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- ❑ РЕЗУЛЬТАТЫ РОССИЙСКИХ  
ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

## PHARMACOECONOMIC ANALYSIS OF THROMBO ASS IN TREATMENT OF PATIENTS WITH PREVIOUS CARDIOVASCULAR EVENTS

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**Abstract:** For many years antiplatelet therapy is the basis for the prevention of cardiovascular diseases. Acetylsalicylic acid is the "gold standard" among all antiplatelet drugs. However, ASA administration has an adverse effect in the form of development of NSAID-induced gastropathy. To reduce this effect various forms of production of medicines ASA are used. In this study the pharmacoeconomic assessment of drugs Thrombo ASS, Cardiomagnyl and Aspirin Cardio in patients with previous cardiovascular diseases was conducted. According to the results of conducted cost-minimization analysis determined that the treatment scheme with the use of Thrombo ASS is characterized by the lowest cost compared with Cardiomagnyl and Aspirin Cardio. The results of the budget impact analysis suggest that therapy drugs Thrombo ASS leads to budget savings up to 33 million rubles calculated for all patients with cardiovascular diseases in Moscow compared with alternatives.

**Key words:** acetylsalicylic acid, Thrombo ASS, Cardiomagnyl, Aspirin Cardio, NSAID-induced gastropathy, infarction, stroke, cardiovascular diseases, antiplatelet drugs, budget impact analysis, cost-minimization analysis, cost analysis, pharmacoeconomics

### Introduction

According to the World Health Organization (WHO), cardiovascular diseases (CVD) are the leading cause of morbidity and mortality worldwide. CVD is the leading reason of death annually [1]. Despite other conditions this group of diseases includes ischemic heart disease (infarction) and cerebrovascular disease (stroke). Patients who have undergone these events who undergone long-term treatment requiring catastrophic costs. That's why infarction and stroke is not only social, but economic burden as for a patient and his family, as for the healthcare system and society overall. Despite the fact that the pharmaceutical market funds to prevent the consequences of atherosclerosis has increased significantly, leading position in the treatment and prevention of CVD and its consequences, occupies acetylsalicylic acid [7,9,21]. ASA is recognized as the gold standard for antiplatelet therapy. Its effectiveness is proven in numerous randomized trials and under-confirmed by experience of practical application during the last hundred years. A meta-analysis of published and undertaken by the expert group Antithrombotic Trialists Collaboration, 2002, showed that the use of ASA lowers the sum frequency of infarction, stroke and cardiovascular death by 23% [4]. According to the results of another study it was found that the appointment of acetylsalicylic acid reduce the risk of repeated infarction by 49% and stroke by 46% [5]. Nevertheless, with proven clinical efficacy, there is the problem of rejection of the application of the ASA drugs. It is explained by the fact, that ASA like all non-steroidal anti-inflammatory drugs (NSAID), has no side effects, adversely affecting the mucous membranes of the digestive tract. Such effects are called NSAIDs-associated or NSAID-induced gastropathy. NSAID-

induced gastropathy is a general term that includes, according to various data sources, effects, adverse effects of nonsteroidal anti-inflammatory drugs on the mucous membranes of the gastrointestinal tract, ranging from dyspepsia to gastrointestinal bleeding. Gastrointestinal effect is dose-dependent [6] and is due to the direct irritant effect on the mucous membrane of the stomach. To ensure a balance between therapeutic effect and possible side effects from the gastrointestinal tract, the dose of ASA should be minimally effective. The optimal dose of aspirin is 75-150 mg/day. [6,7,8,9]. In this regard, the efforts of pharmacologists focused on the creation of the ASA drugs minimally affect the gastric mucosa. The first means were the preparations, enteric-coated tablets resistant to gastric juice. Due to this coating, the acetylsalicylic acid is absorbed in the small intestine rather than the stomach without irritating the mucosa [8,10]. One of these drugs – Thrombo ASS — acetylsalicylic acid, in the form of enterosoluble tablets, to minimize the risk of complications from the stomach [10]. According to domestic authors, in a study that included 80 patients with coronary artery disease, myocardial infarction in history and high risk of gastropathy, resulting in a 3-month therapy with ASA enteric-coated form or a preparation containing the nonabsorbable antacid, not been a single documented case of ulcerative lesions of the stomach or gastrointestinal bleeding [10]. Therefore, for long-term therapy it is recommended to use ASA in the form of shapes, coated or combined with an antacid.

