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Original Article

Prognostic Impact of Insulin-Treated and Non–Insulin-Treated Diabetes in Patients with a Reduced Ejection Fraction After ST-Elevation Myocardial Infarction

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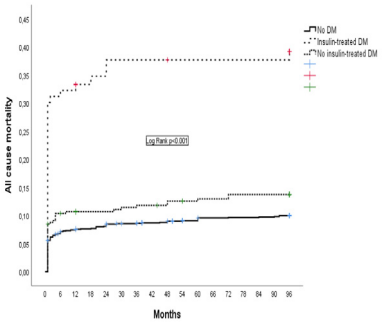
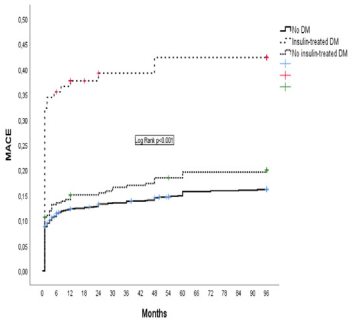
Diabetes treatment and prognosis after STEMI

- 2,230 STEMI patients treated with primary PCI
- Insulin treated DM N=103
- Non-insulin treated DM N=358
- No DM N=1769 patients
- Follow-up 8-years



Insulin-treated DM- HR 1.76 (1.15-2.69)



Insulin-treated DM HR 1.72(1.15-2.62)

Insulin-treated DM- independent predictor for mortality and MACE
Non-insuliin treated DM- not an independent predictor

ABSTRACT

Background: Insulin- and non–insulin treated diabetes (ITDM and NITDM) have different prognostic impact in patients with myocardial infarction and/or heart failure. The aim of this study was to analyze the prognostic impact of ITDM and NTIDM on the incidence of all-cause mortality and major adverse cardiovascular events (MACE— cardiovascular death, nonfatal infarction, nonfatal stroke, and target vessel revascularization) in the 8-year follow-up of patients with ST-segment

RÉSUMÉ

Contexte : Le diabète entraîne des répercussions pronostiques différentes chez les patients ayant subi un infarctus du myocarde et (ou) atteints d'insuffisance cardiaque selon qu'il est traité à l'insuline (DTI) ou non (DNTI). Le but de cette étude consistait à analyser les répercussions pronostiques du DTI et du DNTI sur l'incidence de la mortalité toutes causes confondues et les événements cardiovasculaires indésirables majeurs (ECIM — décès d'origine cardiovasculaire,

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elevation myocardial infarction (STEMI) with a reduced ejection fraction (EF).

Methods: **We analyzed 2230 consecutive STEMI patients treated with primary percutaneous coronary intervention and with EF < 50%. Echocardiographic examination was performed after primary percutaneous coronary intervention . Patients were divided into 3three groups: those with ITDM, those with NITDM, and those with no DM. Patients presenting with cardiogenic shock were excluded.**

Results: **The incidence of DM was 20.7%; among the patients with DM, 103 (22.3%) had ITDM. Patients with ITDM and NITDM had a higher incidence of mortality and MACE, compared with patients without DM. Also, at 8-year follow-up, the incidences of all-cause mortality and MACE were significantly higher in patients with ITDM vs patients with NITDM (37.8% vs 13.1%, *P* < 0.001 and 40.8% vs 18.9%, *P* < 0.001, respectively). Multivariable analysis showed ITDM to be an independent predictor for long-term mortality (hazard ratio 1.76, 95% confidence interval 1.15-2.69), and MACE (hazard ratio 1.72, 95% confidence interval 1.15-2.62).**

Conclusions: **ITDM was an independent predictor of the occurrence of long-term mortality and MACE in patients with STEMI and reduced EF. NITDM was not an independent predictor for the occurrence of adverse events in analyzed patients.**

infarctus non mortel, accident vasculaire cérébral non mortel et revascularisation du vaisseau cible) chez des patients ayant subi un infarctus du myocarde avec élévation du segment ST (STEMI) avec fraction d'éjection réduite, suivis pendant 8 ans.

Méthodologie : **Nous avons analysé 2 230 patients consécutifs ayant subi un STEMI traités par intervention coronarienne percutanée primaire dont la fraction d'éjection était < 50 %. Les patients s'étaient prêtés à un examen échocardiographique après l'intervention. Ils ont été répartis en trois groupes : ceux dont le diabète était traité à l'insuline (DTI), ceux dont le diabète n'était pas traité à l'insuline (DNTI) et ceux qui n'étaient pas atteints de diabète. Les patients ayant présenté un choc cardiogène ont été exclus.**

