

Genetic Determinants of CYP2C19 Gene *2 and *3 Loss of Function Alleles and Response to Anti Platelet Therapy (Clopidogrel) and Cardiovascular Events. (A Study in Kashmir, North India)

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Summary

Background: Studies have demonstrated that the mutant *2 and *3 allele of the *CYP2C19* loss-of-function polymorphism is associated with diminished metabolism of clopidogrel and an attenuated platelet response to clopidogrel treatment. Since no such study has been conducted in this region, we examined *CYP2C19* polymorphism in Acute Coronary Syndrome (ACS) patients on clopidogrel treatment, and its effect on the cardiovascular outcomes.

Material and Methods: A total of 100 samples of ACS were included in this study and genotyping of *CYP2C19* *2 and *3 gene polymorphisms was performed by a Polymerase chain reaction-Restriction fragment length polymorphism (PCR-RFLP).

Results: The distribution of *CYP2C19**2 allele wild *1/*1, Heterozygous *1/*2 and homozygous mutant *2/*2 genotypes was 56%, 34% and 10% respectively while for *CYP2C19**3 wild*1/*1 and heterozygous *1/*3 genotypes was 84% and 16% respectively. The frequency of compound heterozygotes (*2/*3) was found in 9% (9 of 100 patients). *CYP2C19* *1/*2 allele was found in 03 of 34 (8.8%) patients who had CV events followed by 2 of 10 (20%) patients with mutant genotype *CYP2C19**2 (*2/*2) on follow up. In the *CYP2C19**3, 31.2% having heterozygous genotype (*1/*3) had CV events as compared to 11.9% with *1/*1 (31% v/s 11.9% $p > 0.05$). In the poor-metabolizer group (*2/*2 or *2/*3), 20.1% of patients had CV events on follow up compared to 15.6% in the extensive metabolizer group (*1/*1), whereas in the intermediate group only 10% of patients had CV events ($p > 0.05$).

Conclusion: We conclude that patients carrying *CYP2C19* loss-of-function alleles had a higher rate of subsequent cardiovascular events as against those with normal allele. Lack of significant events even in presence of variant alleles justifies us to some extent to continue clopidogrel in our patients.

Keywords: Acute Coronary syndrome; *CYP2C19*; Clopidogrel; Poor-metabolizer; Allele

Introduction

The hepatic *CYP2C19* enzyme contributes to the metabolism of many clinically relevant drugs such as antidepressants, benzodiazepines, mephenytoin, some proton pump inhibitors, and clopidogrel. Like many other *CYP450* superfamily members, the *CYP2C19* gene is highly polymorphic, having more than 25 known variant alleles (<http://www.cypalleles.ki.se/cyp2c19.htm>). *CYP2C19**1 represents the wild-type allele. On the basis of their ability to metabolise (S)-mephenytoin or other probe drugs, individuals can be categorized as Extensive Metabolizer (EM), PM (Poor Metabolizer or Ultra rapid Metabolizer (UM) for *CYP2C19*. Heterozygous EMs are sometimes also referred to as Intermediate Metabolizer (IMs) [1]. The majority of the *CYP2C19* PMs are carriers of the variant alleles *2 and *3, which are loss of function alleles (LOF) whereas the *17 variant is a gain of function (GOF) allele associated with increased activity [2]. Studies have shown a marked interethnic variation in the distribution of variant alleles. The allelic frequency of *CYP2C19**2 has been shown to be 15% in Africans, 29–35% in Asians, 12–15% in Caucasians and 61% in Oceanians. The *CYP2C19**3 is mainly found in Asians (5–9% in Asians, less than 0.5% in Caucasians). The allelic frequency of *CYP2C19**17 has been shown to be 16% in Africans, 3–6% in Asians and 16–21% in Caucasians [3].

