# CYP2C19*2 and Other Allelic Variants Affecting Platelet Response to Clopidogrel Tested by Thrombelastography in Patients with Acute Coronary Syndrome

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## Abstract

**Background:** To investigate the contributions of CYP2C19 polymorphisms to the various clopidogrel responses tested by thrombelastography (TEG) in Chinese patients with the acute coronary syndrome (ACS).

**Methods:** Patients were screened prospectively with ACS diagnose and were treated with clopidogrel and aspirin dual antiplatelet therapy. CYP2C19 loss of function (LOF) and gain of function (GOF) genotype, adenosine 5′-diphosphate (ADP)-channel platelet inhibition rate (PIR) tested by TEG and the occurrence of 3-month major adverse cardiovascular events and ischemic events were assessed in 116 patients.

**Results:** High on-treatment platelet reactivity (HTPR) prevalence defined by PIR <30% by TEG in ADP-channel was 32.76% (38/116). With respect to the normal wild type, CYP2C19*2, and *3 LOF alleles, and *17 GOF alleles, patients were classified into three metabolism phenotypes: 41.38% were extensive metabolizers (EMs), 56.90% were intermediate metabolizers (IMs), and 1.72% were poor metabolizers (PMs). Of the enrolled patients, 31.47%, 5.17%, and 0.43%, respectively, were carriers of *2, *3, and *17 alleles. The HTPR incidence differed significantly according to CYP2C19 genotypes, accounting for 18.75%, 41.54%, and 100.00% in EMs, IMs, and PMs, respectively. Eighteen (17.24%) ischemic events occurred during the 3-month follow-up, and there was a significant difference in ischemic events between HTPR group and nonhigh on-treatment platelet reactivity group.

**Conclusions:** Genetic CYP2C19 polymorphisms are relative to the inferior, the antiplatelet activity after clopidogrel admission and may increase the incidence of ischemic events in patients with ACS.

**Key words:** Acute Coronary Syndrome; Clopidogrel Resistance; CYP2C19 Polymorphisms; Platelet Reactivity; Thrombelastography

## Introduction

Percutaneous coronary intervention (PCI) is the first line treatment for the management of coronary artery disease in hospitals with cardiac catheterization,[1] clopidogrel and aspirin combination therapy has been approved to be effective and safe in multiple clinical trials such as clopidogrel versus aspirin in patients at risk of ischemic event,[2] CURE[3] and CREDO.[4] However, clopidogrel response variability and its correlation with antiplatelet efficiency and the incidence of adverse cardiac events have been reported in patients with coronary heart disease (CHD). The poor respondents will have high on-treatment platelet reactivity (HTPR) which might have a higher risk for thrombotic events whereas the risk for bleeding events might be raised in the high respondents with nonhigh on-treatment platelet reactivity (nHTPR) after the admission of clopidogrel. Unfortunately, the mechanism by which factors contribute to HTPR and to what extent HTPR is associated with adverse cardiac events,[5] especially in Chinese population with acute coronary syndrome (ACS), are currently poorly understood. Diverse factors that affect the effectiveness of antiplatelet therapy in patients with coronary artery disease may influence the outcomes of antiplatelet therapy, such as drug-drug interaction,[6,7] genetic factors[8] or drug interaction combined with genetic factors,[9] concomitant diseases, and patient compliance, among which genetic factors are receiving more and more attention. Clopidogrel is a prodrug

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requiring two major biotransformation steps, cytochrome P-450 (CYP) isoenzymes, transforms prodrug an active metabolite that binds irreversibly to the platelet adenosine 5′-diphosphate (ADP) receptor P2Y12.[10] Several functional polymorphisms have been found with genes encoding CYP isoforms which involve in clopidogrel metabolic activation upstream of P2Y12 (e.g., CYP2C19)[11,12] but their influence on the pharmacodynamic response to clopidogrel has not been systematically investigated, especially in Chinese people with ACS.