Résultats : **L'incidence du diabète était de 20,7 %. Parmi les patients diabétiques, 103 (22,3 %) étaient atteints de DTI. L'incidence de la mortalité toutes causes confondues et des ECIM a été plus élevée chez les patients atteints de DTI et de DNTI que chez les patients qui n'étaient pas atteints de diabète. Après 8 ans de suivi, l'incidence de la mortalité toutes causes confondues et des ECIM était également nettement plus élevée chez les patients atteints de DTI que chez ceux atteints de DNTI (37,8 % *vs* 13,1 %; *p* < 0,001 et 40,8 % *vs* 18,9 %; *p* < 0,001, respectivement). L'analyse multivariée a montré que le DTI était un facteur prédictif indépendant de la mortalité à long terme (rapport des risques instantanés [RRA] : 1,76; intervalle de confiance [IC] à 95 % : 1,15 à 2,69) et des ECIM (RRA : 1,72; IC à 95 % : 1,15 à 2,62).**

Conclusions : **Le DTI s'est avéré être un facteur prédictif indépendant de la mortalité à long terme et des ECIM chez les patients ayant subi un STEMI avec fraction d'éjection réduite. Le DNTI n'était pas un facteur prédictif indépendant de la survenue de manifestations indésirables chez les patients analysés.**

Primary percutaneous coronary intervention (pPCI), dual-antiplatelet therapy, and secondary prevention measures have significantly reduced the incidence of mortality and the occurrence of nonfatal adverse events in patients with ST-segment elevation myocardial infarction (STEMI).[1,2] However, mortality caused by STEMI remains relevant and the incidence is up to 10% in the first year. After this period, the risk for mortality and nonfatal adverse events becomes lower, but not negligible.[1,2] Also, some patients with STEMI are at higher risk for the occurrence of adverse events in both short- and long-term follow-up.

Diabetes mellitus (DM) is not only a strong risk factor for coronary artery disease, but also has a strong negative prognostic impact on mortality incidence and other adverse events in all patients with acute myocardial infarction (AMI).[3-13] Data from literature indicate that the negative prognostic impact of DM in patients with AMI differs depending on DM therapy, and that patients with insulin-treated DM (ITDM) have a poorer prognosis compared to not only patients without DM, but also patients with non−insulin-treated DM (NITDM). The short-term mortality incidence in STEMI patients with ITDM is up to 18%, whereas in patients with NITDM, it is around 10%.[4,6,8,13]

Another very strong prognostic marker in patients with AMI is left ventricular systolic function (most frequently defined as the value of the ejection fraction [EF]).[4,5] A well-known finding is that patients with AMI and a reduced EF < 50% are at risk of mortality and other adverse events, and the risk increases with further decline of the EF.[1] At the same time, the presence of DM in patients with a reduced EF can further worsen the prognosis of these patients.

Studies involving patients with heart failure (HF) of various etiologies with a severely reduced EF < 40% and a mildly reduced EF of 40%-49% indicate that patients with ITDM have a higher risk of adverse events, compared to that for patients with NITDM.[11,12] Also, in patients with AMI and HF or EF < 35%, the negative prognostic impact of ITDM appears stronger than the negative prognostic impact of NITDM. However, a point to note is that only a small percentage of STEMI patients included in these studies were treated with pPCI.[4,5] To the best of our knowledge, the prognostic significance of ITDM and NITDM in the long-term follow-up of patients with STEMI treated with pPCI, who had a reduced EF, has not been analyzed in literature.

The present study aims to analyze the impact of ITDM and NITDM on the incidence of all-cause mortality and

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See page 17 for disclosure information.

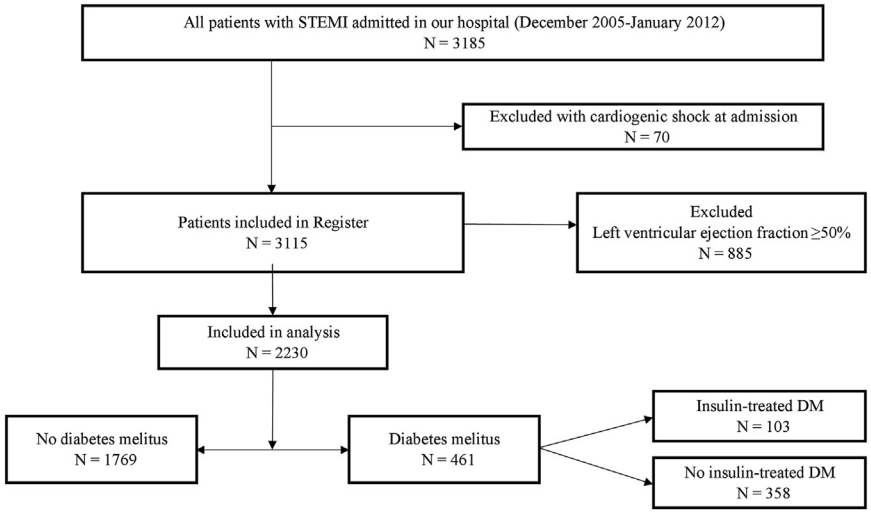

Figure 1. The flowchart of patient selection. DM, diabetes mellitus; STEMI, ST-segment elevation myocardial infarction.

major adverse cardiovascular events (MACE) in the 8-year follow-up of patients with a reduced EF after STEMI.