Clopidogrel is a prodrug whose in vivo metabolite binds to the platelet P2Y₁₂ receptor causing irreversible blockade. The pharmacodynamic response to clopidogrel has substantial interpatient variability [4–7] and patients with coronary disease with lesser degrees of platelet inhibition in response to clopidogrel appear to be at increased risk for cardiovascular events [7–9]. Approximately 85% of

the parent drug is inactivated by human carboxylesterase 1, whereas the remainder is transformed to the intermediate, inactive oxo-clopidogrel by *CYP2C19*, *CYP1A2* and *CYP2B6* [10].

Clopidogrel is an antiplatelet drug used in atherothrombotic diseases, such as myocardial infarction and stroke, which is an inactive prodrug that needs to be bioactivated by a liver enzyme, *CYP2C19*. Several loss-of-function alleles have been previously identified [11]. *CYP2C19**2 and *CYP2C19**3 are the two most frequent variants in Occidentals and Asians, respectively. Major cardiovascular events occur two- to three-times more frequently in patients treated with clopidogrel having decreased *CYP2C19* function compared with wild-type patients after myocardial infarction, stent thrombosis [12–14]. A gene-dose effect seems to occur with the patients heterozygous for one *CYP2C19* variant showing an intermediate clinical response between wild-type patients and patients homozygous for the loss-of-function

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#-Equally Contributed

Received September 03, 2015; **Accepted** October 31, 2015; **Published** November 07, 2015

Citation: Bhat IA, Pandith AA, Faheem S, Yaqoob I, Hafeez I, et al., (2015) Genetic Determinants of CYP2C19 Gene *2 and *3 Loss of Function Alleles and Response to Anti Platelet Therapy (Clopidogrel) and Cardiovascular Events. (A Study in Kashmir, North India). Biol Med (Aligarh) 7: 258. doi: [10.4172/0974-8369.1000258](http://dx.doi.org/10.4172/0974-8369.1000258)

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variants [12]. Identification *CYP2C19* alleles with reduced function has also been associated with reduced responsiveness to, and thus reduced therapeutic benefit of, clopidogrel in cardiovascular patients [12,15-19]. The presence of *CYP2C19* loss of function alleles *2 and *3 may result in lower exposure to Clopidogrel and thus decreased platelet inhibition in clopidogrel treated patients [20]. For this reason FDA issued a Boxed Warning to the clopidogrel label to stress upon the need to identify patients with *CYP2C19* alleles classified as PMs who are considered at an increased risk of adverse cardiovascular outcomes due to reduced effectiveness of clopidogrel [21]. A systematic review and meta-analysis was conducted to examine the association between *CYP2C19* genotype and the clinical efficacy of clopidogrel where it was shown that the presence of at least one loss of function allele was associated with an increased risk of stent thrombosis [22]. Owing to the established role of *CYP2C19* genotype and its relation in anti-platelet (Clopidogrel) therapy, the guiding principles for clopidogrel dosing is still a matter of debate. Besides, ethnic difference exists in both pharmacokinetics and pharmacodynamic and they play an important role in optimization of therapy for the individual patient and drug administration. Since no such study has been conducted in this part, so our investigation will examine the *CYP2C19* polymorphism in our patients on clopidogrel treatment, and its effect on the cardiovascular outcomes in patients with Acute Coronary Syndrome.

Methodology

This study was conducted in Sher-i-Kashmir Institute of Medical Sciences, (Jammu and Kashmir, India) in the Department of cardiology, Immunology and Molecular Medicine and Advanced Centre for Human Genetics for a period of 2 years. Clearance from local SKIMS ethical committee was taken prior to study.