Thus, despite the presence of high prevalence of CVD, as well as their socio-economic importance, a number of issues in the treatment of patients with previous cardiovascular events still remains unresolved, including antiaggregation therapy with ASA. The availability of various forms of release of ASA, in case of equal clinical effectiveness, was the basis for this work.

The purpose of this study is to determine from the perspective of pharmacoeconomic analysis the predominant medications used for the secondary constant-term prevention of cardiovascular events based on the comparison between cost and efficiency, safety and quality of life drugs in the treatment of Thrombo ASS, Cardiomagnyl, Aspirin Cardio.

### The objectives of study:

1. To define the modern approaches of primary and secondary prevention of heart and vascular events;
2. To perform an information search results of RCTs on the effectiveness of modern methods of treatment of this disease;
3. To perform an information search of conducted pharmacoeconomic studies of drugs used for treatment of this nosology;
4. To calculate the annual cost of pharmacotherapy drugs Thrombo ASS, Cardiomagnyl, Aspirin Cardio;
5. To conduct a cost analysis, budget impact analysis, cost-minimization analysis and sensitivity analysis

### The features and methodology of the study

Proven clinical efficacy of different forms of ASA is an undeniable fact, which is an undoubted advantage of the use of Aspirin as antitrombocyte therapy in patients with undergoing cardiovascular events. But it also imposes some restriction on the choice of main method of carrying out the of this pharmacoeconomic study. The availability of comparable clinical effectiveness and different forms of release of ASA, is the basis for the cost-minimization and not allowing to use the cost-effectiveness. Cost-minimization analysis provides an opportunity to assess the difference of applying different forms of the same drugs, in fact, only resorting to the comparison of total amounts of treatment costs. In connection with the given parameters of research, the following drugs Thrombo ASS, Aspirin Cardio and Cardiomagnyl, are almost equal, differing significantly only in the costs spent on the annual rate of pharmacotherapy.

In addition, an important item of expenditure of the patient, long-term using of ASA drugs, are the costs of side effects, in particular NSAID-induced gastropathy. To evaluate this parameter, you must have reliable data about the incidence of adverse events from the gastrointestinal tract. In this regard, at first the first stage of this study out large-scale information retrieval was carried.

It was found that there is a lack of reliable data about the incidence of NSAID-induced gas-tropathy. Found studies [6,7,11] did not meet the requirements for study design, the size of pop-ulation or randomizing, so it is not allowed to grade these data as highest level of reliability and to use it as information sources for pharmacoeconomic analysis. Also during information retrieval the absence of randomized trials assessing QALY was noted. That fact also influenced on the choice of analysis method. In addition, it was found pharmacoeconomic study of ASA drugs made Belousov D. Yu. and Afanasyeva E. V. [12]. In this analysis, pharmacoeconomic assess-ment of two drugs acetylsalicylic acid: Cardiomagnyl and Thrombo ASS was conducted. The authors use the cost minimization method of pre-calculating direct medical costs at the annual rate of pharmacotherapy and correction of side effects, the main one being gastric dyspepsia, as a manifestation of NSAID-induced gastropathy. According to the study, the amount of expenses at the annual Pharma-Thrombo ASS cotherapy drugs significantly lower the cost of therapy drug Cardiomagnyl. However, the final difference in direct costs when using Thrombo ASS is higher than when using drug Cardiomagnyl. In spite, accordingly, confirm the prudent estimates of costs for compensation of gastric dyspepsia, it should be noted that cost data is conventional. This is determined by several factors: firstly, not all statements to various trade names (TN) of Omeprazole contain information confirming its use in NSAIDs – gastropathy, are available in the form of gastric dyspepsia, moreover, most of them indicated daily dose is 20 mg, whereas in the study indicated a dose equal to 40 mg; second, only one TN of Omeprazole with an average re-tail price of 308,68 rubles, while the rose-border price of other products ranges from 12 to 800 rubles per pack. In this regard, and taking into account the previously described observations, the weighted average price per package of Omeprazole, regardless of the TN, will amount to 117 rubles, which is significantly lower than the declared value.

