Gender-related disparities in the treatment and outcomes in patients with non-ST-segment elevation myocardial infarction: results from the Polish Registry of Acute Coronary Syndromes (PL-ACS) in the years 2012–2014

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Abstract

Introduction: Gender-related differences in the treatment of patients with non-ST elevation myocardial infarction (NSTEMI) have been reported in many previous studies despite the fact that an equal approach is recommended in all current guidelines. The aim of the study was to investigate whether gender-related discrepancies in the management of NSTEMI patients have changed.
Material and methods: Between 2012 and 2014 a total of 66,667 patients (38.3% of whom were women) with the final diagnosis of NSTEMI were included into the retrospective analysis of the Polish Registry of Acute Coronary Syndromes (PL-ACS). Differences in clinical profile, treatment, and outcomes were analysed.
Results: Women were older than men and more often had comorbidities. They were less likely to undergo coronary angiography (88.4% vs. 92.1%, $p < 0.05$) as well as percutaneous coronary intervention (59.6% vs. 71.9%, $p < 0.05$). In the general population women had also significantly worse in-hospital prognosis as well as in 12-month follow-up. After the age adjustment the outcomes in women were at least as good as in men. In multivariate analysis females had the same risk as men in-hospital RR = 1.02 (95% CI: 0.97–1.08, $p = 0.45$) and lower in 12-month observation RR = 0.94 (95% CI: 0.92–0.97, $p < 0.0001$).
Conclusions: In comparison with previous reports on NSTEMI patients, gender-related disparities in the treatment and outcomes were radically reduced. Unadjusted mortality rates were still higher in women as a consequence of their older age. After the age adjustment, mortality ratios were similar in both genders. The long-term prognosis seems to be even better in women.

Key words: women, elderly, mortality, non-ST elevation myocardial infarction, invasive treatment.

Introduction

In many previous studies on non-ST-segment elevation myocardial infarction (NSTEMI) patients, gender-related differences in the management and outcomes have been reported. Despite the fact that the guidelines recommend the same therapy for both men and women, significant disparities between genders are still observed in many countries. The differences are particularly notable in acute coronary syndromes without ST-segment elevation due to a variable clinical manifestation as well as different comorbidities. Older patients and women are often excluded from the clinical trials, and thus the results of prior reports were sometimes contradictory. The final impact of sex category on prognosis remains unclear. We sought to investigate whether the gender-related differences in the management and prognosis in NSTEMI patients still persist.

Material and methods

We conducted a retrospective cohort study analysis of the Polish Registry of Acute Coronary Syndromes (PL-ACS). The basic principles of our registry have been published elsewhere [1, 2]. Briefly, a total of 463 hospitals providing care for patients with myocardial infarction contributed to the registry. This analysis covers 3 years, from 2012 to 2014. Data on 66,667 patients were collected in that period. Contribution to the study was voluntary; nevertheless, it comprises more than a half of all NSTEMI cases in Poland in that time. The inclusion criterion was a diagnosis of NSTEMI as a basic clinical condition according to the guidelines of European Society of Cardiology released in 2011. Cases with myocardial ischaemia secondary to other critical conditions were excluded. The study complies with the Declaration of Helsinki and was approved by the PL-ACS Registry committee.

Data were collected from the PL-ACS Registry questionnaires that include variables on demographic factors (gender, age), risk factors (smoking, hypertension, hypercholesterolaemia, diabetes, and obesity), previous cardiovascular history and procedures (myocardial infarction – MI, percutaneous coronary intervention – PCI, coronary artery by-pass grafting – CABG), clinical presentation on admission (Killip class, heart rate, systolic blood pressure, electrocardiographic abnormalities, left ventricular ejection fraction in echocardiography ejection fraction (EF)), in-hospital management (coronary angiography, percutaneous coronary intervention, medical treatment), and medication on discharge. In-hospital, 30-day, 6-month, and 12-month follow-up mortality rates were estimated. Kaplan-Meier survival curves and the log-rank test were used to compare the survival between groups.

Statistical analysis

The gender groups were analysed separately and afterward compared to each other. To investigate the age impact on outcomes additional analyses were conducted in age groups (below 55, between 55 and 64, between 65 and 74, and over 75 years) as well as in consecutive decades of life.

