

Gender-related differences in men and women with ST-segment elevation myocardial infarction and incomplete infarct-related artery flow restoration: a multicenter national registry

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Abstract

Introduction: Little is known about gender-related differences in ST-segment elevation myocardial infarction (STEMI) and incomplete infarct-related artery (IRA) reperfusion after primary percutaneous coronary intervention (pPCI).

Aim: To evaluate gender-related differences in clinical characteristics and prognosis in patients with STEMI and incomplete IRA reperfusion after pPCI.

Material and methods: From 42,752 STEMI patients hospitalized between 2009 and 2011 in Poland we analyzed a group of 984 (36%) females and 1,746 (64%) males with less than Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow following pPCI.

Results: Women were older than men (72.0 ±11.3 vs. 64.0 ±11.7 years; $p < 0.0001$) and in age-adjusted analysis they were more likely to present with hypertension (73.7% vs. 67%; $p = 0.0003$), diabetes (33% vs. 22.6%; $p < 0.0001$) and obesity (28.1% vs. 22.6%; $p = 0.0016$). Heart rate > 100 beats/min was more common in women, while men were more often smokers and presented with sudden cardiac arrest. The most common IRA in women was the left anterior descending artery, and the right coronary artery in men. After adjusting for age statistically significant differences in pharmacotherapy concerned only the use of insulin (OR = 1.31, 95% CI: 1.02–1.68). High risk of death, rehospitalization due to heart failure or cardiac causes, were observed in all patients during the 6-month and 12-month follow-up periods. The risk of heart failure was significantly higher in women than in men. The most significant decrease in survival rates was observed in the in-hospital period.

Conclusions: Among patients with STEMI and post-interventional TIMI flow grade < 3 women have unfavorable baseline characteristics and an adverse short- and long-term prognosis when compared to men.

Key words: primary percutaneous coronary intervention, thrombolysis in myocardial infarction, ST-segment myocardial infarction, gender-related differences.

Summary

Patients with ST-segment elevation myocardial infarction and incomplete infarct-related artery reperfusion after primary percutaneous coronary intervention remain a poorly studied subset. Presented research clearly highlights the gender discrepancy in baseline characteristics, short- and long-term prognosis among patients with ST-segment elevation myocardial infarction and postprocedural suboptimal blood flow. This suggests the need for gender-tailored techniques to minimize post-intervention complications.

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Introduction

Primary percutaneous coronary intervention (pPCI) is the treatment of choice in patients with acute ST-segment elevation myocardial infarction (STEMI) [1]. The main goal of the primary angioplasty is the rapid and sustained blood flow restoration in the infarct-related artery (IRA). In the mid-1980s, the Thrombolysis In Myocardial Infarction (TIMI) Study Group proposed a scoring system (from 0 to 3) referring to levels of epicardial coronary blood flow assessed during PCI [2]. The no-reflow phenomenon referring to TIMI grade < 3 is not so rare as previously thought. It is estimated that 5% to 23% of patients with STEMI fail to achieve TIMI grade 3 flow in the IRA after pPCI [3]. While incomplete reperfusion is an undisputed unfavorable predictor of mortality, there are conflicting reports about the impact of gender on the outcomes in STEMI patients. Some researchers consider women with STEMI as a special patient subset that requires specific attention due to their worse clinical presentation and prognosis compared to men [4]. Other studies suggest that unfavorable differences in outcomes among females mainly originate from their older age, rather than from gender itself [5, 6].

Aim

The purpose of the present study is therefore to analyze differences in clinical characteristics and prognosis between men and women with STEMI undergoing pPCI with final TIMI grade < 3. Currently, there are no convincing data on this specific patient subgroup, although they remain an important and challenging subset in clinical practice.

