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ORIGINAL STUDIES

ESTIMATION OF METFORMIN AND OTHER SUGAR REDUCING THERAPY INFLUENCE ON THE OUTCOMES IN PATIENTS WITH ACUTE CORONARY SYNDROME AND DIABETES MELLITUS TYPE II

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Highlights

• The high mortality rate among patients with acute coronary syndrome on the background of diabetes mellitus type 2 compared with patients without such a history indicates the urgency of the problem. To provide effective metabolic control the treatment of acute coronary syndrome in diabetic patients requires additional efforts. Metformin intake leads to, as it is estimated, a lower hospital mortality risk and after hospital lethality during 6 months.

Aim	To study the influence of hypoglycemic therapy on hospital and long-term prognosis in patients with acute coronary syndrome (ACS) and diabetes type 2.
Methods	The study included 63 patients with ACS and type 2 diabetes. All patients had a clinical examination, assessment of mortality risk and myocardial infarction on GRACE scale (Global Registry of Acute Coronary Events) and TIMI (Thrombolisis In Myocardial Infarction) in-hospital and six months after hospitalization.
Results	Metformin is associated with a lower estimated risk of in-hospital mortality and within 6 months after discharge in patients with acute coronary syndrome on the background of type 2 diabetes and with less risk of adverse cardiovascular events within 14 days of their occurrence in patients with unstable angina pectoris on the background of diabetes. High daily doses of metformin have also been associated with a decrease in the estimated risk of in-hospital mortality and within 6 months after discharge in patients with ACS associated with diabetes. The inverse association between the daily dosage of metformin and the presence of angina pectoris in patients with ACS and diabetes type 2 indicates a protective effect of metformin high daily dosages in relation to the risk of complications within six months after the discharge from hospital.
Conclusion	One of the important aspects of ACS treatment, along with effective therapy, is the impact on concomitant risk factors, including blood glucose control. The main groups of hypoglycemic drugs have currently been identified; their effect on cardiovascular events, long-term effects and long-term prognosis are being investigated.

Keywords Acute coronary syndrome • Diabetes mellitus type 2 • Hypoglycemic therapy • Metformin

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Список сокращений

MI	–	myocardial infarction	STEMI	–	ST elevation myocardial infarction
UA	–	unstable angina (pectoris)			diabetes mellitus
ACS	–	acute coronary syndrome	DM	–	sulfonylurea
NSTEMI	–	non- ST elevation myocardial infarction	SM	–	

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Introduction

Pathologies of cardiovascular system are primary causes of mortality in the Russian Federation (46.3%) according to 2021 data. In 2018 the death rate from coronary heart disease was 52.6% [1]. Diabetes mellitus (DM) is an independent risk factor for atherosclerosis-associated diseases of the circulatory system and more than half of such patients suffer from coronary heart disease. Up to 60% of DM patients have "mute" or low-symptomatic forms of myocardial infarction (MI). Mortality in the development of acute coronary syndrome (ACS) is 2–3 times higher among these patients [2].

Along with the effective therapy, one of the important aspects of ACS treatment is the impact on concomitant risk factors, including blood glucose control [3]. The main groups of hypoglycemic drugs have currently been identified. Their effect on the cardiovascular system is being actively investigated and some standards for the treatment of patients with DM2 and ACS have been developed. It is also necessary to follow the principle of individual treatment and take into account the presence of concomitant pathologies and all the features of the disease course. Despite the fact that the connection between ACS and DM2 has been confirmed, it is still unknown what effect hypoglycemic therapy has on the outcomes of ACS in patients with DM2. It also remains unclear whether antidiabetic drugs affect the future risk of cardiovascular complications in patients with coronary heart disease and vulnerable plaque. It is possible that the concomitant cardioprotective effects of hypoglycemic drugs also affect the prognosis in patients with MI and unstable angina (UA).

The aim of the study is to assess the influence of metformin and other sugar reducing medicine during hospital treatment and long lasting prognosis of patients with ACS on the background of DM 2.

Methods

The study was carried out at the State Medical Institution of the NSO "City Clinical Hospital No. 34" (Novosibirsk, Russia) from November 20, 2018 to April 28, 2019. 63 patients were included in the study. The protocol of the study was approved by the ethical committee of the institution (Protocol No. 15 of 18.09.2018).

