SEMMELWEIS EGYETEM

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Ph.D. értekezések

3391.

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Hormonális szabályozó mechanizmusok

című program

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FACTORS BEYOND TRADITIONAL PREDICTORS INFLUENCING OUTCOMES FOLLOWING ACUTE CORONARY SYNDROME

PhD thesis

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Budapest

2025

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List of Abbreviations

ACEi - Angiotensin-Converting Enzyme Inhibitor,

ACS - Acute Coronary Syndrome

AF - Atrial Fibrillation

aHR - Adjusted Hazard Ratio

ARB - Angiotensin Receptor Blocker

ASA - Acetylsalicylic Acid

BB - Beta-Blocker

CABG - Coronary Artery Bypass Graft

CAD - Coronary Artery Disease

CCB - Calcium Channel Blocker

CCR - Comprehensive Cardiac Rehabilitation

CI - Confidence Interval

CPR - Cardiopulmonary Resuscitation

CVD - Cardiovascular Disease

DBP - Diastolic Blood Pressure

DM - Diabetes Mellitus

ECG – Electrocardiogram

GFR - Glomerular Filtration Rate

HF - Heart Failure

IQR - Interquartile Range

MI - Myocardial Infarction

MINOCA - Myocardial Infarction with Non-Obstructive Coronary Arteries

MWU - Mann-Whitney U Test

NSTEMI - Non-ST-Elevation Myocardial Infarction

PCI - Percutaneous Coronary Intervention

SBP - Systolic Blood Pressure

SD - Standard Deviation

STEMI - ST-Elevation Myocardial Infarction

VSR - Ventricular Septal Rupture

1. Introduction (with the scientific background and the relevant literature)

Coronary artery disease (CAD) stands as the leading cause of mortality worldwide (1). Over recent decades, significant progress has been made in the management of myocardial infarction (MI), notably through advancements in emergency care, refined percutaneous intervention techniques, enhanced equipment, and improved strategies for risk factor modification. These developments have contributed to better patient prognoses (2-6). As a result, the population of individuals living with stable disease after an MI has grown substantially. Despite these improvements, patients who have survived an MI continue to face an elevated risk of future cardiovascular events. Yet, there remains a lack of comprehensive data on the effectiveness of secondary prevention strategies in this group (7, 8).

Comprehensive cardiac rehabilitation serves as an essential component of secondary prevention for patients recovering from acute coronary syndrome. This multidisciplinary, individualized program incorporates physical exercise, management of cardiovascular risk factors, lifestyle adjustments, dietary guidance, smoking cessation support, psychological care, and assistance with returning to work. Numerous studies have demonstrated that cardiac rehabilitation lowers mortality and recurrence rates of myocardial infarction and enhances functional capacity, psychological well-being, and overall quality of life (9-11). Despite its proven effectiveness and strong recommendations (3, 4), participation rates in such programs remain alarmingly low (12, 13). Referral to CCR is a standard procedure during hospitalization for the initial event; enrollment occurs either during the hospital stay or within 30 days after discharge, with rehabilitation provided in institutional or inpatient settings across Hungary. CCR includes counseling on physical activity, support for quitting smoking, guidance on healthy nutrition, weight management, blood pressure and cholesterol control, and advice about following prescribed medications (14-16). In Hungary, the National Health Insurance Fund covers the full cost of the rehabilitation program.

Although cardiovascular mortality has decreased in recent decades, this positive change affects women less than men(17). Women continue to experience poorer outcomes following acute coronary syndrome (ACS), with higher rates of mortality (18). Despite these notable sex-based disparities in prognosis and clinical outcomes, there remains a lack of research exploring the underlying causes, and women are frequently underrepresented in clinical trials, including those supporting US Food and Drug

Administration drug approvals for certain cardiovascular diseases (19). Nonetheless, studies centered on older patient groups have not identified this disparity (20). Women with ACS are generally of more advanced age and tend to have additional comorbidities, such as high blood pressure, abnormal cholesterol, and diabetes (21, 22). Moreover, they are more likely to report atypical or noncardiac chest pain, or to mistake their symptoms for other conditions such as reflux disease (23), as a result, their condition is often misdiagnosed at first, or they may receive a lower standard of care, leading to an initial misdiagnosis or the offering of lower levels of care.

Women tend to delay seeking medical help after the onset of symptoms, and the diagnostic process is often complicated by more subtle or atypical changes in their electrocardiograms and troponin levels (24-29). Additionally, women are more likely to experience non-ST-segment myocardial infarction (NSTEMI), myocardial infarction with non-obstructive coronary arteries (MINOCA), spontaneous coronary artery dissection, coronary artery spasm (30-33), plaque erosion, and coronary thrombosis (34). These conditions can make diagnosis more difficult, delay treatment decisions, and ultimately impact outcomes.

Several smaller studies have indicated that women are less likely to receive timely percutaneous revascularisation (35-38). Female patients also face a greater risk of bleeding complications related to percutaneous coronary intervention (PCI), cardiogenic shock, and mechanical complications. Furthermore, women often present with a higher Killip class at admission(39, 40). During and following hospitalization, women are prescribed guideline-recommended secondary prevention medications less frequently (3, 4, 41) and are less likely to be referred to or participate in cardiac rehabilitation programs (42).

2. Objectives

The principal objective of this research is to evaluate the impact of Comprehensive Cardiac Rehabilitation (CCR) on the mid- and long-term outcomes for early survivors of acute coronary syndrome (ACS) in Hungary. Additionally, the study analyses sex-related differences in the care and prognosis associated with ACS.

The specific objectives pertaining to the rehabilitation aspect of the study are outlined as follows:

1. Assessment of Mortality Rates:
   - To determine the all-cause mortality rates at one year and five years following myocardial infarction (MI) among patients who participated in CCR, as compared to those who did not engage in the program.

2. Evaluation of Participation Rates:
   - To investigate participation rates in CCR among various subgroups of ACS patients, with particular emphasis on those diagnosed with ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI).

3. Examination of CCR Efficacy:
   - To evaluate the efficacy of CCR in improving clinical outcomes, specifically regarding the reduction of recurrent ACS events and overall patient survival rates.

The specific objectives addressing sex-related differences in treatment and prognosis for ACS are as follows:

1. Identification of Mortality Predictor:
   - To analyse factors influencing mortality, which include demographic variables (age, sex) and pertinent clinical characteristics (diabetes, cardiogenic shock).

2. Assessment of Sex Differences in Outcomes:

- To examine sex-related disparities in clinical outcomes among ACS patients, particularly how these differences may affect prognosis and recovery trajectories.

3. Evaluation of Participation Disparities:

- To investigate differences in participation rates in CCR between male and female patients, with the intention of understanding the implications for the development of tailored rehabilitation strategies.

By fulfilling these objectives, this study endeavors to provide valuable insights into the effectiveness of CCR in improving the prognosis of ACS patients and to enhance understanding of the role of sex in patient outcomes.

3. Methods

Data Source

Since January 2014, it is mandatory in Hungary to record all patients presenting with ACS in the National Myocardial Infarction Register. By September 2022, the database contained information on 155,000 events involving over 130,000 patients, forming the basis of our study. We conducted a retrospective analysis using these registry data. Because the database is publicly accessible and strictly anonymized, ethical approval was not required for this research. The study adhered to the human subject protection guidelines of the Local Ethical Committee at the Gottsegen National Cardiovascular Center, ensuring participant safety and privacy throughout the research process.

Study Population and Analytical Cohort

There were 76,153 cases entered into the register from 2014 until 2019.

Regarding sex-related analysis, the average duration of follow-up was 3.6 years (standard deviation: 2.4 years) as of March 25, 2022. Sex was defined as the classification associated with the binary categories of sex assigned at birth.

Our study focused on cardiac rehabilitation and analysed the data of early survivors only; therefore, 66,095 patients were included in our analysis (alive after 30 days of the index event). We excluded those patients who died in the first month following the index event to assess the efficacy of rehabilitation in a population that was stable enough to survive the initial critical period after the MI. The mean time (SD) of follow-up was 4.1 years (2.1 years).

Primary Outcome, statistical analysis

Our primary outcome was all-cause mortality; survival time in days was calculated from the date of the initial diagnosis of MI. Data with a low level of availability, including variables such as smoking and anthropometric measurements, were excluded from the analysis. Baseline characteristics were summarized as median (interquartile range) for continuous variables and as number (percentage) for categorical variables. Differences in individual and disease characteristics between subgroups were assessed using the Mann-Whitney U-test for continuous variables and the $\chi 2$ test for categorical variables. Correlation tests were conducted to eliminate the potential for cross-correlation among the parameters analysed. Binary logistic regression, Cox regression, Kaplan-Meier curves, and a log-rank test were used to assess the difference in all-cause mortality and tendencies for CR referral; $p<0.05$ was considered statistically significant. All statistical analyses were performed in SPSS Statistics, version 29.0.2.0 (IBM Corp.)

