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THE ADVANTAGES OF DUAL ANTIPLATELET THERAPY COMBINATIONS IN PREDICTING RECURRENT CARDIOVASCULAR EVENTS IN OBESE PATIENTS AFTER MYOCARDIAL INFARCTION

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The purpose of the study was to analyze the incidence of recurrent cardiovascular events in obese patients after a myocardial infarction during a 6-month follow-up period, depending on the combination of ticagrelor or clopidogrel with acetylsalicylic acid as a part of dual antiplatelet therapy.

Materials and methods. The study involved 75 patients with acute myocardial infarction with ST segment elevation and concomitant obesity. The patients were divided into 2 subgroups: the first included 31 patients who received the combination of acetylsalicylic acid and ticaglelor, and the second – 44 patients treated with the combination of acetylsalicylic acid and clopidogrel in dual antiplatelet therapy. The GRACE scale was used to stratify the risk of hospital and 6-month mortality. Control of the recurrent cardiovascular events presence was carried out after 6 months.

Results and discussion. Acute myocardial infarction with ST elevation is still the main cause of mortality and invalidisation of able-bodied population. Regardless of the primary percutaneous coronary intervention or thrombolysis, dual antiplatelet therapy remains the main therapeutic strategy, both in the acute ST-elevation myocardial infarction period and in the remote – for the secondary prevention of possible adverse cardiovascular events, and is a combination of acetylsalicylic acid and a $P2Y_{12}$ receptor inhibitor. To date, the issue of the choice of a $P2Y_{12}$ receptor inhibitor in the dual antiplatelet therapy that is used in the treatment of ST-elevation myocardial infarction is an urgent subject of scientific discussion.

While observing patients after a myocardial infarction with concomitant obesity over a period of 6 months, it was found that 28 patients had a recurrent myocardial infarction and / or unstable angina, which was 37.56% of all patients. The analysis of the GRACE scale scores in a cohort of patients with recurrent cardiovascular events revealed that all patients were included in high risk group (> 118 points). In the group of patients who received dual antiplatelet therapy with the involvement of acetylsalicylic acid and ticagrelor in 11 people recorded a repeated myocardial infarction and / or unstable angina, which was 14.76%. At the same time, in a group of patients receiving dual antiplatelet therapy in a combination of acetylsalicylic acid with clopidogrel, re-cardiovascular catastrophes were detected in 17 patients, which was 22.8% of all patients with ST-elevation myocardial infarction on the background of concomitant obesity.

Conclusion. The patients with obesity after a myocardial infarction who are included in the GRACE high risk group are recommended to be treated with the combination of acetylsalicylic acid and ticagrelor as a result of a notable reduction in the risk of recurrent cardiovascular catastrophes compared with the combination of acetylsalicylic acid and clopidogrel.

Keywords: acute myocardial infarction, obesity, dual antiplatelet therapy, clopidogrel, ticagrelor, recurrent cardiovascular event.

Connection of work with scientific programs, plans, topics. The work is based on the research work of the department of Internal Medicine No. 2, Clinical Immunology and Allergology named after academician L. T. Malaya «Predicting the course, improving the diagnostic and treatment of coronary heart disease and hypertension in patients with metabolic disorders», State registration No. 0120U102025 (2020-2022).

Introduction. Despite the diagnostics and treatment of acute myocardial infarction (AMI) have undergone substantial evolution, ST-elevated AMI (STEMI) is still the major cause of death and disability of the

able-bodied population even in the most developed countries [1]. It is well known that the pathogenesis of STEMI is based on atherosclerotic plaque rupture with subsequent adhesion and platelet aggregation, activation of the coagulation cascade and, consequently, myocardial ischemia and necrosis after complete coronary artery (CA) occlusion. Rapid restoration of blood flow in the occlusive segment of the CA by primary percutaneous coronary intervention (PCI) prevents the development of heart failure, preserves ventricular function and reduces mortality [2-5]. However, the COURAGE study found that well-selected and consistently used drug therapy is comparable in effectiveness to invasive myocardial reperfusion [5]. Regardless of PCI or thrombolysis, dual antiplatelet therapy (DAPT) remains the primary treatment strategy in both acute and long-term STEMI for the secondary prevention of possible adverse cardiovascular events and is a combination of acetylsalicylic acid (ASA) and $P2Y_{12}$ – receptor inhibitor. For today, according to the recommendations of the European Society of Cardiology in 2020, the drugs of choice are clopidogrel and ticagrelor [6].

The golden standard of treatment for STEMI patients was clopidogrel up to the moment of ticagrelor appearance. It is now known that, unlike the thienopyridine group of antiplatelet drugs to which clopidogrel belongs, ticagrelor is an active compound which binds directly, without transformation, to $P2Y_{12}$ receptors after absorption from the gastrointestinal tract and entering the bloodstream. This feature determines the rapid antiplatelet effect of ticagrelor [7]. However, the choice of $P2Y_{12}$ receptor inhibitor in DAPT treatment of STEMI is a hot topic of scientific debate.

