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Сравнение эффективности оригинального и воспроизведенного клопидогрела у пациентов с острым коронарным синдромом с подъемом сегмента ST на электрокардиограмме

А. В. Андреева✉, Е. В. Филиппов

Рязанский государственный медицинский университет имени академика И. П. Павлова, Рязань, Российская Федерация

АННОТАЦИЯ

Введение. Вопрос оценки влияния генерических антитромбоцитарных препаратов на исходы острого коронарного синдрома (ОКС) остается до сих пор не решенным, особенно на фоне современной терапии заболевания.

Цель. Оценить терапевтическую эквивалентность оригинального и воспроизведенного препарата клопидогрела у пациентов с ОКС с подъемом сегмента ST (ОКСпST) при наблюдении в течение трех лет.

Материалы и методы. В пилотное одноцентровое открытое ретроспективно-проспективное наблюдательное исследование с 2016 по 2018 гг. были включены пациенты с ОКСпST (n = 94; средний возраст 59,98 ± 7,42 лет; 68,3% мужчин). Критерии включения: подписанное информированное согласие, возраст от 25 до 70 лет; подтвержденный ОКСпST с выполненными коронароангиографией и эндопротезированием коронарных артерий; прием клопидогрела (оригинального или воспроизведенного препаратов). Во время госпитализации по поводу ОКСпST все пациенты получали оригинальный клопидогрел в дозе 75 мг/сут., после выписки пациенты были распределены на две группы: группу оригинального клопидогрела (Плавикс®; n = 63) и группу воспроизведенного клопидогрела (Зилт®, Клопидогрел®; n = 31). В течение 1 года пациенты принимали клопидогрел совместно с ацетилсалициловой кислотой, затем продолжили прием ацетилсалициловой кислоты в виде монотерапии. Медиана наблюдения составила 35,5 ± 3,4 мес., отклик исследования — 100%.

Результаты. Частота развития летальных исходов от всех причин (общая смертность) и частота повторных инфарктов миокарда между сравниваемыми группами статистически значимо не различалась. В то же время у пациентов, принимавших воспроизведенный клопидогрел, частота повторного ОКС была ниже, чем у пациентов принимавших оригинальный клопидогрел (6,45% против 26,98%, p < 0,05). Оригинальный клопидогрел и воспроизведенные препараты хорошо переносились: в обеих группах не было зарегистрировано ни одного случая кровотечения и нежелательных явлений, связанных с приемом антиагреганта.

Заключение. Воспроизведенные препараты клопидогрела у пациентов с ОКСпST по эффективности и безопасности не уступают оригинальному препарату.

Ключевые слова: *клопидогрел; острый коронарный синдром с подъемом сегмента ST; ОКС; ОКСпST; оригинальный препарат; воспроизведенный препарат*

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Comparison of Effectiveness of Branded and Generic Clopidogrel in Patients with ST-Elevation Acute Coronary Syndrome on Electrocardiogram

Anna V. Andreyeva✉, Evgeniy V. Filippov

Ryazan State Medical University, Ryazan, Russian Federation

ABSTRACT

INTRODUCTION: Assessment of the effect of generic antiplatelet drugs on the outcomes of the acute coronary syndrome (ACS) still remains an unresolved issue, especially in terms of modern therapy of the disease.

AIM: To assess therapeutic equivalence of the original and generic clopidogrel drug in patients with ST-elevation ACS (STE-ACS) during a three-year follow-up period.

MATERIALS AND METHODS: The pilot single-center open-label retrospective-prospective observational study between 2016 and 2018 included patients with STE-ASC (n = 94; mean age 59.98 ± 7.42 years; 68.3% of men). Inclusion criteria: signed informed consent, age from 25 to 70 years; confirmed STE-ACS with performed coronary angiography and coronary angioplasty; intake of clopidogrel (branded or generic). During hospitalization for STE-ACS, all patients received branded clopidogrel at a dose of 75 mg/day, after discharge, the patients were divided into two groups: the branded clopidogrel group (Plavix®; n = 63) and the generic clopidogrel group (Zilt®, Clopidogrel®; n = 31). For 1 year, patients took clopidogrel together with acetylsalicylic acid, then continued intake of acetylsalicylic acid as monotherapy. The median follow-up was 35.5 ± 3.4 months, the study response was 100%.

