



## DOES GENDER AFFECT THE OUTCOMES OF PATIENTS IN PROGRAM OF MANAGED CARE FOR ACUTE MYOCARDIAL INFARCTION

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**Background:** There is increasing evidence that cardiac rehabilitation and regular follow-ups are associated with reduced mortality and morbidity. A programme of Managed Care for Patients with Acute Myocardial Infarction was developed in Poland (MC-AMI; in Polish, KOS-zawał), based on current scientific evidence. However, there is a lack of data on possible improvement in long-term prognosis among women after acute myocardial infarction.

**Aims:** To compare the male and female population who participated in MC-AMI, regarding major cardiovascular events, defined as a composite of death, recurrent myocardial infarction, and hospitalization for heart failure, in a 1-year follow-up.

**Methods:** A prospective research study from a single cardiology care centre. The study compared 2 groups: women and men who agreed to participate in the MC-AMI programme.

**Results:** A total of 529 patients were included in the study (167 women and 362 men). In the 12-month follow-up, the difference in major cardiovascular events was not statistically significant for women and men, respectively (11.38% women vs 11.33% men;  $p = 0.98$ ). Cox multivariate regression analysis of the surveyed population showed that coronary heart disease, diabetes mellitus type II, and previous percutaneous coronary intervention were significantly correlated with the primary endpoint.

**Conclusion:** Women participating in the MC-AMI programme did not have a worse prognosis regarding major cardiovascular events, compared with men in a 12-month follow-up. Given the benefits of the MC-AMI programme, the proportion of women participating in the programme should be increased.

**Key words:** MC-AMI; cardiac rehabilitation; major cardiovascular events; MACE; sex differences.

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In Poland, approximately 85,000–90,000 people have an acute myocardial infarction (AMI) every year. Women comprise 48% of patients with AMI (1). Cardiovascular diseases remain a leading cause

### LAY ABSTRACT

Despite the development of new treatment techniques, myocardial infarction remains one of the leading causes of death in Europe. Women account for 48% of patients with myocardial infarction. Due to clinical, economic, demographic and sociological conditions, the long-term prognosis for women after myocardial infarction is worse than for men. A national programme of managed care after myocardial infarction has been introduced in 2019 year in Poland (MC-AMI; in Polish, KOS-zawał). The programme comprises 4 stages: hospitalization and treatment of the acute phase of myocardial infarction; early cardiological rehabilitation; regular follow-up at in-patient clinic; and evaluation of indications for advanced methods of treatment of post-infarction complications. Implementation of this programme in Poland has resulted in a comparable long-term prognosis being achieved for the male and female population. Widespread use of the MC-AMI programme is a promising option to equalize the prognosis for both sexes after a heart attack.

of death across Europe, with approximately 44% of deaths related to coronary heart disease (CHD). Women constitute approximately 33% of patients with CHD (2). In recent years, measures taken to improve the prognosis of patients with acute coronary syndrome include the implementation of cardiac rehabilitation (CR) programmes, and optimization of patient care. However, as Supervia et al. (3) report, the proportion of women participating in such programmes is insufficient. Their review of almost 4,000 publications, found that there are many social and economic obstacles to the process of referring the female population to rehabilitation programmes (3). Every effort should be made to adapt health programmes to the expectations and potential of the female population (e.g. by using home rehabilitation, or online rehabilitation).

Despite, a well-functioning network of interventional cardiology departments and a high proportion of invasive procedures in Poland (percutaneous coronary intervention (PCI) 59% vs coronary artery bypass graft (CABG) 1.9% vs thrombolysis 1%), mortality at 1-year follow-up remains high (total 19.4%; in-hospital mortality 10.5%; mortality after discharge 8.9%) (4). However, after AMI, women continue to have a worse prognosis than men (1).

According to the Polish Registry of Acute Coronary Syndromes (PL-AMI) only 22% of patients participate in CR in the first 12 months after a myocardial infarction (5). Early CR is an important component of the therapeutic process after myocardial infarction. Multiple meta-analyses have reported that CR reduces overall mortality in patients with coronary artery disease (CAD) (6–9). Early and regular follow-up in the outpatient clinic after AMI reduces the risk of readmission to hospital (10). Based on the scientific evidence and results from national registers, the Polish Cardiac Society, the National Health Foundation and Ministry of Health of Poland created a programme of Managed Care for Patients with Acute Myocardial Infarction (MC-AMI; in Polish, KOS-zawal) (11). The programme includes treatment of the acute phase of myocardial infarction, early CR, ambulatory care in the first year after the myocardial infarction, qualification and possible implantation of cardiac implantable electronic devices (CEID).

