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Long-term outcome and risk assessment in premature acute myocardial infarction: A 10-year follow-up study

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ABSTRACT

Background: Premature acute myocardial infarction (AMI) is a rare disease carrying significant morbidity and mortality. Existing data on outcome in these patients is based on retrospective analysis of angiographic reports or refer to time periods with incomparable treatment regimes, making them unusable for risk assessment in times of widespread use of reperfusion therapy. Aim of this study was to assess the outcome of premature AMI in a prospectively recruited study population enrolled in the times of modern reperfusion therapy.
Methods: We included 102 consecutive AMI survivors (≤40 years) in this prospective multicentre study. Outcome was assessed via retrieval query of the Austrian Death Registry and the centralized patient management system of Vienna.
Results: During a median follow up time of 10.3 years (IQR:8.9–11.1), 23% of all patients experienced MACE, of those 6% died, 17% experienced re-AMI and 5% patients an ischemic stroke. Furthermore, forty patients underwent cardiac re-catheterization and twenty-five needed recurrent revascularization. MACE were associated among the classic cardiovascular risk factors with elevated levels of HbA1c (adj. HR 1.32; 95%CI 1.06–1.64; $P = 0.012$), total cholesterol (adj. HR 2.16; 95%CI 1.27–3.48; $P = 0.004$), and c-reactive protein (adj. HR 1.67; 95%CI 1.29–2.17; $P = 0–003$) for an increase of 1-standard deviation.
Conclusion: Although myocardial re-infarction was the driving force of morbidity in premature myocardial infarction, we observed an excellent long-term survival opposed to previous reports. We found that persistence risk factors rather than the clinical risk profile at baseline influences the outcome in these patients, emphasizing the importance of secondary prevention in young patients after AMI.

1. Introduction

Although premature myocardial infarction is a rare disease with a prevalence of 2% to 6% of all acute myocardial infarctions (AMI), it carries a high morbidity that translates into excessive public healthcare expenses due to the wide range of years lived with disability (YLDs) [1]. The clinical profile of patients with premature AMI is depicted by intensive cigarette consumption, metabolic syndrome and an age specific risk lipid phenotype that characterized by a predominance of elevated triglyceride-rich lipoproteins [2–5].

Prognosis in premature myocardial infarction is difficult to assess, as most evidence is based on retrospective analysis of angiographic reports [6–8], only short-term follow up [6,9] and is mostly limited to patient cohorts from decades before the widespread implementation of reperfusion therapy [2,10,11]. Moreover, most studies characterized outcomes of premature myocardial infarction against older patient cohorts, a study design that is not suitable to identify those young patients at higher risk for recurrent events [10]. Available data from the pre-PCI era reveal a markedly high mortality, but treatment options have substantially changed and its uncertain if occurrence of myocardial infarction at a young age still carries the particularly ominous prognosis and requires an more aggressive approach to management different from that used in older patients [12,13]. Effective prevention in these patients needs a reasonable strategy based on knowledge of re-event rate, predictors of outcome and importance of different modifiable risk factors.

Therefore, we aimed to assess the outcome of premature myocardial infarction in a prospectively recruited very young study population (≤40 years of age) enrolled in the era of well-established percutaneous

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coronary intervention therapy. Furthermore, we aimed to identify clinical factors associated with an unfavourable outcome and to assess the prognostic value of modifiable conventional risk factors in patients with premature AMI.

2. Material and methods

2.1. Study population

We prospectively enrolled patients with acute myocardial infarction at a very young age (≤40 years of age) for this multicenter case-control study. All patients were recruited at the Vienna General Hospital, a university-affiliated tertiary care center, or the Wilhelminen Hospital Vienna between September 2004 and March 2008 as previously published [5]. Myocardial infarction was diagnosed according to the respective guideline of the *European Society of Cardiology* [14]. The study protocol complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical University of Vienna. Upon enrollment study participants completed a study questionnaire encompassing variables such as medical history and medication, family history, life style, physical activity, and biometric data, administered and reviewed by a physician. All participants gave written informed consent.

2.2. Clinical risk factory and laboratory measurements

Traditional cardiovascular risk factors were recorded according to the respective guidelines as previously described [15]. Family history for acute myocardial infarction and life-style characteristics were assessed via the patients' questionnaire. Family history was interpreted as positive, if any first-degree relatives have experienced acute myocardial infarction before the age of 55 for men or 65 for women. Patients were classified as diabetics if they either had a history of diabetes, received medication for diabetes, or if HbA1c values exceeded 6%. Arterial hypertension was diagnosed if patients had a history of hypertension, if they were already taking antihypertensive medication, or if the blood pressure was greater equal 135/85 mmHg at rest in at least two measurements. Refractory arterial hypertension was defined as hypertension at hospital discharge despite antihypertensive medication. Venous blood samples of each patient were obtained within 48 h from infarction. Blood draws were taken after 12–14 h overnight fasting and subsequently analysed according to the local laboratory standard procedures. Total cholesterol (TC), HDL-cholesterol (HDL-C), and triglycerides (Tg) were measured enzymatically as described previously [16–18]. LDL-cholesterol (LDL-C) was calculated according to the Friedwald formula. In cases of severe hypertriglyceridemia (Tg ≥400 mg/dL), LDL-C was measured directly as previously described [19].