Study subjects

A total of 100 samples were included in this study which comprised of confirmed cases of ACS which were selected from Department of Cardiology, SKIMS. Blood samples were taken from the patients after a written pre informed consent was obtained. Demographic and clinic-pathological characteristics of each patient were recorded in a Questionnaire. Patients were followed over a period of 2 years in Cardiology Out-patient Department (OPD) and also through telephonically to check the compliance of the drug and cardiovascular events like death from any cardiovascular cause, ACS, fatal and non-fatal MI. The patients were included on criteria like ACS with or without undergoing PCI, ST Elevation Myocardial Infarction (STEMI), Non ST Elevation Myocardial Infarction (NSTEMI) and those with Unstable Angina (USA). The patients who include history of bleeding diathesis, stroke less than 3 months platelet count $<70000/\text{mm}^3$, hematocrit $<30\%$ were excluded from the study. Written informed consent was obtained from all the study participants. Patients recruited for the study were put on clopidogrel 300 mg after diagnosed ACS followed by 75 mg OD, and Patients undergoing PCI received 600 mg followed by 150 mg OD for atleast for 7 days and 75 mg later for a period of one year.

DNA extraction and polymerase chain reaction (PCR)

2 -5 ml of blood sample was taken from each patient and stored at -20°C for DNA analysis. Genomic DNA was isolated using standard proteinase-K digestion, phenol/chloroform extraction, and ethanol precipitation method from whole-blood samples of both cases and controls. The primers used were *Cyp19*2* F-5'AAATTGTTTCCAATCATTAGCT-3' and R-5'ACTTCAGGGCTTGGTCAATA-3' whereas for *Cyp19*3* F-5'-

CAGAGCTT GGCA TATTGTAT C-3' and R-5'GTAAACACACA ACTAGTCAA TG-3' producing 321 bp and 271bp PCR products respectively. PCR was carried out in a final volume of 25 μL containing 50 ng genomic DNA template, 1x PCR buffer (Biotools, B and M Labs, Madrid, Spain) with 2 mmol/L MgCl_2 , 0.4 mmol/L of each primer (Genscript, Piscataway, NJ), 50 mmol/L dNTPs (Biotools, B and M Labs), and 0.5 U Taq Polymerase (Biotools, B and MLabs). For PCR amplification, the standard protocol was used as follows: one initial denaturation step at 94°C for 7 minutes, followed by 35 denaturation cycles of 30 seconds at 94°C , 30 seconds of annealing at 53°C , and 30 seconds of extension at 72°C , followed by a final elongation cycle at 72°C for 5 minutes.

Restriction Fragment Length Polymorphism (RFLP)

Two principle alleles of *CYP2C19*2* (rs4244285) and *CYP2C19*3* (rs4986893) were analyzed by PCR-RFLP. Exon 4 and Exon 5 of *CYP2C19* were amplified by PCR that contain the *CYP2C19* *2 and *3 polymorphisms respectively. 681G>A in Exon 5 of *CYP2C19*(*2) creates an aberrant splice site and destroys *SmaI* restriction site and 636G>A in *CYP2C19*3* gene, creates a premature stop codon and abolishes *BamHI* restriction site. 10 μL of PCR amplified DNA were digested with 5 Units of each *SmaI* and *BamHI* (Fermentas Life Sciences, USA) restriction enzymes for both polymorphisms *CYP2C19* *2 and *3 respectively while keeping the other conditions as per instructions of manufacturer. The digested products were electrophoresed using 2% agarose gel and visualized by Ethidium Bromide staining. The PCR products (271bp) of *3 yielded two bands of 175bp and 96bp in wild type and three products of 96, 175 and 271bp in heterozygous variants (Figure 1A). The PCR product (321bp) encompassing allele *2 digested into two smaller bands of 109bp and 212bp in wild type individuals whereas heterozygous variants for this allele yielded three bands of 321, 212 and 109bp and in homozygous variants the PCR product would not be digested (Figure 1B).

