Impact of diabetes mellitus on outcomes in patients with myocardial infarction according to varying degrees of left ventricular systolic dysfunction

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ABSTRACT

Background: Diabetes mellitus (DM) is known to contribute to unfavorable short- and long-term outcomes in patients with myocardial infarction (MI). Particularly poor outcomes are associated with left ventricular systolic dysfunction after an MI. Our study aimed to compare the short- and long-term outcomes of MI in patients with DM and varying degrees of left ventricular systolic dysfunction with the corresponding outcomes in a non-diabetic control group.

Methods: This analysis focused on patients with MI registered in the Polish National Registry of Acute Coronary Syndrome between 2009 and 2011. For this analysis, diabetic patients were additionally stratified into three subgroups depending on the degree of left ventricular systolic dysfunction, as assessed during their hospitalization for MI. Subsequently, the 30-day, 12-month, and 36-month outcomes in the diabetic study subgroups were compared with those in the corresponding non-diabetic subgroups.

Results: This analysis encompassed a nationwide cohort of 58 123 patients. Twelve- and 36-months mortality was greater in diabetic patients than in non-diabetic patients. The highest 36-months mortality (46.64%) was in the group of patients with DM and reduced ejection fraction (EF) <40%. Multivariate analysis showed diabetes and low EF to be independent risk factors for 36-month mortality, increasing the risk of death by 35% for diabetes and by 30% for each 5-percentage point EF decrease. Higher mortality was observed in older patients, smokers, and patients with ischemic heart disease before the index hospitalization.

Conclusions: Both diabetes and reduced EF proved to be independent risk factors for increased mortality over a long-term follow-up after MI.

Key words: diabetes mellitus, ejection fraction, heart failure, myocardial infarction

INTRODUCTION

Non-cardiovascular comorbidities, depending on their severity, may render the prognosis for heart failure (HF) patients clinically challenging [1]. The correlation between diabetes mellitus (DM) and the risk of myocardial infarction (MI) has been thoroughly documented in the literature. DM increase the risk of hospitalisation for HF [2]. DM patients more commonly require extensive in-hospital treatment for MI compared to non-DM patients [3]. Diabetes worsens short- and long-term outcomes in patients with MI [4–6]. Left ventricular systolic dysfunction is an independent risk factor for mortality after MI [5]. Consequently, ejection fraction (EF) and HF symptoms included in the New York Heart Association (NYHA) functional classification are pivotal indicative criteria

WHAT'S NEW?

Worse prognosis has been observed in patients with myocardial infarction (MI) and previously diagnosed or new-onset diabetes mellitus compared with their non-diabetic counterparts. Moreover, diabetes was shown to be an independent risk factor for hospitalization for heart failure. However, up until now, there have been no large-population studies assessing the long-term effects of diabetes on the long-term prognosis for patients with various degrees of post-MI left ventricular systolic dysfunction. We evaluated a nationwide prospective cohort of over 58 000 MI patients in terms of long-term outcomes over three years.

for cardioverter-defibrillator implantation as primary prevention of sudden cardiac death [6–8]. Our study aimed to compare the short- and long-term outcomes of MI in patients with diabetes mellitus with varying degrees of left ventricular systolic dysfunction (quantified in terms of EF values) with the corresponding outcomes in a non-diabetic control group.

METHODS

Data of 58 123 consecutive patients who were hospitalized for MI (ST-segment elevation MI [STEMI] or non-ST-segment elevation MI [NSTEMI]) between January 2009 and December 2011 were obtained from the Polish National Registry of Acute Coronary Syndrome (PL-ACS). This Registry was initiated by the Silesian Centre for Heart Diseases in Zabrze and maintained in cooperation with the Ministry of Health and the National Health Fund as part of the National Program for the Prevention and Treatment of Cardiovascular Diseases. This vast nationwide Registry contains detailed data on over 640 000 patients hospitalized for the acute coronary syndrome (ACS) in Poland. It is not only the largest registry in Europe, but also it contains the most recent data relating to epidemiology, treatment, and outcomes in patients with ACS. Registry entry criteria were described elsewhere [9]. The investigation conformed to the principles outlined in the Declaration of Helsinki and was carried out in accordance with the local ethics department's policy. The Ethics Committee of the Medical University of Warsaw was informed about the study (AKBE/81/2019).

The study population consisted of patients with diabetes (type 1, type 2, and new-onset, i.e. diagnosed during hospitalization) and patients without diabetes who constituted the control group. In line with the classification adopted within the Registry, patients with DM were defined as patients who received diabetes treatment (insulin, oral medications, or diet) before hospitalization, patients with new-onset diabetes were defined as those whose fasting blood glucose levels exceeded 7 mmol/l (≥126 mg/dl) in two measurements or blood glucose levels exceeded ≥11.1 mmol/l (≥200 mg/dl) following an oral glucose tolerance test conducted after the acute phase of MI [10].

The study population was stratified by EF values and assessed in terms of short- and long-term MI treatment outcomes. For this analysis, patients were further stratified into three subgroups based on the degree of left ventricular systolic dysfunction measured during their index hospitalization for MI. Left ventricular systolic dysfunction, expressed using EF, was determined by echocardiography. Based on the last measurement of the degree of left ventricular systolic dysfunction assessed during hospitalization, diabetic and non-diabetic patients were stratified into the following subgroups:

- heart failure with reduced ejection fraction (HFrEF; <40%)
- heart failure with mid-range ejection fraction (HFmrEF; 40%–49%)
- heart failure with preserved ejection fraction (HfpEF; ≥50%).

Short-term (in-hospital and within 30 days post-discharge) and long-term (after 12 and 36 months) outcomes were assessed. Clinical endpoints are included in Supplementary material, *Table S1*.

Statistical methods

Continuous variables were presented as means and standard deviations (SD). Categorical variables were presented as percentages and absolute values. The chi-square test for frequency data and Student's t-test for continuous data were used to test the differences between the groups. The association between the groups and long-term mortality was analyzed using the Kaplan-Meier method for multiple group comparisons. Parameters from Table 1 and EF were included in the multivariable Cox proportional hazard model (the backward elimination method) to adjust the impact of diabetes on mortality at 36 months, and the results were expressed as hazard ratios (HRs) and 95% confidence interval (CI). Additional models were calculated to assess the impact of DM on 3-year mortality in different EF groups, and the impact of mildly reduced (40%–49%) and reduced (<40%) EF on 3-year mortality in dependence of diabetic status. Statistical significance was set at $P<0.05$. All reported P-values are two-sided. Analyses were performed with the use of Statistica version 13 (TIBCO Software Inc., Palo Alto, CA, USA) and NCSS 2020 Statistical Software, LLC (Kaysville, Utah, USA).

