ORIGINAL ARTICLE

Asesement of myocardial infarction therapy development in diabetics

Anna Polewczyk[1], Marianna Janion[1,2], Mariusz Gąsior[3], Marek Gierlotka[3], Lech Poloński[3]

1 II Cardiology Department, Świętokrzyskie Center of Cardiology, Poland
2 Health Sciences Faculty, Jan Kochanowski Arts and Biology University, Kielce, Poland
3 Silesian Center of Heart Diseases, Zabrze, Poland

KEY WORDS

diabetes, invasive treatment, myocardial infarction

ABSTRACT

INTRODUCTION A considerable development of myocardial infarction treatment including invasive strategy and supportive pharmacotherapy ought to result in prognostic benefits for the high risk diabetic population.

OBJECTIVES The aim of the present study was the evaluation of myocardial infarction treatment efficacy in diabetics from Świętokrzyskie province.

PATIENTS AND METHODS Two groups of diabetics hospitalized because myocardial infarction were compared: group 1 included 183 patients treated during the years 1992–1996, group 2 was comprised of 168 patients treated in the years 2005–2006.

RESULTS Population of diabetic patients treated in the years 2005–2006 was older and presented more coronary risk factors than patients hospitalized in the years 1992–1996. A significant more frequent use of myocardial infarction reperfusion treatment in diabetic patients was demonstrated. In 1992–1996, fibrinolytic therapy was used in 18% of diabetics, while currently the reperfusion strategy was performed in 47.2% of the study patients including fibrinolysis in 8.5% of patients, primary percutaneous coronary intervention in 38.7% of patients. In both study groups a comparably high mortality observed during the hospitalization and the 6-month follow-up incidence was observed. In the years 1992–1996 a significant decrease of mortality among diabetics who were treated by fibrinolytic methods compared to diabetics treated by conservative methods, was observed. In the years 2005–2006 in-hospital and long-term mortality were significantly reduced among diabetics who had undergone invasive therapy.

CONCLUSIONS A significant development of myocardial infarction treatment in diabetics, particularly in those who underwent reperfusion methods, was demonstrated. The absence of reduction in overall mortality ought to be attributed to the worse clinical characteristics of recently treated patients and lower frequency of reperfusion treatment in high risk patients.

Correspondence to:
Anna Polewczyk, MD, PhD, II Oddział Kardiologii, Świętokrzyskie Centrum Kardiologii, Wojewódzki Szpital Zespolony, ul. Grunwaldzka 45, 25-736 Kielce, Poland,
phone: +48-41-367-15-08,
fax: +48-41-367-14-56,
e-mail: annapolewczyk@wp.pl
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INTRODUCTION Diabetes is well documented risk factor of arteriosclerosis in almost all organs. Arteriosclerosis involving coronary, cerebral and peripheral arteries cause about 80% of deaths, and it is responsible for hospitalization of 75% of diabetic patients.[1] It is known that myocardial infarction occurs more frequently than in persons with normal blood glucose level. The recent studies evidenced that significant increase of risk of cardiovascular events occurs in patients with glucose intolerance, even before diabetes diagnosis. Metabolic disturbances such as hyperglycemia, hyperinsulinemia, insulin resistance and dyslipidemia cause impaired arterial function involving both endothelial cells and the media, and lead to blood coagulation system disturbances and systemic of inflammatory state.[2] The volume of arteriosclerotic plaques and the extent of lesions are larger in diabetics compared to non diabetic patients at similar age. Additionally, arteriosclerosis of peripheral arteries occurs in diabetics more frequently.[3] Significant

TABLE 1 Clinical characteristics of diabetic patients hospitalized because of myocardial infarction (group 1: 1992–1996 and group 2: 2005–2006)

