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- МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ ФАРМАКОЭКОНОМИЧЕСКОГО МОДЕЛИРОВАНИЯ
- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ
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A PHARMACOECONOMIC ANALYSIS OF DUAL ANTIPLATELET THERAPY WITH ACETYLSALICYLIC ACID AND TICAGRELOR IN PATIENTS WITH ACUTE CORONARY SYNDROME UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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Summary

Introduction. *On average, about 520,000 cases of acute coronary syndrome (ACS) are registered annually in Russia, and 41,136 patients in 2013 underwent percutaneous coronary intervention (PCI). Every year Russia loses from 100,000 to 120,000 years of life of the working-age population, predominantly male, which leads to a significant loss of the working-age population of the country and presents a significant threat to social and economic welfare of society [8]. The use of more effective antiplatelet therapy in ACS patients can improve outcomes, thus contributing to the reduction in cardiovascular mortality and improving long-term prognosis.*

Objectives. *The aim of this study was to perform a comparative pharmacoeconomic analysis of ticagrelor + ASA and clopidogrel + ASA therapy in patients with ACS undergoing PCI in the context of the Russian health system.*

Results. *Analysis of effectiveness revealed that effectiveness of ticagrelor + ASA treatment regimen was higher. Cost-effectiveness analysis showed that ticagrelor + ASA was a dominant therapy considering average prices in Russia by the results of tenders, as well as ticagrelor price planned for registration in the Essential Medicines List and prices for clopidogrel registered in the Essential Medicines List. According to the results of budget impact analysis, the use of ticagrelor + ASA regimen leads to money saving considering average prices in the Russian Federation by the results of tenders, as well as ticagrelor price planned for registration in the Essential Medicines List and price of Clopidogrel registered in the Essential Medicines List.*

Conclusion. *Therapy of acute coronary syndrome patients managed with PCI with combination of ticagrelor and ASA is economically preferable in comparison with therapy with combination of clopidogrel and ASA*

Keywords*: acute coronary syndrome, budget impact analysis, clinical and economic analysis, cost analysis, cost-effectiveness analysis, effectiveness analysis, percutaneous vascularization, pharmacoeconomics.*

Introduction

The term 'acute coronary syndrome' (ACS) covers a range of different acute atherothrombotic events, including non-ST segment elevation myocardial infarction, ST segment elevation myocardial infarction and unstable angina. Almost all cases of ACS are associated with atherosclerotic plaque disruption or breach in its integrity leading to platelet activation and aggregation, which results, in turn, in the formation of a thrombus and coronary artery obstruction.

According to statistical materials of the Ministry of Health of the Russian Federation, 156,818 patients with acute myocardial infarction and 32,347 (20.6%) patients with repeated myocardial infarction [7] were registered in 2013 in Russia, which indicates that more effective therapies have to be implemented in the practical healthcare.

It is of great importance that mortality from MI in Russia is high and it does not decline during last decade among people of the working age[8]. Every year Russia loses from 100,000 to 120,000 years of life of the working-age population, predominantly male, which leads to a significant loss of the working-age population of the country and presents a significant threat to social and economic welfare of society [8]. The use of more effective antiplatelet therapy in ACS patients can improve outcomes, thus contributing to the reduction in cardiovascular mortality and improving long-term prognosis.

Ticagrelor (Brilinta® produced by AstraZeneca) is a novel oral antiplatelet medicine representing a new chemical class of cyclopentyl-triazolo-pyrimidines (CPTP), $P2Y_{12}$ receptor antagonist.

Ticagrelor is an active substance, which means that it needs no metabolic activation in the liver and has direct action on platelet ADP binding $P2Y_{12}$ receptors, while thienopyridines must at first undergo hepatic biotransformation to be converted to an active metabolite. For this reason ticagrelor has a rapid onset of action in contrast to clopidogrel being a pro-drug and having a delayed antiplatelet action [1].

Study aim

The aim of our study was to perform a cost-effectiveness and budget impact analysis of ticagrelor + ASA therapy in comparison with clopidogrel+ASA therapy in patients with ST-elevation ACS undergoing PCI in the context of the Russian health system.

To achieve this aim the tasks were successively completed:

1. Search for and selection of relevant clinical studies for comparative pharmacoeconomic analysis of the two treatment regimens (ticagrelor + ASA and clopidogrel + ASA) in patients with ST-elevation ACS undergoing PCI.
2. Determination of effectiveness parameters for the two treatment regimens based on the published data of clinical studies.
3. Calculation of total cost for ACS patients management on one-year time horizon, including costs of 9 months course of treatment for the two regimens.
4. Calculation of cost-effectiveness ratio (CER) and incremental cost-effectiveness ratio (ICER).
5. Determination of budget impact.

