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GLUCOSE CONTROL IN PATIENTS WITH MYOCARDIAL INFARCTION

Key words: myocardial infarction, hyperglycemia.

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Aim: to investigate homeostasis markers of unfavourable prognosis and to define target glucose levels in patients with large-focal myocardial infarction (MI) and hyperglycemia (HG) without previous carbohydrate metabolism disorders.

Methods. Results of the examination of 185 patients with acute large-focal MI without previous carbohydrate metabolism disorders are presented in the article. Patients were divided into 2 groups: with HG (study group, n = 106) and without HG (control group, n = 79). Clinical, laboratory and instrumental investigations were performed. The obtained data were processed with the statistical software packages Excel, Statistica (version 10.0, StatSoft, Inc., USA), SPSS (version 16.0, SPSS Incorporation, USA).

Results. Patients with MI and HG were characterized by more severe systemic inflammation, hemostasis disturbances and changes in hormonal state, and myocardial necrosis markers than patients without HG. In patients with MI and HG without previous carbohydrate metabolism disorders a blood glucose level decrease below 8.0 mmol/l was associated with proinflammatory cytokine concentration reduction, D-dimer level decrease and reduction of initially elevated amount of nitrates and nitrites. In patients with MI and HG a blood glucose level decrease to 4.5–6.1 mmol/l and to 6.2–8.0 mmol/l did not affect inflammation parameters, the total amount of nitrates and nitrites, D-dimer level, incidence of complications, in-hospital mortality, unstable angina rate, recurrent myocardial infarction incidence and mortality during a 36-month follow-up.

Conclusions. Stress HG in case of acute MI leads to unfavourable prognostic changes in inflammation, hemostasis and hormonal parameters, biochemical markers of myocardial necrosis. Specific features of MI course and homeostasis parameter changes have been revealed depending on the dynamics of glycemia in the acute period of MI.

Background

The medical and social significance of cardiovascular diseases is extremely high in all countries, as they make the main contribution to the formation of the patterns of morbidity, disability and mortality. According to the national registries of the European Society of Cardiology countries the in-hospital mortality of unselected patients with ST-segment elevation caused by myocardial infarction (MI) varies between 4 and 12 % [1]. One of the most serious problems in MI is hyperglycemia (HG). The development of MI-associated HG significantly increases the risk of adverse outcomes [1, 2]. Angeli et al. [3] performed a systematic review and meta-analysis of 24 observational studies to investigate the association between HG and mortality in patients with acute coronary syndrome. In-hospital, 30-day and long-term mortality were analyzed separately. HG significantly increased the risk of in-hospital (OR 3.62, 95 % CI: 3.09–4.24; p < 0.0001, I2 = 0.0 %; 15 studies, 10673 patients), 30-day (OR 4.81, 95 % CI: 2.18–10.61, p < 0.0001, I2 = 92.2 %; 4 studies, 101447 patients), and long-term (up to 108 months) mortality (OR 2.02, 95 % CI: 1.62–2.51; p < 0.0001, I2 = 79.4 %; 12 studies, 102099 patients). In patients without a prior diagnosis of diabetes admitted to hospital for acute coronary syndrome, HG increases the risk of both short and long-term mortality.

Thus, the study of the problem of HG development in patients with acute large-focal MI is an important task of modern emergency cardiology, taking into account the significant contribution of acute forms of coronary

heart disease to the patterns of mortality, morbidity and disability of the adult population, and high unfavourable prognostic significance of glycemia level increase in this category of patients. It is relevant to identify the factors explaining the adverse effect of hyperglycemia on the course and prognosis of myocardial infarction, as well as to determine optimal management of the patients with acute large-focal myocardial infarction complicated by the development of hyperglycemia without a history of carbohydrate metabolism disorders.

Aim of the research: to investigate homeostasis markers of unfavourable prognosis and to define target glucose levels in patients with MI and HG without previous carbohydrate metabolism disorders.