The currently known results of the clinical studies, do not give the possibility, with confidence, to protect or to challenge the high incidence of NSAID-induced gastropathy a drug Acetylsali-cylic acid.

### Therefore, for analysis, the following cost structure was identified:

1. The costs incurred cardiovascular events (providing inpatient and emergency care at infarction or stroke);
2. The annual cost of pharmacotherapy;
3. The costs of NSAID-induced gastropathy.

As an example gastropathy was used for ulcer disease of stomach and duodenum (12PCS). The choice was due to the fact that this side effect is one of the most striking manifestations of NSAID-induced gastropathy, and has fixed standards of treatment. The frequency of manifestations of this effect for each drug was labeled as “rare” ( $>1/10000$ ,  $<1/1000$ ). Such an assumption was equal for all analyzed drugs and accepted on the basis of the average weighted evaluation of instructions for use. It was made despite the indication in the instructions a significantly greater frequency of occurrence in drug Cardiomagnyl ( $>1/1000$ ,  $<1/100$ ) and a significantly lower frequency of existence of this reaction from drugs Thrombo ASS ( $>1/100$ ), due to the lack of data obtained during the information search, as well as to eliminate discrepancies in the instructions for use, which vary in completeness of the description of drug.

**Table 1.** The incidence of gastric ulcer when use of ASA drugs according to the instructions for use

Trade name	Thrombo ASS	Cardiomagnyl	Aspirin Cardio
The frequency of GU and 12PCS	In exceptional cases	Sometimes ( $>1/1000$ , $<1/100$ )	Rarely ( $>1/10000$ , $<1/1000$ )

### Costs analysis

At this stage of the study the estimation of direct medical costs of the use of drugs Thrombo ASS, in comparison with drug Cardiomagnyl and Aspirin Cardio was performed. Taking into account the results of the information retrieval and recommendations of the leaflets, we have analyzed the time horizon of compared alternatives as 365 days and defined daily dose of ASA and data from the IMS Health on the costs of analyzed of drugs. (table 2). All calculations were carried out taking into account the dosage prescribed by the leaflet. Thus, as the maximum daily doses for drugs Thrombo ASS and Aspirin Cardio, a value of 100 mg and for drug Cardiomagnyl, the values of 75 and 150 mg were used.

A cost analysis was conducted based on the basic cost of pharmacotherapy, compensation costs for the treatment of cardiovascular events, gastric ulcer and duodenal ulcer. The cost of providing inpatient and emergency care in stroke was **28 9714,80 rubles** и **20 072,49 rubles**, respectively; when infarction – **37 5196,58** and **17 422,70 rubles**, respectively. The cost of hospital treatment in GU and 12PCS amounted to **15 395,46 rubles**. These calculations are made on the basis of operating in the territory of the Russian Federation of standards of rendering medical assistance at the time of the study [13,14,15,16].

The results of the analysis of costs per trade name are presented in table.

As it is seen in the table 3 minimal sum of costs during stroke and infarction on pharmacotherapy with Thrombo ASS and it equals 310 674,89 rubles and 437 617,83 rubles.

Results of costs analysis for infarction and stroke treatment is presented on the figure 1 and 2.

Thus, the sum of direct costs on the annual treatment course with previous CVD, 437 617,83 rubles and 310 674,89 rubles – for Thrombo ASS, 438 623,30 rubles and 311 220,94 rubles – for Aspirin Cardio, 438 070,59 rubles and 311 110,89 rubles – for Cardiomagnyl (75 mg), 438 702,98 rub. and 311 758,28 rub. – for Cardiomagnyl (150 mg), during stroke and infarction.

