

## Mortality of women with ST-segment elevation myocardial infarction and cardiogenic shock – results from the PL-ACS registry

### Śmiertelność kobiet z zawałem serca z uniesieniem odcinka ST i wstrząsem kardiogenym – wyniki z rejestru PL-ACS

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**Key words:** cardiogenic shock, revascularization strategy, optimal treatment, mortality, sex-related differences.

**Słowa kluczowe:** wstrząs kardiogeny, strategia rewaskularyzacji, optymalne leczenie, śmiertelność, różnice zależne od płci.

#### Abstract

**Introduction:** Gender-related differences are well elucidated in ST-segment elevation myocardial infarction (STEMI) patients. However, data on patients with cardiogenic shock (CS) are scarce and do not indicate the cause-effect relationship.

**Aim of the research:** To evaluate the differences between women and men with CS complicating STEMI and to identify factors which determine the prognosis in the female group.

**Material and methods:** A total of 3589 consecutive patients with CS were selected from a large, multicenter national registry on 57 400 consecutive STEMI patients.

**Results:** Women had a greater time delay from symptom onset to treatment (admission within the first 2 h, 37.1% vs. 44.8%;  $p < 0.001$ ). They were also less likely to undergo interventional treatment (40.4% vs. 48.1%;  $p < 0.001$ ) and to receive coronary stenting (86.8% vs. 90.1%;  $p = 0.045$ ), glycoprotein IIb/IIIa inhibitors (15.3% vs. 20.1%;  $p < 0.001$ ) and clopidogrel (46.3% vs. 53.6%;  $p < 0.001$ ). In the female patients in-hospital and 12-month mortality were higher than in their male counterparts (55% vs. 45.8%;  $p < 0.001$  and 72.5% vs. 63.8%;  $p < 0.001$ , respectively). Women with cardiogenic shock were less likely to receive optimal therapy than men, which resulted in a poor clinical outcome.

**Conclusions:** This should encourage medical professionals to apply advanced therapeutic strategies without gender bias. Only if there are no gender-related discrepancies in the management of patients with cardiogenic shock may the beneficial impact of invasive treatment be fairly assessed and the hypothesis that more guideline-adherent treatment of women results in better outcomes be validated.

#### Streszczenie

**Wprowadzenie:** Wstrząs kardiogeny (CS), obarczony wysoką śmiertelnością szpitalną, jest jednym z najgorzej rokujących powikłań zawału serca niezależnie od sposobu leczenia. U chorych z zawałem serca z uniesieniem odcinka ST (STEMI) różnice zależne od płci są dobrze udokumentowane. Stwierdzono korzystne efekty stosowania angioplastyki wieńcowej. Nie ma jednak danych na temat podgrupy osób ze wstrząsem kardiogenym.

**Cel pracy:** Ocena różnic w przebiegu klinicznym i rokowaniu pomiędzy kobietami a mężczyznami ze STEMI powikłanym CS oraz analiza czynników determinujących rokowanie u kobiet.

**Materiał i metody:** Do badania włączono 3589 kolejnych pacjentów z CS, których wybrano z dużego, wielośrodkowego narodowego rejestru 57 400 pacjentów ze STEMI.

**Wyniki i wnioski:** Kobiety miały większe opóźnienie od początku objawów do rozpoczęcia leczenia (przyjęcie w ciągu 2 godzin: 37,1% vs 44,8%;  $p < 0,001$ ). Rzadziej były kwalifikowane do leczenia inwazyjnego (40,4% vs 48,1%;  $p < 0,001$ ), rzadziej stentowano u nich tętnice wieńcowe (86,8% vs 90,1%;  $p = 0,045$ ), stosowano inhibitory IIb/IIIa (15,3% vs 20,1%;  $p < 0,001$ ) i klopidogrel (46,3% vs 53,6%;  $p < 0,001$ ). Kobiety miały większą niż mężczyźni śmiertelność szpitalną i roczną

(55% vs 45,8%;  $p < 0,001$  i 72,5% vs 63,8%;  $p < 0,001$ ). Kobiety z CS rzadziej otrzymywały optymalne leczenie, co skutkowało gorszym rokowaniem.

