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The role of *CYP2C19*2* variant and other factors in clopidogrel resistance in Montenegrin ACS patients

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Abstract

Clopidogrel, an antiplatelet drug, has been widely prescribed for the treatment of acute coronary syndrome (ACS) for over two decades. Despite the fact that the drug proved to be effective in the majority of patients, in some, due to an inadequate response, the recurrence of adverse cardiovascular events represents a significant problem. These interindividual differences in response to clopidogrel may be due to genetic variations, concomitant therapy and associated diseases. The purpose of this study is to examine the association of the *CYP2C19*2* loss of function variant, as well as other variables such as demographic characteristics, concomitant diseases and therapy with resistance, i.e. reduced drug efficacy in the Montenegrin cohort. The study included a total of 196 patients diagnosed with ACS who were on clopidogrel therapy. Patients were monitored for a one- year period, after the introduction of therapy, and divided into two groups: effective and ineffective clopidogrel therapy group. Genotyping for the *CYP2C19*2* variant was performed using the real-time qPCR method. Our results show that atrial fibrillation (AF) is associated with impaired efficacy of clopidogrel in reducing the occurrence of adverse CV events during one year after the diagnosis of ACS ($p = 0.040$). There was no statistically significant difference between the effective and ineffective therapy group concerning *CYP2C19*2* allele and genotype distribution ($p = 0.438$, $p = 0.328$) respectively. In conclusion, our findings indicate that AF could be potential non-genetic cause of ineffective clopidogrel therapy in ACS patients.

Keywords

*acute coronary syndrome, CYP2C19*2, atrial fibrillation, clopidogrel*

Introduction

Acute coronary syndrome (ACS) represents one of the main causes of mortality in the modern age and is responsible for 1.8 million deaths annually, worldwide. Although the incidence of ACS generally increases with age, recent data show that ACS occurs far more often in men than in women below the age of 60 years, but women make up the majority of patients over 75 years of age (Bueno, 2018). The role of traditional cardiovascular risk factors in the development of ACS is undeniable and quite well-known (Imbalzano, 2018; Lamelas, 2017). Therefore, in addition to prevention and healthy lifestyle education, it is very important to apply best suited treatment, as soon as possible, after the damaging incident has already occurred. It is considered that genetic studies are very important in the investigation of innate mechanisms responsible for a specific response to drugs (Kapur et al., 2010), which is the basis of a personalized medical approach. Additionally, molecular research has shown that there are a large number of candidate genes that are associated with the development and occurrence of complex diseases (Avdic et al., 2022) such as ACS. One of the meaningful aspects of personalized medicine is pharmacogenetic testing, which is defined as the use of genetic information in assessing how an individual will respond to a certain drug (Whirl-Carillo et al., 2012; Hansen et al., 2022).

Despite the development of new drugs, due to the lower cost and lower bleeding risk, clopidogrel (in combination with aspirin) remains one of the first choices for the treatment of ACS (Li et al., 2021). Clopidogrel inhibits ADP-induced platelet aggregation by selectively binding to the platelet purinergic receptor P2RY12, acting as powerful antithrombotic medication (Committee, 1996). However, it was also found that despite regularly intake of clopidogrel, the expected anti-platelet-aggregation effect is not achieved in many patients and adverse cardiovascular (CV) events occur, which can be defined as clopidogrel resistance (CR) (Wiviott et al., 2004).The existence of interindividual differences in clopidogrel response may be the result of various factors, including genetic ones, such as variations in genes involved in the pharmacodynamics and pharmacokinetics of the drug, but also non-genetic ones, such as comorbidities, older age and interactions with other drugs (Pereira et al., 2019).

Clopidogrel is a prodrug whose activation requires metabolic transformation by Cytochrome P 450 (CYP 450) enzymes in the liver. CYP2C19 enzyme is a CYP isoform that plays a key role in the conversion of clopidogrel into an active metabolite, through two sequential oxidation processes (Han et al., 2017; Ferri et al., 2013). Polymorphisms in the *CYP2C19* gene can result in a reduction or complete loss of enzyme activity or on the other hand, enhanced drug metabolism, i.e. in an increase in enzyme function. Therefore, both the loss of function (LoFA) and gain of function alleles have been defined (Pereira el al., 2019; Klein et al., 2018). The most common LoFA variant is *CYP2C19*2* (rs4244285; 681G>A). It was demonstrated that this LoFA variant is associated with reduced activity of clopidogrel, weaker antiplatelet effect and increased adverse cardiovascular events (Wang et al., 2016). However, despite clopidogrel pharmacogenetics being recognized by the Food and Drug Administration as a major tool in introducing the practice of personalized antiplatelet therapy, the actual clinical application has not seriously taken off (Holmes et al., 2010). The purpose of our study was to investigate whether the *CYP2C19*2* variant

and non-genetic factors, as well as comorbidities and concomitant therapy, are associated with adverse CV events i.e. effectiveness of clopidogrel therapy in Montenegrin ACS patients.