The following inclusion criteria were chosen for the study: 1) DM 2 in accordance with the criteria of the World Health Organization (1999); 2) ACS (MI or unstable angina) according to the criteria of the Russian Society of Cardiology (2017); 3) signing of informed consent to participate in the study.

The study did not include: 1) children and adolescents under 18; 2) patients who were placed to another outpatient clinic so their prognosis could not be assessed; 3) renal insufficiency or impaired renal function (creatinine clearance less than 60 ml/min); 4) diabetic ketoacidosis. Research design was a series of cases, open.

The doctor diagnosed “acute coronary syndrome" according to a set of criteria developed by the European and Russian Cardiological Societies (2017) [4]. "Diabetes mellitus" was diagnosed by the attending physician in accordance with the criteria of ADA, EASD (2018).

All patients underwent a clinical examination: collection of complaints, anamnesis, examination, laboratory diagnostics (general clinical, biochemical and immunological blood tests, instrumental examinations such as ECG, and EchoCG), calculation of glomerular filtration rate according to the formula CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) 2009 in modification 2011) [5]. ECG was used to determine the presence of cicatricial changes in the myocardium, cardiac arrhythmias, and signs of ischemia.

The endpoints were recorded during the hospital stage (deaths due to cardiovascular and other causes, repeated MI, early post-infarction angina pectoris, acute cerebrovascular accident, acute cardiac rhythm and conduction disturbances, and III–IV acute heart failure according to Killip). The endpoints were also determined in 6 months post-hospital period: repeated hospitalizations for cardiovascular reasons during six months of outpatient follow-up, acute cerebrovascular accident, fatal outcomes for cardiovascular and other reasons.

To determine the risk of repeated adverse cardiovascular events within two weeks after ACS the TIMI scale for non-ST elevation myocardial infarction (NSTEMI) was used. The baseline risk level of the scale is 4.7%. A high score in NSTEMI according to this scale indicates an increased risk of adverse cardiovascular events such as MI, early postinfarction angina pectoris, which may require revascularization, and a high risk of cardiovascular death.

It is also possible to determine the risk of adverse cardiovascular events within 30 days for ST elevation myocardial infarction (STEMI) on the TIMI scale. The basic risk level is 0.8% provided there are no risk factors within the scale. In addition the use of the scale gives the opportunity to predict the risk of death for the long-term period (3 years) as well as the development of chronic heart failure.

The risk of MI and death development at the hospital stage and within six months after ACS can be calculated by the GRACE scale [6]. The use of the scale makes it possible to assess hospital mortality, the development of MI as well as the risk of these events within six months after the primary cardiovascular event. These data make it possible to choose personalized therapy for a patient with ACS and to determine its intensity. The risk according to GRACE scale is assessed as low at values less than 109 points (mortality less than 1%),

moderate – at 109–140 (mortality 1–3%) points, high – more than 140 points (mortality more than 3%).

The patients were treated according to the recommendations for the patients diagnosed with NSTEMI (the electrocardiogram (2015)) and the clinical recommendations for "ST elevation myocardial infarction" (2016). Percutaneous transluminal coronary angioplasty with stenting was performed in 23 (36.5%) patients.

Statistical analysis

The IBM SPSS Statistics 23 program (IBM Corp., USA) was used to carry out the statistical analysis. The Kolmogorov-Smirnov method was applied to distribute the quantitative features (mean value (M) and standard deviation (SD)). The Student t-test was chosen to compare the samples. If normal distribution was absent, the median was calculated (Me 25%; 75%). Spearman's rank correlation coefficient (r) was used to assess the closeness of the relationship between the two features. The Mann–Whitney U-test was used to compare two independent samples. Qualitative features were evaluated with Pearson's χ^2 criterion and the z-criterion. The critical significance level of the null hypothesis (p) was <0.05.

Results

63 patients were enrolled in the analysis. They were hospitalized with STEMI and NSTEMI, and DM 2. As can be seen from the presented clinical data (Table 1) the group of patients with STEMI included 4 patients, the group NSTEMI consisted of 59 participants. 20 (31.7%) patients had already undergone percutaneous coronary intervention before hospitalization. Excess body weight was observed in 57 (90.5%) patients.

