CYP2C19 Poor Metabolizer Is Associated With Clinical Outcome of Clopidogrel Therapy in Acute Myocardial Infarction But Not Stable Angina

Ho-Sook Kim, PhD*; Kiyuk Chang, MD, PhD*; Yoon-Seok Koh, MD; Mahn-Won Park, MD; Yun-Seok Choi, MD, PhD; Chul-Soo Park, MD, PhD; Minkyung Oh, PhD; Eun-Young Kim, MD, PhD; Ji-Hong Shon, MD, PhD; Jae-Gook Shin, MD, PhD; Ki-Bae Seung, MD, PhD

Background—More intensive platelet suppression is required in patients with acute myocardial infarction (AMI) than in those with stable angina because of differential platelet activation between AMI and stable angina. In this context, CYP2C19 genotype leading to reduced active metabolite formation may profoundly affect the clinical outcome of clopidogrel therapy in patients with AMI compared with those with stable angina.

Methods and Results—Effects of CYP2C19 genotypes on the clinical outcome of clopidogrel therapy were evaluated in 2188 patients (532 patients with AMI and 1656 patients with stable angina) undergoing percutaneous coronary intervention. The primary clinical outcome was a composite of major adverse cardiac and cerebrovascular events defined as death from any cause, nonfatal myocardial infarction, or stroke during 1 year of clopidogrel therapy. Compared with extensive metabolizer, the CYP2C19 poor metabolizer was significantly associated with higher risk of major adverse cardiac and cerebrovascular events in patients with AMI (hazard ratio, 2.88; 95% confidence interval, 1.27–6.53; P=0.011). However, this finding was not seen in patients with stable angina. A significant interaction between CYP2C19 genotypes and disease subsets of AMI and stable angina was identified with respect to major adverse cardiac and cerebrovascular events (adjusted interaction P=0.045). The patients with AMI showed lower percent inhibition of P2Y12 compared with patients with stable angina in CYP2C19 poor metabolizer or CYP2C19 intermediate metabolizer genotype groups but not in CYP2C19 extensive metabolizer genotype group.

Conclusions—CYP2C19 poor metabolizer is associated with poor clinical outcome of clopidogrel therapy in Asian patients with AMI but not in those with stable angina possibly because of differential requirement of platelet suppression in patients with AMI and stable angina.

Clinical Trial Registration Information—URL: clinicaltrials.gov. Identifier: NCT01239914.

Key Words: acute myocardial infarction □ angina, stable □ clopidogrel □ CYP2C19 protein, human □ pharmacogenetics

C lopidogrel on top of aspirin improves clinical outcomes in patients with acute coronary syndrome and those undergoing percutaneous coronary intervention (PCI).1 Although clopidogrel has been extensively prescribed, inter-individual variation in clinical responses has fueled research into personalized pharmacotherapy for patients undergoing drug-eluting stent (DES) implantation.2,3 Clopidogrel has to be biotransformed into its active thiol metabolite to exert its antiplatelet effects; this is accomplished by hepatic cytochrome P450 isoenzymes such as CYP2C19.4 The CYP2C19 loss-of-function (LOF) alleles (*2 and *3 alleles) result in less formation of active thiol metabolite, causing lack of platelet aggregation inhibition, which translates into a higher rate of subsequent cardiovascular events than noncarriers.5

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Despite its robust association with poor cardiovascular outcomes of clopidogrel therapy, clinical use of the CYP2C19 genotype as a predictive biomarker for personalized antiplatelet therapy remains debatable. Although the CYP2C19 LOF alleles have been consistently associated with worse clinical outcome of clopidogrel therapy in patients with acute myocardial infarction (AMI), its clinical effect in patients with stable angina is undefined. Because intense platelet activation is one of the key components of the biological process in the presence of inflamed and ruptured coronary plaques in patients with AMI, more aggressive platelet suppression is generally recommended in patients with AMI compared with those with stable angina. Therefore, CYP2C19 genotypes are expected to be associated with differential antiplatelet effects and the clinical outcomes of clopidogrel therapy in patients with AMI and stable angina. However, no reports have analyzed the presence of interaction between CYP2C19 genotype and clinical presentations of AMI or stable angina for the clinical outcome of clopidogrel therapy in similar cohorts undergoing DES implantation. Therefore, our objective was to evaluate whether the effects of CYP2C19 genotypes on the clopidogrel responses are different between patients with stable angina and AMI.