Furthermore, to identify patients with abnormal responses to antiplatelet drugs via platelet function testing is critical to clinical outcomes. There are some platelet function tests, such as light transmittance aggregometry (LTA), thrombelastography (TEG), vasodilator-stimulated phosphoprotein assay, and platelet function analyzer (PFA-100, Plateletworks, and VerifyNow System). Unfortunately, clopidogrel-mediated platelet inhibition (PI) is assay-dependent.[13] Currently, LTA and TEG are the most commonly used tests in China. Conventional LTA was once the gold standard of platelet function testing that has been used widely due to low medical cost, however, this is a time-consuming technique which requires specially trained staffs to conduct the tests, large amount of specially prepared platelet-rich plasma with poor reproducibility.[14] TEG gets more commonly used. It is a dynamic test for the process of blood coagulation and fibrinolysis by measuring the physical properties of the thrombus with whole blood. It holds higher reproducibility despite the high expense.

This study aimed to investigate the correlation between HTPR rate using TEG test and the incidence of major adverse cardiovascular event (MACE) rate in Chinese ACS patients; then to determine the contribution of CYP2C19 polymorphisms by testing the residual platelet reactivity after clopidogrel administration in Chinese ACS patients.

## METHODS

### Study population

From June 2014 to January 2015, we screened 510 patients presented in ED to rule out ACS, among which 116 patients (aged 18–80 years) were diagnosed with ACS by quantitative coronary angiography and enrolled into this study with patient consent per human subjects study protocol approved by Peking University Ethics Committee. The exclusion criteria included contraindications to clopidogrel, aspirin, heparin, and contrast agents as well as quantitative coronary angiography; severe cardiac dysfunction and left ventricular ejection fraction (%) of 30% or less; severe renal with glomerular filtration rate ≤25 ml·min$^{-1}$·1.73 m$^{-2}$ or hepatic function failure with aspartate aminotransferase and alanine transaminase ≥80 U/L; serious infection, systemic immune system diseases, malignant tumor, hematologic diseases; pregnancy, lactation, and long-term use of contraceptive agents; history of bleeding or cerebrovascular disease-related accident within the last 3-month; major operation within the last 1-month and the use of a glycoprotein IIb/IIIa antagonist

before the procedure. All patients were administered, 75 mg/d clopidogrel, with a loading dose of 300 mg clopidogrel in addition to the other available medical therapy, including aspirin, statins, β-blockers, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB), or calcium channel blockers. Baseline characteristics, risk factors, and medical history of the patients were recorded.

### Genetic analysis

After TEG testing, dropped heparin-anticoagulated whole blood was collected by the hemostasis laboratory. Blood sample genomic DNA was isolated using the DNA Extractor AxyPrep-96 (Axygen Scientific Inc., California, USA). Single nucleotide polymorphisms CYP2C19*2 (681G > A, rs4244285), CYP2C19*3 (636G > A, rs4986893), and CYP2C19*17 (806C > T, rs12248560) were identified by ligase detection reaction-real time polymerase chain reactions analysis system (Perkin-Elmer Gene Amp PCR Systems 9600, Perkin-Elmer Shanghai Inc., Shanghai, China), and GENESCAN™672 and GeneMapper (ABI3730 DNA Analyzer, Applied Biosystems, California, USA) of the system were used to analyze the CYP2C19 alleles. Duplicate samples and negative controls were included to ensure the accuracy of genotyping.

### Platelet function detection

Four milliliter of citrated whole blood and 4 ml of heparin-anticoagulated whole blood were drawn at least 3 days after the administration of the first clopidogrel maintenance dose. These samples were sent to the hemostasis laboratory and thromboelastography was performed within 3 h after blood collection according to the manufacture's instruction (TEG 5000, Haemoscope Corporation, Heamoscope, illinois, USA) by trained technicians of the hospital. Platelet reactivity was measured using the TEG platelet mapping system. TEG utilizes four channels to detect the effects of APT activity via the arachidonic acid and ADP pathways. The platelet inhibition rate (PIR) in ADP channel was recorded. A TEG PIR of less than 30% after the maintenance dose of clopidogrel reached steady state was defined as HTPR, while patients with nHTPR had PIR of at least 30% according to the instruction and previous study.[15]

