Gender-related differences in long-term outcome among high-risk patients with myocardial infarction treated invasively

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A b s t r a c t

Introduction: Treating acute myocardial infarction (AMI) with percutaneous coronary intervention (PCI) has an impact on improving long-term outcome. However, patients with other comorbidities are challenging, and are considered as a high-risk population.

Aim: To assess gender-related differences in long-term prognosis after AMI among high-risk patients.

Material and methods: The single-center registry encompassed 4375 AMI patients treated with PCI. The following high-risk groups were selected: age > 70 group (n = 1081), glomerular filtration rate (GFR) < 60 group (n = 848), diabetes mellitus (DM) group (n = 782), low ejection fraction (EF) group (n = 560) defined as EF < 35%, and incomplete coronary revascularization (ICR) group (n = 2008). Within each group, comparative analysis of long-term mortality with respect to gender and age was performed.

Results: There were no significant differences in long-term mortality with respect to gender among groups with age > 70 (29.0% vs. 30.3%) and GFR < 60 (37.2% vs. 42.3%) (both p = NS respectively for men vs. women). In the DM group (24.8% vs. 30.8%; p = 0.06) and EF < 35% group (36.3% vs. 44.5%; p = 0.07) there was a trend towards significance. The ICR group showed a higher mortality rate with respect to gender (19.7% vs. 27.3%; p < 0.001). Differences in survival assessed by the log-rank test were significant among ICR and EF < 35% groups.

Conclusions: Female gender is related to higher long-term mortality among high-risk groups, but a statistically significant difference was observed only in patients with ICR and those with EF < 35%. Female gender may be associated with worse prognosis in diabetic patients, but it needs evaluation. However, worse prognosis in women was not independent and was associated mainly with other comorbidities and worse clinical characteristics.

Key words: coronary artery disease, percutaneous coronary intervention, female, mortality, incomplete coronary revascularization.

Introduction

Acute myocardial infarction (AMI) is a serious consequence of coronary artery disease and one of the major causes of all deaths [1]. Wider availability of percutaneous coronary intervention (PCI) decreased mortality caused by AMI, but patients with other comorbidities are still considered as a high-risk population because of worse prognosis despite invasive treatment. Some of these disorders were deemed as independent risk factors causing death among patients with AMI [2]. Gender-related differences with respect to mortality among AMI patients have been investigated in several studies [3, 4]. Some of them claimed that female gender is associated with worse prognosis after AMI [5]. A few studies compared mortality in both genders among patients with other concomitant disorders, such as impaired renal function where mortality between genders did not differ [6]. Others have demonstrated that older age [7], prevalence of diabetes mellitus (DM) and hypertension could be contributive factors to unfavorable prognosis and excessive mortality in women.

Aim

The aim of this study was to assess the potential gender-related differences among high-risk patients treated in the acute phase of myocardial infarction with PCI.

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Material and methods

Data acquisition

This is a prospective single-center registry of consecutive AMI patients with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) treated with PCI between 2001 and 2009. The computerized database included demographics, laboratory values, characteristics of AMI, presence of concomitant diseases, angiographic findings, revascularization procedure, in-hospital complications and mortality. Data concerning long-term outcome were collected in a database of the National Fund of Health and clinical follow-up. The mean follow-up period was 34 months and the data were collected from 94% of patients enrolled in the study.

Selection of patients

The study population consisted of 4375 patients diagnosed with AMI (women n = 1292 and men n = 3083) admitted to our department, with diagnosis of STEMI or NSTEMI, who were treated during the acute phase with PCI.

Clinical AMI criteria evaluated on admission were: chest pain persisting for > 20 min, ST segment elevation of at least 0.1 mV in 2 or more continuous electrocardiographic leads, or non-diagnostic electrocardiogram with enzymatic confirmation of AMI. The biochemical criterion of myocardial infarction was elevated troponin I or T above the upper limit of normal. The patients were mainly admitted from referral hospitals with no upper age limit. Previous administration of fibrinolytic treatment was allowed.

Definitions

A sex-related comparative analysis was performed in five high-risk groups selected from the whole study population: patients with diabetes mellitus (DM group; n = 782), low ejection fraction defined as EF < 35% (EF < 35 group; n = 560), a population with incomplete coronary revascularization (incomplete coronary revascularization (ICR) group; n = 2008), aged > 70 (n = 1081), and those with glomerular filtration rate (GFR) < 60 ml/min/1.73 m² (GFR < 60 group; n = 848).