4. Results

Effect of a Comprehensive Cardiac Rehabilitation Program on the prognosis of early survivors of acute coronary syndrome

Patient characteristics

Data from 66,095 patients were analysed; their median age was 66 years, 61% were male, the prevalence of diabetes mellitus was 33%, 18% of patients had a history of ACS, and 5% had prior surgical revascularisation (CABG). 0.7% of the whole patient group was in cardiogenic shock on admission. The type of ACS was ST-elevation myocardial infarction (STEMI) in 44.1% of cases. The remaining patients had non-ST-elevation MI (NSTEMI). Patients were admitted directly to a PCI-capable hospital in 79% of cases (STEMI: 88%, NSTEMI: 73%), coronary angiography was performed in 87% (STEMI: 93%, NSTEMI: 82%), and percutaneous intervention occurred in 72% (STEMI: 86%, NSTEMI: 61%). Total ischaemic time (a time interval measured in Hungary as part of the mandatory ACS reporting, and defined as the time interval from onset of pain to the opening of the infarct-related artery in the catheterization laboratory in those patients undergoing acute PCI) in the case of STEMI was 265 minutes (MED, IQR: 170-490 minutes), and pain-to-first-medical-contact time was 120 minutes (MED, IQR:55-300 minutes). Cardiogenic shock evolved during hospitalization in 2.1%, and mechanical ventilation was needed in 3.5% of all cases (Table 1).

Clinical Outcomes

1-year mortality of the entire group of 30-day survivors was 10.9%, and 5-year mortality was 28.2%. Despite the officially mandatory CCR referral referred to above, only 21% of patients actually attended cardiac rehabilitation, and repeated acute coronary syndrome occurred in 10% (Table 1). Determinants of all-cause mortality in the whole patient group of early survivors were female sex (hazard ratio (HR): 0.95, 95% confidence interval (95% CI): 0.90-0.99), direct admission to a PCI-capable hospital (HR: 0.80, 95% CI: 0.76-0.85), percutaneous revascularisation (HR: 0.53, 95% CI: 0.50-0.56), participation in a comprehensive cardiac rehabilitation program (HR 0.76, 95% CI: 0.72-0.81), age (HR: 1.42/5 years of age, 95% CI: 1.40-1.43), diabetes mellitus (HR: 1.41, 95%CI: 1.35-1.48), cardiogenic shock during the index event (HR: 1.21, 95% CI: 1.02-1.43), need for mechanical ventilation (HR: 2.40, 95% CI: 2.12-2.73), reinfarction in the follow-up

period (HR: 1.93, 95% CI 1.79-2.07), elevated serum creatinine level on admission (HR: 1.06/every 10 micromol/l elevation, 95% CI: 1.06-1.06) and atrial fibrillation on admission (HR: 1.59, 95% CI: 1.24-2.04). Detailed analyses of mid-term (1 year) and long-term (5 years) mortality were done for the whole group of early survivors, as well as for STEMI and NSTEMI sub-groups (Cox-regression, Table 2).

Both timely percutaneous revascularisation and participation in a comprehensive cardiac rehabilitation program were strongly linked to better overall patient outcomes within specific subgroups. The most significant mortality reduction was achieved for STEMI patients at one year, with a 42% lower risk of death. Despite these benefits, participation in cardiac rehabilitation remained low, with only 21.2% of all patients attending. STEMI patients had the highest participation rate at 29%, whereas individuals with diabetes and those with NSTEMI were least likely to take part in the program—and this subgroup also experienced the highest observed mortality rates (17% and 43% for 1-year and 5-year mortality).

Attendance was lowest among NSTEMI patients who did not undergo PCI, at just 8.7%. This group also faced the highest mortality rates (20.9% and 46% 1-year and 5-year mortality**,** respectively) (Table 3, Graph 1).

We conducted a binary logistic regression analysis to identify factors contributing to non-participation in rehabilitation programs. These factors were higher age (age over 66.1 years, HR: 1.11, 95% CI: 1.07-1.16), NSTEMI (HR: 1.79, 95% CI: 1.72-1.87), male sex (HR: 1.11, 95% CI: 1.06-1.15), lack of PCI (HR: 2.51, 95% CI: 2.37-2.66), direct patient admission to a non-PCI-capable facility (HR: 1.22, 95% CI: 1.15-1.30) and resuscitation during the index event (HR: 1.65, 95% CI: 1.33-2.04). In summary, the patients least likely to participate in comprehensive cardiac rehabilitation were older men with NSTEMI, especially those admitted to hospitals without PCI facilities who did not undergo PCI. (Table 2 and Table 4)

Sex-related differences

An extensive review included 76,153 patients, with a median age of 67.4 years; 40% of participants were female, and women were on average seven years older than men upon admission. Across the entire study population, mortality rates were 12.1% at 30 days, 21.5% at one year, and 37% at five years following presentation. Detailed baseline demographics are presented in Table 5, while the adjusted determinants of mortality assessed through multivariable statistical analysis are outlined in Table 6.

Sex differences in baseline characteristics and outcomes

All patients

Differences in risk factors and presentation: Women tended to have a less favorable cardiovascular risk profile than men. On admission, women were on average seven years older than men, which partly explains the higher rates of diabetes mellitus and hypertension found among female patients. Conversely, active smoking was more prevalent among men (30.2% in men vs. 19% in women). Men also more frequently had a prior history of myocardial infarction (19.2% vs. 15.9% in women) and previous percutaneous revascularisation procedures (17.2% for men vs. 13% for women). Prior surgical revascularisation was likewise more common in men (5.6%) than in women (3.4%).

At admission, women were more likely to have atrial fibrillation, with a rate of 10.3% compared to 8% in men. Acute heart failure was also more common among female patients, as 17.2% presented with Killip class II-IV, versus 13.3% of men. Cardiogenic shock was detected in 1.7% of women and 1.4% of men. Furthermore, women had a lower glomerular filtration rate (GFR), averaging 62 ml/min/1.73 m^2, compared to 76 ml/min/1.73 m^2 in men.

NSTEMI occurred more often in women, occurring in 57.6% of cases compared to 54.6% in males. Similarly, MINOCA was identified at a higher rate in females - 6.9% versus 4% in males.

Men were more frequently admitted directly to hospitals equipped for PCI, with 80% compared to 73.1% for women. Additionally, the likelihood of being either directly admitted or later transferred to a PCI-capable center during an acute coronary syndrome event was higher among men (89.8%) than women (83.1%).

Differences in treatment: men were more likely than women to undergo coronary angiography (87% vs. 78.1%) as well as PCI (72.9% compared to 62.5%). This pattern persisted for both types of myocardial infarction: in cases of STEMI, 86% of men received angiography versus 78.2% of women, and for NSTEMI, 61.8% of men underwent the procedure compared to only 50.9% of women.

The ischaemic time was generally longer for women than for men (median patient onset of pain-to-first-medical-contact time was 110 minutes versus 130 minutes, median first-medical-contact-to-balloon time (a time recorded in Hungary that measures the time from first medical contact whatsoever (e.g., ambulance arrival) to the opening of the artery in the catheterization laboratory. This time interval (different and longer than the "door to balloon time" commonly reported in the US) was 125 minutes versus 135 minutes; median total ischaemic time was 255 minutes versus 290 minutes in case of STEMI, first medical contact to-balloon time was longer in case of NSTEMI (402 minutes versus 431 minutes). Additionally, coronary artery bypass grafting (CABG) was more commonly performed in men (2.8%) than in women (1.8%).

Compared to men, women received less optimal (i.e., guideline-consistent) drug treatment at discharge (angiotensin-converting enzyme inhibitor (ACEi)/ angiotensin receptor blocker (ARB) use 75.5% versus 81.1%, beta-blocker administration 78.5% versus 81.4%, acetylsalicylic acid (ASA) use 81.3% versus 87.3%, and statin drug administration 80.8% versus 86%). Among patients who survived beyond 30 days after the index event, there was no significant difference between sexes in participation in comprehensive cardiac rehabilitation programs.

Differences in complications: women experienced a higher rate of bleeding events following percutaneous coronary intervention (PCI), with 1.7% affected compared to 1.1% of men. Fatal bleeding incidents were also more frequent among women (0.2% versus 0.1%). Additionally, the need for mechanical ventilation was slightly higher at 7.8% for women versus 7.7% for men, and cardiogenic shock occurred more often in female patients during treatment (7.3% compared to 5.7% in men).

When compared to men, women had higher unadjusted rates of all-cause mortality: at 30 days, the rate was 14.8% for women versus 10.4% for men; at one year, 26.1% versus 18.8%; and at five years, 42.4% for women compared to 33.3% for men.

Multivariable Cox regression analysis revealed that, for the overall patient cohort, female sex was an independent predictor of mortality. Specifically, being female was linked to a

higher risk of death at 30 days (adjusted hazard ratio [aHR] 1.06 (1.01-1.11)), but showed a slight protective effect at five years (aHR: 0.97 (0.94-1.00)), as detailed in Table 6.

The influence of sex on the development of chronic heart failure remains uncertain due to limited available data, underscoring the need for further investigation in this area. Notably, women experienced fewer recurrent acute coronary syndrome episodes during follow-up, with a rate of 8.5% compared to 9.1% in men (see Table 5-7).

Age-adjusted analysis

Age is widely recognized as an important, unmodifiable risk factor for cardiovascular disease. At the time of hospital admission, female patients were generally older than males, with a median age difference of 7.3 years (see Table 5). This age gap is further highlighted in the age distribution chart (Graph 2). In Hungary, the overall life expectancy is 74.4 years, with females averaging 77.8 years and males 70.9 years(43). The older age at which women typically present may negatively impact their prognosis and survival, although their overall longevity might offer some advantages for outcomes. For deeper insight, the analysis subdivided patients based on age groups.