Methods

Study Population

All patients were prospectively and consecutively enrolled from 2 affiliated hospitals of The Catholic University of Korea (Seoul St. Mary’s Hospital and Yeouido St. Mary’s Hospital) between January 2005 and December 2009 by the inclusion criteria of obtaining a written informed consent for a genetic association study and whole blood, >18 years of age, a diagnosis of AMI or stable angina, and DES implantation.

AMI was diagnosed if patients had higher serum level of myocardial necrosis markers (creatinine kinase MB, troponin I or T) than the upper normal limit and if patients had either chest pain consistent with AMI or typical electrocardiographic changes in >2 contiguous leads showing pathological Q waves (≥0.04 second in duration) with persistent ST-segment elevation or ST-segment depression >0.1 mV. Patients with stable angina and silent myocardial ischemia were grouped together in the registry. Stable angina was diagnosed if patients had chest pain with an unchanged pattern during the preceding 2 months. Silent myocardial ischemia was defined as objectively documented myocardial ischemia without a history of angina or angina equivalents. Patients who experienced any previous MI within a year were not included in the angina group. This study was approved by the institutional review boards of both the participating hospitals.

Platelet Function Test

To evaluate the effect of clopidogrel on platelet aggregation, we measured P2Y12 platelet reaction units (PRU) using the VerifyNow P2Y12 test (Accumetrics, San Diego, CA). To reflect a patient’s full dose of clopidogrel on the day of discharge. Patients undergoing elective PCI for an angina were discharged on day 2 after index PCI, and those undergoing PCI for AMI were discharged on day 5 after index MI. The PRU values were estimated by an increase in light transmittance from the ADP-induced platelet aggregation. The percent inhibition of platelet reactivity was estimated as follows: % inhibition=[(baseline PRU−postdrug PRU)/baseline PRU]×100. Because of the availability of the VerifyNow P2Y12 test since June 2008, a limited number of patients (n=491) underwent platelet function test during the study period. No other selection bias was observed.

Genotyping

Genotypes of CYP2C19 in this study were determined by single-base extension methods. Analytic validation of the Korean population had been established previously and published by the PharmacoGenomics Research Center (Inje University College of Medicine, Busan, Korea). Genomic DNA was used in genotyping for the presence of the major Korean alleles, including CYP2C19*2 (rs4244285), CYP2C19*3 (rs4986893), and CYP2C19*17 (rs12248560), using an ABI PRISM genetic analyzer and its associated GeneMapper software. All tested genotypes satisfied Hardy–Weinberg equilibrium and showed no statistical significance for all single-nucleotide polymorphisms tested (P>0.05) in this study. Primers for amplification and sequencing of each allele and polymerase chain reaction conditions are listed in Tables I and II in the online-only Data Supplement.

The CYP2C19 alleles were classified into 3 genotype groups according to the number of CYP2C19 LOF alleles: CYP2C19 extensive metabolizer (CYP2C19 EM, CYP2C19*1/*1), and heterozygous for CYP2C19*17 allele, CYP2C19 intermediate metabolizer (CYP2C19 IM, CYP2C19*1/*2, and CYP2C19*1/*3), and CYP2C19 poor metabolizers (CYP2C19 PM, CYP2C19*2/*2, CYP2C19*2/*3, and CYP2C19*3/*3). In the present study, no subjects with homozygous CYP2C19*17/*17, a genotype causing increased CYP2C19 enzyme activity, were identified in 2188 Korean patients. Thirty-three patients with CYP2C19*1/*1, 14 with CYP2C19*2/*17, and 6 with CYP2C19*3/*17 were grouped as CYP2C19 EM in the study.

Statistical Analysis

Two-sided tests were performed using SAS software version 9.2 (SAS Institute, Cary, NC). Baseline characteristics of the patients were summarized as means±SD for continuous variables and percentages for discrete variables. Baseline characteristics were analyzed for differences between patients with stable angina and those with AMI using the Wilcoxon rank-sum test for continuous variables after testing for normality and the χ² or Fisher exact test for categorical variables, as appropriate. The primary clinical outcome was a composite of major adverse cardiac and cerebrovascular events (MACCE), defined as death from any cause, nonfatal MI (nonprocedural/spontaneous), or stroke during 1-year follow-up.

Clinical characteristics and genotypes were compared between patients with AMI and stable angina using χ² test, and effects of CYP2C19 genotype on MACCE were compared between patients with and without MACCE using a univariable Cox proportional hazards model.