Diagnosis of glucose abnormalities was based on WHO criteria for venous plasma [8]. The patients in the DM group were classified based on reported current or previous use of antidiabetic medications (insulin or oral hypoglycemic agents). New onset DM was diagnosed when fasting plasma glucose level was 7.0 mmol/l or greater on at least 2 separate occasions during hospitalization. Diabetes mellitus was also recognized based on oral glucose tolerance test (OGTT) results if fasting glycemia was ≥ 7.0 mmol/l or the 2-hour postload glucose level was ≥ 11.1 mmol/l.

The estimated glomerular filtration rate was calculated on the basis of serum creatinine level on admission before catheterization, according to the abbreviated Modification of Diet in Renal Disease Study Group Equation proposed by the National Kidney Foundation [9].

Multivessel disease was defined as the presence of > 2 major epicardial coronary arteries or their major branches (diameter ≥ 2 mm) with stenosis of at least 70% (for left main > 50%), assessed during initial coronary angiography. Complete revascularization was defined when no total occlusion and no residual stenosis of > 70% (for left main > 50%) was found in any major coronary artery or their major branches at discharge.

Treatment protocol

In all patients, coronary angiography and PCI of the infarct-related artery (IRA) were performed immediately after hospital admission using standard techniques. All patients received a single dose of oral aspirin (300–500 mg) and 5000–10000 U of intravenous heparin (patients were given extra boluses as appropriate to achieve activated clotting time > 250 ms). After diagnostic angiography, PCI of the infarct-related artery was performed. The aim of PCI was to restore Thrombolysis in Myocardial Infarction flow grade 3 with residual stenosis lower than 30%, which denotes a successful procedure. After the procedure all patients started receiving 75–150 mg of aspirin daily indefinitely, 300–600 mg of clopidogrel just before PCI as a loading dose, followed by 75 mg of clopidogrel daily. Moreover, angiotensin receptor blockers/angiotensin-converting enzyme inhibitors, β-blockers and statins were prescribed unless contraindicated.

Outcomes

The endpoint for this analysis was death from any cause.

Statistical analysis

Continuous data were expressed as means with standard deviations ± SD unless otherwise specified. Categorical data were presented as numbers and percentages. Comparative analysis between groups was performed using Student's t-test for continuous variables and the χ^2 test for dichotomous parameters. Survival curves were constructed using the Kaplan-Meier method and differences in survival were assessed by the log-rank test (Figure 1). Independent predictors of death were identified with the multivariate Cox regression model and expressed as hazard ratios with 95% confidence intervals. All tests were double-sided and a p-value of < 0.05 was considered statistically significant. All the analyses were performed using the software package Statistica version 6.1 (StatSoft, Tulsa, OK, USA).

Ethics

All clinical data were obtained as a result of the diagnostic procedures and therapy, which were in accordance with appropriate guidelines for myocardial infarction. All patients provided written consent for hospitalization, invasive treatment, and use of their data for research purposes. The study protocol was in line with the ethical standards.