Categorical data are summarised as frequency and percentage while continuous data as median or arithmetic mean ± standard deviation (SD). Differences in categorical variables were tested by χ^2 test with Pearson modification whereas in continuous variables with Student's *t*-test. A two-sided *p*-value ≤ 0.05 was considered significant. A logistic regression was used to identify variables that independently contributed to mortality. The relative risk (RR) and 95% confidence intervals (CI) were calculated.

Results

Women constituted 25,542 (38.3%) of the study population. They were older than men, and they predominated in the over 70 age group (Figures 1 and 2). They more often had a history of arterial hypertension, diabetes, and obesity. On the contrary, they less often were smokers and had histo-

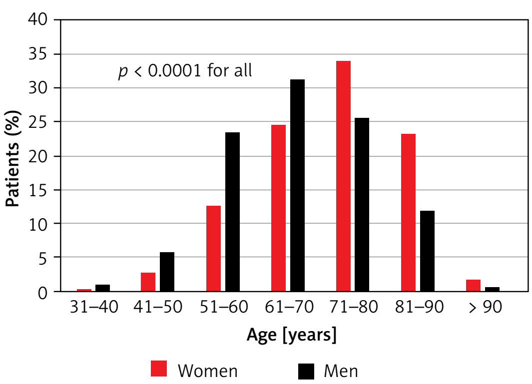

Figure 1. Age histogram of patients with non-ST elevation myocardial infarction in 2012–2014

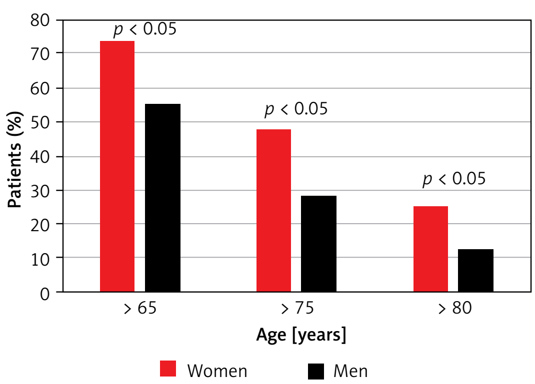

Figure 2. The elderly contribution in patients with non-ST elevation myocardial infarction in 2012–2014

ry of prior myocardial infarction or revascularisation therapy either by PCI or CABG (Table I).

Mild gender disparities in medical therapy were observed. Men more often were administered aspirin, clopidogrel, and statin while women received more calcium channel blockers (CCB). There were no differences in administration of β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and nitrates (Table II).

Women less frequently underwent coronary angiography (88.4% vs. 92.1% in men; $p < 0.0001$) and PCI (59.6% vs. 66.1% in men; $p < 0.0001$). The ratio of patients managed invasively to those treated medically was age-dependent and was the lowest in patients over 75 years old. Interestingly, the differences in PCI utilisation were especially noticeable among patients under 55 years old (59.6% vs. 71.9 % in men; $p < 0.0001$) (Table III). In women the risk of stroke (0.3% vs. 0.2% in men; $p < 0.05$), bleeding complications (1.5% vs. 1.0% in men; $p < 0.05$), as well as cardiovascular death (3.1% vs. 2.3% in men; $p < 0.05$) was higher than in men.

The unadjusted in-hospital and 12-month mortality rates remained far higher in women – in

Table I. Clinical characteristics of patients with non-ST elevation myocardial infarction in 2012–2014

Factor	Women *n* (%)	Men *n* (%)	*P*-value
Hypertension	20,568 (80.5)	31,219 (75.9)	< 0.05
Diabetes	9623 (37.3)	11,999 (29.2)	< 0.05
Hypercholesterolaemia	11,262 (44.1)	18,067 (43.9)	0.67
Smoking	3340 (13.1)	10,989 (26.7)	< 0.05
Obesity	6391 (25.0)	7807 (19.0)	< 0.05
Previous MI	5681 (22.2)	10,728 (26.1)	< 0.05
Previous PCI	4301 (16.8)	8534 (20.8)	< 0.05
Previous CABG	1092 (4.3)	2755 (6.7)	< 0.05

MI – myocardial infarction, PCI – percutaneous coronary intervention, CABG – coronary artery by-pass grafting.

