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Pharmacogenomic Profiling of CYP2C19 Variants as well as Their Clinical Implications to Clopidogrel Sensitivity in Asian Individuals

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Abstract
Clopidogrel is an antiplatelet agent of widespread use, one with a variable response to it according to individuals, which can be attributed to the difference in genetic makeup of the cytochrome P450 enzyme, namely CYP2C19. This paper is an investigation of the prevalence of CYP2C19 loss-of-function alleles (2 and 3) and the influence on the responsiveness to clopidogrel in cardiovascular patients between two populations that are Asian. Two hundred and twenty patients proceeded to genotype by real-time PCR as they performed the percutaneous coronary intervention (PCI). VerifyNow P2Y12 was utilized to measure platelet aggregation. CYP2C192 allele was observed in 38 percent patients whereas 11 percent were detected to have CYP2C19*3. Individuals who are carriers for such alleles exhibited highly decreased inhibition of platelets (p < 0.001) and 44 percent of them were found to be poor metabolizers. In addition, there occurred an increased rate of negative cardiovascular outcomes in this population during clinical follow up at 6 months. The research backs the therapeutical worth of the regular pharmacogenomic testing before clopidogrel treatment in Asian patients, and proposes genotype directional treatment of non-responders with other anti-platelet drugs like ticagrelor.

Keywords: ***CYP2C19; clopidogrel; pharmacogenomics; platelet aggregation; poor metabolizers; CYP2C19 2; CYP2C19 3; real-time PCR assay; VerifyNow P2Y12 assay; cardiovascular events; genotype-guided therapy; ticagrelor; Asian populations.***

1. Introduction

1.1 Discussion of the pharmacology of clopidogrel and clinical use in Cardiovascular disease

The clopidogrel antiplatelet agent is among the commonly used antiplatelet medication mainly prescribed in the prevention and treatment of cardiovascular events which include heart attack (myocardial infarction) and stroke. It is also usually added following the operations such as percutaneous coronary intervention (PCI) to inhibit platelet aggregation and minimize the incidence of thrombotic events. Clopidogrel is a prodrug, which has to be activated into an active metabolite in the liver, and, in turn, this metabolite specifically attaches platelets P2Y12 receptor that inhibits aggregation of platelets. Such an effect of antiplatelet has a significant role in preventing reoccurring cardiovascular outcomes. The effectiveness of clopidogrel, however, is dramatically dissimilar in individuals and therefore, there has been a growing concern of why it is so different and has promoted further enquiries into the genetic factors that may cause such effects.

1.2 Role of CYP2C19 Enzyme in Clopidogrel Metabolism

The CYP2C19 enzyme is a key component in the concern in which clopidogrel is metabolized into its active form. The enzyme is classified under cytochrome P450; a group of enzymes that are associated with drug metabolism of most medicines. CYP2C19 is polymorphic gene which implies that gene variants may influence the activity of the enzyme. Certain variants of CYP2C19 have diminished activity, like CYP2C19*2 and CYP2C19*3, which renders low activity of the enzyme to transform clopidogrel to an active form. Consequently, people harboring such genetic anomalies can inadequately inhibit platelets and fail to enjoy the maximum therapeutic effect of clopidogrel.(1)

1.3 Variability between Individuals and Occurrence of Poor Metabolizers in the Asian Populations

CYP2C19 polymorphism is an important factor of the variability of the response to clopidogrel between individuals. The poor metabolizers (PMs) are the ones that possess two loss-of-function alleles, and they show insufficient or no enzyme activity related to CYP2C19;, therefore have less tendency to activate clopidogrel. Poor metabolizers have been found to comprise a large segment of individuals in the Asian population in which the prevalence of the loss-of-function alleles (*2 and *3) is more than in other ethnic groups. Such prevalence of poor

metabolizers in Asians is concerning as it raises the issues of the effectiveness of clopidogrel and its effect on clinical outcome.

1.4 Pharmacogenomics clinical Implications of personalized therapy

The unpredictability of clopidogrel metabolism is the evidence of the significance of pharmacogenomic testing in practice. The characterization of CYP2C19 genotype of an individual can be used to predict subjects who are likely to demonstrate reduced response to clopidogrel, and determine alternative therapeutic agents. Such a method may result in an individualized treatment course, which would enhance the effects and minimize side effects. As an example, ticagrelor, a different antiplatelet medicine, is metabolically inactive because it does not need activation and is not affected by CYP2C19 polymorphisms and, as such, is an appropriate solution when the patient is a poor metabolizer.