Material and methods

This was prospective study that included 196 patients who were observed in the Cardiology Clinic, Clinical Center of Montenegro, between September 2021 and January 2023, and who were diagnosed with ACS. All patients were prescribed clopidogrel during hospitalization at an initial dose of 75 mg per day and they took the drug for one year after being discharged from the Cardiology department. Information on demographic data was obtained directly from the patients during hospitalization, while data on associated diseases, and additional therapy they were taking were obtained from the medical history. The exclusion criteria were: age younger than 18 and older than 80, malignant disease, pregnancy and chronic autoimmune disease. The present study was approved by the Ethical Committee of the Clinical Center of Montenegro (approval number: 03/01-9928/1) and is in according with the principles of the Helsinki Declaration. Signed informed consent was obtained from all the subjects.

Demographic data and biochemical parameters

Data about the patient's sex, age, and lifestyle choices were obtained from interviews with the patients. The following biochemical parameters were collected from the patients' medical history: glucose, cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), urea, creatinine, fibrinogen and D-dimer. Data on associated diseases-comorbidities (hypertension, diabetes mellitus and atrial fibrillation) as well as concomitant therapy (pantoprazole, metformin, statins and angiotensin-converting enzyme (ACE) -inhibitors) were also taken.

Monitoring of clinical outcomes

All patients were monitored over a period of one year, through periodic phone calls, in person or through close relatives who provided their contact number, then during regular medical controls and interviews to obtain information about the general medical condition of the patient and about the clinical indicators of the effectiveness of clopidogrel therapy, namely: stent thrombosis, reinfarction, percutaneous coronary interventions (PCI) outcome and death. Based on the obtained data, two groups of patients were formed. First, in which adverse cardiovascular events were recorded and the other in which no adverse CV events were recorded during the period of monitoring and taking therapy. The first group was designated as a group with an ineffective therapeutic response, while the second was designated as a group with an effective therapeutic response.

Genotyping

Blood samples were collected from all patients in the EDTA blood collection tubes and genomic DNA was extracted manually by a commercial extraction kit (QIAamp DNA Mini kit, Qiagen, Germany) according to the manufacturer's protocol. Quantification of DNA was carried out by a Qubit 2.00 (Thermo Fisher Scientific, USA) fluorometer. Genotyping for single nucleotide polymorphism (SNP) *CYP2C19*2* (681G>A,

rs4244285) was performed using real-time quantitative polymerase chain reaction (qPCR) and Taqman probes (Applied Biosystems; Thermo Fisher Scientific, Inc., HS) according to the manufacturer's protocol.

Statistical analysis

Depending on the variables types and the normality of the distribution, results have been presented as frequency (percent), median (range) and mean±sd. Of the methods for testing the statistical hypotheses, we used: t-test, Mann-Whitney test, chi-square test and Fisher's exact test. All p-values less than 0.05 were considered significant. Statistical data analysis was performed using IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA) and R-4.0.0 software (The R Foundation for Statistical Computing, Vienna, Austria).

Results and Discussion

Demographic characteristics

Our study involved a total of 196 patients diagnosed with ACS. According to the occurrence of adverse CV events during the follow-up period of one year, two groups of subjects were defined. There were 29 patients in the ineffective therapy group and they had an adverse CV event during the follow-up period, while there were 167 patients in the group with effective therapy without adverse CV outcome recorded during one year. The majority of patients with ACS were males 67.9% and 62.1% respectively, while 32.1% and 37,9% were female patients. The mean age of ineffective group patients was 65.2±8.7, while patients in the effective therapy group had a mean age of 65.4±8.5 There were no significant differences in body mass index (BMI) values and smoking between the two groups, nor the alcohol consumption, coffee drinking and physical activity (all $p > 0.05$). The demographic characteristics, daily activities and lifestyle habits of the studied groups are shown in Table 1.

Biochemical and clinical characteristics of the groups

The biochemical characteristics of the two groups of patients suggested that there were no significant differences between the two groups of patients in terms of glucose values, total cholesterol, LDL-c, HDL-c, urea, creatinine, fibrinogen and D-dimer. Additionally, no significance was found for associated diseases, i.e. hypertension and diabetes mellitus, as well as about the administration of concomitant therapy, i.e. taking other drugs such as pantoprazole, metformin, statins and ACE inhibitors (all $p > 0.005$). On the other hand, we found a statistically significant association between atrial fibrillation (AF) and ineffective clopidogrel therapy, i.e. in patients with ACS who had AF, adverse CV events occurred significantly more often, $p = 0.040$, Table 2.