Patients under 50 years

Higher rates of diabetes mellitus and active smoking were observed among females, who also presented with more advanced circulatory failure and elevated creatinine levels upon admission, suggesting poorer renal function despite the limitations of this indicator. The incidence of NSTEMI and MINOCA was notably higher in this group. Overall, the patterns of revascularisation were less favorable for females. Shock during hospitalization was more common among them, and they participated less often in rehabilitation programs. The use of ACEi or ARB was also less common, potentially due to concerns regarding childbearing potential.

The multivariable analysis identified several major factors linked to higher all-cause mortality, including diabetes mellitus, impaired renal function, the presence of shock during treatment, and the need for mechanical ventilation—each contributing to poorer outcomes in both the medium and long term. Furthermore, PCI emerged as a protective factor in this context (Table 8)

Patients over 80 years

Women tended to be older and showed a higher prevalence of diabetes mellitus and hypertension, while men tended to have higher rates of hyperlipidaemia, active smoking, and a history of cardiovascular disease. Upon admission, females had a higher rate of circulatory failure, while males demonstrated worse renal function and had a higher incidence of prehospital cardiac arrest. Although STEMI occurred more commonly in women, they were less likely to receive revascularisation procedures than men. Furthermore, mechanical ventilation was required more often for men, and they also had a higher frequency of recurrent acute coronary syndrome events. Unadjusted mortality data indicated that women faced poorer short- and mid-term survival, while men were more likely to receive optimal pharmacological therapy upon discharge. Multivariable analysis identified diabetes mellitus, atrial fibrillation, impaired renal function, STEMI diagnosis, shock, and mechanical ventilation as significant predictors of higher all-cause mortality. Conversely, PCI was shown to provide a protective effect for mid- and long-term outcomes. An additional predictor of worse long-term outcomes was prehospital cardiac arrest (Table 9).

Mortality, subgroup analysis

Among patients younger than 50 years, mortality rates showed no significant differences; however, men who did not undergo PCI experienced higher all-cause mortality.

For patients aged between 50 and 80 years old, women experienced higher rates of mortality across the short, medium, and long term. For those with NSTEMI, there were no differences in mortality between sexes. In non-diabetic individuals, long-term mortality was similar for both sexes, but men who did not undergo PCI faced significantly poorer long-term outcomes.

Tables

Table 1

Determinants of long-term mortality of early survivors - descriptive statistics, univariate analysis (44)

	whole patient group, number of cases (%), range (IQR)	5-year survivals, number of cases (%), range (IQR)	5-year deceased, number of cases (%), range (IQR)	p (χ^2, T-test, MWU)
age (years)	66.1 (57.5-75.4)	63.2 (54.8-71.5)	74.9 (65.9-82.1)	<0.01
male sex	40875 (61.1%)	30404 (63.3%)	10471 (55.4%)	<0.01
diabetes mellitus	21974 (32.8%)	13928 (29%)	8046 (42.6%)	<0.01
PCI – during the index event	48184 (72%)	37608 (78.3%)	10576 (56%)	<0.01
direct admission to the catheter centre	53038 (79.3%)	40059 (83.4%)	12979 (68.7%)	<0.01
admission to the catheter centre – during the index event	59964 (89.6%)	44936 (93.6%)	15028 (79.5%)	<0.01
coronarography- during the index event	58228 (87%)	44317 (92.3%)	13911 (73.6%)	<0.01
CPR – during the index event	1076 (1.6%)	683 (1.4%)	393 (2.1%)	<0.01
atrial fibrillation on admission	5031 (7.5%)	2283 (4.8%)	2748 (14.5%)	<0.01
shock on admission	496 (0.7%)	280 (0.6%)	216 (1.1%)	<0.01
anamnestic myocardial infarction	11727 (17.5%)	6846 (14.3%)	4881 (25.8%)	<0.01
anamnestic CABG	3059 (4.6%)	1711 (3.6%)	1348 (7.1%)	<0.01
heart rate on admission	80 (70-91)	78 (69-90)	83 (72-98)	<0.01
systolic blood pressure on admission	136 (120-152)	138 (120-153)	133 (119-150)	<0.01
GFR on admission	74 (54-91)	80 (62-94)	57 (40-79)	<0.01
serum creatinine on admission	80 (63-101)	77 (60-94)	93 (71-125)	<0.01
pain-to-first medical contact (minutes) – STEMI patients only	120 (55-300)	119 (55-286)	128 (60-330)	<0.01
first medical contact-to-needle (minutes) -STEMI patients only	126 (87-199)	124 (85-192)	140 (95-232)	<0.01

total ischaemic time (minutes) – STEMI patients only	265 (170-490)	260 (168-477)	300 (186-555)	<0.01,
shock during treatment	1406 (2.1%)	744 (1.5%)	662 (3.5%)	<0.01
mechanical ventilation	2361 (3.5%)	1216 (2.5%)	1145 (6.1%)	<0.01
intra-aortic balloon pump catheter therapy	715 (1.1%)	400 (0.9%)	315 (1.7%)	<0.01
mechanical complications can be related to infarction	401 (0.5%)	237 (0.5%)	164 (0.9%)	<0.01
STEMI diagnosed	29510 (44.1%)	23216 (48.4%)	6294 (33.3%)	<0.01
NSTEMI diagnosed	37395 (55.9%)	24790 (51.6%)	12605 (85.3%)	<0.01
cardiac rehabilitation	14180 (21.2%)	11332 (23.6%)	2848 (15.1%)	<0.01
reinfarction	6746 (10.1%)	3975 (8.3%)	2771 (14.7%)	<0.01
1-year mortality	7277 (10.9%)	887 (6.3%)	6390 (12.1%)	<0.01
2-year mortality	11132 (16.6%)	1451 (10.2%)	9681 (18.4%)	<0.01
3-year mortality	14412 (21.5%)	2012 (14.2%)	12400 (23.5%)	<0.01
4-year mortality	16937 (25.3%)	2458 (17.3%)	14479 (27.5%)	<0.01
5-year mortality	18899 (28.2%)	2848 (20.1%)	16051 (30.4%)	<0.01

Table 2

Determinants of mid- and long-term mortality of early survivors - multivariate analysis, Cox-regression (44)

parameter	adjusted hazard ratio of 1-year-mortality (aHR, 95% CI)	adjusted hazard ratio of 5-year-mortality (aHR, 95% CI)
Determinants of mid- and long-term mortality of early survivors, whole patient cohort		
female sex	NS	0.95 (0.92-0.98), p<0.01
age (/five years)	1.33 (1.32-1.35), p<0.01	1.34 (1.33-1.35), p<0.01
diabetes mellitus	1.25 (1.18-1.32), p<0.01	1.31 (1.27-1.36), p<0.01
direct admission to the catheter centre	0.84 (0.79-0.90), p<0.01	0.85 (0.82-0.89), p<0.01
PCI occurred	0.52 (0.49-0.56), p<0.01	0.62 (0.59-0.64), p<0.01
cardiogenic shock during the index event	1.26 (1.08-1.46), p=0.03	1.19 (1.07-1.33), p<0.01
mechanical ventilation during the index event	2.86 (2.55-3.20), p<0.01	1.99 (1.83-2.16), p<0.01
mechanical complication (VSR, MR, tamponade)	1.58 (1.21-2.07), p<0.01	1.61 (1.35-1.93), p<0.01
repeated ACS after the index event	1.11 (1.02-1.20), p<0.01	1.34 (1.31-1.44), p<0.01
participation in a rehabilitation program	0.68 (0.63-0.74), p<0.01	0.79 (0.75-0.82), p<0.01
serum creatinine on admission (/ten micromol/L)	1.03 (1.03-1.03), p<0.01	1.03 (1.03-1.03), p<0.01
atrial fibrillation on admission	NS	1.37 (1.13-1.65), p<0.01
Determinants of mid- and long-term mortality of early survivors of STEMI patients		
female sex	NS	NS
age (/five years)	1.36 (1.33-1.39), p<0.01	1.37 (1.35-1.38), p<0.01
diabetes mellitus	1.28 (1.15-1.41), p<0.01	1.32 (1.24-1.40), p<0.01
direct admission to the catheter centre	0.78 (0.68-0.90), p<0.01	0.86 (0.79-0.94), p<0.01
PCI occurred	0.52 (0.46-0.59), p<0.01	0.61 (0.56-0.66), p<0.01
cardiogenic shock during the index event	NS	NS
mechanical ventilation during the index event	3.38 (2.79-4.10), p<0.01	2.11 (1.83-2.42), p<0.01
mechanical complication (VSR, MR, tamponade)	NS	NS

repeated ACS after the index event	NS	1.43 (1.30-1.57), p<0.01
participation in a rehabilitation program	0.58 (0.51-0.66), p<0.01	0.72 (0.67-0.78), p<0.01
serum creatinine on admission (/ten micromol/L)	1.03 (1.02-1.03), p<0.01	1.03 (1.03-1.03), p<0.01
atrial fibrillation on admission	NS	NS
Determinants of mid- and long-term mortality of early survivors of NSTEMI patients		
female sex	NS	0.63 (0.59-0.65), p<0.01
age (/five years)	1.32 (1.30-1.34), p<0.01	1.32 (1.31-1.33), p<0.01
diabetes mellitus	1.24 (1.16-1.32), p<0.01	1.31 (1.25-1.36), p<0.01
direct admission to the catheter centre	0.85 (0.80-0.92), p<0.01	0.85 (0.81-0.89), p<0.01
PCI occurred	0.53 (0.49-0.57), p<0.01	0.62 (0.59-0.65), p<0.01
cardiogenic shock during the index event	1.31 (1.08-1.59), p<0.01	1.21 (1.05-1.40), p<0.01
mechanical ventilation during the index event	2.61 (2.26-3.00), p<0.01	1.92 (1.73-2.13), p<0.01
mechanical complication (VSR, MR, tamponade)	1.78 (1.27-2.50), p<0.01	1.79 (1.43-2.25), p<0.01
repeated ACS after the index event	1.12 (1.02-1.23), p=0.02	1.36 (1.29-1.44), p<0.01
participation in a rehabilitation program	0.78 (0.70-0.86), p<0.01	0.85 (0.80-0.90), p<0.01
serum creatinine on admission (/ten micromol/L)	1.03 (1.02-1.03), p<0.01	1.03 (1.03-1.03), p<0.01
atrial fibrillation on admission	NS	1.31 (1.25-1.36), p<0.01