	Group 1 (n = 183)	Group 2 (n = 168)	p
Age (years ±SD)	65.3 ±9.2	69.7 ±10.8	<0.0001
Female gender (%)	42.1	50.6	0.11
Myocardial infarction history (%)	25.1	17.3	0.08
Hypertension (%)	51.4	75	<0.001
Hypercholesterolemia (%)	31.7	56.6	<0.0001
Cigarette smoking (%)	35	17.3	<0.001
Myocardial infarction localization			
anterior wall	36.6	41.7	0.31
inferior wall	44.8	47	0.65
EF			
normal range	38.7	14.3	<0.001
40–50%	37.1	62.2	<0.001
20–40%	24.2	21.9	0.82
<20%	0	1.7	0.14
Killip class			
1 (%)	23.0	48.8	<0.0001
2 (%)	53.0	31.6	<0.001
3 (%)	12.5	9.5	0.35
4 (%)	11.5	10.1	0.66

Abbreviations: EF – ejection fraction, SD – standard deviation

differences in arteriosclerotic plaque composition between diabetic and non diabetic patients were observed: the main body of the plaque in diabetics consists of lipids, and inflammatory infiltrates contain more macrophages.[4] Ulcerative arteriosclerotic lesions which are prone to clot formation were also more frequently observed.[5] Abnormal vascular remodeling with the absence of compensatory expansion of arteriosclerotic vessel lumen were demonstrated.[6] Furthermore, in diabetic patients with coronary artery occlusion, collateral circulation is underdeveloped.[7] In the light of the data concerning pathophysiology and pathways of vascular abnormalities in diabetes, it is not surprising that of more severe acute coronary events occur in diabetics. Has the considerable development in myocardial infarction treatment observed in the recent years resulted in better prognosis for this particularly high risk group of patients?

The aim of the present study was a comparative retrospective analysis of myocardial infarction treatment efficacy in diabetics from Świetokrzyskie province hospitalized in the years 1992–1996 and from June 2005 to February 2006.

PATIENTS AND METHODS The group of 881 patients with myocardial infarction hospitalized in 1992–1996, and 889 patients who was treated in 2005–2006 because of acute coronary syndromes with ST – segment elevation (STE ACS) underwent a comparative evaluation. In the population treated during 1992–1996, 183 diabetic patients who made up group 1 underwent a detailed analysis. Group 2 comprised of 168 diabetics, selected from patients hospitalized in the years 2005–2006, underwent the same analysis. In the years 1992–1996, the inclusion criteria for the study were based on presence of at least two out of the three following symptoms: typical infarction pain, ECG changes typical of transmural infarction, elevated serum aspartate transaminase level. An inclusion criteria for the study in 2005–2006 years was the vector ST elevation over 0.2 mV in point J of V_1–V_3, or over 0.1 mV of other leads (at least two proper precordial leads) with characteristic elevation of myocardial necrosis markers i.e., troponin T and(or) creatine kinase MB fraction. Diabetes diagnosis was based on the previous diabetes history or performed twice glycose measurements >126 mg/dl on fasting or >200 mg/dl at any daytime. Source data concerning a myocardial infarction history during hospitalization in 1992–1996 were obtained from the Department of Cardiology of the Provincial Hospital in Kielce. Data regarding to the years 2005–2006 came from the Polish Registration Office of Acute Coronary Events PL-ACS[8], but the information concerning long-term prognosis (6-month follow-up) was based on data obtained from the Provincial Registry Office and the Świętokrzyski Branch of the National Health Fund.

TABLE 2 Clinical parameters and treatment strategy in diabetics in the years 2005–2006

Treatment strategy n = 168	Conservative n = 83	Fibrinolysis n = 13	PCI n = 72	p*	p**
Age (years ±SD)	73.3 ±9.0	70.0 ±11.9	65.6 ±11.1	<0.001	0.02
Female gender	62.7	46.2	37.5	0.24	<0.002
Killip class on admittion					
1	39.8	69.2	55.6	<0.05	<0.05
2	27.7	23.1	37.5	0.7	0.18
3	15.7	7.7	2.8	0.46	<0.008
4	16.9	0	4.2	0.11	0.01
EF					
normal range	6.5	25	18.5	0.08	<0.0008
40–50%	60.9	62.5	63.1	0.7	<0.005
20–40%	32.6	0	16.9	0.1	0.61