RESULTS: There were no statistically significant differences between the compared groups in all-cause mortality rate (overall mortality) and incidence of recurrent infarctions. At the same time, the frequency of recurrent ACS was lower in patients taking generic clopidogrel than in those taking branded clopidogrel (6.45% versus 26.98%, $p < 0.05$). The branded clopidogrel and generic drugs were well tolerated: no cases of bleeding or adverse events associated with intake of the antiplatelet drug, were recorded.

CONCLUSION: Generic clopidogrel preparations are not inferior to the branded drug in terms of efficacy and safety in patients with STE-ACS.

Keywords: *clopidogrel; ST segment elevation acute coronary syndrome; ACS; STE-ACS; branded drug; generic drug*

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ECO•VECTOR

LIST OF ABBREVIATIONS

ACS — acute coronary syndrome
ASA — acetylsalicylic acid
CI — confidence interval
HR — hazard ratio
MI — myocardial infarction
STE ACS — ST segment elevation acute coronary syndrome

INTRODUCTION

Clopidogrel is a second-generation inhibitor of platelet adenosine diphosphate receptor (type P2Y12); one of the main antiplatelet agents used to treat patients with ST segment elevation acute coronary syndrome (STE-ACS) [1, 2].

In 2011, Plavix® (branded clopidogrel from Sanofi-Aventis Group, France) was one of the best-selling medical drugs in the world [3]. According to some authors, half of patients in Russia (55.9%) who suffered acute coronary syndrome, were adherent to dual antiplatelet therapy with clopidogrel and acetylsalicylic acid (ASA) for the recommended 12 months [4–6], with *the leading reason for refusal of clopidogrel being its high cost* [7].

One possible solution to this problem is the use of generic drugs, which are equivalent in composition to the branded drug, but are considerably lower in cost [8]. A disadvantage of this approach is that up to the moment there are practically no research that would evaluate the therapeutic equivalence of the branded and generic clopidogrel in patients with STE-ACS. There are only single works comparing the effect of clopidogrel from different manufacturers on platelet aggregation [9, 10] and also investigating the effect of the drugs in patient *with non-ST-segment elevation* ACS [11, 12].

The **aim** of this study to evaluate the therapeutic equivalence and adverse outcomes between the branded and generic clopidogrel in patients with ST segment elevation acute coronary symptom over a three-year follow-up.

MATERIALS AND METHODS

The pilot single-center open-label retrospective-prospective observational study conducted on the base of the cardiology department with an intensive care ward for patients with acute myocardial infarction (MI) of the Regional Clinical Cardiology Dispensary (RCCD) of Ryazan, included patients with STE-ACS who underwent inpatient treatment from 2016 to 2018. The study was approved by the Local Ethics Committee of the RCCD (Protocol No. 12 of December 18, 2019).

Inclusion criteria: signed informed consent; age from 25 to 70 years; confirmed STE-ACS with performed coronary angiography and coronary artery endoprosthetics; intake of clopidogrel (branded or generic).

Exclusion criteria: arterial hypertension with systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg) not controlled by antihypertensive drugs; thrombolytic therapy; life expectancy less than 1 year; erosive-ulcerative lesions of the gastrointestinal tract; marked disorders in renal (estimated glomerular filtration rate < 30 ml/min./1.73 m^2) and liver (severe liver failure — 10–15 points on the Child–Pugh scale) functions; hemorrhagic syndrome; intake of more than 10 units of alcohol per week or history of alcoholism; drug addiction; participation in any clinical trials of drugs in the past 30 days; known inefficiency of/intolerance to clopidogrel.

Patients underwent a standard examination, including complete blood count, clinical urine analysis, blood biochemistry, electrocardiography, coagulogram, glomerular filtration rate calculation, cardiac ultrasound, and coronary angiography.

All patients received a comparable therapy for STE-ACS according to the 2016 Clinical recommendations of the Ministry of Healthcare of the Russian Federation and 2017 Clinical recommendations of the European Society of Cardiology, which included ASA, clopidogrel, angiotensin-converting enzyme inhibitor, beta-blockers, heparin/enoxaparin, nitroglycerin, statins, amiodarone (for paroxysmal atrial fibrillation).

