



ORIGINAL PAPER

DOI: <https://doi.org/10.20883/jms.2018.268>

Women and men diagnosed with acute coronary syndrome – sex-related differences

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ABSTRACT

Introduction. Coronary artery disease (CAD) is one of the most important causes of death in both men and women. There are many gender differences among patients with CAD, including risk factors and acute coronary syndrome (ACS) outcomes. The latest reports showed that mortality due to CAD is higher in women than in men. Cardiac biomarkers play an important role in risk stratification and choice of treatment strategy in patients with ACS, however some of cardiac biomarkers show worse sensitivity and specificity in women.

Aim. The aim was to investigate the sex-related differences in patients with acute coronary syndrome and to compare their sex-related risk of in-hospital mortality.

Material and Methods. Single-center study of patients diagnosed with ACS who underwent percutaneous coronary intervention (PCI). Patients were diagnosed and treated according to ESC Guidelines. Statistical analysis was performed using StatSoft Statistica.

Results. Of the 297 patients included in this study, 32% were women and 68% were men. There were 26.94% STEMI patients, 22.22% NSTEMI patients and 50.84% unstable angina patients. Compared with males, females were significant older (68.2 ± 10.6 vs. 64.8 ± 11.0 ; $p = 0.0175$). Levels of biomarkers of myocardial injury were significantly lower in women: CK-MB ($p = 0.0241$), troponin I ($p = 0.0417$) and CK ($p = 0.0035$) than in men. Women were less frequently treated with PCI or CABG ($p = 0.0016$) but the in-hospital outcomes (cardiogenic shock, sudden cardiac arrest or cardiac death) were similar in both groups ($p = 0.8557$).

Conclusions. Women with ACS were older and have higher incidence of non-ST-elevation ACS than men. In-hospital mortality show no significant difference between genders. Women were less likely to receive invasive treatment.

Keywords: acute myocardial infarction, coronary artery disease, in-hospital mortality.

Introduction

Coronary artery disease (CAD) is one of the most important causes of death in Europe in both men and women [1]. According to the European Society of Cardiology (ESC) guidelines, the definition of acute coronary syndrome (ACS) includes unstable angina (UA), ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) [2, 3]. There are many gender differences among patients with CAD, including risk factors, clinical presentation

and ACS outcomes [4]. Statistically women develop CAD ca. 10 years later than men [5], therefore this disease was believed to be 'a men's domain'. One of the reasons for this is the atheroprotective effect of estrogen [6]. However, some latest reports have concluded that mortality due to CAD is higher in women than in men [7], and that women with ACS have higher rates of in-hospital complications and risk of death than men [4]. Less specific symptoms of CAD in women [8] cause

significant diagnostic difficulties. Cardiac biomarkers, such as cardiac troponins and MB fraction of creatine kinase (CK-MB), being important indicators of myocardial injury [9], play an important role in risk stratification and choice of treatment strategy in patients with ACS. Blood tests for these biomarkers in women show worse sensitivity and specificity than in men [10]. Because diagnosis and risk stratification of ACS is more difficult in women, a multimarker approach may be appropriate in female population. Sex-related differences in patients with ACS require searching for a strategy providing better risk stratification and aiding choice of treatment.

Aim

The aim of this study was to investigate sex-related differences in clinical status, biomarker profile, echocardiographic parameters and treatment strategy in patients with ACS and to compare their sex-related risk of in-hospital mortality.

Material and Methods

This study analyzed data from a prospective single-center registry of patients with ACS. 297 consecutive patients were included; they were admitted to hospital between the 1st January and 31st December 2014 and diagnosed with ACS. All the patients were diagnosed and treated according to the ESC Guidelines [2, 3]. The exclusion criteria were end-stage renal disease, severe liver disease and pregnancy. On admission, the patients underwent physical examination, ECG and had blood collected for laboratory tests, and the investigators collected demographic data and medical history. All patients underwent coronary angiography – immediately, if they presented with a persistent chest pain, a significantly elevated troponin concentration and/or ECG changes; or within 24 hours after admission, if not. Pharmacological therapy in accordance to ESC

guidelines [2, 3] was initiated in all the patients. The primary endpoint was defined as occurrence of cardiogenic shock, sudden cardiac arrest or cardiac death during hospitalization. This study was conducted according to the Declaration of Helsinki, and it was approved by the Ethics Committee of Poznan University of Medical Sciences.

Continuous data is presented as mean and standard deviation (SD). The patients were divided into three groups according to diagnosis. Both sexes were compared within each of the groups. Statistical analysis was performed using Statistica 10, StatSoft. Probability distribution of continuous variables was tested with Lilliefors and Shapiro-Wilk tests, and it was found non-normal for all the variables. Mann-Whitney U test was used for continuous variables with non-normal distribution. Chi square tests were used for categorical variables. The data is expressed as mean values with standard deviation for continuous variables and percentages for categorical variables. A p value of < 0.05 was considered statistically significant for all the tests.