RESULTS

DM patients (n = 11 689) comprised 20% of the study cohort, whereas non-diabetic patients (n = 46 434) comprised 80%. Ninety-seven percent of patients with DM were diagnosed with DM type 2. A total of 41.75% of diabetic patients and 52.07% of controls were diagnosed with STEMI

Table 1. Baseline clinical characteristics

	Non-DM	DM	*P*-value
Number of patients	46 434	11689	
STEMI, n (%)	24 180 (52.07)	4880 (41.75)	<0.001
NSTEMI, n (%)	22 254 (47.93)	6809 (58.25)	
Age, years, mean (SD)	64.4 (12.1)	68.4 (10.4)	<0.001
Male gender, n (%)	15 233 (67.19)	5224 (55.31)	<0.001
BMI, kg/m^2, mean (SD)	27.2 (4.3)	29.7 (5.1)	<0.001
Hypertension (BP ≥140/90 mm Hg), n (%)	31 752 (68.38)	9915 (84.82)	<0.001
Hypercholesterolemia, n (%)	19 050 (41.03)	5605 (47.95)	<0.001
Chronic kidney disease, n (%)	2017 (4.34)	1310 (11.21)	<0.001
Former smoker, n (%)	12 739 (27.43)	3983 (34.07)	<0.001
Current smoker, n (%)	16 076 (34.62)	2047 (17.51)	<0.001
Family history of CVD, n (%)	5284 (11.38)	1500 (12.83)	<0.001
Past MI, n (%)	5835 (12.57)	2331 (19.94)	<0.001
Past PCI, n (%)	3476 (7.49)	1411 (12.07)	<0.001
Past CABG, n (%)	1001 (2.16)	492 (4.21)	<0.001
Coronary artery disease, n (%)	5027 (10.83)	2486 (21.27)	<0.001
Heart failure, n (%)	2854 (6.15)	1264 (10.81)	<0.001
Past stroke, n (%)	1474 (3.17)	701 (6.00)	<0.001
PAD, n (%)	1849 (3.98)	730 (6.25)	<0.001
Chronic lung disease, n (%)	1743 (3.75)	582 (4.98)	<0.001

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CVD, cardiovascular disease; DM, patients with diabetes; MI, myocardial infarction; Non-DM, patients without diabetes; PAD, peripheral artery disease; PCI, percutaneous coronary intervention

Table 2. Invasive cardiac procedures and in-hospital mortality by diabetic status

	Non-diabetic (n = 46 434)	Diabetic (n = 11 689)	*P*-value
Cardiac catheterization, n (%)	43 781 (94.29)	11 689 (91.45)	<0.001
Percutaneous coronary intervention, n (%)	36 979 (79.64)	87 22 (74.62)	<0.001
Coronary artery bypass surgery, n (%)	1236 (2.66)	380 (3.25)	<0.001
Death, n (%)	1527 (3.29)	564 (4.83)	<0.001

(*P* <0.001). The EF ≥50%, EF 40%–49%, and EF <40% subgroups accounted for 53% (n = 30 780), 29% (n = 17 067), and 18% (n = 10 376) of the study cohort, respectively. The average EF values in the diabetic and control groups were 46% and 48%, respectively.

Table 1 presents the clinical characteristics of diabetic and non-diabetic patients. DM patients were usually older, were less likely to be male, and were more likely to suffer from chronic kidney disease in comparison with non-diabetic patients. In addition, DM patients were more likely to have a history of MI, stroke, HF, coronary artery disease, and peripheral vascular disease. Moreover, the diabetic group had a higher proportion of former smokers, whereas the non-diabetic group had a higher proportion of current smokers. Non-diabetic patients were more likely to have a history of hypertension and hypercholesterolemia.

In both groups, coronary angiography was performed in over 90% of cases involving MI. However, it was more frequently performed in the non-diabetic group than in the diabetic group (94.29% vs. 91.45%; *P* <0.001). Furthermore, non-diabetic patients underwent coronary angioplasty more often than patients with diabetes (79.64% vs. 74.62%; *P* <0.001). Likewise, patients with DM were more often qualified for coronary bypass surgery during hospitalization than non-diabetics (3.25% vs. 2.66%; *P* <0.001). Table 2 presents the number and percentage of diabetic and non-diabetic patients who underwent coronary angiography, coronary angioplasty, and coronary artery bypass surgery, as well as those who died in the hospital.

In multivariate analysis, diabetes (HR, 1.35; 95% CI, 1.30–1.42) and reduced EF (HR, 1.30; 95% CI, 1.29–1.31) proved to be independent risk factors for increased mortality within 36 months of the follow-up. Moreover, mortality was elevated in older patients (HR, 1.35; 95% CI, 1.33–1.36, for each 5-year age interval), smokers (former smokers: HR, 1.11; 95% CI, 1.07–1.17; current smokers: HR, 1.24; 95% CI 1.17–1.31), and patients with a history of ischemic heart disease (HR, 1.22; 95% CI, 1.16–1.28). Additionally, multivariate analysis showed hypercholesterolemia, hypertension, and higher body mass index (BMI) to be independent factors for lower mortality.