During hospitalization for STE-ACS, all patients received the branded clopidogrel at a dose of 75 mg/day. After the discharge, the patients were divided into two groups:

- ***group of branded clopidogrel*** (Plavix®; n = 63);
- ***group of generic clopidogrel*** (Zylt®, Clopidogrel®; n = 31).

Patients of both groups were taking clopidogrel at a dose of 75 mg/day together with ASA within 1 year, after which continued intake of ASA as monotherapy. The clinical and demographic characteristics of the patients are given in Table 1, coronary artery lesion according to coronary angiography in Table 2, and the treatment administered in Table 3.

Table 1. Baseline Clinical and Demographic Characteristics of Patients of Compared Groups

Parameters	Branded clopidogrel	Generic clopidogrel	p
n	63	31	–
Age, M ± SD, years	59.98 ± 7.42	57.55 ± 9.5	*0.176*
Men, n (%)	43 (68.3%)	26 (83.9%)	*0.139*
Clinical Characteristics			
Body mass index, M ± SD, kg/m^2	29.05 ± 4.92	26.7 ± 3.92	***0.022***
Systolic blood pressure, M ± SD, mm Hg	136.1 ± 23.17	134.63 ± 19.24	*0.768*
Diastolic blood pressure, M ± SD, mm Hg	83.18 ± 12.77	82.57 ± 11.25	*0.824*
Heart rate, M ± SD, beat/min.	77.26 ± 14.36	76.6 ± 12.1	*0.828*
Left ventricular ejection fraction, M ± SD, %	53.0 ± 7.97	51.58 ± 8.68	*0.437*
Anterior location of myocardial infarction, n (%)	35 (55.6)	22 (71.0)	*0.182*
Lower location of myocardial infarction, n (%)	26 (41.3)	9 (29.0)	*0.268*
Comorbidity			
Essential hypertension, n (%)	51 (81.0)	26 (83.9)	*0.99*
Cerebrovascular disease, n (%)	11 (17.5)	8 (25.8)	*0.415*
Urolithiasis and/or chronic pyelonephritis, n (%)	13 (20.6)	10 (32.3)	*0.307*
Obesity, n (%)	9 (14.3)	3 (9.7)	*0.745*
Type 2 diabetes mellitus, n (%)	12 (19.0)	4 (12.9)	*0.567*
Chronic obstructive pulmonary disease, n (%)	6 (9.5)	4 (12.9)	*0.725*
Chronic heart failure, n (%)	4 (6.4)	1 (3.2)	*0.999*
Persisting atrial fibrillation, n (%)	2 (3.2)	1 (3.2)	*0.999*

Table 2. Coronary Artery Lesion Based on Coronary Angiography Data in Patients of Compared Groups at the Time of Inclusion into Study

Parameters	Branded clopidogrel	Generic clopidogrel	p
n	63	31	–
Anterior interventricular artery, n (%)	35 (55.6)	16 (51.6)	*0.826*
Right coronary artery, n (%)	38 (60.3)	16 (51.6)	*0.507*
Circumflex artery, n (%)	26 (41.3)	7 (22.6)	*0.107*
Others, n (%)	24 (38.1)	8 (25.8)	*0.258*
The type of Coronary Bed Lesion by the Number of Arteries Involved			
Multi-vessel lesion, n (%)	41 (65.1)	15 (48.4)	*0.179*
Single-vessel lesion, n (%)	22 (34.9)	16 (51.6)	*0.179*
Results of Percutaneous Coronary Intervention			
Mean number of stents per person, M ± SD	1.16 ± 0.41	1.13 ± 0.35	*0.37*

Table 3. Pharmacological Treatment of Compared Groups in the Course of Study (n (%))

Parameters	Branded clopidogrel	Generic clopidogrel	p
n	63	31	–
Proton pump inhibitors	32 (50.8)	17 (54.8)	*0.827*
Angiotensin-converting enzyme inhibitors	52 (82.5)	27 (87.1)	*0.766*
Angiotensin II receptor blockers	5 (7.9)	1 (3.2)	*0.66*
Beta-adrenoblockers	57 (90.5)	28 (90.3)	*0.99*
Diuretics	15 (23.8)	6 (19.4)	*0.79*
Long acting nitrates	36 (57.1)	12 (38.7)	*0.125*
Statins	56 (88.9)	28 (90.3)	*0.99*
Acetylsalicylic acid	51 (81.0)	26 (83.9)	*0.99*
Spironolactone	43 (68.3%)	15 (48.4)	*0.074*
Compliance > 80%, n (%)	63 (100)	31 (100)	*1.0*

The formed groups were comparable in the main clinical parameters, concomitant diseases, the kind of the coronary artery lesion and medications taken. The exception was the body mass index, which appeared to be higher in patients receiving Plavix® than in those prescribed generic clopidogrel (by 8.8%, p = 0.022; Table 1).