Materials and Methods

Study population, inclusion and exclusion criteria, data collection, and definitions

In the present study, we included 2230 consecutive STEMI patients with an EF $<$ 50% hospitalized between December 2005 and January 2012. All patients were included in the prospective Clinical Center of Serbia STEMI Register (CCSSR). The purpose of the prospective CCSSR has been published previously.[14] In brief, all consecutive STEMI patients, aged $\geq$ 18 years, who were admitted to the coronary care unit after being treated with pPCI in the catheterization lab of the center were included in the CCSSR. All included patients received written information of their participation in the CCSSR. Their verbal and written consent from every patient also was obtained.[14] Patients with cardiogenic shock at admission were excluded from the CCSSR. For the purpose of this study, patients with EF $\geq$ 50% were excluded from the analysis.

The flowchart of patient selection is presented in Figure 1.

Coronary angiography and pPCI were performed via the femoral approach in all patients. All patients were pretreated with loading doses of aspirin (300 mg) and clopidogrel (600 mg) before the procedure. Selected patients also were given the glycoprotein IIb/IIIa receptor inhibitor tirofiban (infusion started in the catheter laboratory). After the procedure, patients were treated in keeping with the current guidelines.[14]

Demographic, baseline clinical, laboratory, angiographic, and procedural data were collected and analyzed. An echocardiographic examination was performed during hospitalization, in the first 3 days after pPCI. The left ventricular EF was calculated according to the biplane method. Baseline kidney function (blood for creatinine analysis was drawn before iodine contrast administration) was assessed using the Modification of Diet in Renal Disease equation, and a value of the estimated glomerular filtration rate $<$ 60 ml/min per m^2 was considered as chronic kidney disease (CKD). Patients were divided into 3 groups: those with no DM, those with ITDM, and those with NITD. The diabetic status of the patients was determined at hospital admission by the attending physician by careful assessment of past medical history and based on the use of oral antidiabetic drugs or insulin. Also, in the ITDM or NITD group, we also included patients in whom DM was diagnosed during hospitalization (new-onset DM) and treatment was started.

Patients were followed up at 8 years after the index event. Follow-up data were obtained through telephone interviews and at outpatient visits. We analyzed all-cause mortality and composite endpoint major adverse cardiovascular events, which included cardiovascular death, nonfatal reinfarction, nonfatal ischemic stroke, and target vessel revascularization. The cause of death was obtained from death certificates or discharge forms (if the patient had been hospitalized). Cardiovascular death included any death due to a cardiac cause (fatal recurrent myocardial infarction, low-output HF, fatal arrhythmia, and/or sudden death), and death caused by noncoronary vascular causes, such as ischaemic cerebrovascular disease.[14] Recurrent myocardial infarction was defined according to the Fourth Universal Definition for Myocardial Infarction from the European Society of Cardiology.[15] Target vessel revascularization was defined as ischemia-driven percutaneous revascularization of the target vessel performed for thrombosis, restenosis, or other complications. Computed tomography was used to diagnose (ischemic) stroke. The emergency hospital neurologist was responsible for the diagnosis and treatment of stroke.[14]

Ethics

The study protocol was approved by the Ethics Committee of the University of Belgrade, Faculty of Medicine (approval number 470/II-4, February 21, 2008). The study was conducted in keeping with the principles outlined in the Helsinki Declaration. Written informed consent was obtained from all patients for their participation in the CCSSR.

Statistical analysis

Categorical variables were expressed as frequency and percentage. Baseline continuous variables were expressed as the median, with 25th and 75th quartiles, and were compared using Kruskal-Wallis analysis of variance (when we compared 3 group of patients—those with no DM, those with ITDM, and those with NITDM) and the Mann-Whitney test (when we compared 2 groups of patients—ITDM and NITDM). Analysis for normality of data was performed using the Kolmogorov-Smirnov test. Baseline differences between categorial variables were tested using the Pearson χ^2 test. The Kaplan-Meier method was used for constructing the probability curves for 8-year mortality and MACE for all 3 analyzed groups, whereas the difference between patients was tested using the log-rank test. The Cox proportional hazard model (backward method with the entrance $P < 0.1$) was used to identify univariable and multivariable predictors for the occurrence of all-cause mortality and MACE.

Two-tailed P-values < 0.05 were considered statistically significant. We used SPSS statistical software, version 19, for statistical analysis (SPSS, Chicago, IL).

