Pharmacoeconomics in Dual Antiplatelet Therapy after Acute Ischemic Syndrome

Mindaugas Stonis[1]*, Gintarė Martinkutė[1,2], Simona Ripkauskaitė[1], Emilija Šabatina[1], Vilius Ripkauskas[1,3] and Vacis Tatarūnas[4]

[1]*Faculty of Medicine, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*

[2]*Departament of Cardiology, Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania*

[3]*Departament of Surgery, Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania*

[4]*Laboratory of Molecular Cardiology, Institute of Cardiology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*

*Corresponding Author: Mindaugas Stonis, Faculty of Medicine, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania.

Abstract

The acute coronary syndrome (ACS) is resulting in high healthcare sector expenditure and is also a life-threatening illness. Therefore, there is a need for an effective and economically optimal treatment strategy to address it. A comparison of 12-month patient treatment costs after ACS between two antiplatelet medication strategies was made in this pilot study. Our findings suggest that clopidogrel and aspirin therapy is the less expensive treatment option as compared to ticagrelor and aspirin whilst also showing non-inferior treatment effectiveness.

Keywords: Acute Coronary Syndrome; Clopidogrel; Ticagrelor; Dual Antiplatelet Therapy; Pharmacoeconomic

Introduction

Every year, about 185000 patients are hospitalized for ACS in Lithuania. Despite the decreasing incidence of acute coronary syndrome (ACS), the mortality rate from ACS in Lithuania remains extremely high at 36% [1]. Significant funds of the health care system are allocated for the treatment of ACS worldwide. During recent years (according to the American Heart Association and European Society of Cardiology guidelines), dual antiplatelet therapy, consisting of P2Y12 receptor blocker ticagrelor or prasugrel combined with aspirin is preferred over clopidogrel [2-4]. These recommendations are based on the recent data, showing that clopidogrel is less effective in reducing coronary artery events as compared to newer generation drugs ticagrelor or prasugrel, mainly during in-hospital period [5]. However, patients receiving ticagrelor and prasugrel have increased rates of bleeding events [5]. Even reduction of daily dosages of these new generation drugs may not prevent bleeding [6]. In the patients with bleeding, ticagrelor or prasugrel is switched to clopidogrel [7].

The effectiveness of the medications mentioned varies between patients [8]. That is why the aim of our study was to evaluate factors influencing the cost of treatment of ACS according to our pharmacoeconomic model in patients receiving the older generation drug clopidogrel or the newer generation drug ticagrelor and to display that clopidogrel is more cost-effective while being safe and effective treatment option.

Methods

A retrospective study was performed involving 50 patients at the Lithuanian University of Health Sciences Hospital Kaunas Clinics Cardiology Clinic. Based on the previous data, showing that *CYP4F2* gene variants may influence effectiveness of antiplatelet therapy with ticagrelor, all the studied patients were screened for *CYP4F2* (rs2108622) variant [9]. All patients underwent percutaneous transluminal coronary angioplasty (PTCA) and stenting and received single loading dosages of antiplatelet drugs (clopidogrel 600 mg + aspirin 300 mg or ticagrelor 180 mg + aspirin 300 mg) before the intervention. Maintenance dosages (clopidogrel 75 mg + aspirin 100 mg or ticagrelor 90 mg bidaily + aspirin 100 mg) were prescribed for at least 12 months.

Patients who used clopidogrel and aspirin or ticagrelor and aspirin were included into the pharmacoeconomic model. The cost of treatment included these components: inpatient treatment of ACS expenses, outpatient dual antiplatelet therapy cost and price of re-hospitalization for complications of dual antiplatelet therapy.

Statistical analysis

Kruskal-Wallis and Pearson-Chi square tests were used for nonparametric and categorical variables accordingly. A stepwise multivariate logistic regression method was used to determine the factors that influence aforementioned treatment price. Statistically significant data were considered when $p < 0.05$.