There is a lack of data on possible improvement in long-term prognosis among women after AMI who participate in early CR and follow-up visits in an outpatient clinic. The aim of this study is to compare the male and female population participating in the MC-AMI programme regarding major cardiovascular events (MACE), defined as a composite of death, recurrent myocardial infarction, and hospitalizations for heart failure during a 1-year follow-up period. The MC-AMI programme was created to improve the level of secondary prevention of cardiovascular diseases in Poland. MACE objectively assesses the level of implementation guidelines for secondary prevention of cardiovascular diseases.

## METHODS

This is a prospective research study from a single cardiology care centre, where the MC-AMI programme is included as standard care. The study groups included all patients with AMI from 1 November 2017 to 31 August 2018 who agreed to participate in the MC-AMI programme. The study compares 2 groups: the female population (group 1,  $n=167$ ) and the male population (group 0,  $n=362$ ). All patients were  $\geq 18$  years old. Treatment was based on guidelines (12). Myocardial infarction was diagnosed in line with the Third Universal Definition of Myocardial Infarction (13). Coronary angiography was performed via either the radial or the femoral artery, using a standard technique (12). The type of stent used was chosen by the invasive cardiologist. Standard post-myocardial infarction pharmacotherapy was used according to the European Society of Cardiology (ESC) recommendations (12), unless contraindicated. Transthoracic echocardiography was performed to assess the left ventricular ejection fraction (LVEF) using the modified Simpson's biplanar method (12).

### Stages of the MC-AMI programme

The MC-AMI programme comprises the following 4 integrated modules:

- treatment of acute coronary syndrome according to ESC guidelines (*module I*),
- early CR in outpatient or stationary conditions (*module II*),
- qualification for CEID implantation (*module III*),
- 12 months of follow-up in a cardiology outpatient clinic (*module IV*).

The programme included those patients with non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), who agreed to participate in MC-AMI.

### Assumptions of the rehabilitation programme

Each patient began CR within 14 days after AMI. CR was preceded by a coordinating visit. During the coordinating visit, basic laboratory parameters (C-reactive protein (CRP), creatinine, electrolytes and morphology) were monitored. Patients qualified for outpatient or in-hospital CR based on peri-infarction and comorbidities. CR was performed in an outpatient CR facility (22 days) or in-hospital CR ward (hospitalization up to 35 consecutive days). The key criterion for in-hospital rehabilitation was: condition after cardiac surgery, complicated course of interventional or surgical treatment, LVEF  $\leq 35\%$ , LVEF  $> 35\%$  and NYHA III, diabetes mellitus (DM) type II, or chronic obstructive pulmonary disease (COPD). Follow-up electrocardiogram (ECG), transthoracic echocardiography (TTE), 6-min walk test (6MWT) and treadmill test were performed in all patients during CR. The rehabilitation programme included interval training on an ergometer, group and individualized, supervised physical training, as well as a psychological programme, including group therapy and relaxation sessions. Moreover, educational sessions on lifestyle modification and control of coronary risk factors were included in the programme. After completion of the CR, the patients were monitored at outpatient clinics for the subsequent 12 months. Control visits were scheduled every 3–4 months. During the visit, each patient was evaluated for the indication for implantable cardioverter-defibrillator (ICD) and cardiac resynchronisation therapy (CRT) implantation.

### Study aim

This study compares the male and female populations participating in the MC-AMI programme regarding major cardiovascular events (MACE), defined as a composite of death, recurrent myocardial infarction, and hospitalization for heart failure during a 1-year follow-up period. MACE is the primary endpoint. Exact dates of deaths, myocardial infarction, and repeat hospitalization for heart failure, were obtained from the National Health Foundation. Hospitalization for heart failure was defined as admission to a healthcare facility lasting  $> 24$  h due to worsening of symptoms of heart failure and followed by specific treatment for heart failure.

### Ethics approval

The study protocol was approved by the ethics committee of the Medical University of Silesia in Katowice, Poland.

