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THE EFFECTIVENESS AND COST-EFFECTIVENESS OF DIFFERENT ANTITHROMBOTIC THERAPY REGIMENS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS DURING 1 YEAR OF FOLLOW-UP AFTER AN EXACERBATION OF CORONARY HEART DISEASE ACCORDING TO THE STUDY ORACLE II

<i>Background</i>	To analyze the effectiveness and cost-effectiveness of various antiplatelet therapies in patients with type 2 diabetes mellitus who have experienced acute coronary syndrome based on one-year follow-up data.
<i>Materials and Methods</i>	The article presents data on the characteristics of different antithrombotic therapy regimens in patients with type 2 diabetes after an episode of acute coronary syndrome from the perspective of efficacy and cost-effectiveness under real-world clinical practice conditions using material from the open prospective observational study ORACLE II (2014–2017). Data were collected for 368 patients divided into three groups depending on their chosen antithrombotic therapy. Due to significant differences found in clinical characteristics among these groups, a propensity score matching process was performed according to key differing variables – gender, age, hemoglobin level at admission, and frequency of percutaneous coronary intervention during index hospitalization.
<i>Results</i>	Based on adjusted data, adverse cardiovascular outcomes occurred in 9 patients (17.6%) taking ticagrelor, compared to 21 (41.2%) among patients receiving clopidogrel and 14 (27.5%) among those undergoing antiplatelet therapy de-escalation ($p = 0.031$). In conducting pharmacoeconomic analysis, the cost-effectiveness ratio was evaluated using the cost-effectiveness analysis. Drug costs over the observation period were higher for patients taking ticagrelor – 2723703,45 rubles versus 445880,76 rubles for those taking clopidogrel. However, in real-world clinical practice settings in Russia, economic benefits were observed with ticagrelor use due to subsequent reductions in hospitalizations and thus direct medical expenses covered by mandatory health insurance (MHI). Total costs related to subsequent hospitalizations resulting from adverse cardiovascular events over one year of observation amounted to 755773,47 rubles for patients taking ticagrelor and 2209545,53 rubles for those taking clopidogrel. Thus, total costs per patient during the one-year period following the index event were 14819,09 rubles in the ticagrelor group and 43324,42 rubles in the clopidogrel group.
<i>Conclusion</i>	Considering current Russian clinical practice, ticagrelor is currently more effective than clopidogrel as an antiplatelet agent both in terms of preventing further adverse cardiovascular events and its overall cost-effectiveness in patients experiencing acute coronary syndrome and having type 2 diabetes.
<i>Keywords</i>	Acute Coronary Syndrome, Diabetes Mellitus Type 2, Antithrombotic Therapy, Cost-Effectiveness, Pharmacoeconomic Analysis.
<i>For citations</i>	Chichkov Y. M., Minushkina L. O., Brazhnik V. A., Kosmacheva E. D., Khasanov N. R., Chichkova M. A. et al. The Effectiveness and Profitability of Different Antithrombotic Therapy Regimens in Patients with Type 2 Diabetes Mellitus During 1 Year of Follow-Up after an Exacerbation of Coronary Heart Disease According to the Study ORACLE II. <i>Kardiologiya</i> . 2025;65(8):22–30. [Russian: Чичков Ю. М., Минушкина Л. О., Бражник В. А., Космачева Е. Д., Хасанов Н. Р., Чичкова М. А. и др. Эффективность и рентабельность разных режимов антитромботической терапии у больных с сахарным диабетом 2-го типа в течение 1 года наблюдений после обострения ишемической болезни сердца по данным исследования ОРАКУЛ II. <i>Кардиология</i> . 2025;65(8):22–30].
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Introduction

Currently, during dual antiplatelet therapy following an episode of acute coronary syndrome (ACS), preference is given to more potent P2Y₁₂ receptor inhibitors such as ticagrelor and prasugrel. Ticagrelor is among the most commonly used platelet aggregation inhibitors in dual antiplatelet therapy regimens for patients who have experienced ACS both worldwide and in Russia [1, 2]. Prasugrel is used much less frequently in our country. The guidelines also discuss the possibility of antiplatelet therapy de-escalation (substitution of the strongest inhibitor of platelet P2Y₁₂-receptors, ticagrelor, with clopidogrel) in patients at high risk of bleeding [2]. An important issue remains regarding the efficacy of ticagrelor compared to clopidogrel in patients with type 2 diabetes mellitus [3]. There is a view that antiplatelet therapy de-escalation should not be recommended in these patients if they have had an exacerbation of coronary heart disease [2, 4, 5].