Genotyping classification

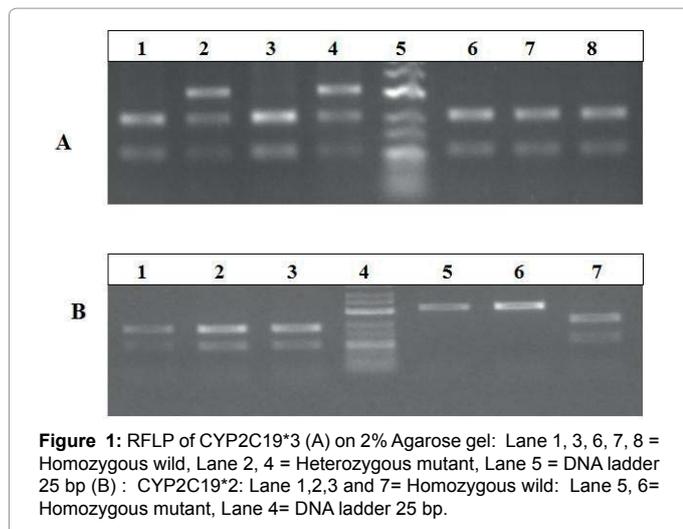
Patients were classified into different metabolizer phenotype groups. Patients with two *CYP2C19*2* or *CYP2C19*3* alleles (*2/*2 or *2/*3) were classified as having the poor- metabolizer phenotype, those with one *CYP2C19*2* or *CYP2C19*3* allele (*1/*2 or *1/*3) were classified as having the Intermediate - metabolizer phenotype and those without *CYP2C19*2* or *CYP2C19*3* allele (*1/*1) were classified as having extensive-metabolizer phenotype.

Statistical Analysis

All continuous variables of study have been shown in terms of Mean \pm SD and the categorical variables in terms of frequency and percentage. The standard statistical tests like T-test. Chi square test and Fischer -exact test have been used to analyze the data, moreover odds ratio with 95% confidence interval have been calculated at appropriate places. All the results obtained have been discussed on 5% level of significance (p value <0.05) considered as significant, also suitable statistical charts have been used to represent the data, SPSS version 20 was used for analysis.

Results

The mean age of our patients was 61.1 ± 8 (range 43 to 75) and majority of patients belonged to age groups of 50-60(38%) and 60-70 years (39%) where 80% of patients were males and 20% females. Hypertension and diabetes mellitus was present in 84% and 39% of patients respectively. Our study included 71% patients with ST Elevation



Myocardial Infarction (STEMI), 20% Non-ST elevation Myocardial Infarction (NSTEMI) and 9% of patients were having unstable Angina (USA) Table 1.

Table 1 shows all the clinical details of Acute Coronary Syndrome (ACS) patients classified with cardiovascular events in different conditions. Ninety two patients went for Coronary Angiography (CAG) after Acute Coronary syndrome (ACS) while as in eight patients CAG could not be done due to financial constraints. Of the 92 patients 69(75%) had single vessel disease (SVD), 13 (14%) of patients had double vessel disease (DVD) and 10 patients had triple vessel disease (TVD).

In our study 15 patients had Cardiovascular events (CV) on follow up in which there were 04 deaths (possible stent thrombosis), 06 patients had definite stent thrombosis, 02 patients had probable stent thrombosis (who presented with MI in the same territory), 02 patients had MI in the same territory who had not undergone percutaneous coronary intervention (PCI) after coronary angiography (CAG) and 01 patient had instant restenosis (ISR) and presented with ACS. The cardiovascular events were noticed over a study period mostly during the first year of follow up.

The distribution of CYP2C19*2 allele wild *1/*1 (no loss of function), heterozygous *1/*2 (Loss of function allele) and homozygous mutant *2/*2 (Total loss of function) genotypes were 56%, 34% and 10% respectively and CYP2C19*3 wild*1/*1, and heterozygous *1/*3 genotypes were 84% and 16% respectively. No patient had homozygous mutant *3/*3 genotype. The frequency of compound heterozygotes (*2/*3) was found in 9% (9 of 100 patients) Table 2.