Effectiveness Analysis

Analysis of effectiveness was the first phase of the cost-effectiveness analysis undertaken in our study. Such analysis involves collection of necessary data on drug effectiveness and selection of the effectiveness measure that satisfies conditions of the study.

The effectiveness data used in our study were derived from the subanalysis of PLATO clinical study for patients with ACS undergoing PCI, including more

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than 8000 patients [4]. The study evaluated benefits of ticagrelor + ASA therapy in patients with ACS undergoing PCI. The main end-points from this substudy used for calculation of expenses in our analyses are given in table 1 [4].

Table 1. Kaplan-Meier estimates of events rate

End-point	Clopidogrel	Ticagrelor	HR (95% CI)	p
Primary end-point: CV death/MI/ Stroke	10,8%	9,4%	0,87 (0,75 – 1,01)	0,07
Secondary end-points:				
CV death/MI	10,2%	8,4%	0,82 (0,71 – 0,96)	0,01
All-cause mortality/MI	11,3%	9,8%	0,87(0,75 – 1,0)	0,05
MI	5,8%	4,7%	0,8 (0,65 – 0,98)	0,03
Stroke	1,0%	1,7%	1,63 (1,07 – 2,48)	0,02
Major bleeding	9,2%	9,0%	0,98 (0,83 – 1,14)	0,76
Definite, probable, possible stent thrombosis	4,3%	3,3%	0,75 (0,57 – 0,99)	0,04
All-cause mortality:	6,1%	5,0%	0,82 (0,67-1,00)	0,05
CV death	5,5%	4,5%	0,83 (0,67-1,02)	0,07
Non-CV death	0,7%	0,5%	0,77 (0,40-1,48)	0,43

The outcome measure in our analysis was LYG (Life Years Gained).

$$LYG = \frac{K}{100}$$

Where: LYG – Life Years Gained
K – number of patients alive

$$K = 100 - n$$

n – number of patients with cardiovascular death

The use of ticagrelor + ASA treatment regimen in patients with ACS undergoing PCI resulted in the increase of Life Years Gained compared to Clopidogrel + ASA treatment regimen: 0.955 LYG vs. 0.945 LYG per patient, respectively (the time horizon of the analysis corresponded to the average duration of observation in the PLATO study - 1 year).

Cost analysis

Cost analysis was the next phase of our pharmacoeconomic analysis. In analysis we determined cost for ticagrelor + ASA compared to clopidogrel + ASA in patients with ACS undergoing PCI. The total cost was a combination of cost of antiplatelet therapy, other direct medial cost, and indirect costs caused by productivity loss due to premature mortality.

The time horizon of this study corresponded to the average length of follow-up of patients in the PLATO study - 1 year.

The cost of medical services was calculated based on the data derived from the medical services tariff agreement under the Moscow territorial program of compulsory health insurance for 2014 and for the planned period of 2015 and 2016 dated on 12.25.2014. The cost of concomitant drug therapy (means not antiplatelet) was calculated based on medicinal product prices available at open electronic resource http://www.pharmindex.ru, as there are no recorded prices for the part of concomitant therapy drugs, for ticagrelor and clopidogrel on the basis of tender prices from IMS Health database, and EDL registered prices.

As part of one-year therapy, ticagrelor was initially administered as a 180-mg loading dose, then followed by 90-mg dose twice daily for 280 days; clopidogrel was initially administered as a 300-mg or 600-mg loading dose, then followed by 75-mg dose once daily for 280 days.

The cost of 280 days of treatment using clopidogrel + ASA and ticagrelor + ASA amounted to 22,279 rubles and 31,107 rubles, respectively, based on average prices in Russia by tender results, and to 25,678 rubles and 39,857 rubles, respectively, based on ticagrelor price planned for registration in the EDL and price of clopidogrel registered in the EDL. The calculations of daily drug cost and course cost are given in tables 2 and 3.

Table 2. Cost of mg of preparation

Price of one mg, RUR		
	Tender price	EDL price
Clopidogrel 300 mg tablets	0.615	0.608
Clopidogrel 75мг mg tablets	1.049	1.211
Ticagrelor	0.615	0.788

In addition to the cost of drug therapy, we also calculated the cost of additional medical services and additional medicines needed for correction of adverse events caused by ticagrelor and clopidogrel.

