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Clopidogrel Response Variability: Impact of Genetic Polymorphism and Platelet Biomarkers for Predicting Adverse Outcomes Poststenting

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The aim of this study was to triage platelet reactivity and adverse vascular outcomes after dual antiplatelet therapy due to percutaneous coronary intervention (PCI) dependent on CYP2C19*2 and CYP2C19*3 genotypes in patients with coronary artery disease. Fifty-five patients with coronary artery disease were studied serially pre-PCI and post-PCI. Platelet reactivity was assessed by conventional light transmission aggregometry, VerifyNow Analyzer, and thromboelastography with platelet mapping. Genetic testing was performed with allele-specific real-time polymerase chain reaction. Adverse events included vascular death, acute myocardial infarction, repeated PCI, definite stent thrombosis, and angina recurrence. The common genotype (GG) was found in 39 patients, heterozygous polymorphism CYP2C19 (GA) G681A allele was detected in 14 patients, and the rare homozygous polymorphism CYP2C19 (AA) G681A allele was exhibited in 2 patients. There were no CYP2C19*3 (Trp212Ter) carriers among index patients. The platelet reactivity was higher in patients with heterozygous and homozygous carriers compared with GG genotype. The largest differences were observed among GG, GA, and AA genotypes, which correlated with the average values of platelet aggregation ($P = 0.02$). There was a significant link between adverse events and high platelet reactivity assessed by light transmission aggregometry ($P = 0.002$). We found a trend between different genotype and VerifyNow readings ($P = 0.057$); moreover, their cumulative impact on adverse events was significant ($P = 0.041$). Platelet reactivity is higher in patients with heterozygous and homozygous carriers of CYP2C19*2 versus common genotype and may predict an increased risk of clopidogrel response variability and/or experiencing adverse cardiac events.

Keywords: clopidogrel, coronary artery disease, genetic polymorphism, antiplatelet therapy, platelet reactivity

INTRODUCTION

Platelet activation and aggregation play a pivotal role in the development of ischemic events in acute coronary syndrome and during percutaneous coronary intervention (PCI).[1] Dual antiplatelet therapy with aspirin and clopidogrel in patients with acute coronary syndrome and PCI significantly reduce the number of such adverse vascular events.

In recent years, enormous attention has been paid to antiplatelet drug resistance. According to several

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reports, the incidence of aspirin resistance ranges from 5% to 45% and that of clopidogrel ranges from 4% to 30%.[2,3] Since the mid-1990s, studies have been conducted to demonstrate heterogeneity of platelet response to aspirin treatment and variability of clopidogrel response.[3–9] Mechanisms of aspirin and clopidogrel resistance are multifactorial, and are still not clear. This can be due to clinical factors (patients' weight, age, diabetes, unauthorized dose reduction or premature withdrawal of the drug, poor absorption, and drug–drug interactions) and cellular mechanisms (accelerated platelet pool formation, decreased metabolic activity, upregulation of P2Y12 or P2Y1, impaired activation P2Y1, and insufficient suppression of catecholamine-induced platelet activation), or other reasons. Despite a large amount of data being available on the clinical significance of gene polymorphisms as a cause of resistance to antiplatelet therapy, currently, this association is not quite clear. There are different genetic variants, but polymorphisms of CYP2C19 system are the most evidence based. Numerous genome-wide studies and their meta-analyses conducted in healthy subjects revealed the link between CYP2C19 system (allele 2 and allele 3) and clopidogrel response variability. Patients who are the carriers of CYP2C19*2 and CYP2C19*3 alleles had a diminished antiplatelet response due to impaired active metabolite formation in the hepatic system, resulting in genetically determined clopidogrel resistance.[10,11]

The aim of our study was to assess the laboratory criteria of antiplatelet therapy effectiveness and the impact of the CYP2C19*2 and *3 genetic polymorphism on the incidence of major adverse cardiac events (MACEs) in patients with stable coronary artery disease after PCI.