### Follow-up and study endpoints

The patients were followed up at 1-, 3-month after the coronary angiography, respectively, and the clinical outcomes after the patients discharged were recorded. The primary endpoint was MACE, which were a composite of cardiac death, nonfatal myocardial infarction (MI), and target lesion revascularization (TLR). Cardiac death was defined as any mortality caused by cardiac diseases. A five-fold increase in creatine kinase and troponin levels, over the upper normal limit plus the occurrence of ischemic symptoms, was defined as nonfatal MI. TLR was defined as ischemia driven PCI or coronary artery bypass graft on the target lesion. Secondary endpoints included definite stent thrombosis, unstable angina (UA), nonfatal stroke, and major bleeding. Definite stent thrombosis was defined according to the definition of the Academic Research Consortium with

angiographic evidence of thrombotic stent occlusion.[16] UA was defined as the occurrence of ischemic symptoms in 1-month requiring a hospital stay but without an increase in creatine kinase and troponin levels. Nonfatal stroke was defined as ischemic stroke caused by thrombosis or hypotension and hemorrhagic stroke because of intracranial or subarachnoid hemorrhage. Major bleeding was defined as intracranial bleeding or clinically overt bleeding associated with a decrease in hemoglobin of 5 g/dl according to the *Thrombolysis in Myocardial Infarction criteria*.[17]

### Statistical analysis

The data were expressed as numbers and frequencies for categorical variables, and as the mean ± standard deviation (SD) for continuous variables. For comparisons among groups, the Chi-squared test was used for categorical variables, and the unpaired Student's *t*-test or the one-way analysis of variance (ANOVA) was used for continuous variables. The observed genotype frequencies were compared with those expected for a population being in Hardy–Weinberg equilibrium, using a Chi-squared test with 1 degree of freedom. Statistical significance is considered at $P < 0.05$ for Student's *t*-test or Chi-squared test between two groups, at $P < 0.016$ for three groups Chi-squared test. All statistical analyses were carried out using SPSS 18.0 (SPSS Inc., Chicago, Illinois, USA).

## Results

### Platelet reactivity detection in all patients and baseline characteristics in high on-treatment platelet reactivity and nonhigh on-treatment platelet reactivity groups

One hundred and sixteen patients were included in this study, among which we identified 38 (32.76%) patients with HTPR. Demographic characteristics of the study population according to clopidogrel response status are in Table 1. There were no significant differences in the baseline characteristics between the HTPR and nHTPR groups, including sex, age, body mass index (BMI), smokers, incidence of diabetes mellitus, hypertension, dyslipidemia, prior MI, prior PCI, and platelet counts ($P > 0.05$). Moreover, the administration of a β-receptor antagonist, statins, $Ca^{2+}$ antagonist, and ACEI/ARB, proton pump inhibitors did not alter residual platelet reactivity ($P > 0.05$).

### Genotyping results

Genotype distribution and allele frequencies of the genetic variations studied are in Table 2. Among the 116 patients studied, 58 (50.00%) were carriers of at least one CYP2C19*2 loss of function (LOF) allele and 12 (10.34%) were carriers of at least one CYP2C19*3 LOF allele, for CYP2C19*17 gain of function (GOF) allele, only one heterozygous carriers was detected. The distribution of all the CYP genetic variants did not deviate from Hardy–Weinberg equilibrium.

On the basis of the distribution of genotypes, the patients were divided into extensive metabolizers (EMs) without LOF mutation allele (LOF noncarriers), which is also the CYP2C19*1/*1 (681GG/636GG) wild-type genotype, intermediate metabolizers (IMs) carrying only one LOF mutation allele (CYP2C19*2 or CYP2C19*3) with or without GOF mutation allele, and poor metabolizers (PMs) carrying two LOF mutation alleles (CYP2C19*2 and CYP2C19*3), accounting for 41.38%, 56.90%, and 1.72% of all cases, respectively.