Table 3

The relationship between participation rates in Comprehensive Cardiac Rehabilitation (CCR) and the mid- and long-term prognosis of patients (44)

Patient group	Number of patients	Participation rate in CCR	Participants		Non-Participants	
			1-year-mortality	5-year-mortality	1-year-mortality	5-year-mortality
All patients	66905	21.2% (14180)	6.3% (887)	20.1% (2848	12.1% (6390)	30.4% (16051)
STEMI patients	29510 (44.1%)	28.9% (8516)	4.7% (396)	16.1% (1369)	9.1% (1912)	23.5% (4925)
NSTEMI patients	37395 (55.9%)	15.1% (5664)	8.7% (491)	26.1% (1479)	14.1% (4478)	35.1% (11126)
STEMI patients with PCI	25463 (38.1%)	31.3% (7976)	4.2% (333)	14.9% (1192)	7% (1228)	20.2% (3533)
Non-PCI STEMI patients	4047 (6%)	13.3% (540)	11.7% (63)	32.8% (177)	19.5% (684)	39.7% (1392)
NSTEMI patients with PCI	22721 (33.9%)	19.3% (4386)	6.5% (286)	22.2% (974)	8.8% (1612)	26.6% (4877)
Non-PCI NSTEMI patients	14674 (21.9%)	8.7% (1278)	16% (205)	39.5% (505)	21.4% (2866)	47.6% (6249)

Table 4

Binomial logistic regression model for participation in cardiac rehabilitation program, parameters that made participation more unlikely (44)

parameter	AOR, 95% CI, p-value
age over 66.1 years (median value of early survivors)	1.12 (1.07-1.16), p<0.01
NSTEMI diagnosis	1.79 (1.72-1.87), p<0.01
admission to the hospital without a catheter lab	1.22 (1.15-1.30), p<0.01
resuscitation during the index event	1.65 (1.33-2.04), p<0.01
PCI not occurred	2.51 (2.37-2.66), p<0.01
male sex	1.11 (1.06-1.15), p<0.01

Table 5

Comparison of baseline characteristics of patients presenting with acute coronary syndrome in Hungary (2014-2019). All-cause mortality was assessed as of March 25,2022, with an average follow-up period of 3.6 years (45)

	all patients, number of cases (%), or median and IQR	females, number of cases (%), or median and IQR	males, number of cases (%), or median and IQR	p-value (χ^2, T-test, MWU)
Sex distribution	76153	30552 (41.1)	45601 (59.9)	<0.01
Risk factors				
age (years)	67.4 (58.5-76.8)	72.3 (62.7-80.6)	65 (56.1-73.4)	<0.01
diabetes mellitus	25783 (33.9)	11083 (36.3)	14700 (32.2)	<0.01
hypertension	60447 (79.4)	25676 (84)	34771 (76.3)	<0.01
hyperlipidaemia	22647 (29.7)	9040 (29.6)	13607 (29.8)	<0.01
anamnestic myocardial infarction	13614 (17.9)	4861 (15.9)	8753 (19.2)	<0.01
anamnestic CABG	3578 (4.7)	1039 (3.4)	2539 (5.6)	<0.01
anamnestic PCI	11811 (15.5)	3979 (13)	7832 (17.2)	<0.01
active smoking	19581 (25.7)	5796 (19)	13785 (30.2)	<0.01
Admission				
prehospital CPR	2513 (3.3)	839 (2.7)	1674 (3.7)	<0.01
atrial fibrillation on admission	6780 (8.9)	3150 (10.3)	3630 (8)	<0.01
Killip I on admission	62959 (82.7)	24429 (80)	38530 (84.5)	<0.01
Killip II on admission	8674 (11.4)	4076 (13.3)	4598 (10.1)	<0.01
Killip III on admission	(2622) (3.4)	1183 (3.9)	1439 (3.2)	<0.01
Killip IV on admission	1162 (1.5)	517 (1.7)	645 (1.4)	<0.01

GFR on admission (ml/min/1.73 m^2)	71 (49-89)	62 (41-82)	76 (55-92)	<0.01
serum creatinine on admission (umol/l)	82 (64-107)	76 (58-103)	86 (69-109)	<0.01
ACS characteristics, treatment				
STEMI diagnosed	33843 (44.4)	12948 (42.4)	20895 (45.8)	<0.01
NSTEMI diagnosed	42310 (55.6)	17604 (57.6)	24706 (54.6)	<0.01
PCI – during the index event	52316 (68.7)	19091 (62.5)	33225 (72.9)	<0.01
direct admission to the catheter centre	58830 (77.3)	22333 (73.1)	36497 (80)	<0.01
admission to the catheter centre – during the index event	66368 (87.2)	25397 (83.1)	40971 (89.8)	<0.01
coronarography- during the index event	63517 (83.4)	23863 (78.1)	39654 (87)	<0.01
pain-to-first medical contact (minutes) – STEMI patients only	120 (55-300)	130 (60-341)	110 (50-280)	<0.01
first medical contact-to-balloon (minutes) -STEMI patients only	128 (88-202)	135 (92-213)	125 (85-196)	<0.01
total ischaemic time (minutes) – STEMI patients only	268 (170-495)	290 (185-540)	255 (165-470)	<0.01
pain-to-first medical contact (minutes) – NSTEMI patients only	206 (83-540)	215 (90-569)	200 (80-521)	0.13
first medical contact-to-balloon (minutes) - NSTEMI patients only	413 (191-823)	431 (197-868)	402 (190-789)	0.01
total ischaemic time (minutes) – NSTEMI patients only	582 (290-960)	600 (282-990)	575 (292-945)	0.09
angiography and PCI	52316 (68.7)	19091 (62.5)	33225 (72.9)	<0.01
angiography and PCI, STEMI	28094 (83)	10127 (78.2)	17967 (86)	<0.01
angiography and PCI, NSTEMI	24222 (57.2)	8964 (50.9)	15258 (61.8)	<0.01
only angiography, without PCI	11021 (14.7)	4772 (15.6)	6429 (14.1)	<0.01
angiography and CABG	1843 (2.4)	555 (1.8)	1288 (2.8)	<0.01
angiography without PCI or CABG	9178 (12.3)	4217 (13.8)	5141 (11.3)	<0.01
MINOCA	3908 (5.1)	2093 (6.9)	1815 (4)	<0.01

CABG operation	1843 (2.4)	555 (1.8)	1288 (2.8)	<0.01
bleeding event during the index event	1019 (1.3)	511 (1.7)	508 (1.1)	<0.01
lethal bleeding during the index event	110 (0.1)	58 (0.2)	52 (0.1)	<0.01
CPR – during the index event	3939 (5.2)	1750 (5.7)	2189 (4.8)	<0.01
shock during treatment	4835 (6.3)	2219 (7.3)	2616 (5.7)	<0.01
mechanical ventilation	5903 (7.8)	2393 (7.8)	3510 (7.7)	<0.01
mechanical complications related to infarction	701 (0.9)	334 (1.1)	367 (0.8)	<0.01
Outcomes				
cardiac rehabilitation	14355 (18.9)	5524 (18.1)	8831 (19.4)	<0.01
cardiac rehabilitation – early survivors (after 30 days of index event)	14240 (21.2)	5448 (20.9)	8792 (21.4)	0.18
recurrent ACS episode	6749 (8.9)	2594 (8.5)	4155 (9.1)	<0.01
30-days mortality	9248 (12.1)	4522 (14.8)	4726 (10.4)	<0.01
1-year mortality	16525 (21.7)	7964 (26.1)	8561 (18.6)	<0.01
2-years mortality	20380 (26.8)	9617 (31.5)	10763 (23.6)	<0.01
3-years mortality	23660 (31.1)	11047 (36.2)	12613 (27.7)	<0.01
4-years mortality	26185 (34.4)	12122 (39.7)	14063 (30.8)	<0.01
5-years mortality	28147 (37)	12950 (42.4)	15197 (33.3)	<0.01
Optimal drug therapy at discharge				
ACEi/ARB	60060 (78.9)	23055 (75.5)	37005 (81.1)	<0.01
Beta-receptor blocker	61116 (80.3)	23987 (78.5)	37129 (81.4)	<0.01
ASA-therapy	64665 (84.9)	24850 (81.3)	24850 (87.3)	<0.01
statin therapy	63884 (83.9)	24686 (80.8)	39198 (86)	<0.01