* p value for comparison between conservative and fibrinolysis treatment
** p value for comparison between conservative and PCI treatment

Abbreviations: PCI – percutaneous coronary intervention, others – see TABLE 1

Statistical analysis Continuous parameters were presented as mean values ±standard deviation or the median and interquartilic interval, depending on the distribution of data. The statistical significance of differences among mean values was evaluated using the t-Student or the U Mann-Whitney tests. Categoric parameters were compared using the χ^2 test. Statistical analyses and calculations were performed using the STATISTICA PL program, version 6.1 (StatSoft Inc).

RESULTS Women made the majority of diabetic patients hospitalized for myocardial infarction in the years 1992–1996 and 2005–2006. It should also be emphasized that patients with myocardial infarction hospitalized in 2005–2006 were about five years older than those from the years 1992–1996, and it is notable that the incidence of hypertension and hypercholesterolemia in diabetics treated during 2005–2006 years was significantly increased. The analysis of myocardial infarction localization in diabetics treated in 1992–1996 and 2005–2006 did not show significant differences between the study populations.

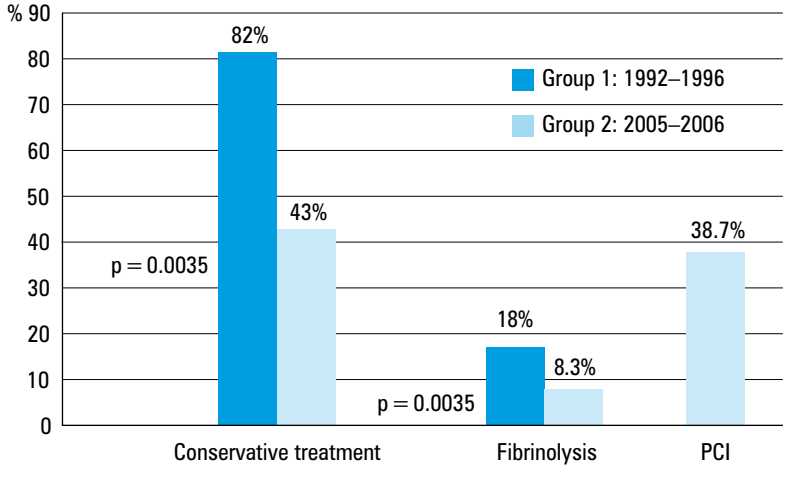


FIGURE 1 Comparison of myocardial infarction strategy management in diabetics. Abbreviations: PCI – percutaneous coronary intervention

In group II, slightly lower values of left ventricular ejection fraction (EF) (significantly large number of patients with EF value of 40–50% compared to the previous period) were showed, which however did not considerably influence on cardiac function evaluated according to the Killip-Kimball classes (TABLE 1).

The analysis of acute myocardial infarction treatment showed a significant increase in the frequency of reperfusion therapy in diabetics with myocardial infarction. In Świetokrzyskie province fibrinolytic therapy was introduced in the years 1992–1996, but mechanical reperfusion was not used then. Only 18% of diabetics were treated with fibrinolysis (82% of them were treated conservatively). In the recent years, in the age of invasive strategies development, primary angioplasty were performed in 38.7% of diabetes patients, and 8.3% of diabetics were treated with fibrinolysis (conservative therapy was administered to 43% of the study patients) (FIGURE 1).

The detailed analysis of the diabetes population qualified for reperfusion therapy showed that invasive treatment was provided to the youngest patients (mean age 65.6 ±11.1), more frequently to men, with a normal left ventricular ejection fraction, and those who represented circulation system efficiency class I according to the Killip classes (TABLE 2).