Diabetes increased the risk of death in all EF subgroups. The strongest effect was observed in the EF 40%––49% subgroup. On the other hand, low EF (<40%) doubled the risk of death in both diabetic and control groups in comparison with the risk of death in the preserved-EF

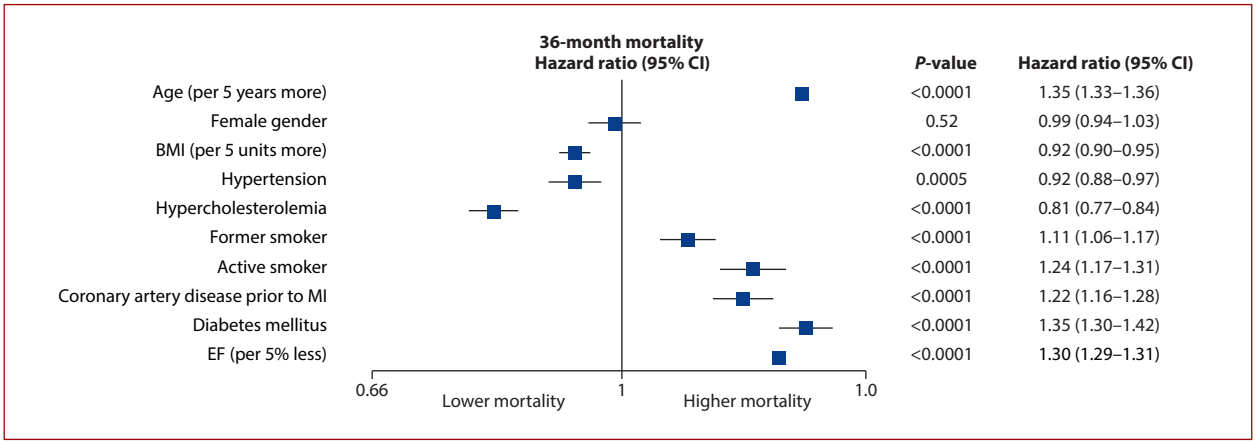

Figure 1. Multivariate analysis

Abbreviations: BMI, body mass index; CI, confidence interval; EF, ejection fraction; MI, myocardial infarction

Table 3. The adjusted hazard ratio for death at 36 months for patients with DM vs. non-DM stratified by EF. Parameters used for adjustment: age, sex, body mass index, hypertension, hypercholesterolemia, smoking, history of coronary artery disease before index myocardial infarction

EF	HR (95% CI)
≥50%	1.41 (1.30–1.54)
40%–49%	1.42 (1.31–1.54)
<40%	1.25 (1.17–1.34)

Abbreviations: HR, hazard ratio; CI, confidence interval; other — see Figure 1 and Table 1

Table 4. The adjusted hazard ratio for death at 36 months for patients with mildly reduced (40%–49%) and reduced (<40%) EF in control and diabetic groups. Parameters used for adjustment: age, sex, body mass index, hypertension, hypercholesterolemia, smoking, history of coronary artery disease before index myocardial infarction

	Control HR (95% CI)	Diabetes HR (95% CI)
EF 40%–49% (vs. ≥50%)	1.57 (1.48–1.67)	1.63 (1.48–1.79)
EF <40% (vs. 40%–49%)	1.93 (1.88–1.99)	1.86 (1.78–1.95)
EF <40% (vs. ≥50%)	2.37 (2.24–2.51)	2.11 (1.94–2.30)

Abbreviations: see Figure 1 and Table 3

Table 5. Total mortality (including in-hospital mortality) in DM and non-DM stratified by EF

Total mortality over the follow-up period	Control	DM	Control	DM	Control	DM
	EF ≥50% (n = 25 388)	EF ≥50% (n = 5 292)	EF 40%–49% (n = 13 393)	EF 40%–49% (n = 3 674)	EF <40% (n = 7 653)	EF <40% (n = 2 723)
30 days, n (%)	313 (1.23)	101 (1.91)	437 (3.26)	163 (4.44)	1045 (13.65)	411 (15.09)
	P <0.001		*P* <0.001		*P* = 0.06	
12 months, n (%)	1140 (4.49)	387 (7.31)	1151 (8.59)	499 (13.58)	2034 (26.58)	857 (31.47)
	P <0.001		*P* <0.001		*P* <0.001	
36 months, n (%)	2405 (9.47)	795 (15.02)	2169 (16.20)	927 (25.23)	2928 (38.26)	1270 (46.64)
	P <0.001		*P* <0.001		*P* <0.001	

Abbreviations: see Figure 1 and Table 1

subgroups (EF >50%). All multivariate analysis results are presented in Figure 1 and Tables 3 and 4.

All patients completed a 3-year follow-up. The total mortality rate over 36 months (including in-hospital mortality) is shown in Table 5. Kaplan-Meier curves show the total risk of death during the 36-month follow-up in all evaluated groups (Figure 2).

Analysis of cardiovascular events after hospital discharge

Long-term (12- and 36-month) follow-up after hospital discharge demonstrated a higher risk of re-infarction and stroke in all three EF subgroups of diabetic patients than in non-diabetic patients. Diabetic patients from all three EF subgroups were also more likely to be hospitalized for HF than non-diabetic patients. This observation was true for both the short-term (30-day) and long-term (12- and 36-month) follow-ups. Diabetes was also associated with higher rates of end-stage renal disease and the resultant need for dialysis in all EF subgroups. The diabetic subgroup with the lowest EF of <40% showed that the rates of coronary angiography, coronary angioplasty, or coronary artery bypass grafting (CABG), within the 12- and 36-month follow-up periods, were no higher than those in the control group. Cardiovascular events over the 30-day, 12-month, and 36-month post-discharge follow-up have been presented in Table 6.

After hospital discharge, there was no difference in the 30-day mortality in the EF <40% and EF 40%–49%

Table 6. Three-year post-discharge outcomes in non-diabetic and diabetic patients stratified by ejection fraction