The risk of death was assessed in all patients during hospitalization in the cardiology department according to the TIMI and GRACE scales regardless of further treatment tactics. The distribution of patients according to the degree of risk on the GRACE scale is presented in Table 2.

Most of the patients (44.4%) had a moderate risk on the GRACE scale. The majority of patients (90.5%) took various hypoglycemic drugs during inpatient treatment. The therapy was prescribed before ACS at the outpatient stage of treatment for the period from 3 months to 10 years. The distribution of patients receiving hypoglycemic drugs was as follows: n = 25 (39.7%) – metformin monotherapy from 500 to 2,000 mg per day, n = 10 (15.9%) – insulin monotherapy, n = 6 (9.5%) – a combination of insulin and a tablet form of sulfonylurea (SM) or a dipeptidyl peptidase inhibitor-4, n = 4 (6.3%) – a combination of metformin and a tablet drug from the SM group, n = 12 (19.0%) – monotherapy of the tablet form of the drug SM and n = 6 (9.5%) – without therapy.

The comparison of patients' subgroups receiving various hypoglycemic drugs according to clinical, anamnestic and laboratory characteristics is presented in Table 3.

It was determined that in patients taking SM drugs BMI is higher than in patients following the therapy with a combination of metformin and SM drugs. The participants in the insulin monotherapy subgroup were more likely to have MI, the duration of diabetes and fasting blood glucose levels were higher compared to patients in the metformin monotherapy subgroup.

Complications after the hospital stage were registered in 31 (39.7%) patients: early post infarction angina – 3 cases, pulmonary edema – 1 case, conduction disorders such as blockage of the Gis bundle legs – 17, atrial fibrillation – 7, ventricular extrasystole – 3 cases (Table 4).

Long-term outcomes (after 6 months) were assessed in 58 out of 63 patients included in the study and the response was 92.1%. During this period 7 deaths occurred (12.1%), 4 (57.1%) of which were due to cardiovascular causes (1 case – acute myocardial infarction (1.7%) and 3 cases of acute heart failure (5.2%)) and 3 (42.9%) cases due to other causes (1 case of nosocomial pneumonia (1.7%), 1 case – community-acquired pneumonia (1.7%), 1 case – disseminated intravascular coagulation syndrome (1.7%)). Repeated hospitalization was registered in 21 (36.2%) cases. The reasons for repeated hospitalization were unstable angina – 33%, MI – 5%, arterial

Table 1. Characteristics of the examined patients

Index	n (%)
Total number of patients (m/f)	63 21/42 (33.3/66.7)
Age, years, Me (25%; 75%)	69.0 (63.0; 77.0)
Body mass index, kg/m^2, Me (25%; 75%)	32.0 (28.8; 35.4)
Myocardial infarction/unstable angina	16/47 (25.4/74.6)
ST elevation/absence	4/59 (6.4/93.6)
Q-positive/absence	5/58 (7.9/92.1)
Increased troponin I	16 (25.4)

Table 2. Distribution of patients with acute coronary syndrome and type 2 diabetes risk class according to GRACE scale

Patients, (n)	High risk, n (%)	Moderate risk, n (%)	Low risk, n (%)
63	9 (14.3)	28 (44.4)	26 (41.3)

hypertension – 10%, stenting – 14%, coronary angiography – 24%, other – 14%.

The number of days from initial hospitalization to death/re-hospitalization was also recorded (Table 5).

A significant inverse correlation was found between metformin intake and the received GRACE scores (r = -0.332; p = 0.008). The daily dose of metformin is inversely associated with GRACE scores (r = -0.518; p = 0.003) and inversely associated with the presence of complaints of chest pain and/or shortness of breath 6 months after the first hospitalization (r = -0.377; p = 0.034) (Table 6).

Since patients with unstable angina prevailed among the examined individuals, a correlation analysis was carried out for this subgroup of patients (Table 7).