METHODS

Patients

The study was conducted at the Bakoulev Centre for Cardiovascular Surgery (Moscow, Russia). The study design was approved by the Ethics Committee of the center. All patients provided a written informed consent. Our study included 55 patients with stable coronary artery disease. All patients underwent elective PCI with DES implantation during dual antiplatelet therapy (aspirin and clopidogrel). Patient demographics and baseline clinical characteristics are presented in Table 1. The risk factors for CAD were defined as current smoking, diabetes mellitus, hypertension (>140/90 mm Hg or use of antihypertensive

Table 1. Baseline clinical characteristics of the study population.

Variables			
Total patients, n = 55	G/G	G/A	A/A
Men/women, n (%)	37 (67)/2 (3.6)	11 (20)/3 (5)	0/2 (3.6)
Age, yrs	59.69 ± 7.14	66.5 ± 7.36	54.63 ± 2.3
Weight, kg	89.38 ± 15.34	86.17 ± 14.1	98
Body mass index, kg/m^2	29.43 ± 4.68	28.82 ± 5.42	35
Smoker, n (%)	21 (38)	12 (21.8)	0
Diabetes mellitus, n (%)	10 (18)	4 (7)	1 (1.8)
Hypertension, n (%)	37 (67)	13 (23.6)	2 (3.6)
Prior myocardial infarction, n (%)	18 (32.7)	10 (18)	1 (3.6)
Prior PCI, n (%)	10 (18)	4 (7)	0
Laboratory data prior PCI			
Hemoglobin, g/L	145.69 ± 12.27	145.35 ± 16.88	135
Platelet count, μ/ml	247.58 ± 58.42	242 ± 60.8	320
Fasting glucose, mg/L	5.83 ± 1.94	5.09 ± 0.55	7.4
Creatinine, mg/dL	91.97 ± 15.61	85.42 ± 9.1	75
Total cholesterol, mmole/L	4.72 ± 1.23	5.58 ± 1.77	6.5
High-density lipoprotein, mmole/L	0.84 ± 0.19	0.92 ± 0.27	1.32
Low-density lipoprotein, mmole/L	2.75 ± 0.92	2.79 ± 1.12	5.3
Triglycerides, mmole/L	1.43 ± 0.7	3.71 ± 5.54	1.15

Values are expressed in percent (%) or mean ± SD.

medications), dyslipidemia (a low-density lipoprotein cholesterol level of ≥3.0 mmole/L or a triglyceride level of ≥2.3 mmole/L or the use of medications for dyslipidemia) and a family history of myocardial infarction. Ten patients had a 1-vessel lesion (18.2%), 19 patients had a 2-vessel lesions (34.5%), and 26 patients (47.3%) were diagnosed with multivessel coronary disease. Exclusion criteria were allergy to aspirin and/or clopidogrel, acute coronary syndrome, recent injuries or massive surgical procedure within 1 month of enrollment, platelet count outside the 100 and 450 × 10^9/L range, hematocrit <30%, hemoglobin <100 g/L, and renal dysfunction (a serum creatinine level of ≥2.0 mg/dL or the use of hemodialysis).

Study design

All patients received aspirin (100 mg once daily) for at least 7 days before PCI, or 325 mg of loading dose on the day of intervention. Clopidogrel 600-mg loading dose was received at least 24 hours before elective PCI. Platelet function tests [light transmission aggregometry (LTA) with 5 μM adenosine diphosphate (ADP), VerifyNow P2Y12 and Aspirin Assay, Thromboelastography with "Platelet Mapping" Kit] were performed before, immediately after PCI, and then serially at 30 days, 3 months, 6 months, and 12 months after elective PCI. Blood sampling pre-PCI was performed just before coronary intervention. All patients underwent PCI with drug eluting stent implantation (Sypher, Cordis, Johnson & Johnson, USA or Taxus, Boston Scientific, USA).