Frequency distribution of CYP2C19*2 and CYP2C19*3 having different metabolizer phenotypes in ACS patients on clopidogrel and their relation to Cardiovascular Events are shown in detail in Table 3. CYP2C19 *1/*2 allele (loss of function allele) was found in 03 of 34 (8.8%) patients who had CV events, only 2 of 10 (20%) patients with mutant genotype CYP2C19*2 (*2/*2) had CV events on follow up and patients with wild genotype *1/*1, 10 of 56 (17.9%) had CV events. In the CYP2C19*3, 15 out of 16 patients (31.2%) having heterozygous genotype (*1/*3) had CV events as compared to 10 out of 84 (11.9%) with *1/*1 type (31% v/s 11.9% p value 0.061). The distribution of these genotypes among the CV events did not match statistical significance (p<0.05) (Table 3).

In the poor-metabolizer group of patients 20.1% of patients had CV events on follow up compared to 15.6% in the extensive metabolizer group of patients, whereas in the intermediate group only 10% of patients had CV events (Figure 1). All these figures were not statistically significant (p <0.05) (Table 3).

Discussion

Clopidogrel is an antiplatelet drug used in atherothrombotic diseases, such as myocardial infarction and stroke, which is an inactive prodrug that needs to be bioactivated by a liver enzyme, CYP2C19. Several loss-of-function alleles have been previously identified [11]. CYP2C19*2 and CYP2C19*3 are the two most frequent variants in Occidentals and Asians, respectively. CYP2C19 alleles are associated with reduced conversion of clopidogrel to its active metabolite. Many studies support the observations regarding reduced-function of CYP2C19 polymorphisms and platelet aggregation among clopidogrel-treated subjects [20,23,24]. Ethnic difference also exists and they play an important role in optimization of therapy for the individual patient and drug administration. To our knowledge this study is the first from the subcontinent, to investigate the CYP2C19 polymorphism in our patients on clopidogrel treatment, and its effect on the cardiovascular outcomes in patients with acute coronary syndrome.

The present report observed frequency of wild CYP2C19*2, heterozygous *1/*2 and mutant homozygous *2/*2 genotypes as 56%, 34% and 10% respectively while as for CYP2C19*3 wild*1/*1 and heterozygous*1/*3 genotypes were 84% and 16% respectively. Homozygous mutant *3/*3 contributing for loss of function was not found in any case of our study. Nine percent (9%) were compound heterozygotes (*2/*3).

In a study conducted by Dirk et al. [14] on a large sample size, 1805 patients, (73%) were CYP2C19 wild-type homozygotes (*1/*1), 633 (25%) were CYP2C19*2 heterozygotes (*1/*2), and 47 (2%) were homozygous (*2/*2) for the mutant CYP2C19 *2 allele. Despite comparatively small sample size, we observed high frequency of mutant CYP2C19 *2 allele as against Dirk et al. (2% v/s 10% our study). Simon et al. [12] also observed the same pattern of CYP2C19 *2 allele frequency as Dirk et al. [14] and thus both differing more on the frequency of mutant allele *2/*2 (2% Dirk et al. [14] v/s 2.5% Tabossam et al. [12] v/s 10% our study). For CYP2C19*3 allele, although genotype distribution frequency differs from our report (*1/*1; 84%, *1/*3; 16% our study v/s 99% and 1% Tabossam et al. [12]) but both studies report a similar finding where no subject were having mutant (*3/*3) genotype. Prasanthi et al. [25] in northeastern patients of India found 36%, 24% for *1/*1 and *1/*2 respectively with CYP2C19*2 allele and 60% in CYP2C19*3 had *1/*1 genotype which show a complete disagreement with our cohort giving a more evidence for the ethnic difference of this polymorphic gene.

Our patients carrying CYP2C19*2 heterozygous allele *1/*2 had 8.8% CV events and homozygous mutant genotype *2/*2 carriers had 20% against 17.9% CV events in patients with wild genotype *1/*1. Likewise genotype *1/*3 in CYP2C19*3 had 31.2% CV events as compared 11.9% with *1/*1 (31% v/s 11.9%), however, all these figures did not match statistical significance thus disagreeing with many studies [20, 24].