Material and methods

Study population Data derive from the prospective, nationwide Polish Registry of Acute Coronary Syndromes (PL-ACS) implemented by the Silesian Centre for Heart Diseases and the Polish Ministry of Health. Its methodology and an analysis of the first 100,193 patients have been previously described [7]. In practice, the registry is an ongoing, multicenter, observational study of consecutively hospitalized Polish patients representing the entire ACS spectrum (unstable angina, NSTEMI, or STEMI). A detailed protocol with inclusion and exclusion criteria, methods and logistics, and definitions of all the fields in the registry dataset had been precisely defined before the registry was launched. Patients are continuously enrolled after the diagnosis of acute coronary syndrome (ACS) is confirmed. In the current study we analyzed a total of 42,752 STEMI patients hospitalized between 2009 and 2011 in Poland. The selected group consisted of 2,730 patients with less than TIMI grade 3 flow following pPCI. Patients with cardiogenic shock on admission were excluded. There were 948 (36%) women and 1,746

(64%) men in the analyzed group. Baseline characteristics, pharmacotherapy, complications during hospitalization, in-hospital and long-term mortality, were compared between women and men. The primary end-points were in-hospital, 30-day, 6-month and 12-month mortality. Major adverse cardiac events (MACE) were defined as cardiovascular death, myocardial infarction, stroke, or major bleeding. The follow-up data were obtained from the National Health Fund (NHF) and updated for all subjects included.

Data definitions According to the protocol, STEMI was defined as the presence of serum cardiac necrosis markers together with the ST-segment elevation consistent with myocardial infarction (MI) of ≥ 2 mm in adjacent chest leads and/or ST-segment elevation of ≥ 1 mm in two or more standard leads or new left bundle branch block (LBBB).

Statistical analysis

Continuous variables are presented as mean \pm standard deviation (SD) and compared by Student's *t*-test. The quantitative data were presented as numbers and percentages and compared with the χ^2 test. Additionally, age-adjusted odds ratios with confidence intervals for women vs. men were calculated for each parameter using logistic regression. Follow-up mortality was analyzed using the Kaplan-Meier method and the log-rank test. Variables with a *p*-value < 0.05 were considered statistically significant. Calculations were performed using NCSS 12 Statistical Software (NCSS, LLC, Kaysville, Utah, USA) and R statistical package, version 2.15.3 (R Development Team, Vienna, Austria).

Results

Out of 40,637 patients with STEMI 34,457 (92.3%) were treated with pPCI. In this group, 2,730 (7.9%) patients achieved less than TIMI grade 3 post-procedural flow. The numbers of patients with particular TIMI grades were as follows: 753 (2.2%) TIMI 0, 414 (1.2%) TIMI 1 and 1563 (4.5%) TIMI 2. There was no gender-specific difference in the incidence of individual TIMI grades.

Clinical and angiographic characteristics of patients

It was found that women were older than men by an average of 8 years. Moreover, they were more likely to present well-known risk factors such as hypertension, diabetes, and obesity. Men were more often smokers and had a history of MI and coronary artery bypass grafting (CABG). There were no gender-related differences in the time to presentation to the emergency room after symptom onset. However, most of the patients presented to the emergency room 3–12 h since symptoms onset. In men, cardiac arrest was significantly more common at admission, while tachycardia occurred more often in females.

After adjustment for age, female gender was no longer an independent risk factor for hyperlipidaemia, atrial fibrillation (AF), heart rate > 100 beats/min, anterior MI, and sudden cardiac arrest (SCA) during hospitalization.

The vessel responsible for myocardial infarction was most commonly the left anterior descending (LAD) artery in women, whereas it was the right coronary artery (RCA) or an aorto-coronary bypass in men. However, the latter turned out to be irrelevant after the age-adjusted analysis (odds ratio (OR) for aorto-coronary bypass occlusion in men: 0.5, 95% confidence interval (CI): 0.23–1.12).

Culprit lesions were identified in 1726 men and in 931 women. Other cases were considered as MI with no obstructive coronary artery disease (MINOCA, Table I).

In-hospital complications

There was no gender-related difference in the incidence of: myocardial infarction (0.7% in males vs. 0.8% in females, $p = 0.71$), pulmonary edema (3% vs. 3.4%, $p = 0.59$), stroke (0.5 vs. 0.7% in females, $p = 0.39$), intracranial hemorrhage (0% vs. 0.1%, $p = 0.77$) or target lesion revascularization during hospitalization (1.4% vs.