### Relationship of genotypes and phenotypes with residual platelet reactivity

In the study population, carriers of at least one LOF allele (PMs and IMs) had higher residual platelet reactivity compared to noncarriers (EMs), PMs and IMs had higher incidence of

### Table 1: Demographic characteristics of the study population according to residual platelet reactivity

| Characteristics | Overall (*n* = 116) | HTPR (*n* = 38) | nHTPR (*n* = 78) | *P* |
|---|---|---|---|---|
| Age, years | 64.45 ± 11.20 | 65.47 ± 10.7 | 63.95 ± 11.53 | 0.494 |
| Male, *n* (%) | 87 (75.00) | 27 (71.05) | 60 (76.92) | 0.493 |
| BMI (kg/m²) | 25.61 ± 3.59 | 25.34 ± 3.48 | 25.74 ± 3.66 | 0.573 |
| Smoker, *n* (%) | 57 (49.14) | 15 (39.47) | 42 (53.85) | 0.146 |
| DM, *n* (%) | 47 (40.52) | 16 (42.11) | 31 (39.74) | 0.808 |
| Hypertension, *n* (%) | 78 (67.24) | 28 (73.68) | 50 (64.10) | 0.302 |
| Dyslipidemia, *n* (%) | 47 (40.52) | 17 (44.74) | 30 (38.46) | 0.518 |
| Prior MI, *n* (%) | 25 (21.55) | 11 (28.95) | 14 (17.95) | 0.176 |
| Prior PCI, *n* (%) | 35 (30.17) | 11 (28.95) | 24 (30.77) | 0.841 |
| Platelet count (10⁹/L) | 184.56 ± 68.08 | 185.43 ± 56.76 | 184.16 ± 73.05 | 0.935 |
| β-receptor antagonist, *n* (%) | 43 (37.07) | 12 (31.58) | 31 (39.74) | 0.393 |
| ACEIs or ARBs, *n* (%) | 23 (19.83) | 8 (21.05) | 15 (19.23) | 0.817 |
| CCBs, *n* (%) | 17 (14.66) | 3 (7.89) | 15 (19.23) | 0.114 |
| Statins, *n* (%) | 56 (48.28) | 16 (42.11) | 40 (51.28) | 0.353 |
| PPIs, *n* (%) | 5 (4.31) | 2 (5.26) | 3 (3.85) | 1.000 |
| Platelet inhibition rate | 50.08 ± 29.57 | 18.22 ± 8.55 | 65.60 ± 22.94 | 0.000 |

HTPR: High on-treatment platelet reactivity; nHTPR: Nonhigh on-treatment platelet reactivity; BMI: Body mass index; DM: Diabetes mellitus; PCI: Percutaneous coronary intervention; MI: Myocardial infarction; ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; CCBs: Calcium channel blockers; PPIs: Proton pump inhibitor.

HTPR than EMs, (2 [100%] vs. 9 [18.75%], $P = 0.000$ and 27 [41.54%] vs. 9 [18.75%], $P = 0.000$, respectively) [Figure 1a]. And there are significant statistic difference between the incidence of HTPR of PMs and IMs too, with a $P = 0.000$, PMs had higher residual platelet reactivity than IMs by TEG detecting, which means the CYP2C19 polymorphism was a critical contributor of clopidogrel resistance.

Furthermore, we evaluated the ADP-channel platelet inhibition by TEG (TEG-PI) of each phenotype. It showed that the TEG-PI of EMs was significantly higher than that in PM and IM patients (12.25% ± 12.23% and 43.72% ± 28.30% vs. 60.39% ± 28.34%, respectively, $P < 0.05$ for each comparison [Figure 1b]; however, no statistical difference in TEG-PI was found between the EM and the IM phenotype (12.25% ± 12.23% vs. 43.72% ± 28.30%, $P = 0.123$) [Figure 1b]. And we also compared the difference of TEG-PIR after clopidogrel between CYP2C19*2 carriers or CYP2C19*3 carriers and LOF noncarriers and it turned out that there was significant difference with a $P = 0.004$ and $0.033$, respectively, but no significant difference between CYP2C19*2 carriers and CYP2C19*3 carriers. Which means both of CYP2C19*2 and CYP2C19*3 are associated with the PI by TEG.