Another significant question concerns the cost-effectiveness of using ticagrelor following an episode of ACS. Most clinical studies show that ticagrelor is a more effective drug than clopidogrel [2, 6]. However, direct medical costs associated with treatment by ticagrelor are significantly higher [7, 8]. Therefore, optimal choice of antiplatelet therapy in patients

with concomitant type 2 diabetes mellitus who have suffered ACS remains a subject of debate.

From 2014 to 2017, a Russian multicenter prospective observational study ORACLE II was conducted focusing on assessing prognostic factors during ACS in real-world clinical practice. The protocol envisaged collection of data concerning administered therapies over the first-year post-hospitalization. These findings formed the basis for conducting our own pharmacoeconomic analysis comparing different modes of antithrombotic therapy in patients after experiencing CHD exacerbation.

Aim

The aim of this research was to analyze results obtained within one year of observation, considering not only therapeutic effectiveness but also economic feasibility when choosing antiplatelet therapy for patients with type 2 diabetes mellitus who had undergone acute coronary syndrome.

Materials and methods

The present study used data from the multicenter prospective ORACLE II study [9] in patients with type 2 diabetes who had undergone acute coronary syndrome (ACS) and were indicated for myocardial revascularization procedure. Data of 410 patients

Central illustration

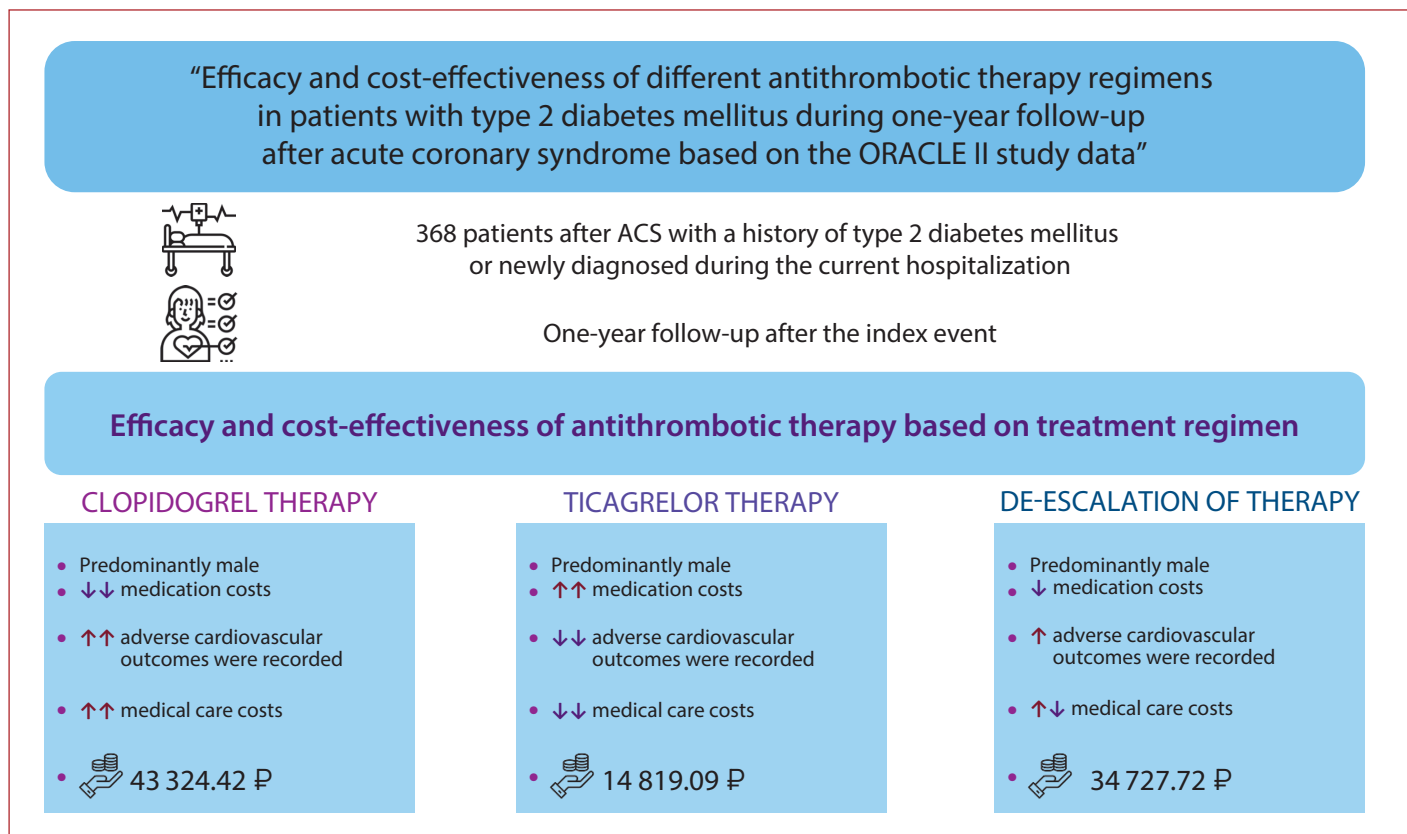


Table 1. Clinical characteristics of patients with acute coronary syndrome and concomitant type 2 diabetes