Table II. Medication on discharge

Factor	Women *n* (%)	Men *n* (%)	*P*-value
Aspirin	21,898 (88.7)	35,904 (89.5)	< 0.05
Clopidogrel	18,893 (76.5)	31,072 (77.5)	< 0.05
β-Blocker	16,593 (76.6)	24,079 (76.4)	0.42
ACEI/ARB	18,779 (76.1)	30,767 (76.7)	0.05
Statin	17,340 (85.0)	25,702 (85.6)	< 0.05
Nitrate	2577 (10.4)	4151 (10.4)	0.73
CCB	3675 (14.9)	5112 (12.7)	< 0.05

ACEI – angiotensin-converting enzyme inhibitors, ARB – angiotensin receptor blockers, CCB – calcium channel blockers.

Table III. Invasive treatment

Age groups	Coronary angiography			Percutaneous coronary intervention		
	Women *n* (%)	Men *n* (%)	*P*-value	Women *n* (%)	Men *n* (%)	*P*-value
< 55 years	1542 (93.6)	5195 (95.0)	< 0.05	980 (59.5)	3929 (71.9)	< 0.05
55–64 years	4717 (94.0)	12189 (94.4)	0.38	3270 (65.2)	8958 (69.3)	< 0.05
65–74 years	6233 (91.9)	10366 (92.8)	< 0.05	4170 (61.5)	7305 (65.4)	< 0.05
≥ 75 years	10097 (83.5)	10124 (87.5)	< 0.05	6808 (56.3)	7006 (60.5)	< 0.05

the years 2012–2014 the in-hospital mortality rate was 3.3% in women vs. 2.5% in men; $p < 0.0001$, while the 12-month mortality rate was 15.1% in women vs. 12.8% in men: $p < 0.0001$, respectively.

When analysing the mortality according to age there were no differences in the in-hospital mortality between genders (Figure 3). Women had even better long-term prognosis. In the seventh, eighth, and ninth decades of life their 12-month mortality rates were lower than in men (Figure 4).

Mortality analysis adjusted to age groups is presented in Figure 5. When analysing only patients who underwent PCI there were no differences between genders in the short-term prognosis whereas women had lower mortality rates in the age group of 65 to 74 years. Mortality analysis adjusted to strategy of treatment is presented in Figure 6. Multivariable analysis was performed, and there were no differences between gender in in-hospital observation (RR = 1.02, 95% CI: 0.97–1.08,