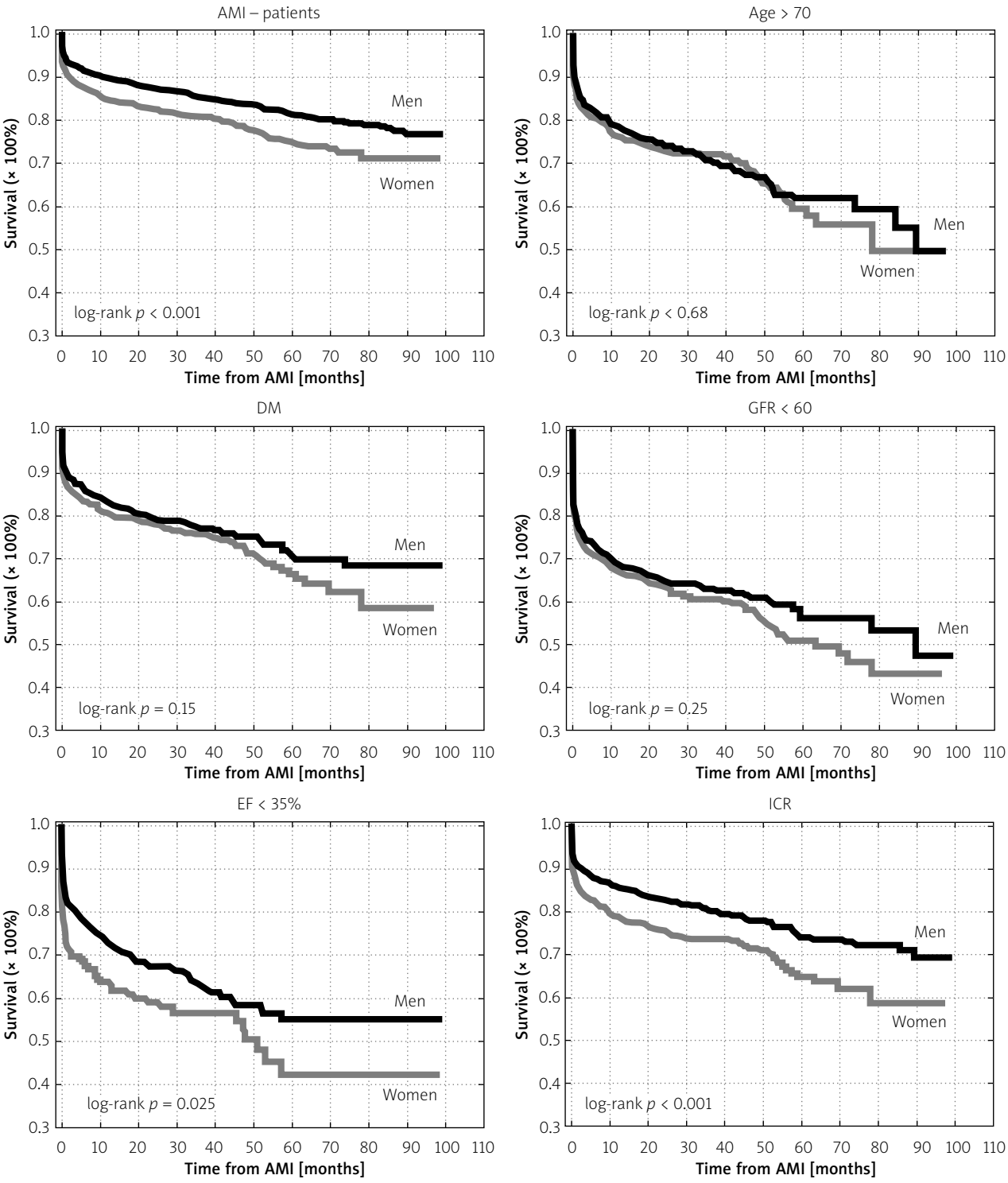

Figure 1. Kaplan-Meier survival curves for particular high-risk study groups

AMI – acute myocardial infarction, GFR – glomerular filtration rate, EF – ejection fraction, DM – diabetes mellitus, ICR – incomplete coronary revascularization

Results

Baseline characteristics

Among 4375 patients enrolled in our analysis, 1292 (29.53%) patients were women and 3083 (70.47%) patients were men. The women were approximately 6 years older than the men. Moreover, 38.0% of the females were > 70 years old compared to 19.1% of men.

Differences in baseline clinical characteristics between study groups with respect to gender are presented in Table I and comparative analysis of laboratory data is presented in Table II.

Compared to men, the women in each group were older and more frequently showed hypertension, hyperlipidemia, diabetes mellitus and a glomerular filtration rate under 60 ml/min/1.73 m². The comparative analysis between men and women in all high-risk subgroups revealed no significant differences with respect to pharmacotherapy in hospital and at discharge (antiplatelet therapy, fibrinolysis, β-blockers, angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, and statins).

No differences were observed in terms of angiographic or procedural characteristics.

Outcome

Total mortality rate in the entire study population was 15.0% vs. 20.2% for men and women respectively. In-hospital, 30-day and 1-year death rates were 5.4% vs. 8.2%, 5.7% vs. 8.8%, and 10.1% vs. 15.0% respectively ($p < 0.001$ in all cases). Mortality rates for each high-risk group are shown in Table III.

A worse outcome was observed at each time point among females in the ICR group. Moreover, this relationship became more pronounced over time.

An opposite relationship was observed in the EF < 35% study group. In this population the biggest differences were recorded during in-hospital and 30-day observation, where the outcome in female gender became similar to the outcome of male gender over time.

Independently of follow-up time there were no statistically significant differences in outcomes between genders in other high-risk groups. According to multivariate