Methods

The clinical study included 185 patients with acute large-focal MI who were hospitalized in intensive care units of city clinical hospitals in Minsk. MI was diagnosed on the basis of clinical, electrocardiographic and biochemical criteria developed by the specialists of the American College of Cardiology and the European Society of Cardiology. HG was diagnosed in accordance with the recommendations of the American College of Cardiology upon detecting a blood glucose level ≥ 8.0 μmol/l in the patients hospitalized in the intensive care unit on the first day of MI [2]. Depending on the development of HG, 2 study groups were formed. The main group included 106 patients with MI and HG, the comparison group consisted of 79 patients with MI without HG.

The patients' enrollment in the study was carried out on the basis of informed consent and in the absence of the following criteria: MI and history of carbohydrate metabolism disorders, noncoronogenic myocardial diseases, previous cardiosurgical or interventional surgery, acute infectious diseases and exacerbation of chronic inflammatory diseases, advanced liver and kidney diseases, oncological pathology, thermal and chemical burns, disseminated intravascular coagulation, autoimmune diseases, immunodeficiency, the presence of transplanted organs and tissues, postoperative hypoinsulinemia, vitamin-B12-deficiency anemia.

Laboratory methods of investigation included determination of the level of cardiospecific enzymes. The concentration of troponin I was determined using a kit for quantitative rapid diagnosis of Triage (Biosite Diagnostics, Inc.), creatine phosphokinase (CK) and creatine phosphokinase MB isoenzyme (CK-MB), using the Konelab 30i automatic biochemical analyzer manufactured by Termo Electron Corporation (Finland). The blood glucose level was assessed by a highly specific hexokinase method using commercial sets GLUCOSE «E-D» (Russia). The level of glycated hemoglobin was determined by a competitive enzyme immunoassay using commercial kits of Glycohemoglobin HbA-test from Human. Sets of DRG International, Inc. were used to study the concentration of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), cortisol, leptin, insulin, C-peptide, total nitrates and nitrites (NO_3/NO_2) (USA) using the ELISA method. The D-dimer concentration was determined by an enzyme immunoassay using the TECHNOZYMD-Dimer kit from Technoclone GmbH (Austria). The level of fibrinogen was evaluated by Clauss' method.

The processing of the obtained data was carried out with the help of statistical software packages Excel, Statistica (version 10.0, StatSoft, Inc., USA), SPSS (version 16.0, SPSS Incorporation, USA). To determine the quantitative characteristics, the distribution parameters were estimated using the Shapiro-Wilk test. A quantitative comparison of the two independent groups with a normal distribution was performed using the Student's t-test, in the case of disparity between the variable distribution and the normal distribution, the Mann-Whitney criterion was used in the study groups. When comparing independent groups by qualitative characteristics, differences between groups were assessed using the exact Fisher test, or χ^2 test. When comparing the two dependent groups by the quantitative characteristic, a parametric method was used with Student's t-criterion calculated for the dependent groups in the case of the normal distribution of the variable. In the abnormal distribution, the Wilcoxon test was calculated. Evaluation of the relationship between the two characteristics was carried out using correlation analysis (Pearson and Spearman methods). Differences in the groups were considered significant with the probability of an error-free forecast of 95.5 % ($p < 0.05$).

The groups studied did not differ significantly in age and sex composition, prevalence of the main factors of cardiovascular risk. The proportion of patients with MI and HG who were smoking among the patients was 54.7 % (n = 58) and statistically did not differ significantly from this index in the group of patients without HG (51.9 % (n = 41)). The frequency of arterial hypertension in the main group of patients was 90.6% (n = 96) and did not differ significantly from the corresponding frequency in the group without HG (86.1 % (n = 68)). A family history of early coronary heart disease was detected in 19.8 % (n = 21) of patients with MI and HG, which corresponded the frequency of this factor in the group with MI without HG (15.2 % (n = 12)). The value of body mass index in the group of patients with MI and HG was 27.7 (26.0–30.0) kg/m^2 and did not differ significantly from the corresponding index in the comparison group (27.0 (25.1–29.0) kg/m^2).