Treatment group	Clopidogrel (n=218)	Ticagrelor (n=82)	Antiplatelet therapy de-escalation (n=68)	p
Clinical characteristics				
Male sex, n (%)	104 (47.7)	43 (52.4)	36 (52.9)	0.645
Age, years	67.92±11.29	65.33±10.66	63.94±9.17	0.015
BMI, kg/m ²	29.87±5.78	29.45±4.42	30.70±5.18	0.371
STEMI, n (%)	51 (23.4)	30 (36.6)	30 (44.1)	0.003
PCI at an index event, n (%)	80 (36.7)	67 (81.7)	41 (60.3)	<0.001
Killip II–IV, n (%)	63 (28.9)	19 (23.1)	10 (14.7)	0.074
Hypertension, n (%)	204 (93.6)	78 (95.1)	64 (94.1)	0.503
CHD, n (%)	172 (78.9)	59 (72.0)	54 (79.4)	0.402
History of MI, n (%)	89 (40.8)	27 (32.9)	28 (41.2)	0.428
History of PCI, n (%)	34 (15.6)	12 (14.6)	15 (22.1)	0.398
AF, n (%)	45 (20.6)	12 (14.6)	7 (10.3)	0.134
Stroke, n (%)	36 (16.5)	5 (6.1)	8 (11.8)	0.115
History of CHF, n (%)	142 (65.1)	38 (46.3)	44 (64.7)	0.016
Dyslipidemia, n (%)	150 (68.8)	53 (64.6)	48 (70.6)	0.811
History of PAD, n (%)	70 (32.1)	22 (26.8)	22 (32.4)	0.907
Smokes, n (%)	35 (16.1)	16 (19.5)	18 (26.5)	0.024
Hemoglobin, g/l	130.97±20.92	138.01±17.20	136.18±19.34	0.012
Glucose, mmol/l	10.56±4.35	12.20±5.44	11.46±4.78	0.023
Glucose is higher than 7.2 mmol upon admission, n (%)	164 (75.2)	69 (84.1)	53 (77.9)	0.141
Creatinine, µmol/L	103.27±50.05	100.08±26.79	101.91±57.79	0.875
eGFR <60 ml/min/1.73 m ²	103 (47.2)	36 (43.9)	25 (36.8)	0.537
MACE	57 (26.1%)	26 (31.7%)	15 (22.1%)	0.400

BMI – body mass index, STEMI – ST-segment elevation myocardial infarction, PCI – percutaneous coronary intervention, CHD – coronary heart disease, MI – myocardial infarction, AF – atrial fibrillation, CHF – chronic heart failure, PAD – peripheral arterial disease, eGFR – estimated glomerular filtration rate.