Results

Of the 297 patients included in this study, 96 (32%) were women and 201 (68%) were men. There were 80 (27%) patients with STEMI, 66 (22%) with NSTEMI and 151 (51%) with UA. Men presented significantly more frequently with STEMI, and women with UA. Female sex was associated with a higher incidence of non-ST-elevation acute coronary syndrome (NSTEMI) (UA and NSTEMI) (82% vs. 69%, $p = 0.0378$). Incidence of NSTEMI was similar in both groups (**Table 1**). Women were older and had significantly higher systolic blood pressure on admission. They were more likely to have lower red blood cells count and hemoglobin level, and higher count of blood platelets. There were no significant differences in body mass index (BMI), heart rate on admission, and comorbidities such as arterial hypertension

Table 1. Incidence of types of acute coronary syndrome (ACS)

Diagnosis	All patients (n = 297)	Men (n = 201) (68%)	Women (n = 96) (32%)	p
STEMI (%)	80	31 (n = 63)	18 (n = 17)	0.0378
NSTEMI (%)	66	22 (n = 44)	23 (n = 22)	
UA (%)	151	47 (n = 94)	59 (n = 57)	

STEMI – ST-segment elevation myocardial infarction; NSTEMI – non-ST-segment elevation myocardial infarction; UA – unstable angina

and diabetes mellitus between genders (**Table 2**). Higher left ventricular ejection fraction (LVEF) ($p = 0.0001$), smaller end-diastolic diameter of left ventricle ($p < 0.0001$), smaller diameter of left atrium ($p = 0.0001$), thinner intraventricular septum ($p = 0.0009$) and posterior wall of left ventricle ($p = 0.0042$) were observed in female gender (**Table 3**). Women had significantly lower blood concentrations of troponin I, creatine kinase-myocardial band (CK-MB) and lower creatine kinase activity (CK); but there was no significant difference in concentrations of CK-MB mass between both genders (**Table 4**). In detailed analysis of ischaemic cardiac enzymes in separate groups of ACS patients, there were no significant differences observed in levels of troponin, CK-MB mass,

CK-MB, CK between men and women (**Table 5**). All patients underwent coronary angiography. Of the patients, 66% were qualified for percutaneous coronary intervention (PCI), 4% for coronary artery bypass grafting (CABG) and 30% for conservative treatment. Percutaneous coronary intervention was performed in 142 (70.65%) men and 54 (56.25%) women ($p = 0.0016$), coronary bypass grafting was conducted more often in men (11 (5.47%) vs. 1 (1.04%); $p = 0.0015$). Conservative treatment was carried out in 48 (23.88%) men and 41 (42.71%) women ($p = 0.0015$). Female gender was less likely to receive invasive treatment (**Figure 1**). Women and men did not differ significantly as to endpoint occurrence (6.25% vs. 6.47% respectively, $p = 0.86$).

Table 2. Baseline characteristics of the investigated patients

	All patients (n = 297)	Men (n = 201) (68%)	Women (n = 96) (32%)	P
Characteristics				
Age (years)*	65.9	65.0 ± 11	68.0 ± 11	0.0174
BMI (kg/m ²)*	27.9	28.0 ± 4.52	27.6 ± 4.21	0.7294
Medical history				
Diabetes mellitus (%)	30.07	29	32	0.7994
Heart failure (%)	28.62	33	20	0.0286
Arterial hypertension (%)	77.7	75	83	0.1613
Clinical presentation				
SBP (mm Hg)*	145 ± 27	142 ± 27	149 ± 27	0.0340
HR adm (bpm)*	74 ± 18	73 ± 18	76 ± 17	0.0689
RBC (10 ¹² /L)*	4.66 ± 0.56	4.74 ± 0.58	4.51 ± 0.49	0.0004
HGB (mmol/L)*	8.70 ± 1.09	8.93 ± 1.06	8.23 ± 0.88	< 0.0001
PLT (10 ⁹ /L)*	230 ± 73	222 ± 71	249 ± 74	0.0002
WBC (10 ⁹ /L)*	9.23 ± 6.13	9.05 ± 3.02	9.61 ± 9.89	0.0906
ESR (mm/h)*	17 ± 18	14 ± 18	23 ± 18	< 0.0001
Glc adm (mmol/L)*	7.43 ± 2.97	7.34 ± 2.70	7.62 ± 3.50	0.4564
Anemia (%)	7.77	8	7.29	0.9850

* mean values and SD

BMI – body mass index; SBP – systolic blood pressure; HR adm – heart rate at admission;; RBC – red blood cells count; HGB – hemoglobin; PLT – platelet count; WBC – white blood cells count; ESR – erythrocyte sedimentation rate, Glc adm – glucose at admission.

