In-hospital daily insulin dose predicts long-term adverse outcome in patients with diabetes with ST-elevation myocardial infarction treated with successful primary percutaneous angioplasty

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Abstract

Introduction: Early initiation of reperfusion therapy including primary percutaneous coronary revascularization (PPCI) has been recognized as a crucial factor determining clinical outcomes in the acute phase of myocardial infarction. In unstable patients with type 2 diabetes mellitus (T2D) the clear benefit from PPCI was proven. We aim to evaluate the prognostic value of factors describing glycometabolic state on admission in patients with T2D undergoing PPCI in acute ST-elevation myocardial infarction (STEMI).
Material and methods: Prospective analysis of clinical and laboratory variables (mean daily short acting exogenous insulin dose (DID), admission blood glucose, glycated hemoglobin (HbA_{1c}), microalbuminuria) was performed in 112 consecutive patients with T2D with STEMI who underwent PPCI. Women comprised 58% of the group.
Results: Insulin dosing was targeted to obtain a mean daily glucose level < 7.8 mmol/l. During 12-month follow-up 33 (29.5%) major adverse cardiac events (major adverse cardiac events (MACE) consisting of death, reinfarction, and repeated target vessel revascularization) were reported. Microalbuminuria was present in 68 (60.5%) patients. The mean HbA_{1c} level was 7.9%. In the multivariate logistic regression model only DID > 44 IU remained an independent risk factor for MACE (p = 0.02, OR = 5.2).
Conclusions: In patients with diabetes with STEMI treated with PPCI, simple measurement of DID during hospitalization can add valuable prognostic information about the future risk of MACE.

Key words: diabetes, primary percutaneous coronary intervention, daily insulin dose, ST-elevation myocardial infarction.

Introduction

The prevalence of type 2 diabetes (T2D) among patients presenting with ST-elevation myocardial infarction (STEMI) is estimated to be as high as 21–45% [1–4]. The presence of hyperglycemia and high glycated hemoglo-

bin (HbA_{1c}) concentrations at the time of STEMI are associated with more diffuse coronary atherosclerosis, larger infarct size and worse outcomes [5–8].

Patients with T2D suffering from STEMI have higher in-hospital and long-term mortality [9–12]. Early initiation of reperfusion therapy including primary percutaneous coronary revascularization (PPCI) has been recognized as a crucial factor determining clinical outcomes in the acute phase of myocardial infarction. In unstable patients with T2D the clear benefit from PCI was proven. Even after adjustments to the more diffuse character and distribution of coronary atherosclerosis seen in patients with T2D, the advantage of an early invasive strategy was clear and more significant than in normoglycemic patients [13]. Even though the implementation of PPCI in STEMI reduced the total mortality rate, the risk of cardiovascular death among people with diabetes is still higher than in normoglycemic individuals [14, 15]. Time to treatment delays connected with diabetic neuropathy and more often seen atypical manifestation of STEMI [16], diffuse character of coronary atherosclerosis [12], proinflammatory state [17], high platelet activity and platelet resistance [18], and more pronounced reperfusion injury [19, 20] are the main postulated reasons for the differences in prognosis.

It has been suggested that the type of pharmacological treatment of diabetes may modify the clinical course during and after myocardial infarction in subjects with T2D [6]. Results of DIGAMI trials have shown that intensive glycemic control reduced long-term mortality in patients with T2D and acute myocardial infarction [8]. There is an ongoing debate on the way of achieving a satisfactory level of glycemic control in the acute phase of STEMI. We still are not convinced whether we should use insulin or oral agents [21]. The predictors of long-term outcome in this subset of patients treated with PPCI concerning metabolic control have not been fully described to date.

Therefore, the aim of this study was to analyze the association between the parameters of metabolic control during the acute phase of STEMI in patients with T2D undergoing PPCI and subsequent adverse events during 12 months of follow-up.