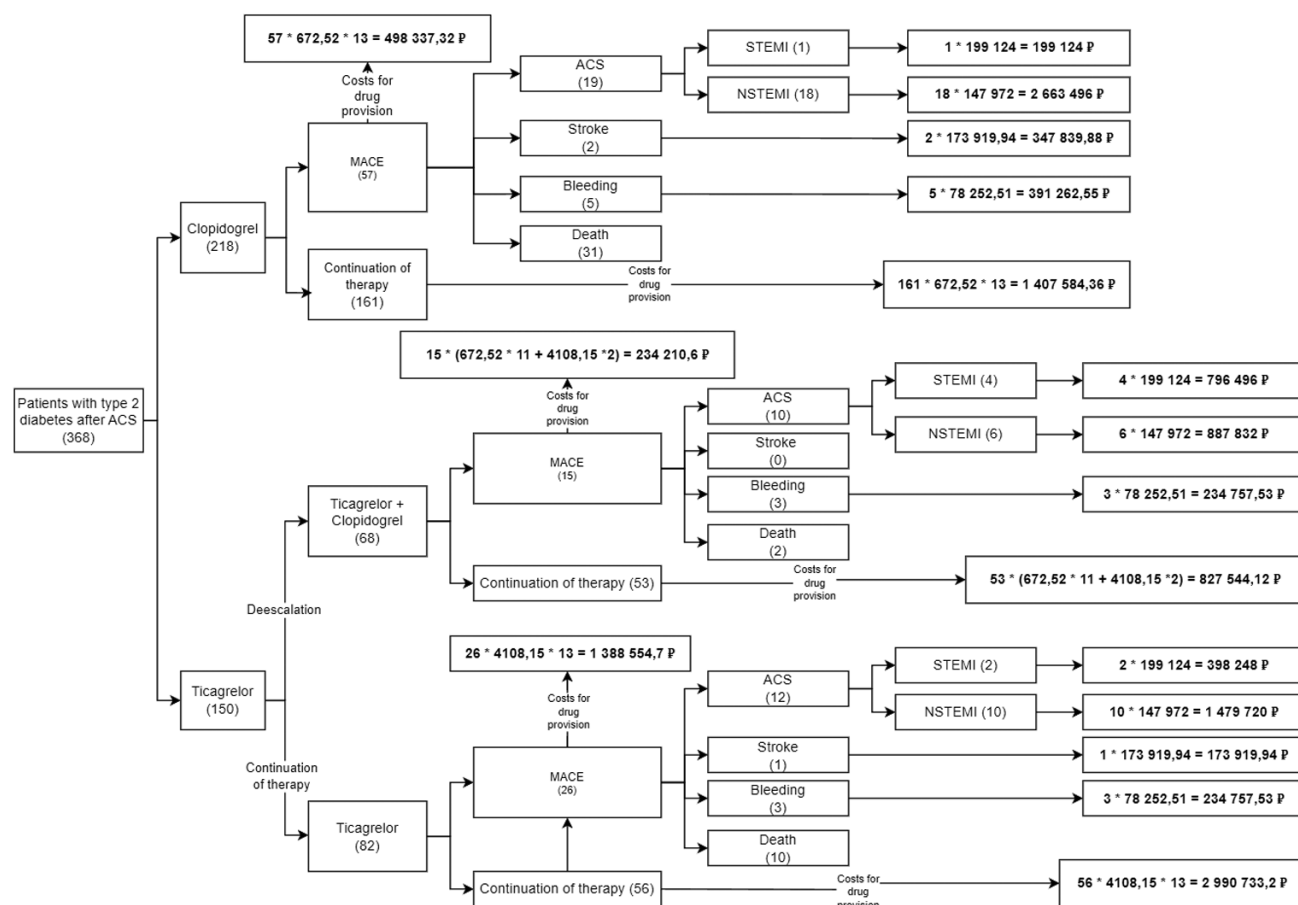
meeting these criteria were analyzed, out of which 368 patients who underwent percutaneous coronary intervention (PCI), were discharged from hospital and continued dual antiplatelet therapy (DAPT) within one year after index event were included into this analysis. The inclusion period was between 2014 and 2017. Patients were followed up for a further one-year period. Detailed inclusion criteria are described in previous publications [9, 10]. This analysis did not include patients receiving anticoagulants at discharge or those for whom it was impossible to obtain information on outpatient use of antiplatelet drugs.

