Cardiovasc Prev Pharmacother. 2019 Oct;1(2):63-70
https://doi.org/10.36011/cpp.2019.1.e8
eISSN 2671-700X

Cardiovascular Prevention and Pharmacotherapy

Original Article

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CYP2C19 Polymorphisms and Smoking Status Affects Responsiveness to the Platelet P2Y12 Receptor Antagonist Clopidogrel

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OPEN ACCESS

Received: Aug 29, 2019
Accepted: Oct 9, 2019

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ABSTRACT

Background: The "comparison of triflusal and clopidogrel effects in secondary prevention of stroke based on cytochrome P450 2C19 (CYP2C19) genotyping (MAESTRO)" study was a prospective, multicenter, randomized, open-label, and blind genotype trial. We performed a subgroup analysis of the MAESTRO study to explore the relationship between VerifyNow P2Y12 assay with regard to CYP2C19 polymorphisms and smoking status in patients with non-cardiogenic ischemic stroke who underwent clopidogrel treatment.
Methods: For the study, patients treated with clopidogrel and who underwent VerifyNow P2Y12 assay was selected from the MAESTRO study.
Results: Of the 393 patients in 18 hospitals, 256 (65%) patients in 12 hospitals were entered for this subgroup analysis. P2Y12 reaction unit (PRU) was significantly lower and percent inhibition (% INH) was higher in the current smoking group than in the nonsmoking group ($p<0.001$). The same results were also observed in the good genotype group when compared with the poor genotype group ($p<0.001$). Among the groups, significant lower PRU and higher % INH was demonstrated in current smoking with good genotype group. However, there was no difference in PRU and % INH between current smoking with poor genotype group and nonsmoking with good genotype group, suggesting that clopidogrel activity was concurrently related to CYP2C19 polymorphisms and smoking status.
Conclusions: Regarding secondary stroke prevention, patients who were current smokers and had a poor genotype for clopidogrel metabolism may benefit from clopidogrel treatment similar to that in patients who were nonsmokers and had a good genotype.

Keywords: Clopidogrel; Polymorphism, genetic; Polymorphism, Single nucleotide; Smoking; Stroke

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Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Lee KY; Data curation: Han SW, Lee KY; Formal analysis: Han SW, Nam HS, Lee KY; Funding acquisition: Lee JH, Lee KY; Investigation: Han SW, Kim YJ, Seo WK, Yu S, Nam HS, Yoon SS, Kim SH, Lee JY, Lee JH, Hwang YH, Lee J, Lee KA, Lee KY; Methodology: Kim YJ, Kim SH, Hwang YH, Lee KA, Lee KY; Project administration: Kim YJ, Lee KY; Resources: Lee J, Lee KY; Supervision: Lee KY; Validation: Yu S, Nam HS, Lee KA, Lee KY; Visualization: Yu S, Lee KA; Writing - original draft: Han SW; Writing - review & editing: Lee KY.

INTRODUCTION

The "comparison of triflusal and clopidogrel effects in secondary prevention of stroke based on cytochrome P450 2C19 (CYP2C19) genotyping (MAESTRO)" study was a prospective, multicenter, randomized, open-label, and blind genotype trial.[1] It was designed to compare the efficacy and safety of antiplatelet agents for the secondary prevention of ischemic stroke based on CYP2C19 polymorphisms. The major finding of the MAESTRO study was that in the clopidogrel treatment group, a good CYP2C19 genotype for clopidogrel metabolism was associated with a 31% decrease in the relative risk of recurrent stroke. A 41% decrease in the relative risk of recurrent ischemic stroke in the good CYP2C19 genotype group was observed, although these values were bounded by a wide confidence interval.

Several studies have shown that cigarette smoking could influence the antiplatelet effect of clopidogrel by affecting the activity of the cytochrome P450 (CYP) system.[2][3] Clopidogrel requires oxidation by the hepatic CYP system to generate the active metabolite and CYP2C19 plays a major role in the metabolism of clopidogrel.[4] In the "Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events" trial, a smoking–clopidogrel paradox was observed among patients with a recent minor stroke or transient ischemic attack.[5] Compared with nonsmokers, smokers treated with clopidogrel had secondary stroke prevention at 90 days from clopidogrel treatment. Recently, it has also been shown that enhanced clopidogrel response in smokers is not a universal effect but is rather dependent on genotype status.[6]

The VerifyNow P2Y12 assay is a whole blood optical detection test based on the measurement of the increase in light transmission. It is intended to directly measure the effects of clopidogrel on the P2Y12 receptor and to overcome the limitations of the conventional optical platelet aggregation assay.[7] The outcomes are expressed as P2Y12 reaction unit (PRU) and percent inhibition (% INH), with high PRU and low % INH indicating clopidogrel resistance (CR).[8] There is emerging evidence pertaining to the relationship between CR and functional outcome, stroke recurrence, and mortality following ischemic stroke. However, there is no evidence as yet, based on VerifyNow assay in relation to CYP2C19 polymorphisms and smoking status, that CR is more clinically informative at predicting recurrent vascular events after ischemic stroke.[9][10]

In this context, we performed a subgroup analysis of the MAESTRO study to explore the relationship between VerifyNow P2Y12 assay with regard to CYP2C19 polymorphisms and smoking status in patients with non-cardiogenic ischemic stroke who underwent clopidogrel treatment.