Material and methods

Patients

The study enrolled 112 patients with T2D, at mean age 66 ±9.9 years (range: 34–84 years), admitted to our department with STEMI; 65 women comprised 58% of the group. The patients were recruited from a consecutive cohort of STEMI patients admitted to our institution based on a pre-existing or new diagnosis of T2D. Ninety-seven subjects (86.6%) had T2D diagnosed before and 15 (13.4%) patients during the index hospitalization. Previous diagnosis of T2D was accepted if they had been informed of this diagnosis and were on prescribed non-pharmacological (diet and exercise only) and/or pharmacological treatment. New cases were diagnosed during the hospitalization according to WHO criteria [22]. Patients in cardiogenic shock upon admission and those with a recent history of coronary revascularization (≤ 3 months) were excluded. Approval to conduct this study was obtained from the local university's review board and written informed consent was obtained from all patients.

Immediately after admission all the patients, regardless of their previous glucose-lowering therapy, were switched to intensive insulin therapy for at least 3 days (human short-acting insulin was given in continuous intravenous infusion). The target range for mean blood glucose concentrations during the first 3 days of hospitalization was 5.7–7.8 mmol/l, and the daily insulin dose was adjusted to achieve this range in all patients. The analyzed parameter DID was calculated as the mean daily dose of insulin from the first 3 days of hospitalization. Blood glucose concentration < 3 mmol/l was defined as hypoglycemia.

Diagnosis of ST-elevation myocardial infarction

The STEMI was diagnosed according to the standard ACC/AHA criteria [23]. All the patients underwent immediate coronary angiography and successful PPCI within the infarct-related artery (IRA). The PPCI was considered successful if residual stenosis in the IRA at the end of the procedure was < 30%, and epicardial flow on the TIMI scale was graded 3. The use of coronary stents and periprocedural GP IIb/IIIa blockers administration was left to the decision of the operator.

Clinical data collection

Demographic data, general medical history and specific diabetes history (duration and type of glucose-lowering therapy treatment) were recorded using a standardized patient data collection form. During long-term follow-up, any health problems or adverse events were recorded as they were detected by the cardiologist or stated by the patient. A blood sample was taken immediately after admission to the emergency room for: creatinine kinase (CKMB), glucose, creatinine, C-reactive protein (CRP), total cholesterol, HDL cholesterol, and triglycerides measurement. Plasma glucose concentration was measured using the oxidase method. The HbA_{1c} was measured using the DCA 2000 (Bayer) instrument (normal range 4.1–6.5%). Mi-

croalbuminuria was measured from a single urine sample taken at admission using a semi-qualitative method based on the albumin-to-creatinine ratio. In patients in whom recurrence of angina was recognized during the follow up period, and in whom repeated coronary angiography was performed, restenosis in a previously treated vessel was defined as new stenosis > 50% of the particular segment reference diameter.

Long-term observation

At hospital discharge and during follow-up, the glucose-lowering therapy was individualized and all the changes were recorded. As a cardiovascular pharmacological treatment all patients were prescribed β-blockers, angiotensin-converting enzyme inhibitors, acetylsalicylic acid, thienopyridine and statins (unless contraindicated). Subjects were followed up for a mean of 1 year (388 ±224 days), with outpatient visits scheduled every 6 months. At each visit a standardized health check-up was carried out by the cardiologist at our department.

The primary endpoint of the study was the occurrence of major adverse cardiac events (MACE) within 1 year after STEMI. The combined endpoint of MACE was defined as death, recurrent nonfatal myocardial infarction or the need for repeated coronary revascularization (either percutaneous or surgical).

Statistical analysis

For statistical analysis the cohort was divided into subgroups according to the occurrence of study endpoints. The pilot sampling of the study cohort allowed for calculating the variability of daily short acting exogenous insulin dose (DID). Then the minimal number of enrolled patients was calculated in order to achieve the statistical power > 0.8 with the assumption that the rate of study end point occurrence in 12-month observation will be 30% based on previously published data [7, 24, 25].