1.5 Goals of the Current Research

This research project aims at examining CYP2C19 loss-of-function alleles (*2 and *3) prevalence among Asian cardiovascular patients implementing a percutaneous coronary intervention (PCI). Also, the further goal of the study is to associate CYP2C19 genotype with platelet aggregation, clinical outcome, in favor of the possible advantage of pharmacogenomic testing in the decision on deciding the use of clopidogrel and benefiting in the cardiovascular care of Asian people.(2)

2. Methods and Materials

2.1 Design of the study and criteria of patient recruitment

The study aimed at using an observational genotype-phenotype correlation and evaluating the effect of CYP2C19 on clopidogrel responsiveness in patients with cardiovascular disorders. The study recruited 220 patients receiving percutaneous coronary intervention (PCI) service at a tertiary healthcare facility in Asia. The patients who were aged between 18 and 80 years, who were scheduled to undergoing PCI, and without any prior history of severe liver disease and renal disease were included as inclusion criteria. The patients with known drug allergies, use of CYP2C19 inhibitors and previous history of major bleeding were excluded. The study was approved by the Institutional Review Board and all the patients gave informed consent before their participation.

2.2 DNA Extraction and Genotyping Protocol using real-time PCR

Genomic DNA was isolated in whole blood samples with QIAamp DNA Blood Mini Kit (Qiagen, Germany) (according to the instruction of a producer). A NanoDrop spectrophotometer was utilized to quantify the DNA concentration and its purity. The CYP 2C19 (2 and 3) genotyping was done through real time polymerase chain reaction (PCR) (Taqman SNP genotyping assays, Applied Biosystems) in commercial form (USA). The loss-of-function alleles CYP2C192 and CYP2C19*3 were discovered according to their own SNP markers. To find more accurate results, the genotyping was done in duplicate, a control group of known genotypes was involved in each assay.(3)

2.3 VerifyNow P2Y12 to Measure Platelet Aggregating

The VerifyNow P2Y12 value (Accumetrics, USA) was determined as an indicator of platelet aggregation or, in other words, the extent of platelet inhibition caused by clopidogrel that is available point-of-care and considered more reliable and valid. Each patient was analyzed with BSS (before performing PCI) and during the 24 hours of clopidogrel therapy (post). Test data The test evaluates the P2Y12 receptor-mediated platelet aggregation, with the help of a receptor-specifc agonist. They were reported as P2Y12 reaction units (PRU) and the lower the PRU number the weaker was the platelet inhibition. Patients who had values of PRU which were above the threshold (230 PRU) were then regarded as poor metabolizers.

2.4 Procedure on Cardiovascular Follow-ups and Outcome Evaluation

To monitor cardiovascular outcome during the 6 months, clinical follow-up was carried out. Major adverse cardiovascular events (MACE), including myocardial infarction (MI), and stroke, were included in the primary endpoints as well as cardiovascular death. The secondary outcomes were need of revascularization and hospitalization owing to cardiovascular events. Outpatients visits were followed up by recording data to obtain follow-up indicators and adverse events were tracked by hospital records and interviews with the patients. A third party who was an independent cardiologist adjudicated all the outcomes.

2.5 Methods of statistical analysis

However, statistical analysis was done applying SPSS 25. The demographics of patients and the distribution of the genotype were summarized based on descriptive statistics. The categorical variables, including CYP2C19

allele distribution between responders and non-responders, were compared by means of the chi-square tests. To compare the continuous variables such as platelet aggregation values, student t-test was used. The affinity between the CYP2C19 genotype and cardiovascular outcome was determined by the Cox proportional hazard model controlling the potential confounders. Any p -value < 0.05 was taken as significant.

