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Sex differences in the non-invasive risk stratification and prognosis after myocardial infarction

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Abstract

Background: Women have unfavorable prognosis after myocardial infarction (MI). This text describes sex differences in mortality and in the power of risk predictors in contemporarily-treated MI patients.
Methods: A population of 4141 MI patients (26.5% females) was followed up for 5 years. Effects of sex and age on total mortality were investigated by multivariable Cox analysis. Mortality predictors were investigated by receiver-operator characteristics analysis. Stepwise multivariable Cox regression was used to create sex-specific predictive models.
Results: Thirty-day mortality was 1.5-fold higher in women. However, sex was not a significant mortality predictor in a model adjusted for age. Predictors for 5-year mortality performed differently in male and female patients. In women, a sex-specific model provided better risk stratification than a sex-neutral model.
Conclusion: The unfavorable prognosis of female MI patients can be explained by advanced age. Sex-specific predictive models might improve risk stratification in female survivors of acute MI.

Keywords: Myocardial infarction; Risk stratification; Gender; ECG

Introduction

Myocardial infarction (MI) is a major cause of morbidity and mortality in the developed world [1,2]. The mortality risk in women suffering from MI is higher than that in men [3]. One obvious explanation for this disparity is that on average, women are about 10 years older than men at the time of MI. Other factors, such as gender bias in clinical approach to MI treatment [4], inadequate MI diagnosis in women due to atypical presentation [5], and lower rate of revascularization procedures in women [6] have also been discussed to explain the unfavorable outcome of MI in women.

Sex differences in the physiology of coronary artery disease (CAD), such as a higher prevalence of non-obstructive CAD in women [7], may also contribute to the outcome differences. Furthermore, interventional treatments recommended by the guidelines [1,2,8,9] might be less effective in females than in males due to the smaller diameter of the coronary arteries in the former [10].

Patients surviving the acute MI phase are at risk of subsequent death due to re-infarction, arrhythmia, or heart failure. Corresponding non-invasive risk predictors are presently intensively researched [11]. While left-ventricular ejection fraction remains the core of current post-MI risk assessment, its limits are well recognized and several other parameters have been evaluated for their potential to improve risk stratification [11–18]. A systematic analysis of sex differences in the predictive power of these parameters has not yet been reported.

This study re-assessed the mortality risk in contemporarily-treated MI patients of either sex and investigated whether the

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risk prediction in acute MI survivors might be improved by sex-specific predictive models.

Methods

Study cohort

The present study used data of patients enrolled in two separate cohort studies, namely the ISAR study [19] and the ART study [20]. Enrolment took place between January 1996 and March 2005 with last follow-up in May 2010. Patients were recruited at two centers in Munich (Klinikum rechts der Isar and Deutsches Herzzentrum München). We included patients suffering from acute MI within 4 weeks before enrolment. MI diagnosis was defined as two or more of (i) chest pain for ≥20 min, (ii) creatine kinase-MB above the doubled upper normal limit of our laboratory, (iii) ST-segment elevation of 0.1 mV in two or more limb leads and/or 0.2 mV in two or more contiguous precordial leads at the time of hospital admission. In the present analysis, we have not applied any upper age limit and also included patients who were not in sinus rhythm.

The study consisted of two parts, dealing with sex differences in the outcome (part A), and sex differences in the power of risk predictors (part B). Fig. 1 shows the patient flow. Part A involved all patients admitted to the hospital with acute MI (cohort A), whereas part B included only patients who (1) survived the first month after admission, (2) had no indication for secondary prevention implantable cardioverter/defibrillator (ICD) therapy, and (3) had a Holter ECG available (cohort B).

For parts A and B, the primary endpoint was all-cause mortality at 30 days and at 5 years, respectively.

The study was approved by the local ethics committee. Oral (ISAR study) or written (ART study) informed consent was obtained from all patients or from their legal caregivers.