Cumulative event rates were estimated and compared for all patient cohorts and separately for the stable angina and AMI patient groups by the Kaplan–Meier method. In addition, a landmark analysis with a prespecified landmark set at 1 month (within the first months post-PCI and thereafter) was performed using the Kaplan–Meier method to provide separate descriptions of the early and late relative effects of CYP2C19 genotype on the clinical outcome of clopidogrel therapy. In a multivariable, stepwise Cox proportional hazards model for clinical outcomes during 1-year follow-up was developed from the covariates with a P value set at 0.05 for entering and 0.1 for exclusion. The statistical significance of each covariate associated with clinical outcome was analyzed by the Wald test and described as hazard ratios (HRs) with 95% confidence intervals (CIs). In the multivariable analysis, the clinical characteristics were dichotomized as ≤65 or >65 years of age, body mass index ≤25 or >25 kg/m², and coadministration of proton pump inhibitors, including omeprazole, esomeprazole, or lansoprazole, which inhibit the CYP2C19 enzyme activity. In this study, proton pump inhibitor coadministration was analyzed only for the cases in which proton pump inhibitor administration was started in the period between 2 days before and 1 month after PCI and continued for >7 days. The proportional hazard assumption was tested using a time-dependent Cox proportional hazards model, including final covariates. Our model satisfied the proportional hazards assumption.

To evaluate the interaction between CYP2C19 genotype and diagnosis at PCI (AMI or stable angina), formal tests for interaction were conducted using the final Cox proportional hazards models.
Baseline characteristics of the study population

In this study, complete follow-up data for major clinical events were collected from 98.1% of the 2188 study patients. The patients were categorized into 2 groups: the stable angina group (n=1656), 75.7% of total patients; 86% presented with stable angina and 14% with silent myocardial ischemia and the AMI group (n=532, 24.3% of total patients; 61% presented with ST-segment–elevation MI and 39% with non–ST-segment–elevation MI). Patients were started on a loading dose of either 600 mg (80% in the stable angina group, 84% in the AMI group) or 300 mg (20% in the stable angina group, 16% in the AMI group) clopidogrel on the first day of clopidogrel treatment. All patients continued on a daily maintenance dose of clopidogrel of 75 mg. Fifty-six patients (2.5%) were treated with glycoprotein IIb/IIIa inhibitors at the time of PCI and ≤12 hours thereafter.

The distribution of the baseline characteristics between AMI and stable angina groups is shown in Table 1. The proportions of men, current smokers, and chronic renal failure were higher in patients with AMI. Slightly more patients with stable angina received a higher clopidogrel loading dose. Older age, higher body mass index, and higher prevalence of hypertension, diabetes mellitus, hypercholesterolemia, and previous PCI were observed in patients with stable angina. Other baseline characteristics were comparable between patients with stable angina and AMI.

In 1656 patients with stable angina, the composite of death, nonfatal MI, or stroke occurred in a total of 42 (8.7%) patients and death in 35 (2.1%) patients, whereas in 532 patients with AMI, the composite outcomes occurred in a total of 45 (8.4%) patients and death in 36 (6.9%) patients during the 1-year follow-up after PCI. The frequencies of all genotypes in this study were consistent with previous reports and our pharmacogenomics database for the Korean ethnic population.10 The frequencies of CYP2C19 genotypes were not significantly different between patients with stable angina and AMI (Table 1).

Effect of CYP2C19 Genotypes on Clinical Outcome

The effects of CYP2C19 genotype in the AMI and stable angina groups were analyzed separately. The carriers of CYP2C19*2/*2 and *2/*3 had statistically significant higher HRs for MACCE (HR, 2.99 [1.13–7.53] and 2.98 [1.04–8.58]; P=0.027 and 0.043, respectively) compared with CYP2C19*1/*1 only in patients with AMI but not in patients with stable angina (Table 2). The HRs for MACCE in patients with CYP2C19*3/*3 genotype or CYP2C19*17 allele were not statistically significant compared with those with CYP2C19*1/*1 because of the small number of subjects with CYP2C19*3/*3 and CYP2C17*1/*17 (n=6 and 8 in patients with AMI and n=17 and 25 in patients with stable angina).