**Wnioski:** Należy zachęcać lekarzy do stosowania nowoczesnego postępowania bez względu na płeć pacjenta. Tylko wtedy korzyść z leczenia inwazyjnego może być w pełni oceniona, a hipoteza o przynoszącym korzyści leczeniu zgodnym z wytycznymi będzie mogła zostać zweryfikowana.

## Introduction

Cardiogenic shock (CS) complicates approximately 4.2–7.7% of ST-segment elevation myocardial infarctions (STEMI) and results in a very high in-hospital mortality rate ranging from 47% to 70%. The STEMI patients aged 65 or more, with left ventricular ejection fraction (EF)  $< 35\%$ , elevated creatinine kinase activity, diabetes or impaired fasting glucose, a history of prior myocardial infarction or multivessel coronary artery disease are prone to CS development. The risk of shock is also higher in female patients with history of stroke, heart failure and atherosclerosis of lower extremities [1]. The history of cardiac arrest and neurological defects as well as no reperfusion therapy also affect the prognosis. The main cause of CS in the early hours of STEMI is acute left ventricular failure resulting from a massive necrosis or some combination of a moderate necrosis and muscle freezing in the adjacent areas. Mechanical complications of MI as well as other rare cause are also reported [2]. The SHOCK trial clearly showed benefits from the use of an early revascularization strategy. This effect was observed only in patients below 75 years of age [3, 4]. It has become a source of controversy over the optimal treatment of elderly patients. Dzavik *et al.* reported that in patients over 75 years the in-hospital mortality was 48% in those who underwent early revascularization vs. 81% in the conservative treatment group ( $p = 0.003$ ) [5]. Dauerman *et al.* reported lower mortality in patients treated invasively compared to those treated conservatively, but this effect also affected patients aged 75 years or more [6, 7]. Similar conclusions were drawn from the Polish Registry of Acute Coronary Syndromes (PL-ACS). The mortality was lower in patients with CS treated with percutaneous coronary intervention (PCI) versus conservative treatment (54.6% vs. 69.9%,  $p < 0.001$ ) [8]. In addition, between 2003 and 2009 the improvement in STEMI patients' prognosis resulted from the extent of revascularization techniques, improved logistics, and the efficiency of drug therapy [9], especially abciximab [10]. The SHOCK trial showed that survival was not related to gender, diabetes, ST-segment elevation index, right heart catheterization, pulmonary capillary wedge pressure, use of intraaortic balloon pump (IABP), thrombolysis, the use of glycoprotein IIb/IIIa inhibitors, inotropes and vasopressors, or a history of prior MI, PCI and coronary artery bypass grafting (CABG) [11]. Gender-related differences are well elucidated in STEMI patients, but data on patients with CS are

scarce and do not indicate the cause-effect relationship. There have been no proposals on the improvement in prognosis in women with CS complicating STEMI. In the present study gender- and age-related issues in the management of cardiogenic shock were studied and possible improvement in prognosis in the female group is discussed.

## Material and methods

Data were derived from the Polish Registry of Acute Coronary Syndromes (PL-ACS). The basic principles of our registry have been reported previously and are available on-line [8]. Briefly, this is an ongoing, nationwide, multicenter, prospective, observational study of all patients with acute coronary syndromes. The study group was extracted from a population of 57 400 consecutive STEMI patients included between May 2005 and November 2008 and followed up until January 2010. A total of 3589 (6.3%) patients were included in the final analysis. The inclusion criteria were STEMI and CS defined as a systolic blood pressure of less than 90 mm Hg for at least 30 min secondary to myocardial dysfunction.