During the first year of follow-up after the index event, the following adverse cardiovascular events were recorded: death from all causes, recurrent ACS, acute cerebrovascular accident, and major bleeding episodes.

In this pharmacoeconomic study, we applied cost-of-illness analysis and cost-effectiveness analysis methods as well as calculation of incremental cost-effectiveness ratio.

To estimate economic costs associated with clinical outcomes and related medical expenses for each selected antiplatelet regimen, a decision tree model was utilized based on a one-year observation period.

Figure 1. Analysis of treatment costs over 1-year follow-up period considering adverse outcomes



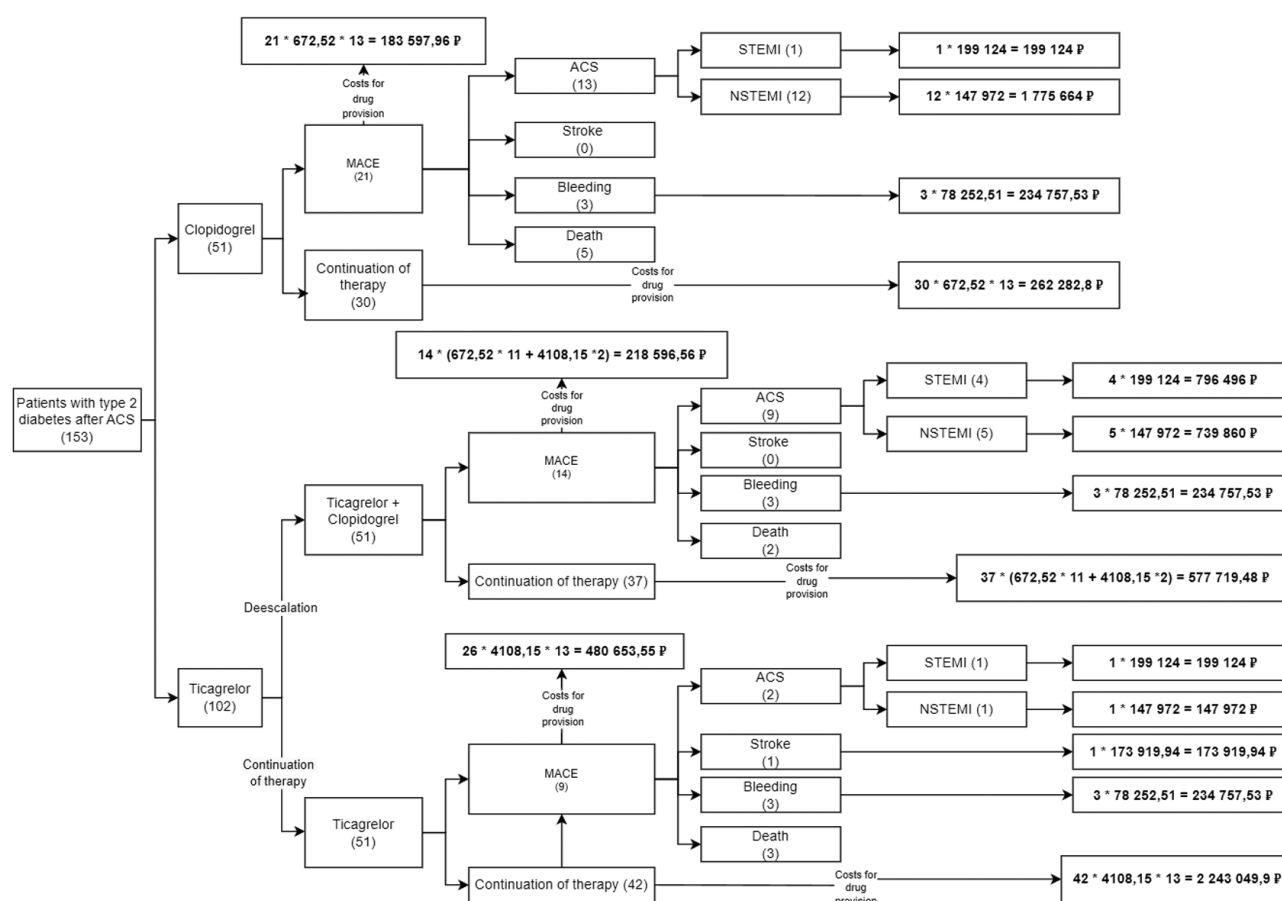
The model is grounded on data obtained during our own observational multicenter ORACLE II study conducted in state healthcare institutions in Moscow, Kazan, Astrakhan, and Krasnodar cities.