Results

In patients with large-focal MI without previous carbohydrate metabolism disorders (the proportion of patients with HG was 57.3 % (n = 106)), a high prevalence of stress HG was established, the unfavorable prognostic significance of which was proved for a short- and long-term prognosis [1, 2, 4].

In the group of patients with MI and HG, a more pronounced activation of proinflammatory cytokines was revealed in comparison with the group of patients with MI without HG, which was manifested by significantly higher levels of IL-6 (2.6 (1.6–5.0) и 0.8 (0.4–1.4) pg/ml; $p < 0.001$), TNF-α (7.5 (2.6–20.3) и 3.0 (0.7–7.3) pg/ml; $p < 0.05$) (Figure 1–4), which is reported to be associated with increased lethality, the development of recurrence

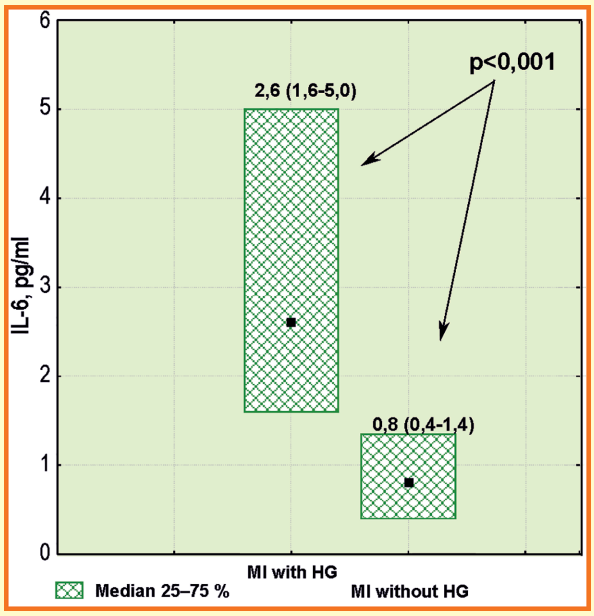

Figure 1. IL-6 levels in patients of the study groups.

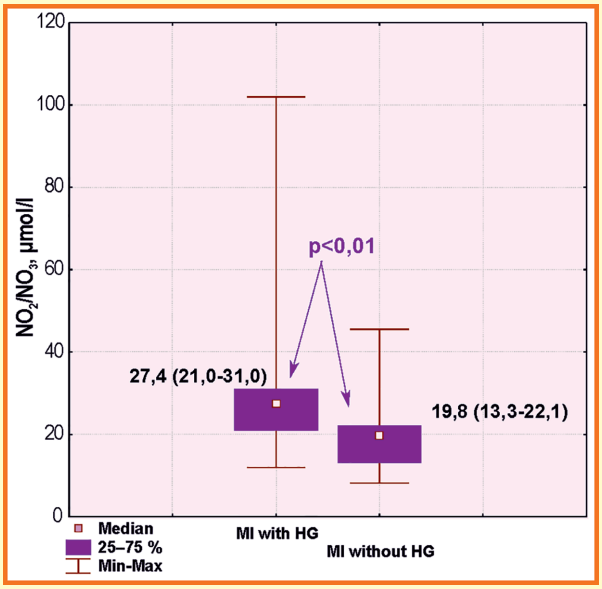

Figure 3. Content of nitrates and nitrites in patients of the study groups.

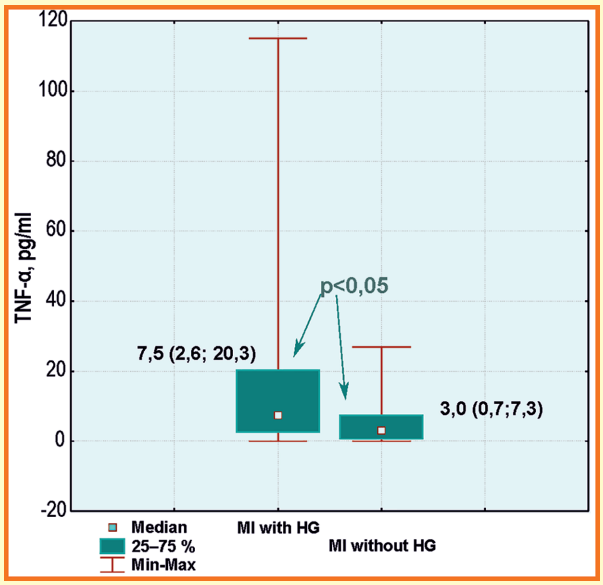

Figure 2. TNF-α in patients of the study groups.