Continuous variables with normal distribution are presented as mean ± SD or as median (25% percentile, 75% percentile) in the case of non-normal distribution. Categorical variables are presented as percentages and compared with the χ^2 test. Comparison of means for continuous data variables was performed by *t*-test in the case of normal distribution or Mann-Whitney in the case of non-normal distribution as indicated by the Kolmogorov-Smirnov test. Subsequently, receiver operating characteristic (ROC) curves were plotted for numerical variables significant in univariate analysis in order to identify optimal cutoff values. The population was subdivided into subgroups below and above the ROC-derived threshold and Kaplan-Meier MACE-free survival curves were constructed for such subgroups. The differences in survival rates were analyzed using the log-rank test. The impact of DID, HbA_{1c} and baseline glucose levels on survival were evaluated using a multivariate logistic regression model (enter method). A *p* value (two-tailed) < 0.05 was considered statistically significant. All analyses were performed using MedCalc 8.02 (Frank Schoonjans, 2005).

Results

Baseline clinical and biochemical characteristics of the patients are summarized in Table I. Mean duration of known T2D was 6.0 ±5.7 years. Fifty-four (48.2%) patients suffered from anterior STEMI and 58 (51.8%) from inferior STEMI. The time frame from onset of chest pain to PPCI initiation was 3.7 ±1.8 h. One-vessel disease was diagnosed in 42 (37.5%), whereas three-vessel disease was found in 29 (25.9%) patients. Complete occlusion of IRA (TIMI 0 flow) was present in 83 (74.1%) patients. Coronary stent implantation was performed in 87 (77.7%) patients (more than 1 stent was implanted in 12 (10.7%) procedures) and 25 (22.3%) received plain balloon an-

Table I. Baseline characteristics of patients and follow-up results (*n* = 112)

Subjects	Results *n* (%)
Past medical history:	
Diagnosis of diabetes prior to admission	97 (86.6)
History of myocardial infarction	28 (25.0)
Previous coronary angioplasty	3 (2.7)
Hypertension	82 (73.2)
Obesity (body mass index > 30 kg/m^2)	26 (23.2)
Current smoking	41 (36.6)
Mean baseline biochemical data:	
Total cholesterol > 5.2 mmol/l	53 (47.3)
Microalbuminuria	68 (60.7)
Creatinine > 115 µmol/l	18 (16.1)
Prevalence of clinical events during follow-up period:	
Composite major adverse cardiac event	33 (29.5)
Death	12 (10.7)
Reinfarction	18 (16.1)
Repeat target vessel revascularization	21 (18.8)
Coronary artery bypass grafting	3 (2.7)
Percutaneous coronary intervention	18 (16.1)

gioplasty. The GP IIb/IIIa inhibitor abciximab was introduced in 84 (75%) patients undergoing PPCI, and 28 patients received the loading dose of clopidogrel (300 mg) prior to PPCI. The mean duration of hospitalization was 7.8 ±3.0 days. Final post-procedural TIMI 3 flow after PPCI was achieved in 92 patients (82.1%); TIMI 2 in 6 (5.4%), TIMI 1 in 10 (8.9%), TIMI 0 in 4 (3.6%).

Primary percutaneous coronary revascularization safety analysis

Per protocol PPCI was successful in all patients in terms of mechanical recanalization of the infarct-related coronary artery. Periprocedural complications, mostly transient, were observed in 33 (29.5%) patients. They consisted of coronary flow disturbances defined as the no-reflow phenomenon that was observed in 22 (19.6%) patients. Life-threatening arrhythmias during PPCI occurred in 3 (2.7%) patients. Cardiogenic shock developed in 4 patients (3.6%) during 24 h after PPCI, of which 1 patient died. One patient during the first 24 h after PPCI presented focal neurologic symptoms consistent with stroke. Minor bleeding complications connected with the puncture site were noted in 3 (2.7%) cases, and in 1 case blood transfusion was required.

Study endpoints analysis

During the follow-up period 33 patients (29.5%) experienced the primary end point (MACE), predominantly recurrent angina resulting in repeated revascularization (PCI and/or bypass surgery), which was performed in 21 (18.8%) patients (Table I). 12 patients (10.7%) died during follow-up.

Univariate analysis

Treatment of type 2 diabetes

Before the index hospitalization the majority of our cohort was treated with oral hypoglycemic agents. None of the patients was prescribed glitazones because they were not available in Poland at the time of enrollment. There were 32 patients treated with sulphonylureas (SU), 16 with metformin, and 10 with SU in combination with metformin. 39 out of 97 patients (40.2%) were treated with insulin. The remaining 15 (13.4%) patients did not have any treatment for T2DM before the hospitalization.