Table I. Baseline characteristics

Parameter	Men 1746 (64%)	Women 984 (36%)	P-value	Age-adjusted odds ratio for females (95% CI)
Age, mean \pm SD	64.0 \pm 11.7	72.0 \pm 11.3	< 0.0001	–
Older than 65 years	807 (46.2%)	734 (74.6%)	< 0.0001	–
Age < 65 years	939 (53.8%)	250 (25.4%)	< 0.0001	–
Arterial hypertension	1170 (67%)	725 (73.7%)	0.0003	1.22 (1.02–1.47)
Diabetes	394 (22.6%)	325 (33%)	< 0.0001	1.55 (1.29–1.86)
Hyperlipidemia	690 (39.5%)	389 (39.5%)	0.99	1.09 (0.92–1.29)
Ever smoked	1238 (70.9%)	337 (34.3%)	< 0.0001	0.28 (0.24–0.34)
Obesity (BMI > 30 kg/m ²)	395 (22.6%)	276 (28.1%)	0.0016	1.54 (1.27–1.86)
Renal failure	106 (6.1%)	74 (7.5%)	0.14	0.84 (0.61–1.17)
Previous myocardial infarction	269 (15.4%)	115 (11.7%)	0.0073	0.68 (0.53–0.87)
Previous PCI	174 (10%)	66 (6.7%)	0.0039	0.76 (0.56–1.03)
Previous CABG	50 (2.9%)	10 (1%)	0.0016	0.4 (0.2–0.8)
Congestive heart failure	104 (6%)	79 (8%)	0.038	0.99 (0.73–1.37)
Dominant symptom type:				
Chest pain	1601 (91.7%)	903 (91.8%)	0.95	1.07 (0.79–1.44)
Dyspnea	34 (2%)	27 (2.7%)	0.18	1.28 (0.74–2.2)
Cardiac arrest	43 (2.5%)	10 (1%)	0.0085	0.46 (0.23–0.95)
EKG on admission:				
Sinus rhythm	1587 (90.9%)	841 (85.5%)	< 0.0001	0.86 (0.67–1.11)
AF	124 (7.1%)	115 (11.7%)	< 0.0001	1.14 (0.86–1.52)
HR > 100 min ⁻¹	179 (10.3%)	143 (14.5%)	0.0009	1.45 (1.13–1.86)
Infarct location:				
Anterior	713 (40.8%)	457 (46.4%)	0.0045	1.15 (0.98–1.36)
Inferior	865 (49.5%)	426 (43.3%)	0.0017	0.83 (0.71–0.98)
Symptom onset-to-admission time:				
0–3 h	567 (33.8%)	297 (31.5%)	0.23	0.93 (0.78–1.11)
3–12 h	679 (40.5%)	390 (41.4%)	0.66	1.00 (0.85–1.19)
> 12 h	432 (25.7%)	256 (27.2%)	0.43	1.08 (0.89–1.3)
Infarct-related artery:				
LM	29 (1.7%)	13 (1.3%)	0.49	0.8 (0.4–1.59)
LAD	679 (38.9%)	463 (47.1%)	< 0.0001	1.29 (1.09–1.52)
RCA	727 (41.6%)	353 (35.9%)	0.0031	0.83 (0.7–0.99)
SVG	31 (1.8%)	8 (0.8%)	0.042	0.5 (0.23–0.12)
Post-procedural TIMI grade:				
TIMI 2	1021 (58.5%)	542 (55.1%)	0.085	0.93 (0.78–1.09)
TIMI 0 or 1	725 (41.5%)	442 (44.9%)	0.085	1.08 (0.91–1.28)

BMI – body mass index, CI – confidence interval, PCI – percutaneous coronary intervention, CABG – coronary artery bypass surgery, EKG – electrocardiogram, AF – atrial fibrillation, HR – heart rate, LM – left main coronary artery, LAD – left anterior descending artery, RCA – right coronary artery, TIMI – Thrombolysis in Myocardial Infarction, SVG – saphenous vein graft.

1.2%, $p = 0.73$). Sudden cardiac death, bleeding, acute mitral regurgitation (AMR), free wall rupture (FWR) and infarct-related ventricular septal defect (VSD) were more common in females. After adjusting for age, the only significant complication occurring more often in women was VSD (Table II).