Indirect costs were estimated as costs associated with gross domestic product (GDP) loss due to premature mortality with one year horizon (Table 4).

Table 4. Calculation of indirect cost

GDP per capita in 2013, rubles	498,179
Average time before retirement, years	*4,61*
Mortality in clopidogrel + ACA group, events per patient per year	*0,055*
Loss of GDP per patient for one year in clopidogrel +ASA group, rubles	126,313
Mortality in ticagrelor + ACA group, events per patient per year	0,045
Loss of GDP per patient for one year in clopidogrel +ASA group, rubles	103,347

Therefore, it was found that due to lower cardiovascular mortality rate in case of ticagrelor + ASA is accompanied by higher degree of prevention of GDP loss and lower indirect expenses then in case of treatment clopidogrel + ASA.

Expenses on management of different events during the span of one year for ticagrelor and clopidogrel groups based on established normative tariffs are given in table 5.

The final cost analysis values are presented in Table 6 [2;4;5; 6].

Therefore, the cost of treatment per patient, based on average prices in Russia by tender results and based on ticagrelor price planned for registration in the EDL and price of clopidogrel registered in the EDL, was lower in ticagrelor + ASA treatment group compared to clopidogrel + ASA treatment group (1-year time horizon).

Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) is used to estimate the cost of a unit of effectiveness associated with the medical technologies under comparison. This analysis allows to determine whether the cost of an intervention corresponds to its effectiveness, and to select the most advantageous alternative with the lowest cost-effectiveness ratio (CER). This alternative is called a dominant.

In case when a new technology is more effective and more expensive, it is necessary to determine an incremental cost-effectiveness ratio (ICER), which means the amount of additional investments required to achieve an additional unit of effectiveness with the use of more effective technology.

The performed cost-effectiveness analysis in patients with ACS undergoing PCI showed that the number of life years gained (LYG) per patient was 0.945 in ticagrelor + ASA treatment group and 0.955 in clopidogrel + ASA treatment group, cost-effectiveness ratios for the treatment regimens being compared , with the data on life years gained (LYG) used as an effectiveness measure, were as follows (1-year time horizon):

- based on average prices in Russia by tender results: 747,773 rubles in ticagrelor + ASA group compared to 783,274 rubles in clopidogrel + ASA group.
- based on ticagrelor price planned for registration in the EDL and price for clopidogrel registered in the EDL: 756,935 rubles in ticagrelor + ASA group compared to 786,871 rubles in clopidogrel + ASA group.

Pharmacoeconomic analysis of ticagrelor + ASA treatment regimen and clopidogrel + ASA treatment regimen in patients with ACS undergoing PCI

Table 3. Calculation of course cost of clopidogrel and ticagrelor

Average tender price							
Clopidogrel, RUR						***22,279***	
	INN	Course, days	Dose, mg	Patients share	Dose, mg	Cost, RUR	
						Daily	Course
1.	Clopidogrel, loading dose	1	300	0,647	300	119	119
2.	Clopidogrel, loading dose	1	600	0,353	600	130	130
3.	Clopidogrel, maintenance dose	280	75	1	21000	79	22 029
					Total	328	22,279
Ticagrelor, RUR					***31,107***		
	INN	Course, days	Daily dose, mg	Course dose, mg	Cost, RUR		
					Daily	Course	
1.	Ticagrelor, loading dose	1	180	180	111	111	
2.	Ticagrelor, maintenance dose	280	180	50400	111	30,996	
				Всего:	221	31,107	
EDL prices							
Clopidogrel, RUR						***25,678***	
	INN	Course, days	Dose, mg	Patients share	Dose, mg	Cost, RUR	
						Daily	Course
1.	Clopidogrel, loading dose	1	300	0,647	300	118	118
2.	Clopidogrel, loading dose	1	600	0,353	600	129	129
3.	Clopidogrel, maintenance dose	280	75	1	21000	91	25,431
					Всего:	338	25,678
Ticagrelor, RUR					***39,857***		
	INN	Course, days	Daily dose, mg	Course dose, mg	Cost, RUR		
					Daily	Course	
1.	Ticagrelor, loading dose	1	180	180	142	142	
2.	Ticagrelor, maintenance dose	280	180	50400	142	39,715	
				Total:	284	39,857	

Table 5. Calculation of expenses on management of events occurring during one year.