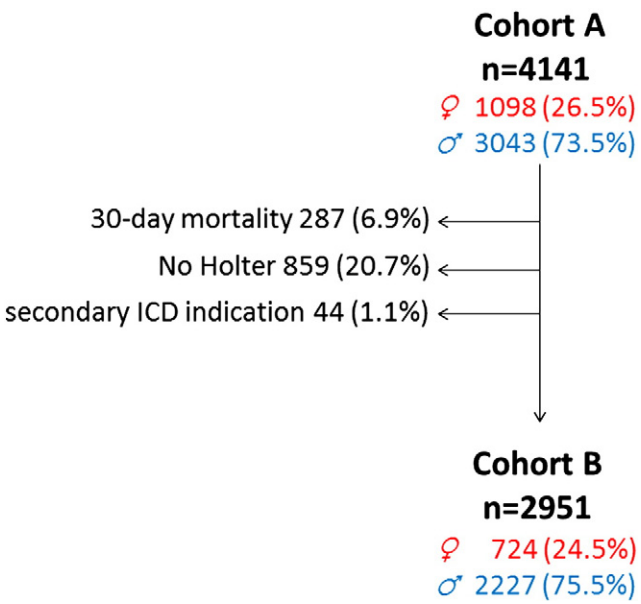

Fig. 1. Patient flow chart. (Color illustration online.) ICD: implantable cardioverter/defibrillator.

Clinical variables

At admission, a standard 12-lead ECG was recorded and blood pressure, heart rate, serum creatinine and cardiac enzymes were measured in all patients. Left ventricular ejection fraction (LVEF) was quantified either by angiography or by echocardiography. Patients were considered to have diabetes if already diagnosed or if receiving treatment with diet, oral medication or insulin or if fasting blood glucose concentration repeatedly exceeded 11 mmol/L.

Holter and ECG variables

Holter ECGs were recorded during the initial hospitalization for MI using equipment by Oxford instruments (n = 829, 3 channels), Reynolds Medical (n = 1925, 3 channels), and Mortara Instrument (n = 197, 12 channels). The recordings were automatically analyzed by corresponding analytical systems. Subsequently, visual verification and, where appropriate, manual correction was made of QRS detections and classifications (normal, ventricular ectopic, and supraventricular ectopic) by experienced technicians.

Risk predictors derived from the Holter ECG included mean heart rate, number of ventricular premature complexes (VPCs) per hour, heart rate variability triangular index (HRVTI) [12], heart rate turbulence [21] slope (TS) and onset (TO), heart rate deceleration capacity (DC) [22], and Holter-derived nocturnal respiratory rate [16,17]. QRS width and corrected QT interval (QTc; calculated according Bazett's formula) were obtained from a standard 12-lead ECGs.

Follow-up and endpoints

Clinical follow-up appointments were scheduled approximately every 6 months. If a patient did not attend a planned appointment, contact was made via mail, telephone or through the attending general practitioner. If none of these channels were successful, the local population registry either provided a new address of the patient or confirmed that the patient was deceased. If a patient could neither be contacted nor his/her death confirmed during the first year of follow-up, he/she was considered lost to follow-up. If this happened later in follow-up, the patient was censored at the time of last contact.

Statistics

Continuous variables are presented as median and interquartile range (IQR). Categorical data are presented as absolute frequencies and percentages. Survival curves were estimated by the Kaplan–Meier method and compared using the log-rank test. Univariable and multivariable Cox proportional hazards models were used to assess the association of predictors with mortality. Receiver-operator characteristics (ROC) curves were used to evaluate the predictive power of continuous parameters and risk scores and quantified by calculating the area under the curve (AUC). Optimum dichotomies of continuous variables were determined as the maximum of the log-rank statistics. The sensitivities achieved by the different models at a fixed specificity of 90% were compared by the McNemar test [23]. A stepwise multivariable Cox regression was performed separately in men and women to investigate whether sex