On-admission pharmacotherapy

In the primary analysis, women were less likely to receive acetylsalicylic acid (ASA), glycoprotein (GP) IIb/IIIa inhibitors, angiotensin-converting enzyme inhibitors (ACEI), β -blockers and statins, while the usage of diuretics and insulin was more common in women than in men. After adjusting for age, statistically significant differences concerned only the use of insulin (OR = 1.31, 95% CI: 1.02–1.68). In 9.4% of men and 11.9% of women ASA was not used (Table III).

Follow-up

High risk of death, rehospitalization due to heart failure or cardiac causes and MACE were observed in all patients during the 6-month and 12-month follow-up periods. After age adjustment the risk of heart failure was significantly higher in women than in men (Table IV).

In-hospital and long-term mortality

The mortality was significantly higher in women than in men in each follow-up period. The most significant de-

crease in survival rates was observed in the in-hospital period (Figure 1).

Discussion

The major finding of our study is that women with STEMI and post-procedural suboptimal coronary blood flow have unfavorable clinical presentation and higher mortality rate in each follow-up period, compared to men. To the best of our knowledge, this is the first report on gender-related differences in a large population of STEMI patients with incomplete reperfusion, as many other published papers focused on determining the predictive factors of suboptimal flow after pPCI with no gender specification [3, 8]. Moreover, available data comparing outcomes in men and women with STEMI remain controversial, with some authors reporting worse prognosis in females and others showing no sex differences in clinical endpoints [4, 9, 10]. These discrepancies can be partly explained by different inclusion criteria and size of study populations [10]. However, it seems that the most confounding factor when comparing the outcomes of men versus women with STEMI is age. Existing data indicates a potential interaction between age and gender as in most studies females were older than men and thus had more comorbidities affecting overall results [11]. Similarly, in our study women with suboptimal blood flow after pPCI were older than men by an average of 8 years and had more well-known risk factors for cardiovascu-

Table II. In-hospital complications

Parameter	Men 1746 (64%)	Women 984 (36%)	P-value	Age-adjusted odds ratio for females (95% CI)
Bleeding	40 (2.3%)	40 (4.1%)	0.0083	1.31 (0.82–2.1)
AMR	1 (0.1%)	5 (0.5%)	0.047	7.8 (0.88–68.73)
FWR	5 (0.3%)	9 (0.9%)	0.027	2.43 (0.78–7.55)
VSD	2 (0.1%)	8 (0.8%)	0.010	7.4 (1.49–36.87)
Cardiac death	201 (11.5%)	162 (16.5%)	0.0003	1.05 (0.83–1.34)

CI – confidence interval, AMR – acute mitral regurgitation, FWR – free wall rupture, VSD – ventricular septal defect.

Table III. In-hospital pharmacotherapy

Parameter	Men 1746 (64%)	Women 984 (36%)	P-value	Age-adjusted odds ratio for females (95% CI)
Acetylsalicylic acid	1582 (90.6%)	867 (88.1%)	0.039	0.83 (0.64–1.08)
Clopidogrel	1725 (98.8%)	970 (98.6%)	0.62	0.9 (0.44–1.85)
GP IIb/IIIa inhibitor	725 (41.5%)	350 (35.6%)	0.0022	0.92 (0.78–1.1)
β -Blocker	1274 (73%)	660 (67.1%)	0.0011	0.86 (0.72–1.03)
ACEI	1170 (67%)	610 (62%)	0.0082	0.9 (0.76–1.07)
ARB	34 (2%)	15 (1.5%)	0.42	0.73 (0.38–1.37)
Statin	1398 (80.1%)	752 (76.4%)	0.025	0.9 (0.74–1.11)
Diuretics	374 (21.4%)	278 (28.3%)	< 0.0001	1.13 (0.93–1.37)
Aldosterone antagonist	146 (8.4%)	102 (10.4%)	0.080	1.22 (0.92–1.61)
Insulin	182 (10.4%)	139 (14.1%)	0.0039	1.31 (1.02–1.68)
Oral antihyperglycemic agents	92 (5.3%)	57 (5.8%)	0.56	1.04 (0.73–1.48)

CI – confidence interval, GP – glycoprotein, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker.