Results

We completed 8-year follow-up in 1823 (81.7%) patients. The median follow-up was 78 ± 18 months. Among 2230 patients analyzed, 461 (20.7%) patients (20.7%) had DM. Among the patients with DM, 103 (22.3%) had ITDM, and 358 (77.7%) had NITDM. The mean age of all analyzed patients was 61 (53, 70) years, and 632 patients (28.3%) were female. Overall, 948 patients (42.6%) had an EF < 40%, whereas 1282 (57.4%) patients had an EF ranging from 40% to 49%.

Compared to patients with no DM, patients with ITDM and NITDM were older and more likely to be female; they more often presented with Killip class > 1, complete atrioventricular block, and atrial fibrillation; they were more likely to have baseline CKD, multivessel disease on the initial angiogram, a postprocedural TIMI flow < 3 and a lower EF. When we compared patients with ITDM and NITDM, we found that patients with ITDM more often presented with Killip class>1, complete atrioventricular block, and AF, as well as that they more often had CKD, multivessel coronary artery disease, a postprocedural thrombolysis in myocardial infarction (TIMI) flow < 3, and a lower EF. The in-hospital mortality incidence was significantly higher in patients with ITDM and NITDM, when compared to that in patients with no DM. Also, among patients with DM, in-hospital mortality was significantly higher in patients with ITDM, as compared to patients with NITDM. Baseline characteristics, laboratory, angiographic, and procedural characteristics, in-hospital mortality, and therapy at discharge, in patients with no DM, with ITDM, and with NITDM, are presented in Table 1.

At 8-year follow-up, all-cause mortality and MACE were registered in a total of 252 (11.3%) and 379 (16.9%) patients, respectively. Causes of mortality were predominantly cardiovascular in all of the analyzed groups; noncardiovascular causes of death (most often cancer, pneumonia, sepsis, ileus, and dementia) were registered in 19 patients (7.5% of all deaths). All-cause mortality and MACE rates at 8-years of follow-up in patients with ITDM were 37.8% and 40.8%; in patients with NITDM, these rates were 13.1% and 18.9%, and in patients without DM, they were 9.4% and 15.2%, respectively.

All-cause mortality and MACE rates in patients with ITDM, NITDM, and without DM are presented in Table 2. Kaplan-Meier curves showing 8-year all-cause mortality (curve a) and MACE (curve b) are presented in Figure 2. After adjustment to variables defined in the univariate analysis, as predictors of 8-year mortality and MACE, ITDM remained an independent predictor of all-cause mortality and MACE in 8-year follow-up (patients with no DM were used as a reference group). Predictors for the occurrence of 8-year mortality and MACE are presented in Table 3.

Discussion

In our study, we found that STEMI patients with ITDM had a higher burden of cardiovascular diseases, and a higher incidence of long-term all-cause mortality and MACE, as compared with that in patients without DM, and also with patients with NITDM. The difference in the incidence of MACE was caused predominantly by higher cardiovascular mortality; no significant difference occurred in the incidence of nonfatal recurrent ischemic events among these 3 groups of patients (those with ITDM, those with NITDM, and those with no DM). In the multivariable analysis ITDM, but not NITDM, was an independent predictor of mortality and composite endpoint MACE in the 8-year follow-up.

Baseline characteristics of analyzed patients

The clinical characteristics of our patients from all 3 analyzed groups are in keeping with the data found in the literature,[4,12,13] and the differences in the percentage of patients with ITDM and NITDM can be explained by the difference in patient selection, ie, the different study design. According to data from literature, among the patients with DM, around 30% are patients with ITDM,[7,8,16-18] which is also the case with our findings. A common finding is that patients with DM are older and develop coronary disease earlier, have more comorbidities, as well as poorer angiographic findings, compared with patients without DM. This finding suggests that patients with diabetes have a higher atherosclerotic burden.[7,8] Patients with ITDM are usually older, as compared to patients with NITD; however, this was not the case in our study, but patients with ITDM did have more comorbidities, poorer angiographic findings, and they presented more often with signs of HF and/or heart rhythm disorders, which is also in keeping with the findings in the literature.[4,13,18]

Prognostic impact of ITDM and NITD in patients with myocardial infarction and/or HF

Data from the literature indicate that the overall risk of adverse events in patients with AMI and ITDM is increased, as compared to that in not only patients without DM, but also those with NITDM.[4,8,9,13,19] In a study by Hoebers et al., wherein over 4000 STEMI patients treated with pPCI were included, ITDM was found to be an independent predictor of

Table 1. Baseline clinical, laboratory, angiographic, procedural characteristics, therapy at discharge, and intrahospital mortality of the study patients