Patients with CYP2C19 PM showed higher cumulative event rates of death, nonfatal MI, or stroke at 1 year after PCI than in those with CYP2C19 IM and EM, although the differences did not reach statistical significance (P=0.068; Figure 1A). However, the same analysis in AMI and stable angina groups yielded different results. In the AMI group, the cumulative event rate in CYP2C19 PM genotype was significantly higher than that in CYP2C19 EM and CYP2C19 IM genotypes (15.5% event rate in CYP2C19 PM versus 5.6% in CYP2C19 EM and 7.9% in CYP2C19 IM; Figure 1B). However, the effect of CYP2C19 genotypes on event rate was not apparent in the stable angina group, and there was no difference between patients with CYP2C19 PM and with EM and IM (P=0.783; Figure 1C). The HR for primary outcome of CYP2C19 PM compared with CYP2C19 EM was estimated to be 2.88 with 95% CI of 1.27 to 6.53 in patients with AMI (P=0.011; Table 2), and it was not significantly different in patients with stable angina (HR, 1.26; 95% CI, 0.52–3.06). There were no significant differences between CYP2C19 EM and CYP2C19 IM in analyses of the overall population or the AMI group (Figure 1A and 1B; Table 2).

The post hoc power calculation based on our actual data of Table 2 revealed a power of >0.85 in 3 CYP2C19 genotype groups stratified by AMI and stable angina (a power of 0.909 for CYP2C19 EM versus IM and >0.999 for CYP2C19 EM versus PM in AMI group; a power of 0.981 for CYP2C19 EM
versus IM and 0.859 for CYP2C19 EM versus PM in stable angina). These results demonstrate that our data set had sufficient statistical power to detect the effects of CYP2C19 genotype on MACCE.

No effects of CYP2C19 genotype on stent thrombosis were observed because of the low rate of stent thrombosis in this study population (Table III in the online-only Data Supplement). The effect of CYP2C19 genotype on MACCE was further analyzed within the first month after PCI and from 1 month to 1 year. The cumulative event rate of AMI patients with CYP2C19 PM was significantly higher than those of CYP2C19 EM and IM within the first month after PCI (event rate, 8.9% versus 1.0% versus 4.3%; \( P = 0.007 \); Figure 2A).

However, the statistical significance of the difference in the cumulative event rate among those genotype groups was not maintained after the first 1 month to 1 year after PCI (7.3% versus 4.7% versus 3.8%; \( P = 0.405 \); Figure 2B).

In the multivariable Cox proportional analyses, ≥65 years of age, AMI diagnosed at PCI, chronic renal failure, and coadministration of proton pump inhibitors, as well as CYP2C19 PM genotype, were identified to be associated with the clinical outcome of MACCE for the 2188 patients (Table 3). Cox proportional hazards models adjusted for demographic and clinical factors identified a significant interaction between CYP2C19 genotype and disease subsets with respect to the primary outcome (adjusted \( P = 0.045 \) for
the interaction between diagnosis at PCI and CYP2C19 genotype; Table 4). After multivariable adjustment, CYP2C19 PM genotype was associated with a significantly increased HR of MACCE in AMI (adjusted HR, 2.66; 95% CI, 1.28–5.54) but not associated with HR of MACCE in patients with stable angina (adjusted HR, 1.29; 95% CI, 0.54–3.12).

### Effect of Genotypes on the Platelet Reactivity

The effects of CYP2C19 genotype on the antiplatelet effect of clopidogrel were evaluated in 491 patients having the results from the VerifyNow P2Y12 test. The P2Y12 inhibition percentage showed gene dose response according to the number of CYP2C19 LOF allele. Patients with CYP2C19 EM showed the most potent antiplatelet effect compared with those with CYP2C19 IM and CYP2C19 PM (Figure 3A). The percentage inhibition of platelet reactivity was further analyzed in patients with AMI and stable angina stratified by CYP2C19 genotypes (Figure 3B). Patients with AMI showed lower percent inhibition of P2Y12 compared with patients with stable angina in CYP2C19 PM or CYP2C19 IM genotype groups (P=0.053 in CYP2C19 PM and 0.022 in CYP2C19 IM). However, patients with CYP2C19 EM showed no significant difference in the percent inhibition of platelet reactivity between stable angina and AMI.