### Cost-minimization analysis

As the use of all drugs ASA does not have statistically significant differences in mortality and disability of patients who suffered cardiovascular events, the next step pharmacoeconomic research was the analysis of cost-minimization analysis. This type of pharmacoeconomic analysis is a special case of cost-effectiveness analysis, which carried out a comparative assessment of two or more interventions, characterized by the same efficiency and security, but different cost. In the pharmacoeconomic study, it is recommended to change the cost-minimization analysis in a comparative study of different forms or from different conditions of use of one drug or one medical technology. Cost-minimization analysis is calculated by the following formula [18]:

$$CMA = DC1 - DC2, \quad (1)$$

CMA — difference of costs,

DC1 — direct costs of 1 method,

DC2 – direct costs of 1 method,

The table below shows data about how much cost you can save if you transfer one patient on drug therapy Thrombo ASS:

**Table 4.** Cost-minimization analysis

Trade name	Costs differences	
	Stroke (rubles)	Infarction (rubles)
Aspirin Cardio	1 005,47	1 003,26
Cardiomagnyl (75 mg)	452,76	451,00
Cardiomagnyl (150 mg)	1 083,39	1 085,15

**Table 2.** Cost of drugs and dosing scheme

Form of presentation	Price of a pack	Price of 1 mg	Mean price of 1 mg	Mean price of daily dosage
Thrombo ASS				
tablets 50 mg №28	50,43 rubles	0,04 rubles	0,03 rubles	2,53 rubles
tablets 50 mg №100	146,70 rubles	0,03 rubles		
tablets 100 mg №28	55,56 rubles	0,02 rubles		
tablets 100 mg №100	160,93 rubles	0,02 rubles		
Aspirin Cardio				
tablets 100 mg №28	236,27 rubles	0,08 rubles	0,04 rubles	5,45 rubles
tablets 100 mg №56	137,66 rubles	0,02 rubles		
tablets 300 mg №20	85,90 rubles	0,01 rubles		
Cardiomagnyl				
tablets 75mg+15mg №30	188,19 rubles	0,07 rubles	0,04 rubles	3,84 rubles <sup>1</sup>
tablets 75mg+15mg №100	293,20 rubles	0,03 rubles		5,69 rubles <sup>2</sup>
tablets 150mg+30mg №30	166,96 rubles	0,03 rubles		
tablets 150mg+30mg №100	332,33 rubles	0,02 rubles		

\* – the average price of the maximum daily dose recommended by the leaflet

1 –cost of maximum daily dose of drug Cardiomagnyl, according to the assumption, equal to 75 mg

2 –the cost of daily dose of drug Cardiomagnyl, according to the manual, equal to 150 mg. From the data presented in the table 2 with the minimal cost of mean daily dosage of Thrombo ASS –2,53 rubles.

**Table 3.** Results of direct costs analysis

Trade name	Pharmacotherapy	Costs for stroke treatment	Costs for infarction treatment	Compensation of side effects	Total costs on stroke	Total costs on infarction
TA	864,84 rubles	309 794,65 rubles	436 737,59 rubles	15,40 rubles	310 674,89 rubles	437 617,83 rubles
AK	1 403,33 rubles	309 802,22 rubles	436 747,36 rubles	15,40 rubles	311 220,94 rubles	438 623,30 rubles
KM 75 mg	1 294,79 rubles	309 800,70 rubles	436 745,39 rubles	15,40 rubles	311 110,89 rubles	438 070,59 rubles
KM 150 mg	1 942,19 rubles	309 800,70 rubles	436 745,39 rubles	15,40 rubles	311 758,28 rubles	438 702,98 rubles