Clinical and laboratory follow-up

After undergoing laboratory sampling and elective PCI, all patients received standard medical therapy and were followed up for a maximum of 30 months (mean 20.1 ± 7.8 months) or until the occurrence of the first clinical endpoint. For laboratory assessment of platelet function in the follow-up period, LTA with 5 μM ADP was evaluated in 30 days, 3 months, 6 months, 12 months after PCI. The composite endpoints included cardiac death, acute myocardial infarction, repeated PCI, stent thrombosis, or angina recurrence.

Platelet function assessment

Potency of dual antiplatelet therapy was evaluated using the following methods:

Light transmission aggregometry

Platelet aggregation was assessed in platelet rich plasma at 37°C with a BIOLA Aggregometer 230 LA (BIOLA Ltd., Moscow, Russia). ADP was used as an agonist at a concentration of 5 μM. Aggregation was expressed as the percentage change in light transmittance from the baseline, with platelet-poor plasma as a reference. Aggregation with 5 μM ADP >45% was defined as laboratory criteria of resistance to dual antiplatelet therapy.

VerifyNow Analyzer

The VerifyNow (Accumetrics, CA) point-of-care system is based on turbidimetric optical detection of platelet aggregation in the whole blood. For the VerifyNow assay, the blood samples for the P2Y12 and Aspirin cartridge were drawn into 1.8-mL blood collection tubes containing 3.2% sodium citrate. The results are reported in P2Y12 reaction units (PRU), which represent the amount of ADP-induced aggregation. PRU levels >208 and percentage of P2Y12 inhibition >23 was defined as criteria of resistance to antiplatelet therapy according to the manufacture's recommendation.

Thromboelastography and "platelet mapping" kit

Thromboelastography (TEG) and platelet mapping were performed according to the manufacturer's guidelines, using the "platelet mapping" kit (Haemoscope Corp, Niles, IL). The maximum amplitude values were labeled as MA. The percentage platelet aggregation (TEG–ADP% and TEG-AA%) represents platelet aggregation in the presence of specific activators as a percentage of thrombin-initiated aggregation. According to reference values of manufacturer MA 47–65 unites, and the criteria of laboratory resistance were MA TEG-ADP% >50%, TEG-AA% >50%.

Genetic testing

Blood samples for genotyping CYP2C19*2 and CYP2C19*3 using allele-specific real-time polymerase chain reaction were collected in all patients after the main phase of study was completed (during the last visit). Genotyping was performed using kits SNP-Express RV "Clopidogrel 1" and "Clopidogrel 2" ("Lytech." Russia) using iCycler IQ5 (BioRad) according to the manufacturer's protocol. With sample extracted DNA, 2 parallel amplification reactions were carried out with 2 pairs of allele-specific primers.

Statistical analysis

All statistical analysis was performed using "Statistica" version 7 software (StatSoft Inc). Continuous variables are presented as mean ± SD, and categorical variables are presented as frequencies and percentage. Significance of the mean value difference was evaluated using Student t test. Using the Pearson χ^2 test, we compared the categorical variables of the groups. For data that were

Table 2. The occurrence and distribution of composite endpoints (n = 10).

Vascular endpoints	Patients, n (%)
Vascular deaths	0
AMI	1 (1.8%)
Recurrent angina	2 (3.6%)
ST with STEMI	3 (5.4%)
ST with NSTEMI	2 (3.6%)
ST with UA	2 (3.6%)

UA, unstable angina.

normally distributed, 1-way analysis of variance (ANOVA) followed by the Student–Newman–Keuls test was used to identify significant differences among the groups with Bonferroni correction. Cumulative survival curves were constructed using the Kaplan–Meier method. The level of statistical significance was defined as $P < 0.05$.

RESULTS

During our study, the incidence of cumulative endpoints in the overall population (n = 55) was 20% (n = 11) including acute myocardial infarction, recurrent angina, stent thrombosis with ST-elevated myocardial infarction and non-ST-elevated MI development, and stent thrombosis with unstable angina (Table 2).