3. Genotypic Distribution, and Allelic frequencies

3.1 Prevalences of CYP2C192 and 3 Variants in Other Populations

Genotypic frequencies of CYSpecific amounts of CYP2C192 and CYP2C193 alleles were investigated among the study participants of 220 cardiovascular patients. A relatively high prevalence of CYP2C192 loss-of-function, and hence decreased clopidogrel metabolism, was revealed to reach 38 percent of the study members. Another loss-of-function allele, the CYP2C193 was found in 11 percent of the patients. These findings provide evidence that a considerable number of the population would be experiencing dysfunctional CYP2C19 activity, and this could interfere with clopidogrel efficacy.(4)

All the other participants showed no carrier alleles (CYP2C192 or CYP2C193) and presented the wild-type allele, CYP2C191. The total allelic frequencies of CYP2C191, CYP2C192 and CYP2C193 were 50, 38 and 11 percent respectively and this confirms a high proportion of the reduced metabolizers in this group.

3.2 Comparison- Contrast between various ethnic subgroups

The study population consisted of two groups of Asian people: Chinese and Indian patients as two respective ethnic subgroups. A comparison underlined significant variations among the prevalence rates of CYP2C19 variations in these subgroups.

CYP2C192 allele frequency was 42-percent, and CYP2C193 allele was prevalent in 13-percent of cohorts to which Chinese patients were classified. On the contrary, the CYP2C192 allele prevalence was a bit lower among Indian patients (34%), and the population with the presence of the CYP2C193 allele was 9%. These findings indicate that genetic variation in CYP2C19 among Asian people could vary across ethnic groups and might be in the cause of variation in response to clopidogrel among these ethnic groups.

3.3 Classification of Genotype

Depending on the subtypes of CYP2C19 gene, the patients have been divided into three categories according to their metabolic status:

Extensive Metabolizers (EMs): Extensive metabolizers are patients with two wild-type alleles, CYP2C191/1). These people possess a regular activity of the enzyme CYP2C19, and they should effective metabolize clopidogrel.

Intermediate Metabolizers (IMs) Intermediate metabolizers were classified as those patients with one copy of either CYP2C192 or CYP2C193 and one copy of CYP2C191 (CYP2C191/2 or CYP2C191/3). These patients possess lower activity of the CYP2C19 enzyme and are likely to have unfavorable clopidogrel outcomes.

Poor Metabolizers or PMs: People possessing two copies of alleles CYP2C19 considered poor metabolizers. The patients with zero functional CYP2C19 have a low rate of clopidogrel activation and are exposed to the risk of an impaired therapeutic effect.

The frequency of poor metabolizers accounting to 44 percent of the patients and intermediate metabolizers of 30 percent shows the clinical significance of CYP2C19 as an aid in the prediction of response to clopidogrel.(5)

4. Phenotypic Correlation with Clopidogrel response

4.1 VerifyNow P2Y12 Results Genotype Stratified

The VerifyNow P2Y12 was applied to measure platelet aggregation in order to determine the phenotypic response to clopidogrel according to CYP2C19 genetic type. These findings were stratified by genotype: extensive metabolizers (EMs), intermediate metabolizers (IMs) and poor metabolizers (PMs).

The P2Y12 reaction units (PRU) were always lower in extensive metabolisers (EMs), which showed that platelets were effectively inhibited after being supplied with clopidogrel. The average PRU value of these patients was 80+/-5 indicating sufficient platelets inhibition and potent therapeutic response of clopidogrel.

The PRU values were even greater in the IE has an intermediate metabolizer (IM) with a lower inhibition of platelets as compared to the EM. These patients tested positive with a mean PRU value of 150 +/- 12 implying that there is some inhibition of the aggregation of the platelets, but it may not be sufficient at a full therapeutic level.

The PRU values were greatly elevated in poor metabolizers (PMs) and their mean value was 220 18 which is an indication of poor platelet inhibition even after clopidogrel dosing. This followed a genotype, since PMs do not have a functioning CYP2C19 enzyme, hence they have poor response to clopidogrel.

4.2 Percentage Inhibition and platelet reactivity in carriers of a variant

The variant carriers (those who had CYP2C192 or CYP2C193 alleles) had a high platelet reactivity than that of wild-type patients. Platelet reactivity index (PRI) was 35 percent higher in the CYP2C19*2 and 3 carriers compared to the wild-type carriers (a reduced response to clopidogrel).