In the poor-metabolizer group of patients 20.1% of patients had CV events on follow up compared to 15.6% in the extensive metabolizer group of patients, whereas in patients in the intermediate group only 10% of patients had CV events. All these figures were not statistically

Characteristic	Patients		Cardiovascular event		p value	
	N=100	%	NO	YES		
Age (yr)	40-50	13	13.0	13(100%)	0(0%)	0.038
	50-60	38	38.0	34(89.5%)	4(10.5%)	
	60-70	39	39.0	30(76.9%)	9(23.1%)	
	70-80	10	10.0	8(80%)	2(20%)	
	Mean ± SD	61.44 ± 8.0				
Gender	Male	80	80.0	68(85%)	12(15%)	1.0
	Female	20	20.0	17(85%)	3(15%)	
Hypertension	Yes	84	84.0	71(84.5%)	13(15.5%)	0.555
	No	16	16.0	14(87.5%)	2(12.5%)	
Diabetes Status	Non Diabetics	61	61.0	52(85.2%)	9(14.8%)	0.574
	Diabetics	39	39.0	33(84.6%)	6(15.4%)	
Smoking Status	Smokers	82	82.0	71(86.6%)	11(13.4%)	0.586
	Non smokers	18	18.0	14(77.8%)	4(22.2%)	
Type of ACS	STEMI	71	71.0	59(83.1%)	12(16.9%)	0.465
	NSTEMI	20	20.0	17(85%)	03(15%)	
	USA	09	9.0	09(100%)	(0)0%	
PCI	PCI	82	82.0	69(84.1%)	13(15.9%)	0.18
	Non-PCI	18	18.0	16(88.9%)	2(11.1%)	
Coronary Arteries with significant disease	SVD	69	69.0	62(89.9%)	07(10.1%)	0.009
	DVD	13	13.0	08(61.5%)	05(38.5%)	
	TVD	10	10.0	07(70%)	03(30%)	
Previous MI	No Previous MI	85	85.0	76(89.4%)	9(10.6%)	0.034
	Previous MI	15	15.0	9(60%)	6(40%)	
Previous PCI	No previous PCI	86	86.0	76(88.4%)	10(11.6%)	0.024
	Previous PCI	14	14.0	9(64.3%)	5(37.7%)	
LV function	Normal LV function	60	60.0	55(91.7%)	5(8.3%)	0.024
	LV dysfunction (< 45%)	40	40.0	30(75%)	10(25%)	

Table 1: Clinical details of Acute Coronary Syndrome (ACS) patients classified with cardiovascular events in different conditions. STEMI: ST Elevation Myocardial Infarction, NSTEMI: Non- ST Elevation Myocardial Infarction, USA: Unstable Angina, SVD: Single Vessel Disease, DVD: Double Vessel Disease, TVD: Triple Vessel Disease, LV: Left Ventricular, MI: Myocardial infarction, PCI: percutaneous coronary intervention

CYP2C19 allele	Genotype	Frequency of genotype n
CYP2C19*2 Allele (rs4244285)	*1/*1 (GG)	56 (0.56)
	*1/*2(AG)	34 (0.34)
	*2/*2 (AA)	10(0.10)
CYP2C19* 3 Allele (rs4986893)	*1/*1 (GG)	84(0.84)
	*1/*3 (AG)	16(0.16)
Compound heterozygous	*2/*3	09 (0.09)

Table 2: Frequency of genotypes with CYP2C19*2 and CYP2C19*3.

significant ($p > 0.05$) and these results were consistent with study of Guillaume [19].

The previous studies other than conducted by Guillaume et al. [19] had shown attenuated benefits of clopidogrel among carriers of loss of function alleles. Our study matched the results of the study conducted by Guillaume et al. [19], although poor metabolizer group of patients had increased frequency of CV events than extensive metabolizer group but could not achieve significance. All these results can be explained to some extent by potential pleiotropic effects of loss of function alleles (independent of their effects on active metabolite of clopidogrel). Moreover since variation of non-CYP genes may also have effect on responsiveness to clopidogrel and the likelihood of ischemic events.