Endpoints (in this analysis) were all-cause mortality, MI, recurrent ACS.

Patients' adherence to taking antiplatelet drugs, renin-angiotensin-aldosterone system blockers, beta-blockers, statins, mineralocorticoid receptor antagonists was evaluated in the Morisky–Green test (the version actual at the time of study) [13]. Compliance below 80% was considered unsatisfactory.

The mean follow-up period in the study was 35.5 ± 3.4 months. The study response was 100%.

The obtained data were processed using Statistica 13.0 (Stat Soft Inc., USA) and Excel 2016 (Microsoft Corporation, USA). The distribution of variables was assessed using Shapiro–Wilk test. Quantitative data are presented in the table as the arithmetic mean and standard deviation (M ± SD, since the data distribution was normal), qualitative parameters are presented as frequencies (in percent). The statistical significance of differences between quantitative parameters was assessed using Student's t-test for unrelated samples. The statistical significance of differences between qualitative parameters was analyzed using Fisher's exact test. The efficacy of the generic and branded clopidogrel was calculated by endpoints (based on the hypothesis of therapeutic equivalence of the drugs): no worse — $p < 0.05$, superior to the original clopidogrel — $p < 0.001$.

RESULTS

When analyzing the efficacy and safety of the branded and generic drugs, the following results were obtained (Figure 1). The frequency of all-cause deaths (overall mortality) and of recurrent MI between the compared groups had no statistically significant differences. At the same time, in patients who were prescribed generic clopidogrel, the incidence of ACS was lower than in patients prescribed the branded clopidogrel (6.45% vs. 26.98%, p = 0.027).

In the group of generic clopidogrel, no cases of coronary artery restenosis, acute cerebrovascular accidents, deaths from cardiovascular diseases, bleedings or other serious adverse reactions were recorded, while in the group of the branded drug their incidence was 4.76%, 3.17%, 15.87%, 0% and 0%, respectively (p > 0.05).

DISCUSSION

Confirmation of equal clinical efficacy of generic drugs is an important step in their post-registration development [14]. In the presented work, the therapeutic efficacy of the branded and generic clopidogrel are compared in patients with STE-ACS over a three-year follow-up.

It was found that the frequency of all-cause death (overall mortality) and the incidence of recurrent MI had no statistically significant difference between the compared groups, no differences were either obtained in the incidence of coronary artery restenosis, acute cerebrovascular accidents and death from cardiovascular diseases. The branded and generic clopidogrel preparations were well tolerated; not a single case of

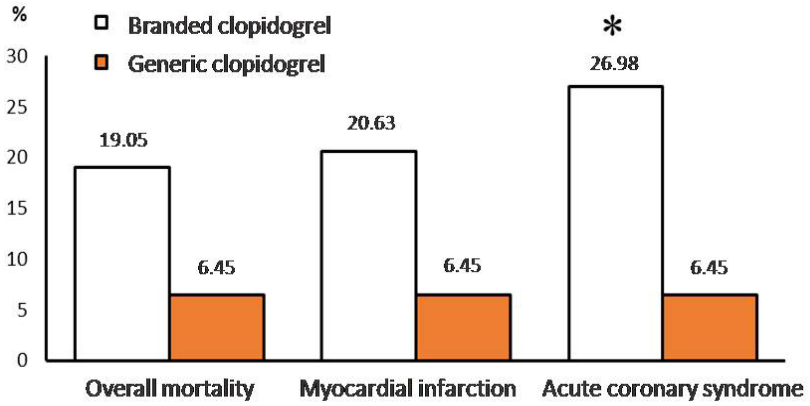

Fig. 1. Frequency of outcomes in patients with ST-segment elevation acute coronary syndrome prescribed branded and generic clopidogrel.
Note: * — $p < 0.05$, statistically significant differences between the compared groups

bleeding and adverse events associated with intake of the antiplatelet drug was recorded. The data obtained evidence the *comparability of the branded and studied generic clopidogrel preparations*.