Results and Discussion

The study sample consisted of 50 patients, of whom 19 (38%) had recurrent events. In the whole sample, there were 37 men (74%) and 13 women (26%). Stent restenosis was observed in 5 (10%) patients, of whom 4 (8%) patients had bare metal stents. Timings for restenosis to occur were: range 2 - 12, median 3 months. Restenosis was significantly more common in the users of alcohol ($\chi^2 = 10.784$, $p = 0.001$). No complications associated with the use of antiplatelet agents, such as stent thrombosis, were observed.

Clopidogrel group consisted of 26 (52%) and ticagrelor of 24 (48%) subjects. The treatment price in ticagrelor group was: range 1980 - 11945, median 4269 Eur and clopidogrel: range 1594 - 7945, median 3883Eur. The 12-month treatment after ACS was more expensive in ticagrelor group ($p < 0.0001$). Clopidogrel was more frequently prescribed to women ($p = 0.037$). Treatment cost in female: range 1594 - 10134, median 3883 Eur and male: range 1594 - 11945, median 4269 Eur, patient groups did not differ significantly ($p = 0.13$).

We performed more detailed analysis. Patients were stratified into two groups based on the treatment cost: more than 4,000 euros and less than 4,000 euros. Totally there were 27 (54%) and 23 (46%) patients, respectively. Assessing all factors included in the multiple binary regression, it was shown that male gender (HR 14.053, 95% CI: 1.470 - 134.379, $p = 0.022$), smoking (HR 10.516, 95% CI: 1.328 - 83.291, $p = 0.026$) and *CYP4F2* rs2108622 A allele (HR 3.966, 95% CI: 1.019 - 15.438, $p = 0.047$) increased the odds ratios for 12-month patient treatment to be more expensive than 4000 EUR.

Conclusion

Smoking, male gender, and *CYP4F2* variant A significantly increased the odds ratios for patient's treatment to be more expensive during 12-month therapy after ACS. The treatment with clopidogrel and aspirin was less expensive and it was similarly effective as compared to ticagrelor and aspirin dual antiplatelet therapy. Stent thrombosis was not observed in a represented patient sample thus, this pilot study may not represent the correct cost of treatment in patients with stent thrombosis. There is still a need for more comprehensive studies.

Conflicts of Interest

There are no conflicts of interest.

Bibliography

1. Amsterdam EA., *et al.* "2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines". *Journal of the American College of Cardiology* 64.24 (2014): e139-e228.

2. Roffi M., *et al.* "2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)". *European Heart Journal* 37.3 (2016): 267-315.

3. Capodanno D., *et al.* "ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy: JACC Guideline Comparison". *Journal of the American College of Cardiology* 72 (2018): 2915-2931.

4. Castini D., *et al.* "Real-world clopidogrel utilization in acute coronary syndromes: patients selection and outcomes in a single-center experience". *Therapeutic Advances in Cardiovascular Disease* 11.12 (2017): 323-331.

5. Shoji S., *et al.* "Ischemic and Bleeding Events Among Patients With Acute Coronary Syndrome Associated With Low-Dose Prasugrel vs Standard-Dose Clopidogrel Treatment". *JAMA Network Open* 3.4 (2020): e202004.

6. Bagai A., *et al.* "In-hospital switching between clopidogrel and prasugrel among patients with acute myocardial infarction treated with percutaneous coronary intervention: insights into contemporary practice from the national cardiovascular data registry". *Circulation: Cardiovascular Interventions* 7.4 (2014): 585-593.

7. Grodecki K., *et al.* "Gender-related differences in post-discharge bleeding among patients with acute coronary syndrome on dual antiplatelet therapy: A BleeMACS sub-study". *Thrombosis Research* 168 (2018): 156-163.

8. Tatarunas V., *et al.* "The impact of CYP2C19 and CYP4F2 variants and clinical factors on treatment outcomes during antiplatelet therapy". *Pharmacogenomics* 20.7 (2019): 483-492.