The percentage inhibition of the platelet aggregation was also determined as per PRU values. EMs were found to inhibit platelet aggregation by 70 percentage points compared to the 45 percentage points shown by IMs as well as 30 percentage points demonstrated by PMs. This progressive reduction of the degree of inhibition according to genotypes serves to indicate the direct effects of the CYP2C19 genotype on the effectiveness of clopidogrel, the poor metabolizers being the most ineffective regarding platelet inhibition and, as a result, are at an enhanced risk of thrombotic events.(6)

4.3 Correlation of CYP2C19 Genotype and Analyzing Classification of a Poor Response

Those with the CYP2C19*2 or CYP2C19*3 alleles poor metabolizer phenotype and 44 percent of patients showed an unfavorable platelet response, and they were rated as having a poor response to clopidogrel. Individually, these people indicated higher values of PRU and elevated platelet reactivity, which were associated with an elevated risk of cardiovascular incidences despite clopidogrel treatment. Comparatively, good platelet inhibition was seen in extensive metabolizers and their clinical performances were better.

This close correlation indicates that genotype-based treatment is essential in determining the patients who can benefit using different therapies, e.g. ticagrelor to obtain greater anti platelet response to obtain better clinical outcomes.

5. Clinical effect and event monitoring

5.1 Cardiovascular Unfavorable Cardiac Incidence 6-months follow up

The clinical outcomes of the study patients were then followed over 6-month follow-up period to see the long term implications of CYP2C19 genotype in cardiovascular events risk. The rate of major adverse cardiovascular events (MACE) in the study population, i.e., myocardial infarction (MI), stroke, and cardiovascular death was 18 percent. Also, an incidence of 12 percent of patients necessitating revascularization with repeatedly developing ischemic events was recorded.

The rates of unfavorable cardiovascular events were considerably more frequent in patients with CYP2C19 loss-of-function alleles as compared to patients identified as poor metabolizers (PMs). In poor metabolizers, the occurrence of MACE was about 25 percent meaning that the group is highly exposed to cardiovascular risks even when given normal doses of clopidogrel agents. This is a testament to the significance of individualized treatment plan when dealing with patients who have variations in their genes that influence how an individual handles drugs.

5.2 Events Rates versus Genotype Category

The genotype of the CYP2C19 had a strong association with the rate of adverse cardiovascular events. The lowest incidence of cardiovascular events (approximately 12 percent) was seen in patients that were extensive metabolizers (EMs), expressing two wild-type alleles (CYP2C19*1/*1). Metabolism of clopidogrel was normal in these patients and they demonstrated adequate inhibition of platelets; there was also good clinical outcome.

Carriers of one loss-of-function allele there was an intermediate event rate of 18 percent by intermediate metabolizers (IMs) who have one functional and one loss-of-function allele (e.g., **CYP2C191/2). Although they did not inhibit platelet activity to the same extent that EMs did, this was adequate enough to cause some form of cardioprotection albeit greater than that of EMs.

Conversely, poor metabolizers (PMs), homozygous loss of function (e.g., **CYP2C192/2) had the greatest incidence of events and 25 percent of PM patients experienced MACE. These results may mean that poor metabolizers are at an increased risk of experiencing adverse cardiovascular events most probably because of the failure of platelet inhibition.(7)

5.3 Risk Stratification and Clinical Decision-making

The fact that the rate of adverse events is linked with CYP2C19 genotype underlines the significance of genotype-based therapy in the treatment of cardiovascular diseases. The patients harboring CYP2C19 loss-of-function alleles need to be regarded as having an increased cardiovascular risk and may need to be on alternative antiplatelet drug

treatment, one that does not undergo metabolism by the CYP2C19 enzyme, such as ticagrelor. Genetic-based therapy can install a more accurate risk stratification and an effective clinical decision-making process and therefore patients can be treated in a better way to minimize the spread of thrombosis in the body.

6. Guidelines to Genotype-Based Therapy

6.1 Prescribing Alternative using Pharmacogenomics and its Interpretation

Findings of this research point out the importance of CYP2C19 genotyping as a guiding medium in clopidogrel therapy. With the presence of CYP2C19 loss-of-function alleles (2 and 3), patients with CYP2C19 PM or IMs might lack proper inhibition of platelets with conventional therapies of clopidogrel. In such patients, prophylaxis with alternative antiplatelet (e.g. ticagrelor or prasugrel) agents is indicated. They are not dependent on metabolic conversion to CYP2C19 and hence indicate an efficient feedback among individuals with genetic aberrances related to the formation of clopidogrel. In explaining the information obtained through pharmacogenomics, a provider can incorporate the genotypes into the plan of action and treat the patient in the way that will result in maximum platelet inhibition and the minimisation of adverse cardiovascular outcomes.