	Follow-up	Non-DM, EF ≥50% (n = 25 075)	DM, EF ≥50% (n = 5191)	Non-DM, EF 40%–49% (n = 12 956)	DM, EF 40%–49% (n = 3511)	Non-DM, EF <40% (n = 6608)	DM, EF <40% (n = 2312)
Death, n (%)	30 days	107 (0.43)	34 (0.65)	113 (0.87)	42 (1.19)	185 (2.75)	80 (3.38)
		P = 0.03		*P* = 0.08		*P* = 0.12	
	12 months	910(3.62)	315 (6.04)	788 (6.05)	367 (10.36)	1110 (16.51)	501 (21.18)
		P <0.001		*P* <0.001		*P* <0.001	
	36 months	2175 (8.65)	723 (13.86)	1806 (13.86)	795 (22.44)	2002 (29.77)	914 (38.65)
		P <0.001		*P* <0.001		*P* <0.001	
Myocardial infarction, n (%)	30 days	215 (0.85)	58 (1.11)	152 (1.17)	58 (1.64)	116 (1.73)	42 (1.78)
		P = 0.07		*P* = 0.03		*P* = 0.87	
	12 months	984 (3.91)	341 (6.54)	644 (4.94)	298 (8.41)	495 (7.36)	226 (9.56)
		P <0.001		*P* <0.001		*P* <0.001	
	36 months	1720 (6.84)	575 (11.02)	1143 (8.77)	501 (14.14)	771 (11.47)	361 (15.26)
		P <0.001		*P* <0.001		*P* <0.001	
Stroke, n (%)	30 days	39 (0.16)	18 (0.34)	44 (0.34)	14 (0.40)	28 (0.42)	17 (0.72)
		P = 0.004		*P* = 0.61		*P* = 0.07	
	12 months	241 (0.96)	82 (1.57)	201(1.54)	76 (2.15)	130 (1.93)	74 (3.13)
		P <0.001		*P* = 0.01		*P* <0.001	
	36 months	656 (2.61)	216 (4.14)	453 (3.48)	172 (4.86)	320 (4.76)	151 (6.38)
		P <0.001		*P* <0.001		*P* = 0.002	
Hospitalization for heart failure, n (%)	30 days	183 (0.73)	63 (1.21)	189 (1.45)	104 (2.94)	330 (4.91)	169 (7.15)
		P <0.001		*P* <0.001		*P* <0.001	
	12 months	864 (3.43)	380 (7.28)	816 (6.26)	426 (12.03)	1390 (20.67)	614 (25.96)
		P <0.001		*P* <0.001		*P* <0.001	
	36 months	1541 (6.13)	661 (12.67)	1463 (11.23)	726 (20.50)	2018 (30.01)	867 (36.66)
		P <0.001		*P* <0.001		*P* <0.001	
Hospitalization for renal failure, n (%)	30 days	2904 (11.54)	728 (13.95)	1726 (13.25)	547 (15.44)	1119 (16.64)	479 (20.25)
		P <0.001		*P* <0.001		*P* <0.001	
	12 months	10 831 (43.06)	2630 (50.40)	6034 (46.32)	1861 (52.54)	3696 (54.97)	1417 (59.92)
		P <0.001		*P* <0.001		*P* <0.001	
	36 months	13 981 (55.58)	3400 (65.16)	7703 (59.13)	2366 (66.80)	4570 (67.97)	1696 (71.71)
		P <0.001		*P* <0.001		*P* <0.001	
Cardiac catheterization, n (%)	30 days	1608 (6.39)	364 (6.98)	906 (6.95)	245 (6.92)	376 (5.59)	135 (5.71)
		P = 0.12		*P* = 0.94		*P* = 0.83	
	12 months	6426 (25.55)	1449 (27.77)	3366 (25.84)	974 (27.50)	1549 (23.04)	570 (24.10)
		P <0.001		*P* = 0.046		*P* = 0.29	
	36 months	8132 (32.33)	1893 (36.28)	4241 (32.55)	1241 (35.04)	2065 (30.71)	758 (32.05)
		P <0.001		*P* = 0.005		*P* = 0.23	
PCI, n (%)	30 days	1411 (5.61)	325 (6.23)	784 (6.02)	207 (5.84)	300 (4.46)	109 (4.61)
		P = 0.080		*P* = 0.70		*P* = 0.77	
	12 months	5077 (20.18)	1166 (22.35)	2558 (19.63)	728 (20.55)	1094 (16.27)	403 (17.04)
		P <0.001		*P* = 0.22		*P* = 0.39	
	36 months	6144 (24.42)	1467 (28.11)	3095 (23.76)	921 (26.00)	1385 (20.60)	523 (22.11)
		P <0.001		*P* = 0.006		*P* = 0.12	
CABG, n (%)	30 days	256 (1.02)	84 (1.61)	146 (1.12)	52 (1.47)	76 (1.13)	34 (1.44)
		P <0.001		*P* = 0.09		*P* = 0.24	
	12 months	1460 (15.80)	420 (8.05)	822 (6.31)	272 (7.68)	402 (5.98)	131 (5.54)
		P <0.001		*P* = 0.004		*P* = 0.43	
	36 months	1624 (6.46)	476 (9.12)	932 (7.15)	302 (8.53)	458 (6.81)	158 (6.68)
		P <0.001		*P* = 0.006		*P* = 0.83	
ICD, n (%)	30 days	8 (0.03)	1 (0.02)	13 (0.10)	3 (0.08)	54 (0.80)	22 (0.93)
		P = 0.63		*P* = 0.80		*P* = 0.56	
	12 months	48 (0.19)	9 (0.17)	86 (0.66)	22 (0.62)	417 (6.20)	135 (5.71)
		P = 0.78		*P* = 0.80		*P* = 0.39	
	36 months	108 (0.43)	19 (0.36)	205 (1.57)	57 (1.61)	634 (9.43)	190 (8.03)
		P = 0.51		*P* = 0.88		*P* = 0.04	
CRT-D, n (%)	30 days	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	6 (0.09)	3 (0.13)
		-		-		*P* = 0.62	
	12 months	2 (0.01)	0 (0.00)	7 (0.05)	1 (0.03)	72 (1.07)	22 (0.93)
		P = 0.52		*P* = 0.56		*P* = 0.42	
	36 months	11 (0.04)	1 (0.02)	17 (0.13)	7 (0.20)	133 (1.98)	45 (1.90)
		P = 0.35		*P* = 0.82		*P* = 0.63	

Table 6 (cont.). Three-year post-discharge outcomes in non-diabetic and diabetic patients stratified by ejection fraction