The impact of clinical factors on composite endpoint occurrence

In our study, the rate of MACE was independent of underlying clinical factors (weight, sex, diabetes mellitus, smoking, and the severity of coronary atherosclerosis). However, it should be noted that in 3 patients adverse vascular events occurred after premature discontinuation of clopidogrel, while the remaining 52 patients received dual antiplatelet therapy for >1 year. Importantly, the risk of stent thrombosis in patients truly receiving clopidogrel and aspirin is diminishing over time by the end of the 1-year follow-up. The main adverse endpoints during the 2-year follow-up were less severe angina recurrence and mild myocardial infarction without stent thrombosis. Statistical analysis confirms the trend toward reducing the incidence of stent thrombosis over time (MP $\chi^2 = 7.35$; $P = 0.025$).

Effect of different platelet function test values on composite endpoints

We have analyzed the following parameters of platelet function: 5 μM ADP-induced aggregation with LTA; MA, aggregation arachidonic acid and ADP using TEG; ARU, PRU and presence of P2Y12 by the VerifyNow Assay.

As shown in Table 3, the ANOVA revealed a significant association between 3 platelet function test parameters and the incidence of adverse endpoints. Vascular complications were more common in patients with 5 μM ADP residual platelet aggregation above 48.0 ±

Table 3. The impact of platelet biomarkers on composite adverse outcomes.

Platelet function tests		Mean values in patients without composite endpoints	Mean values in patients with composite endpoints	*P*(*F*)
TEG	MA	60.1 ± 0.60	59.2 ± 1.82	0.52
	AA aggregation%	25.00 ± 2.74	30.55 ± 9.01	0.434
	ADP aggregation%	24.20 ± 2.15	40.28 ± 8.47	0.010
LTA	Prior PCI	38.42 ± 1.81	48.09 ± 4.60	0.028
	Immediately after PCI	51.29 ± 1.95	59.36 ± 3.44	0.064
	30 d	41.5 ± 1.63	49.0 ± 10.0	0.18
	3 mos	38.62 ± 1.51	28.33 ± 16.17	0.134
	6 mos	36.95 ± 1.70	24.67 ± 12.45	0.056
	12 mos	36.86 ± 2.23	24.3 ± 12.73	0.100
VerifyNow	PRU	146.3 ± 8.92	225.4 ± 21.27	<0.001
	Base PRU	382.0 ± 6.62	407.8 ± 15.9	0.100
	% Of P2Y12 inhibition	45.77 ± 3.12	27.36 ± 4.18	0.007

Values presented as mean ± SE; significant differences at $P < 0.05$.
F, Fisher ratio test; MA, maximum amplitude.

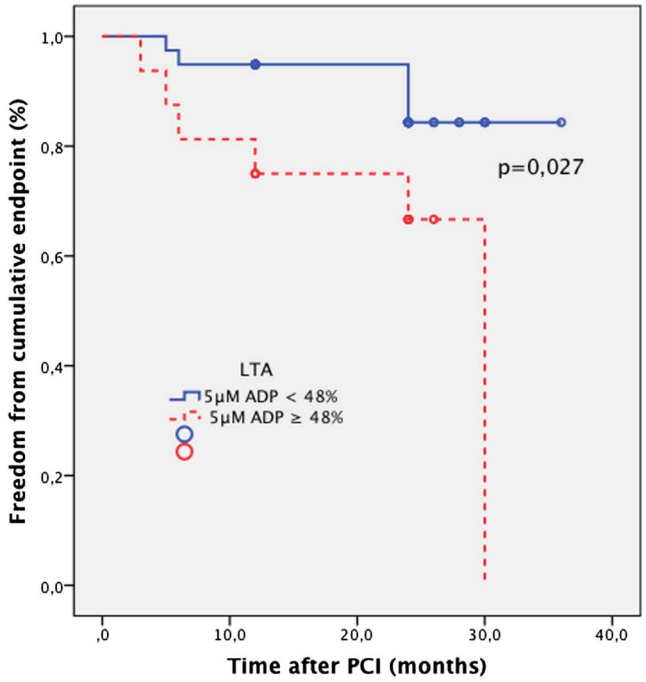

FIGURE 1. Freedom from MACE endpoints dependent on platelet aggregation assessed by LTA.

