Evaluation of CYP2C19, P2Y12, and ABCB1 polymorphisms and phenotypic response to clopidogrel in healthy Indian adults

Kannan Sridharan, Rachna Kataria, Drishti Tolani, Shital Bendkhale, Nithya J. Gogtay, Urmila M. Thatte

Abstract:
Introduction: CYP2C19 and P2Y12 polymorphisms have been claimed to alter the pharmacodynamic response to clopidogrel. ABCB1 polymorphism has been associated with the efflux of clopidogrel resulting in decreased bioavailability. Due to paucity of data from Indian population, the present study was undertaken to evaluate the association of genetic polymorphisms of CYP2C19, P2Y12, and ABCB1 with inhibition of platelet aggregation (IPA) by clopidogrel.

Methods: Healthy adults (n = 90) of either gender were administered single dose of 300 mg clopidogrel. Baseline, 4 h postdose, and day 7 assessment of platelet aggregation and genotype of CYP2C19, P2Y12, and ABCB1 were carried out using standardized laboratory methods. The difference in the maximum platelet aggregation (MPA) between baseline and 4 h postdose was considered as delta‑MPA (DMPA), and percentage change of MPA at 4 h from baseline was considered as IPA. Those with an IPA of <30% were considered as poor responders. Inferential statistics was applied to find out significant difference of these parameters between various groups of genetic polymorphisms.

Results: Mean (standard deviation [SD]) of MPA (%) at baseline, 4 h postdose, and day 7 were 78 (5), 56 (16), and 71 (8), respectively. Similarly, mean (SD) of DMPA (%) and IPA (%) were 23 (17) and 29 (21), respectively. A total of 54/90 (60%) cases were found to be poor responders to clopidogrel. A wild genotype (*1/*1) of CYP2C19 was observed in 35 (40.2%), 42 (48.3%) had *1/*2, 2 (2.3%) individuals had *1/*3, and 8 (9.2%) had *2/*2 mutant genotypes. Although statistically not significant (P = 0.09), a trend was observed in having decreased inhibition values (both MPA and IPA) as we proceed from wild genotype (*1/*1) to mutant genotypes in the order of *1/*2, *1/*3, and *2/*2. Similarly, in P2Y12, a wild haplotype (H1/H1) was present in 77 (89.5%) and 9 (10.5%) individuals had H1/H2 type. A statistically significant difference in DMPA and IPA was observed with more IPA by clopidogrel in individuals with H2 haplotype. No association was observed between the carriers and noncarriers of mutant (T) allele of ABCB1.

Conclusion: A trend of decrease in the IPA with CYP2C19 genotypes and an increase in the same with the H2 haplotype of P2Y12 following clopidogrel in Indian healthy adults were observed. Assessment of genetic polymorphisms of the same may aid in personalizing the therapy with clopidogrel.

Key words: Antiplatelet drugs, clopidogrel, genotype, pharmacogenetics, phenotype

Clopidogrel is an inhibitor of platelet aggregation. It antagonizes the activity of adenosine diphosphate (ADP) and is used in clinical practice since 1997 for the management of patients with myocardial infarction, ischemic stroke, and peripheral arterial disease. Clopidogrel binds to ADP receptor (P2Y12), and genetic polymorphisms in P2Y12 gene (H1 and H2) haplotypes affect the phenotypic response to the drug.[3] Furthermore, clopidogrel is a prodrug depending on CYP2C19 for conversion to an active metabolite, 2-oxo-clopidogrel.[3] Polymorphisms in CYP2C19 (*1, *2, and *3) have been shown to affect antiplatelet response of clopidogrel in various studies.[3] ABCB1 C3435T has been shown to hinder with the intestinal absorption of clopidogrel, thereby reducing its antiplatelet activity.[3] However, studies from the Western population were inconclusive regarding

How to cite this article: Sridharan K, Kataria R, Tolani D, Bendkhale S, Gogtay NJ, Thatte UM. Evaluation of CYP2C19, P2Y12, and ABCB1 polymorphisms and phenotypic response to clopidogrel in healthy Indian adults. Indian J Pharmacol 2016;48:350-4.
the changes in the phenotypic effect of this exact mutation in the ABCB1. In recent, platelet aggregation methods have been standardized and the phenotypic activity of clopidogrel can be established by analyzing its activity to decrease the platelet aggregation. Considering the paucity of Indian data regarding the influence of CYP2C19, P2Y12, and ABCB1 genetic polymorphisms on the antiplatelet effect of clopidogrel, we conducted this study in healthy Indian adults.