### Clinical outcomes

The three-month follow-up was completed in all patients. There were total of 20 events in all patients at 3-month [Table 3]. Eighteen (17.24%) ischemic events occurred during the follow-up, including 3 (7.89%) nonfatal MI and 7 (18.42%) UA in the HTPR group; and 2 (2.56%) nonfatal MI and 6 (7.69%) UA in the nHTPR group, resulting in a statistically significant difference between the two groups ($P < 0.05$). Two (1.72%) major bleeding occurred, but there was no significant difference between HTPR group and nHTPR group although both of major bleeding samples were in the nHTPR group. For MACE (nonfatal MI) rate, there was no significant different between HTPR and nHTPR group. No cardiac death, TLR, nonfatal stroke, or stent thrombosis has been detected in patients on 3-month follow-up.

Furthermore, we checked the difference of clinical outcomes among PMs, IMs, and EMs [Table 4], 1 (50%) MACE was found in PM group while 10 (20.83%) in EM group but no statistically significant difference was found between the two groups. No major bleeding events were found either in PM group or in EM group.

## Discussion

Available studies that tested various clopidogrel responses and aimed at analyzing the contributions of different risk factors to the various clopidogrel responses were mostly based on patients with stable CHD[2-4,18] not in ACS patients
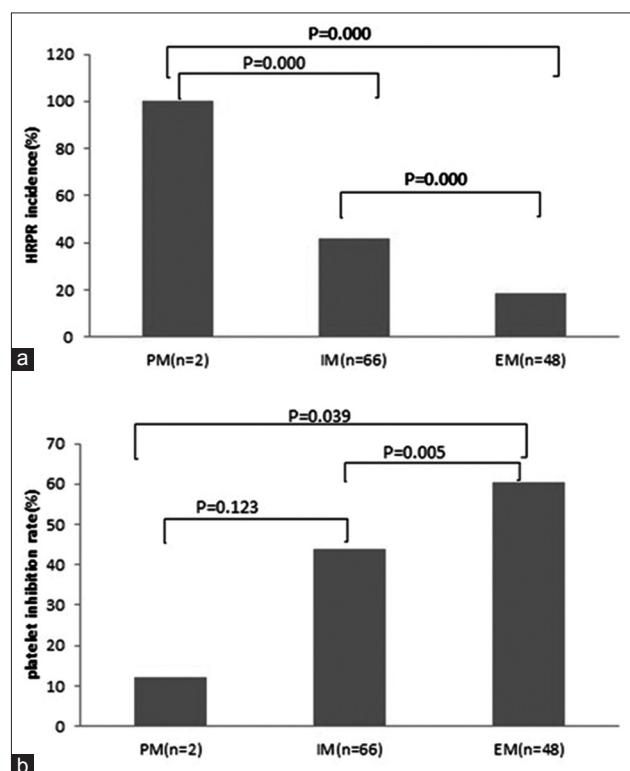
**Figure 1:** Comparison of the high on-treatment platelet reactivity incidence (a) and the adenosine diphosphate-induced platelet inhibition rate (b) by thrombelastography detecting after clopidogrel among patients with acute coronary syndrome with different phenotype of CYP2C19*2, CYP2C19*3, and CYP2C19*17. HTPR: High on-treatment platelet reactivity; PM: Poor metabolizers; IM: Intermediate metabolizers; EM: Extensive metabolizers.