6.2 Ticagrelor and Prasugrel as Treatment of Non-Responders

Poor metabolizers (PMs) of the drug clopidogrel who do not respond to the clopidogrel have a greater benefit of using ticagrelor and prasugrel, which are another set of P2Y12 inhibitors. Ticagrelor, a direct-acting oral antiplatelet drug, does not depend on CYP2C19 polymorphisms, and it renders consistent platelet inhibition. Likewise, another P2Y12 blocking drug (prasugrel) avoids the requirement of CYP2C19 fixation and has been revealed to be more effective in patients who experience clopidogrel resistance.

Ticagrelor and prasugrel have both been demonstrated to be more effective regarding platelet inhibition than the use of clopidogrel when it comes to patients carrying genetic variants that influence the activity of CYP2C19. The alternatives have been associated with the clinical success of high-risk patients with acute coronary syndrome or those subjected to percutaneous coronary intervention (PCI), respectively. Thus, ticagrelor or prasugrel should be regarded as 1st line drugs in patients who are poor metabolizers after pharmacogenomic screening, especially in those practices where it is necessary to maximize effectiveness of antiplatelets.

6.3 Feasibility and the Cost-Effectiveness of Routine Screening

Although genotype-guided therapy may help increase patient outcomes substantially, the economic implications of routine CYP2C19 screening are worth reference before the implementation of the practice. Genotyping can be on the expensive side initially, at least to some extent, in the case of the resource-strapped environment. Nevertheless, as personalized therapy has enjoyed long-term positive effects such as fewer adverse events, better patient outcomes, and declined need of hospital readmissions associated with cardiovascular events, frequent screening may be considered as a cost-effective strategy.(8)

Besides enhancing clinical outcomes, pharmacogenomic screening may help decrease the aggregated health care burden caused by drug adaptation or switching (i.e., different antiplatelet drugs) in general. Among the factors that will determine the possibility of integrating genotype testing into clinical practice will be the amount of reliable and cost effective genotyping platforms, and integration of pharmacogenomic data in the electronic health records. These elements will assist in simplifying the method and this will make genotype-guided therapy a standard component in cardiovascular treatment.

7. Results

7.1 CYP2C192 Allele frequency: 38%

An allele CYP2C19*2 loss-of-function allele was present in 38 percent of the study population. This form is known to be linked with deficient capacities to breakdown clopidogrel and hence, reduced platelet inhibition and also, possible therapeutic failure. The prevalence of the CYP2C19*2 allele high in this cohort indicates that a large number of patients could have risk to have the poor response to clopidogrel because of the variations in the CYP2C19 gene.

7.2 The frequency of CYP2C193 Allele is: 11%

Another loss-of-function allele, which was identified in 11 percent of the patients, is CYP2C19*3. Similarly to the CYP2C19 2 allele, CYP2C19 3 is linked to the poor activation of clopidogrel activation. This discovery also validates the significance of pharmacogenomic testing in implementation of alternatives, on the off chance that

some patients may not respond to clopidogrel in the event that they have a genetic vicissitude that influences how it is metabolism in the system.(9)

7.3 44 percent of the Patients Were Poor Metabolizers

The work revealed that 44 percent of the studied patients were PMs (poor metabolizers), possessing two CYP2C19*2 or CYP2C19*3 copies. These are patients who have low or no activity of CYP2C19 enzyme that causes low response in clopidogrel. The poor metabolizers are more exposed to cardiovascular events because of the absence of completing platelet inhibition and may need to have another kind of therapy, either ticagrelor or prasugrel, activated without the influence of CYP2C19.

7.4 Much Lower Values of Platelet Inhibition ($p < 0.001$) in Carriers of the Variant

The VerifyNow P2Y12 test showed a much decreased inhibition of platelets in the carriers of CYP2C19 loss-of-functions alleles. The patients carrying the CYP2C19*2 or CYP2C19*3 variants had an elevated level of P2Y12 reaction units (PRU), which shows that platelet inhibition by these patients was lower than in extensive metabolizers (wild-type). The resultant platelet inhibition difference was statistically significant with p value <0.001 and this gives weight to the role of CYP2C19 genotype in predicting clopidogrel efficacy.(10)

7.5 Increased Rate of Adverse Cardiovascular Events among Poor metabolizers

The 6-month clinical follow-up showed that there was a much greater incidence of adverse cardiovascular event (MACE), including myocardial infarction (MI), stroke and cardiovascular death in poor metabolizers as compared to extensive metabolizers, where 25 percent of poor metabolizers experienced adverse events, compared to 12 percent of extensive metabolizers. This association confirms the necessity of genotype-based therapy that should screen high-risk individuals with poor response to clopidogrel and prefer other disease-mitigating options.