Kaplan-Meier analysis showed that insulin treatment before STEMI was a risk factor for the occurrence of MACE (p =0.004, HR = 3.3, 95% CI: = 1.8 to 23.9).

Mean plasma glucose concentration at admission was 13.1 ±6.9 mmol/l and HbA_{1c} was 7.6 ±1.4%. In the acute phase of STEMI our therapeutic goal of glycemic control (mean daily glycemia < 7.8 mmol/l) was achieved in all patients with intensive, intravenous insulin therapy. Within the first 3 days of hospitalization episodes of moderate hypoglycemia occurred in 4 (3.6%) patients.

Predictors of major adverse cardiac events in univariate and multivariate analysis

Composite MACE occurred in 33 (29.5%) patients. In univariate analysis high DID (p = 0.0001; ROC cutoff 44 UI; AUC = 0.7; 95% CI: 0.56–0.81), the presence of microalbuminuria (p = 0.047; OR = 2.6; 95% CI: 1.1–6.5) and de-novo diagnosis of T2D (p = 0.006; OR = 5.1; 95% CI: 1.7–15.4) were predictive of adverse long-term prognosis. High values of DID showed a strong relationship with high glucose levels at admission (r = 0.60, p < 0.0001) and a mild correlation with the duration of T2D (r = 0.3; p = 0.03).

We found no correlation between gender, obesity, history of hypertension, hypercholesterolemia and previous acute coronary syndrome (ACS) and long-term outcomes. Except for DID, no other metabolic parameter related to T2D correlated with MACE (Table II).

In the logistic regression analysis only DID > 44 IU was found to be an independent predictor of MACE (p = 0.02, OR = 5.2, 95% CI: 1.3–20.7) af-

Table II. Comparison of means of selected variables related to T2D that could influence occurrence of MACE

Parameter	No MACE *N* = 79 (70.4%) (mean ± SD)	MACE *N* = 33 (29.5%) (mean ± SD)	Value of *p**
Age [years]	63.6 ±9.4	62.5 ±11.0	NS
Baseline GLC [mg/dl]	225.7 ±106.3	255.9 ±162.6	NS
HbA_{1c} (%)	7.7 ±1.5	8.1 ±2.0	NS
DID [IU]	30.3 ±13.4	42.7 ±18.4	0.0001
T2D duration [years]	7.1 ±5.8	6.4 ±4.8	NS

**ROC – receiver operating characteristics, MACE – major adverse cardiac event, GLC – glucose, DID – daily insulin dose, T2D – type 2 diabetes mellitus*

ter successful PPCI. The Kaplan-Meier curve plotted for occurrence of composite MACE according to the DID also showed significant differences in event-free survival (Figure 1).

Discussion

The results of our study indicate that PPCI in STEMI is an efficacious and safe method of restoring patency of IRA in patients with diabetes, and the long-term mortality rate of 10.7% in our group was low. These observations are concordant with previously published data [7, 16, 26, 27].

In our study the only independent predictor of long-term adverse outcome was DID. The DID correlated with baseline glucose levels, reflecting the degree of metabolic imbalance and glycemic control deregulation in the acute phase of STEMI. There is evidence that baseline hyperglycemia is a better predictor of in-hospital than long-term mortality [28]. Numerous trials have confirmed the relationship between the severity of T2D expressed as a need for insulin supplementation and mortality as well as occurrence of serious cardiovascular events after STEMI [29, 30]. The need for high daily doses of insulin in order to achieve proper metabolic control may be a marker of the T2D severity, insulin resistance and hyperinsulinemia, which is often accompanied by obesity. In our study we found only a mild correlation between BMI and DID, which does not by itself explain the high requirement for insulin supplementation.