**Table 2: Genotype distribution and allele frequency of investigated genetic variations**

| Items | CYP2C19*2 | CYP2C19*3 | CYP2C19*17 |
|---|---|---|---|
| Noncarriers, $n$ (%) | 58 (50.00) | 104 (89.66) | 115 (99.14) |
| Heterozygous carriers, $n$ (%) | 43 (37.07) | 12 (10.34) | 1 (0.86) |
| Homozygous carriers, $n$ (%) | 15 (12.93) | 0 (0.00) | 0 (0.00) |
| Carriers of at least one allele, $n$ (%) | 58 (50.00) | 12 (10.34) | 1 (0.86) |
| Allele frequency (%) | 31.47 | 5.17 | 0.43 |

**Table 3: Clinical outcomes at the 3-month follow-up in HTPR and nHTPR groups ($n$ (%))**

| Items | HTPR ($n=38$) | nHTPR ($n=78$) | Total ($n=116$) |
|---|---|---|---|
| Nonfatal MI | 3 (7.89) | 2 (2.56) | 5 (4.31) |
| Cardiac death | 0 (0) | 0 (0) | 0 (0) |
| TLR | 0 (0) | 0 (0) | 0 (0) |
| MACE | 3 (7.89) | 2 (2.56) | 5 (4.31) |
| UA | 7 (18.42) | 6 (7.69) | 13 (11.21) |
| Nonfatal stroke | 0 (0) | 0 (0) | 0 (0) |
| Stent thrombosis | 0 (0) | 0 (0) | 0 (0) |
| Major bleeding | 0 (0) | 2 (2.56) | 2 (1.72) |
| Ischemic events* | 10 (26.32) | 8 (10.26) | 18 (15.52) |
| Total events | 10 (26.32) | 10 (12.82) | 20 (17.24) |

HTPR: High on-treatment platelet reactivity; nHTPR: Nonhigh on-treatment platelet reactivity; MI: Myocardial infarction; MACE: Major adverse cardiovascular events; UA: Unstable angina; TLR: Target lesion revascularization. *$P=0.031$ for Ischemic events between HTPR and nHTPR groups.

which require much more effective therapy, thus we conducted this study to detecting the clopidogrel response in Chinese ACS patients. In our study, 32.76% of the enrolled ACS patients showed HTPR after clopidogrel (clopidogrel resistance) measured by TEG. With a cutoff PIR of 30%, the results were in agreement with Sambu et al.'s study by short TEG[19] and others despite the different assays used.[18,20] And we found a significant association the ischemic events (nonfatal MI and UA) at 3-month after discharge between HTPR and nHTPR rate defined by TEG with a incidence rate of 26.32% and 10.26%, respectively [Table 3], which was much higher than the previous study of Chinese CHD people followed for 1-year[21] (18.42% and 7.69% in HTPR and nHTPR group respectively.). In our study, the MACE rate (which turned to be nonfatal MI) was higher than the previous study in Chinese CHD population, which might probably due to the different patients' comorbidity or our sample size. For patients with ACS that needed to be treated in the coronary care unit, these CHD patients had a more comorbid illness or had severe CAD, which might contribute to the high incidence rate of ischemic events at 3-month.

CYP2C19 is an important member of the CYP family that converts clopidogrel into an active metabolite; its LOF variants encoded by CYP2C19 mutated alleles have lost their enzymatic activities, while GOF variants can enhance the enzymatic activities. The most frequent LOF variant alleles are CYP2C19*2 and CYP2C19*3. The most frequent GOF variant allele is CYP2C19*17. Thus, the three variant alleles in Chinese ACS population were investigated in this study. Among which, CYP2C19*17 variant allele has seldom been reported in Chinese people with ACS. In our studied population, we found one CYP2C19*17 carrier out of 116, with an allele frequency of 0.43% [Table 2]. PMs, IMs, and Ems carrying the status of these three variant alleles, are 1.72%, 56.90%, and 41.38%, respectively [Table 4]. The incidence of genetic mutation was found higher than that of Caucasian and African (18–45% and 2–15% for IMs and PMs, respectively)[22] but in agreement with Japanese

