Pharmacoeconomic Analysis of Antiplatelet Therapy in the Treatment of Acute Coronary Syndrome and Diabetes Mellitus in Ukraine

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Abstract

Aim: This study aims to improve the results of treatment patients with acute coronary syndrome (ACS) and diabetes mellitus (DM) using more effective antiplatelet therapy. **Materials and Methods:** It was analyzed the Cochrane database, the randomized, double-blind PLATO study, comparing the use of cyclooxygenase inhibitors in combination with ticagrelor (180 mg once, followed by 90 mg 2 g/day) and clopidogrel (300 or 600 mg once, with subsequent administration of 75 mg 1 g/day) in the treatment of patients with ACS and DM. Cyclooxygenase inhibitors prescribed 300 mg once, followed by appointment 75–100 mg 1 p/day. It was carried out the cost-effectiveness analysis based on the results of a randomized clinical trial and one-factor sensitivity analysis. **Results and Discussion:** The results of the "cost-effectiveness" analysis of antiplatelet therapy in treating patients with ACS and DM in Ukraine showed the most favorable is the scheme with clopidogrel. To achieve a unit of efficiency in the case of application of scheme with ticagrelor, it is necessary to attract 1398.30 dollars USA, and for the scheme with clopidogrel - 1335.12 dollars USA $ 1340.13 USA (ICER = $ 66.59/1 extra life saved). The study indicates if the wholesale price is reduced by 12%, the scheme with the ticagrelor becomes dominant. **Conclusion:** Research results are used to develop effective models of reimbursement value provided by theme dicaland pharmaceutical care for patients with diabetes and ACS for implementing social model of compulsory medical insurance in Ukraine.

Key words: Acute coronary syndrome, antiplatelet therapy, cost-efficiency, diabetes, medicines, sensitivity analysis

INTRODUCTION

One of the areas of the social state programs is to provide measures for combating cardiovascular disease and diabetes mellitus (DM). In Ukraine, in 2017, was introduced government program about reimbursement cost of medicines, which aims to stabilize the epidemiological situation, reducing morbidity and mortality due to cardiovascular disease and diabetes.[1]

There is a great need in scientific research, such as a pharmacoeconomic analysis of treatment patients with acute coronary syndrome (ACS) and diabetes. According to the scientific literature, the use of more effective antiplatelet therapy in patients with ACS and DM can improve the results of treatment, and as a consequence of reducing mortality from cardiovascular complications.[2] Early pharmacotherapy of ACS is aimed at preventing myocardial infarction and involves the use of antiplatelet drugs (anti-aggregators) and anticoagulants. At present, antiplatelet agents use cyclooxygenase inhibitors, adenosine diphosphate-dependent platelet aggregation inhibitors (clopidogrel, prasugrel, and

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ticagrelor), and inhibitors of glycoproteins IIb/IIIa (tirofiban, abciximab, etc.).[3,4].For the above purpose of our study, pharmacoeconomic analysis of antiplatelet therapy in the treatment of ACS and diabetes was conducted. To achieve this goal, it was necessary to solve the following tasks:

- To determine the effectiveness of antiplatelet therapy based on the results of the published clinical research data;
- To calculate the direct and indirect costs associated with the provision of medical and pharmaceutical assistance to patients with ACS and DM;
- To carry out the cost-effectiveness analysis (CEA) based on the results of a randomized clinical trial;
- To conduct a one-factor sensitivity analysis.

It should be noted that the results obtained pharmacoeconomic analysis with practical application value for healthcare reform in Ukraine. Thus, based on the results of the study, changes were made to the National List of Essential Medicines.

MATERIALS AND METHODS (METHODS, COST ANALYSIS, AND DATA ANALYSIS)

It was analyzed the Cochrane database on the effectiveness and safety of antiplatelet therapy regimens in patients with ACS and DM for the pharmacoeconomic analysis. There randomized, double-blind, PLATO study, comparing the use of cyclooxygenase inhibitors in combination with ticagrelor (180 mg once, followed by 90 mg 2 g/day) and clopidogrel (300 or 600 mg once, with subsequent administration of 75 mg 1 g/day) in the treatment of patients with ACS and DM. Cyclooxygenase inhibitors prescribed 300 mg once, followed by appointment 75–100 mg 1 p/day.[5] Consequently, taking into account PLATO research data in subsequent calculations, it was taken the use of antiplatelet therapy for 1 year. Characteristics of the results of a randomized clinical trial PLATO on the effectiveness of treatment regimens are presented in Figure 1.

It has been established that in the case of applying ticagrelor in patients with ACS and DM, mortality rate from cardiovascular disease, myocardial infarction, stroke is 14.1%, and for clopidogrel - 16.2%. That is, 859 patients per 1000 patients with ACS and DM who received ticagrelor survivor (the

number of survived lives). Only 838 survived, using clopidogrels.