*Association of CYP2C19*2 with clopidogrel effectiveness*

The genotype analysis showed that there was not a significant difference between the two groups in genotype distribution. There was no observable allelic nor genotype association between effective and ineffective therapy group ($p > 0.005$). Genotype distribution, allelic and genotype association with two groups were presented in Table 3.

Table 1. Demographic characteristics and lifestyle activity of two groups

Variables	Total (n=196)	Ineffective therapy group (n=29)	Effective therapy group (n=167)	p- value
Sex, n (%)				
Male	133 (67.9)	18 (62.1)	115 (68.9)	
Female	63 (32.1)	11 (37.9)	52 (31.1)	0.470
Age, mean±SD	65.4±8.5	65.2±8.7	65.4±8.5	0.910
BMI, mean±SD	27.3±4.38	26.7±4.89	27.4±4.29	0.410
Smoking, n (%)	99 (50.5)	15 (51.7)	84 (50.3)	0.887
Alcohol intake, n (%)	76 (38.8)	10 (34.5)	66 (39.5)	0.607
Coffee, n (%)	133 (67.9)	21 (72.4)	112 (67.1)	0.569
Physical activity, n (%)	127 (64.8)	17 (58.6)	110 (65.9)	0.451

BMI- body mass index

Table 2. Biochemical parameters, comorbidities and concomitant therapy of two therapy groups

Variables	Total (n=196)	Ineffective therapy group (n=29)	Effective therapy group (n=167)	p- value
Glucose, median (range)	6.3 (3.4-24.1)	6.3 (3.4-11.3)	6.3 (3.4-24.1)	0.796
Cholesterol, mean±SD	4.84±1.39	5.11±1.35	4.79±1.40	0.269
LDL-c, median (range)	2.83±1.17	2.98±1.15	2.80±1.17	0.455
HDL-c, median (range)	1.17±0.38	1.14±0.38	1.17±0.38	0.685
Urea, median (range)	6.58 (2.40-73.0)	6.60 (4.10-73.0)	6.50 (2.40-60.9)	0.363
Creatinine, median (range)	82.0 (37.0-686)	83.0 (54.0-188)	82 (37-686)	0.997
Fibrinogen, median (range)	3.6 (2.0-9.5)	3.4 (2.0-5.3)	3.6 (2.0-9.5)	0.237
D-dimer, median (range)	1.06 (0.02-16.1)	0.83 (0.02-5.02)	1.1 (0.09-16.1)	0.681
Comorbidities, n(%)				
Hypertension	96 (49.0)	13 (44.8)	83 (49.7)	0.628
Diabetes mellitus	62 (31.6)	7 (24.1)	55 (32.9)	0.347
Atrial fibrillation	29 (14.8)	8 (27.6)	21 (12.6)	**0.040**
Concomitant therapy, n(%)				
Pantoprazole	138 (71.9)	23 (82.1)	115 (70.1)	0.191
Metformin	29 (15.1)	5 (17.9)	24 (14.6)	0.660
Statins	110 (57.3)	17 (60.7)	93 (56.7)	0.692
ACE inhibitor	68 (35.4)	13 (46.4)	55 (33.5)	0.187

SD-standard deviation; LDL-c –low density lipoprotein cholesterol; HDL-c –high density lipoprotein cholesterol

Table 3. *CYP2C19*2* allele and genotype frequency and association with effectiveness of clopidogrel therapy

*CYP2C19*2* polymorphism	Total (n=196)	Ineffective th. group (n=29)	Effective th. group (n=167)	p- value
GG	132 (67.3)	20 (69.0)	112 (67.1)	
GA	60 (30.6)	9 (31.0)	51 (30.5)	0.328
AA	4 (2.0)	0 (0.0)	4 (2.4)	
A allele	68 (17.3)	9 (15.5)	59 (17.7)	0.438
G allele	324 (82.7)	49 (84.5)	275 (82.3)	
Null	64 (32.7)	9 (31.0)	55 (32.9)	0.244
Active	132 (67.3)	20 (69.0)	112 (67.1)	

We did not find an association between the *CYP2C19*2* gene variant and the ineffectiveness of clopidogrel therapy, i.e. occurrence of adverse CV events. Our groups with effective and ineffective clopidogrel therapy did not differ statistically in terms of distribution of *CYP2C19*2* genotypes. Obtained genotypic frequency for *CYP2C19*2* homozygotes (*2/*2) and heterozygotes (*1/*2) in the Montenegrin population was about 2% and 30%, respectively, which is in accordance with findings in other studies on Caucasian subjects (Hulot et al, 2006; Dorji et al, 2019). Similar to our study, findings observed by Ahmed et al (2022), indicate that there was no statistically significant difference in response to clopidogrel in relation to *CYP2C19*2* intermediate and poor metabolizer genotypes, in the Pakistani group of subjects. A large study conducted by Pare et al. (2010) showed that there was no significant difference in the effect of clopidogrel in reducing primary efficacy outcomes in subjects who were heterozygotes and recessive homozygotes for *CYP2C19*2* compared to those who were not carriers of this variant.