### Discussion

This large study investigates the effects of CYP2C19 genotypes on the clinical outcome of clopidogrel therapy, analyzed in an Asian population with cardiovascular disease, in which all study patients underwent PCI with exclusive placement of DES and were treated with clopidogrel for >1 year. In our Korean patient population with higher statistical power from the standpoint of higher frequencies of CYP2C19 LOF alleles, CYP2C19 PM genotype was significantly associated with a higher risk of MACCE compared with CYP2C19 EM/IM genotypes only in patients with AMI but not in patients with stable angina. In line with this finding, P2Y12 percentage inhibition showed significant difference between the patients with stable angina and AMI with the CYP2C19 PM and IM genotypes, although only a subpopulation of these patients were analyzed with the VerifyNow P2Y12 test.
 Clinically, patients with the 2 different indications of PCI, such as AMI and stable angina, are exposed to different conditions particularly during the early post-PCI period. Patients with AMI receive urgent coronary revascularization on highly thrombotic and inflamed plaques, whereas patients with stable angina are clinically at less risk and usually undergo a PCI stratified by CYP2C19 genotype. The horizontal line within each box represents mean, and the bottom and top borders of each box represent 25th and 75th percentiles, respectively. The single horizontal bars above and below the box indicate 90th and 10th percentiles. The P values were calculated using the Wilcoxon rank-sum test. AMI indicates acute myocardial infarction; EM, extensive metabolizer; IM, intermediate metabolizer; and PM, poor metabolizer.

Figure 3. Effect of CYP2C19 genotypes on the platelet reactivity. Platelet reactivity was measured using the VerifyNow test in 491 patients after a maintenance dose of 75 mg clopidogrel. A, P2Y12 inhibition percentage according to the CYP2C19 genotype. B, P2Y12 inhibition percentage according to diagnosis at PCI stratified by CYP2C19 genotype. The horizontal line within each box represents mean, and the bottom and top borders of each box represent 25th and 75th percentiles, respectively. The single horizontal bars above and below the box indicate 90th and 10th percentiles. The P values were calculated using the Wilcoxon rank-sum test. AMI indicates acute myocardial infarction; EM, extensive metabolizer; IM, intermediate metabolizer; and PM, poor metabolizer.

Clinically, patients with the 2 different indications of PCI, such as AMI and stable angina, are exposed to different conditions particularly during the early post-PCI period. Patients with AMI receive urgent coronary revascularization on highly thrombotic and inflamed plaques, whereas patients with stable angina are clinically at less risk and usually undergo a programmed PCI as in our study population. In contrast to patients with angina, the risk of MACCE was significantly higher in patients with CYP2C19 PM genotype than in those with CYP2C19 EM and IM among the 532 patients with AMI. Furthermore, we identified a remarkable interaction between CYP2C19 genotype and the diagnosis of PCI beyond simply comparing the predictability of CYP2C19 PM for MACCE in the separate strata of angina and AMI. From these results, the CYP2C19 PM genotype seems to be a good predictive biomarker of clopidogrel treatment failure for the clinical outcome in patients with AMI undergoing PCI but not in patients with stable angina undergoing PCI.

Our findings are collectively supported by the heterogeneity of study populations in clinical trials observing the effect of CYP2C19 genotypes on clinical outcome and our landmark analysis. Study populations showing positive associations between CYP2C19 LOF alleles and poor clinical outcomes of clopidogrel therapy, such as in the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI), Appraisal of Risk Factors in Young Ischemic Patients Justifying Aggressive Intervention (AFIJI), and Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), were largely composed of patients with AMI, whereas those showing negative associations, such as Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Atrial Fibrillation Clopidogrel Trial for Prevention of Vascular Events (ACTIVE-A), were not at such a high risk. In these trials, 74.9% of CURE subjects presented with unstable angina, and only 14.5% underwent PCI with placement of a bare-metal stent, and the ACTIVE-A trial was composed of patients with atrial fibrillation.

In addition, our landmark analysis in which the effect of CYP2C19 PM genotype in patients with AMI was statistically significant within the first 1 month after PCI but not after 1 month further strengthens our conclusion (Figure 2), considering that patients in the early phase of AMI experience greater proinflammatory and prothrombotic conditions. However, patients with AMI may have an increased risk of late thrombotic complications beyond 1 month after PCI because underlying plaque morphology could lead to delayed healing at ruptured plaque compared with that of patients with stable angina. On the contrary, CYP2C19*2 polymorphism has been reported to be associated with subclinical thrombus formation after DES implantation and clopidogrel therapy, although no significant increase in major adverse cardiac events was observed. Our landmark analysis and these reports suggest that AMI patients with CYP2C19 LOF alleles during clopidogrel therapy may have an increased chance of developing intrastent thrombus formation without clinical significance beyond 1 month, which need another intravascular imaging or clinical outcome study.

