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Original Article

Incidence of major adverse cardiovascular events with genotype test guided antiplatelet treatment strategy after percutaneous coronary intervention

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ABSTRACT

Objective: To estimate the incidence of major adverse cardiovascular events (MACE) with genotype test-guided antiplatelet therapy in patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndrome.
Methods: Patients who had undergone PCI for acute coronary syndrome as well as stable coronary artery disease were recruited. Salivary samples were obtained from these patients and genotyped for CYP2C19*2, CYP2C19*3 variations by sequencing method (GAAP x method). Patients were categorized as normal (GG, GG) (29%), intermediate (AG) (52%) or poor metabolizes (homozygous variant AA) (19%). Dual antiplatelets were given based on the genotyping data. Poor metabolizes received newer agent (ticagrelor), intermediate metabolizes received double-dose of clopidogrel and normal metabolizes received therapeutic doses of clopidogrel. All subjects were followed-up for six months.
Results: Based on the genotyping data of CYP2C19*2 and CYP2C19*3 variations, it was found that most patients were categorized as 'intermediate' (78, 51.65%), followed by 'normal' (43, 28.48%) and 'poor' metabolizes (30, 19.87%). Only 3 (1.5%) of 151 patients reported MACE at follow-up.
Conclusions: Genotyping for CYP2C19 variations to assess clopidogrel resistance in patients undergoing PCI and subsequent drug selection helps reduce MACE after coronary intervention.

1. Introduction

Antiplatelets are the cornerstone in preventing major adverse cardiac events (MACE) post percutaneous coronary intervention (PCI). Clopidogrel is a P2Y12 receptor antagonist which, upon administration, is metabolized to its active form by hepatic cytochrome P450 system. Platelet inhibition level and inhibition rate of clopidogrel are dose dependent.[1,2] Subgroup enzymes CYP2C19 and CYP3A4/5 of cytochrome P450 enzymes family are most commonly involved in clopidogrel metabolism.[3–5]

Genetic polymorphisms in CYP2C19 impairs clopidogrel metabolism in healthy volunteers and in patients. This poor metabolizer phenotype has also been associated with an increased risk of cardiovascular (CV) events. The CYP2C19*2 genetic variant, 681 G > A (rs4244285), was identified as a major determinant of prognosis in young patients who received clopidogrel treatment after myocardial infarction (MI).[6] Furthermore, patients carrying any two CYP2C19 loss-of-function alleles [*2, *3 (rs4986893), *4 (rs28399504), or *5 (rs56337013)] had higher rates of CV events than patients lacking these alleles.[3,4,7,8] Based on the variable pharmacodynamic response to clopidogrel, patients have been classified as non-responders, poor responders or resistant to clopidogrel. In addition, factors such as age, diabetes, renal failure, and cardiac failure also influence clopidogrel response.[3,7] Evidence shows that the prevalence of clopidogrel resistance in India is in line with the global scenario.[9–11] Based on these findings, Ray, in his review article, suggested the use of higher loading doses of clopidogrel (600 mg) or more potent P2Y12 receptor agents (e.g. prasugrel, ticagrelor, cangrelor) as strategies to overcome clopidogrel resistance.[12]

Switching between P2Y12 receptor antagonists is frequently seen in clinical practice[13,14] as prasugrel and ticagrelor used early-on after a PCI are de-escalated to clopidogrel maintenance to decrease the risk of bleeding and reduce treatment costs.[15] A line of

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evidence shows that CYP2C19 genotyping to guide this de-escalation is effective in optimizing the clinical outcomes in patients undergoing PCI.[16–18] The present study aimed to evaluate the efficiency of genotype test-guided antiplatelet therapy (de-escalating ticagrelor to clopidogrel) on major adverse cardiac outcomes (MACE) in patients undergoing PCI.

2. Methods

2.1. Patient selection and recruitment

This was a non-randomized prospective study conducted at a tertiary-care teaching hospital in India. The study protocol was approved by the hospital ethics committee. Written informed consent was obtained from all study participants before their participation in the trial.

