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ORIGINAL ARTICLE

CO-EXISTENCE OF *CYP2C19**1/*2 AND *ABCB1c*.3435 CT GENOTYPE HAS A POTENTIAL IMPACT ON CLINICAL OUTCOME IN CAD PATIENTS TREATED WITH CLOPIDOGREL

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ABSTRACT

Clopidogrel, is a standard treatment in the prevention of major adverse cardiovascular events (MACE) in patients with coronary artery disease (CAD). Clopidogrel response is highly variable, mainly due to the presence of polymorphisms in the genes involved in drug metabolism. The aim of this study was to evaluate the association between the presence of the *ABCB1* C3435T and *CYP2C19**2 polymorphism and the clinical outcome in patients with CAD treated with clopidogrel. A total of 96 patients with CAD were included in the study. Genomic DNA from peripheral blood was extracted from all patients with standard phenol/chloroform protocol. The genotyping was performed by Real-Time PCR using TagMan assays. The frequency of the reduced-function allele, in both genes, was higher in patients with negative outcome (36.36% vs 21.15%). A negative clinical outcome and an increased risk for MACE was observed in patients with concomitant inheritance of the *CYP2C19* *1/*2 and *ABCB1* CT genotype vs patients with other genotypes (22.73% vs 9.62%; OR 3.455; 95% CI= [0.936-12.743], p=0.05722. A trend towards higher risk of MACE was also noted in carriers of the *CYP2C19*1/*1* and *ABCB1* CC/CT genotype. Our results support the data on the association of the *CYP2C19 *2* alone, or in combination with the *ABCB1* C polymorphism with the increased risk of MACE. The results also indicate that the presence of *ABCB1* C343T polymorphism might be potentially considered as independent predictor of MACE in patients on clopidogrel. However, these results are preliminary and should be confirmed on a larger number of patients.

***Key words*:** *ABCB1,* clopidogrel, *CYP2C19,* coronary artery disease, *P*-glycoprotein, pharmacogenetics

INTRODUCTION

Cardiovascular diseases are a leading cause of death worldwide. Coronary artery disease (CAD) is the most common type of cardiovascular disease, and for those patients, Percutaneous Coronary Intervention (PCI) with stenting is the standard of care. However, in many cases post-operative patients develop major cardiovascular events (MACE) as cardiac death, myocardial infarction, stroke, and stent thrombosis which are serious concerns (1). According to guidelines, antiplatelet therapy is the first-line option in primary and secondary prevention of most cardiovascular diseases, followed by a thrombotic event, but despite successful treatment, the possibilities for recurrent ischemic events still exist (2, 3). Therefore, the use of drug-eluting stents in combination with dual antiplatelet therapy of aspirin and clopidogrel significantly reduces the incidence of ischemic events and stent thrombosis in patients with CAD (4).

Clopidogrel (adenosine diphosphate receptor $P2Y_{12}$ blocker) is a prodrug that needs to be converted into an active drug by several hepatic cytochrome P450 (CYP) enzymes. For this reason, the activity of these enzymes is assumed as the primary determinant for therapeutic response to this drug. *CYP2C19* plays a key role in the metabolic transformation. The *CYP2C19* gene is highly polymorphic, and therefore the association between *CYP2C19* gene variants and clopidogrel efficacy appears to be clinically actionable. The presence of certain *CYP2C19* polymorphisms can lead to variations in the level of functional proteins that influence the degree of clopidogrel metabolites and promote different inter-individual clopidogrel responses (5, 6). Specifically, the presence of any dysfunctional *CYP2C19* allele (*2,*3,*4,*5) is associated with adverse cardiovascular events, whereas the presence of *CYP2C19* allele (*17) is associated with increased risk of bleeding (7, 8). Guidelines recommend the testing of *CYP2C19*2 *3* and **17* in order to avoid adverse outcomes in patients with CAD treated with clopidogrel (9). According to the presence of reduced-

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function alleles, patients are classified into two clinically significant categories: intermediate metabolizers and poor metabolizers. Due to the insufficient activity of the enzyme these patients are suggested to consider alternative P2Y12 inhibitors (ticagrelor and ticlopidine) (10).