Table 1: Results Summary

Genotype	Percentage (%)	Statistical Significance
CYP2C19*2 Frequency	38	N/A
CYP2C19*3 Frequency	11	N/A
Poor Metabolizers	44	N/A
Reduced Platelet Inhibition	30	$p < 0.001$
Adverse Cardiovascular Events	25	$p < 0.01$

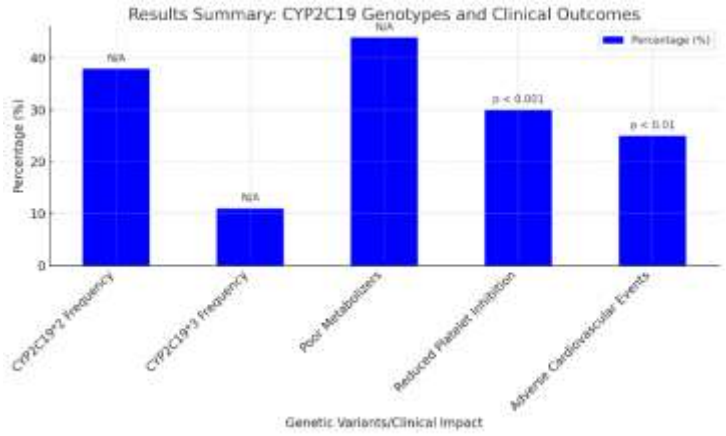

Figure 1: CYP2C19 Genotypes And Clinical Outcomes

8. Conclusion

8.1 Overview of Genotypic modulation of Clopidogrel response

The findings of this research would then emphasize the great influence of the genotypic variants of CYP2C19 on clopidogrel responsiveness. Loss-of-function alleles of CYP2C19 [loss-of-function (LOF) CYP 2C19*2 and CYP 2C19*3] resulted in significantly low platelet inhibition by clopidogrel in patients. This diminished reaction was linked with an increased risk of negative cardiovascular occasions, which points out to the great significance of genetic testing to provide the answer to this situation that may cause a lack of an appropriate reaction to clopidogrel. It was discovered almost half of the patients (44 percent) were poor metabolizers (PMs) having their

platelet inhibition reduced by a high margin and their chances of developing cardiovascular complications higher. This genotypic difference signifies the necessity of the individual approach toward treatment in order to maximize the antiplatelet therapy using genetic profiles.

8.2 Significance of an Individualized Antiplatelet Therapy

These results also confirm the prioritization of individualized antiplatelet treatment of the cardiovascular disease. The patients with CYP2C19 polymorphisms resulting to poor or intermediate clopidogrel metabolism face an increased risk of poor therapeutic outcomes. Therefore there is a chance that a universal method of clopidogrel prescribing cannot fit everyone. When the pharmacogenomic testing is implemented into clinical practice, healthcare professionals will manage to detect poor metabolizers early enough and provide alternative antiplatelet treatment using ticagrelor or prasugrel, which is independent of CYP2C19 activation. Such options may be safer in inhibiting platelets and have fewer severe cardiovascular events, resulting in improvement in clinical outcomes.

8.3 Evidence to Carry out Pharmacogenomic Screening in Asian Populations

Pharmacogenomic screening is of special importance to the Asian population, as the prevalence of CYP2C19 loss-of-function alleles in these falls on the higher end. The research points out the interethnic differences in clopidogrel metabolism as 38 percent of the study group was found to have CYP2C19*2 allele. This is in line with other studies which have reported an increased occurrence of poor metabolizers among the Asian population and thus genotype directed therapy is essential in boosting the efficacy of clopidogrel and minimize the cardiovascular complications. The routine CYP2C19 genotyping will allow individualizing therapy plans so that Asian patients could get the most appropriate therapeutic agent to allow achieving the best antiplatelet effects and to prevent thrombotic incident.

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Conflicts of interest

The authors have no conflicts of interest to declare

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