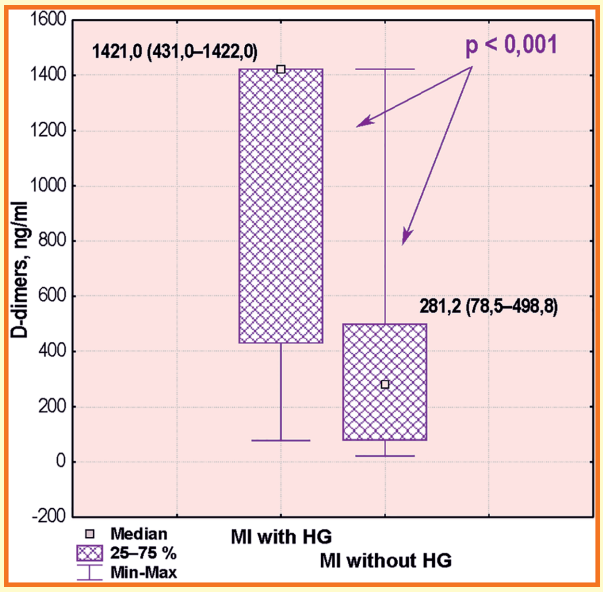

Figure 4. Plasma concentration of D-dimers in patients of the study groups.

and repeated MI, unstable angina, heart failure and heart rhythm disturbances in the post-infarction period [4, 5].

Based on the results of the studies, an increase in the concentration of inflammatory markers in circulating blood has been determined in the patients with MI, higher levels of pro-inflammatory cytokines being observed in the patients with MI and DM versus the patients with no history of type II diabetes [6, 7]. However, according to the results of in vitro studies, in animals and in the human population, stress HG can lead to a more pronounced oxidative shift than long-term chronic HG. According to the results of our study, higher values of the total amount of nitrates and nitrites (27.4 (21.0–31.0) и 19.8 (13.3–22.1) µmol/l; $p < 0.05$) were determined in the group of patients with MI and HG (Figure 3), which was associated with activation of prooxidant indices and could be treated as a factor aggravating the course of myocardial infarction [8].

In the group of patients with MI and HG higher values of serum insulin concentration (30.4 (23.4–43.4) and 12.4 (8.2–20.0) µIU/ml; $p < 0.001$) were revealed against a higher proportion of patients with over- threshold values of insulin in comparison with the group of patients with MI without HG, it being an indirect evidence of more pronounced insulin resistance in patients with MI and HG. Oxidative stress, in its turn, can be a trigger of inflammation and subsequent insulin resistance, which can contribute to the increase in the level of glycemia. Thus, it was established that proinflammatory cytokines of TNF-α and IL-6 were able to alter the components of the insulin signal system and glucose metabolism, which led to the

development of insulin resistance in target tissues and could aggravate the existing HG [9]. Based on the results of the study, a direct moderate correlation was found between the IL-6, TNF-α concent-rations and insulin values (r = 0.33, p < 0.05 and r = 0.38, p < 0.01, respectively).

In the group of patients with MI and HG in comparison with the group of patients with MI without HG, higher values of D-dimers were found (1421.0 (431.0–1422.0) and (281.2 (78.5–498.8) ng/ml; p<0.001) (Figure 4). An increase in D-dimer levels is characteristic of increased intravascular hemocoagulation and is associated with a higher risk of mortality, development of unstable angina, repeated MI, and stroke [10]. Higher levels of fibrinogen were found in the group of patients with MI and HG as compared to the group of patients with MI without HG (4.1 (3.5–5.0) и 3.5 (3.0–4.2) g/l, p<0.001).