Table I. Baseline clinical characteristics of the study groups

High-risk group/variable	Men	Women	*P*-value
GFR < 60:	*N* = 422	*N* = 426	
Age [years]	66.923 ±9.52	70.220 ±9.39	< 0.001
Smoking, *n* (%)	257 (60.9)	141 (33.1)	< 0.001
Hypertension, *n* (%)	265 (62.8)	310 (72.8)	0.002
Hyperlipidemia, *n* (%)	185 (43.9)	230 (54.0)	< 0.001
Previous myocardial infarction, *n* (%)	127 (30.1)	119 (28.0)	0.50
Previous CABG, *n* (%)	17 (4.0)	19 (4.4)	0.77
Previous PCI, *n* (%)	46 (10.9)	57 (13.4)	0.27
Thrombolysis, *n* (%)	31 (7.3)	29 (6.8)	0.78
IIb/IIIa inhibitor, *n* (%)	76 (18)	86 (20.2)	0.42
DM:	*N* = 432	*N* = 350	
Age [years]	64.104 ±9.66	67.914 ±9.15	< 0.001
Smoking, *n* (%)	242 (56.0)	103 (29.4)	< 0.001
Hypertension, *n* (%)	300 (69.4)	281 (80.3)	< 0.001
Hyperlipidemia, *n* (%)	215 (49.8)	184 (52.6)	0.45
Previous myocardial infarction, *n* (%)	126 (29.2)	97 (27.7)	0.67
Previous CABG, *n* (%)	16 (3.8)	13 (3.8)	0.99
Previous PCI, *n* (%)	67 (15.5)	44 (12.6)	0.25
Thrombolysis, *n* (%)	34 (7.9)	23 (6.6)	0.49
IIb/IIIa inhibitor, *n* (%)	78 (18)	53 (15)	0.26
EF < 35%:	*N* = 405	*N* = 155	
Age [years]	63.490 ±10.92	68.779 ±11.03	< 0.001
Smoking, *n* (%)	243 (60.0)	65 (42.0)	< 0.001
Hypertension, *n* (%)	216 (53.3)	105 (67.7)	< 0.001
Hyperlipidemia, *n* (%)	167 (41.2)	89 (57.4)	< 0.001
Previous myocardial infarction, *n* (%)	168 (41.5)	54 (34.8)	0.15
Previous CABG, *n* (%)	21 (5.2)	7 (4.5)	0.77
Previous PCI, *n* (%)	39 (9.6)	19 (12.2)	0.36
Thrombolysis, *n* (%)	22 (5.4)	11 (7.1)	0.44
IIb/IIIa inhibitor, *n* (%)	79 (19.5)	35 (22.6)	0.42
AGE > 70:	*N* = 590	*N* = 491	
Age [years]	75.241 ±4.40	76.472 ±4.55	< 0.001
Smoking, *n* (%)	281 (47.6)	111 (22.6)	< 0.001
Hypertension, *n* (%)	343 (58.1)	360 (73.3)	< 0.001
Hyperlipidemia, *n* (%)	304 (51.5)	246 (50.1)	0.65
Previous myocardial infarction, *n* (%)	157 (26.6)	104 (21.2)	0.039
Previous CABG, *n* (%)	17 (2.9)	13 (2.7)	0.84
Previous PCI, *n* (%)	59 (9.9)	53 (10.8)	0.61
Thrombolysis, *n* (%)	33 (5.6)	20 (4.1)	0.26
IIb/IIIa inhibitor, *n* (%)	68 (11.5)	69 (14.1)	0.20
ICR:	*N* = 1405	*N* = 603	
Age [years]	62.015 ±10.55	67.314 ±9.85	< 0.001
Smoking, *n* (%)	926 (65.9)	240 (39.8)	< 0.001
Hypertension, *n* (%)	762 (54.2)	430 (71.3)	< 0.001
Hyperlipidemia, *n* (%)	683 (48.6)	341 (56.6)	< 0.001
Previous myocardial infarction, *n* (%)	399 (28.4)	134 (22.2)	0.003
Previous CABG, *n* (%)	74 (5.3)	16 (2.7)	0.01
Previous PCI, *n* (%)	150 (10.7)	51 (8.5)	0.13
Thrombolysis, *n* (%)	94 (6.7)	28 (4.7)	0.09
IIb/IIIa inhibitor, *n* (%)	212 (15.1)	94 (15.6)	0.78