	Follow-up	Non-DM, EF ≥50% (n = 25 075)	DM, EF ≥50% (n = 5191)	Non-DM, EF 40%–49% (n = 12 956)	DM, EF 40%–49% (n = 3511)	Non-DM, EF <40% (n = 6608)	DM, EF <40% (n = 2312)
ICD/CRT-D, n (%)	30 days	8 (0.03)	1 (0.02)	13 (0.10)	3 (0.08)	60 (0.89)	25 (1.06)
		$P = 0.63$		$P = 0.80$		$P = 0.47$	
	12 months	51 (0.20)	9 (0.17)	93 (0.71)	23 (0.65)	487 (7.24)	156 (6.60)
		$P = 0.65$		$P = 0.68$		$P = 0.29$	
	36 months	119 (0.47)	20 (0.38)	219 (1.68)	63 (1.78)	756 (11.24)	235 (9.94)
		$P = 0.38$		$P = 0.69$		$P = 0.08$	
Cardiac rehabilitation, n (%)	30 days	3452 (13.72)	610 (11.69)	1796 (13.79)	303 (8.55)	699 (10.40)	203 (8.58)
		$P < 0.001$		$P < 0.001$		$P = 0.01$	
	6 months	6134 (24.38)	1152 (22.08)	3440 (26.40)	655 (18.49)	1363 (20.27)	391 (16.53)
		$P < 0.001$		$P < 0.001$		$P < 0.001$	
	12 months	6454 (25.66)	1234 (23.65)	3590 (27.56)	708 (19.99)	1443 (21.46)	414 (17.51)
		$P = 0.002$		$P < 0.001$		$P < 0.001$	
Dialysis, n (%)	30 days	37 (0.15)	23 (0.44)	34 (0.26)	20 (0.56)	26 (0.39)	24 (1.01)
		$P < 0.001$		$P = 0.005$		$P < 0.001$	
	12 months	121 (0.48)	67 (1.28)	91 (0.70)	68 (1.92)	83 (1.23)	65 (2.75)
		$P < 0.001$		$P < 0.001$		$P < 0.001$	
	36 months	171 (0.68)	110 (2.11)	132 (1.01)	102 (2.88)	112 (1.67)	85 (3.59)
		$P < 0.001$		$P < 0.001$		$P < 0.001$	

Abbreviations: CABG, coronary artery bypass grafting; CRT-D, cardiac resynchronization therapy device; ICD, implantable cardioverter-defibrillator; PCI, percutaneous coronary intervention; other — see Figure 1 and Table 1

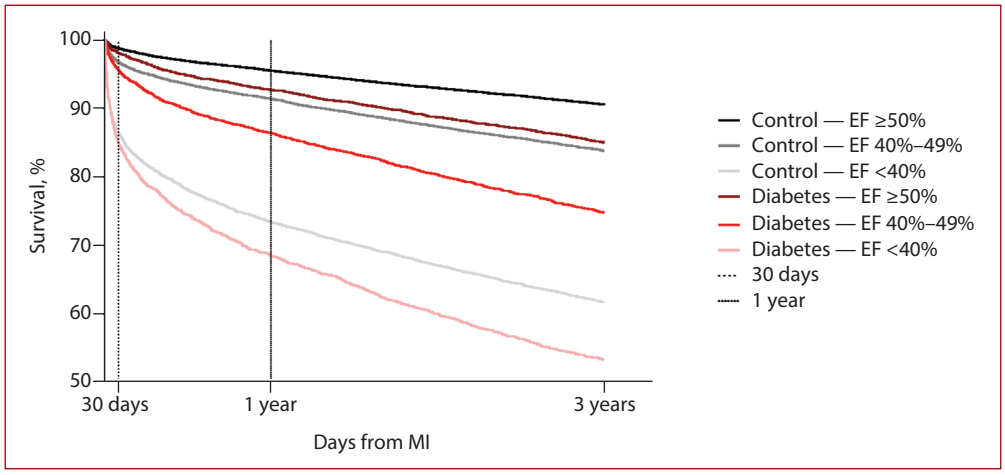

Figure 2. 36-month mortality in diabetic and control groups stratified by ejection fraction

Abbreviations: see Figure 1

subgroups, regardless of diabetes status. However, in the EF ≥50% subgroup, the 30-day mortality was significantly higher in patients with diabetes ($P = 0.03$).

Similarly, in terms of left ventricular systolic dysfunction, 12- and 36-month post-discharge mortality was significantly higher in all diabetic subgroups compared with that in the control subgroups ($P < 0.001$). For non-diabetic patients, the annual mortality rates after hospital discharge in the EF ≥50%, EF 49%–50%, and EF <40% subgroups were 3.62%, 6.05%, and 16.51%, respectively. The 12-month post-discharge mortality rates in the corresponding diabetic EF subgroups were considerably higher at 6.04%, 10.36%, and 21.18%, respectively. Ultimately, the highest 36-month mortality (38.65%) was found in patients with diabetes and an EF of <40%.

No significant differences were observed between patients with and without DM across all subgroups over the 30-day and 12-month follow-up periods in terms of the use of implantable cardiac defibrillators (ICD) or cardiac resynchronization therapy devices (CRT-D). This is in contrast with the 36-month follow-up data, in which non-diabetics from the EF <40% subgroup had higher rates of ICD implantation procedures compared with patients with DM from the EF <40% subgroup ($P < 0.05$). There was no difference in the rates of CRT-D implantation between diabetic and non-diabetic patients.

Unexpectedly, patients with diabetes participated less often in cardiac rehabilitation than patients in the control group over the 1-year follow-up. Despite proven benefits of cardiac rehabilitation, the proportions of diabetic

patients from EF ≥50%, 40%–49%, and <40% subgroups who underwent this type of treatment were lower, 23.65%, 19.99%, and 17.51%, respectively, than in the corresponding non-diabetic subgroups (25.66%, 27.56%, and 21.46%, respectively).

DISCUSSION

The present study attempted to assess the long-term prognosis for diabetic patients who were treated for MI. The outcomes in diabetic patients with reduced left ventricular EF were particularly unfavorable, compared with those in non-diabetic patients with similar EF values.

Long-term outcomes of diabetic patients after MI in the era of thrombolytic treatment have been assessed previously. The GUSTO-I study reported the annual mortality among diabetic patients with STEMI to be 14.5%, compared to 8.9% in non-diabetics [11]. Similar observations come from the OASIS and Valiant trials [12–13]. Also, the contemporary literature includes studies demonstrating a poor prognosis for diabetic patients undergoing treatment for MI [14]. Diabetic patients with MI are at a higher risk of adverse events than non-diabetic patients with MI (HR, 1.40; 95% CI, 1.20–1.64; *P* <0.001). Multivariate analysis results indicated that acute revascularization and medical therapy with aspirin and inhibitors of the renin-angiotensin system may improve patients' prognoses [14]. DM patients with reduced EF are more commonly found to receive insulin or no anti-diabetic treatment compared to DM with normal range EF. Conversely, a tendency towards oral anti-diabetic medication is observed in normal EF range DM patients [3]. New classes of antidiabetic drugs, such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1-RAs), are nowadays recommended in diabetes mellitus type 2 (DM2) patients with cardiovascular disease to improve outcomes [15]. Empagliflozin decreased the death rate from cardiovascular causes, non-fatal MI, and stroke and death from any cause in patients with DM2 at high risk for cardiovascular events, as compared with placebo [16]. In the LEADER Trial, Liraglutide reduced the risk of death from cardiovascular causes, MI and stroke in patients with DM [17].