**Methods**

**Study Ethics and Participants**

The study was initiated following approval from the Institutional Ethics Committee of Seth GS Medical College and KEM Hospital (EC/OA-29/2011) and was registered in the Clinical Trial Registry of India (CTRI/2011/06/001795). As no literature exists regarding the change of delta-maximum platelet aggregation (DMPA) and inhibition of platelet aggregation (IPA) by clopidogrel in Indian population, no formal sample size calculation was undertaken. Adults between 18 and 40 years of age of either gender with an uneventful medical and surgical history, normal hematological (hemoglobin, red blood corpuscle count, white blood cell count, and platelet count) and biochemical (random blood glucose, blood urea, serum creatinine, total and direct bilirubin, aspartate aminotransferase, and alanine aminotransferase) parameters, and a MPA of at least 70% as assessed by platelet reactivity index were recruited in the study after obtaining the written informed consent.

**Study Procedure**

Eligible study participants were asked to come after an overnight fast and a standardized breakfast was given to all the study participants. After half an hour, 20 ml of blood was withdrawn for assessment of baseline MPA and genotyping of CYP2C19, P2Y12, and ABCB1. They were immediately administered 300 mg clopidogrel (4 tablets of Clopivas 75 mg, batch number D 10392 manufactured by Cipla Ltd.). After 4 h of drug administration, 10 ml of blood was withdrawn for postdose MPA. The study participants were closely observed for any adverse event for 8 h, and then discharged from the hospital. Telephonic follow-up of the study participants for any adverse event was done for 24 h period, and the participants were asked to come for a follow-up on day 7 for MPA assessment and any adverse event.

**Genotyping Methods**

Genotyping of CYP2C19, P2Y12, and ABCB1 were carried out as per the methodology described by Adithan et al.,[7] Braun et al.,[8] and Hu et al.,[9] respectively. The primer sequence used for identification of the same is shown in Table 1.

**Phenotyping Method**

Platelet aggregatory response to ADP (20 µM) was studied using the turbidimetric method described by Born[10] on a chronolog platelet aggregocorder.

**Endpoints and Statistical Analyses**

The exact difference in the MPA between baseline and 4 h postdose was considered as DMPA and percentage reduction in the 4 h postdose MPA as compared to baseline was considered as IPA. Those with an IPA of <30% were categorized as poor responders.[11] All the numerical data were assessed for normality using Kolmogorov–Smirnov test. The differences in DMPA and IPA were evaluated between the individuals with various genotypes of CYP2C19 using one-way analysis of variance, and unpaired Student’s t-test was used for the same among P2Y12 haplotypes. Kruskal-Wallis H test was used to assess the statistical significance of DMPA and IPA between various genotypes of ABCB1. Mann–Whitney U-test was applied for assessing the difference of predose, DMPA and IPA between noncarriers (CC) and carriers of T alleles (TC + TT). Chi-square test was used to assess the proportion of poor responders between different genotypes. Trend analysis for the assessment of poor responder status between CYP2C19 genotypes was performed by Chi-square test for trend. Statistical analysis was performed in SPSS version 17.0 (SPSS Inc., Illinois, Chicago, USA). P < 0.05 was considered statistically significant.

**Results**

**Demographic Details**

A total of 90 participants (male:female, 2:1) were enrolled in the present study with the median (range) of age in years of 21 (18–35). None of the study participants had any adverse event with clopidogrel.

**Genotyping**

CYP2C19 genotyping was available for 87 participants, of whom 35 (40.2%) had the wild genotype (*1/*1), 42 (48.3%) had *1/*2, 2 (2.3%) individuals had *1/*3, and 8 (9.2%) had *2/*2 mutant genotypes. P2Y12 genotyping results were available for 86 participants of which wild haplotype (H1/H1) was present in 77 (89.5%) and 9 (10.5%) individuals had H1/H2 and none with H2/H2 type. ABCB1 genotyping results were available only for 55 study participants. A total of 47 (85.5%) participants were identified to carry T allele (23/35 [41.8%] had CT, 24/55 [43.7%]) and the remaining (8/55 [14.5%]) were identified to harbor CC genotype (noncarriers of T allele).