Janka *et al.* [31] found that a high degree of insulin resistance and need for higher DID correlated with increased risk of both coronary and non-coronary vascular events. There are data that suggest worse survival after PCI among insulin-treated patients [32]. Because of the established role of insulin treatment in the acute phase of STEMI [11], in our group all patients were switched to insulin treatment in the acute phase so we could not compare whether insulin treatment was superior or inferior to the oral hypoglycemic drugs regimen. Patients with STEMI and no previous diagnosis of diabetes have a high prevalence of insulin resistance both during the hospital stay and 3 months thereafter [33]. We found a higher rate of cardiovascular events in the subgroup of patients who were diagnosed with T2D during the index hospitalization. These results are in accordance with previous observations demonstrating that newly diagnosed T2D was a strong risk factor for both mortality and major cardiovascular events during 1-year follow-up after myocardial infarction [34]. It is generally accepted that in this subset of patients the first major cardiovascular event is often preceded by long-term, undiagnosed hyperglycemia [35]. It has also been observed that patients

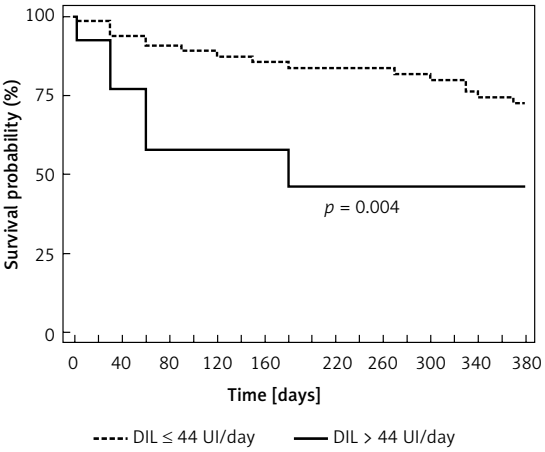

Figure 1. Kaplan-Meier curve plotted for occurrence of composite MACE according to DID

with de-novo diagnosed T2D present with more pronounced proinflammatory activity that can induce rupture of atherosclerotic plaques and partially explain the observed excess of cardiovascular events [36].

The most prevalent adverse cardiovascular event was the need for repeated target vessel revascularization due to significant clinical or angiographic restenosis. Poor metabolic control of diabetes is a well-known risk factor of restenosis after percutaneous coronary interventions [37]. As shown in the long-term observation of the DIGAMI 2 trial, there was generally no difference in outcome between oral glucose-lowering drugs and insulin, but an excess of non-fatal myocardial infarctions and strokes was observed in the insulin-treated subgroup while use of metformin tended to be protective [38]. Insulin stimulates an exaggerated healing process which can be responsible for excessive neointima hyperplasia after angioplasty. This process can justify a higher frequency of MACE in patients with T2D requiring high DID in STEMI. To date, such a relationship has been described in peripheral balloon angioplasties [39] and coronary interventions but never in the setting of the acute procedure [40, 41]. The adverse effect of high insulin concentrations during the course of acute coronary syndrome is not limited to the population with overt diabetes but was also proven for normoglycaemic individuals with recognized hyperinsulinemia [42]. The reasons for the adverse clinical course after PPCI in STEMI in patients requiring high doses of insulin supplementation have never been elucidated to date. Our study provides a clue about the importance of measuring the DID as a simple, easy to measure parameter predictive of MACE in long-term observation. In our opinion, DID as a parameter embraces more pathophysiological information than standard indicators of metabolic imbalance such

as glycemia or HbA_{1c} levels. In this specific setting, DID can link the information concerning metabolic status that is more often worse than in elective interventions and at the same time give us a clue for the future restenosis risk prediction because high insulin concentrations, whether endogenous or exogenous, promote neointimal hyperplasia.

This study has several limitations. Possible differences in pharmacological cardiovascular treatment prior to the STEMI were not analyzed. The total number of patients in this single-center study is limited. However, patients were unselected and probably representative for our daily practice population. In addition, we did not measure insulin levels or insulin resistance. Therefore, we can only speculate about the degree of hyperinsulinemia and that the patients who needed a higher daily dose of insulin to normalize blood glucose concentration were more insulin resistant than the others. Multi-center study design could include more patients, but a variable strategy of STEMI treatment and different operators' experience level might emerge as new limiting factors.

In conclusion, the accurate assessment of cardiometabolic risk in patients with T2D with STEMI treated with PPCI may require novel approaches. In this setting a simple measurement of DID can add valuable prognostic information about the future risk of MACE.

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