4.6% ($P = 0.028$)—measured by LTA, PRU level above 225 ± 21 ($P < 0.001$) and percentage of P2Y12 inhibition below 27.3 ± 4.18 ($P = 0.007$) using the VerifyNow Assay. According to the TEG data, a significant association was found between the values—ADP% and development of complications ($P = 0.01$), but the determination of platelet function safety cut-offs is difficult for this method. Survival analysis revealed that patients with values of TEG-ADP% >40% have no significant differences but only a trend in the frequency of MACE ($P = 0.07$). Actuarial freedom from composite endpoints was significantly lower in patients with the level of LTA 5 μM ADP ≥48% ($P = 0.027$) (Figure 1) and the level of PRU ≥225 ($P = 0.00046$) according to the VerifyNow Assay (Figure 2).

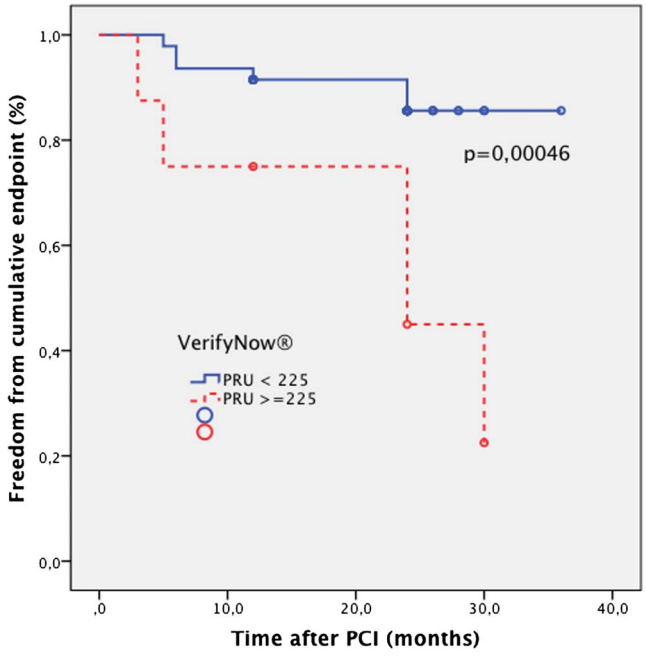

FIGURE 2. Freedom from composite endpoints dependent on the PRU values.

The impact of baseline clinical characteristics and risk factors on platelet reactivity

There was no correlation between different platelet function measurements (LTA with 5 μM ADP, ADP-induced aggregation by TEG, MA, PRU, and % of P2Y12 inhibition) and clinical risk factors such as (sex, smoking history, diabetes, hypertension, or number of affected arteries). Also, the history of prior myocardial infarction had no impact on the level of on-treatment platelet reactivity. The only platelet biomarker that significantly correlated with baseline platelet count ($P = 0.016$) was MA measured by TEG.

The influence of genetic factors on composite endpoint occurrence

After the main phase of the study was completed (during the last visit), we collected blood samples for genotyping CYP2C19*2 and CYP2C19*3 using an allele-specific polymerase chain reaction, after which all patients were divided into 3 groups:

1. CYP2C19*1/*1 (GG)—normal genotype;
2. CYP2C19*1/*2 (GA)—heterozygous carriers;
3. CYP2C19*2/*2 (AA)—homozygous carriers.

In our study, 39 patients had normal CYP2C19*1/*1 genotype (GG), 14 patients were heterozygous (GA), and 2 patients exhibited homozygous (AA) genotype. All 55 patients had no CYP2C19*3 allele (Trp212Ter). Carriage of CYP2C19*2 allele had a significant impact on average levels of TEG-ADP% $P(t) = 0.007$, LTA with 5 μM ADP prior stenting $P(t) = 0.05$, and PRU values $P(t) = 0.022$. As shown in Table 4, the ANOVA did not reveal a convincing evidence of the effects of CYP2C19*2 carriage on cumulative endpoints [Maximum probability (MP) $\chi^2 = 12.83$; $P = 0.38$].