Cost analysis

The direct medical and indirect costs of antiplatelet therapy in patients with ACS and DM were calculated. As you know, direct medical costs are directly related to the treatment (cost of the schemes, the cost of bed-days during stay in a hospital). There were selected trade names of drugs, which had a level of therapeutic equivalence – "A".[6] The cost of treatment was calculated on the basis of the declared wholesale prices for medicines by the state on November 20, 2017.[7,8] Recalculation of UAH in USD USA was carried out according to the rate of the National Bank of Ukraine on 20.11.2017, where 1 USD USA = 26.50 UAH. Due to the lack of official information about the cost of bed-days in public healthcare facilities, we analyzed price from the private health care centers. It is established that the minimum cost of bed-days in hospital is $ 11.89 USA (https://medikom.ua/price/). According to data from literature sources, the average length of stay of patients with ACS and DM is 27 bed-days.[9] The cost of bed-days during treatment patients with ACS and DM in the hospital is $ 321.03 USA. At the same time, when conducting thorough pharmacoeconomic analysis, it is necessary to take into account also the indirect costs associated with payment for days of disability on the leaves of disability from the social insurance fund, the total loss of society due to the absence on the workplace (loss of gross domestic product [GDP] of the country). Characteristics of indirect costs for one patient ACS and DM are given in Table 1.

The processing of the obtained statistical indicators was carried out using special software (Microsoft Office Excel).

RESULTS

The results of the economic evaluation of the cost of the antiplatelet therapy ACS and DM, presented in the PLATO randomized clinical trial are given in Table 2.

Comparing the values of the cost of applying ACS and DM for 1 year, it was found that the cost of the scheme 1 is 1/2 times higher than the cost of schemes 2 and 3. The

Table 1: Indirect costs of treating patients with ACS and diabetes		
Types of expenses	**Characteristics of expenses**	**Data source**
Expenses for days of disability	Average salary for various types of economic activity in Ukraine in 2017 amounted to $ 258.42 USA. The estimated loss of one day was $ 8.61. USA	The State Statistics Service of Ukraine, literary data[10]
Loss of GDP as a result of disability	In Ukraine, the nominal GDP in 2016 per year - $ 2107.47 USA GDP per person per day - $ 5.77 USA	The State Statistics Service of Ukraine, literary data[10]

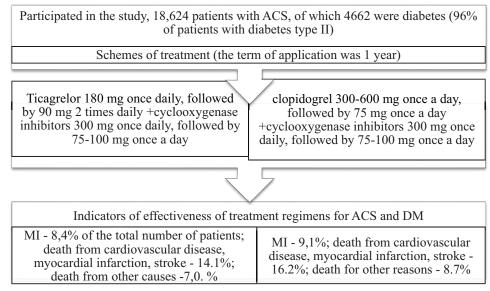ACS: Acute coronary syndrome, GDP: Gross domestic product

Figure 1: Characteristics of the results of the updated clinical trial PLATO

INN	ATC	Wholesale price of medicines	The cost of single dose UAH	Cost of a daily dose, UAH	Total cost of treatment per patient per year, UAH
Table 2: The results of the economic evaluation of the cost of the treatment of ACS and DM					
Scheme No. 1: Ticagrelor 180 mg once daily, followed by 90 mg 2 times daily+cyclooxygenase inhibitors 300 mg 1 time per day, followed by appointment 75–100 mg once a day					
Ticagrelor	B01AC24	71.73	2.56	1.28	469.76
Acetylsalicylic acid	B01A C06	3.51	0.19	0.06	22.09
Total					491.85
Scheme No. 2: Clopidogrel 300 mg once daily, followed by 75 mg once daily+cyclooxygenase inhibitors 300 mg once daily, followed by administration of 75–100 mg once a day					
Clopidogrel	B01AC04	29.34	4.20	1.05	387.45
Acetylsalicylic acid	B01A C06	3.51	0.19	0.06	22.09
Total					409.54
Scheme No. 3: Clopidogrel 600 mg once daily, followed by 75 mg once a day+cyclooxygenase inhibitors 300 mg once daily, followed by administration of 75–100 mg once a day					
Clopidogrel	B01AC04	29.34	8.4	1.05	391.65
Acetylsalicylic acid	B01A C06	3.51	0.19	0.06	22.09
Total					413.74

ACS: Acute coronary syndrome, DM: Diabetes mellitus

results of calculations of direct medical and indirect costs for one patient with ACS and DM during the year are given in Table 3.

The analysis of the cost of antiplatelet therapy in the treatment of ACS and DM allowed to establish that from the point of view of minimizing budget expenditures, the use of schemes 2 and 3 (USD 1118.83 and 1123.03 USD) compared with scheme 1 - $ 1201.14 USA. The estimated budget savings can be about $ 82.31 USA, $ 78.11 USA per patient.