population (40.0%, 45.2%, and 14.8% for EMs, IMs, and PMs, respectively)[23] and other studies of Chinese population (39.31%, 47.59%, and 13.10% for EMs, IMs, and PMs, respectively).[24] In our population carriers of at least one LOF alleles (CYP2C19*2 or *3) or one LOF allele and one GOF allele at the same time had higher residual platelet reactivity compared to noncarriers, which shows a significant gene and HTPR rate association in ACS patients (PMs > IMs > EMs, $P < 0.016$) [Figure 1a]. These observations are in accordance with previous studies.[21,22,25-27] EMs TEG-PIR (60.39%) were higher than that of IMs (43.72%) and PMs (12.25%) significantly but there was no difference of TEG-PIR, between PMs (12.25%) and IMs (43.72%) [Figure 1b].

The HTPR rate in this study was higher than the previous studies in Chinese CHD population (32.76% vs. 20.67%)[24] which probably due to the difference of study population, different assays used for detecting platelet function may contribute to this observation, in additional to our small sample size. It is reported that the platelet function tests are highly test-specific,[28] and even for the same testing method, the optimal cut-off value for the inferior response is also controversial.[29] A standard definition for antiplatelet drug response has not been fully established. Using TEG to assess the residual platelet reactivity after clopidogrel administration is chosen due to its reproducibility. In addition, TEG provides an overall assessment of ex vivo hemostatic function, thus the interaction of all the components of coagulation, including thrombin, platelets, fibrin, and clotting factors is considered in the test, which provides a graphical representation of the speed and strength of clot formation as well as clot stability. Processing wise, it uses whole blood for the test, minimizing the lab workload. All these features provide an advantage of the TEG method over other platelet function tests such as Multiple Platelet Function analyzer and LTA. In summary, TEG provides specific and reliable results of the residual platelet activity after clopidogrel admission. Nevertheless, further studies are needed to compare those methods by bigger samples.

### Study limitations
The small sample size and short follow-up period are the limitations of this study. The duration of follow-up was 3-month and a follow-up of 12 or even 24–36 months will provide more information for MACE rate. Moreover, it is noted that only part of the genetic polymorphisms that are considered in this study for clopidogrel resistance, the impact of other CYP P450 metabolism enzymes, such as CYP1A2, 2B6, and 2C9, and other allelic variants of 2C19 on platelet reactivity were excluded in this study. There is one patient with CYP2C19*17 mutation, thus the impact of CYP2C19*17 to clopidogrel response is inconclusive, this may be due to the infrequent CYP2C19*17 allele mutation observed low in the Asian population. Furthermore, other comorbidity, like diabetes and BMI as well as the interactions between clopidogrel and other drugs, such as statins, $Ca^{2+}$ antagonist, and ACEI, and their effects on PI in different groups were not considered in this study.

**Table 4: Clinical outcomes at the 3-month follow-up in different phenotype groups (*n* (%))**

| Items | PM (*n* = 2) | IM (*n* = 66) | EM (*n* = 48) | Total (*n*=116) |
|---|---|---|---|---|
| Nonfatal MI | 0 (0) | 2 (3.03) | 3 (6.25) | 5 (4.31) |
| Cardiac death | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| TLR | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| MACE | 0 (0) | 2 (3.03) | 3 (6.25) | 5 (4.31) |
| UA | 1 (50.00) | 5 (7.58) | 7 (14.58) | 13 (11.21) |
| Nonfatal stroke | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Stent thrombosis | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Major bleeding | 0 (0) | 2 (3.03) | 0 (0) | 2 (1.72) |
| Ischemic events | 1 (50.00) | 7 (10.61) | 10 (20.83) | 18 (15.52) |
| Total events | 1 (50.00) | 9 (13.85) | 10 (20.83) | 20 (17.24) |

MI: Myocardial infarction; MACE: Major adverse cardiovascular events; UA: Unstable angina; TLR: Target lesion revascularization; PM: Poor metabolizer; IM: Intermediate metabolizer; EM: Extensive metabolizer.

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