Relationship between platelet biomarkers and cyp2c19 genotypes

LTA with 5 μM ADP and PRU had the most significant impact on adverse endpoints. In patients with normal genotype (GG), the mean values of platelet aggregation had no impact on the possible occurrence

Table 4. The impact of CYP2C19*2 genetic variants on composite endpoint occurrence.

Genetic variants	No composite endpoints	AMI	Recurrent angina	ST + STEMI	ST + NSTEMI	ST + UA	Total
G/G	33	0	2	2	1	1	39
%	84.6	0.00	5.1	5.1	2.6	2.6	
G/A	10	1	0	1	1	1	14
%	71.4	7.14	0.0	7.1	7.1	7.1	
A/A	1	0	0	1	0	0	2
%	50.0	0.0	0.0	50.0	0.0	0.0	
Total	44	1	2	3	2	2	55

A/A, homozygous carriage; G/A, heterozygous carriage; G/G, normal genotype; SA, stable angina; UA, unstable angina.

of post-PCI complications. In contrast, CYP2C19*2 (GA + AA) carriers had an increased average value of platelet aggregation, whereas maximum values were observed in a group with MACE (Table 5, Figure 3).

There was a borderline correlation between PRU values and allelic variants of CYP2C19*2 carriage ($P = 0.057$); however, the occurrence of complications was heavily dependent on PRU values ($P < 0.001$). Assessment of PRU values and CYP2C19*2 (GA + AA) polymorphism cumulative impact on MACE revealed a significant association ($P = 0.041$). The average PRU values in patients with heterozygous and homozygous carriage of CYP2C19*2 were higher compared with those of normal genotype patients, who also exhibited an increased risk of MACE (Table 6, Figure 4).

DISCUSSION

Our study revealed no significant relationship between conventional clinical factors such as weight, sex, diabetes mellitus, smoking, hypertension, and frequency of adverse endpoint occurrence during PCI in patients with CAD. The most likely causes of discrepancies with the previous data[12,13] may be due to a small sample size of our study, and a high incidence of patients with risk factors—particularly smokers and overweight individuals, which is so common in Russia. It should be noted again that in 3 patients vascular complications occurred after premature unauthorized discontinuation of clopidogrel, whereas the rest of the patients received dual antiplatelet therapy for >1 year. The index data are in agreement with the previous evidence and suggest that early discontinuation of antiplatelet agents may cause up to 50% of further adverse events.[5] We also demonstrated that laboratory criteria of high on-treatment platelet reactivity [5 μM ADP-induced aggregation >48% ($P = 0.027$), or PRU >225 according to VerifyNow] had high impact on adverse endpoints occurrence ($P = 0.00046$). Importantly, risk factors per se did not influence the values of platelet biomarkers. These findings are consistent with those of previous studies in patients with stable CAD after

Table 5. Cumulative impact of 5 μM ADP-induced aggregation and CYP2C19*2 polymorphism on composite endpoints (Newman–Keuls test).

	Mean values of 5 μM ADP-induced aggregation			
Groups	Group 1; 37.52 ± 2.13 *P*(*F*)	Group 2; 41.13 ± 3.49 *P*(*F*)	Group 3; 37.67 ± 5.26 *P*(*F*)	Group 4; 60.60 ± 1.72 *P*(*F*)
1		0.808	0.979	0.001
2	0.808		0.553	0.002
3	0.979	0.553		0.001
4	0.001	0.002	0.001	

Group 1, normal CYP2C19 genotype (GG) and no composite endpoints; group 2, normal CYP2C19 genotype (G/G) and composite endpoints; group 3, polymorphism CYP2C19 (G/A + A/A) and no composite endpoints; group 4, polymorphism CYP2C19 (G/A + A/A) and composite endpoints.