**Phenotyping**

Mean (standard deviation [SD]) of MPA (%) at baseline, 4 h postdose, and day 7 were 78 (5), 56 (16), and 71 (8), respectively. Similarly, mean (SD) of DMPA (%) and IPA (%) were 23 (17) and 29 (21), respectively. A total of 54 subjects (60%) were found to be poor responders to clopidogrel.

### Table 1: Poor responder status with CYP2C19 genotypes and P2Y12 haplotypes

| Gene     | Genotype haplotype | Poor responders, n (%) | Normal responders, n (%) |
|----------|--------------------|------------------------|--------------------------|
| CYP2C19* | *1/*1 (n=35)       | 20 (57.1)              | 15 (42.9)                |
|          | *1/*2 (n=42)       | 25 (59.5)              | 17 (40.5)                |
|          | *1/*3 (n=2)        | 2 (100)                | 0                        |
|          | *2/*2 (n=8)        | 7 (87.5)               | 1 (12.5)                 |
| P2Y12*   | H1/H1 (n=77)       | 49 (63.6)              | 28 (36.4)                |
|          | H1/H2 (n=9)        | 3 (37.5)               | 5 (62.5)                 |
| ABCB1*   | CT/TT (n=47)       | 29 (61.7)              | 18 (38.3)                |
|          | CC (n=8)           | 5 (62.5)               | 3 (37.5)                 |

*P > 0.05 (not significant) by Chi-square test. No statistically significant difference was observed in the number of poor responders between the various genotypes of CYP2C19 and ABCB1 or haplotypes of P2Y12.
Association of Genotyping and Phenotyping

Figure 1 depicts the mean (SD) of DMPA (%) and IPA (%) for different groups of CYP2C19 (*1/*1, *1/*2, *1/*3, and *2/*2). Although statistically not significant (P = 0.09), a trend of decreased inhibition values (both MPA and IPA) was observed as we proceed from wild genotype (*1/*1) to the mutant genotypes in the order of *1/*2, *1/*3, and *2/*2. Furthermore, the proportion of poor responders was not significantly different between the various CYP2C19 genotypes (P = 0.1) [Table 2]. Mean (SD) of DMPA (%) and IPA (%) among carriers (23.8 [17.5] and 30 [22.2]) of any of the mutant alleles (*2/*3) and noncarriers (*1/*1) (21 [15.4] and 27 [19.2]) was not found statistically significant (P = 0.17) [Figure 2].

Figure 3 illustrates the difference in mean (SD) of DMPA (%) and IPA (%) for the haplotypes of P2Y12 (H1/H1 and H1/H2). A statistically significant difference was obtained in both DMPA (P = 0.03) and IPA (P = 0.02) between individuals with H1/H1 and H1/H2 haplotypes. Individuals with H2 haplotype were found to have more IPA following clopidogrel administration. However, the proportion of poor responders was not significantly different (P = 0.2) between the haplotypes [Table 2]. A total of two participants had a combination of mutant alleles in CYP2C19 (*2/*3) and P2Y12 (H2), with the DMPA (%) of 9, 42 and IPA (%) of 13, 59, respectively.

With regard to genotyping of ABCB1, Table 2 depicts the various parameters of platelet aggregation values. It can be observed that there was no significant difference in predose, DMPA or IPA between carriers and noncarriers of T allele. However, when analyzed by genotype group (wild, hetero mutant and homo mutant), a statistically significant reduction in DMPA and IPA was observed for hetero mutant (CT) as compared to wild (CC) and homo mutant (TT) types. A total of 34/55 (61.8%) individuals were identified as poor responders and the proportion of poor responders was not significantly different when analyzed based on either the carrier status or genotype group [Table 2].

Discussion

The present study was done to find out the association of genetic polymorphisms of CYP2C19, P2Y12, and ABCB1 with phenotypic response of inhibiting platelet aggregation following a single dose of 300 mg clopidogrel in healthy adult Indians. We found a trend of decrease in platelet inhibition among individuals with mutant genotypes of CYP2C19. On the other hand, those with H2 haplotype (H1/H2) in P2Y12 had a profound IPA. Nearly 60% of the study participants have been found to be poor responders to clopidogrel, and there was no significant difference observed between various CYP2C19 genotypes or P2Y12 haplotypes or ABCB1 genotypes.