Despite increased prevalence of heterozygous and mutant allele in

our population, we could not see significant CV events in our patients on the basis of CYP2C19 *2 and CYP2C19*3 alleles (loss of function alleles), which justifies us to some extent to continue clopidogrel in our patients, the majority of which belong to low economic class who may not be able to afford the antiplatelet agents like prasugrel and ticagrelor. The FDA has added boxed warning to clopidogrel which is for patients who do not effectively metabolize the drug (poor metabolizers). However this study with comparatively less sample size prompts us to enroll more patients to elucidate whether such approach can be applied to the patients of this geographical area.

Conclusion

We conclude that patients carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events as against those

Allele	Genotype	Cardiovascular Event		Total	P VALUE
		NO	YES		
CYP2C19*2 (rs4244285)	*1/*1 (GG)	46(82.1%)	10(17.9%)	56	0.460
	*1/*2 (AG)	31(91.1%)	03(8.8%)	34	
	*2/*2 (AA)	8(80%)	2(20%)	10	
	TOTAL	85	15	100	
CYP2C19*3 (rs4986893)	*1/*1 (GG)	74(88.1%)	10(11.9%)	84	0.61
	*1/*3 (AG)	11(68.8%)	5(31.2%)	16	
	Total	85(85%)	15(15%)	100	
Compound heterozygote	*2*/3	7	2	9	0.404
Metabolizer Phenotype	Extensive	43(84.4%)	8(15.6%)	51	0.570
	Intermediate	27(90%)	03(10%)	30	
	Poor	15(78.9%)	04(20.1%)	19	
	Total	85	15	100	

Table 3: Frequency distribution of CYP2C19*2 and CYP2C19*3 having different metabolizer phenotypes in ACS patients on clopidogrel and their relation to cardiovascular events.

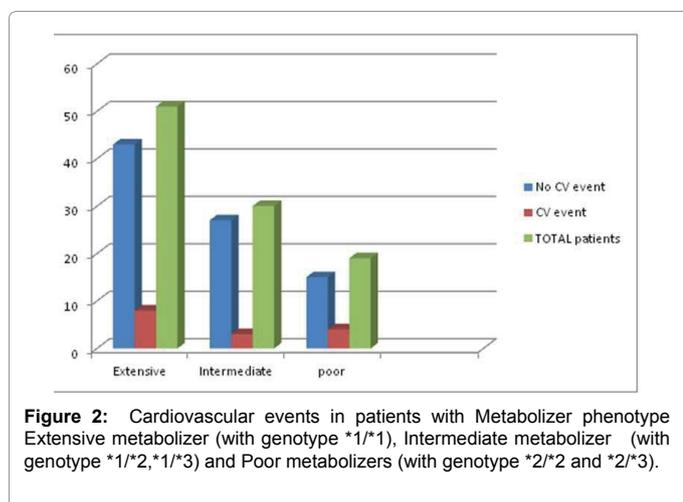


Figure 2: Cardiovascular events in patients with Metabolizer phenotype Extensive metabolizer (with genotype *1/*1), Intermediate metabolizer (with genotype *1/*2,*1/*3) and Poor metabolizers (with genotype *2/*2 and *2/*3).

with normal allele. These events in *CYP2C19* loss-of-function alleles were particularly marked among the patients undergoing percutaneous coronary intervention. Lack of significant events even in presence of variant alleles justifies us to some extent to continue clopidogrel in our patients.

Acknowledgment

We acknowledge with warm thanks the cooperation of the patients of this study as well as the SKIMS administration for funding this study.

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Citation: Bhat IA, Pandith A A, Faheem S, Yaqoob I, Hafeez I, et al., (2015) Genetic Determinants of CYP2C19 Gene *2 and *3 Loss of Function Alleles and Response to Anti Platelet Therapy (Clopidogrel) and Cardiovascular Events. (A Study in Kashmir, North India). Biol Med (Aligarh) 7: 258. doi: [10.4172/0974-8369.1000258](https://doi.org/10.4172/0974-8369.1000258)

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