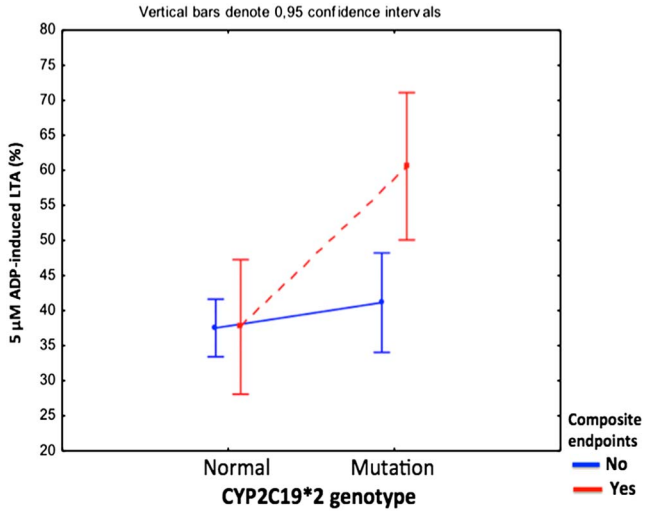

FIGURE 3. Cumulative impact of 5 μM ADP-induced aggregation and CYP2C19*2 polymorphism on MACE.

PCI. The POPULAR trial revealed that increased platelet reactivity is a major risk factor of ischemic events, which is also in agreement with the index data. According to this study, only 3 tests significantly correlated with adverse ischemic outcomes: LTA, VerifyNow, and PlateletWorks. High on-treatment platelet reactivity consistent values: platelet aggregation >42.9% with 5 μM ADP ($P < 0.001$) according to LTA, PRU over 236 according to the VerifyNow ($P < 0.001$), >80.5 according to PlateletWorks test ($P = 0.005$).[14]

One of our tasks was a "blind" determination of CYP2C19*2 and CYP2C19*3 alleles and evaluation of their impact on platelet biomarkers and clinical outcomes. It is well established that clopidogrel is a prodrug that requires biotransformation into active thiol metabolite in the hepatic system. To become active, clopidogrel undergoes transformation with the involvement of different cytochrome P450 system isoenzymes.[15] Isoenzymes CYP2B6, CYP2C9, CYP3A4 \5, and CYP1A2 play a minor role in the biotransformation of clopidogrel.[16–18] In contrast, CYP2C19 plays a crucial role[19–21] for clopidogrel metabolism. The presence of CYP2C19 681 G > A (*2) polymorphism results in a loss of enzyme activity. Other genetic variances of CYP2C19 polymorphism (*3—*8), which are also associated with reduced enzyme activity, have a lower incidence, and therefore, their clinical relevance is uncertain.[10] Several studies suggested the association between genetic polymorphism, antiplatelet potency of clopidogrel, and clinical outcomes. It was shown that the carriers of CYP2C19*2 and CYP2C19*3 allelic variants receiving clopidogrel are at a high risk of developing cardiovascular events compared with patients with wild-type CYP2C19 allele.[22] Studies revealed that patients being homozygous for the CYP2C19*2 allele have a 2.4-fold higher cardiovascular event rate (including cardiac death) compared with noncarriers,[23] and a 3.4-fold increased incidence during PCI.[24] There is an ongoing debate with regard to whether or not CYP2C19*2 homozygous patients have an increased risk of ischemic events. Mega et al[24,25] carried out a meta-analysis comprising 9685 cardiac patient after PCI, and it was demonstrated that the number of advert ischemic events is increasing both in homozygous and in heterozygous patients. However, in our study, analysis of MACE in groups with different allele variants of CYP2C19*2 revealed no significant difference in adverse events. According to our data, for patients with homozygous and heterozygous carriages of CYP2C19*2, the mean values of different platelet biomarkers were significantly higher compared with those holding normal genotype. However, the CYP2C19*2 polymorphism accounts only for 5%–12% of the cases with high ADP-induced aggregation values.[26,27]

Table 6. Cumulative impact of PRU levels and CYP2C19*2 polymorphism on composite endpoint (Newman–Keuls test).