Direct effects of angioplastic method application, evaluated using the TIMI scale, showed excellent results – the TIMI-3 flow in the intramyocardial artery was present in 95.4% of diabetic patients. The high frequency of stent application (86.2% bare metal stents and 4.6% drug eluting stents) ought to be emphasized. The analysis of pharmacotherapy used in myocardial infarction in the recent more than ten years demonstrated the introduction of new antiplatelet drugs and statins into the treatment, considerably more frequent use of β-adrenolytic drugs

TABLE 3 Comparison of in-hospital pharmacotherapy in diabetic and nondiabetic patients (group 1: 1992–1996, and group 2: 2005–2006)

	Group 1 (n = 183 [%])	Group 2 (n = 168 [%])	p
ASA	88.0	95.8	0.009
Ticlopidin	–	27.4	–
Clopidogrel	–	39.9	–
GP IIb/IIIa inhibitor	–	14.3	–
Anticoagulants	71.0	77.4	0.17
Heparin	71.0	33.9	<0.0001
LMWH	–	63.7	–
β-adrenolytics	41.5	73.8	<0.0001
ACEI	75.4	79.2	0.4
Statins	–	70.8	–
Nitrates	89.1	59.5	<0.0001

Abbreviations: ACEI – angiotensin converting enzyme inhibitors, ASA – acetylsalicylic acid, GP – glycoprotein, LMWH – low-molecular-weight heparin

and acetylsalicylic acid (ASA), and administering low-molecular weight heparin treatment as antithrombotic therapy. What should be noted is the equally frequent in both groups use of angiotensin converting enzyme inhibitors and a considerable decrease in nitrate administration in the years 2005–2006 (TABLE 3).

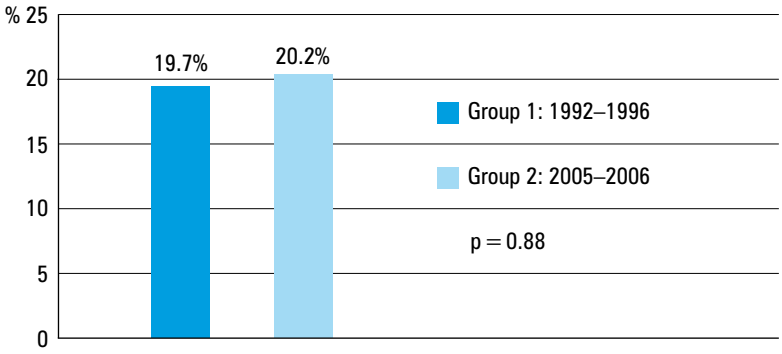
In-hospital mortality was similarly high in both groups (FIGURE 2).

The highest in-hospital mortality in both study groups was observed in diabetics with acute myocardiual infarction, treated conservatively. A significant reduction in the rate of in-hospital mortality was observed in the 1992–1996 group of diabetes patients who received fibrinolytic treatment (22.7% vs. 6.1%, p = 0.035). In the 2005–2006 group, a significant reduction in mortality resulting from use of invasive methods (32.5% vs. 8.3%, p <0.001) with a tendency to a slight decrease in death rate in diabetics treated with fibrinolytic methods, was observed (FIGURE 3).

The global analysis of long-term prognoses in diabetics hospitalized because of myocardial infarction also showed an equally high morality during the 6-month follow-up in both study groups. The decidedly worst long-term outcomes of conservative treatment for myocardial infarction in diabetes patients were confirmed. In the 1992–1996 group of patients, a remarkable reduction in mortality in diabetics treated with fibrinolysis (30.7% vs. 9.1%, p = 0.01 after 6 months) was observed. In the 2005–2006 diabetes group a significant reduction in mortality was noticed in patients treated with invasive methods (41% vs. 15.3%, p = 0.01 after 6 months), and there was a tendency to a slightly increased mortality after the use of fibrinolysis (41% vs. 15.4%, p = 0.085 after 6 months) (FIGURE 4).