Table II. Laboratory data

High-risk group/variable	Men	Women	*P*-value
GFR < 60:	*N* = 422	*N* = 426	
Creatinine on admission [µmol/l]	160.784 ±100.04	129.923 ±77.36	< 0.001
Glucose on admission [mmol/l]	10.434 ±5.42	11.78 ±6.66	0.002
Uric acid [µmol/l]	438.749 ±127.66	418.577 ±149.82	0.07
Ejection fraction (%)	39.384 ±10.98	41.126 ±10.22	0.025
Incomplete revascularization, *n* (%)	247 (58.5)	228 (53.5)	0.16
TIMI flow < 3 after PCI of IRA, *n* (%)	87 (20.6)	77 (18.1)	0.36
Multivessel coronary artery disease, *n* (%)	167 (39.6)	305 (71.6)	< 0.001
DM:	*N* = 432	*N* = 350	
Creatinine on admission [µmol/l]	110.430 ±90.64	101.003 ±60.33	0.10
Glucose on admission [mmol/l]	12.546 ±8.53	12.983 ±5.72	0.43
Uric acid [µmol/l]	368.321 ±125.82	380.212 ±152.26	0.28
Ejection fraction (%)	39.868 ±9.59	42.126 ±9.14	< 0.001
GFR < 60 ml/min/ 1.73 m^2, *n* (%)	96 (22.2)	167 (47.7)	< 0.001
Incomplete revascularization, *n* (%)	247 (57.2)	212 (60.6)	0.34
TIMI flow < 3 after PCI of IRA, *n* (%)	76 (17.6)	49 (14.0)	0.17
Multivessel coronary artery disease, *n* (%)	327 (75.7)	262 (74.8)	0.80
EF < 35%:	*N* = 405	*N* = 155	
Creatinine on admission [µmol/l]	106.114 ±60.06	108.329 ±64.01	0.70
Glucose on admission [mmol/l]	10.241 ±8.34	10.793 ±4.92	0.46
Uric acid [µmol/l]	407.594 ±139.41	402.841 ±161.91	0.76
Ejection fraction (%)	27.362 ±5.56	27.471 ±5.10	0.83
GFR < 60 ml/min/ 1.73 m^2, *n* (%)	98 (24.2)	82 (52.9)	< 0.001
Incomplete revascularization, *n* (%)	263 (64.9)	98 (63.2)	0.71
TIMI flow < 3 after PCI of IRA, *n* (%)	89.5 (22.1)	34 (21.9)	0.96
Multivessel coronary artery disease, *n* (%)	310 (76.5)	119 (76.8)	0.94
AGE > 70:	*N* = 590	*N* = 491	
Creatinine on admission [µmol/]	105.979 ±52.19	93.749 ±39.88	< 0.001
Glucose on admission [mmol/l]	9.018 ±4.68	10.57 ±5.81	< 0.001
Uric acid [µmol/l]	386.049 ±155.25	363.64 ±144.97	0.029
Ejection fraction (%)	40.134 ±9.51	41.474 ±9.28	0.026
GFR < 60 ml/min/ 1.73 m^2, *n* (%)	172 (29.1)	234 (47.7)	< 0.001
Incomplete revascularization, *n* (%)	360 (61.0)	269 (54.8)	0.04
TIMI flow < 3 after PCI of IRA, *n* (%)	95 (16.1)	100 (20.4)	0.09
Multivessel coronary artery disease, *n* (%)	456 (77.3)	344 (70.0)	0.012
ICR:	*N* = 1405	*N* = 603	
Creatinine on admission [µmol/]	94.559 ±37.41	89.143 ±53.67	0.010
Glucose on admission [mmol/l]	8.852 ±4.36	10.211 ±4.92	< 0.001
Uric acid [µmol/l]	370.14 ±142.01	339.652 ±125.64	< 0.001
Ejection fraction (%)	41.885 ±9.62	42.585 ±9.32	0.15
GFR < 60 ml/min/ 1.73 m^2, *n* (%)	232 (16.5)	214 (35.5)	< 0.001
TIMI flow < 3 after PCI of IRA, *n* (%)	246 (17.5)	127 (21.0)	0.08
Multivessel coronary artery disease, *n* (%)	1321 (94.0)	555 (92.0)	0.13

analysis, worse prognosis in women was not independent and was associated mainly with other comorbidities and their worse clinical characteristics (Table IV).

Discussion

In this population-based study we found that female patients with ICR and/or EF < 35% exhibit a less favorable outcome after invasive treatment performed in the acute phase of AMI. Moreover, our data reflected a trend toward worse long-term survival among women compared to men with diabetes mellitus. Another important finding was that female gender showed a similar outcome to male gender among patients aged > 70, as well as those with GFR < 60.

Our study did not show significant interaction between sex and long-term outcome among patients over the age of 70. This finding is consistent with many studies that presented similar death rates in men and women in advanced age [7, 10, 11]. The protective role of estrogens, including regulation of particular metabolic factors such as lipids, the coagulant system, inflammatory markers or promotion of the vasodilatory effect expires after the menopause, which may explain the lack of difference in outcome between genders in this advanced age subgroup of AMI patients [12].

Cheng *et al.* [4] found that advanced age in women contributed to a higher 30-day mortality rate in compar-