Characteristics	ITDM N = 103	NITDM N = 358	P*	No DM N = 1769	P†
Age, y	63 (57, 72)	64 (58, 73)	0.971	60 (52,70)	< 0.001
Female	37 (35.9)	131 (36.6)	0.901	459 (25.9)	< 0.001
BMI	27.3 (24.5, 29.7)	26.8 (24.8, 29.4)	0.644	25.9 (24.2, 27.8)	0.493
Previous MI	22 (21.3)	49 (13.7)	0.037	197 (11.1)	0.009
Previous angina	10 (9.7)	38 (10.6)	0.791	126 (7.1)	0.032
Previous stroke	8 (7.7)	25 (7.9)	0.786	69 (3.9)	< 0.001
Hypertension	80 (77.7)	295 (82.1)	0.277	1130 (63.9)	< 0.001
HLP	58 (56.3)	225 (62.8)	0.230	1030 (58.2)	0.192
Smoking	29 (28.2)	112 (31.3)	0.544	965 (54.6)	< 0.001
Family hystory	20 (19.4)	85 (23.7)	0.356	577 (32.6)	< 0.001
Pain duration, h	3 (1.5, 5)	3 (2, 5.5)	0.861	2.5 (1.5, 4.5)	< 0.001
Atrial fibrillation on initial ECG	20 (19.4)	21 (5.9)	<0.001	147 (8.3)	0.950
Complete AV block	18 (17.4)	11 (3.1)	<0.001	86 (4.9)	0.086
Killip class > 1	49 (47.5)	76 (21.1)	<0.001	262 (14.8)	< 0.001
Systolic arterial BP at admission	130 (110, 150)	140 (130, 160)	<0.001	130 (120, 150)	< 0.001
Heart rate at admission	80 (70, 100)	82 (75, 97)	0.235	80 (70, 90)	< 0.001
Multivessel disease	89 (5.1)	239 (66.7)	0.002	991 (56)	< 0.001
3-vessel disease	61 (59.2)	128 (35.7)	<0.001	455 (25.7)	< 0.001
LM stenosis	10 (9.8)	30 (8.4)	0.679	113 (6.9)	0.030
Postprocedural flow TIMI < 3	16 (15.5)	23 (6.4)	0.003	94 (5.3)	0.019
Stent implanted	92 (89.4)	325 (90.8)	0.958	1634 (92.4)	0.091
Acute stent thrombosis	4 (3.9)	4 (1.1)	0.058	22 (1.2)	0.261
Glycoprotein IIb/IIIa inhibitor	42 (40.1)	112 (31.2)	0.078	701 (39.6)	0.007
CK MB max	1788 (952, 4003)	1673 (708, 3054)	0.102	2389 (1598, 4025)	0.024
Troponin max	53 (12.6, 119)	27.4 (7.8, 96.2)	0.219	37.5 (11.9, 103)	0.045
Hemoglobin at admission, g/L	141 (124, 158)	150 (138, 159)	0.081	141 (131, 152)	< 0.001
Baseline CKD	38 (36.9)	85 (23.7)	0.008	282 (15.9)	< 0.001
LVEF	40 (34, 45)	42 (39, 45)	<0.001	44 (40, 49)	< 0.001
LVEF < 40%	66 (64.1)	178 (49.7)	<0.001	704 (39.7)	< 0.001
LVEF 40%−49%	37 (35.9)	180 (50.3)	<0.001	1065 (60.2)	< 0.001
Therapy at discharge‡					
Beta-blockers	60 (3.4)	284 (79.3)	0.085	1432 (80.9)	0.077
ACE inhibitors	58 (3.3)	275 (76.8)	0.275	1349 (76.2)	0.015
Statin	62 (3.5)	271 (75.7)	0.162	1430 (80.8)	0,779
Diuretic	25 (1.4)	82 (22.9)	0.080	320 (18.1)	< 0.001
Calcium antagonist	1 (0.9)	13 (36.3)	0.823	64 (3.6)	0.589
Amiodarone	1 (0.9)	5 (1.4)	0.934	54 (3.1)	0.065
In-hospital mortality	24 (23.3)	24 (6.7)	< 0.001	82 (4.6)	< 0.001

Values are n (%), or median (interquartile range), unless otherwise indicated.

ACE, angiotensin-converting enzyme; AV, atrioventricular; BBB, bundle branch block on electrocardiogram (ECG) at admission; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CK-MB, creatine kinase MB isoform; DM, diabetes mellitus; HF, heart failure; HLP, hyperlipidemia; IQR, interquartile range; ITDM, insulin-treated diabetes mellitis; LAD, left anterior descendent; LM, left main artery; LVEF, left ventricular ejection fraction; med, median; MI, myocardial infarction; NITDM, non−insulin treated diabetes mellitus; TIMI, thrombolysis in myocardial infarction; WBC, white blood cell count at admission.

* P-value for patients with NITDM and ITDM.

† *P*-value over the 3 groups.

‡ All patients were on aspirin and clopidogrel.