The intestinal absorption of clopidogrel is mediated by ATP-dependent drug efflux pump, and P-glycoprotein, transporting a high variety of molecules across the extra- and intra-cellular membranes. Although it is expressed mostly on the intestinal epithelial cells, an increased expression can alter the bioavailability of clopidogrel. The P-glycoprotein is encoded by the *ABCB1* gene located on chromosome 7 (11). Among several single nucleotide polymorphisms (SNPs) that were examined within this gene, the *ABCB1* C3435T has been shown to have an effect on absorption of clopidogrel (12). Namely, individuals carrying the loss of function allele variant were associated with lower levels of the active drug metabolite and were considered to have a high rate of adverse clinical outcomes (13, 14). However, recent studies have presented conflicting results on the association of the *ABCB1* C3435T and adverse events in patients treated with clopidogrel.

It is known that the pharmacodynamic response of clopidogrel can vary among individuals. Nearly 25% of patients treated with standard doses of clopidogrel experience low ex vivo inhibition of ADP-induced thrombocyte aggregation. The precise mechanism of resistance of clopidogrel is still unclear, although additional factors including epigenetics, demographics, complications and drug-drug interactions may also be involved in the response heterogeneity (15).

The aim of this study was to evaluate the association between the presence of the *ABCB1* C3435T and *CYP2C19**2 polymorphisms and the clinical cardiovascular outcome in post-operative patients with coronary artery disease treated with clopidogrel.

MATERIALS AND METHODS

Study population

A total of 96 patients were included the study. Samples from all patients were derived from the Special Hospital for Surgical Diseases "Filip II" in Skopje, R.N. Macedonia. The demographic and clinical characteristics of the patients enrolled in the study are presented in Table 1.

Table 1. Demographic and clinical characteristics of the patients with coronary artery disease treated with clopidogrel.

Parameter	Total number of patients (N=96)	Patients with positive outcome (N=52)	Patients with negative outcome (N=44)
Demographic characteristics			
Age	60.42±9.05	60.64±9.19	60.16±9.22
Male	59 (61.46%)	33 (63.46%)	26 (59.09%)
Clinical characteristics			
History of myocardial infarction	27 (28.13%)	10 (19.23%)	17 (38.64%)
History of diabetes	48 (50%)	24 (46.15)	24 (54.54%)
NYHA classification*			
Class I	22 (22.92%)	15 (28.85%)	7 (15.91%)
Class II	31 (32.29%)	14 (26.92%)	17 (38.64%)
Class III	41 (42.71%)	22 (42.31%)	19 (43.18%)
Class IV	2 (2.08)	1 (1.92%)	1 (2.27%)
Diagnosis**			
105-06	4 (4.17%)	3 (5.77%)	1 (2.27%)
120-23	54 (56.25%)	32 (61.54%)	22 (50%)
125	17 (17.71%)	8 (15.38%)	9 (20.45%)
135	3 (3.13%)	1 (1.92%)	3 (6.82%)
165-66, 170-74	17 (17.71%)	8 (15.38%)	9 (20.45%)

NYHA classification*
Class I No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
Class II Slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III Marked limitation of physical activity. Comfortable at rest but less than ordinary activity results in fatigue, palpitation or dyspnea.
Class IV Unable to carry out any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Diagnosis**
105-06 mitral and aortal stenosis (rheumatic etiology)
120-23 angina, acute myocardial infarction, complications after myocardial infarction
125 – atherosclerotic cardiovascular disease
135 – aortal stenosis (nonrheumatic etiology)
165-66, 170-74 atherosclerosis, aortal aneurism, other peripheral vascular diseases, arterial embolism and thrombosis

Table 2. Genotype frequencies of *ABCB1* and *CYP2C19* in patients treated with clopidogrel