On the basis on multivariate analysis of 6-months mortality in study groups, it was shown that the most important prognostic factors were: age progression, myocardial insufficiency on hospital admission according Killip class and nonuse of invasive treatment (odds ratio of death during 6-month follow-up: 0.35 (95% CI 0.22–0.58, p <0.0001) (FIGURE 5).

FIGURE 2 Comparison of in-hospital mortality in diabetics and patients with normal glycemiae



DISCUSSION Increased incidence of diabetes observed in the recent years is a poor prognostic factor for patients with severe cardiovascular complications which frequently occurring in the course of metabolic disturbances accompanying glycemic imbalance. However, the current significant development of myocardial infarction therapy including mainly progress of reperfusion approaches ought to improve prognosis of high risk patients. A comparative analysis of 2 groups of diabetic patients treated because of myocardial infarction 1992–1996 and 2005–2006 years showed that the latter was on initially higher risk group. These patients were older (69.7 vs. 65.3 years, p <0.0001) and significantly more often suffered from hypertension (75% vs. 51.4%, p <0.001) and dyslipidemia (56.6% vs. 31.7%, p <0.0001).

The comparative analysis of acute myocardial infarction treatment in both study groups demonstrated a significant increase of new therapeutic methods in diabetic patients, in accordance with the development of new reperfusion techniques. In the 2005–2006 years 47% of patients were qualified for reperfusion therapy, fibrinolytic methods were used in 8.3% of them, and

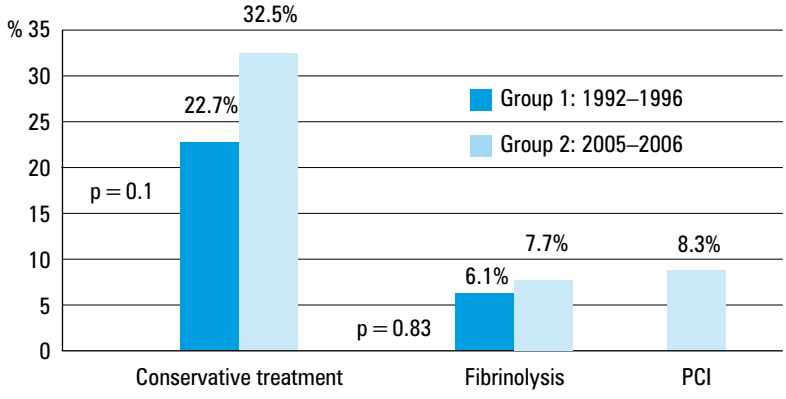


FIGURE 3 Comparison of in-hospital mortality in diabetics and patients with normal glycemiae depending on treatment strategy. Abbreviation – see FIGURE 1

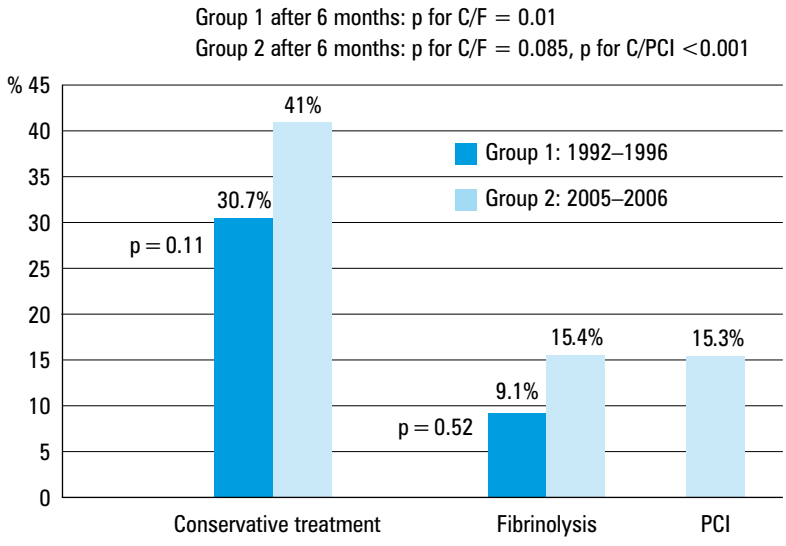
coronary angioplasty was performed in 38.7% of patients, while in the years 1992–1996 only 18% of diabetics underwent fibrinolytic therapy (p = 0.0035).