Eligible patients were aged 18 years and above, had undergone PCI for acute coronary syndrome as well as chronic coronary syndrome and required antiplatelet therapy as a part of therapeutic management. Patients were excluded if they presented with a: (i) history of PCI; (ii) history of coronary artery bypass surgery (CABG); (iii) history of using clopidogrel, nonsteroidal anti-inflammatory drugs, and anticoagulants.

2.2. Study procedure

As per the hospital protocol, and in accordance with the current clinical practice guidelines, all the patients were given ticagrelor and aspirin after the procedure. Principal investigator/study coordinator discussed the implications of pharmacogenetic testing and study objectives with the potential patients, and requested them to participate in the study. Consenting patients provided a written informed consent to participate in the study, and study-specific screening was performed on these patients. In all, 151 patients were recruited from this single study center.

At index procedure, saliva samples were collected from the study participants for genotyping CYP2C19 *2 and CYP2C19*3 variation using the Xcode life sciences saliva collection kit[19] and the were sent to 'The XCode Life Sciences Private Limited' laboratory for analysis. The Principal investigator/study coordinator reviewed the results and according to their CYP2C19 *2 and CYP2C19*3 variations, categorized the patients as "normal" (GG, GG), "intermediate" (AG), or "poor" metabolizes (homozygous variant AA). Based on pharmacogenetic testing, antiplatelets were switched to double-dose and single-dose clopidogrel in intermediate and normal metabolizes, respectively. According to the study protocol, patients categorized as normal metabolizes were prescribed therapeutic doses of clopidogrel, and those categorized as intermediate metabolizes were prescribed double the therapeutic dose of clopidogrel. All poor metabolizes were continued on ticagrelor. In patients who were switched from ticagrelor to clopidogrel was given 300 mg of loading dose of clopidogrel 12 h after last dose of ticagrelor. Patients were followed-up for a period of six months. Patients were evaluated during their scheduled clinic visits and were also advised to contact the study personnel if they experienced any adverse events during the study period.

2.3. Study endpoints

The primary clinical outcome was MACE, defined as a composite of CV death, nonfatal MI, definite/probable stent thrombosis (ST), revascularization, stroke or transient ischemic attack (TIA), and clinically significant bleeding event.[20,21]

2.4. Statistical analysis

Continuous and quantitative variables were summarized using descriptive statistics. Categorical data were presented as frequency count (n) and percentages (%). All statistical analyses were performed using SAS (version 9.4).

3. Results

3.1. Patient demography and baseline characteristics

In all, 176 patients were screened and 151 patients were recruited. All enrolled subjects completed the study, which included 128 (84.8%) males and 23 (15.2%) females. Mean age of the male and female population was 54.59 ± 11years and 55.9 ± 11.5 years, respectively. The clinical features and risk factors are presented in Table 1. Diabetes (29.1%) and hypertension (25.2%) were the most commonly seen comorbidities in the study population. Many patients (39.1%) presented with anterior wall myocardial infarction (AWMI), and inferior wall myocardial infarction (IWMI) (22.5%).

Based on the genotyping data of CYP2C19*2 and CYP2C19*3 variations, over half of the patients were categorized as 'intermediate' (78, 51.65%), followed by 'normal' (43, 28.48%) and 'poor' (30, 19.87%). Similar trend was observed in the male and female subgroups (Table 2).

3.2. Major adverse cardiac outcomes

No major bleeding episodes were reported in all patients (151) during the study period and follow-up. Three patients (2.0%) presented with MI, as was confirmed by elevated cardiac troponin levels. Of these three, one patient on ticagrelor presented with probable stent thrombosis and was found to be non-compliant to the antiplatelet treatment. The other two patients were on clopidogrel and had lesions in the non-culprit vessels with patented stents. All these patients underwent coronary angiography (CAG) to confirm the same.