This pharmacoeconomic study accounted only for direct medical expenditures covered by budgetary funds and compulsory health insurance system. These included costs directly linked to providing medical care such as medication supply, medical services, and patient accommodation in case an unfavorable cardiovascular event occurred during clinical trial monitoring. Direct non-medical costs were excluded since initially all participants received disability benefits due to permanent loss of work capacity. Indirect costs (economic damage caused by illness) were also omitted because fatalities registered among pensioners. To update the cost data, drug prices and treatment costs including high-tech interventions were taken as valid for 2024. It should be noted that for maintaining current relevance of the study, pricing parameters of essential medicines listed in the Vital and Essential Drugs List (VEDL) and costs of specialized high-tech medical assistance refer to data for 2024. According to the federal VEDL list for 2024, maximum retail price of original clopidogrel preparation is 672,52 rubles per package cov-

ering 28 days of treatment, while ticagrelor's equivalent amounted to 4108,15 rubles [11]. In accordance with Russian Government program of guaranteed free medical care provision for citizens in 2024 [11], medical service costs varied depending on patient condition and type of coronary artery lesion. Specifically, PCI with stenting for STEMI cases cost 199124 rubles, whereas for NSTEMI cases it totaled 147972 rubles [12]. Additionally, according to completed case payment rates set by mandatory health insurance scheme, hospitalization costs for stroke reached 173919,94 rubles, while gastrointestinal hemorrhage-related admission costs stood at 78252,51 rubles [13, 14].

Statistical processing of data was performed using SPSS version 23.0 software. For continuous variables, distribution analysis and its normality test (Shapiro-Wilk test) were carried out. Continuous variables mean values along with standard deviation ($M \pm SD$) were calculated. Significance testing employed t-tests for normally distributed parameters, Mann-Whitney U test for abnormally distributed ones, and Pearson chi-square test for discrete variables. All differences were considered significant if p-value was less than 0.05. Group balancing across differing clinical characteristics was achieved through propensity score meth-

Figure 2. Costs for treating patients over a one-year follow-up period with consideration of adverse outcomes after equalizing groups by main clinical parameters



od calculating propensity measure derived via regression analysis.

Results

The clinical characteristics of the patients included in the study are presented in Table 1. A total of 368 patients with type 2 diabetes mellitus who had an episode of acute coronary syndrome exacerbation (myocardial infarction or unstable angina) and were discharged from hospital after the index event were analyzed. All patients received dual antiplatelet therapy according to clinical guidelines. In the examined group, 218 patients received a combination of acetylsalicylic acid (ASA) and clopidogrel for one year following ACS, 82 patients received ASA and ticagrelor, and 68 patients initially received ASA and ticagrelor at discharge but then their treatment was changed to ASA and clopidogrel.

Comparison between observed groups revealed significant differences. Patients prescribed clopidogrel during initial hospitalization were older, had lower hemoglobin levels and glucose on admission, less frequently experienced STEMI, and underwent fewer PCIs during the index event. The antiplatelet therapy

de-escalation group was the youngest by age. Adverse cardiovascular events in corresponding groups are shown in Figure 1.

Since the groups differed clinically at baseline, before proceeding with pharmacoeconomic analysis we performed propensity score matching based on key differing variables – gender, age, hemoglobin level upon admission, and frequency of PCI during index hospitalization. After statistical processing, three groups of 51 patients each were obtained that did not significantly differ in main parameters (Table 2).

Pharmacoeconomic analysis

Cost analysis of treatment was conducted in three groups of patients taking clopidogrel and ticagrelor as well as those who experienced antiplatelet therapy de-escalation during the observation period (Fig. 2). It is worth noting that on average according to our study data, antiplatelet therapy de-escalation occurred after only two months of regular DAPT intake following an index event.