Table 2. All-cause mortality and composite endpoint major adverse cardiovascular events (MACE) in study patients

Event	ITDM N = 103	NITDM N = 358	P*	No DM N = 1769	P†
8 years					
All-cause death	39 (37.8)	47 (13.1)	< 0.001	166 (9.4)	< 0.001
MACE	42 (40.8)	68 (18.9)	< 0.001	269 (15.2)	< 0.001
Cardiovascular death	36 (34.9)	43 (12)	< 0.001	154 (8.7)	< 0.001
Nonfatal recurrent infarction	9 (8.7)	18 (5.1)	0.226	96 (5.5)	0.943
TVR	19 (18.4)	39 (10.9)	0.607	116 (6.5)	0.070
Nonfatal stroke	3 (2.9)	6 (1.7)	0.250	23 (1.3)	0.022

Values are n (%), unless otherwise indicated.

DM, diabetes mellitus; ITDM, insulin-treated DM; NITDM, non−insulin-treated DM; TVR, target vessel revascularization.

* *P*-value for patients with NITDM and ITDM.

† *P*-value over the 3 groups.

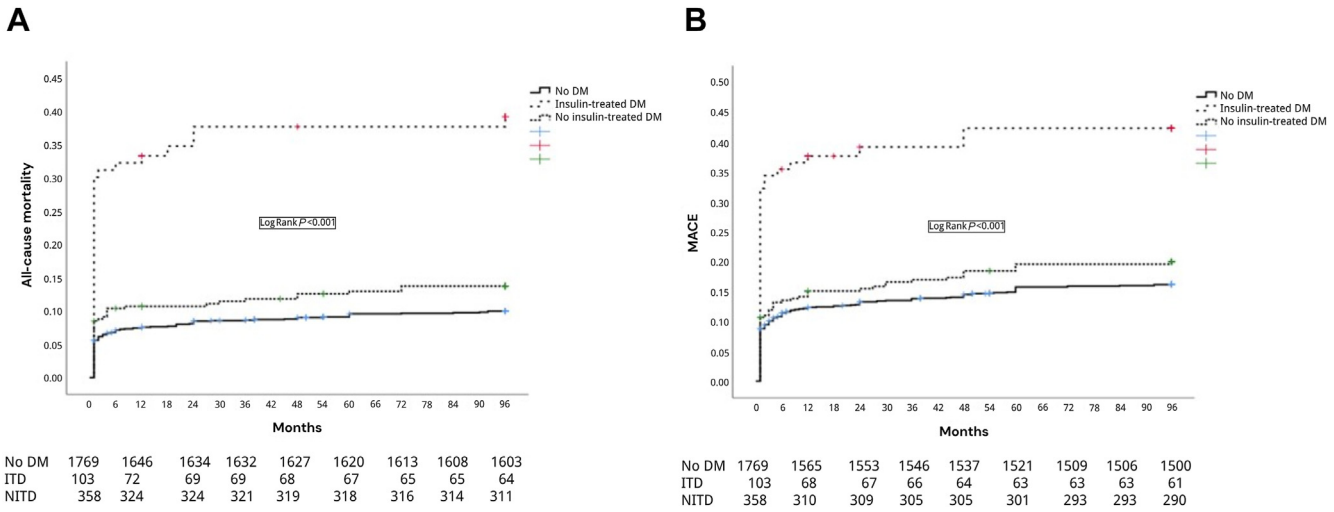

Figure 2. Kaplan-Meier curves showing (**A**) 8-year all-cause mortality and (**B**) major adverse cardiovascular events (MACE). Register = Clinical Center of Serbia STEMI Register. DM, diabetes mellitus; ITD, insulin-treated diabetes; NITD, non-ITD.

long-term mortality (up to 5 years), whereas the long-term mortality incidences were similar in patients with NITDM vs those without DM.[13] Similar are the results of the study by Antoniucci et al., in which the 6-month mortality incidence in patients treated with pPCI was the highest in the ITDM group (26%), and it was similar in patients with NITDM vs nondiabetic patients (7% vs 4%, respectively).[20] Also, patients with STEMI and ITDM have a higher risk of MACE during the short- and long-term follow-up periods, as compared with patients with NITDM.[8,18] Finally, a meta-analysis by Bundhun et al. included 21 studies wherein patients who underwent PCI were included (without data on what percentage of patients had acute coronary syndrome). The results of this meta-analysis showed that mortality, as well as the occurrence of MACE in 1-year and in long-term follow-up after PCI, were significantly higher in patients with ITDM, as compared to the incidence in patients with NITDM.[21]