We analyzed the prognosis for MI patients based on the degree of left ventricular systolic dysfunction (expressed in terms of EF). Stolfo et al. concluded that the EF assessed at hospital discharge proved to be a better predictor than the EF recorded earlier during hospitalization [18]. Our study results were based on the last measurement of EF made during hospitalization. Solomon et al. [19] revealed that most of the observed functional improvement occurred by day 14 after MI. The improvement in left ventricular EF after MI begins within three days of coronary revascularization [19]. Stolfo et al. [18] evaluated EF at three different time points after STEMI (<24 hours after coronary angioplasty, at hospital discharge, and three months after MI) and reported that the independent predictors of decreased EF (<35%) 3 months after revascularization are creatinine levels on hospital admission, peak troponin I levels, and EF during hospitalization. In our analysis, patients with DM from all evaluated EF ranges fared worse than their non-diabetic counterparts in the long-term follow-up, as evidenced by increased risks of mortality, stroke, re-infarction, hospitalization for HF, and end-stage renal failure requiring dialysis. The mortality rate in patients with HF, or reduced EF after MI, was twice as high as in patients with preserved or mid-range EF and no symptoms of HF [20, 21].

Yet another important observation from our study concerns the prognosis for patients with mid-range ejection fraction. Our study revealed that patients with EF of 40%–49% have a much worse prognosis than those with preserved EF regardless of their diabetic status. Multivariate analysis results showed that patients with EF of 40%–49% from both the diabetic and control groups had an over 50% higher risk of death compared with the groups with an EF of ≥50%. There have been no data in the current literature that are consistent with our findings.

Our study proves beyond any doubt that patients with diabetes are more prone to cardiovascular events and hospitalization prompted by HF. Re-infarction was more common among diabetic patients in all three EF subgroups. Similarly, the EPHESUS study assessed the impact of diabetes on the prognosis for patients with MI with reduced EF. Diabetes was also identified as an independent risk factor for the onset of another MI, but not necessarily resulting in death. However, no correlation was found between diabetes and the incidence of fatal MI during 2.5 years of follow-up [22]. In our study, diabetes correlated with the rate of hospitalizations for HF across all three EF subgroups. In an observational registry, ACS exacerbated by HF was shown to result in significantly worse outcomes than ACS without HF over a 6-month follow-up. HF was associated with reduced hospitalization and 6-month survival rates across all ACS subsets. ACS patients who were diagnosed with HF on admission had an approximately threefold decrease in their 6-month post-discharge survival rate (mortality rates of 8.5% in those with an admission diagnosis of HF vs. 2.8% in those without HF, respectively; *P* <0.001) and were also more likely to be re-hospitalized (23.6% vs. 15.7%, respectively, *P* <0.001) [23]. Similarly, Hung et al. [24] showed that the incidence of death in patients with MI complicated by HF was greater than in patients without HF after a 1-year follow-up. Development of HF within 90 days of the index MI hospitalization yielded an adjusted HR of 2.7 for 1-year mortality in 90-day survivors.

Every 5% reduction in EF increases the risk of cardiac arrest or sudden cardiac death by 21% in the first 30 days after MI [5]. Similarly, our patients with reduced EF had a much higher 30-day mortality rate (15.09% in DM and 13.65% in non-DM patients) compared with patients with mid-range EF (4.04% in DM and 3.36% in non-DM patients). We concluded that a reduction in EF increased 36-month mortality by 30% for each 5% decrease in EF.

Future investigations after the implementation of new recommendations will be interesting. SGLT-2 inhibitors in addition to standard care found a new place for both diabetic and non-diabetic patients with cardiovascular disease. Dapagliflozin or empagliflozin are recommended for patients with symptomatic HF and EF≤40% despite optimal medical therapy to reduce the risk of hospitalization and death. This first-class recommendation of the ECS guidelines results from recently conducted studies [25, 26].

We identified the following three parameters as independent factors for lower mortality: BMI, hypercholesterolemia, and hypertension. Higher BMI and lower mortality in chronic coronary artery disease and ACS patients are considered a "BMI paradox". Our observations are consistent with those resulting from analysis of other large registries [27, 28]. In the registry, which is a collection of data on 64 436 patients who underwent coronary angiography due to ACSs, the relation between BMI and mortality was U-shaped, the lower risk of mortality was noted in moderately overweight patients (BMI of 26.5–28 kg/m^2) [27]. In-hospital mortality was also assessed in over 50 000 patients hospitalized for STEMI in the United States [28]. Using patients with BMI between 30 kg/m^2 and 35 kg/m^2 as a reference, risk-adjusted in-hospital mortality rates were significantly higher only for patients with BMI of ≥40 kg/m^2 (HR, 1.64; CI, 95% 1.32–2.03).

Epidemiological data about the association between hypertension and prognosis in patients with ACS are inconclusive [29]. Some studies showed an unfavorable association between hypertension and in-hospital [30], 30-day [31], or long-term prognosis [32], whereas other studies demonstrated no association between hypertension and long-term mortality or even showed higher mortality in normotensive patients [33]. The possible explanation of lower mortality in patients with hypertension and hypercholesterolemia may be associated with the use of angiotensin-converting enzyme inhibitors, β-blockers, and statins in the period before hospitalization.

Our analysis of the 36-month data revealed that a greater proportion of non-diabetic patients in the EF <40% subgroup received an ICD compared with diabetic patients (P <0.05), despite the current guidelines. By way of explanation, diabetes may curtail the effectiveness of ICDs in patients with reduced EF [34]. In addition, in a recent meta-analysis [35] including a combined total of 3359 patients from MADIT I, MADIT II, DEFINITE, and SCD-HeFT studies, ICD implantation reduced overall mortality in non-diabetic patients but not in patients with DM. It is, therefore, imperative that prospective research studies be performed on whether to implant ICDs in patients with diabetes and reduced EF.