In performing the “cost-of-disease” analysis, total costs were considered based on the amount spent per patient treated with specific medication over a year

Table 2. Clinical characteristics of patients with acute coronary syndrome and concomitant type 2 diabetes after group balancing procedure

Clinical characteristics	Treatment group	Clopidogrel (n=218)	Ticagrelor (n=82)	Antiplatelet therapy de-escalation (n=68)	
Male sex, n (%)		29 (56.8)	28 (54.9)	28 (54.9)	0.954
Age, years		67.42±9.35	67.44±9.45	66.57±9.67	0.213
BMI, kg/m ²		30.15±5.15	29.12±4.20	30.89±5.46	0.203
STEMI, n (%)		34 (66.7)	29 (56.9)	30 (58.8)	0.127
PCI at an index event, n (%)		38 (74.5)	38 (74.5)	38 (74.5)	0.999
Killip II–IV, n (%)		13 (25.5)	10 (19.6)	8 (15.7)	0.441
Hypertension, n (%)		50 (98.0)	49 (96.1)	51 (100)	0.978
CHD, n (%)		38 (74.5)	39 (76.5)	40 (78.4)	0.457
History of MI, n (%)		20 (39.2)	17 (33.3)	20 (39.2)	0.801
History of PCI, n (%)		10 (19.6)	9 (17.6)	12 (23.5)	0.785
AF, n (%)		10 (19.6)	11 (21.6)	3 (5.9)	0.057
Stroke, n (%)		9 (17.6)	3 (5.9)	7 (13.7)	0.240
History of CHF, n (%)		30 (58.8)	28 (54.9)	33 (64.7)	0.623
Dyslipidemia, n (%)		45(88.2)	36 (70.6)	43(84.3)	0.752
History of PAD, n (%)		12 (23.5)	14 (27.4)	17 (33.3)	0.541
Smokes, n (%)		35 (16.1)	16 (19.5)	18 (26.5)	0.579
Hemoglobin, g/l		135.6±20.24	137.1±18.61	136.8±19.56	0.776
Glucose, mmol/l		11.97±5.710	11.61±4.635	11.86±5.143	0.837
Glucose is higher than 7.2 mmol upon admission, n (%)		40 (78.4)	41 (80.4)	40 (78.4)	0.923
Creatinine, мкмоль/л		101.5±6.74	99.2±2.39	100.6±3.31	0.737
eGFR <60 ml/min/1.73m ²		14 (27.4)	12 (23.5)	13 (25.5)	0.567
MACE		21 (41.2%)	9 (17.6%)	14 (27.5%)	0.031

BMI — body mass index, STEMI — ST-segment elevation myocardial infarction, PCI — percutaneous coronary intervention, CHD — coronary heart disease, MI — myocardial infarction, AF — atrial fibrillation, CHF — chronic heart failure, PAD — peripheral arterial disease, eGFR — estimated glomerular filtration rate.

in accordance with registered adverse cardiovascular events.

The overall sum of funds expended for each group is presented in Table 3. For simplification purposes, only patients who underwent emergency PCI on a single coronary artery due to an index episode were selected for this analysis.

When conducting a cost-effectiveness analysis, we evaluated coefficients CER and ICER which allow us to determine the ratio between treatment costs and achieved effectiveness for a given drug therapy (CER) as well as additional incremental costs per unit increase in efficiency (ICER). Effectiveness was defined as the number of patients without any adverse cardiovascular events within one year of observation (see Table 4). The calculation formula used in this work for

determining the cost-effectiveness indicator (CER) is shown below (1):

$$(1) \text{ CER} = \text{DC} / \text{Ef},$$

where CER – cost-effectiveness ratio; DC – direct costs of ongoing treatment; Ef – treatment effectiveness (number of patients without reported adverse cardiovascular events).

To assess the incrementality factor in terms of increased expenditure per additional efficiency unit, the ICER metric was calculated using the following formula (2):

$$(2) \text{ ICER} = \text{DC ticagrelor} - \text{DC clopidogrel} / \text{Ef ticagrelor} - \text{Ef clopidogrel},$$

where ICER – cost efficiency increment indicator; DC ticagrelor – direct medical costs of ticagrelor treatment; DC clopidogrel – direct medical costs of clopi-