2.3. Clinical follow-up and study endpoints

Mortality was determined via retrieval query of the Austrian Death Registry. Austrian law stipulates that all deaths of Austrian citizens (also in foreign countries, if reported to Austrian officials) have to be recorded in the central Austrian death registry, which allows an almost complete follow up of all patients [20]. A systematic exploration of the centralized patient management system of Vienna (AKIM- AKH-Informationsmanagement) was performed to obtain information on re-hospitalizations, acute myocardial re-infarction, and stroke. This system offers a comprehensive chronological overview of patient data, documents, diagnoses and services as well as laboratory results acquired in Vienna general hospital as well as in every hospital of the Vienna hospital association (KAV). MACE was defined as composite endpoint of all-cause death, myocardial re-infarction and stroke and selected as primary study endpoint.

2.4. Statistical analysis

Continuous data were presented as medians and interquartile ranges and compared using Mann– Whitney statistics. Discrete data were presented as counts and percentages and analysed using a $\chi 2$ test. Univariate and multivariate Cox proportional hazard regression analysis were used to determine the impact of traditional cardiovascular risk factors and different laboratory factors on MACE. To account for potential confounding effects, we adjusted for: age, body-mass index, hypertension, Hba1c, eGFR and active smoking. Results were presented as the hazard ratio (HR) for a 1-standard deviation (SD) increase of continuous variables with the respective 95% confidence intervals (95% CI). The discriminatory power of the respective variables was assessed using receiver operating characteristic (ROC) analysis. Estimated GFR was calculated using the Cockcroft-Gault formula. Two-sided *P*-values below 0.05 indicated statistical significance. SPSS 23.0 was applied for statistical analysis (IBM corp., Chicago, USA).

3. Results

3.1. Baseline characteristics and clinical endpoints

Overall 102 premature myocardial infarction patients were enrolled during the initial study period. Twenty-three per cent of all patients ($n = 24$) experienced MACE during a median follow-up of 10.3 years (IQR: 8.9–11.1). Of those, seventeen (17%) experienced re-myocardial infarction, five patients (5%) experienced an ischemic stroke and six patients (6%) died. Cardiovascular causes accounted for four of the observed deaths (Fig. 1). We identified 40 patients (39%) that underwent cardiac re-catheterization and 25 of these patients (24%) needed recurrent revascularization (Fig. 2). Detailed baseline characteristics and distribution of conventional risk factors for patients grouped by the occurrence of MACE are shown in Table 1.

3.2. Established cardiovascular risk factors and major-adverse cardiovascular events

We observed a high prevalence of established cardiovascular risk factors in our young study population e.g. active smoking (71%), arterial hypertension (39%) and DM II (27%). Patients experiencing MACE displayed a significantly higher BMI (28.4 [IQR 26.5–33.1] vs. 27.0 [23.7–29.7]; $p = 0.0030$) as well as HbA1c (5.7% [IQR 5.5–7.6] vs. 5.5% [IQR 5.3–5.7]; $p = 0.019$). There was no statistical significance in allocation of male gender ($p = 0.14$), positive family history for CAD ($p = 0.90$), active smoking ($p = 0.56$) between patients with and without MACE.

In the univariable Cox regression analysis DM II was the strongest predictor of outcome among conventional risk factors with a crude hazard ratio (HR) of 2.36 (95% CI, 1.07–5.28, $p = 0.036$). This effect was even more pronounced after adjustment for potential confounders with an adjusted HR of 4.12 (95% CI, 1.33–12.80, $p = 0.014$). Concomitantly HbA1c predicted outcome with a crude hazard ratio of 1.27 (95% CI, 1.06–1.54, $p = 0.011$) and an adjusted HR of 1.32 (95% CI, 1.06–1.64, $p = 0.012$). Beside diabetes only refractory hypertension at discharge had a significant predictive value in the crude analysis. Detailed results of the univariable and multivariate Cox regression analysis for conventional risk factors and laboratory measurements variables are displayed in Table 2.

3.3. Enzymatic infarct size and major-adverse cardiovascular events

Peak values of creatine kinase, creatine kinase myoglobine binding isoenzyme and troponin levels were utilized to reflect severity of

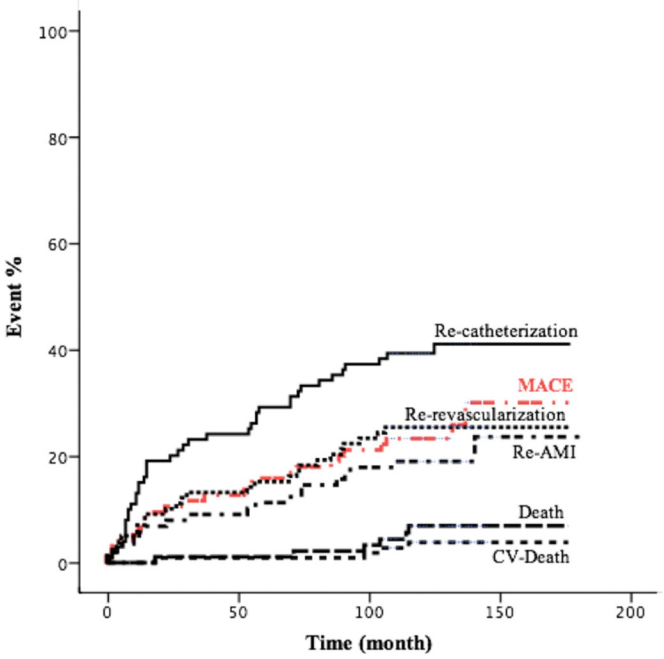

Fig. 1. Kaplan Meier Time-to-Event curve for the occurrence of cardiovascular death, all-cause death, repeated acute myocardial infarction (Re-AMI), re-vascularization, major adverse cardiac events (MACE) and re-catheterization.

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