### Statistical analysis

The continuous parameters are expressed as mean  $\pm$  standard deviation or median and interquartile range, depending on the normality of data distribution. The significance of differences between means was tested using Student's *t* test or unpaired ANOVA rank test, Kruskal-Wallis and Mann-Whitney or  $\chi^2$  test as appropriate. Mortality was analyzed using the Kaplan-Meier method, and the log-rank test. Multivariate analysis of factors influencing mortality was performed by the Cox proportional hazard method. A  $p$ -value  $\leq 0.05$  was considered significant (two-sided). Calculations and statistical analyses were performed using Statistica PL version 6.1 (StatSoft, Inc.).

## Results

### Baseline characteristics

Women were older than men, more of them were over 65 years of age, and more women than men had arterial hypertension, diabetes and obesity. Women less frequently than men had a history of myocardial infarction, coronary angioplasty and smoking. Initial cardiac arrest affected more men than women, while it occurred more commonly during the in-hospital course in the female group. Women more frequently

**Table 1.** Baseline characteristics

Parameter	Females N = 1435 (40.0%)	Males N = 2154 (60.0%)	P-value
Age, mean ± SD	72.7 ±12.0	65.4 ±11.9	< 0.001
Patients ≥ 65 years old	1088 (75.8%)	1146 (53.2%)	< 0.001
Arterial hypertension	764 (53.2%)	1000 (46.4%)	< 0.001
Diabetes mellitus	484 (33.7%)	477 (22.1%)	< 0.001
Hypercholesterolemia	408 (28.4%)	595 (27.6%)	0.59
Smoking	227 (15.8%)	932 (43.3%)	< 0.001
Obesity (BMI > 30 kg/m <sup>2</sup> )	332 (23.1%)	307 (14.3%)	< 0.001
Prior MI	203 (14.1%)	406 (18.8%)	< 0.001
Prior PCI	19 (1.3%)	57 (2.6%)	0.007
Prior CABG	34 (2.4%)	70 (3.2%)	0.12
<b>Admission ECG:</b>			
Sinus rhythm	1046 (72.9%)	1587 (73.7%)	0.60
AF	189 (13.2%)	210 (9.7%)	0.001
Pacemaker	19 (1.3%)	27 (1.3%)	0.85
Other	181 (12.6%)	330 (15.3%)	0.023
<b>Symptom onset-to-admission time [h]:</b>			
0–2	525 (37.1%)	949 (44.8%)	< 0.001
2–6	427 (30.2%)	640 (30.2%)	0.99
6–12	154 (10.9%)	193 (9.1%)	0.082
> 12	309 (21.8%)	337 (15.9%)	< 0.001
<b>Cardiac arrest:</b>			
Before admission	259 (18%)	626 (29.1%)	< 0.001
During hospitalization	688 (47.9%)	787 (36.5%)	< 0.001
No cardiac arrest	486 (33.9%)	738 (34.3%)	0.81

BMI – body mass index (kg/m<sup>2</sup>), MI – myocardial infarction, PCI – percutaneous coronary intervention, CABG – coronary artery bypass grafting, AF – atrial fibrillation.

had atrial fibrillation. Fewer women than men were admitted during the first 2 h of the chest pain, and more women than men were admitted to hospital after 12 h from the symptom onset (Table 1).

### Treatment strategy

Women were treated conservatively more frequently than men. Coronary angiography, PCI and CABG were performed less frequently in women. In women the revascularization strategy was applied after 12 h more often ( $p = 0.046$ ). Fewer women received IABP. There were no differences in in-hospital complications. Women received less glycoprotein IIb/IIIa inhibitors and clopidogrel. The increased use of insulin in women was observed (Table 2). There were no differences in the invasive treatment according to age groups except in women older than 80 (Table 3).

### Mortality

In-hospital, 30-day, and 12-month mortality was higher in women with CS than in men with CS (Table 4). In age subgroups there were no differences in mortality between males and females (Table 5). In the multivariable analysis adjusted for age and cardiovascular risk factors female sex did not influence mortality (Table 6).