Upon that, these results are comparable with the results of evaluating the equivalence of clopidogrel preparations in another pathology. Thus, a population-based observational study in patients with ACS showed that at 1 year of therapy, 17.6% of patients prescribed branded clopidogrel and 17.9% of patients prescribed generic clopidogrel, experienced fatal outcome and ACS (there were no statistically significant differences between the groups, $p > 0.05$) [15].

In the prospective single-center, open-label study in patients with non-STE ACS, no overall mortality, MI, revascularization, stent thrombosis, thrombolysis in MI and bleedings were recorded in patients during in-hospital stay or 1 month of follow-up when receiving branded or generic clopidogrel [11].

The meta-analysis by D. Caldeira, et al. (2012) included three studies involving 760 patients of 2 randomized controlled trials and 1 cohort study. The hazard risk (HR) for major cardiovascular events was 1.01 (95% confidence interval (CI) 0.67–1.52) [16].

At the same time, in the given study it was found that in patients who were prescribed *generic clopidogrel, the ACS incidence was statistically significantly lower* than in patients who were prescribed the branded clopidogrel. Compliance of patients in the study was comparable, therefore the obtained results are unlikely to be associated with adherence to treatment.

Similar results were obtained in a number of other studies. Analysis of the frequency of adverse (undesirable) reactions after taking the branded clopidogrel and its generics, according to the Food and Drug Administration Adverse Event Reporting System, showed a decrease in patient mortality *when taking generics* (HR 0.38; 95% CI 0.32–0.43; $p < 0.0001$ for the entire observation period and HR 0.40; 95% CI 0.37–0.45; $p < 0.004$ for 2010–2017). In contrast, cardiac (HR 1.12; 95% CI 1.0–1.25; $p < 0.06$), hemorrhagic (HR 1.45; 95% CI 1.33–1.57; $p < 0.0001$) and cutaneous (HR 1.20; 95% CI 1.00–1.44; $p < 0.05$) adverse events *developed more frequently with the use of generics*. The authors associated the higher mortality rate with the use of the branded clopidogrel with the fact that generic manufacturers were reluctant to report fatal cases [17].

In a retrospective study it was found that the use of generic clopidogrel bisulfate (n = 254) compared with the use of branded clopidogrel (n = 185) was associated with a decrease in antiplatelet resistance (from 44% to 31%, $p < 0.01$) and a decrease in the mean resistance index (from 5.06 ± 4.55 to 3.32 ± 4.03, $p < 0.01$). No statistically significant differences in the prevalence of secondary events were found between the studied drugs [18].

CONCLUSION

In the course of the present work, it was shown that the studied generic drugs of clopidogrel in patients with acute coronary syndrome with ST segment elevation on the electrocardiogram are not inferior to the branded clopidogrel in the efficacy and safety. It is necessary to conduct larger multi-center randomized clinical trials that could confirm the results of this work, which is important for the public healthcare.

Limitations of the study: all limitations characteristic of a pilot study and a small sample are also present in this study (intake of the branded clopidogrel by all

patients during in-hospital period of the study, small sample size, short follow-up period, lack of a more thorough control of adherence to treatment throughout the entire follow-up period).

ADDITIONALLY

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ОБ АВТОРАХ

*** Андреева Анна Викторовна**;
ORCID: https://orcid.org/0000-0002-2941-9679;
eLibrary SPIN: 6809-4395; e-mail: andreeva_anna76@mail.ru

Филиппов Евгений Владимирович, д.м.н., профессор;
ORCID: https://orcid.org/0000-0002-7688-7176;
eLibrary SPIN: 2809-2781; e-mail: dr.philippov@vk.com

AUTHORS' INFO

*** Anna V. Andreyeva**;
ORCID: https://orcid.org/0000-0002-2941-9679;
eLibrary SPIN: 6809-4395; e-mail: andreeva_anna76@mail.ru

Evgeniy V. Filippov, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-7688-7176;
eLibrary SPIN: 2809-2781; e-mail: dr.philippov@vk.com

* Автор, ответственный за переписку / Corresponding author