CYP2C19 / **Genotype**	***ABCB1***	**Positive outcome N=52**	**Observed Frequency (%)**	**HWE Frequency (%)**	**Negative outcome N=44**	**Frequencies (%)**	**Expected Frequencies (%)**	**OR**	**95%**	**p value**
***ABCB1* CC homozygotes**										
*1/*1	CC	9	17.31	17.7	11	4.84	5.4	1.00		
*1/*2	CC	3	5.77	5.0	2	4.55	3.4	0.545	0.074-4.008	0.54819
*2/*2	CC	0	0	0.4	0	0	0.6	0.826	0.015-45.693	1.0000
ABCB1 CT heterozygotes										
*1/*1	CT	19	36.54	32.9	11	25	11.1	1.00		
*1/*2	CT	5	9.62	16.8	10	22.73	9.7	3.455	0.936-12.743	0.05722
*2/*2	CT	3	5.77	2.2	2	4.55	2.1	1.152	0.166-7.990	0.88644
ABCB1 TT homozygotes										
*1/*1	TT	10	19.23	19.6	4	9.09	8.6	1.00		
*1/*2	TT	3	5.77	5.1	3	6.82	7.8	2.500	0.346-18.039	0.35720
*2/*2	TT	0	0	0.3	1	2.27	1.8	7.00	0.237-206.784	0.14323

Clopidogrel was administrated to all patients by the following regimen: a loading dose of 600 mg, on the first day of the treatment, and maintenance dose of 75 mg daily for up to 15 months. The follow up period was > 12 months. The primary endpoint of this study was the occurrence of the first clinical sign of the following MACE. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics committee of the Faculty of Pharmacy- Skopje.

DNA isolation

Genomic DNA was isolated from leucocytes obtained (PBMCs) from 3ml peripheral blood collected by venepunction in vacutainers containing EDTA (Ethylenediaminetetraacetic acid) as an anticoagulant. DNA isolation was performed using the standard phenol/chloroform extraction protocol. Subsequently, the concentration of the obtained DNA was measured with the NanoDrop 2000c UV – Vis spectrophotometer (ThermoFisher Scientific, Wyman Street Waltham, MA USA). DNA purity was verified by UV absorption at 260/280 nm, while DNA integrity was assessed using 1% agarose gel containing ethidium bromide. DNA samples were stored at 4°C.

Genotyping

The genotyping analysis for both polymorphisms *(CYP2C19*2* and *ABCB1* C3435T) was done by Real-Time PCR using the allelic discrimination method on the MxPro 3005P instrument (Agilent technologies, Santa Clara, CA, USA). The amplification and the detection of the specific SNPs alleles were performed using specific TaqMan Drug Metabolism Genotyping Assays according to manufacture recommendations (ThermoFisher Scientific, Foster City, CA, USA). The presence of the SNPs was determined using the MxPro Software v.5.1.

Statistical analysis

The obtained data was analyzed using SPSS software. Genotype distribution for the studied polymorphisms was in correlation with the Hardy-Weinberg equilibrium, according to the X^2 test. X^2 and Fischer exact probability test were used to compare the genotype distributions and allelic frequencies between the patient population and positive/negative outcome. Odds ratios (OR) were calculated with 95% confidence interval limit (95% CI). P value ≤0.05 was considered as statistically significant.

RESULTS

By comparison of the results obtained from the genotyping and clinical presentation of the disease we observed that a negative clinical outcome is more frequent in the subgroup of patients treated with clopidogrel that carry the *CYP2C19* *1/*2 genotype together with the *ABCB1* CT genotype. These results indicate that those patients are at an increased risk of adverse cardiovascular events vs patients who are homozygotes for the normal allele (22.73% vs 9.62%; OR 3.455; 95% CI= [0.936-12.743], p=0.05722 (Table 2). Consequently, allelic distribution of the reduced-function allele, in the *CYP2C19* and *ABCB1* genes, was higher in patients with worse cardiovascular outcome (36.36% vs 21.15%) (Table 3, Figure1). Additionally, in the subgroup of patients presented with the *CYP2C19*1/*1* genotype and co-existence of the *ABCB1* CC or CT genotype, we noted a trend towards higher risk of MACE occurrence compared to patients with the TT genotype (OR=1.316 TT→CT; OR=3.056 TT→CC).