Few large-scale reports have addressed the effect of CYP2C19 genotype on the clinical outcome of clopidogrel therapy expressed as major adverse cardiac events or MACCE in Asian populations, which have higher frequencies of the CYP2C19 LOF allele (CYP2C19*2 and *3) compared with those of other ethnic populations. In patients with AMI of this study, only the carriers of 2 LOF alleles of CYP2C19 (ie, CYP2C19 PM genotype) had poorer clinical outcomes than noncarriers of CYP2C19 LOF alleles (ie, CYP2C19 EM genotype). Although our AMI population had sufficient statistical power to detect the effects of CYP2C19 genotype on MACCE, the incidence of MACCE in patients with only 1 LOF allele of CYP2C19 (ie, CYP2C19 IM genotype) was not significantly different compared with noncarriers of CYP2C19 LOF alleles. Interestingly, the incidence of adverse cardiac events during clopidogrel therapy in Asians was not higher than that in whites, despite their higher frequencies of CYP2C19 LOF
alleles. Furthermore, higher cutoff PRU values for adverse cardiac events in Asians compared with whites have been reported. Despite the same treatment, bleeding incidence is higher in Asians than in whites. Asians may require less potent antiplatelet effects for the prevention of MACCE compared with whites. Thus, although the CYP2C19 IM could have an influence on major adverse cardiac events or MACCE after clopidogrel therapy in whites, only the CYP2C19 PM genotype may be a predictor of clinical outcome of clopidogrel therapy in the Asian population with AMI. Further confirmation of these findings is required in another large Asian population of patients with AMI.

Higher loading and maintenance dose of clopidogrel results in more rapid and greater inhibition of platelet reactivity than standard dosage. It was reported recently that 225 mg clopidogrel in CYP2C19*2 heterozygotes resulted in comparable platelet inhibition compared with standard 75 mg dose in non-carriers. However, in CYP2C19*2 homozygotes, even 300 mg clopidogrel did not result in comparable degrees of platelet inhibition compared with standard 75 mg dose in non-carriers. Accordingly, patients with the CYP2C19 PM genotype would benefit from more potent ADP receptor blockers such as prasugrel or ticagrelor rather than a higher dose of clopidogrel, especially in patients with acute coronary syndromes receiving PCI.

Several metabolic enzymes, such as CYP2B6, CYP2C9, CYP3A5, PON1, and CYP2C19, have been reported to contribute to the formation of the clopidogrel thiol active metabolite. However, except CYP2C19, other genetic polymorphisms were not associated with clinical outcome of clopidogrel therapy. Among transports, ABCB1 C3435T single-nucleotide polymorphism was reported to be associated with increased rate of cardiovascular events. However, the relationship between the ABCB1 C3435T single-nucleotide polymorphism and P-glycoprotein expression/activity is controversial among different ethnic groups. Thus, the polymorphisms in other genes except CYP2C19 were not included in this study. In conclusion, the CYP2C19 PM genotype is significantly associated with higher risk of MACCE during clopidogrel therapy in Asian patients with AMI but not with stable angina, especially within the first 1 month after PCI.

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Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

It has been well established that the loss-of-function alleles of CYP2C19 genotype are reliable predictors of the clinical outcome of clopidogrel therapy in patients undergoing percutaneous coronary intervention (PCI). However, limited evidence is available on whether the effects of CYP2C19 genotypes on clopidogrel responses are different between patients with elective PCI from stable angina and those undergoing emergency PCI from acute myocardial infarction with intense platelet activation. We evaluated the effect of CYP2C19 genotype on the risk of cardiovascular events in 2188 Korean patients, who have higher frequency of CYP2C19 loss-of-function alleles and lower frequency of CYP2C19 gain-of-function alleles, undergoing PCI with the use of drug-eluting stents and receiving clopidogrel therapy. Only CYP2C19 poor metabolizer (2 loss-of-function alleles) was associated with higher risk of primary outcome in patients undergoing emergency PCI from acute myocardial infarction but not in those with elective PCI from stable angina. Significant interaction between CYP2C19 genotype and disease subsets was also identified with respect to major adverse cardiac and cerebrovascular events. The patients with acute myocardial infarction showed lower percent inhibition of P2Y12 compared with patients with stable angina in CYP2C19 poor metabolizer or CYP2C19 intermediate metabolizer genotype group. These findings suggest that only CYP2C19 poor metabolizer is associated with poor clinical outcome of clopidogrel therapy in Asian patients with acute myocardial infarction but not with stable angina possibly because of differential requirement of platelet suppression in each disease setting.
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# SUPPLEMENTAL MATERIAL