Similar results can be found in studies wherein patients with HF and/or a reduced EF were analyzed, especially in cases with ischemic etiology. In a study by Rossello et al., patients who had suffered myocardial infarction complicated with HF of with EF $< 35\%$ were analyzed. In this study, the highest total and cardiovascular mortality during an approximately 3-year follow-up was registered in patients with ITDM, whereas patients with NITDM had a significantly lower incidence of mortality, albeit higher, compared to that in patients without DM. ITDM significantly increased the risk of mortality, compared to not only nondiabetic patients but also those with NITDM. However, both ITDM and NITDM were independent predictors of mortality in this study, with the independent and negative prognostic impact of ITDM being stronger, as compared to that of NITDM.[4] Also, patients with ITDM had a higher risk of nonfatal events during follow-up, compared with patients with NITDM and patients without DM. The difference in the results between our study and the cited study can be explained by the different populations of analyzed patients, and the small number of patients who were treated with pPCI.[4] In a study by Schupp et al., patients with HF with a mid-range EF (40%-49%) and ITDM had a higher risk of 30-month mortality, as compared to NITDM patients.[11] In a post-hoc analysis—Systolic Heart Failure Treatment with the Inhibitor Ivabradine Trial (SHIFT), patients with sinus rhythm, an EF $\leq 35\%$, and with ITDM were shown to have a 33% higher risk of cardiovascular death or hospitalization due to HF exacerbation as compared to patients with NITDM.[22] Also, the post-hoc analysis of the Studies of Left Ventricular Dysfunction (SOLVD) study showed that the presence of DM generally adversely affected the prognosis of patients with left ventricular systolic dysfunction, if it was of ischemic etiology, whereas DM had no prognostic impact in patients with nonischemic etiology.[23]

Possible mechanisms for higher adverse events rates in patients with ITDM

Numerous and still insufficiently explained mechanisms that could explain the worse prognostic impact of ITD on patients with AMI and/or HF, as compared to the prognostic impact of NITDM. Data from experimental and nonrandomized studies showing that the use of insulin in the treatment of DM led to the progression of cardiovascular diseases, especially in patients with previous macrovascular complications. The introduction of insulin therapy in patients with DM (DM type 2, which also includes our patients) is a surrogate marker for poor glycemic management with oral medication and for a longer duration of DM. Patients with ITDM also have an elevated concentration of glycosylation end products, which have an atherogenic and proinflammatory effect,[8,9,12,18] and iatrogenic hyperinsulinemia also itself has a proinflammatory effect.[20] Insulin is also thought to enhance fibrinogen production, and (iatrogenic) hyperinsulinemia may have a procoagulant effect, lead to overactivation of signal-transducing pathways that affect the progression of atherosclerosis, disrupt the balanced synthesis and release of endothelial mediators.[4,18,21] Insulin treatment in type 2 DM has been associated with platelet hyperreactivity.[21] Also, patients with ITDM usually have more severe

Table 3. Predictors for 8-year all-cause mortality and major adverse cardiovascular events (MACE; Cox regression model)

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause mortality				
Age, y	1.04 (1.02−1.06)	< 0.001	1.05 (1.03−1.06)	< 0.001
Postprocedural TIMI < 3	5.31 (3.951−7.29)	< 0.001	2.89 (2.07−4.31)	< 0.001
Killip > 1 at admission	4.98 (3.85−6.39)	< 0.001	2.80 (2.14−3.62)	< 0.001
ITDM	4.51 (3.12−6.51))	< 0.001	1.76 (1.15−2.69)	0.008
AF at admission	3.81 (2.18−5.15)	< 0.001	1.74 (1.33−2.54)	0.001
CKD	3.68 (2.81−4.16)	< 0.001	1.42 (1.01−1.95)	0.042
3-vessel disease	2.27 (1.76−2.96)	< 0.001	1.32 (1.02−1.76)	0.038
Previous infarction	1.73 (1.06−2.12)	0.002	1.27 (1.08−2.16)	0.026
Complete AV block at admission	1.40 (1.05−1.60)	0.020		
NITDM	1.40 (0.99−1.97)	0.056		
Anemia at admission	1.37 (0.92−1.89)	0.167		
Troponin level max.	1.0 (0.99−1.02)	0.670		
Left main stenosis	0.97 (0.61−1.55)	0.972		
		MACE		
Age, y	1.04 (1.02−1.06)	< 0.001	1.02 (1.01−1.03)	< 0.001
Postprocedural TIMI < 3	3.64 (2.75−4.82)	< 0.001	2.37 (1.57−3.20)	< 0.001
Killip > 1 at admission	3.07 (2.18−4.32)	< 0.001	2.03 (1.56−2.48)	< 0.001
ITDM	3.06 (2.47−3.79)	< 0.001	1.72 (1.15−2.62)	0.006
Complete AV block at admission	2.23 (1.69−2.96)	< 0.001	1.36 (1.01−1.43)	0.028
CKD	2.32 (1.85−2.92)	< 0.001	1.31 (0.99−1.72)	0.061
Previous infarction	1.71 (1.32−2.24)	< 0.001		
3-vessel disease	1.66 (1.34−2.6)	< 0.001		
NITDM	1.25 (0.94−1.64)	0.121		
Left main stenosis	1.33 (0.92−1.92)	0.120		