CEA

The CEA is used to estimate the unit cost of performance. This analysis allows you to determine how much the cost of one or another intervention corresponds to its effectiveness, and also to choose the most preferred alternative, in which the cost/efficiency ratio (CER) will be minimal. Such an alternative is called dominant. When the new technology is more efficient and more expensive, it is necessary to determine the incremental cost-efficiency ratio (ICER), which implies which additional investment requires one

Table 3: Total cost of antiplatelet therapy in treatment of ACS and DM per patient

Indexes	Scheme 1	Scheme 2	Scheme 3
Cost of application of antiplatelet therapy regimens per patient, USD USA	491.85	409.54	413.74
Cost of bed days (27 days)	321.03	321.03	321.03
Total direct medical expenses per patient, USD USA	812.88	730.57	734.77
Expenses for payment of days of disability	232.47	232.47	232.47
Loss of GDP as a result of disability	155.79	155.79	155.79
Total amount of indirect costs per patient, USD USA	388.26	388.26	388.26
Total cost per patient, USD USA	1201.14	1118.83	1123.03

Table 4: Pharmacoeconomic analysis by cost-effectiveness method based on the results of a randomized, double-blind study PLATO

Indexes	Scheme 1	Scheme 2	Scheme 3
Total cost per 1000 patients, USD USA	1201140.00	1118830.00	1123030.00
Number of saved lives per 1000 patients (Ef)	859	838	838
Additional efficiency unit (additional saved lives)	21	-	-
Cost-efficiency (CEA), USD US for 1 saved life	1398.30	1335.12	1340.13
Cost of an additional efficiency unit (ICER), USD US $ 1 for an extra saved life	66.59	-	-

additional efficiency unit with the use of more efficient technology. Therefore, to obtain more accurate results of the pharmacoeconomic analysis, it is necessary to take into account the indicators of clinical efficacy, namely, the number of survived lives per 1000 patients. Further, calculations were made of total costs, based on the number of survivals per 1000 patients per year presented in the randomized, double-blind, PLATO blind study [Table 4].

It has been established that the use of scheme 1 requires higher costs to achieve the efficiency unit. The cost-efficiency indicator for scheme 1 is $ 1398.30 USA/1 saved life, and for scheme 2 and scheme 3 are $1335.12 USA/1 saved life and $ 1340.13 USA/1 saved life accordingly. The incremental cost-efficiency indicator for scheme 1 in relation to schemes 2 and 3 is $ 66.59 USA/1 extra saved life.

Sensitivity analysis

To determine the stability of the study results, a one-factor sensitivity analysis for pharmacoeconomically substantiated antiplatelet therapy in the treatment of ACS and DM was performed. The main purpose of univariate analysis is to estimate the magnitude of influence factor on a particular amount of research. Given the financial and economic crisis in Ukraine, namely, the devaluation of the UAH and, as a consequence, the rise in prices for drugs, the analysis of the sensitivity of the results was made taking into account the values of the fluctuation the price on the ticagrelor. For this purpose, the wholesale price decreased with subsequent recalculation indicator CEA [Table 5].

Table 5: Univariate sensitivity analysis results of stability antiplatelet therapy in patients with ACS and diabetes (detail study)

№	Decrease in wholesale prices, %	CEA, dollars USA per 1 saved life
1	Beginning data	1398.30
2	5	1371.29
3	10	1343.98
4	12	1334.37

It is established that at the reduced wholesale selling price on 12%, the scheme No. 1 with ticagrelor becomes the dominant one.

DISCUSSION

Analysis of published literary sources from 2013 to 2016 showed that 20 pharmacoeconomic studies were based on data on the clinical efficacy and safety of ticagrelor before clopidogrel received from the PLATO study.[11-17] The subject of comparison was most often (81%) generic clopidogrel and the entire cohort of patients with ACS, without division into treatment tactics (81%). In the structure of published pharmacoeconomic studies predominates (95%) retrospective time orientation of research, with a long-time horizon (over 1 year - 88% of foreign studies). In the course of research, 71% of cases and the CEA were used, 52% of the researchers additionally conducted a cost–utility analysis. In the cost analysis, 62% of authors consider only direct medical expenses, 19% take into account direct medical and indirect costs.[11-17]

In foreign pharmacoeconomic studies, based on the calculated ICER, quality of life (QALY), and WTP, ticagrelor was considered a cost-effective alternative to clopidogrel due to its low ICER and always higher QALY. Thus, the additional cost of 1 year of QALY turned out to be lower than "the threshold of willingness of society to pay."[11]

The analysis of foreign pharmacoeconomic studies of ticagrelor suggests it as a cost-effective method for treating patients with ACS, depending on the treatment tactics. Ticagrelor data on the economic efficiency may be helpful in revising the guidelines for managing patients with ACS, taking into account the peculiarities of national health systems and the availability of Hi-Tech pharmaceutical care.

CONCLUSION

The results of the "cost-effectiveness" analysis of antiplatelet therapy in treating patients with ACS and DM in Ukraine suggested that the most favorable, from the socioeconomic point of view, is the scheme 2 with clopidogrel. To achieve a unit of efficiency in the case of application of scheme 1, it is necessary to attract 1398.30 dollars USA, for the schemes 2 and 3 - 1335.12 dollars USA $ 1340.13 USA (ICER = $ 66.59/1 extra life saved). When the wholesale price is reduced by 12%, the scheme with the ticagrelor becomes dominant. Research results used to develop effective models of reimbursement (compensation) value provided by the medical and pharmaceutical care for patients with diabetes and ACS conditions for implementing social model of compulsory medical insurance in Ukraine.

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