## Table 1. Primers for amplification of each allele and multiplexed PCR conditions.

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<tr>
<th>Tested alleles</th>
<th>Forward (5’—3’)</th>
<th>Reverse (5’—3’)</th>
<th>Size(bp)</th>
<th>PCR Temp.</th>
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1) Lee SS et al. Ther Drug Monit. 2007 Aug;29(4):455-9  

## Table 2. Primers used in the multiplex SBEa methods for detection of CYP2C19*2,*3,*17, CYP3A4*18, CYP3A5*3, CYP2B6*4, *6, and *9 alleles, and P2Y12 742T>C, MDR 2677G>A, 2677G>T and MDR 3435C>T.

<table>
<thead>
<tr>
<th>Primer</th>
<th>Sequence</th>
<th>Concentration in SNaPshot reaction (nM)</th>
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<td>(T) TTGTGTCTTCTGTTCTCAAAAG</td>
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<td>(T)28CAAAAAAACTTGGCCTTACCTGGAT</td>
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a SNaPshot reaction for detecting duplication in a separate well
Table 3. Stent thrombosis (ST) in angina patients and AMI patients at 12 months according to functional allelic variants of CYP2C19 gene

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<th>CYP2C19 genotypes</th>
<th>AMI Without ST (n=528)*</th>
<th>With ST (n=4)*</th>
<th>P value†</th>
<th>Stable angina Without ST (n=1646)*</th>
<th>With ST (n=10)*</th>
<th>P value†</th>
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<td>187(35.4)</td>
<td>0(0.0)</td>
<td>0.161</td>
<td>631(38.3)</td>
<td>1(10.0)</td>
<td>0.103</td>
</tr>
<tr>
<td>*1/*17</td>
<td>8(1.5)</td>
<td>0(0.0)</td>
<td></td>
<td>25(1.5)</td>
<td>0(0.0)</td>
<td></td>
</tr>
<tr>
<td>*2/*17</td>
<td>2(0.4)</td>
<td>0(0.0)</td>
<td></td>
<td>11(0.7)</td>
<td>1(10.0)</td>
<td></td>
</tr>
<tr>
<td>*3/*17</td>
<td>2(0.4)</td>
<td>0(0.0)</td>
<td></td>
<td>4(0.2)</td>
<td>0(0.0)</td>
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</tr>
<tr>
<td>*1/*2</td>
<td>193(36.6)</td>
<td>2(50.0)</td>
<td></td>
<td>565(34.3)</td>
<td>5(50.0)</td>
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</tr>
<tr>
<td>*1/*3</td>
<td>59(11.2)</td>
<td>0(0.0)</td>
<td></td>
<td>177(10.8)</td>
<td>2(20.0)</td>
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</tr>
<tr>
<td>*2/*2</td>
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<td>2(50.0)</td>
<td></td>
<td>134(8.1)</td>
<td>1(10.0)</td>
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<tr>
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<td>30(5.7)</td>
<td>0(0.0)</td>
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<td>82(5.0)</td>
<td>0(0.0)</td>
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<tr>
<td>*3/*3</td>
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<td>0(0.0)</td>
<td></td>
<td>17(1.0)</td>
<td>0(0.0)</td>
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<tr>
<td>CYP2C19 Classified</td>
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<td></td>
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<tr>
<td>EM</td>
<td>199(37.7)</td>
<td>0(0.0)</td>
<td></td>
<td>671(40.8)</td>
<td>2(20.0)</td>
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<tr>
<td>IM</td>
<td>252(47.7)</td>
<td>2(50.0)</td>
<td></td>
<td>742(45.1)</td>
<td>7(70.0)</td>
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<tr>
<td>PM</td>
<td>77(14.6)</td>
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<td></td>
<td>233(14.2)</td>
<td>1(10.0)</td>
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<tr>
<td>IM and PM</td>
<td>329(62.3)</td>
<td>4(100.0)</td>
<td>0.302</td>
<td>975(59.2)</td>
<td>8(80.0)</td>
<td>0.216</td>
</tr>
</tbody>
</table>

*Values are number (%). †P values were calculated using the fisher's exact test