As a result of the analysis of the relationship between proinflammatory cytokines and homeostatic parameters, it was revealed that IL-6 levels on the first day of MI in patients without a history of carbohydrate metabolism disorders were characterized by the pre-sence of a direct moderate correlation with fibrinogen values (r = 0.31, p < 0.05), and D-dimer plasma concent-rations (r = 0.45, p < 0.001). A direct moderate correlation with fibrinogen values (r = 0.29, p < 0.05) and D-dimer plasma concentrations (r = 0.32, p < 0.05) was also established for proinflammatory cytokine values of TNF-α. The revealed correlation dependence proves the involvement of the proinflammatory cytokine activation, which is characteristic of patients with MI and HG, in the enhancement of hemocoagulation disorders.

The group of patients with MI and HG was characterized by a tendency to higher values of biochemical markers of myocardial necrosis, which was reflected in higher plasma concentrations of CK (1656 (914–2870) U/ l versus 423 (205–1001) U/ l, p < 0.001), CK-MB (188 (80–312) U/ l versus 44 (26–114) U/ l, p < 0.001) and troponin I (10.1 (1.7–29.9) ng/ml versus 1.7 (0.4–5.1) ng/ml, respectively, p < 0.001) (Figure 5), which is associated with the subsequent development of the MI complications and an increase in mortality [11, 12].

Given the adverse effect of HG on the course and prognosis of the disease in patients with MI, it is relevant to determine the optimal target values of glycemia against vascular accidents.

The original Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study was the first multicenter, randomized trial, in which the effect of glycemic control on the outcome of myocardial infarction was studied. DIGAMI randomized hyperglycemic patients (average glucose at randomization > 275 mg/dl) to either standard therapy or intravenous glucose-insulin infusion titrated to achieve a prespecified target of 126–196 mg/dl during the acute phase, followed by multidose subcutaneous insulin injections for 3 months. Following randomization, clinically and statistically lower glucose levels were achieved in the glucose control patients (≈ 173 mg/dl) versus control (≈ 211 mg/dl) at 24 hours, and a significant difference was maintained through discharge. Lower mortality was observed in the glucose control patients (vs. control) at discharge and at 3 months, but this mortality difference only reached statistical significance after 1 year

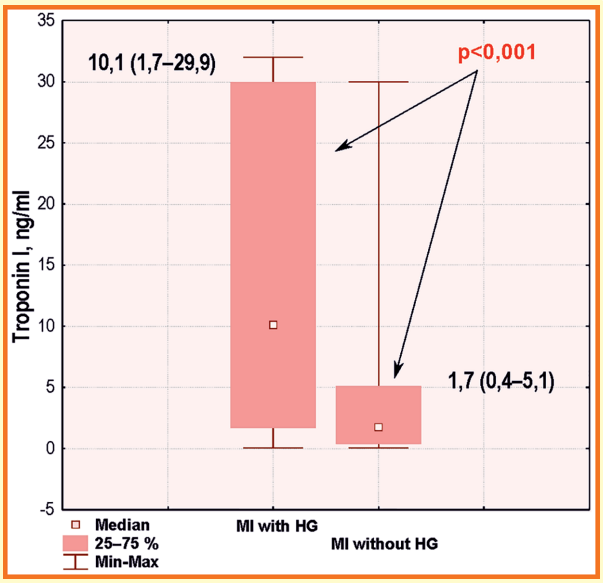

Figure 5. Values of troponin I in patients of the study groups.

of follow-up. Whether this mortality reduction was due to acute glucose lowering in-hospital, chronic glucose control postdischarge, or both could not be determined. Statistically significant differences in mortality in patients in the study group compared with those in the control group were observed after 1 year. These differences persisted, but tended to increase during 3.4 (1.6–5.6) years. Ritsinger et al. [13] tracked the mortality of patients included in the DIGAMI study during the long-term follow-up (up to 20 years after randomization). The average survival rate in the study group was significantly higher (7.0 (1.8–12.4) years) than in the control group (4.7 (1.0–11.4) years) (p = 0.027).