Based on the results from the CYP2C19/ABCB1 genotyping, patents were divided into three groups according to combined genotype/phenotype: extensive metabolizers (EM), intermediate metabolizers (IM) and poor metabo-

Table 3. Allelic distribution of the *ABCB1* and *CYP2C19* polymorphisms in CAD patients treated with clopidogrel

Allele	Patients with positive outcome (N=52)	Patients with negative outcome (N=44)
	number of patients	
***CYP2C19**1/ *ABCB1* C**	36	34
***CYP2C19**1/ *ABCB1* T**	37	28
***CYP2C19**2/ *ABCB1* C**	11	14
***CYP2C19**2/ *ABCB1* T**	11	16

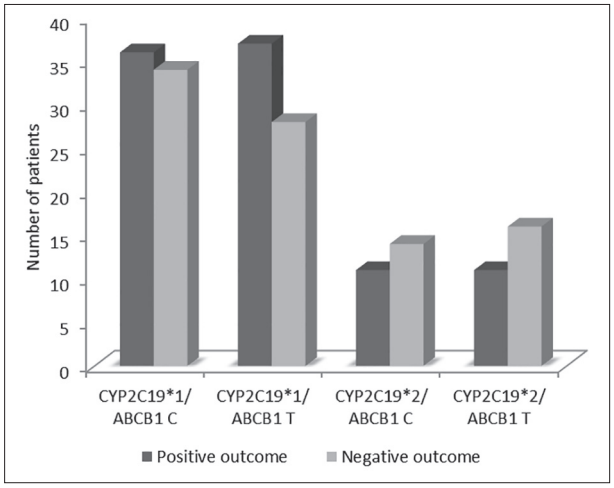

Figure 1. Allelic distribution of *ABCB1* and *CYP2C19* in patients with CAD treated with clopidogrel

lizers (PM) (Table 4). Patients carrying normal function alleles were classified as extensive metabolizers, patients carrying at least one or two loss-of-function allele were classified as intermediate metabolizers, whereas the patients carrying two loss-of-function alleles were classified as poor metabolizers. In the subgroup of patients with negative outcome, the presence of intermediate metabolizers was more frequent compared to the subgroup of patients with positive outcome (0.7272 vs 0.5192; p=0.02805). The frequency of patients referred to as poor metabolizers was higher in the subgroup with a positive outcome (0.2272 vs 0.3077; p=0.22842), but without statistical significance (Table 4). Therefore, the patients classified as intermediate metabolizers, carrying at least one loss-of-function allele were assumed to have higher risk of adverse cardiovascular events or MACE.

DISSCUSION

The main goal of optimal antiplatelet therapy for patients with acute coronary disease and/or undergoing percutaneous coronary intervention is to reduce the incidence of cardiovascular events. The clinical outcome of clopidogrel, as a well-established antiplatelet therapy, has high inter-individual variability within patients

Although recent studies present contradictory data, our results support the association between the presence of the *CYP2C19 *2,* alone or in combination with the *ABCB1* C and an increased risk for adverse cardiovascular events compared to the carriers of the alternative alleles. The concomitant inheritance of the genotype *CYP2C19*1/*2* and *ABCB1 CT* have shown a significant trend toward increased risk for MACE. These finding are line with data presented in the studies conducted on a larger sample size. (16-18)**.**

According to another study *ABCB1* C3435T and *CYP2C19* *2 polymorphisms are recognized as significant, independent predictors for the primary endpoint of cardiovascular death, myocardial infarction or stroke. The presented results indicate that the risk for MACE is higher in patients, either as carriers of a *CYP2C19* or *ABCB1* reduced-function allele, or both (19). In our study it was also demonstrated that patients with normal *CYP2C19* genetic status and presence of the *ABCB1* CT/CC genotype have a higher incidence of MACE, indicating that the presence of the *ABCB1* C allele could be a potential negative predictor for disease outcome in patients treated with clopidogrel.