Table 6

Factors predicting mortality in patients with acute coronary syndrome in Hungary (2014-2019). All-cause mortality was assessed as of March 25,2022, with an average follow-up period of 3.6 years (45)

	Binary logistic regression model	Cox-regression model		
parameter	adjusted odds ratio of mortality (AOR, 95% CI)	adjusted hazard ratio of 30-days-mortality (aHR, 95% CI)	adjusted hazard ratio of 1-year-mortality (aHR, 95% CI)	adjusted hazard ratio of 5-year-mortality (aHR, 95% CI)
female sex	0.93 (0.89-0.97)	1.06 (1.01-1.11)	NS	0.97 (0.94-1.00)
age (/5 years of age increasing)	1.46 (1.44-1.47)	1.26 (1.24-1.27)	1.31 (1.30-1.32)	1.33 (1.32-1.34)
diabetes mellitus	1.46 (1.40-1.52)	1.16 (1.11-1.22)	1.22 (1.17-1.26)	1.28 (1.25-1.32)
serum creatinine level on admission (/10 mikromol/l increasing)	1.07 (1.06-1.07)	1.03 (1.03-1.03)	1.03 (1.03-1.03)	1.03 (1.03-1.03)
admission to the hospital with a catheter lab	0.78 (0.74-0.82)	0.90 (0.85-0.95)	0.89 (0.85-0.93)	0.88 (0.86-0.91)
STEMI diagnosis	1.06 (1.02-1.11)	1.55 (1.48-1.63)	1.31 (1.26-1.36)	1.13 (1.09-1.16)
cardiogenic shock on admission	1.52 (1.15-2.02)	1.34 (1.06-1.70)	1.30 (1.09-1.56)	1.35 (1.17-1.56)
cardiogenic shock during the index event	2.29 (2.01-2.60)	2.39 (2.21-2.59)	2.09 (1.95-2.23)	1.94 (1.83-2.06)
resuscitation during the index event	3.42 (2.54-4.59)	2.15 (1.65-2.81)	2.60 (2.10-3.20)	2.79 (2.34-3.31)
PCI, if positive angiography findings	0.47 (0.44-0.49)	0.54 (0.51-0.57)	0.52 (0.50-0.55)	0.58 (0.56-0.60)
need for mechanical ventilation during the index event	4.29 (3.87-4.74)	2.90 (2.70-3.11)	2.81 (2.64-2.98)	2.34 (2.22-2.47)
mechanical complication (VSR, tamponade, perforation)	1.84 (1.45-2.36)	1.47 (1.29-1.70)	1.57 (1.39-1.78)	1.67 (1.50-1.86)

Table 7

Mortality rates by sex of patients presenting with acute myocardial infarction in Hungary (2014-2019). Age-adjusted analysis with presentation of various subgroups (45)

			Without age-adjustment			Aged under 50 years			Aged 50-80 years			Aged over 80 years		
		all patients (%, N)	females (%, N)	males (%, N)	p-value (χ^2)	females (%, N)	males (%, N)	p-value (χ^2)	females (%, N)	males (%, N)	p-value (χ^2)	females (%, N)	males (%, N)	p-value (χ^2)
All patients	30 days	12.1% (9248)	14.8% (4522)	10.4% (4726)	<0.01	2.2% (42)	2.6% (157)	0.28	10.4% (2115)	9.2% (3166)	<0.01	28.8% (2365)	27.1% (1403)	0.03
	1 year	21.7% (16525)	26.1% (7964)	18.8% (8561)	<0.01	4.4% (85)	4.3% (258)	0.85	18.9% (3852)	17.1% (5873)	<0.01	49.1% (4027)	47% (2430)	0.02
	5 years	37% (28147)	42.4% (12950)	33.3% (15197)	<0.01	8.2% (160)	9% (543)	0.31	33.1% (6757)	31.6% (10871)	<0.01	73.6% (6033)	73.1% (3783)	0.58
STEMI	30 days	12.8% (4333)	16.9% (2187)	10.3% (2146)	<0.01	3.1% (33)	2.9% (112)	0.85	12.3% (1094)	9.9% (1540)	<0.01	35.7% (1060)	31.7% (494)	0.01
	1 year	19.6% (6641)	25.3% (3275)	16.1% (3366)	<0.01	5.6% (61)	4.6% (176)	0.17	19% (1690)	15.7% (2444)	<0.01	51.4% (1524)	47.9% (746)	0.03

	5 years	31.4% (10627)	38.3% (4964)	27.1% (5663)	<0.01	9% (97)	8.9% (340)	0.96	30.5% (2712)	27.3% (4237)	<0.01	72.6% (2155)	69.8% (1086)	0.04
NSTEMI	30 days	11.6% (4915)	13.3% (2335)	10.4% (2580)	<0.01	1% (9)	2% (45)	0.06	8.9% (1021)	8.6% (1626)	0.46	24.9% (1305)	25.1% (909)	0.83
	1 year	23.4% (9884)	26.6% (4689)	21% (5195)	<0.01	2.8% (24)	3.7% (82)	0.22	18.8% (2162)	18.2% (3429)	0.19	47.8% (2503)	46.5% (1684)	0.24
	5 years	41.4% (17520)	45.4% (7986)	38.6% (9534)	<0.01	7.3% (63)	9.1% (203)	0.11	35.2% (4045)	35.2% (6634)	0.96	74.1% (3878)	74.5% (2697)	0.62
diabetics	30 days	14.8% (3809)	17.1% (1900)	13% (1909)	<0.01	4.6% (17)	3.6% (37)	0.40	13% (1016)	11.5% (1369)	<0.01	30.1% (867)	29% (503)	0.04
	1 year	27% (6955)	30.8% (3416)	24.1% (3539)	<0.01	7% (26)	6.6% (68)	0.80	24.3% (1907)	21.8% (2603)	<0.01	51.5% (1483)	50.1% (868)	0.37
	5 years	46% (11855)	51.1% (5661)	42.1% (6194)	<0.01	15.7% (58)	13.7% (140)	0.34	43.2% (3383)	39.5% (4718)	<0.01	77.1% (2220)	77.1% (1336)	0.95

non-diabetics	30 days	10.8% (5439)	13.5% (2622)	9.1% (2817)	<0.01	1.6% (25)	2.4% (120)	0.06	8.7% (1099)	8% (1797)	0.02	28.2% (1498)	26.1% (900)	0.04
	1 year	19% (9570)	23.4% (4548)	16.3% (5022)	<0.01	3.7% (59)	3.8% (190)	0.95	15.5% (1945)	14.6% (3270)	0.02	47.8% (2544)	45.4% (1562)	0.03
	5 years	32.3% (19292)	37.4% (7289)	29.1% (9003)	<0.01	6.5% (102)	8% (403)	0.40	26.8% (3374)	27.4% (6153)	0.24	71.1% (2447)	71.7% (3813)	0.57
PCI	30 days	7.9% (4125)	9.6% (1833)	6.9% (2292)	<0.01	1.9% (27)	2.4% (119)	0.28	7.5% (1054)	6.6% (1675)	<0.01	20.8% (752)	18.6% (498)	0.03
	1 year	14.5% (7570)	17.2% (3269)	13% (4301)	<0.01	4.1% (58)	3.8% (189)	0.61	13.8% (1936)	12.5% (3177)	<0.01	35.3% (1275)	34.9% (935)	0.76
	5 years	28.1% (14661)	31.9% (6088)	25.9% (8573)	<0.01	7.7% (110)	8.1% (405)	0.66	26.7% (3745)	25.5% (6485)	0.01	61.8% (2233)	62.8% (1683)	0.39
non-PCI	30 days	10.3% (1146)	10.7% (507)	10.1% (639)	0.28	0.6% (2)	2.3% (16)	0.05	9.1% (303)	9.7% (479)	0.36	19.5% (202)	20.3% (144)	0.65

	1 year	22.2% (2463)	22.5% (1067)	22% (1396)	0.51	1.4% (5)	4.5% (31)	0.01	19.8% (660)	21.1% (1044)	0.15	38.7% (402)	45.3% (321)	0.01
	5 years	40.4% (4477)	40.1% (1897)	40.7% (2580)	0.52	5.5% (20)	10% (69)	0.01	35.5% (1185)	40.1% (1986)	<0.01	66.7% (692)	74.2% (525)	<0.01