	Clopidogrel			Ticagrelor		
	Rate of events	Cost per event, RUR	Weighted expenses, RUR	Rate of events	Cost per event, RUR	Weighted expenses, RUR
Cost of repeated MI	5,8%	528,830	30,672	4,7%	528,830	24,855
Cost of stroke	1,0%	128,458	1,285	1,7%	128,458	2,184
Cost of bleeding	9,2%	175,355	16,133	9,0%	175,355	15,782
Cost of stent thrombosis	4,3%	85,650	3,683	3,3%	85,650	2,826
Total			51,772			45,674

allow us to conclude that ticagrelor + ASA is a dominant therapy compared to clopidogrel + ASA therapy.

Table 6 Cost Analysis Results for ticagrelor + ASA in patients with ACS undergoing PCI compared to clopidogrel + ASA, rubles

Cost Analysis Parameter	Clopidogrel + ASA	Ticagrelor + ASA
1. Direct medical expenses for primary ACS event (except antiplatelet therapy cost):	591 603	579 669
1.1 Emergency medical services costs	17,423	17,423
1.2 Specialized inpatient care costs	375,197	375,197
1.3 Outpatient care costs	136,211	136,211
1.4 Medical care costs attributable to recurrent myocardial infarction	30,672	24,855
1.5 Medical care costs attributable to stroke	1,285	2,184
1.6 Medical care costs attributable to bleeding events	16,133	15,782
1.7 Medical care costs attributable to stent thrombosis	3,683	2,826
1.8 Cost of correction of drug side effects	10,999	5,191
2. Cost of antiplatelet therapy:		
2.1 Based on average prices in Russia by tender results	22,279	31,107
1.2 Based on ticagrelor price planned for registration in EDL and prices of clopidogrel registered in the EDL	25,678	39,857
3. Indirect Costs	126,313	103,347
Total cost:		
Based on average prices in Russia by tender results	740,194	714,123
Based on ticagrelor price planned for registration in the EDL and price for clopidogrel registered in EDL	743,593	722,873

Budget Impact Analysis

This type of analysis involves assessment of all types of costs associated with the introduction into actual practice of a new medical technology or medicine, taking into consideration its effectiveness. The final result is expressed as an amount of money that will be either saved or spent as a result of the use of the medical technology being evaluated. The technology with a lower cumulative economic effect is considered to be the preferred one in budget impact analysis.

We analyzed the budget impact in relation to the budget of the country. On average, about 520,000 cases of ACS are registered every year in Russia [8]. According to available data [5], 41,136 patients underwent PCI. Calculation of budget impact for care for ACS patients managed with PCI annually in Russian Federation depending on ticagrelor ore clopidogrel use and variant of prices calculated is given in table 7.

The performed budget impact analysis showed that ticagrelor + ASA treatment regimen leads to cost savings in the amount of 1,072,450,794 rubles compared to clopidogrel + ASA treatment regimen, in terms of average prices in Russia by the results of tenders. In terms of ticagrelor price planned for registration in the EDL and price of clopidogrel registered in the EDL, the use of Ticagrelor + ASA treatment regimen also leads to cost savings in the amount of 852,324,600 rubles (1-year time horizon).

Conclusion

The results of pharmacoeconomic analysis of treatment regimens ticagrelor + ASA and clopidogrel + ASA in patients with ACS undergoing PCI allow us to make the following conclusion: based on average prices in Russia by the results of tenders as well as based on Ticagrelor price planned for the registration on the EDL and price of clopidogrel registered in the EDL, ticagrelor + ASA is a dominant therapy as compared to clopidogrel + ASA therapy since it shows better therapeutic effectiveness, saves financial resources and is characterized by a lower cost effectiveness ratio.

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Table 7. Calculation of budget impact for care for ACS patients managed with PCI annually in Russian Federation

With use of average tender prices			
	Direct expenses, rubles	**Indirect expenses, rubles**	**Total expenses, rubles**
Clopidogrel + ASA	25,252,581,706	5,196,028,409	30,448,640,116
Ticagrelor + ASA	25,124,863,350	4,251,295,971	29,376,159,322
Cost-saving, RUR			1,072,450,794
With use of planned for EDL registration price for ticagrelor and EDL registered price for clopidogrel			
	Direct expenses, rubles	**Indirect expenses, rubles**	**Total expenses, rubles**
Clopidogrel + ASA	25,392,409,499	5,196,028,409	30,588,437,908
Ticagrelor + ASA	25,408,817,337	4,251,295,971	29,736,113,308
Cost-saving, RUR			852,324,600

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