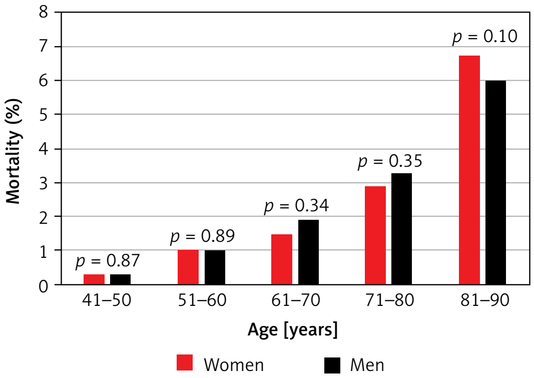

Figure 3. In-hospital mortality rates in consecutive decades of life

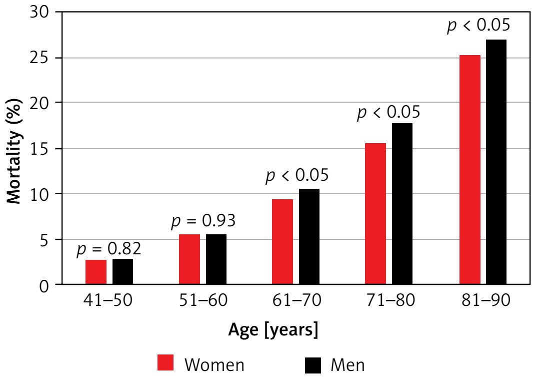

Figure 4. 12-month mortality rates in the consecutive decades of life

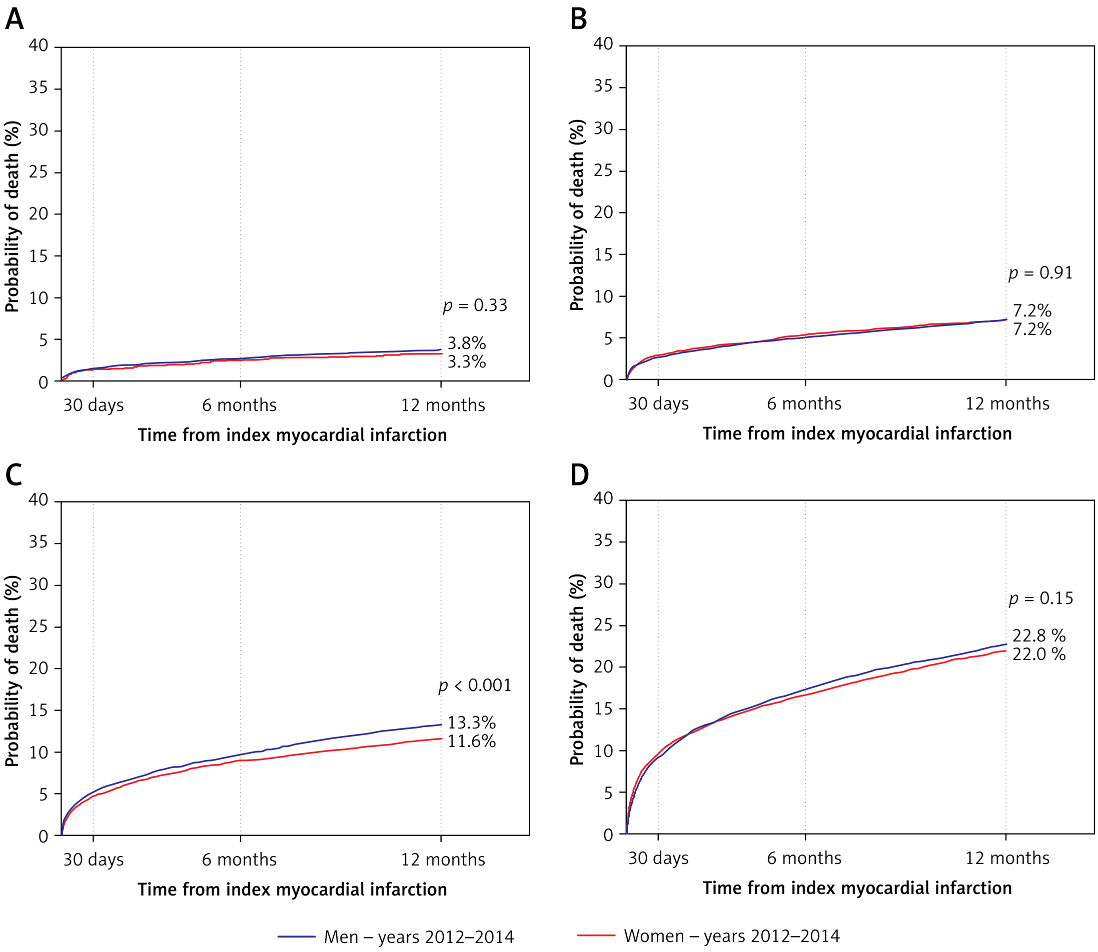

Figure 5. 12-month mortality in age groups: **A** – age < 55, **B** – age 55–64, **C** – age 65–74, **D** – age ≥ 75 years

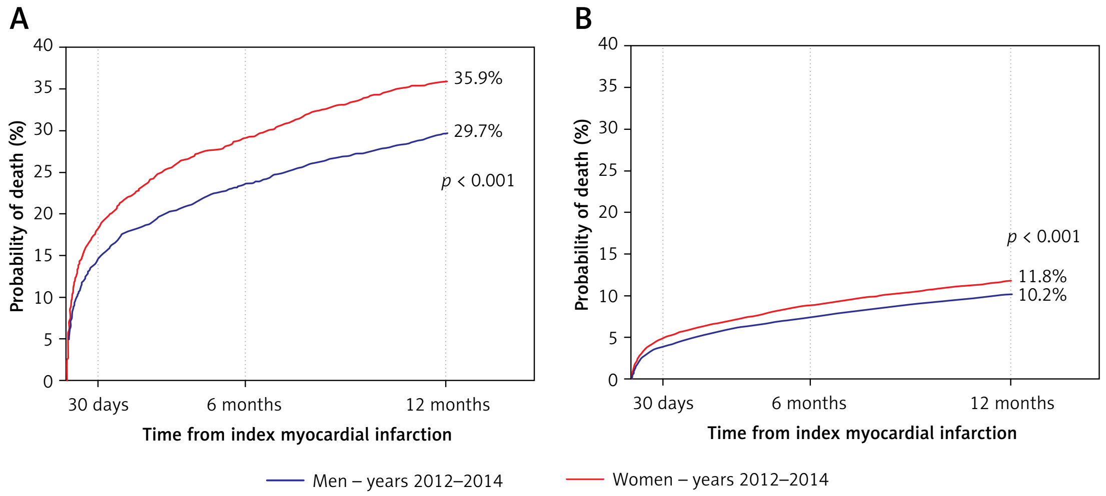

Figure 6. 12-month mortality adjusted to strategy of treatment: **A** – conservative strategy, **B** – invasive strategy