Table 3. Echocardiography parameters

Parameter	All patients (n = 297)	Male (n = 201) (68%)	Female (n = 96) (32%)	P
LVEF (%)*	49.85 ± 10.73	48.27 ± 10.62	53.13 ± 10.25	0.0001
LVEDd (mm)*	50.73 ± 6.85	52.2 ± 6.9	47.66 ± 5.63	< 0.0001
LAD (mm)*	40.32 ± 5.93	41.33 ± 6.01	38.20 ± 5.15	0.0001
RVD (mm)*	28.32 ± 4.53	28.89 ± 4.55	27.15 ± 4.28	0.0027
Ao (mm)*	32.35 ± 5.05	33.12 ± 5.17	30.78 ± 4.46	< 0.0001
PW (mm)*	10.6 ± 1.56	10.78 ± 1.70	10.23 ± 1.13	0.0042
IVS (mm)*	10.93 ± 1.58	11.13 ± 1.54	10.52 ± 1.58	0.0009

* mean values and SD

LVEF – left ventricular ejection fraction; LVEDd – left ventricular end-diastolic diameter; LAD – left atrium diameter; RVD – right ventricular diameter; Ao – aortic bulb diameter; PW – posterior wall of left ventricle; IVS – intraventricular septum diameter.

Table 4. Cardiac biomarkers

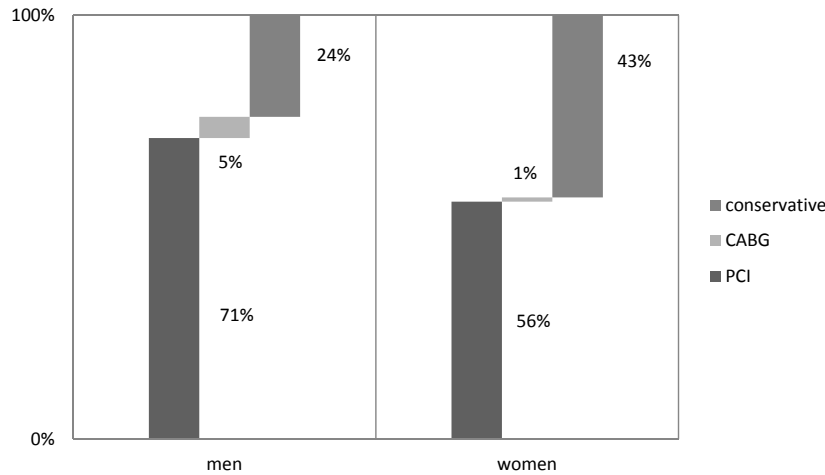
Cardiac biomarkers	All patients (n = 297)	Male (n = 201) (68%)	Female (n = 96) (32%)	p
TnI (ng/mL)	14.447	18.615	5.611	0.0417
CKMB mass (ng/mL)	22.59	26.06	15.58	0.0779
CKMB (ng/mL)	49.22	56.83	31.29	0.0241
CK (U/L)	326	370	234	0.0035

TnI – Cardiac Troponin I; CK-MBmass – mass concentration of creatine kinase-MB, CK-MB – creatine kinase-myocardial band; CK – creatine kinase.

Table 5. Cardiac biomarkers characteristic among types of ACS and gender

Biomarker	API			NSTEMI			STEMI		
	Male	Female	p	Male	Female	p	Male	Female	p
TnI (ng/mL)	0.081	0.162	0.8433	2.667	7.267	0.3967	56.622	22.165	0.1369
CK-MBmass (ng/mL)	2.57	2.16	0.5707	31.53	27.36	0.8789	71.95	50.72	0.1966
CK-MB (ng/mL)	18.87	18.64	0.7704	29.00	36.11	1.0000	110.31	65.38	0.1394
CK (U/L)	135	116	0.1036	177	368	0.4924	854	522	0.0739

TnI – Cardiac Troponin I; CK-MBmass – mass concentration of creatine kinase-MB, CK-MB – creatine kinase-myocardial band; CK – creatine kinase.

**Figure 1.** Treatment qualification ($p = 0,002$). CABG – coronary artery bypass grafting, PCI – percutaneous coronary intervention

Discussion

The hereby-presented analysis shows a number of interesting information referring to effect of gender on course and treatment of ACS. The main finding is that female sex was associated with a higher incidence of non-ST-elevation ACS and lower of ST-segment elevation acute coronary syndrome (STE ACS) than male gender. In-hospital mortality was not different between men and women despite lower levels of injury markers, lower prevalence of heart failure and higher ejection fraction in women. But women were less likely receiving invasive treatment.