Based on the results of subsequent studies, it was found that HG correction in patients with pathological conditions requiring intensive care and reanimation had a positive effect on the outcome of the disease. However, there are a sufficient number of scientific papers questioning the appropriateness of strict glycemic cont-rol in this category of patients [2, 13, 14, 15]. It was found that a decrease in the level of glycemia in patients with MI is an independent factor in the reduction of mor-tality, while the use of insulin is associated with an improvement in the prognosis only in the case of effec-tive correction of HG [2, 15]. On this basis, the need for further study of glycemic control in patients with MI and HG without a history of carbohydrate metabolism disorders is particularly relevant.

In our study we studied the effect of reducing the level of glycemia in the acute period of the disease on the course of acute myocardial infarction and laboratory parameters in patients with HG.

A decrease in blood glucose level below 8.0 μmol/l on the first day of hospitalization in patients with MI and HG was accompanied by a decrease in the concent-ration of proinflammatory cytokines (IL-6 concentration (2.8 (1.6–5.4) and 0.8 (0.2–2.1) pg/ml, Wilcoxon test, (p < 0.01), D-dimer level (1422 (527–1422) and 302 (110–1063) ng/ml,

Wilcoxon test, p < 0.001) and initially elevated NO_3/NO_2 values (29.0 (27.4–37.4) and 16.2 (11.5–25.0) μmol/l, Wilcoxon test, p < 0.001).

In a subgroup of patients with MI and HG with a decrease in glycemia to 4.5–6.1 mmol/l compared with a subgroup of patients with MI and HG with a decrease in glycemia to a level of 6.2–8.0 μmol/l in assessing IL-6 levels (0,9 (0,1–2,2) and 0,7 (0,3–2,0) pg/ml), the total amount of nitrates and nitrites (18.2 (11.5–28.4) and 16.1 (14.0–22.9) μmol/l) and D-dimers (328 (88–1190) and 276 (110–936) ng/ml) were not statistically significant in the acute period of the disease.

As a result of the analysis of the incidence of complications at the hospital stage, there were no significant differences in the relative weight of patients with complicated myocardial infarction (31.4 % (n = 16) and 25.0 % (n = 10) in the compared subgroups), life-threatening arrhythmias (ventricular fibrillation, sustained ventricular tachycardia, complete atrioventricular blockade, asystole) (3.9 % (n = 2) and 5.0 % (n = 2)), recurrent coronary events (postinfarction angina, relapse of MI) (11,8 % (n = 6) and 10.0 % (n = 4)), acute heart failure (5.9 % (n = 3) and 5.0 % (n = 2)), risk of mortality (the ratio of mortality risk in the subgroup with a decrease in glycemia to 4.5–6.1 μmol/l was 1.19 (95 % confidence interval 0.19–7.47, p> 0.05)), as well as in the incidence of adverse cardiovascular events during 36 months of follow-up (Figure 6).

Conclusions

As a result of the study, a high prevalence of HG in patients with large-focal MI without a history of carbohydrate metabolism was established. Patients with MI and HG were characterized by more severe systemic inflammation, homeostasis disturbances and changes in hormonal state as compared to patients without HG. In patients with MI and HG without previous carbohydrate metabolism disorders blood glucose level decrease below 8.0 μmol/l was associated with proinflammatory cytokine concentration reduction, D-dimer level decrease and a reduction of initially elevated amount of nitrates and nitrites. In patients with MI and HG blood glucose level decrease to 4.5–6.1 μmol/l and to 6.2–8.0 μmol/l did not affect inflammation parameters, the total amount of nitrates and nitrites, D-dimer level, complications incidence, in-hospital mortality, unstable angina rate, recurrent myocardial infarction incidence and mortality during a 36-month follow-up. Thus, in patients with acute large-focal MI and HG and without the impairment of carbohydrate metabolism in past history, it is advisable to reach a blood glucose level of 4.5–8.0 μmol/l.