Table III. Mortality

High-risk group/variable	Men	Women	*P*-value
GFR < 60:	*N* = 422	*N* = 426	
Total mortality, *n* (%)	157 (37.2)	180 (42.3)	0.13
In-hospital mortality, *n* (%)	84 (19.9)	89 (20.9)	0.72
30-day mortality, *n* (%)	86 (20.4)	92 (21.6)	0.67
1-year mortality, *n* (%)	130 (30.8)	138 (32.4)	0.62
DM:	*N* = 432	*N* = 350	
Total mortality, *n* (%)	107 (24.8)	108 (30.8)	0.06
In-hospital mortality, *n* (%)	42 (9.7)	41 (11.7)	0.38
30-day mortality, *n* (%)	48 (11.1)	48 (13.7)	0.27
1-year mortality, *n* (%)	75 (17.4)	80 (22.9)	0.05
EF < 35%:	*N* = 405	*N* = 155	
Total mortality, *n* (%)	147 (36.3)	69 (44.5)	0.07
In-hospital mortality, *n* (%)	59 (14.6)	41 (26.5)	0.001
30-day mortality, *n* (%)	61 (15.1)	37 (23.9)	0.014
1-year mortality, *n* (%)	107 (26.4)	55 (35.5)	0.034
AGE > 70:	*N* = 590	*N* = 491	
Total mortality, *n* (%)	171 (29.0)	149 (30.3)	0.63
In-hospital mortality, *n* (%)	68 (11.5)	65 (13.2)	0.39
30-day mortality, *n* (%)	71 (12.0)	64 (13.0)	0.62
1-year mortality, *n* (%)	122 (20.7)	114 (23.2)	0.32
ICR:	*N* = 1405	*N* = 603	
Total mortality, *n* (%)	277 (19.7)	165 (27.3)	< 0.001
In-hospital mortality, *n* (%)	111 (7.9)	71 (11.8)	0.05
30-day mortality, *n* (%)	115 (8.2)	74 (12.3)	0.004
1-year mortality, *n* (%)	195 (13.9)	125 (20.7)	< 0.001

ison to men. Nonetheless, this study was not designed to determine the long-term outcomes in patients undergoing PCI due to AMI. This observation is in contrast to MacIntyre *et al.* [13], who found that survival rate in advanced age is more favorable for women > 75 years old. It could be, however, difficult to compare the above results with our findings because of differences regarding the length of follow-up and treatment strategy used in these studies. The literature presents some studies which confirmed the association between age and outcome after AMI among both genders. Otten *et al.* [7] found in their study that 1-year mortality for women < 65 years old was higher in comparison with their male counterparts, whereas 1-year mortality for women who were > 65 years old in comparison with > 65-year-old men was similar. Moreover, they observed that mortality between genders is age dependent and found that the

Table IV. Independent predictors of death in the high-risk groups of AMI patients

High-risk group/variable	Hazard ratio (95% CI)	*P*-value
GFR < 60 group:		
Male gender	0.859 (0.689–1.071)	0.176
Diabetes mellitus	1.242 (0.988–1.560)	0.063
Left ventricle ejection fraction < 35%	2.617 (2.074–3.303)	< 0.001
Age > 70 years	1.391 (1.114–1.737)	0.004
Incomplete coronary revascularization	1.969 (1.541–2.515)	< 0.001
DM group:		
Male gender	1.060 (0.840–1.336)	0.624
GFR < 60 ml/min/1.73 m^2	3.483 (2.740–4.428)	< 0.001
Left ventricle ejection fraction < 35%	2.497 (1.965–3.171)	< 0.001
Age > 70 years	1.272 (1.007–1.607)	0.043
Incomplete coronary revascularization	1.890 (1.466–2.436)	< 0.001
EF < 35% group:		
Male gender	0.991 (0.734–1.336)	0.950
GFR < 60 ml/min/1.73 m^2	2.996 (2.243–4.001)	< 0.001
Diabetes mellitus	1.133 (0.854–1.503)	0.387
Age > 70 years	1.229 (0.923–1.634)	0.158
Incomplete coronary revascularization	1.562 (1.149–2.125)	0.004
Age > 70 group:		
Male gender	1.057 (0.842–1.327)	0.635
GFR < 60 ml/min/1.73 m^2	2.933 (2.325–3.700)	< 0.001
Diabetes mellitus	0.998 (0.793–1.255)	0.985
Left ventricle ejection fraction < 35%	2.335 (1.838–2.965)	< 0.001
Incomplete coronary revascularization	1.770 (1.381–2.268)	< 0.001
ICR group:		
Male gender	0.946 (0.772–1.160)	0.597
GFR < 60 ml/min/1.73 m^2	3.132 (2.557–3.836)	< 0.001
Diabetes mellitus	1.237 (1.013–1.510)	0.037
Left ventricle ejection fraction < 35%	2.745 (2.245–3.357)	< 0.001
Age > 70 years	1.538 (1.258–1.881)	< 0.001

AMI – acute myocardial infarction, CI – confidence interval, DM – diabetes mellitus, EF – ejection fraction, GFR – glomerular filtration rate, ICR – incomplete coronary revascularization.

less favorable outcome in young women in comparison with the same aged men is statistically significant. Similar observations (although regarding in-hospital mortality) have been made by other authors such as Zheng *et al.* [14] and Vakili *et al.* [15], who found that the unadjusted mortality of patients < 75 years of age was 1.6% among men and 5.5% among women ($p = 0.001$) while the mortality of > 75-year-old patients was 8.4% among older men compared with 14.6% among women ($p = 0.212$). After multivariable logistic regression analysis the hazard ratio for in-hospital mortality was 2.33 (95% CI: 1.2–4.6, $p = 0.016$).