## Statistical analysis

Statistical analysis was performed using SPSS v.25.0 software (IBM Corp, Armonk, NY, USA). Quantitative variables were described as means and standard deviations (SD) (normally distributed parameters) or medians and 25–75 percentile limits (non-normally distributed parameters), while qualitative parameters were described as number and percentage. Student's *t*-test was used for normally distributed, while Mann–Whitney *U* for comparison of non-normally distributed continuous variables throughout the analyses. The assumption of a normal distribution was tested using the Shapiro–Wilk test. For categorical variables, including categorical endpoints of mortality, MACE and AMI, the Pearson  $\chi^2$  test was applied. Relative risk ratios (RR) were calculated with 95% confidence intervals (95% CI). All independent variables with  $p < 0.1$  in the univariate model were included in the Cox proportional hazard model using Wald's step-backward approach. MACE constituted the dependent variable in the Cox proportional hazard model. Kaplan–Meier survival curves for females (group 1) and males (group 0) were determined, and log-rank tests were calculated. A  $p$ -value  $< 0.05$  was considered statistically significant.

## RESULTS

A total of 529 patients were included in the study; women comprised 31.6% of the study population (167 women vs 362 men). A comparable proportion of men and women declined to participate in the MC-AMI programme (23% vs 25%,  $p = 0.14$ ). Arterial hypertension (AH) (80.2%), hyperlipidaemia (73.9%), CHD (51.0%), and DM (31.8%) were frequently observed in the study group. Less than half of the respondents had a history of smoking (40.6%). There were no differences in the study groups in terms of age and comorbidities (Table I). No differences were observed in the AMI treatment method in the study groups (Table II). A

**Table I.** Baseline characteristics of study groups ( $n = 529$ )

Characteristics	Men		Women		<i>p</i> -value
	Mean (SD)		Mean (SD)		
Age, years	65.69 (10.64)		67.80 (10.17)		0.867
LVEF (%)	45.37 (10.53)		45.24 (11.83)		0.890
	<i>n</i> = 362	<i>n</i> (%)	<i>n</i> = 167	<i>n</i> (%)	<i>p</i> -value
Previous CHD	186	51.38	84	50.30	0.817
Hypertension	288	79.56	136	81.44	0.615
DM II	107	29.56	61	36.53	0.11
DM I	2	0.55	2	1.20	0.579
Hyperlipidaemia	262	72.38	129	77.25	0.236
PAD	43	11.88	15	8.98	0.322
Previous stroke	16	4.42	10	5.99	0.438
CKD	54	14.92	38	22.75	0.027
Smoking	149	41.16	66	39.52	0.721
Previous STEMI	58	16.02	23	13.77	0.504
Previous NSTEMI	65	17.96	28	16.77	0.738
Previous UA	50	13.81	28	16.77	0.373
Previous PCI	118	32.60	50	29.94	0.542
Previous CABG	42	11.60	21	12.57	0.748

CABG: coronary artery bypass grafting; CHD: coronary heart disease; CKD: chronic kidney disease; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; NSTEMI: non-ST elevation myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-elevation myocardial infarction; UA: unstable angina.

**Table II.** Method of treatment in study groups

Treatment	Total		Men		Women		<i>p</i> -value
	<i>n</i> = 529	<i>n</i> (%)	<i>n</i> = 362	<i>n</i> (%)	<i>n</i> = 167	<i>n</i> (%)	
PCI-LAD/D	211	39.90	153	42.27	57	34.13	0.076
PCI-RCA	162	30.60	106	29.28	56	33.53	0.324
PCI-Cx/OM	120	22.70	80	22.10	40	23.95	0.636
PCI bypass	13	2.50	8	2.21	5	2.99	0.588
Failed PCI	3	0.60	2	0.55	1	0.60	0.947
PCI-LM	3	0.60	3	0.83	0	0.00	0.238
Application of eptifibatide	51	9.60	38	10.50	13	7.78	0.326
Urgent CABG	51	9.60	43	11.88	8	4.79	0.01

CABG: coronary artery bypass grafting; Cx: left circumflex artery; D: left diagonal branch artery; LAD: left anterior descending artery; LM: left main coronary artery; OM: left obtuse marginal artery; PCI: percutaneous coronary intervention; RCA: right coronary artery.

comparable percentage of women and men participated in outpatient cardiac rehabilitation (46.71% vs 40.06%,  $p = 0.15$ ). Approximately half (51.2%) of the women and 58.29% of the men qualified for in-hospital CR ( $p = 0.13$ ).