Table 3. Total cost of treatment

Cost	Treatment group	Clopidogrel (n=51)	Ticagrelor (n=51)	Antiplatelet therapy de-escalation (n=51)
Drug supply costs		445 880.76 ₺	2 723 703.45 ₺	796 315.02 ₺
Costs of treatment of recurrent ACS		1 974 788.00 ₺	347 096.00 ₺	1 536 356.00 ₺
Costs of stroke treatment		0.00 ₺	173 919.94 ₺	0.00 ₺
Costs of treating bleeding		234 757.53 ₺	234 757.53 ₺	234 757.53 ₺
Total cost of clinical outcomes		2 209 545.53 ₺	755 773.47 ₺	1 771 113.53 ₺
Total cost per 1 person		43 324.42 ₺	14 819.09 ₺	34 727.72 ₺
Costs of drug provision and compulsory medical insurance		2 655 426.29 ₺	3 479 476.92 ₺	2 567 428.55 ₺

ACS – acute coronary syndrome; ACA – acute cerebrovascular accident; MHI – mandatory health insurance.

Table 4. Pharmacoeconomic analysis data

Cost	Treatment group	Clopidogrel (n=51)	Ticagrelor (n=51)	Antiplatelet therapy de-escalation (n=51)
Ratio CER		88 514.21 ₺	82 844.69 ₺	69 389.96 ₺
Ratio ICER		19 590.25 ₺		x
Ratio ICER		x	21 678.44 ₺	

grel treatment; Ef ticagrelor – reflects the effectiveness of treatment when using ticagrelor; Ef clopidogrel – reflects the effectiveness of treatment when using clopidogrel.

Discussion

In this pharmacoeconomic study, the ICER value (ticagrelor-clopidogrel) was determined at 19590,25 rubles while the ICER value (ticagrelor-antiplatelet therapy de-escalation) reached 21678,44 rubles. According to International Monetary Fund data, Russia’s nominal GDP per capita in 2023 was USD 14,404, or approximately 1,197,477 rubles. The willingness-to-pay threshold in Russia amounts to approximately 3,592,430 rubles

Among patients with type 2 diabetes, treatment with ticagrelor after acute coronary syndrome led to higher pharmaceutical expenditures, but fewer long-term adverse cardiovascular events, thereby reducing overall direct healthcare expenditures under MHI coverage. Therefore, ticagrelor-based treatment appears both clinically and economically more effective than clopidogrel, including in the context of antiplatelet therapy de-escalation in post-ACS patients with type 2 diabetes.

Similar findings have been previously reported across various countries based on PLATO trial results and regional health system evaluations. An Iranian study demonstrated a quality-adjusted life expectancy

gain of 7.2 years despite higher initial treatment costs with ticagrelor [8].

Comparable conclusions emerged from interpretations of the PLATO study conducted in Poland. Overall direct medical costs related to ticagrelor were also found to exceed those of clopidogrel, yet annual healthcare expenditures excluding pharmacotherapy remained lower among clopidogrel users, resulting in better economic outcomes such as significantly reduced QALY thresholds compared to the willingness-to-pay limit [7].

In Australia, direct medical costs for ticagrelor-treated patients exceeded those of clopidogrel recipients, although longer-term adjusted life years favored ticagrelor usage, proving economically optimal in preventing further adverse cardiovascular events post-ACS [15].

Researchers in Spain and Thailand arrived at similar conclusions regarding the relationship between higher upfront financial burdens of ticagrelor and improved survival rates along with quality-adjusted life gains [16, 17].

However, previous studies analyzed mixed populations of diabetic and non-diabetic patients, whereas our current investigation focused exclusively on individuals with type 2 diabetes – a key risk factor exacerbating the course and prognosis of ACS. Given these pharmacoeconomic insights, trends regarding antiplatelet agents appear consistent in terms of both effectiveness and cost-efficiency within Russian healthcare set-

tings. These findings could potentially inform future clinical practice standards and recommendations specifically tailored to the management of these patients.

Study Limitations. This observational study did not involve randomization. Therapy decisions made during outpatient stages followed the then-existing guidelines. The relatively small sample size precluded full adjustment for all disparate variables between groups.

Conclusion

In the context of Russian real-world clinical practice, ticagrelor is currently superior to clopidogrel as

an antiplatelet agent, both for the prevention of subsequent adverse cardiovascular events and in terms of economic feasibility among patients with acute coronary syndromes and concomitant type 2 diabetes..

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