The purpose of the study was to analyze the recurrent cardiovascular events incidence in obese patients after myocardial infarction within 6 months of follow-up, depending on the combination of ticagrelor or clopidogrel with acetylsalicylic acid in dual antiplatelet therapy.

Materials and methods. The study involved 75 patients with AMI with ST segment elevation and concomitant obesity aged 62.48 ± 3.21 years, who were treated in the infarction department of the City Clinical Hospital No. 27.

All experiments were conducted in accordance with the Council of Europe Convention “On the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine Application of Biological and Medicine Achievements (ETS No. 164)” dated 04.04.1997, and the Helsinki Declaration of the World Medical Association (2008). Each study patient signed an informed consent to participate in the study and all measures to ensure anonymity of patients were taken.

The patients were divided into 2 subgroups: the first group included 31 patients receiving the combination of ASA and ticagrelor, and the second group included 44 patients treated with the combination of ASA and clopidogrel as DAPT. The diagnosis of AMI was established on the basis of clinical-anamnestic and laboratory-instrumental studies using the criteria recommended by the European Society of Cardiology in 2012 and in accordance with the Order of the Ministry of Health No. 455 dated 02.07.2014 “Unified clinical protocol of emergency, primary, secondary (specialized) and tertiary (highly specialized) medical care and medical rehabilitation of patients with acute coronary syndrome with elevation of the ST segment”. The presence of obesity was established according to the WHO classification, 1997 at a BMI > 30 kg / m2, which was determined by the formula:

BMI (kg / m²) = body weight / (height) ²

Exclusion criteria were acute and chronic inflammatory processes, Q-negative acute myocardial infarction, diffuse connective tissue diseases, cancer, concomitant thyroid diseases, the presence of symptomatic hypertension.

The GRACE (Global Registry of Acute Coronary Events) scale was used to stratify the risk of hospital and 6-month mortality. Risk factors include age, Killip’s acute heart failure class, hemodynamic parameters (heart rate and systolic blood pressure), blood creatinine, conduction abnormalities, increased cardiospecific enzymes, and ST segment elevation on the patient’s electrocardiogram at admission.

Monitoring for recurrent cardiovascular events was performed after 6 months.

Statistical processing of the obtained data was performed using the statistical program package “Microsoft Excel”. The obtained data are presented as the arithmetic mean and the statistical error of the arithmetic mean ($\bar{X} \pm S\bar{x}$). Differences between groups in a distribution close to normal were assessed using Student’s t-test. Differences at $p < 0.05$ were considered statistically significant.

Results and discussion. Observation of patients after myocardial infarction on the background of concomitant obesity for 6 months revealed that 28 people developed recurrent myocardial infarction and / or unstable angina (UA), which accounted for 37.56% of all patients.

Analysis of the GRACE scores in a cohort of patients with recurrent cardiovascular events showed that all patients were at high risk. According to the distribution of patients according to the risk of 6-month mortality, 69.3% of patients were in the high-risk group and had a score more than 118 points ($p < 0.05$ comparing with both low and medium risk), 26.7% of patients with AMI and concomitant obesity, who had

a range of 89 up to 118 points got to the middle-risk group (p <0.05 comparing with low risk) and only 4% of patients, who received a score of 88 points or less, resulted in a low-risk of 6-month mortality and recurrence of coronary events on the GRACE scale. The data are presented in **table 1.**

Table 1 – The risk of 6-month mortality and recurrent coronary events by the GRACE scale among the patients with acute myocardial infarction and obesity

GRACE, points	Patients with AMI and obesity (n=75)
high risk (> 118 points)	52 (69.3%)
middle risk (89-118 points)	20 (26.7%)
low risk (≤88 points)	3 (4%)

According to the combinations of ASA with ticagrelor or clopidogrel included in DAPT, we investigated the development of cardiovascular events in obese patients six months after STEMI. In the group of patients who received DAPT with the involvement of ASA and ticagrelor in 11 people the recurrent MI and / or UA was observed, which amounted to 14.76%. At that time, in the group of patients receiving DAPT in combination with ASA and clopidogrel, recurrent cardiovascular catastrophes were found in 17 people, which was 22.8% of all patients with STEMI on the background of concomitant obesity. The data is given in **table 2**.

Therefore, in the group of patients treated with ASA and ticagrelor, there is a lower number of recurrent coronary events than in the group of patients receiving ASA with clopidogrel (p <0.05).