The benefits of reperfusion treatment in diabetic patients were observed in cases with prevalence of fibrinolytic methods. At the start of this study, there were concerns, that fibrinolytic therapy in diabetics might result in high number of retinal hemorrhages and diabetic retinopathy. However the GUSTO-1 study demonstrated that diabetic patients had more benefits from fibrinolytic therapy compared to those who did not have any carbohydrate disturbances, without the increased incidence of retinal hemorrhage.

No differences in the blood flow according to the TIMI scale were observed and, reocclusion and reinfarction were more common observed. However, complete reperfusion on the microcirculation level, rarely occurred. This was probably caused by lower fibrinolytic efficacy resulting from enhanced activation of blood coagulation system and impaired endogenous fibrinolysis.[9,10]

The present study confirmed high efficacy of fibrinolytic therapy in diabetic patients hospitalized in the years 1992–1996. This therapy resulted in only slight decrease in mortality as shown in the 2005–2006 years. A significant reduction of death number (compared to conservative treatment) was observed in diabetic patients who underwent invasive methods during hospitalization. This effect persisted during the 6-months follow-up (reduction of 63% of 6-month follow up mortality).

FIGURE 4 Comparison of long-term prognoses dependent on treatment strategy in diabetics. Abbreviations: p for C/F – p value for comparison between conservative and fibrinolysis treatment; p for C/PCI – p value for comparison between conservative and percutaneous coronary intervention (PCI) treatment



According to the current recommendations concerning the treatment of acute coronary events including myocardial infarction, primary angioplasty is the best strategy in diabetics. The comparative study of primary angioplasty and fibrinolytic therapy efficacy demonstrated the prevalence of invasive methods in the study groups of patients.

In the GUSTO IIb study a lower number of reinfarctions in diabetics who had undergone primary percutaneous coronary interventions (PCI) was found, compared to patients who had received fibrinolytic therapy during 30-day follow-up. A significant reduction in mortality in the PCI group was not observed which was probably caused by less common stent implantation and the GP IIb/IIIa inhibitors.[11]

The analysis of diabetics with the STEMI-ACS included to the PAMI study showed, that primary angioplasty in this group was used more rarely than in subjects without glycemic disturbances (88% of diabetics vs. 91% of normoglycemic subjects). The initial angioplasty effectiveness was, however, similar in both study groups – the TIMI 3 flow was present in 92% of diabetics and in 93% of non diabetic patients and residual occlusion was found in 20% of cases in both study groups. Despite these positive results, within hospital and 6-month follow-up mortality was significantly increased in diabetics and amounted to 4.5% vs. 2.6%, and 7.7% vs. 4.2%, respectively. This fact was attributed to more frequent occurrence of no-reflow phenomenon in diabetics.[12] It was also evidenced that GP IIb/IIIa inhibitor treatment increased the efficacy of primary angioplasty in diabetic subjects.[13]

The present study showed real-life benefits of invasive methods in myocardial infarction treatment in diabetic subjects. A significant reduction in the in-hospital and long-term mortality undoubtedly resulted from the development of new reperfusion methods.