The second high-risk group in our study, where female gender presented a similar outcome to male, was the population of patients with GFR < 60. Impaired renal function expressed by GFR < 60 ml/min/1.73 m² is a known risk factor for worse outcome in a population of patients after AMI. The association between gender and long-term outcome in this subset of patients however is still unclear. There are a limited number of studies analyzing the relation of gender differences with prognosis in AMI patients with GFR < 60. Furthermore, these investigations produced contradictory results.

Our study showed that in the GFR < 60 group there was no significant impact of gender on the outcomes among patients after AMI with concomitant impaired renal function.

This observation confirms the results obtained by the authors of the KAMIR study [6]. Choi *et al.* analyzed a large number of ST-elevation myocardial infarction (STEMI) patients (7679 patients) in a multi-center registry and found no significantly higher hazard ratio of 1-year mortality in either women or men ($p < 0.903$). According to their results, risk of death was proportionally higher with decreasing GFR in both genders. Damman *et al.* [16] in a single-center study of STEMI patients found that GFR had prognostic significance for mortality in both male and female patients. The authors of this prospective investigation calculated the 3-year mortality rate according to the presence of GFR < 60 ml/min in patients. As shown in the results, reduced renal function was associated with increased 3-year mortality in male patients and was also associated with a twofold increase in mortality hazard in female patients.

The differences in survival between men and women with renal disorders might lie at the basis of pathophysiological disparities of renal diseases that were present in both genders.

There are several investigations concerning the pathophysiological basis of chronic kidney disease in relation to gender in the literature. According to them, the possible explanation of this observation might be related to serum phosphorus levels [17] and, going further, changes in renal regulation of phosphorus due to differences in estradiol between males and females [18]. Higher serum phosphorus levels have been reported in women and have been associated with negative effects on renal function and less favorable outcome. Hyperphosphatemia might contribute to hypocalcemia and calcium deposition. The real consequences of this phenomenon might be caused by calcium build-up in tissues, especially in artery walls, which may predispose to greater atherosclerosis of vessels and a worse long-term outcome in women.

What is more, it was noted that a greater possibility of hyperphosphatemia is associated with sex hormone effects on renal phosphorus handling, especially in women after menopause. This reflects the influence of low estradiol levels after the menopause on a higher serum phosphorus level. In comparison, due to estradiol deriving from testosterone, men have higher levels of serum estradiol than post-menopausal women.

These reports are related to chronic kidney disease without taking GFR into consideration, and therefore they do not affect AMI patients. Based on the data mentioned above, renal disorders are associated with worse outcome in women. Our investigation along with the KAMIR study presents different results, i.e. a similar prognosis in both gender groups. A possible explanation for these differences from other studies may be related to lesser known cardiovascular and pathophysiological factors, which could affect the outcome independently of renal function or even inversely.

Different results were also presented by Sederholm Lawesson *et al.* [19] in their single-center investigation. According to them, outcomes between genders were significantly different due to concomitant GFR < 60 ml/min and more strongly associated with female gender. Moreover, they found that the risk of 1-year mortality is reduced by 63% when GFR is increased by each 10 ml/min/1.73 m². These results can be explained by the pathophysiological hypothesis, which claims that female sex is correlated with higher serum phosphorus level, as cited above. This result is different to the results of our study and the KAMIR investigation. A potential explanation for this difference might be attributed to the differences in baseline characteristics and in-hospital management.

A different connection between gender and outcome was observed in the group with concomitant diabetes mellitus. This comorbidity is a well-established risk factor for cardiovascular death and myocardial infarction [20, 21]. The results obtained from our study reflect a trend toward worse long-term survival in women than in men within a subgroup with diabetes mellitus. Several studies have also evaluated mortality in the presence of diabetes among female and male patients after AMI treated with PCI. Most of them, however, encompassed in-hospital mortality and early outcome. The Global Registry of Acute Coronary Events (GRACE) [22] showed that in-hospital case-fatality among patients with acute coronary syndrome and concomitant diabetes mellitus is almost twice as high as that of patients without this disease. The authors of this trial reported that diabetic patients

remained at significantly increased risk for death during acute phase hospitalization. Mehilli *et al.* [23] reported that females with DM had higher mortality risk ($p = 0.02$) in comparison to men ($p = 0.17$) in a cohort of patients with stable and unstable angina, whereas in a group of nondiabetic women and men no difference in 1-year mortality was found. The reason for higher mortality in women with DM compared to their male counterparts is presumably multifactorial and may be associated with smaller vessel size of coronary arteries, a greater amount of inflammatory factors, a worse risk factor burden and a less aggressive treatment strategy [12].