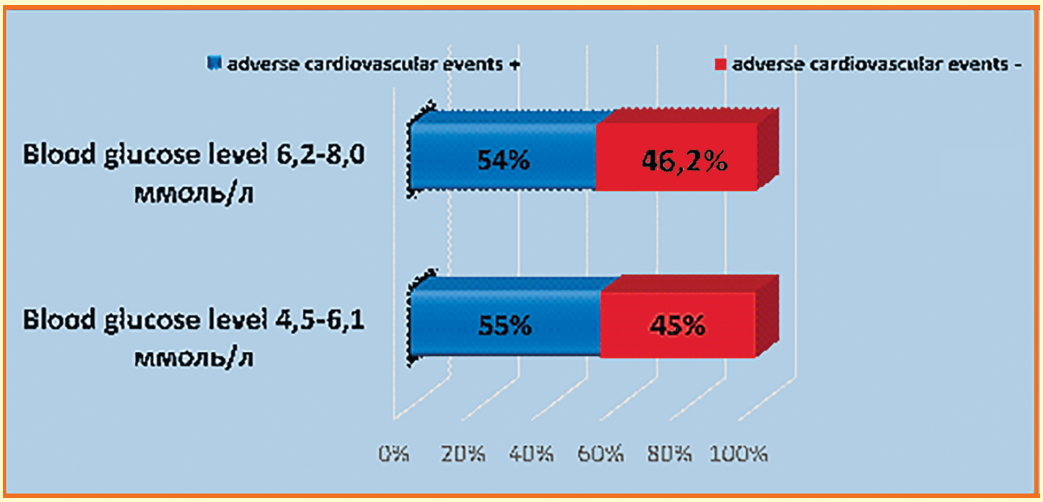

Figure 6. Distribution of patients depending on the development of adverse cardiovascular events based on the results of a 36-month follow-up.

References

[1] Ibanez B., James S., Agewall S., Antunes M. J., Bucciarelli-Ducci C., Bueno H., Caforio A.L.P., Crea F., Goudevenos J. A., Halvorsen S., Hindricks G., Kastrati A., Lenzen M.J., Prescott E., Roffi M., Valgimigli M., Varenhorst C., Vranckx P., Widimský P. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Rev Esp Cardiol (Engl Ed)*, 2017, vol.70, no. 12, pp. 1082. doi: 10.1016/j.rec.2017.11.010.

[2] Deedwania P., Kosiborod M., Barrett E., Ceriello A., Isley W., Mazzone T., Raskin P. Hyperglycemia and acute coronary syndrome. A scientific statement from the american heart association diabetes committee of the council on nutrition, physical activity, and metabolism. *Circulation*, 2008, vol. 117, no. 12, pp. 1610–1619.

[3] Angeli F., Verdecchia P., Karthikeyan G., Mazzotta G., Del Pinto M., Repaci S., Gatteschi C., Gentile G., Cavallini C., Reboldi G. New-onset hyperglycemia and acute coronary syndrome: a systematic overview and meta-analysis. *Curr Diabetes Rev*, 2010, vol. 6, no. 2, pp. 102–110.

[4] Smirnova E.S., Grigorenko E.A., Mitkovskaya N.P. Stress induced hyperglycemia in patients with acute myocardial infarction. *Vestsi Natsyyanal'nai akademii navuk Belarusi. Seriya meditsinskikh navuk* [Proceedings of the National Academy of Sciences of Belarus. Medical series], 2017, no. 4, pp. 60–69 (in Russian).

[5] Zykov M.V., Barbarash O.L., Karetnikova V.N., Kashtalap V.V. *Ispol'zovanie biomarkerov – zitokinov v diagnostike i prognozirovanii techeniya infarkta miokarda* [Use of biomarkers-cytokines in diagnosis and prognostication of myocardial infarction course]. Kemerovo, 2011. 24 p. (in Russian).