Our results do not contradict the data of the world medical literature. Thus, according to the results of the analysis of the ATLANTIC study, which involved patients with STEMI, it was found that between the groups where the loading dose of ticagrelor was first received at the prehospital stage and in the hospital, there were no significant differences in the incidence of adverse cardiovascular events in the form of cardiovascular death (CVD), stroke or emergency revascularization, as well as the occurrence of bleeding within 30 days of observation [8]. At the same time, the ONSET/OFFSET study demonstrated significantly earlier antiplatelet activity and potency of ticagrelor compared to clopidogrel, which is due to the direct connection of the active compound to $P2Y_{12}$ platelet

Table 2 – Characteristics of obese patients after myocardial infarction according to the development of recurrent coronary events during 6-month follow-up

	Patients with MI and obesity (n=75)		
	After treatment (n=75)	DAPT ASA + ticagrelor (n=31)	DAPT ASA + clopidogrel (n=44)
Development of recurrent MI and / or UA 6 months after MI	28 (37.56%)	11 (14.76%), p<0.05	17 (22.8%)

Note: p<0.05 – in comparison with the second subgroup (DAPT ASA + clopidogrel)

receptors [9, 7, 10]. Analyzing the effectiveness of ticagrelor and clopidogrel in the PLATO study, it was shown that the frequency of the primary endpoint events in the group of patients treated with ticagrelor compared with those treated with clopidogrel was significantly lower – 9.8% versus 11.7%. The use of ticagrelor in combination with ASA was associated with an absolute reduction in the risk of CVD, recurrent myocardial infarction or acute cerebrovascular accident by 1.9%, together with a relative risk reduction of these events by 16% compared with the use of clopidogrel [11-14].

Conclusion. The majority of patients (69.30%) with obesity after myocardial infarction were included in the high risk group for six-month mortality according to the number of points on the GRACE scale. In 37.56% of patients with acute myocardial infarction with ST segment elevation and concomitant obesity, a recurrent coronary event occurred in the form of myocardial infarction or unstable angina in the presence of high scores on the GRACE scale. The cohort of obese patients after myocardial infarction, included in the high-risk group according to the six-month mortality scale, is recommended to be treated with a combination of acetylsalicylic acid and ticagrelor, taking into account a pronounced reduction in the risk of recurrent cardiovascular accidents, p<0.05).

Perspectives of further research. Based on the analysis of the prevention of thrombotic situations in obese and non-obese patients after AMI, further research rests on the problem of hemorrhagic complications and remains open today. In this regard, not only the effectiveness, but also the safety of antithrombotic therapy is of great importance.

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ПЕРЕВАГИ КОМБІНАЦІЙ ПОДВІЙНОЇ АНТИТРОМБОЦИТАРНОЇ ТЕРАПІЇ У ПРОГНОЗУВАННІ ПОВТОРНИХ КАРДІОВАСКУЛЯРНИХ ПОДІЙ У ПАЦІЄНТІВ З ОЖИРІННЯМ ПІСЛЯ ПЕРЕНЕСЕНОГО ІНФАРКТУ МІОКАРДА

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Резюме. *Мета дослідження.* Проаналізувати частоту виникнення повторних серцево-судинних подій у хворих з ожирінням після перенесеного інфаркту міокарда протягом 6-місячного терміну спостереження залежно від комбінації тикагрелору або клопідогрелю з ацетилсаліциловою кислотою в складі подвійної антитромбоцитарної терапії.

Матеріали та методи дослідження. В дослідженні прийняли участь 75 хворих на STEMI та супутнє ожиріння. Хворих було розподілено на 2 підгрупи: до першої увійшов 31 хворий, які отримували комбінацію АСК+тикагрелор, а до другої – 44 пацієнта, що лікувалися комбінацією АСК+клопідогрель в складі подвійної антитромбоцитарної терапії. Для стратифікації ризику госпітальної та 6-місячної летальності була використана шкала GRACE. Контроль наявності повторних кардіоваскулярних подій здійснювався через 6 місяців.

Результати. При спостереженні за хворими після перенесеного інфаркту міокарда на тлі супутнього ожиріння протягом 6 місяців було виявлено, що у 28 осіб (37,56%), що входили до групи високого ризику за GRACE (>118 балів), розвинувся повторний інфаркт міокарда та/або нестабільна стенокардія. У групі хворих, які отримували подвійну антитромбоцитарну терапію із залученням ацетилсаліцилової кислоти та тикагрелору в 11 осіб (14,76%) зафіксовано повторний інфаркт міокарда та/або нестабільну стенокардію, у той час, коли в групі хворих, що отримували подвійну антитромбоцитарну терапію у комбінації ацетилсаліцилової кислоти з клопідогрелем, повторні серцево-судинні катастрофи було виявлено у 17 осіб (22,8%).

Висновки. Хворим з ожирінням після перенесеного інфаркту міокарда, що увійшли до групи високого ризику за шкалою GRACE, доцільно проводити лікування з залученням комбінації ацетилсаліцилової кислоти та тикагрелору внаслідок більш виразного зменшення ризику виникнення повторних серцево-судинних катастроф, порівняно з комбінацією ацетилсаліцилової кислоти та клопідогрелю.

Ключові слова: гострий інфаркт міокарда, ожиріння, подвійна антитромбоцитарна терапія, клопідогрель, тикагрелор, повторна кардіоваскулярна подія.

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