Table 8

Sex distribution and mortality predictors in myocardial infarction patients under 50 years old in Hungary (2014-2019) (45)

	sex differences			multivariable analysis	
	females, number of cases (%), or median and IQR	males, number of cases (%), or median and IQR	p-value (χ^2, T-test, MWU)	adjusted hazard ratio 1-year mortality	adjusted hazard ratio 5-years mortality
Sex distribution	1945 (24.3)	6046 (75.7)			
Risk factors					
Age (years)	45 (42-48)	45 (42-48)	0.60		
Diabetes mellitus	370 (19)	1025 (17)	0.04	1.79 (1.40-2.29)	1.91 (1.61-2.27)
Hypertension	1105 (56.8)	3363 (55.6)	0.45		
Hyperlipidaemia	1406 (23.3)	424 (21.8)	0.37		
Anamnestic myocardial infarction	156 (8)	559 (9.2)	0.26		
Anamnestic CABG	17 (0.9)	52 (0.9)	0.35		
Anamnestic PCI	153 (7.9)	534 (8.8)	0.38		
Active smoking	3496 (57.8)	1088 (55.9)	<0.01		
Admission					
Prehospital CPR	73 (3.8)	231 (3.8)	0.19		2.92 (1.05-8.14)
Atrial fibrillation	19 (1)	66 (1.1)	0.87		
Killip I	1751 (90)	5566 (92.1)	0.02		
Killip II	122 (6.3)	334 (5.5)			
Killip III	34 (1.7)	75 (1.2)			
Killip IV	20 (1)	43 (0.7)			
Glomerular filtration rate (ml/min/1.73 m^2)	99 (84-107)	98 (81-108)	0.71		
Serum creatinine (umol/l)	78 (64-90)	61 (47-74)	<0.01	1.28 (1.01-1.63)	1.22 (1.04-1.45)
ACS characteristics, treatment					
STEMI diagnosis	1080 (55.5)	3808 (63)	<0.01		
NSTEMI diagnosis	865 (44.5)	2238 (37)	<0.01		
Coronary angiography	1790 (92)	5711 (94.5)	<0.01		
PCI, if positive angiography findings	1424 (79.7)	5007 (87.9)	<0.01	0.47 (0.36-0.61)	0.58 (0.49-0.70)

Angiography and PCI - STEMI	936 (90.9)	3412 (93)	0.02		
Angiography and PCI - NSTEMI	488 (64.6)	1595 (78.7)	<0.01		
MINOCA	229 (11.8)	380 (6.3)	<0.01		
CABG operation	101 (0.5)	70 (1.2)	<0.01		
Bleeding event after PCI	9 (0.5)	20 (0.3)	0.62		
Lethal bleeding event after PCI	1 (0.1)	3 (0.1)	0.89		
CPR – during the index event	64 (3.3)	158 (2.6)	0.08		
Shock during treatment	67 (3.4)	147 (2.4)	0.02	3.24 (2.35-4.45)	3.19 (2.40-4.24)
Mechanical ventilation	97 (5)	258 (4.3)	0.18	13.52 (9.50-19.24)	5.94 (4.43-7.97)
Mechanical complications related to infarction	7 (0.4)	36 (0.6%)	0.22		
Outcomes					
Cardiac rehabilitation	419 (21.5)	1434 (23.7)	0.05		
Cardiac rehabilitation – early survivors (after 30 days of index event)	419 (22)	1430 (24.3)	0.04		
Recurrent ACS episode	146 (7.5)	506 (8.4)	0.23		
30-days mortality	42 (2.2)	157 (2.6)	0.28		
1-year mortality	85 (4.4)	258 (4.3)	0.85		
2-years mortality	111 (5.7)	341 (5.6)	0.91		
3-years mortality	132 (6.8)	417 (6.9)	0.87		
4-years mortality	144 (7.4)	482 (8)	0.42		
5-years mortality	160 (8.2)	543 (9)	0.31		
Optimal drug therapy at discharge					
ACEi/ARB	1557 (80.1)	5125 (84.8)	<0.01		
Beta-receptor blocker	1644 (84.5)	5195 (85.9)	0.16		
ASA-therapy	1814 (93.3)	5658 (93.6)	0.62		
Statin therapy	1735 (89.2)	5491 (90.8)	0.05		

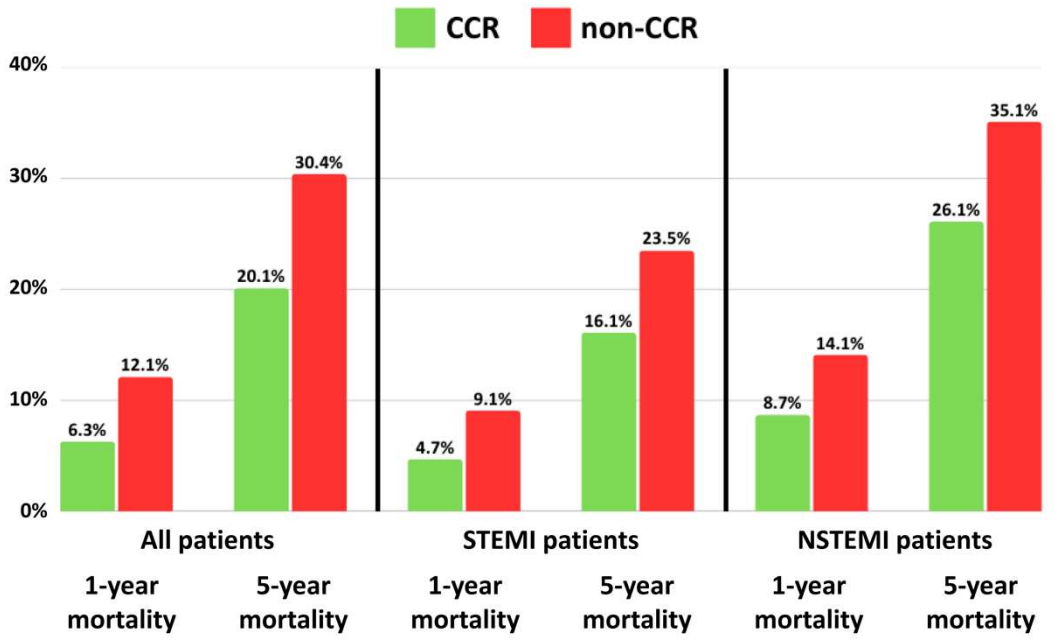
Table 9

Sex distribution and mortality predictors in myocardial infarction patients over 80 years old in Hungary (2014-2019) (45)

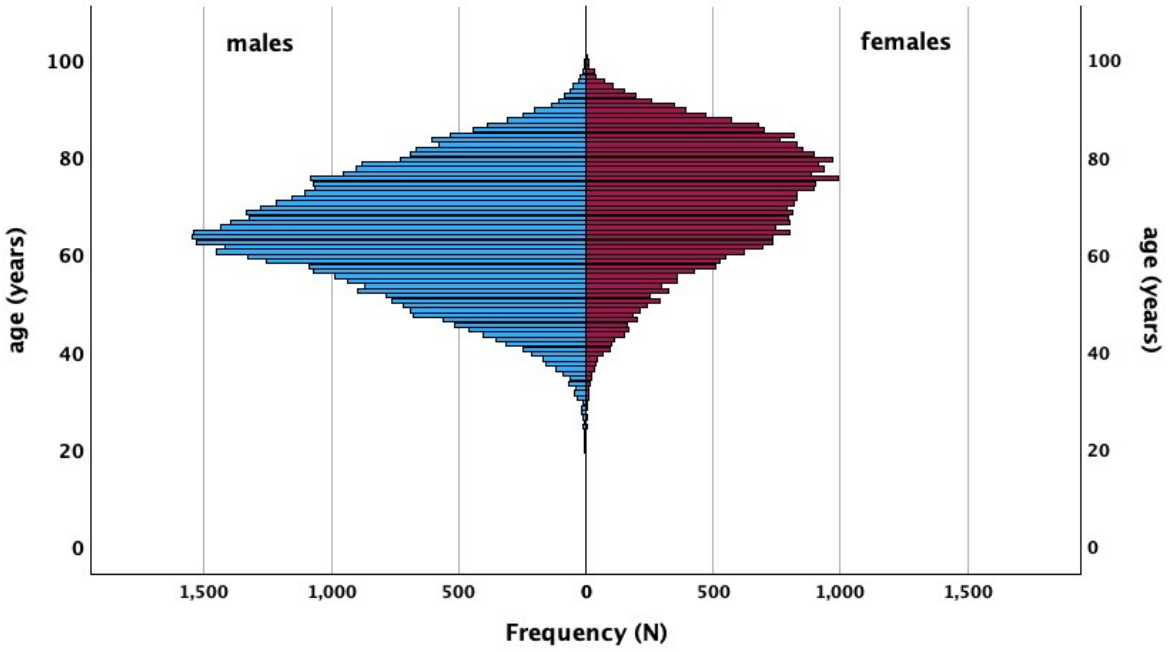
sex differences				multivariable analysis	
	females, number of cases (%), or median and IQR	males, number of cases (%), or median and IQR	p-value (χ^2, T-test, MWU)	adjusted hazard ratio 1-year mortality	adjusted hazard ratio 5-years mortality
Sex distribution	8202 (61.3)	5187 (38.7)			
Risk factors					
Age (years)	85 (82-88)	84 (82-87)	<0.01		
Diabetes mellitus	2881 (35.1)	1732 (33.5)	0.05	1.10 (1.05-1.16)	1.14 (1.10-1.19)
Hypertension	7362 (89.8)	4459 (86.2)	<0.01		
Hyperlipidaemia	2192 (26.7)	1482 (28.6)	<0.01		
Anamnestic myocardial infarction	1572 (19.2)	1391 (26.9)	<0.01		
Anamnestic CABG	276 (3.4)	457 (8.8)	<0.01		
Anamnestic PCI	999 (12.2)	1031 (19.9)	<0.01		
Active smoking	145 (1.8)	231 (4.5)	<0.01		
Admission					
Prehospital CPR	159 (1.9)	129 (2.5)	0.02		1.31 (1.03-1.69)
Atrial fibrillation	1658 (20.2)	1003 (19.4)	0.13	1.35 (1.16-1.57)	1.40 (1.24-1.58)
Killip I	5877 (71.7)	3876 (74.9)	<0.01		
Killip II	1575 (19.2)	847 (16.4)			
Killip III	436 (5.3)	276 (5.3)			
Killip IV	172 (2.1)	111 (2.1)		1.30 (1.05-1.61)	
Glomerular filtration rate (ml/min/1.73 m^2)	43 (30-60)	49 (36-65)	<0.01		
Serum creatinine (umol/l)	95 (71-128)	111 (86-145)	<0.01	1.44 (1.36-1.52)	1.37 (1.32-1.43)
ACS characteristics, treatment					
STEMI diagnosis	2967 (36.2)	1556 (30.1)	<0.01	1.40 (1.33-1.48)	1.21 (1.16-1.27)