Table IV. Multivariate analysis of factors influencing in-hospital mortality

Factor	RR (95% CI)	*P*-value
Invasive treatment	0.31 (0.29–0.33)	< 0.0001
Hypercholesterolaemia	0.73 (0.69–0.77)	< 0.0001
Hypertension	0.73 (0.69–0.78)	< 0.0001
Previous PCI	0.80 (0.73–0.88)	< 0.0001
Previous CABG	0.80 (0.71–0.91)	0.0006
Current smokers	1.02 (0.94–1.10)	0.6776
Female (vs. male)	1.02 (0.97–1.08)	0.4485
Previous MI	1.07 (1.01–1.14)	0.0255
Diabetes	1.09 (1.03–1.15)	0.0021
Time to admission > 12 h	1.09 (1.03–1.16)	0.0030
EF = 35–50%	1.10 (1.01–1.20)	0.0240
ST-T abnormalities on ECG	1.16 (1.07–1.27)	0.0007
Obesity	1.18 (1.10–1.26)	< 0.0001
Other than sinus rhythm on ECG	1.19 (1.12–1.27)	< 0.0001
Age (on each decade)	1.63 (1.59–1.68)	< 0.0001
EF < 35%	2.31 (2.11–2.53)	< 0.0001
Prehospital cardiac arrest	2.37 (2.09–2.69)	< 0.0001
Killip 3 class	3.67 (3.41–3.94)	< 0.0001
IABP	3.89 (3.23–4.69)	< 0.0001
Killip 4 class	13.2 (12.0–14.4)	< 0.0001

EF – ejection fraction, ECG – electrocardiogram, IABP – intra aortic balloon pomp. Other abbreviations as in Table I.

p = 0.45) (Table IV). On the other hand, female sex was one of the independent factors that improved 12-month prognosis (RR = 0.94, 95% CI: 0.92–0.97, p < 0.0001) (Table V). These results were in accordance with our previous observation in the age groups. One of the most important variables that has a substantial impact on mortality rates is the age of the patients. With each decade of life the relative risk of death increases rapidly; in short-term prognosis RR = 1.63 (95% CI:

Table V. Multivariate analysis of factors influencing 12-month mortality

Parameter	OR (95% CI)	*P*-value
Invasive treatment	0.51 (0.49–0.52)	< 0.0001
Hypercholesterolaemia	0.81 (0.79–0.83)	< 0.0001
Previous CABG	0.84 (0.80–0.88)	< 0.0001
Hypertension	0.85 (0.83–0.88)	< 0.0001
Previous PCI	0.90 (0.87–0.94)	< 0.0001
Female (vs. male)	0.94 (0.92–0.97)	< 0.0001
Obesity	0.99 (0.96–1.02)	0.37
Time to admission > 12 h	1.03 (1.00–1.06)	0.022
Current smokers	1.06 (1.03–1.10)	0.0005
Previous MI	1.12 (1.09–1.15)	< 0.0001
ST-T abnormalities on ECG	1.15 (1.11–1.19)	< 0.0001
Other than sinus rhythm on ECG	1.14 (1.11–1.18)	< 0.0001
Diabetes	1.29 (1.26–1.32)	< 0.0001
EF = 35–50%	1.52 (1.47–1.57)	< 0.0001
Age (each decade)	1.57 (1.55–1.59)	< 0.0001
Prehospital cardiac arrest	1.74 (1.63–1.85)	< 0.0001
Killip 3 class	1.98 (1.91–2.06)	< 0.0001
IABP	2.17 (1.99–2.38)	< 0.0001
EF < 35%	2.67 (2.57–2.78)	< 0.0001
Killip 4 class	4.48 (4.26–4.71)	< 0.0001

Abbreviations as in Tables I and IV.