[6] Oranskiy P.P., Chanferyan R.A. Urovni zitokinov u bol'nych Q-pozitivnym infarktom miokarda v syvorotke krovi i kul'turach mononuklearov krovi [The levels of cytokines in patients with Q-wave myocardial infarction in the serum and the cultures of blood mononuclear cells]. *Zitokiny i vospalenie*, 2009, vol. 8, no. 2, pp. 31–33. doi: 10.1016/j.amjcard.2011.08.029. (in Russian)

[7] Solheim S., Grøgaard H.K., Hoffmann P., Arnesen H., Seljeflot I. Inflammatory responses after percutaneous coronary intervention in patients with acute myocardial infarction or stable angina pectoris. *Scand J. Clin Lab Invest*, 2008, vol. 68, no. 7, pp. 555–562.

[8] Lapshina L.A., Kravchun P.G., Titova A.Yu., Glebova O.V. Znachenie opredeleniya nitritov – nitratov kak markerov disfunkzii endoteliya pri serdechno-sosudistoy patologii [Significance of nitrite – nitrate determination as markers of endothelial dysfunction in cardiovascular pathology]. *Ukr Med Chasopis*, 2009, vol. 74, no. 6, pp. 49–53. (in Russian).

[9] Ceriello A. Cardiovascular effects of acute hyperglycaemia: pathophysiological underpinnings. *Diabetes & Vascular Disease Research*, 2008, vol. 5, no. 4, pp. 260–268. doi: 10.3132/dvdr.2008.038.

[10] Panina A.V., Dovgalevskiy Ya.P., Furman N.V., Puchin'yan N.F., Bogomolova O.S. Prognosticheskoe znachenie povyshennogo urovnya D-dimera plazmy krovi u bol'nych ostrym koronarnym sindromom [Prognostic value of elevated blood plasma D-dimer level in patients with acute coronary syndrome]. *Byul Med Internet-Konf*, 2013, vol. 3, no. 6, pp. 954–954. (in Russian).

[11] Shachnovich R.M. *Ostryy koronarnyy sindrom s pod'yemom segmenta ST : rukovodstvo dlya vrachey* [Acute coronary syndrome with ST-segment elevation]. Moskva, GEOTAR-Media, 2010. 376 p. (in Russian)

[12] Mit'kovskaya N.P., Statkevich T.V, Smirnova E.S., Galizkaya S.S., Balysh E.M., Chervyakova T.A., Troyanova N.V., Kulazhenko I.O. Lechebnaya taktika u pazientov s krupnoochagovym infarktom miokarda i giperglikemiey s poziziy kardioprotekzii [Therapeutic tactics in patients with large-focal myocardial infarction and hyperglycemia from the standpoint of cardioprotection]. *Med panorama*, 2012, no. 3, pp. 17–19. (in Russian).

[13] Ritsinger V., Malmberg K., Mårtensson A., Ryden L., Wedel H., Norhammar A. Intensified insulin-based glycaemic control after myocardial infarction: mortality during 20 year follow-up of the randomised Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) trial. *Lancet Diabetes Endocrinol*, 2014, vol. 2, no. 8, pp. 627–633.

[14] Finfer S., Chittock D.R., Su S.Y., Blair D., Foster D., Dhingra V., Bellomo R., Cook D., Dodek P., Henderson W.R., Hébert P.C., Heritier S, Heyland D.K., McArthur C., McDonald E., Mitchell I., Myburgh J.A., Norton R., Potter J., Robinson B.G., Ronco J.J. Intensive versus conventional glucose control in critically ill patients. *N Engl J. Med*, 2009, vol. 360, no. 13, pp. 1283–1297.

[15] Kosiborod M., Inzucchi S. E., Krumholz H. M., Masoudi F. A., Goyal A., Xiao L., Jones P. G., Fiske S., Spertus J. A. Glucose normalization and outcomes in patients with acute myocardial infarction. *Arch Intern Med*, 2009, vol. 169, no. 5, pp. 438–446.

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