Higher incidence of NSTEMI-ACS in women was observed also in a study^{of} a huge population of

199.690 patients [11]. Kragholm et al. showed that 33.3% of NSTEMI-ACS patients were women, and it has changed minimally over the 17-years observation [12]. We have observed a similar percentage of female patients in ACS patients (32.3%), however this included also STEMI. Our results are consistent with the previous findings showing that ACS women are older than men [12]. Average age at first myocardial infarction (MI) is 64.5 years for men and 70.3 years for women [1]. The incidence of hypertension and diabetes mellitus was similar in men and women, although some previous studies show that women present more frequently with these comorbidities [12, 13], however, cited studies investigated only NSTEMI-ACS. Other sur-

veys showed the prevalence of hypertension and diabetes mellitus with the same frequency in men and women [14]. Incidence of heart failure was lower in women, which is in opposite with the previous studies [12]. Comorbidities occur with similar frequency in both women and men, but other authors show that women have a greater number of comorbidities [15]. Usually there are modifiable risk factors for heart diseases, such as smoking, obesity, hypertension or hyperlipidemia. Differences between studies may mainly be due to different inclusion criteria, whether patients with confirmed or suspected ACS were included.

Referring to a recent study, heart rate may be an important prognostic factor [16] and may help in stratification of risk [17] connected with incidence of ACS. We showed no significant difference in heart rate on admission between men and women. It should be noted that heart rate on admission is considered one of the ACS prognostic factors.

There was no significant difference between genders in BMI, whereas in other studies higher BMI correlated with higher occurrence of ACS and male gender [18]. Previous studies show the impact of obesity on the development of CAD appears to be greater in women than in men [19]. The Framingham Heart Study showed that obesity increased relative risk of CAD by 64% in women, as opposed to 46% in men [20]. Moreover other surveys showed that patients who have higher BMI have higher risk of STEMI than any other type of ACS, but also they have the same risk for in-hospital outcomes [21]. It was also shown that obese patients, especially men, have better prognosis after ACS [22].

We found no difference in mortality between genders. Numerous investigators observed higher early mortality after STEMI in women than in men [21]. In comparison, another analysis showed no differences in early (30 days) mortality in STEMI in women versus in men [23]; and a similar incidence of in-hospital MACE was demonstrated also in NSTEMI-ACS [13]. Long-term mortality was not taken under consideration in our study. What is more, according to other studies, in-hospital outcomes are very rare in NSTEMI patients. Several studies showed that mortality after NSTEMI-ACS is similar in both men and women [13]. Sex-related differences in early mortality after MI are the topics of numerous studies. After

MI, younger women, but not older women, have higher mortality during hospitalization than men of the same age [5]. The younger patients were, the higher the risk of death of female patients was compared to males [5].

We noticed also that women underwent coronary revascularization relatively rarely compare to men, as it was observed in other studies [13]. This observation may be consistent with lower biomarkers level and lower risk-baseline characteristics in women. The majority of women from investigated population were treated conservatively. Other trials explain, that different manifestations of CAD in women are associated with their smaller coronary arteries, higher coronary blood flow, and higher endothelial shear stress, which have major effects on endothelial function and resistance to coronary atherosclerosis [24]. In women complex interactions of focal stenosis, diffuse epicardial coronary narrowing, related endothelial shear stress, and microvascular dysfunction often make diagnostic process difficult by use of standard noninvasive or invasive technologies [24].

Several studies examined relationship between troponin concentration and gender, and showed women to have lower concentrations of troponins [14]; these results are consistent with our findings. However in detailed analysis of every ACS group there were no differences between men and women in level of cardiac biomarkers. According to another survey [25], predictive value of troponin concentration is greater in women than in men, thus knowing the differences and establishing cut-off points separating women and men might be useful. The high sensitivity troponin assay with sex specific diagnostic thresholds may double the diagnosis of myocardial infarction in women and identify those at high risk of reinfarction or death [14]. The risk of under-diagnosing of myocardial infarction in women can contribute to inequalities in the management and treatment of myocardial infarction. In clinical practice it is important, to take into consideration, differences among genders to improve diagnosis and treatment strategy in both men and women.

Limitations of the study

This was prospective single-center registry of patients with ACS, so the number of patients is not very high.

Conclusions

Female sex was associated with a higher incidence of non-ST-elevation ACS and lower of ST-elevation ACS than male gender. In-hospital mortality was not different between men and women despite lower levels of heart injury markers, lower prevalence of heart failure, and higher ejection fraction in women. Women were less likely to receive invasive treatment.

Acknowledgements

Conflict of interest statement

The authors declare no conflict of interest.

Funding sources

There are no sources of funding to declare.

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Acceptance for editing: 2018-06-30
Acceptance for publication: 2018-07-02

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