TA – Thrombo ASS, AK – Aspirin Cardio, KM – Cardiomagnyl



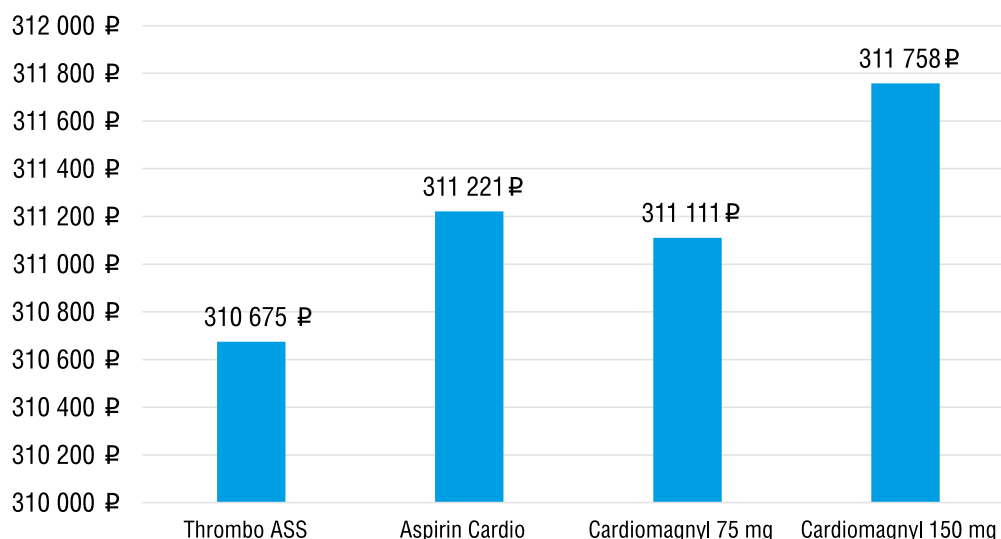


Figure 1. Results of direct costs analysis during stroke

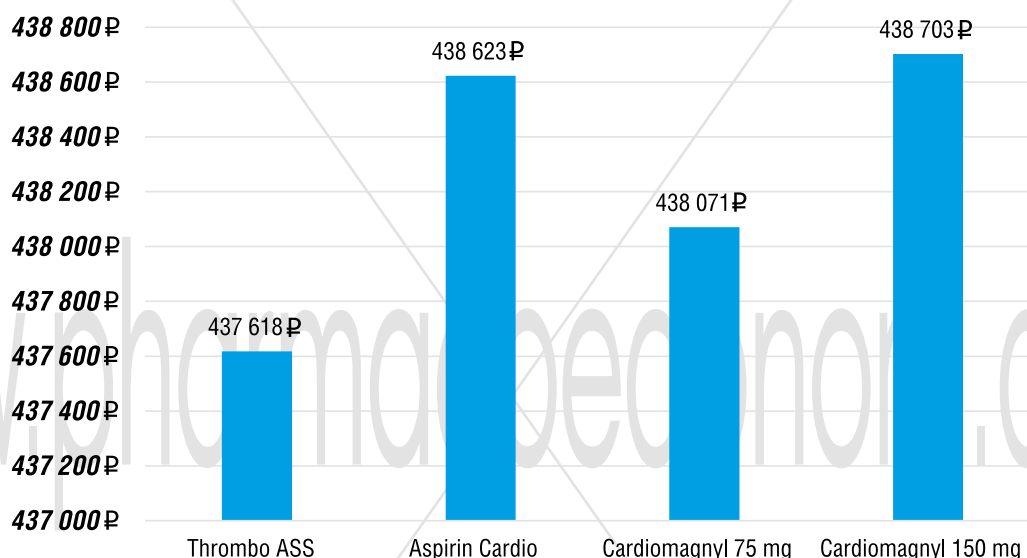


Figure 2. Results of direct costs analysis during infarction.

Based on the performed cost-minimization analysis the usage of Thrombo ASS in patients with previous CVD allows to decrease the costs during the treatment of stroke and infarction by 1 004,37 rubles compared with Aspirin Cardio, by 451,88 rubles compared with Cardiomagnyl 75 mg and by 1 084,27 rubles compared with Cardiomagnyl 150 mg.