Inverse correlations were determined between metformin intake and GRACE scores (r = -0.325; p = 0.024), as well as metformin intake and TIMI scores

Table 3. Clinical, anamnestic and laboratory characteristics of patients with various hypoglycemic therapy

Characteristics	Metformin monotherapy subgroup (1)	Insulin monotherapy subgroup (2)	Subgroup of a combination of insulin and a tablet preparation SM or DPP-4 (3)	Subgroup of a combination of metformin and a tablet preparation SM (4)	Subgroup of monotherapy of the SM tablet preparation (5)	Subgroup without treatment (6)
Age, years, Me (25%; 75%)	67.0 (62.5; 74.0)	73.5 (66.5; 80.0)	64.5 (55.3; 76. 5)	69.0 (59.0; 83.5)	69.5 (68.0; 76.8)	76.5 (53.8; 83.0)
Male, n, %	7 (28.0)	3 (30.0)	2 (33.3)	1 (25.0)	5 (41.7)	3 (50.0)
BMI, kg/m^2, Me (25%; 75%)	31.2 (27.1; 34.4)	31.4 (30.8; 32.3)	32.9 (30.6; 39.3)	26.2 (20.0; 34.3)	35.0 (30.1; 39.2)*	31.3 (25.6; 33.9)
MI/UA, n, %	4/21 (16.0/84.0)	5/5 (50.0 /50.0)**	1/5 (16.7/83.3)	1/3 (25.0/75.0)	3/9 (25.0/75.0)	2/4 (33.3/66.7)
Duration of DM, years, Me (25%; 75%)	6.0 (3.0; 8.0)	18.0 (13.7; 20.0)***	9.5 (6.0; 13.0)	10.5 (6.0; 12.0)	11.0 (7.5; 14.0)	8.0 (4.0; 10.0)
Fasting blood glucose, mmol/L, Me (25%; 75%)	7.4 (6.4; 8.5)	11.8 (9.1; 20.2)#	10.3 (7.4; 25.1)	7.6 (5.7; 8.9)	8.6 (6.1; 9.1)	5.9 (5.0; 14.7)

Note: ** – p^{4-5} = 0,041; ** – p^{1-2} = 0,009; *** – p^{1-2} = 0,005; # – p^{1-2} = 0,001; BMI – body mass index; DM – diabetes mellitus; DPP – dipeptidyl peptidases; MI – myocardial infarction; SM – sulfonylurea; UA – instable angina.*

Table 4. Characteristics of complications during hospital period

Complication, n = 31	n (%)
Early postinfarction angina	3 (4.8)
Pulmonary edema	1 (1.6)
Conduction disturbances	17 (27.0)
Atrial fibrillation	7 (11.1)
Ventricular premature beats	3 (4.8)

Table 5. Characteristics of patient outcomes (n = 99)

Patient outcomes, n = 58	(n, %)
Lethal	7 (12.1)
The number of days from the beginning to the hospital mortality, Me (25%; 75%)	155 (71; 219)
Rehospitalization	21 (36.2)
The number of days from the beginning to the hospital readmission, Me (25%; 75%)	130 (84; 208)

Table 6. Correlation character of hypoglycemic therapy connections with complications of acute coronary syndrome in patients with diabetes type 2

Index	Correlation coefficient	p
Metformin and GRACE scores	-0.332	0.008
Metformin dosage and GRACE score	-0.518	0.003
Metformin Dosage and disturbing breathlessness/chest pain 6 months after first hospitalization	-0.377	0.034

Table 7. Correlation between hypoglycemic therapy and complications of ACS in patients with unstable angina and diabetes type 2

Index	Correlation coefficient	p
Metformin and GRACE scores	-0.325	0.024
Metformin and TIMI score	-0.298	0.013
Metformin dosage (mg/day) and GRACE score	-0.428	0.037

(r = -0.327; p = 0.025). An inverse relationship was found between the daily dose of metformin and the scores on the GRACE scale (r = -0.428; p = 0.037).

Discussion

In ACS many factors are associated with DM2. They are blood glucose, hyper- and hypoglycemia, glycated hemoglobin and they lead to an unfavorable outcome [7]. Nevertheless, ACCORD and ADVANCE studies have shown that strict glycemic control does not have a positive effect on the prognosis in such patients but on the contrary it can lead to episodes of hypoglycemia and increased mortality [8, 9] although many hypoglycemic drugs have a cardioprotective effect [10].