In-hospital and post-discharge care for AMI patients is related to a major adverse cardiovascular events rate reduction by 45% in 3 months [36]. Although cardiac rehabilitation after MI has been proven to reduce cardiovascular mortality by 20%, diabetic patients participated less frequently in cardiac rehabilitation within the first year after their MI (regardless of EF values) [37]. In addition, cardiac rehabilitation after MI improves exercise capacity, which is significantly lower in patients with diabetes compared to that in non-diabetics [38]. Consequently, greater emphasis should be placed on referring diabetic patients for cardiac rehabilitation.

Study strengths and limitations

The strength of this study derives from analyzing an extensive data set and the use of uniform diagnostic and treatment procedures. The percentage of missing values in the PL-ACS registry used in multivariate analyses was low (<0.5%) thus multivariate analyses were performed with the exclusion of patients with missing data. Since this was a non-randomized observational study, the possible interdependence of some variables, including the effects of the patients' medications, is unknown. We were unable to measure the EF after the index hospitalization. Possibly, the inter-observer variability could be an issue in this study, but the huge number of patients we analyzed from the different centers strongly reduces the possibility of its negative impact.

CONCLUSION

We presented data, representing 36-month post-MI follow-up, obtained from a large national ACS Registry. In addition, we conducted outcome analyses as a function of the degree of left ventricular systolic dysfunction after MI. The worst outcome with a 36-month mortality rate of 46.64% was in patients with diabetes and EF below 40%. In our multivariate analysis, diabetes and decreased EF after MI were independent risk factors of mortality during the 36-month follow-up.

Finally, we would like to emphasize that the present study is only an attempt to highlight the common clinical problems posed by MI treatment in patients with comorbid diabetes. Certainly, further research on the group of patients with mid-range EF would be interesting.

Our study is intended to spur a discussion on multivariate aspects of in-hospital and, which is equally important, outpatient treatment to improve the unfavorable prognosis in DM patients with MI.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared

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REFERENCES

1. Correale M, Paolillo S, Mercurio V, et al. Non-cardiovascular comorbidities in heart failure patients and their impact on prognosis. Kardiol Pol. 2021; 79(5): 493–502, doi: 10.33963/KP.15934, indexed in Pubmed: 34125921.
2. Franklin K, Goldberg RJ, Spencer F, et al. Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events. . Arch Intern Med. 2004; 164(13): 1457–1463, doi: 10.1001/archinte.164.13.1457, indexed in Pubmed: 15249356.
3. Niedziela JT, Hiczkiewicz J, Kleinrok A, et al. Prevalence, characteristics, and prognostic implications of type 2 diabetes in patients with myocardial infarction: the Polish Registry of Acute Coronary Syndromes (PLACS) annual 2018 report. Kardiol Pol. 2020; 78(3): 243–246, doi: 10.33963/KP.15189, indexed in Pubmed: 32063598.
4. Aguilar D, Solomon SD, Køber L, et al. Newly diagnosed and previously known diabetes mellitus and 1-year outcomes of acute myocardial infarction: the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial. Circulation. 2004; 110(12): 1572–1578, doi: 10.1161/01.CIR.0000142047.28024.F2, indexed in Pubmed: 15364810.
5. Pouleur AC, Barkoudah E, Uno H, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. N Engl J Med. 2005; 352(25): 2581–2588, doi: 10.1056/NEJMoa043938, indexed in Pubmed: 15972864.
6. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Europace. 2006; 8(9): 746–837, doi: 10.1093/europace/eul108, indexed in Pubmed: 16935866.
7. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2010; 31(20): 2501–2555, doi: 10.1093/eurheartj/ehq277, indexed in Pubmed: 20802248.
8. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008; 29(19): 2388–2442, doi: 10.1093/eurheartj/ehn309, indexed in Pubmed: 18799522.
9. Poloński L, Gasior M, Gierlotka M, et al. Polish Registry of Acute Coronary Syndromes (PL-ACS). Characteristics, treatments and outcomes of patients with acute coronary syndromes in Poland. Kardiol Pol. 2007; 65(8): 861–72; discussion 873, indexed in Pubmed: 17853315.
10. Ryden L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary: The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2006; 28(1): 88–136, doi: 10.1093/eurheartj/ehl260, indexed in Pubmed: 17220161.
11. Mak KH, Moliterno DJ, Granger CB, et al. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol. 1997; 30(1): 171–179, doi: 10.1016/s0735-1097(97)00118-6, indexed in Pubmed: 9207639.
12. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation. 2000; 102(9): 1014–1019, doi: 10.1161/01.cir.102.9.1014, indexed in Pubmed: 10961966.
13. Aguilar D, Solomon SD, Køber L, et al. Newly diagnosed and previously known diabetes mellitus and 1-year outcomes of acute myocardial infarction: the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial. Circulation. 2004; 110(12): 1572–1578, doi: 10.1161/01.CIR.0000142047.28024.F2, indexed in Pubmed: 15364810.
14. Takara A, Ogawa H, Endoh Y, et al. Long-term prognosis of diabetic patients with acute myocardial infarction in the era of acute revascularization. Cardiovasc Diabetol. 2010; 9: 1, doi: 10.1186/1475-2840-9-1, indexed in Pubmed: 20047694.
15. Grant PJ, Cosentino F, Cosentino F, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020; 41(2): 255–323, doi: 10.1093/eurheartj/ehz486, indexed in Pubmed: 31497854.
16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373(22): 2117–2128, doi: 10.1056/NEJMoa1504720, indexed in Pubmed: 26378978.
17. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016; 375(4): 311–322, doi: 10.1056/NEJMoa1603827, indexed in Pubmed: 27295427.
18. Stolfo D, Cinquetti M, Merlo M, et al. ST-elevation myocardial infarction with reduced left ventricular ejection fraction: Insights into persisting left ventricular dysfunction. A pPCI-registry analysis. Int J Cardiol. 2016; 215: 340–345, doi: 10.1016/j.ijcard.2016.04.097, indexed in Pubmed: 27128558.
19. Solomon SD, Glynn RJ, Greaves S, et al. Recovery of ventricular function after myocardial infarction in the reperfusion era: the healing and early afterload reducing therapy study. Ann Intern Med. 2001; 134(6): 451–458, doi: 10.7326/0003-4819-134-6-200103200-00009, indexed in Pubmed: 11255520.
20. Parakh K, Thombs BD, Bhat U, et al. Long-term significance of Killip class and left ventricular systolic dysfunction. Am J Med. 2008; 121(11): 1015–1018, doi: 10.1016/j.amjmed.2008.06.020, indexed in Pubmed: 18954850.
21. Møller JE, Brendorp B, Ottesen M, et al. Congestive heart failure with preserved left ventricular systolic function after acute myocardial infarction: clinical and prognostic implications. Eur J Heart Fail. 2003; 5(6): 811–819, doi: 10.1016/s1388-9842(03)00159-4, indexed in Pubmed: 14675860.
22. Deedwania PC, Ahmed MI, Feller MA, et al. Impact of diabetes mellitus on outcomes in patients with acute myocardial infarction and systolic heart failure. Eur J Heart Fail. 2011; 13(5): 551–559, doi: 10.1093/eurjhf/hfr009, indexed in Pubmed: 21393298.
23. Steg PG, Dabbous OH, Feldman LJ, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation. 2004; 109(4): 494–499, doi: 10.1161/01.CIR.0000109691.16944.DA, indexed in Pubmed: 14744970.
24. Hung J, Teng THK, Finn J, et al. Trends from 1996 to 2007 in incidence and mortality outcomes of heart failure after acute myocardial infarction: a population-based study of 20,812 patients with first acute myocardial infarction in Western Australia. J Am Heart Assoc. 2013; 2(5): e000172, doi: 10.1161/JAHA.113.000172, indexed in Pubmed: 24103569.
25. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Eng l J Med. 2019; 381: 1995–2008, doi: 10.1056/NEJMoa1911303.
26. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020; 383(15): 1413–1424, doi: 10.1056/NEJMoa2022190, indexed in Pubmed: 32865377.
27. Angerås O, Albertsson P, Karason K, et al. Evidence for obesity paradox in patients with acute coronary syndromes: a report from the Swedish Coronary Angiography and Angioplasty Registry. Eur Heart J. 2013; 34(5): 345–353, doi: 10.1093/eurheartj/ehs217, indexed in Pubmed: 22947610.
28. Das SR, Alexander KP, Chen AY, et al. Impact of body weight and extreme obesity on the presentation, treatment, and in-hospital outcomes of 50,149 patients with ST-Segment elevation myocardial infarction results from the NCDR (National Cardiovascular Data Registry). J Am Coll Cardiol. 2011; 58(25): 2642–2650, doi: 10.1016/j.jacc.2011.09.030, indexed in Pubmed: 22152950.
29. Konstantinou K, Tsioufis C, Koumelli A, et al. Hypertension and patients with acute coronary syndrome: Putting blood pressure levels into perspective. J Clin Hypertens (Greenwich). 2019; 21(8): 1135–1143, doi: 10.1111/jch.13622, indexed in Pubmed: 31301119.
30. Fresco C, Avanzini F, Bosi S, et al. Prognostic value of a history of hypertension in 11,483 patients with acute myocardial infarction treated with thrombolysis. GISSI-2 Investigators. Gruppo Italiano per lo Studio della, Sopravvivena nell'Infarto Miocardico. J Hypertens. 1996; 14(6): 743–750, doi: 10.1097/00004872-199606000-00010, indexed in Pubmed: 8793697.