Table IV. Follow-up of patients with STEMI and post-procedural TIMI grade < 3

Parameter	Men 1453 (65%)	Women 766 (35%)	P-value	Age-adjusted odds ratio for females (95% CI)
Six-month follow-up:				
Death	135 (9.3%)	113 (14.8%)	0.0001	1.08 (0.89–1.32)
Reinfarction	46 (3.2%)	27 (3.5%)	0.65	1.09 (0.66–1.8)
Heart failure rehospitalization	96 (6.6%)	97 (12.7%)	< 0.0001	1.5 (1.1–2.03)
Cardiac causes rehospitalization	603 (41.5%)	300 (39.2%)	0.29	0.94 (0.78–1.12)
MACE	698 (48%)	380 (49.6%)	0.48	1.01 (0.85–1.2)
Twelve-month follow-up:				
Death	163 (11.2%)	144 (18.8%)	< 0.0001	1.16 (0.96–1.4)
Reinfarction	61 (4.2%)	37 (4.8%)	0.49	1.08 (0.7–1.67)
Heart failure rehospitalization	129 (8.9%)	113 (14.8%)	< 0.0001	1.33 (1.0–1.75)
Cardiac cause rehospitalization	689 (47.4%)	359 (46.9%)	0.80	1.01 (0.85–1.2)
MACE	791 (54.4%)	448 (58.5%)	0.068	1.11 (0.93–1.32)

CI – confidence interval, MACE – major adverse cardiac events.

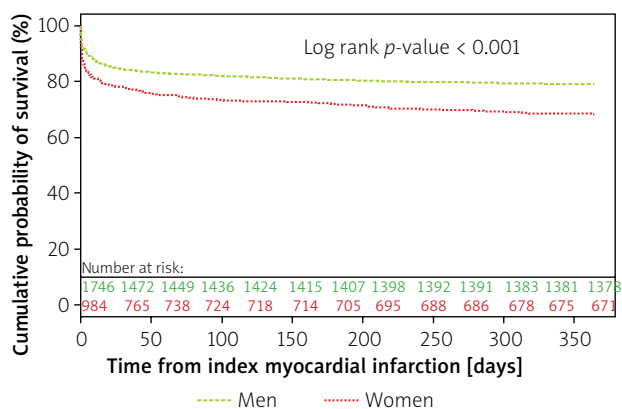


Figure 1. Kaplan-Meier survival curves in patients with STEMI and post-procedural TIMI < 3

lar disease. In addition, some of these factors such as hypertension, diabetes and obesity still occurred more often in women after an age-adjusted analysis. Comorbidities and advanced age deeply influence the clinical presentation. This is confirmed by the fact that among all the analyzed factors after the age-adjusted analysis, only tachycardia occurred more frequently in women. Although it is well documented that women with STEMI have time delays in medical help seeking longer than their male counterparts [12], we did not observe gender-related differences in the symptom onset-to-balloon time in the studied population.

In our study, the incidence of suboptimal coronary blood flow was 7.9%, and it is comparable with other studies which similarly used the criterion of TIMI flow grade < 3 [3, 13, 14]. In a multivariate analysis Gąsior *et al.* found that diabetes and advanced age were independent determinants of post-procedural coronary flow in patients with myocardial infarction [15]. Data analyses from the Primary Angioplasty in Myocardial Infarction (PAMI) trials also revealed age > 70 years, diabetes and

in addition heart failure as important risk factors for final TIMI flow grade < 3 after pPCI [3]. None of the mentioned studies have shown that female sex was a predictor of interventional treatment failure. However, women have narrower coronary arteries than males [16] and it might be considered as a possible obstacle in balloon or stent delivery. According to Watanabe *et al.*, the ratio of stent diameter to vessel diameter (per 0.1 increase) is significantly associated with slow flow following stent implantation [17]. Moreover, low estrogen levels in post-menopausal women contribute to the development of coronary microvascular disease [18] and the no-reflow phenomenon. Some researchers indicate that patients with the LAD as the IRA have fourfold greater risk of the no-reflow phenomenon [15, 19]. As it was previously investigated, acute MI involving the LAD is associated with worse prognosis due to lower ejection fraction and risk of developing heart failure [20]. Consequently, anterior STEMI increases the risk of death and post-infarction heart failure [21]. In our study, LAD occlusion was more common in women, which could contribute to other findings regarding their worse prognosis compared to men.