Our study demonstrated the presence of inverse associations of metformin intake with scores on the GRACE and TIMI scales in patients with ACS on the background of DM2.

It has already been known that metformin intake by patients with DM2 on the background of ACS is directly associated with low hospital mortality from all causes [11]. It is stated that metformin is a first-line drug for DM2 treatment. However, the development of lactic acidosis is a serious side effect because high concentrations of the drug block gluconeogenesis in the liver (more often with renal insufficiency, liver hypoperfusion, tissue hypoxia). At the same time, the use of metformin according to the results of the DIGAMI 2 study reduced mortality from all causes by 35% in contrast to the use of insulin therapy and sulfonylurea derivatives [15].

According to the "Algorithms of specialized medical care for patients with diabetes mellitus" (2019) metformin is contraindicated in patients with DM and ACS due to the risk of lactic acidosis in tissue hypoxia and the unexplored effect on early and long-term clinical outcomes. Although ACS increases the risk of lactic acidosis, the disease develops extremely rarely if to take metformin (in 0.03 cases / 1000 patient-years). The attending physician registers such situations in singular cases. In addition, there are no exact criteria for determining which patient will develop lactic acidosis [1]. In real clinical practice the decision to continue metformin therapy is made by the attending physician after assessing the harm and benefit for a particular patient. It is assumed that the cardioprotective effect of metformin does not depend on its hypoglycemic effect.

Some potential mechanisms of this phenomenon include activation of the protein kinase A (PKA or cAMP-dependent protein kinase) pathway either directly by amplifying AMP kinase, or by stimulating adenosine receptors. All of the above effects inhibit the opening of pores that change the permeability of mitochondria during reperfusion (its opening leads to activation of apoptosis and cardiac muscle death), and provide cardioprotection [12]. AMP kinase acts as an energy sensor and is activated when the level of adenosine triphosphate in the cytoplasm of the cell decreases [14]. It is assumed that metformin provides cardioprotection by inhibiting mitochondrial complex I which reduces myocardial damage as a result of reperfusion. Blocking of the complex prevents the pores that change the permeability of mitochondria from opening and further the release of cytochrome and reactive oxygen species with subsequent apoptosis [13]. Our study revealed that the daily dosage of metformin in patients with DM2 with ACS is inversely associated with the scores obtained on the GRACE scale as well as the presence of angina pectoris 6 months after the first hospitalization. High concentrations of metformin inhibit complex I in endothelial cells and prevent the death of endothelial cells caused by high glucose content by inhibiting the opening of pores [16]. If to use high doses of metformin during reperfusion, the death of H9c2 cells (mycoplasma-free heart myoblasts) decreases. If a single treatment with high doses of metformin in ischemia is used, the infarction zone decreases in vitro and in vivo while therapy with high doses of metformin directly at the time of ischemia reduces reperfusion injury of the myocardium and causes inhibition of complex I activation, which is accompanied by attenuation of pore opening. In contrast to the effect provided by the constant intake of metformin the effect of the drug with a single dose does not depend on AMPK activation. Thus, a single administration of metformin high dose during reperfusion reduces heart damage through complex I modulation [13].

The results of the work indicate metformin positive effect on the prognosis in patients with ACS and DM2. However, further study of the drug is necessary to confirm the benefits of its use for the purpose of secondary prevention among these patients.

Conclusion

Among patients with ACS on the background of DM 2 metformin intake is inversely associated with the estimated risk of death at the hospital stage and within six months after ACS on the GRACE scale. The daily dose of metformin is also inversely related to the estimated risk of death at the hospital stage and within six months after ACS on the GRACE scale in this group of patients.

Conflict of interest

K.Y. Nikolaev declares no conflict of interest. K.I. Bondareva declares no conflict of interest. A.Ya. Kovaleva declares no conflict of interest. G.I. Lifshits declares no conflict of interest.

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Author Contribution Statement

NKYu – contribution to the concept and design of the study, data collection, analysis and interpretation, editing, approval of the final version, fully responsible for the content

BKI – contribution to the concept and design of the study, data collection, analysis and interpretation, editing, approval of the final version, fully responsible for the content

KAYa – data interpretation, editing, approval of the final version, fully responsible for the content

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