidence intervals were presented. Univariate variables with *p*-value ≤ 0.10 were included in the multivariable conditional logistic regression. Multivariable logistic regression analyses were performed to determine if unrecognized MI was an independent predictor of death corrected for age, sex, hypertension, diabetes and heart rate. Due to privacy concerns, only death year was available, which did not enable us to perform a survival analyses. All statistical analyses were performed using Stata version IC 13, StataCorp, College Station, Texas.

3. Results

Fig. 1 shows a flowchart of our study population. Baseline ECGs were available in 152,124 participants. In 20.9% of cases (31,724 out of 152,124) automatic evaluation of the ECG was classified as abnormal. ECGs of 3556 participants (701 participants with "possible" unrecognized MI, 1395 controls and 1460 participants with recognized MI) were reviewed by an interventional after which a matched control group was made. MI was present in 1881 (1.2%) participants. Unrecognized MI was present in 431 (22.9%) and recognized MI in 1450 (77.1%) participants. In the group under the age of 50 years, percentages of unrecognized MI relative to the total number of MI were 34% (92 out of 268) and 55% (83 out of 150) in men and women respectively. Proportions of 20%, 16% and 13% of unrecognized MI relative to the total number of MI were determined among participants with an age of 45, 55 and 65 years and older, respectively. In men and women the percentage of unrecognized MI relative to the total number of MI decreased with age but was significantly higher for women compared to men in from the age of 40 years ($p < 0.001$, Fig. 2).

Table 1 shows the baseline characteristics of participants with unrecognized and recognized MI. Participants with unrecognized MI were younger (55 years versus 62 years, $p < 0.001$) and more often female (50% versus 24%, $p < 0.001$) compared to participants with recognized MI.

3.1. Correlates of unrecognized MI

Compared to recognized MI, classical cardiovascular risk factors were less prevalent in participants with unrecognized MI (Table 1). Participants with unrecognized MI less often had a history of heart failure, atrial fibrillation, chest pain, percutaneous coronary intervention or coronary artery bypass surgery compared to participants with recognized MI. Compared to controls, participants with unrecognized MI more often had a history of hypertension ($p = 0.014$) or diabetes ($p < 0.001$) and reported slightly more often a history of chest pain ($p = 0.081$, Table 1 in Ref. [18]).

Kidney function, as assessed by eGFR was higher in participants with unrecognized MI, and glucose levels were lower in participants with unrecognized MI compared to participants with recognized MI. Total cholesterol, HDL-cholesterol and LDL-cholesterol were higher in participants with unrecognized MI, but the value of triglycerides were lower compared to participants with recognized MI.

The use of blood pressure lowering medication, cholesterol lowering medication and platelet inhibitors was more common in participants with recognized MI compared to participants with unrecognized MI. In participants with unrecognized MI, the use of cholesterol lowering medication was comparable to controls and the use of blood pressure lowering medication and platelet inhibitors slightly higher compared to controls.

In multivariable logistic conditional regression analysis heart rate and diabetes were independent correlates for the presence of unrecognized MI (Table 2). Framingham risk score was not an independent predictor of unrecognized MI ($p = 0.292$).

3.2. Unrecognized MI and mortality

Median follow-up time was 5 years (IQR 3–6 years) in patients with unrecognized MI, 4 years (IQR 3–5 years) in patients with recognized MI

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