Our study showed that women with STEMI and incomplete revascularization have more in-hospital complications. Although previous studies indicate that females after pPCI have more bleeding complications compared to men [22, 23], we did not observe such dependence after adjustment for age. Surprisingly, some complications in the studied group occurred less frequently than in the whole population of patients with STEMI, applying to FWR or VSD [24].

Based on the results, women are less likely to receive guideline-recommended pharmacotherapy during hospitalization. However, these differences are mainly age-dependent as women are almost a decade older than men, with higher prevalence of hemorrhagic complications, diabetes mellitus and renal failure. There are no spe-

cific data to clarify the reason for the surprisingly low percentage of ASA usage; however, we hypothesize that some patients have already used chronic anticoagulation for other reasons such as an artificial heart valve, atrial fibrillation or a history of pulmonary embolism. Moreover, certain patients could have contraindications for ASA administration because of allergy. Similarly, Akhter *et al.* showed that women after ACS were less likely to receive aspirin and GP IIb/IIIa inhibitors, and were less often discharged on aspirin [23]. Several large studies evaluating gender-related differences in STEMI patients also revealed that men receive optimal therapy more often than women (including interventional treatment) [25, 26]. According to our data, 7.7% of females did not undergo pPCI. Although the registry does not allow us to precisely identify the causes, we suspect that it could be explained by MINOCA, subsequent CABG or coronary lesions not amenable to revascularization. No specific analyses were performed among patients with MINOCA as due to the small sample size (20 men and 13 women) they were included in the entire studied population. However, new guidelines of the European Society of Cardiology (ESC) emphasize that MINOCA comprises up to 14% of STEMI patients and requires additional diagnostic tests and tailored therapy which may differ from typical STEMI management [27].

Previous studies clearly indicate that TIMI grade < 3 flow after pPCI in patients with MI leads to poor in-hospital and long-term outcomes [3, 13, 28]. Based on PAMI trials, patients who did not achieve optimal TIMI flow after pPCI had significantly higher rates of in-hospital mortality and in-hospital major adverse cardiac events than those with TIMI grade 3 [3]. Likewise, an increase in early (30-day) mortality with TIMI grade < 3 flow was noted in the GUSTO-IIb trial [29]. Another study by Champney *et al.* revealed that 30-day mortality after STEMI was higher among women and even after adjusting for comorbidities mortality remained about 15–20% higher in younger females than in men [11]. In the present study, after adjustment for age we did not observe a statistically significant difference in mortality between the sexes. Moreover, the survival rates decreased substantially in the early period after STEMI, and then remained moderately stable. Additionally, during the 12-month follow-up period we observed higher risk of heart failure in women, which may be associated with more frequent microvascular and endothelial dysfunction [30].

Study limitations

Although the PL-ACS Registry is a prospective observational study, not all hospitals treating ACS patients in Poland contributed to data collection. Data also vary depending on the center and country region. Thus, the data averaged for Poland may not necessarily reflect the actual

situation in the different regions of the country. Moreover, the imaging protocol was not standardized in individual catheterization laboratories. The catheterization centers participating in the study did not have a core laboratory and therefore the TIMI grade assessment was operator-dependent. However, experimental studies prove the close correlation of individual TIMI grades with the myocardial necrosis area even if the assessment is often subjective. In the present study the effect of vascular access was not analyzed.

Conclusions

Our study shows that among patients with STEMI and incomplete epicardial coronary blood flow restoration following pPCI women have unfavorable baseline characteristics and clinical presentation. They also have an adverse short- and long-term prognosis when compared to men, including higher risk of heart failure development. After adjustment for age the in-hospital and long-term mortality is similar in both sexes, with the greatest decrease in survival during the in-hospital period.

Conflict of interest

The authors declare no conflict of interest.

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