### Discussion

The gender-related differences in coronary heart disease are undeniable. They include age (women are older), risk factors (diabetes, oral contraceptives and hormone replacement therapy) [12], symptoms [13, 14], delay in medical interventions including revascularization [15], more frequent complications [16],

**Table 2.** Treatment strategy

Parameter	Females N = 1435 (40.0%)	Males N = 2154 (60.0%)	P-value
Conservative	688 (47.9%)	871 (40.4%)	< 0.001
Thrombolytic	133 (9.3%)	200 (9.3%)	0.99
Coronary angiography	623 (43.4%)	1108 (51.4%)	< 0.001
PCI	580 (40.4%)	1035 (48.1%)	< 0.001
Stent implantation	508 (86.8%)	936 (90.1%)	0.045
CABG	2 (0.1%)	7 (0.3%)	0.45
PCI + CABG	5 (0.3%)	4 (0.2%)	0.54
<b>Symptom onset-to-balloon time [h]:</b>			
0–2	95 (16.8%)	189 (18.9%)	0.29
2–6	265 (46.7%)	488 (48.7%)	0.45
6–12	89 (15.7%)	157 (15.7%)	0.99
> 12	118 (20.8%)	168 (16.8%)	0.046
<b>Other treatments:</b>			
IABP	111 (7.7%)	220 (10.2%)	0.012
GP IIb/IIIa inhibitor	219 (15.3%)	432 (20.1%)	< 0.001
ASA	1070 (74.6%)	1571 (72.9%)	0.28
Ticlopidine	138 (9.6%)	253 (11.7%)	0.045
Clopidogrel	664 (46.3%)	1155 (53.6%)	< 0.001
Insulin	349 (24.3%)	382 (17.7%)	< 0.001
<b>In-hospital outcomes:</b>			
Re-MI	90 (6.3%)	138 (6.4%)	0.87
Stroke	26 (1.8%)	25 (1.2%)	0.11
Major bleeding	48 (3.3%)	60 (2.8%)	0.34
re-PCI (TLR)	11 (0.8%)	33 (1.5%)	0.041

IABP – intraaortic balloon pump, GP IIb/IIIa – glycoprotein IIb/IIIa, ASA – acetylsalicylic acid, Re-MI – recurrent myocardial infarction, TLR – target lesion revascularization, other abbreviations as in Table 1.

**Table 3.** Invasive treatment according to age

Age [years]	Females N = 1435 (40.0%)	Males N = 2154 (60.0%)	P-value
< 40	8 (73%)	13 (57%)	0.59
≥ 40 and < 50	33 (65%)	99 (59%)	0.46
≥ 50 and < 60	102 (56.4%)	318 (58.4%)	0.64
≥ 60 and < 70	138 (56.1%)	300 (53.9%)	0.58
≥ 70 and < 80	196 (41.8%)	272 (44.8%)	0.32
≥ 80	146 (30.6%)	106 (41.7%)	0.0026

occurrence of CS, increased mortality associated with angioplasty [17], worse long-term results of late revascularization [18–20] and worse clinical outcomes of CABG [17]. These differences can also be seen in the

**Table 4.** Mortality

Parameter	Females N = 1435 (40.0%)	Males N = 2154 (60.0%)	P-value
In-hospital	789 (55%)	986 (45.8%)	< 0.001
30-day	939 (65.4%)	1204 (55.9%)	< 0.001
6-month	1018 (70.9%)	1336 (62%)	< 0.001
12-month	1040 (72.5%)	1375 (63.8%)	< 0.001

etiology, course and prognosis of women with STEMI complicated by CS [21]. In ongoing studies in recent decades gender-related issues in prognosis and treatment strategies were analyzed, but with no comment on CS [22–25]. Many studies have shown that poor clinical outcomes in women are related to suboptimal