4. Discussion

Clinical outcomes of genotype-guided, de-escalation of antiplatelet therapy have not been well reported in Indian patients. Thus, in our study we attempted to find an incidence of clopidogrel resistance in the south Indian population with genotyping. The present study also attempted to minimize the occurrence of MACE due to clopidogrel resistance in patients undergoing PCI by genotype-guided antiplatelet therapy. In our study, 19.87% of patients were found to be poor metabolizes. This was in line with the previous reports that indicated clopidogrel resistance rate to be between 5% and 56% in a similar population.[22] As it has been reported that adverse CV events occur frequently in patients with clopidogrel resistance, our study was designed to treat poor metabolizes with therapeutic doses of newer antiplatelet agent, ticagrelor,[23] and the intermediate metabolizes with double-dose clopidogrel. This strategy is supported by the CURRENT OASIS 7 study[24] and the VASP-02 study,[25] which reported significantly lower rate of CV death, MI and stroke with this treatment regimen. After one-month follow-up, the CURRENT OASIS 7 study reported MACE of 3.9% in the double-dose group vs. 4.5% in the normal dose group. VASP-02 study reported no MACE in any of the groups. However, 19% of minor bleeding episodes in the double-dose (150 mg/day) group, vs. 22.6% in the normal dose (75 mg/day) group after one-month follow-up were reported.[25]

Table 1
Clinical Features and Risk factors.

Characteristics		Total n = 151	%
Coronary risk factors	Diabetes	47	31.1
	Hypertension	38	25.2
	Smoker	47	31.1
	Alcohol use	44	29.1
	Positive family history	12	7.9
Presentation	AWMI	59	39.1
	IWMI	34	22.5
	NSTEMI	7	4.6
	Atypical angina	3	2.0
	Unstable angina	2	1.3
	Chronic stable angina	11	7.3
	IHD	7	4.6
	CAD	1	0.7
Coronary angiography	SVD	93	61.6
	DVD	26	17.2
	TVD	4	2.6
LMCA disease		2	1.3
LV function	Normal	41	27.2
	LV dysfunction	82	54.3

AWMI, anterior wall myocardial infarction; IWMI, inferior wall myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; IHD, ischemic heart disease; CAD, coronary artery disease; SVD, small vessel disease; DVD, double vessel disease; TVD, triple vessel disease; LMCA, left main coronary artery; LV, left ventricular.

Table 2
Categorisation of Patients based on CYP2C19*2 and CYP2C19*3 Variations.

Gender (n)	Category (n)	Age Mean ± SD	%CV	Age Range
Overall (151)	Normal (43)	55.84 ± 1107	19.82	29–80
	Intermediate (78)	54.61 ± 12.41	22.74	24–86
	Poor (30)	53.73 ± 10.56	19.66	36–75
Male (128)	Normal (38)	55.68 ± 11.65	20.93	29–80
	Intermediate (65)	54.63 ± 12.56	22.99	24–86
	Poor (25)	52.84 ± 9.53	18.03	36–73
Female (23)	Normal (5)	57 ± 5.34	9.37	53–65
	Intermediate (13)	54.54 ± 12.17	22.31	40–75
	Poor (5)	58.2 ± 15.3	26.29	42–75

CYP2C19, Cytochrome P450 2C19.

Three out of 151 patients (1.5%) had MACE during six months of follow-up in our study. Of these three patients, one subject was found to be non-compliant with the antiplatelet therapy and had stent thrombosis. The other two subjects developed thrombotic lesions in the non-culprit vessels with patented stents. Our study did not report any major bleeding complications.

Genotyping for CYP2C19 variations in patients undergoing PCI and the genotyping-guided therapeutic intervention strategy presented to be beneficial in minimizing MACE after coronary intervention.

5. Limitations

The present study is a single center, non-randomized study with a limited sample size and follow-up of 6 months.

Sources of funding

None.

Declaration of competing interest

All authors have none to declare.

What is already Known?

Genetic polymorphisms of CYP2C19 impairs clopidogrel metabolism and has been associated with an increased risk of CV events.

What this study adds?

Genotyping for CYP2C19 variations in patients undergoing PCI and subsequent drug selection helps in reducing MACE after coronary intervention.

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