Frequent stent implantation during angioplasty in the study group from 2005–2006 ought to be emphasized. Currently, it is known that the introduction of stents into invasive treatment has significantly decreased risk of restenosis which has been also observed in diabetic patients who had undergone angioplasty (24% vs. 60%, compared to the group who had undergone balloon angioplasty), which in turn resulted in a significant decrease in the revascularization procedure risk during follow-up (14% vs. 31% respectively, p = 0.03).[14] Bare metal stent implantation has not solved problems with worse prognosis for diabetics treated with invasive methods. The introduction of drug-eluting stents has been another attempt aimed at improving the PCI results in diabetics. The SIRUS study confirmed the benefits

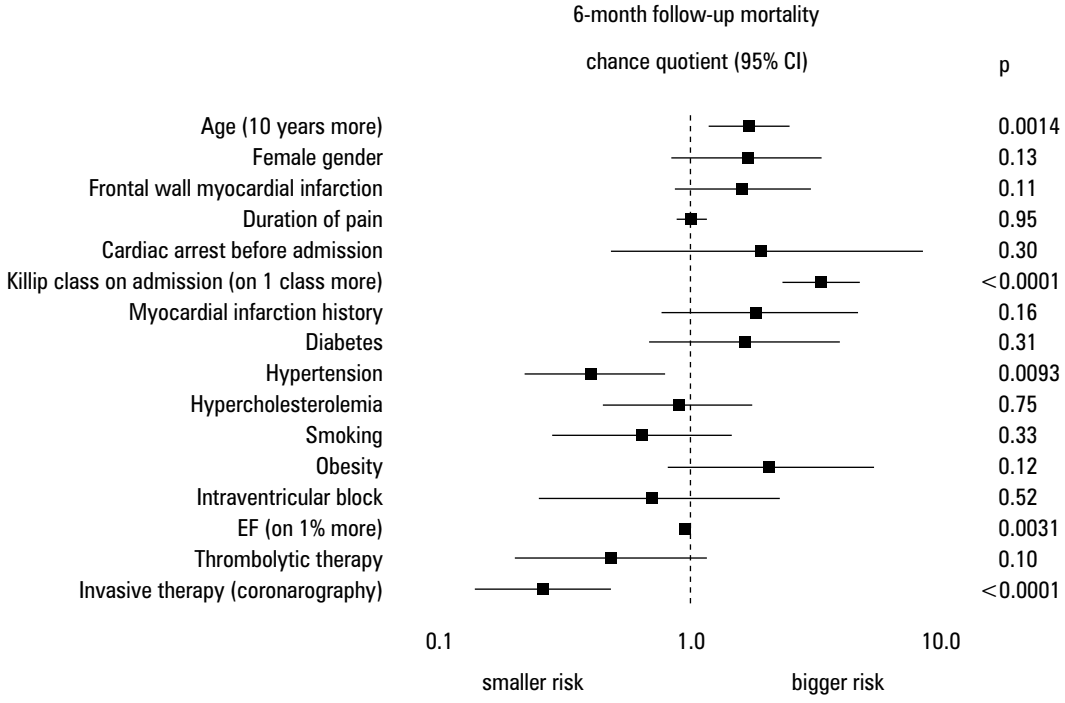


FIGURE 5 Multifactor analysis of 6-month follow-up mortality. Abbreviations: EF – ejection fraction

provided by stents eluting antiproliterative drugs (sirolimus) in diabetic patients.

Rapamycin stent implantation in this study group resulted in reduction in the number of restenosis from 50.5% (bare metal stent) to 17.6% (drug-eluting stent) which in turn led to decrease of severe cardiac adverse events rate (from 25% to 9.2% – in the rapamycin stent group, respectively). However, detailed analysis of diabetic patients subgroups showed that significant reduction of number of restenosis was not observed in patients who required intensive insulin therapy.[15]

Highly promising results were obtained from 9-month study that included diabetics with paclitaxel-coated stents; the frequency of restenosis was 6.4%.[16] The further studies showed however that effects of antiproliferative stents application were not so optimistic; it has been more often demonstrated that diabetes still decides about increasing risk of restenosis, and in spite of restenosis reduction, drug-eluting stents do not decrease coronary event rate.[17,18]