This difference within the cost per patient seems insignificant, but it is necessary to extrapolate the results to the population, suffering from CVD, as the difference in costs will increase significantly.

#### Budget impact analysis

Next was a completed budget impact analysis based on the data about the duration, treatment of patients and number of patients who suffered cardiovascular events in the form of infarction or stroke, depending on the region of the Russian Federation (RF), to assess the economic effects on the budget of the health system [17,19]. Calculation of costs was carried out by using the formula:

$$BIA = Cost1 - Cost2, \quad (2)$$

Where Cost1 - total cost of first health technology (rubl.);

Cost2 – total cost of second health technology (rubl.);

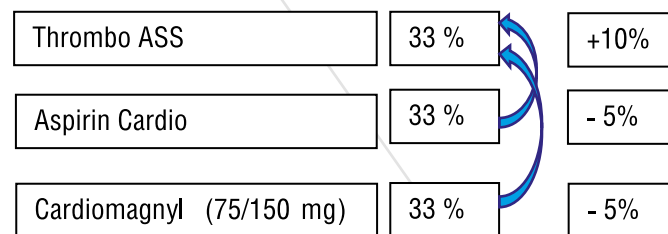
BIA (Budget Impact Analysis) – result of budget impact analysis (rubl.).

Result of budget impact analysis is on the diagram(fig.1):

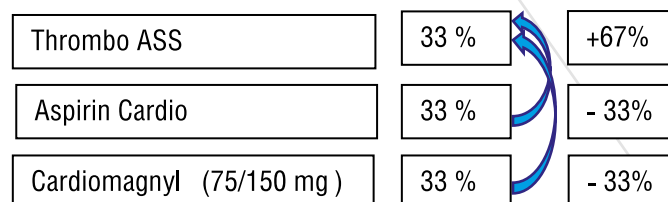
The analysis used two scenarios to compare alternative choices. The first involves the use of pharmacotherapy following drugs: Thrombo ASS, Aspirin Cardio and Cardiomagnyl 75 mg. In the second, Cardiomagnyl is

used in a dosage of 150 mg. moreover, in each scenario, we considered two hypothetical situations of switch of the minimum and maximum number of patient for the use in the treatment of drugs Thrombo ASS (Fig.3):

Figure 3. The scheme of translation of patients during budget impact analysis.



or



In this first scenario there is a transfer of 10% of patient population from the usage of Thrombo ASS to the cohort of the already taking that drug. At the second scenario, there is a transfer of all patients to treatment with Aspirin Cardio and Cardiomagnyl. In both situations, the assumption was made that the distribution of patients taking the ASA drug is the same (33%).

Due to the fact that the study used average prices of the cost of the analyzed drugs, in Moscow, we carried out a calculation for a specific number of patients suffering from CVD, living in Moscow (48 211 people, according to the statistics stick to the disease in 2013 [3]). The following results were obtained, presented in table:

**Table 5.** Results of budget impact analysis

Share of patients taking Thrombo ASS	+ 10%	100%
1 scenario	3 510 347 rub.	23 519 323 rub.
2 scenario	5 034 764 rub.	33 732 917 rub.

These results show that the transfer of additional 10% patients for Thrombo ASS can allow to obtain economy in the frames of the budget of Department of healthcare of Moscow equaling from 3 to 5 million rubles per year, compared with Cardiomagnyl and Aspirin Cardio. The transfer of all patients with previous CVD can reduce the total costs of budget of Department of healthcare of Moscow from 23 to 33 million rubles per year depending the earlier used therapy.

## Conclusions:

1. According to the results of cost-minimization analysis therapy drugs Thrombo ASS is dominant and reduces the amount of direct costs in the treatment of patients with previous CVD compared with Cardiomagnyl and Aspirin Cardio.

2. Conducted budget impact analysis showed that the use of Thrombo ASS leads to budget savings compared with Cardiomagnyl and Aspirin Cardio.

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