Clopidogrel, one of the commonly used agents in the management of thromboembolic disorders has been found to be associated with high inter-individual variability and around one-third of patients were found to be nonresponsive.[12] Among the various factors contributing to this variability,

Table 2: ABCB1 genotype and phenotypic parameters in health subject taking clopidogrel

| Carrier status/ genotype | Groups | Mean (SD) (%) |
|--------------------------|--------|---------------|
|                          |        | Predose       |
|                          |        | DMPA | IPA       |
| Carrier status           |        |      |           |
| Carriers (CT + TT) (n=47) |       | 78 (4.9)* | 23 (17.7)* | 29 (22.2)* |
| Noncarriers (CC) (n=8)   |       | 77 (5)  | 24 (22.1) | 22 (19.8)  |
| Genotype                 |        |      |           |
| Wild (CC) (n=8)          |       | 77 (5)* | 24 (22.1)*| 30 (28.1)* |
| Hetero mutant (CT) (n=23) |      | 79 (5.2) | 18 (17)   | 22 (19.8)  |
| Homo mutant (TT) (n=24)  |       | 78 (4.8)| 28 (17.2) | 36 (22.5)  |

Carriers with noncarriers of mutant allele (T): *Mann-Whitney U-test - P>0.05 (not significant), Analysis as per genotypes: *Kruskal-Wallis H-test - P=0.04 (significant), *Kruskal-Wallis H-test - P=0.03 (significant). SD=Standard deviation, DMPA=Delta-MPA, IPA=Inhibition of platelet aggregation

Figure 1: CYP2C19 genotype and phenotypic parameters (n = 87).
DMPA = Delta-maximum platelet aggregation, IPA = Inhibition of platelet aggregation, P > 0.05 (not significant) using one-way analysis of variance. No statistically significant difference was observed with either DMPA or IPA between the different genotypes of CYP2C19.

Figure 2: Carriers and noncarriers of mutant allele in CYP2C19 genotype and phenotypic parameters (n = 87). DMPA = Delta-maximum platelet aggregation, IPA = Inhibition of platelet aggregation, P = 0.17 (not statistically significant for both DMPA and IPA between the carriers and noncarriers of mutant alleles)
genetic influence of the enzymes involved in activation (CYP2C19) and metabolism (CYP3A4, CYP3A5, and CYP2C9), transport (ABCB1) and pharmacodynamic target (P2Y12) is the widely studied one. Of these, the present study had assessed the influence of CYP2C19 and P2Y12 polymorphisms with their effect on the degree of platelet inhibition. The allele frequencies of *2 and *3 of CYP2C19 in Asian population have been found to be range between 29–35% and 2–9%, respectively. Depending on the activity, those with *1/*1 genotype in CYP2C19 were termed as extensive metabolizers, *1/*2 as intermediate and the rest (*1/*3, *2/*2, *2/*3 and *3/*3) as poor metabolizers. We found majority of the individuals with *1/*2 genotype (48%) followed by *1/*1 (40%) similar to other studies from the West and India. Although statistically not significant, a trend was observed in decreased response to clopidogrel with mutant genotypes as compared to wild although several other authors have established a significant association either in healthy volunteers or patients. A similar trend was also observed in another study with drug-naive patients of acute myocardial infarction from the same population. This can be either attributed to influence of other genetic factors that were not assessed or an inadequate sample size in the present study. Furthermore, because of the aforementioned reason, we did not find any significant difference between carriers and noncarriers of reduced function alleles. Interestingly, Mega et al. had found that carriers of at least one of these reduced function alleles had a relative reduction of 32.4% of the active metabolite of clopidogrel in their plasma as compared to noncarriers. In addition, the authors in the same study had also found 9% decrease in the MPA among carriers of any of these reduced function alleles. Even the United States Food and Drug Administration (US FDA) has recently revised the prescribing information highlighting the impact of CYP2C19 genotyping with clopidogrel response. The US FDA has even issued a "black-box" warning of reduced effectiveness of clopidogrel in patients with *2 alleles and recommends either initiation of clopidogrel at higher dose or other alternative antiplatelet agent. Considering the prevalence of mutant alleles of CYP2C19 in Indian population, it may be worthwhile to do genetic testing to determine the adequate dose of clopidogrel but there is a paucity of data on the cost-effectiveness of this strategy. Studies evaluating the cost-effectiveness of performing pharmacogenetic testing for clopidogrel administration are the need of the hour to determine their clinical utility, especially in Indian setup. We also found a greater IPA with H2 haplotype of P2Y12 similar to earlier studies. Interestingly, H2 haplotype has been found to be a high-risk factor for coronary artery disease and peripheral arterial disease due to an increased ADP-induced platelet aggregation. Although the combination of H2 haplotype with CYP2C19 mutant genotype has been shown to have altered antiplatelet response following clopidogrel response, we had only two patients in the present study leaving no such conclusions. Similarly, we found no significant differences between the carriers and noncarriers of mutant (T) allele of ABCB1. The results are corroborative to other studies and also from a meta-analysis. However, the meta-analysis found an increased risk of early major adverse cardiovascular events in patients with carriers of T allele in ABCB1 at 3435 position.