AF, atrial fibrillation; AV, atrioventricular; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; ITDM, insulin-treated diabetes mellitus; max, maximum; MI, myocardial infarction; NITDM, non−ITDM; TIMI, thrombolysis in myocardial infarction.

and more extensive coronary artery disease and more often coronary chronic total occlusion, compared with patients with no DM or those with NITDM.[10,11] Some authors believe that reperfusion in ITD is less successful despite an optimal TIMI flow,[13,24] which indirectly indicates the presence of microvascular disease or atherothrombotic embolism during the procedure.[5,10,20] In our study, we found the highest percentage of patients with postprocedural TIMI flow < 3 in the group with ITD. However, even after adjusting for this variable, ITD remained an independent predictor of mortality and MACE. Also, the relatively altered myocardium of diabetic patients (diabetic cardiomyopathy) may be more prone to ischemia-reperfusion injury than the myocardium of patients without diabetes.[10] Finally, underutilization of evidence-based therapy after MI has been suggested to explain worse outcomes in patients with DM in some older studies,[25] but our results do not support this theory, because in our study no difference occurred in the therapy at discharge among analyzed patients.

Clinical implications

Our study confirms previous reports on the unfavourable prognostic impact of ITDM in patients with STEMI and a reduced EF, and it also adds to the knowledge in this area by providing information on long-term outcomes in patients with a mildly reduced EF (40%-49%). Differentiation between ITDM and NITD should be taken into account in the individual patients with DM. In patients with STEMI and a reduced EF, the need for insulin therapy provides further prognostic value in diabetic patients and should be taken into account to further predict cardiovascular risk. In addition to the usual treatment that is administered to all patients after STEMI (introducing sodium-glucose transporter inhibitors-2 in all patients with DM, especially those with ITDM and a reduced or mildly reduced EF, should be considered.[4,26]

Study limitations

Our results should be viewed in the context of the study limitations. The study is unicentric, and observational, but it is controlled and prospective. Inclusion of consecutive STEMI patients who underwent primary PCI limits possible selection bias. STEMI patients presenting with cardiogenic shock and STEMI patients who were not treated with pPCI are not included in this CCSSR (this can limit generalizability of our results in all STEMI patients). Patients analyzed in this study were hospitalized between 2005 and 2012. No patients were treated with more recently developed antiplatelet drugs (ticagrelor and/or prasugrel), because these drugs were not available for routine administration to patients at the time of their entry into the CCSSR. We did not use other measures for determining left ventricular systolic function such as myocardial deformation imaging. However, many clinical trials so far have used EF to stratify patients and have demonstrated its benefit in determining the outcome.[11-13] No data on follow-up echocardiographic examinations show whether a certain degree of recovery or deterioration in the left ventricular systolic function has occurred. We did not routinely measure hemoglobin A1c in all patients. Patients with insulin resistance (or some other prediabetic condition) were included in the group of nondiabetic patients. However, they may have developed DM during the 8-year follow-up, which could have affected their long-term prognosis. We

had no data on the specific criteria for initiating insulin therapy in patients with ITDM at admission. We also had no data on the duration of DM or insulin treatment. New-generation oral antidiabetic drugs, such as sodium glucose transporter-2 inhibitors, were unavailable at the time of patient inclusion. Potential confounding factors that are not tested in our analysis may have an impact on the prognosis. The study was not designed to evaluate whether changing pharmacologic treatment during follow-up would have an impact on the long-term outcome in the analyzed patients.

Conclusion

STEMI patients with reduced EF and with insulin- and non−insulin-treated DM had a significantly higher all-cause long-term mortality and MACE rate, as compared to that of patients with no DM. Also, patients with insulin-treated DM had a higher burden of comorbidities, a worse finding on the coronary angiogram, and a higher incidence of the analyzed adverse events, as compared with patients with non−insulin-treated DM. Insulin-treated DM was an independent predictor for the occurrence of long-term mortality and composite endpoint MACE. Non−insulin-treated DM was not an independent predictor for long-term mortality and MACE in the analyzed patients.

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Data Availability

The data presented in this study are available upon request from the corresponding author.

Ethics Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University of Belgrade, Faculty of Medicine (approval number 470/II-4, February 21, 2008).

Patient Consent

The authors confirm that patient consent is not applicable to this article. This registry analysis uses deidentified data; therefore, the institutional review board did not require consent from the patient. Written informed consent was obtained from all patients for their participation in the Register.

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Disclosures

The authors have no conflicts of interest to disclose.

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