	Mean PRU values			
Groups	Group 1; 147 ± 11 *P*(*F*)	Group 2; 144 ± 12 *P*(*F*)	Group 3; 187 ± 20 *P*(*F*)	Group 4; 271 ± 30 *P*(*F*)
1		0.879726	0.135138	0.000065
2	0.879726		0.158258	0.000225
3	0.135138	0.158258		0.023401
4	0.000065	0.000225	0.023401	

Group 1, normal CYP2C19 genotype (GG) and no composite endpoints; group 2, normal CYP2C19 genotype (G/G) and composite endpoints; group 3, polymorphism CYP2C19 (G/A + A/A) and no composite endpoints; group 4, polymorphism CYP2C19 (G/A + A/A) and composite endpoints.

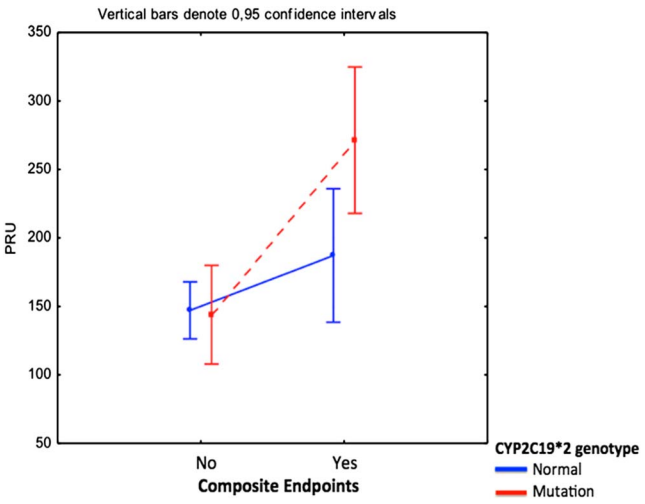

FIGURE 4. Cumulative impact of PRU levels and CYP2C19*2 polymorphism on MACE.

Currently, several studies are conducted or are underway comparing the pharmacogenetic approach to select antiplatelet regimens with traditional methods of applying clopidogrel without preliminary pharmacogenetic testing. There is currently an agreement that the reasonability of genetic or functional test administration for individual selection and correction of antiplatelet therapy has not been proved, and is, therefore, not mandatory. Our data, although small, suggest that laboratory evaluation of platelet reactivity on dual antiplatelet therapy is more reliable than genotyping alone. We demonstrated the impact of laboratory data on MACE, but at the same time, determination of CYP2C19 allelic variants alone has not been proved to be a risk factor of poor prognosis predicting MACE. It seems the idea to evaluate platelet reactivity using LTA, VerifyNow, and "Platelet Mapping" prior to coronary intervention, particularly in high-risk groups holds some promise, and needs to be tested in a randomized trial especially in patients with definite stent thrombosis, complex coronary anatomy, multivessel disease, and those who will use clopidogrel as a single antiplatelet agent. Laboratory resistance in combination with genetic CYP2C19*2 polymorphism may justify the change of clopidogrel to another antiplatelet drug whose metabolism is not associated with the CYP P450 system (e.g., ticagrelor or vorapaxar). In the absence of genetic polymorphism, it may be necessary to analyze other probable causes of high residual platelet reactivity, whose role has been underestimated—especially the influence of proinflammatory factors, hypercholesterolemia, drug–drug interactions, etc.

We conclude that in patients with stable CAD receiving dual antiplatelet therapy, increased baseline mean values of LTA and PRU may indicate an increased risk of MACE after PCI. However, there is no convincing evidence on how different CYP2C19*2 genotypes impact the risk of adverse outcomes. Determination of CYP2C19*2 allelic variants alone as risk factors for vascular complications has not been validated. Elevated platelet reactivity may indeed increase the risk of MACE in heterozygous and homozygous patients. Genetic testing may be substantiated in patients with initially confirmed high platelet biomarkers, but requires validation in randomized trial(s).

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