The proportion of poor responders to clopidogrel was found to be 60% in the present study similar to other studies. Although variant intestinal absorption, efflux transporter (ABCB1) activity, CYP2C19, and P2Y12 activity have been discussed by various authors as reasons for such nonresponsiveness to clopidogrel, we did not find any association between CYP2C19, P2Y12, and ABCB1 polymorphisms with poor responder status. Higher dose (600 mg) of clopidogrel or other antiplatelet drugs has been recommended by various other authors in such individuals.

The study results should be interpreted with the limitations of not having assessed the influence of other genes involved in the pharmacokinetics of clopidogrel; in addition, in CYP2C19 alleles, presence of *17 (has ultra-rapid activity) was not looked at; patients on clopidogrel have not been included and therefore data on clinical endpoints were not available. To conclude, we found a trend of decrease in the IPA with CYP2C19 genotypes and an increase in the same with the H2 haplotype of P2Y12 following clopidogrel in Indian healthy adults. Assessment of genetic polymorphisms of the same may aid in personalizing the therapy with clopidogrel in patients.

Acknowledgments
We would like to thank Dr. Jaideep Gogtay, Medical Director, Cipla Ltd., Mumbai, for offering clopivas tablets and Ms. Juhi Bhargava (undergraduate medical student), Ms. Madhuri Shewale (postgraduate (M.S.) biotechnology student), Dr. Priya Wagh and Dr. Sudharshan Upadhyay (M.Sc. Pharmaceutical Sciences students) for their help in data collection and Ms. Prajakta Gandhe for her help in genotyping of P2Y12. We also thank the Indian Council of Medical Research for funding this study under Ad-Hoc research grant.

Financial Support and Sponsorship
The study was funded by the Indian Council of Medical Research under Ad-Hoc grant.

Conflicts of Interest
There are no conflicts of interest.
References

1. Fontana P, Dupont A, Gandrille S, Bachelot-Loza C, Reny J, Aiach M, et al. Adenosine diphosphate-induced platelet aggregation is associated with P2Y12 gene sequence variations in healthy subjects. Circulation 2003;108:989-95.

2. Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: A systematic review and meta-analysis. JAMA 2011;306:2704-14.

3. Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, et al. Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol 2008;51:1925-34.

4. Taubert D, von Beckerath N, Grimbarg G, Lazar A, Jung N, Goese T, et al. Impact of P-glycoprotein on clopidogrel absorption. Clin Pharmacol Ther 2006;80:486-501.

5. Su J, Xu J, Zhang H, Hu J, Fang R, et al. ABCB1 C3435T polymorphism and response to clopidogrel treatment in patients with stable angina pectoris scheduled for elective coronary stent placement. Thromb Haemost 2003;89:783-7.

6. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature 1962;194:927-9.

7. Müller I, Besta F, Schulz C, Massberg S, Schöning A, Gawaz M. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. Thromb Haemost 2003;89:783-7.

8. Braun OO, Amisten S, Wihlborg AK, Hunting K, Nilsson D, Erlinge D. Residual platelet ADP reactivity after clopidogrel treatment is dependent on activation of both the unblocked P2Y (1) and the P2Y (12) receptor and is correlated with protein expression of P2Y (12). Puri:ncin Signal 2007;3:195-201.

9. Hu YF, Qiu W, Liu ZQ, Zhu LJ, Liu ZQ, Tu JH, et al. Gene sequence variations of the platelet P2Y12 receptor and the P2Y (12) receptor and is correlated with protein expression of P2Y (12). Puri:ncin Signal 2007;3:195-201.

10. Bates ER, Lau WC, Bleske BE. Loading, pretreatment, and interindividual variability issues with clopidogrel dosing. Circulation 2005;111:2557-9.

11. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature 1962;194:927-9.

12. Bates ER, Lau WC, Bleske BE. Loading, pretreatment, and interindividual variability issues with clopidogrel dosing. Circulation 2005;111:2557-9.

13. Jose R, Chandrasekaran A, Sam SS, Gerard N, Chanolean S, Abraham BK, et al. CYP2C9 and CYP2C19 genetic polymorphisms: Frequencies in the South Indian population. Fundam Clin Pharmacol 2005;19:101-5.

14. Dean L. Clopidogrel therapy and CYP2C19 genotype. In: Medical Genetics Summaries. Bethesda (MD): National Center for Biotechnology Information (US); 2012. Available from: http://www.ncbi.nlm.nih.gov/books/NBK84114/.[Last accessed on 2014 Dec 19].

15. Salazar-Flores J, Torres-Reyes LA, Martinez-Cortes G, Rubi-Castellanos R, Sosa-Macias M, Muñoz-Valle JF, et al. Distribution of CYP2D6 and CYP2C19 polymorphisms associated with poor metabolizer phenotype in five Amerindian groups and Western Mestizos from Mexico. Genet Test Mol Biomarkers 2012;16:1098-104.

16. Panchabhai TS, Noronha SF, Davis S, Shinde VM, Khirsagar NA, Coglay NJ. Evaluation of the activity of CYP2C19 in Gujrati and Marwadi subjects living in Mumbai (Bombay). BMC Pharmacol 2006;6:8.

17. Adithan C, Gerard N, Vasu S, Rosemary J, Shashindran CH, Krishnamoorthy R. Allele and genotype frequency of CYP2C19 in a Tamilian population. Br J Clin Pharmacol 2003;56:331-3.

18. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: A cohort study. Lancet 2009;373:309-17.

19. Shahla KK, Shah VK, Pawar P, Dicekar SS, Payannavar S. Polymorphisms of MDR1, CYP2C19 and P2Y12 genes in Indian population: Effects on clopidogrel response. Indian Heart J 2013;65:158-67.

20. Collet JP, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome p450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-62.

21. Ellis KJ, Stouffer GA, McLeod HL, Lee CR. Clopidogrel pharmacogenomics and risk of inadequate platelet inhibition: US FDA recommendations. Pharmacogenomics 2009;10:1799-817.

22. Cavallari U, Trabetti E, Malerba G, Biscuola M, Girelli D, Olivieri O, et al. Gene sequence variations of the platelet P2Y12 receptor are associated with coronary artery disease. BMC Med Genome 2007;8:59.

23. Fontana P, Guassem P, Aiach M, Fiessinger JN, Emmerich J, Reny J. P2Y12 H2 haplotype is associated with peripheral arterial disease: A case-control study. Circulation 2003;108:2971-3.

24. Guha S, Sardar P, Guha P, Roy S, Mookerjee S, Chakrabarti P, et al. Dual antiplatelet drug resistance in patients with acute coronary syndrome. Indian Heart J 2009;61:1925-34.

25. Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Hackeng CM, et al. Cytochrome P450 2C19 681G>A polymorphism and response to clopidogrel treatment in coronary artery disease (CAD) patients: A meta-analysis. PLoS One 2012;7:e46366.

26. Kshirsagar NA, Gogtay NJ. Evaluation of the activity of CYP2C19 genotypes with clopidogrel response. Indian Journal of Pharmacology 2010;48:482-8.

27. Fonata P, Dupont A, Gandrille S, Bachelot-Loza C, Reny J, Aiach M, et al. Adenosine diphosphate-induced platelet aggregation is associated with P2Y12 gene sequence variations in healthy subjects. Circulation 2003;108:989-95.

28. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature 1962;194:927-9.

29. Müller I, Besta F, Schulz C, Massberg S, Schöning A, Gawaz M. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. Thromb Haemost 2003;89:783-7.

30. Bates ER, Lau WC, Bleske BE. Loading, pretreatment, and interindividual variability issues with clopidogrel dosing. Circulation 2005;111:2557-9.

31. Jose R, Chandrasekaran A, Sam SS, Gerard N, Chanolean S, Abraham BK, et al. CYP2C9 and CYP2C19 genetic polymorphisms: Frequencies in the South Indian population. Fundam Clin Pharmacol 2005;19:101-5.