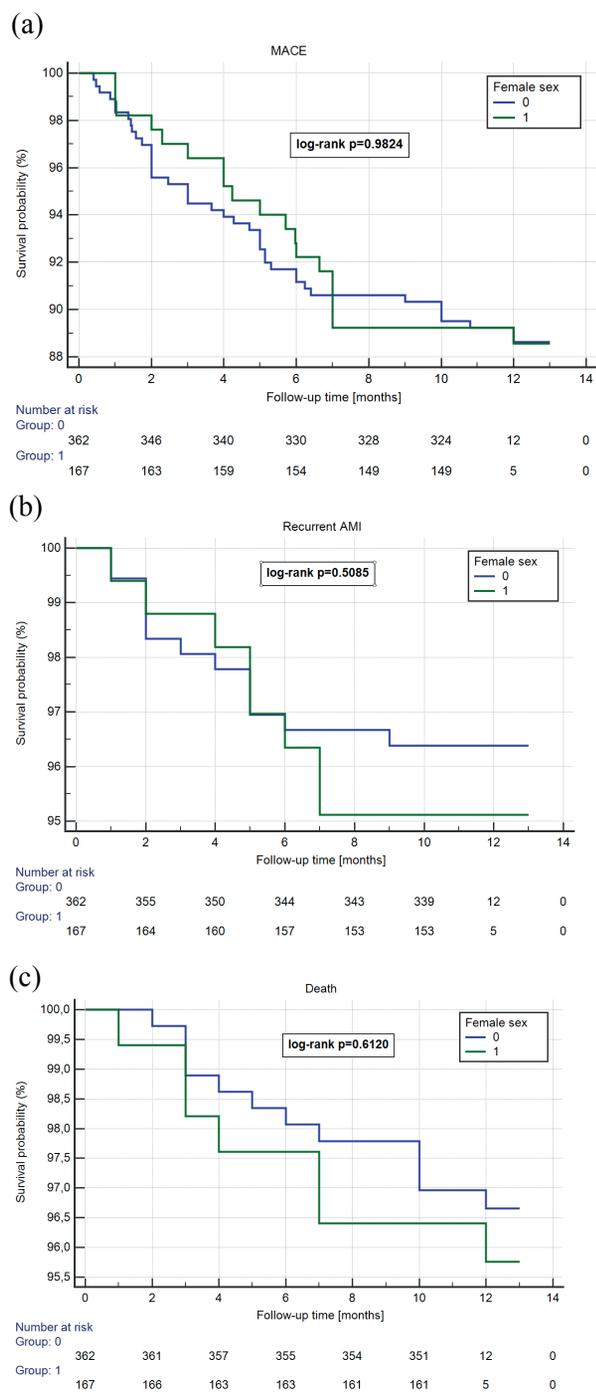
Over the 12-month follow-up, in the study population ( $n = 529$ ), total mortality was 3.6% (4.19% of women vs 3.31% of men), 5.1% of the patients were re-hospitalized because of exacerbation of heart failure (4.19% of women vs 5.52% of men), and 4.0% had another AMI (4.79% of women vs 3.39% of men). In the 12-month follow-up, the incidence of MACE events was not significantly different in the 2 study groups (11.38% women vs 11.33% men;  $p = 0.98$ ) (Fig. 1).

Cox multivariate regression analysis of the surveyed population participating in the MC-AMI programme showed that CHD, DM type II, and previous PCI are significantly correlated with the primary endpoint (Table III). In the Cox multivariate analysis, female sex was associated with a numerically better prognosis in terms of MACE, but this did not reach statistical significance (HR hazard ratio 0.71, 95% CI 0.49–1.03,  $p = 0.07$ ).

**Table III.** Multivariate analysis of independent predictors of major cardiovascular events (MACE) in study population

Variables	RR	95% CI	<i>p</i> -value
Female sex	0.713	0.492–1.033	0.074
Hyperlipidaemia	0.542	0.293–1.006	0.053
CHD	3.644	1.687–7.873	0.001
CKD	0.462	0.201–1.068	0.072
DM II	2.141	1.258–3.642	0.005
eGFR	0.973	0.956–0.990	0.002
LVEF	0.954	0.934–0.975	<0.0001
Multi-vessel disease	2.086	1.208–3.600	0.009
Previous CABG	0.469	0.215–1.026	0.059
Smoking	0.547	0.304–0.984	0.045
Previous PCI	0.429	0.219–0.838	0.013
Previous UA	2.698	1.395–5.217	0.003

CABG: coronary artery bypass grafting; CHD: coronary heart disease; CKD: chronic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; UA: unstable angina; 95% CI: 95% confidence interval; RR: relative risk.