NSTEMI diagnosis	5235 (63.8)	3618 (69.9)	<0.01		
Coronary angiography	4663 (56.9)	3401 (65.7)	<0.01		
PCI, if positive angiography findings	3514 (77.7)	2678 (79.1)	<0.01	0.45 (0.43-0.47)	0.51 (0.49-0.54)
Angiography and PCI - STEMI	1824 (87.2)	1104 (89.9)	0.02		
Angiography and PCI - NSTEMI	1790 (69.6)	1574 (72.9)	0.02		
MINOCA	427 (5.2)	226 (4.4)	<0.01		
CABG operation	58 (0.7)	60 (1.2)	<0.01		
Bleeding event after PCI	183 (2.2)	129 (2.5)	0.55		
Lethal bleeding event after PCI	24 (0.3)	11 (0.2)	0.61		
CPR – during the index event	678 (8.3)	460 (8.9)	0.12		
Shock during treatment	881 (10.7)	542 (10.5)	0.63	3.67 (3.36-4.00)	3.28 (3.03-3.56)
Mechanical ventilation	710 (8.7)	521 (10.1)	<0.01	1.92 (1.75-2.11)	1.68 (1.54-1.83)
Mechanical complications related to infarction	120 (1.5)	60 (1.2)	0.14		
Outcomes					
Cardiac rehabilitation	912 (11.1)	561 (10.8)	0.62		
Cardiac rehabilitation – early survivors (after 30 days of index event)	873 (15)	534 (14.2)	0.28		
Recurrent ACS episode	628 (7.7)	467 (9)	<0.01		
30-days mortality	2365 (28.8)	1403 (27.1)	0.03		
1-year mortality	4027 (49.1)	2430 (47)	0.02		
2-years mortality	4735 (57.7)	2921 (56.5)	0.15		
3-years mortality	5314 (64.8)	3325 (64.3)	0.54		
4-years mortality	5729 (69.8)	3581 (69.2)	0.44		
5-years mortality	6033 (73.6)	3783 (73.1)	0.58		
Optimal drug therapy at discharge					
ACEi/ARB	5227 (63.7)	3451 (66.7)	<0.01		
Beta-receptor blocker	5610 (68.4)	3598 (69.5)	<0.01		
ASA-therapy	5514 (67.1)	3961 (71.3)	<0.01		
Statin therapy	5575 (68)	3679 (71.1)	<0.01		

Graphs

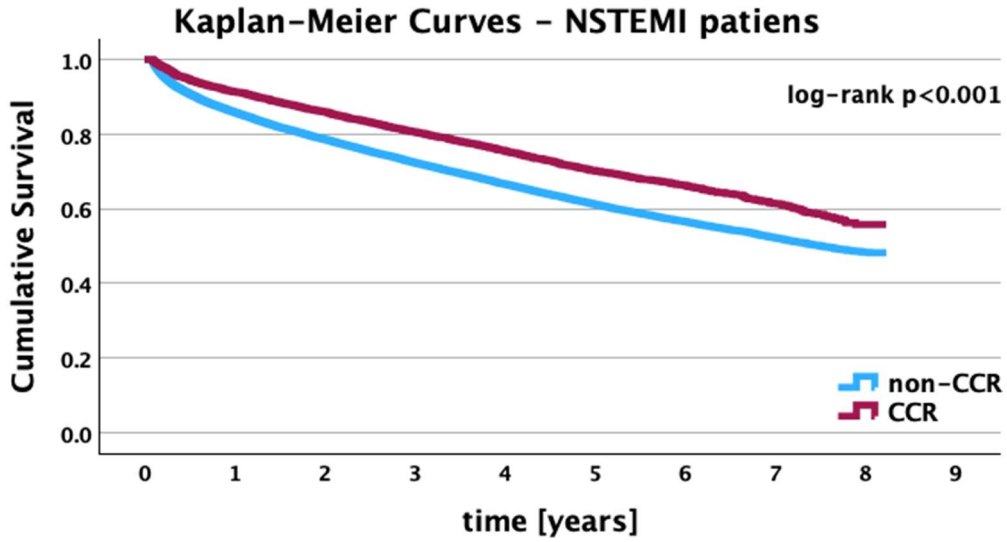


Graph 1 – Analysis of mortality data according to types of acute coronary syndrome and the impact of participating in a comprehensive cardiac rehabilitation (CCR) program (44)

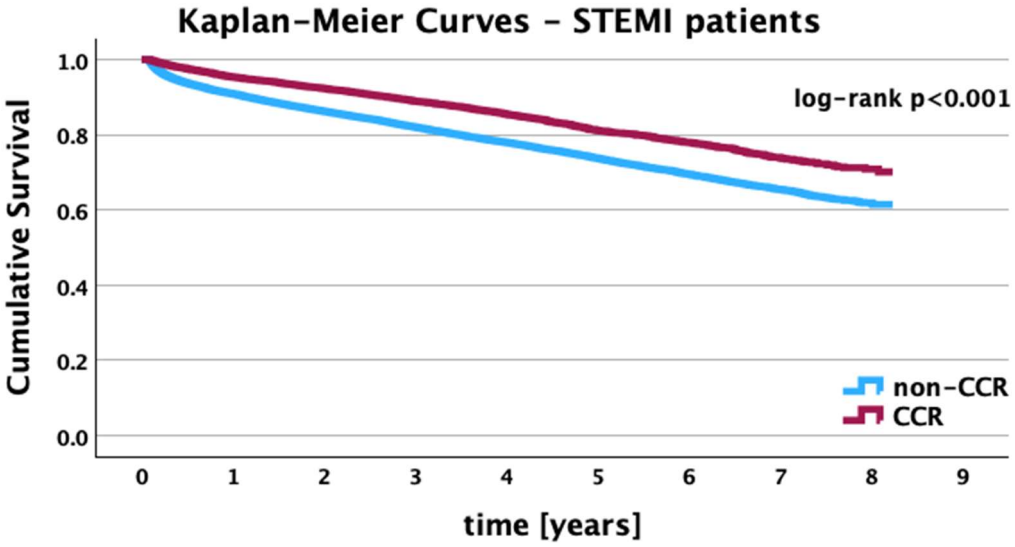


Graph 2

Age and sex distribution of all patients presenting with acute myocardial infarction in Hungary between 2014 and 2019 (45)



Graphs 3 Kaplan-Meier curves, the effect of comprehensive cardiac rehabilitation on survival, NSTEMI patients (44)



Graphs 4 Kaplan-Meier curves, the effect of comprehensive cardiac rehabilitation on survival, STEMI patients (44)

5. Discussion

Participating in a comprehensive cardiac rehabilitation program after myocardial infarction is an accessible and cost-effective way to support secondary prevention [46]. The program typically includes exercise training, lifestyle changes, psychological support, medication optimization, nutritional counseling, and guidance for quitting smoking (47-51). In addition, being involved in CCR has fostered a stronger connection between healthcare providers and patients (52, 53).

In Hungary, cardiac rehabilitation enrollment following ACS presentation typically occurs during the initial hospitalization (14). The analysis includes the data of those participating in early rehabilitation treatment (phase II rehabilitation treatment with direct transfer or early admission after the index event).

Numerous meta-analyses conducted in regions outside of Hungary have consistently demonstrated that early cardiac rehabilitation leads to a short-term reduction in all-cause mortality and decreases in unplanned hospital readmissions and reinfarctions (47, 54-57). Although participation in cardiac rehabilitation is a class I recommendation in the ESC and AHA/ACC guidelines (3, 4), actual enrollment rates remain low in Hungary and elsewhere (3, 4, 13, 58-60). While most studies have focused on the mid-term (one-year) benefits of CCR following ACS (56), only a few early investigations have explored its long-term impact over periods of 10 to 15 years (10-15 years) (61-63).

The National Health Insurance Fund in Hungary covers the cost of comprehensive cardiac rehabilitation at a rate of 10,000 to 13,000 Hungarian Forint per day, which usually lasts 21 days. In contrast, percutaneous revascularisation procedures are reimbursed at 1.8 million Hungarian Forint per index event.