On the other hand, several studies have confirmed the existence of an association between the presence of the *CYP2C19* LoFA, primarily *CYP2C19*2,* and poor prognosis and weaker response to therapy in patients treated with clopidogrel. Thus, a study conducted by Mega et al. 2009, pointed out that among subjects who were treated with clopidogrel, carriers of the *CYP2C19* LoFA had significantly lower levels of the drug's active metabolite and a higher degree of adverse CV events compared to non-carriers. Cedillo-Salazar et al. (2019) reported that reduced efficacy of clopidogrel was significantly associated with the presence of *CYP2C19*2* polymorphism in Mexican patients with ACS. Additionally, some very recent studies found an association between clopidogrel effectiveness and the *CYP2C19*2* variant. Namely, analyzing the role of *CYP2C19*2* polymorphism and non-genetic risk factors for the development of adverse CV events during one year of taking clopidogrel, Yu et al. (2021) found that the *CYP2C19*2* gene variant contributes to the risk for the development of adverse CV events in Uygur patients with ACS treated with dual antiplatelet therapy.

The absence of a statistically significant association between the *CYP2C19*2* variant and reduced efficacy of clopidogrel in our study could be explained by the small number of subjects included in the study, while on the other hand, the different results in studies of this type may be a potential reason why pharmacogenetic testing has

not been introduced into clinical practice. The fact is that there is a discrepancy between the obtained results of different studies, which may be a consequence of the involvement and intertwining of different factors that can contribute to different patient responses to the same therapy.

We did not observe significant differences in the values of biochemical parameters between the effective and ineffective groups, nor regarding the concomitant therapy. On the other hand, we found that there were significantly more patients with AF in the group with an ineffective response to clopidogrel. Defined as a long-term heart rhythm disorder, AF is the most common form of clinical arrhythmia and can often coexist with ACS (Ho et al., 2020). Previous research and clinical practice have shown that the combination of ACS and AF represents a complex situation with a three-dimensional risk: coronary, cardioembolic and hemorrhagic (Limbruno et al., 2020). Establishing adequate therapy in cases of concomitant ACS and AF is a clinical challenge. On the one hand, we have dual antiplatelet therapy (DAPT), usually clopidogrel in combination with aspirin, which have the role of preventing unwanted CV events, while on the other hand, oral anticoagulants (OAS) are used to treat AF. It is known that antiplatelet drugs in combination with anticoagulants increase the risk of bleeding. The study conducted by Lamberts et al. (2013) showed that there is 1.5 times a higher risk of excessive bleeding for aspirin and 1.84 times for clopidogrel, compared to anticoagulant alone. On the other hand, there are very few studies that have examined the association of atrial fibrillation with adverse CV events. Our study is the first to have found an association between adverse cardiac events, which are an indirect sign of ineffective clopidogrel therapy, and AF, in the Montenegrin ACS population. Similar to our results, the study by Moltó-Balado et al. (2023) showed that AF was associated with major adverse cardiovascular events (MACE), although they emphasized that additional information is needed to explain this connection. Additionally, these claims were supported by the findings that AF presents a risk for the development of adverse CV events within one year after the revascularization process (Jung et al., 2022).

The authors wish to acknowledge here, that there are some shortcomings of the study, among other things, a relatively small sample. Also, patients were tested only for the *CYP2C19*2* polymorphism and not the other *CYP2C19* variants, that could lead to an inadequate response to clopidogrel, were not included. Additionally, we were not able to carry out platelet aggregometry testing, as a direct method of testing the antiplatelet activity of clopidogrel.

Conclusion

Despite not finding an association between the *CYP2C19* variant and reduced response to clopidogrel, present study showed a significant association between AF and adverse CV events, markers of inadequate response to clopidogrel treatment during the follow-up period. Our findings suggest that the treatment of patients with ACS and AF needs to be more personalized. Although more research is needed to confirm our findings, we believe that atrial fibrillation in patients with ACS can lead to more frequent occurrence of cardiac events and that the effectiveness of clopidogrel in such conditions is reduced, so perhaps in such setting, this drug should be substituted with another antiplatelet agent.

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Authors' contributions

Svetlana Perović

Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Visualization; Writing – original draft.

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Conceptualization; Methodology; Supervision; Validation.

Saša Perović

Conceptualization; Formal analysis; Investigation; Methodology.

Anđelka Šćepanović

Conceptualization; Investigation; Methodology; Supervision; Validation; Writing – review & editing.

Conflict of interest

Authors declare no conflict of interest.

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