In a large cohort, conducted on 2208 patients with an acute myocardial infarction receiving clopidogrel therapy,

Table 4. Phenotype frequencies of *CYP2C19* and *ABCB1* in clopidogrel treated patients

Phenotype/ Metabolizer	Patients with positive outcome (N=52)			Patients with negative outcome (N=44)			OR	p
	N	Observed Frequency (%)	HWE Frequency (%)	N	Observed Frequency (%)	HWE Frequency (%)		
Normal*	9	0.1731	0.1872	2	0.0454	0.1673	1.000	
Intermediate**	27	0.5192	0.4909	32	0.7272	0.4834	5.333	0.02805
Poor***	16	0.3077	0.3218	10	0.2272	0.3491	2.812	0.22842

*Carrier of CYP2C19*1/*1/ ABCB1 CC genetic polymorphism
**Carrier of CYP2C19*1/*1/ ABCB1 CT genetic polymorphism
CYP2C19*1/*1/ ABCB1 CT genetic polymorphism
CYP2C19*1/*2/ ABCB1 CT genetic polymorphism
CYP2C19*1/*2/ ABCB1 CC genetic polymorphism
***Carrier of CYP2C19*2/*2/ ABCB1 CC genetic polymorphism
CYP2C19*2/*2/ ABCB1 CT genetic polymorphism
CYP2C19*1/*1/ ABCB1 TT genetic polymorphism
CYP2C19*1/*2/ ABCB1 TT genetic polymorphism
CYP2C19*2/*2/ ABCB1 TT genetic polymorphism

Simon et al., presented no significant association between the *ABCB1* and *CYP2C19* polymorphisms and the clinical outcome, but the presence of two *CYP2C19*-deficient alleles and either one or two *ABCB1* variant alleles was associated with rate of events five times higher when compared to patients with the wild-type (20). Another study also supports the evidence that patients who are poor metabolizers are at greater risk of thrombotic events when treated with clopidogrel (17, 21).

Several studies including the TRITON TIMI study evaluated the contribution of *ABCB1* variants in patient carrying the risk allele *CYP2C19*2* and confirmed that clopidogrel response depends on the complex mechanisms of action, including hepatic activation and also that variable response can occur due to other factors such as polymorphisms in other genes involved in clopidogrel pharmacokinetics and pharmacodynamics.

Since this study was conducted on a small sample size, limitations should be considered when interpreting the results. This was the first conducted study in Macedonia to evaluate the concomitant influence of the *ABCB1*3435 CT and *CYP2C19*1/**2 genotypes on clinical cardiovascular outcomes in coronary artery disease patients on clopidogrel treatment. The evaluation was based on occurred major adverse cardiovascular events and plasma concentrations of clopidogrel, and its active metabolites were not monitored during the follow up. Moreover, we cannot completely exclude the probability that other risk factors, such as BMI, smoking status, lifestyle, diet etc., influence the clinical cardiovascular outcome. However, the main limitation of this study was the small number of patients included, leading to restricted statistical significance for some of the results. Additional, larger studies will be of great importance to further evaluate the relation between concomitant inheritance of the *ABCB1* C3435T and *CYP2C19**2 polymorphisms and clopidogrel treatment outcomes.

CONCLUSION

In summary, our results support the previous data on the association between the presence of the *CYP2C19 *2* alone, or in combination with the *ABCB1* C, and the increased risk of MACE compared to the carriers of the wild type alleles. Namely, a higher incidence of major adverse cardiovascular events was detected in patients with concomitant inheritance of the CYP2C19*1/*2 and ABCB1 CT genotype and in patients with normal CYP2C19 genetic status and presence of the *ABCB1 3435*C allele. The results also indicate that the presence of *ABCB1* C343T polymorphism might be potentially considered as an independent predictor of adverse cardiovascular events in patients treated with clopidogrel. However, this was an initial study conducted on a subset of the Macedonian population, and the results should be confirmed with a larger cohort.

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