1.59–1.68, $p < 0.0001$), whereas in long-term prognosis RR = 1.57 (95% CI: 1.55–1.59, $p < 0.0001$).

Discussion

In many previous studies gender-related disparities in the treatment and outcomes of acute coronary syndromes have been reported. There are concerns that women less frequently receive optimal therapy according to the contemporary guidelines [3]. In particular, invasive procedures have been underutilised in the past [4–9]. In the French Registry FAST-MI 2005 the likelihood of having an invasive strategy was 34% lower in women compared to men. Five years later, in FAST 2010, the disproportion between genders was less indicated but still observed (OR = 0.84). Additionally, in many studies an adverse prognosis in women was pronounced [8, 10, 11].

A significant body of evidence indicates that several differences in the demographic and clinical profile among man and women with NSTEMI exist. Women are older and predominate in older groups. Almost half of them are over 75 years old while a quarter are over 80 years old. They more frequently have a history of hypertension, diabetes and renal failure. Moreover, atypical symptoms that delay the diagnosis are more often encountered in women. This implies analyses adjusted for age [12, 13].

The majority of former studies have revealed significant inequalities in the application of recommended medical and invasive therapies. In the report by Blomkalns *et al*. the likelihood of coronary angiography and subsequent invasive treatment in women was up to 30% lower than in men [7]. In our study the differences were diminished substantially, and in the medical treatment they are just minimal.

A similar trend in the application of invasive procedures has been observed. That means that previously reported gender discrimination in that matter is no longer apparent [14–16]. Similarly, the percutaneous coronary intervention (PCI) rate in women was far greater than was reported in previous studies. However, women still tend to have less PCI that their male counterparts. We speculate that non-obstructive coronary artery disease may partially explain this issue [3, 8]. In the French Study ONACI women more frequently had nonsignificant coronary lesions or normal coronary arteries (21% in women vs. 11% in men, $p < 0.001$) [6]. Nonetheless, a widespread invasive strategy implementation is crucial for the improvement in prognosis. In our study it was the strongest independent predictor of decreased mortality.

The most important and still unresolved issue is the persisting gender-related difference in prognosis. Former studies were inconclusive, but in general, unadjusted mortality rates were significantly higher in women. Also, our analysis revealed that unadjusted mortality rates were significantly higher in women. Age-adjusted analyses provided additional data. In both models there were no differences both in the in-hospital and the long-term mortality. Previous observations that mortality in older women is not as high as expected have been verified [3, 16–18]. These results are in contradiction with those from the unadjusted analysis in the general population, but this can be explained by taking into account the influence of the age factor. With each decade of life, the relative risk of death increases, which is in line with the reports by Radovanovic *et al.* [9] and Bucholz *et al.* [19]. Poor prognosis in elderly patients results from many factors, i.e. advanced coronary artery disease, more frequent comorbidities, atypical or late presentation of symptoms, as well as exposure to complications and side effects of treatment [15].

In the subgroup of patients treated with PCI the results were similar. After age classification women had at least the same prognosis as men. Surprisingly, the long-term mortality was even lower in women in several age groups. Finally, female gender did not impact the in-hospital mortality but slightly improved the long-term prognosis. This implies the most important rule in the analysis of any gender-related discrepancies in the field of acute coronary syndromes: the age-adjusted approach. This also provides the novel finding that the prognosis in females with NSTEMI is at least the same as in men when managed according to the guidelines [19–22].

There were several limitations of our study. The PL-ACS Registry is a voluntary, observational study, and not all hospitals treating NSTEMI in Poland participated in data collection. What is more, the absence of some important measures, such as troponin assays, and the retrospective nature of our analysis are also potential weaknesses. On the other hand, PL-ACS is one of the largest contemporary national registries of patients with acute coronary syndromes and provides exceptional data in that issue. Our findings are in accordance with the latest observations in other countries.

In conclusion, our study provides additional data contributing to the ongoing debate on gender-related differences in the management and prognosis in NSTEMI patients. We clearly demonstrated that women, when treated with appropriate access to interventional treatment and modern pharmacotherapy, still have worse short- and long-term prognosis, but this is ascribed mostly to their advanced age. After adjustment for age, those discrepancies no longer exist. Moreover, in some age groups the interventional treatment may be more beneficial in women.

Conflict of interest

The authors declare no conflict of interest.

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