Different conclusions were drawn by Ogita *et al.* [24]. In their study with 4-years follow-up the incidence of cardiac events was similar between male and female gender. Comparable mortality between women and men with acute myocardial infarction treated with PCI with concomitant impaired glucose tolerance (IGT) was also found by Sędkowska *et al.* [25].

No data reporting higher mortality of male patients with diabetes in comparison with female patients were found.

Presence of incomplete coronary revascularization among AMI patients is associated with worse outcome. Moreover, as we confirmed in our investigation, this outcome is also sex-dependent.

The ICR group was one of the two groups with a significant mortality difference between genders in our study. However, we could not compare our results with other publications because of the limited amount of data and lack of studies in this field. There could be many factors which may impact our result. As in other studies, women in our study have more comorbidities than men. This, combined with limited flow through the infarct-related artery, could result in higher mortality. Another possible explanation of this result may involve differences in human physio- and pathophysiology. Women are known to have smaller and stiffer cardiac vessels, and they suffer from endothelial and smooth muscle dysfunction more often [26, 27]. Dickerson *et al.* [28] found in their research that female gender is associated with smaller dimensions of the main coronary arteries, which could also explain our results. Furthermore, women's symptoms of angina are more often atypical compared to men. Women are also more likely to delay seeking care, which could be associated with reduced likelihood of receiving successful reperfusion therapy [27].

The other significantly different group with the prognosis related to gender is the EF < 35% group. In our study, female gender was associated with a less favorable outcome than men in patients with EF < 35%. No data which could validate our results were found. Many studies only confirm that reduced ejection fraction is associated with higher rates of mortality [29–32]. The study of Vakili *et al.* showed that gender has a significant impact on EF and is associated with mortality, but the difference was not statistically significant [30]. Hartikainen *et al.* indicated in their study that reduced EF was a risk factor for nonarrhythmic type of death [33]. The authors of this investigation were able to define a group of patients having 75% of deaths due to a nonarrhythmic mechanism by selecting patients with the lowest EF and omitting patients with the lowest heart rate variability. In the study of Yoon *et al.* [34] the authors found that decreased ejection fraction (lower than 45%) was a major independent predictor ($p < 0.01$) of progressive left ventricular dilatation and no gender dependence was found. The mortality rate was not investigated in this study.

In the ICR group we observed worse prognosis for women in all time intervals and that this relationship deepened over time. An inverse relationship was recorded in the EF < 35% group, where the biggest differences in outcome occurred during the in-hospital and early post-hospital period. Later the prognosis for women becomes more similar to the prognosis for men. In other subsets, regardless of the observation period, outcome differences between genders were statistically non-significant.

In our study population women had higher prevalence of concomitant diseases, but use of pharmacotherapy during interventions, particularly administration of IIb/IIIa inhibitors in female gender, did not differ significantly such use in males. Dziewierz *et al.* [35] in the study of the EUROTRANSFER Registry described how early use of abciximab might be an important determinant of outcomes after PCI. In this study the authors assessed the impact of early administration of abciximab in female and male patients with STEMI transferred for primary PCI on clinical outcomes and patency of infarct-related arteries. The authors found that early use of abciximab led to a reduction in 30-day and 1-year mortality in female gender. What is more, the observed difference was also significant after adjustment for potential confounders. Taking into consideration these results, we can hypothesize that more frequent administration of IIb/IIIa inhibitors, especially in women, might be an important determinant of outcome and may potentially improve their survival.

This study has several limitations. First of all, data were derived from a single-center prospective study, which could have biased the results. On the other hand, the fact that during this nonrandomized observational and single-center study all patients were treated invasively with similar pharmacotherapy at discharge can provide homogeneousness of the study population and represents real-life clinical situations.

There was a lack of precise data for all causes of death in the study population, so we were unable to analyze and fully clarify the potential reasons for differences in mortality in particular study groups. Finally, our study did not resolve the problem of how to improve long-term outcomes of high-risk AMI patients.

Conclusions

Female gender was associated with significantly worse prognosis among AMI patients treated invasively who had incomplete revascularization or left ventricle ejection fraction < 35%. Among diabetic women a trend toward significance was observed. However, according to multivariate analysis worse prognosis in women was not independent and was associated mainly with other comorbidities and their worse clinical characteristics. Other high-risk populations after AMI treated invasively did not reveal that outcome was dependent on any other gender-related interactions.

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Conflict of interest

The authors declare no conflict of interest.

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