31. Dumaine R, Gibson CM, Murphy SA, et al. Thrombolysis in Myocardial Infarction (TIMI) Study Group. Association of a history of systemic hypertension with mortality, thrombotic, and bleeding complications following non-ST-segment elevation acute coronary syndrome. J Clin Hypertens (Greenwich). 2006; 8(5): 315–322, doi: 10.1111/j.1524-6175.2006.05384.x, indexed in Pubmed: 16687939.
32. Lingman M, Herlitz J, Bergfeldt L, et al. Acute coronary syndromes — the prognostic impact of hypertension, diabetes and its combination on long-term outcome. Int J Cardiol. 2009; 137(1): 29–36, doi: 10.1016/j.ijcard.2008.05.055, indexed in Pubmed: 18755519.
33. Abrignani MG, Dominguez LJ, Biondo G, et al. In-hospital complications of acute myocardial infarction in hypertensive subjects. Am J Hypertens. 2005; 18(2 Pt 1): 165–170, doi: 10.1016/j.amjhyper.2004.09.018, indexed in Pubmed: 15752942.
34. Steinberg BA, Al-Khatib SM, Edwards R, et al. Outcomes of implantable cardioverter-defibrillator use in patients with comorbidities: results from a combined analysis of 4 randomized clinical trials. JACC Heart Fail. 2014; 2(6): 623–629, doi: 10.1016/j.jchf.2014.06.007, indexed in Pubmed: 25306452.
35. Sharma A, Al-Khatib SM, Ezekowitz JA, et al. Implantable cardioverter-defibrillators in heart failure patients with reduced ejection fraction and diabetes. Eur J Heart Fail. 2018; 20(6): 1031–1038, doi: 10.1002/ejhf.1192, indexed in Pubmed: 29761861.
36. Wita K, Kułach A, Wita M, et al. Managed Care after Acute Myocardial Infarction (KOS-zawał) reduces major adverse cardiovascular events by 45% in 3-month follow-up - single-center results of Poland's National Health Fund program of comprehensive post-myocardial infarction care. Arch Med Sci. 2020; 16(3): 551–558, doi: 10.5114/aoms.2019.85649, indexed in Pubmed: 32399102.
37. Hedbäck B, Perk J, Wodlin P. Long-term reduction of cardiac mortality after myocardial infarction: 10-year results of a comprehensive rehabilitation programme. Eur Heart J. 1993; 14(6): 831–835, doi: 10.1093/eurheartj/14.6.831, indexed in Pubmed: 8325313.
38. Banzer JA, Maguire TE, Kennedy CM, et al. Results of cardiac rehabilitation in patients with diabetes mellitus. Am J Cardiol. 2004; 93(1): 81–84, doi: 10.1016/j.amjcard.2003.09.017, indexed in Pubmed: 14697472.