To summarize, our findings demonstrate that participation in a Comprehensive Cardiac Rehabilitation program is a significant protective factor, improving the prognosis of 30-day ACS survivors, comparable to the benefits seen with percutaneous coronary intervention or immediate admission to a hospital equipped for PCI (in case of early survivors of ACS) (Graphs 3-4). Promoting greater understanding of these advantages among patients and healthcare providers and expanding access to this highly effective and cost-effective intervention should be a central focus for policymakers. The currently low participation rate also reflects trends observed in other regions (13, 64).

Raising awareness alone, however, may not be enough, since the above-referenced national mandate for CCR referral and the similar AHA/ACA and ESC guidelines are largely unenforced and appear to have little impact on actual participation rates. Policymakers should consider designating CCR participation as an official Quality of Care indicator and linking reimbursement for both the initial hospital stay and 30-day same-diagnosis readmissions to documentation of CCR referral, unless there are clearly stated reasons for non-referral in the medical record. Establishing more outpatient rehabilitation options, introducing telerehabilitation, and expanding home-based services would make CCR more accessible, particularly for younger individuals and those facing mobility challenges. These measures could yield marked improvements in mid- and long-term outcomes. Integrating automatic patient referrals through electronic health record systems may substantially increase the currently low participation rates (65).

Analysis of sex differences in the prognosis and management of ACS

Sex differences

Female patients tended to have a less favorable cardiovascular risk profile, marked by higher rates of diabetes and hypertension, and most importantly, older age. Recent data reveal an increased incidence of diabetes mellitus in women, an observation that contrasts with earlier research (66). This inconsistency highlights the need for further research to understand the factors driving this unexpected trend.

Females were, on average, seven years older at the time of their ACS event and were less likely to receive prompt treatment or revascularisation procedures. This may partly be due to a greater prevalence of MINOCA and NSTEMI among women. Furthermore, female patients experienced higher complication rates during treatment and were less likely to be discharged with guideline-recommended medications. In comparison, men were more often provided with timely percutaneous coronary interventions (PCI). Nevertheless, for those who did not undergo PCI, men showed worse long-term survival rates.

The research underscores notable differences in mortality outcomes between men and women with ACS (see Table 1). While it might be tempting to attribute these disparities solely to healthcare provider bias, the underlying causes are likely multifaceted and cannot be explained by a single factor. Interestingly, although women had higher unadjusted mortality rates, multivariable analysis revealed a five-year survival advantage for females. This finding should be interpreted in the context of women's generally longer life expectancy and that they tend to be older at the time of their ACS event. As such, observed outcome differences are shaped by a combination of sex, treatment quality, and comorbid conditions, rather than by biological differences or provider behavior alone (refer to Graph 1).

Age-adjustment

Diabetes mellitus is strongly linked to an increased risk of all-cause mortality, regardless of the patient's age.

In terms of short-term survival, individuals with STEMI generally experience less favorable outcomes, while those diagnosed with NSTEMI face higher risks in the mid- to long-term. An exception to this pattern is observed among patients younger than 50, for whom no notable difference in long-term survival is found between NSTEMI and STEMI cases (5-year mortality χ^2 p=0.57).

Even among those over 80 years old, percutaneous coronary intervention continues to offer essential survival advantages. There is an urgent need for timely revascularisation strategies for patients experiencing STEMI. Healthcare institutions should focus on minimizing treatment delays to improve patient outcomes. Patients aged over 80, particularly females, tend to demonstrate a less favorable prognosis in both the short and mid-term. Notably, in the case of NSTEMI, no significant difference was observed in mortality rates.

The research also emphasizes that older patients, particularly those over 80, present unique challenges. The higher prevalence of comorbidities in this age group requires a

more nuanced understanding of their treatment needs and the potential barriers to achieving successful outcomes.

The higher prevalence of NSTEMI among younger women, coupled with their longer ischaemic times and reduced likelihood of receiving timely PCI, further complicates their clinical outcomes and underscores the importance of better awareness and education about ACS symptoms for this group. For patients aged 80 and above, data show that a greater proportion of women are diagnosed with STEMI compared to men. However, despite this increased rate, women in this age group are still less likely than men to undergo revascularisation. This disparity highlights the need for further investigation into factors contributing to differences in treatment and outcomes based on sex in this age group (Table 8).

Among diabetic patients, a short-term disparity is evident, with females experiencing a poorer prognosis, similar to the outcomes reported in non-diabetic individuals within both the short and mid-term periods

Regardless of age, both the presence of cardiogenic shock at admission and its development later on are strong indicators of worse outcomes. This underscores the critical importance of early recognition—such as identifying Society for Cardiovascular Angiography & Interventions Shock Stages A and B—and prompt intervention, especially early revascularisation, for managing circulatory failure. Additionally, the requirement for mechanical ventilation is linked to a much poorer prognosis.

Limitations

These analyses were retrospective. It was necessary to implement specific statistical adjustments to account for missing data, including anthropometric measurements, smoking status, treatment durations, and adherence to secondary prevention medication. Furthermore, the socioeconomic backgrounds of the patient population examined remain unknown. There is also a lack of information regarding female-specific cardiovascular risk factors, such as menopausal status, eclampsia, and migraine. The research focused on Hungarian patients, whose cardiovascular risk factors are generally considered less

favorable compared to those in Western Europe or the United States (67, 68). Door-to-balloon time in patients presenting to PCI-capable hospitals is longer in Hungary, compared to Western Europe or the United States (67-69). Lastly, prehospital thrombolysis is rare (69). It is important to note that only all-cause mortality data were available for this research.

6. Conclusions

Participation in CCR is crucial for improving mid- and long-term outcomes following ACS. Policy changes are needed to increase patient participation rates. Future studies and policy directives should focus on identifying and overcoming barriers to participation in cardiac rehabilitation programs. The low participation rate could also be improved by extending outpatient rehabilitation treatment. Lastly, CCR completion rather than CCR referral should be established as a Quality-of-Care marker. Tying this marker to index admission and 30-day readmission reimbursement rates might benefit public health policy-making.

The findings of this research reveal significant sex differences in the management and outcomes of patients with acute coronary syndrome. The elevated mortality rates observed among female patients can be attributed to a combination of factors, including older age, higher rates of comorbidities, and disparities in treatment approaches. Nonetheless, further research is essential. Recognizing the multifaceted nature of these differences is critical for developing effective, sex-sensitive treatment strategies that can enhance outcomes for all acute coronary syndrome patients.

Main findings:

- comprehensive cardiac rehabilitation plays a crucial role in enhancing survival rates among patients post-acute coronary syndrome
- despite the proven benefits of comprehensive cardiac rehabilitation, only 21% of eligible acute coronary syndrome patients participate
- women and older patients face significant treatment disparities, with women experiencing worse outcomes despite having a slight survival advantage in adjusted analyses, this highlights the need for sex-sensitive and age-appropriate treatment protocols
- the study identifies participation in comprehensive cardiac rehabilitation as key predictor of mortality, emphasizing a holistic approach to patient evaluation and management

7. Summary (1 page)

This research investigates the effects of CCR and sex-related differences on the prognosis of patients in Hungary following ACS. Women typically experience inferior outcomes, as evidenced by elevated mortality rates, delays in care, and less aggressive treatment protocols. Several factors contribute to the poorer outcomes observed in female patients, including older age at presentation, a higher prevalence of comorbid conditions, atypical symptomatology, diagnostic challenges (NSTEMI and MINOCA), and lower rates of engagement in secondary prevention. The primary objectives of this study were to evaluate the impact of a CCR program on survival among early post-MI survivors and to analyse sex-related differences in clinical presentation, management practices, and long-term outcomes. The findings suggest that CCR is an effective intervention that enhances survival rates; however, despite established guidelines, participation rates remain alarmingly low, indicating an urgent need for policy reforms.

Sex disparities in outcomes are multifactorial. Some adverse early outcomes may be attributable to biases within the healthcare system, biological factors, or the challenges posed by comorbidities. Our analysis also revealed age-related differences, indicating that younger patients benefit significantly from timely revascularisation, irrespective of sex. Conversely, in the older population, particularly among women, timely revascularisation and adherence to prescribed therapy are essential yet often inadequately addressed. In conclusion, the findings highlight the prognostic significance of CCR post-MI, underscore the persistent sex disparities in management and outcomes, and emphasize the necessity for systemic interventions. These interventions should enhance adherence to clinical guidelines, enforce relevant policies, and improve access to rehabilitation services. Special attention should be directed toward vulnerable groups, including elderly women, diabetic patients, and those with NSTEMI, to mitigate mortality rates and improve long-term prognoses. In summary, enhancing participation in CCR through policy adaptations, the development of outpatient programs, and the utilization of electronic health tools, while addressing sex-specific management gaps, can substantially improve long-term survival and quality of life for patients following myocardial infarction.

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Volume 55,
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ISSN 2211-3355,
https://doi.org/10.1016/j.pmedr.2025.103131.

10. Acknowledgements

I am deeply grateful to my mentor, Prof. Dr. Péter Andréka, and my colleague, Dr. Christian M. Heesch, for their invaluable support. I also thank all the contributors to the National Myocardial Infarction Register for their dedicated efforts and Prof. Dr. András Jánosi for coordinating the program.