Available data concerning pathophysiology of acute coronary events show that restenosis is not the only reason for the worse clinical status and prognosis of myocardial infarction in diabetics. It is important for these patients to perform adequately aggressive antiplatelet and antihypertensive pharmacotherapy to normalize glycemia, hyperlipidemia and blood pressure. Enhanced of blood coagulation activity in diabetics, as the result of platelet activation, indicates that antiplatelet drugs is strongly recommended in myocardial infarction therapy. On the basis of the ISIS-2 and GISSI-3 studies, it was suggested that diabetics ought to receive higher ASA doses.[19] Also, the new antiplatelet drug therapy should improve prognosis in diabetic patients with acute coronary events. The CLARITY-TIMI 28 study (including 16% of diabetics) which evaluated patients with STEMI-ACS, demonstrated benefits of effective reperfusion methods application and decreased risk of myocardial infarction reoccurrence during the 30-day follow-up of the study group receving clopidogrel compared to the placebo group.[20]

Another class of drugs which offer considerable benefits for diabetic patients with the history of myocardial infarction, are β-blokers. In one study, it has been shown that treatment with β-blockers resulted in mortality reduction in 37% of diabetics with acute myocardial infarction, and the long-term administration of these drugs resulted in 43% of cases reduction in the mortality.[21] The activity of statins in diabetes patients was confirmed in the HPS study[22], and the benefits of convertase inhibitor treatment offered to diabetics with the early stage myocardial infarction were demonstrated in other studies[23,24].

The present study showed the marked progress in myocardial infarction pharmacotherapy in diabetics. In the recent years, clopidogrel, statins, ASA and β-blockers have been more commonly used compared to the previous period.

In view of significant changes in current therapy of myocardial infarction, presented in this paper, it is unclear why there has been no overall mortality reduction in diabetic patients. Detailed analysis of each group of patients can help explain this problem. Patients hospitalized in the years 2005–2006 were a high risk group for cardiovascular events, they were about 5 years older, more frequently suffered from hypertension and hypercholesterolemia, and had a slightly lower left ventricular ejection fraction. The additional analysis of this group showed different myocardial infarction therapies depending on the patient's clinical status. The analysis showed that invasive treatment was used in younger patients

(manage 65.6 years compared with 73.3 years, which was the mean age of patients undergoing conservative treatment) and angioplasty was performed less frequently in women and individuals with lower left ventricular ejection fraction in the third and fourth stages of heart failure according to Killip class.

Currently run registers of patients with acute coronary syndromes are showing more and more commonly that in the "real world" qualification for invasive treatment is based on selection of patients. The GRACE data analysis demonstrated increased, according to the GRACE risk-score, in-hospital mortality of patients with acute coronary events. It is also showed, that in patients with STEMI-ACTS, coronary angioplasty was performed the most frequently in a very low risk group of patients (60% of cases), more infrequently in the medium risk group (54% of cases), and the most rarely in the high risk group of patients (41% of cases).[25] Thus, it is not surprising that overall mortality was so high among diabetic patients hospitalized recently because of myocardial infarction.

The present study demonstrated that high mortality resulted from high death rate among patients qualified to conservative treatment. These patients constituted the highest risk group for cardiovascular events; they were older, more frequently females and had lower left ventricular ejection fraction and the symptoms of heart failure.

Conclusions from the presented study are as follow:

1) the present study demonstrated a considerable development in myocardial infarction therapy observed in patients from the highest risk group for acute coronary events: diabetics (wide application of reperfusion therapy with intensive pharmacotherapy)
2) considerable benefits of reperfusion use to diabetes patients were confirmed (a reduction of 75% in in-hospital mortality compared to patients treated conservatively, and a decrease of 63% in the number of deaths during the 6-month follow-up)
3) the absence of the global mortality decrease among diabetics treated for myocardial infarction resulted mainly from the worse clinical status of the 2005–2006 group of patients (older age and the coexistence of other connected with diabetes risk factors for coronary event occurrence), and, probably, the less common of qualifications for reperfusion therapy among patients from the highest risk group.

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