**Table 5.** In-hospital and 12-month mortality according to age

Age	In-hospital			12-month		
	Females N = 1435 (40.0%)	Males N = 2154 (60.0%)	P-value	Females N = 1435 (40.0%)	Males N = 2154 (60.0%)	P-value
< 40	2 (18%)	8 (35%)	0.55	5 (45%)	10 (43%)	0.79
≥ 40 and < 50	19 (37%)	54 (32.1%)	0.50	25 (49%)	79 (47%)	0.80
≥ 50 and < 60	57 (31.5%)	182 (33.4%)	0.64	82 (45.3%)	268 (49.2%)	0.37
≥ 60 and < 70	113 (45.9%)	258 (46.3%)	0.92	154 (62.6%)	356 (63.9%)	0.72
≥ 70 and < 80	263 (56.1%)	322 (53.1%)	0.32	365 (77.8%)	452 (74.5%)	0.20
≥ 80	335 (70.2%)	162 (63.8%)	0.075	409 (85.7%)	201 (82.7%)	0.27

**Table 6.** Multivariate analysis of mortality

Variable	Wald $\chi^2$	Relative risk (95% CI)	P-value
Age (per 10 years more)	139.5	1.25 (1.20–1.30)	< 0.0001
Systolic blood pressure on admission (per 10 mm Hg less)	126.2	1.06 (1.05–1.07)	< 0.0001
Heart rate on admission (per 10 bpm more)	20.7	1.03 (1.01–1.04)	< 0.0001
Symptom-onset-to-admission time 2–6 h	19.5	0.77 (0.68–0.86)	< 0.0001
Admission ECG: LBBB	17.0	1.37 (1.18–1.60)	< 0.0001
Hypercholesterolemia	13.3	0.84 (0.76–0.92)	0.0003
Admission ECG: other than sinus rhythm	12.7	1.18 (1.08–1.29)	0.0004
Symptom-onset-to-admission time 0–2 h	10.4	0.83 (0.75–0.93)	0.0012
Smoking	9.4	0.86 (0.77–0.95)	0.0022
Admission ECG: RBBB	8.4	1.24 (1.07–1.44)	0.0038
Prior MI	7.0	1.16 (1.04–1.29)	0.0081
Obesity (BMI > 30 kg/m <sup>2</sup> )	6.1	1.14 (1.03–1.27)	0.014
Arterial hypertension	2.9	0.93 (0.85–1.01)	0.091
Prior PCI	1.4	0.84 (0.62–1.12)	0.23
Cardiac arrest before admission	1.4	0.94 (0.85–1.04)	0.24
Symptom-onset-to-admission time 6–12 h	0.5	0.94 (0.81–1.10)	0.48
Female sex	0.1	1.02 (0.93–1.11)	0.71
Diabetes mellitus	0.1	0.98 (0.90–1.08)	0.73
Prior CABG	0.002	1.00 (0.77–1.28)	0.97

Abbreviations as in Tables 1 and 2.

treatment [26–29]. Conversely, several lines of evidence indicate that guidelines-compliant treatment in women and men results in significant improvements in outcomes [30]. It is known that a delay in the application of invasive treatment significantly worsens the prognosis of patients with STEMI [31]. All studies cited above, and the study of (S)MASH, confirmed the effectiveness of invasive therapy and the improvement in prognosis of patients with STEMI [32]. The complications profile was similar to other reports [33]. In the present study women were less likely to undergo

PCI, and significantly fewer women underwent coronary stenting during PCI. There were also noted more than 2 h PCI delay and significantly less frequent administration of GP IIb/IIIa inhibitors and clopidogrel in the female group. It may be hypothesized that the discrepancy observed resulted in worse prognosis in the female group. In younger patients who underwent a similar therapeutic approach, the outcomes in women were better and were similar to those in men, even though the rate of bleeding complications was higher in the female group.

## Conclusions

Women with cardiogenic shock were less likely to receive optimal therapy when compared to men, which resulted in a poor clinical outcome. This should encourage medical professionals to apply advanced therapeutic strategies without gender bias. Only if there are no gender-related discrepancies in the management of patients with cardiogenic shock may the beneficial impact of invasive treatment be fairly assessed and the hypothesis that more guideline-adherent treatment of women results in better outcomes be validated.

## Conflict of interest

The authors declare no conflict of interest.

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