**Fig. 1.** Kaplan–Meier curves showing freedom from: (a) major cardiovascular events (MACE), (b) recurrent acute myocardial infarction (AMI), and (c) mortality from any cause in women (group 1) and men (group 0), during 12-month follow-up.

### DISCUSSION

Research confirming the importance of CR in reducing mortality and morbidity has increased in recent years (14–16). However, the full benefits of early coronary revascularization can only be achieved with the sub-

sequent participation of patients in physiological and psychological rehabilitation. After AMI, regular visits to the outpatient clinic reduce the risk of readmission. The risk of hospitalization for heart failure is also reduced (16). The MC-AMI programme is a multistage, coordinated, and comprehensive AMI patient care programme.

This study showed that women who participate in the MC-AMI programme do not have a worse prognosis for the occurrence of MACE, compared with men in the 12-month follow-up. Multivariate analysis showed that female sex was not an independent risk factor in achieving the primary endpoint. However, many studies have reported a worse long-term prognosis for women after AMI (18) and a higher 30-day mortality in women than men (19–21). According to the VIRGO analysis (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients), women are more likely than men to attribute symptoms of myocardial infarction to stress/anxiety (22), resulting in delayed initial medical contact and diagnosis (23). Zachura et al. (1) reported that women with STEMI are more likely to have associated diseases, such as AH, DM, and obesity. In long-term follow-up, mortality after STEMI was significantly higher in women than in men. In addition, women were more often hospitalized for heart failure. As in the our study, female sex was not an independent risk factor for prognosis in long-term follow-up. Other studies did not include participation in CR and regular follow-up as a factor modifying mortality relative to sex. Some studies report that, despite a worse short-term prognosis, the long-term risk of mortality from acute coronary syndrome (ACS) is similar in men and women (24–25). Physical efficiency in women is lower than in men; therefore, the benefits of CR might be greater for women (26).

MC-AMI is the first programme for multi-stage, coordinated care after myocardial infarction in Poland. The initial results show that participation in this programme is associated with a 40% reduction in adverse cardiovascular and cerebrovascular (MACE) events compared with a control group (27). Patients participating in the MC-AMI programme were readmitted to hospital with heart failure (5.1%) and AMI (4.0%) during the 12-month follow-up. This is a much lower level compared with other studies, where the frequency of re-hospitalization after myocardial infarction due to heart failure ranges from approximately 9% (28) to 18% (29), and due to AMI from approximately 8% (28) to 12% (29).

Only 20–50% of patients participate in CR (30). Since early CR is an obligatory item in the MC-AMI programme, without undertaking early CR, participation in the MC-AMI programme cannot be continued. In

Poland, the percentage of patients participating in CR after AMI is comparable with global data; estimated at 22% according to the PL-AMI register. It is of concern that a much smaller percentage of women are recruited for CR compared with men. A Cochrane review of the effectiveness for key outcomes of exercise-based CR, compared with a lack of exercise control, showed that women comprised less than 15% of patients enrolled in the study (31). In the current study, women comprised only 33% of participants in the MC-AMI programme. A comparable percentage of women qualified for outpatient and in-hospital CR (47.9% vs 52.1%). The introduction of innovative models of delivery, such as home-based programmes and telehealth interventions, may increase the number of patients participating in rehabilitation programmes (32-33).

### Study limitations

This is a prospective, but single-centre, study. The main limitation of the analysis is the limited number of cases analysed. A larger number of respondents and a longer observation period would enable collection of more accurate data.

## CONCLUSION

The MC-AMI programme is a multi-stage, coordinated, and comprehensive AMI patient care programme. Women who participate in the MC-AMI programme do not have a worse prognosis for the occurrence of MACE, compared with men in a 12-month follow-up. Given the benefits of the MC-AMI programme, the proportion of women participating in the programme should be increased.

*The authors have no conflicts of interest to declare.*

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