METHODS

The design and method of the MAESTRO study have been published previously.[11] Briefly, patients were eligible if they were 20 years of age or older and had their first non-cardiogenic ischemic stroke. In the clopidogrel treatment group, patients received 75 mg clopidogrel once daily. All patients received appropriate medical treatments at the discretion of the attending neurologist, including anti-hypertensive treatment, statin treatment, and rigorous control of vascular risk factors.

CYP2C19 genotype status was assessed using the Seeplex CYP2C19 ACE Genotyping system (Seegene, Seoul, Korea) and Real-Q CYP2C19 genotyping kit (Biosewoom, Seoul, Korea).

https://doi.org/10.36011/cpp.2019.1.e8

Patients were classified as ultrarapid metabolizer (UM; *1/*17, *17/*17), extensive metabolizer (EM; *1/*1), intermediate (IM)/unknown metabolizer (*1/*2, *1/*3 and *2/*17, *3/*17), or poor metabolizer (PM; *2/*2, *2/*3, *3/*3) based on CYP2C19 genotype status. For the study, patients with UM or EM status were allocated into the good genotype group for clopidogrel metabolism, and patients with IM/unknown metabolizer or PM status were allocated into the poor genotype group.[1)]

CR was tested using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA). Blood samples were obtained from patients 2 and 12 weeks after study enrollment. All patients received 75 mg clopidogrel once daily for at least 7 consecutive days before testing. The assay was performed according to the manufacturer's instructions. In the P2Y12 assay, % INH was calculated for each patient as follows: % INH = ([baseline PRU − post-drug PRU] ÷ baseline PRU) × 100. The PRU specifies the amount of ADP P2Y12 platelet receptor-mediated platelet aggregation and is inversely related to the antiplatelet function.[8)] If the PRU is low, % INH and antiplatelet activity increased. Current smokers were defined as those who smoked regularly during the past month. Nonsmokers were defined as those who never smoked or patients who stopped smoking for >1 month before enrollment. All patients provided written informed consent prior to participation in the study. The study design was approved by the appropriate ethics review board and conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of each participating hospital (Gangnam Severance Hospital, No. 3-2009-0192).

Statistical analyses

Variables were tested for normality using the Kolmogorov–Smirnov test. The baseline parameters of each group were analyzed using 1-way ANOVA with a Tukey's post hoc test for continuous variables, where appropriate. Univariate analyses of demographics, vascular risk factors, and medical history were performed using an independent sample t-test or the Mann–Whitney U test for continuous variables and the χ^2 test for categorical variables. Pearson's and Spearman's correlation coefficients were calculated to evaluate the correlations of PRU and % INH with demographics and vascular risk factors. Descriptive data were expressed as numbers (percent) or mean±standard deviation. Statistical analyses were performed using SPSS version 25.0 for Windows (IBM, Armonk, NY, USA).

RESULTS

A total of 784 patients were included in the MAESTRO study. Clopidogrel was administered to 393 patients (50%). Of the 393 patients in 18 hospitals, 256 (65%) patients in 12 hospitals were entered for this subgroup analysis. The median duration of follow-up was 3.0 years (range, 0–4.5). **Table 1** shows the baseline characteristics of enrolled patients. The mean age was 61 years, and 29% of the patients were women. Fifty-four percent of patients had a history of hypertension, 25% had diabetes, 24% had dyslipidemia, and 38% were current tobacco smokers. The most frequent genotype in all patients was IM (118, 46%), followed by EM (91, 35%), PM (42, 16%), UM (3, 2%), and unknown (2, 1%). Accordingly, 94 (37%) had a good genotype for clopidogrel metabolism and 162 (63%) had a poor genotype. Current smoking patients, who were younger men, had higher hemoglobin and hematocrit levels and lower hypertension and antihypertensive use rates than those for nonsmoking patients, likely related to the differences in habits by gender and age (**Table 1**). There were no other significant differences in the demographics and clinical findings among the groups.

https://doi.org/10.36011/cpp.2019.1.e8

Table 1. Baseline demographics and characteristics of the participants

Genotype	Total (n=256)	Current smoking (n=98, 38%)		Nonsmoking (n=158, 62%)		p value
		Good (n=37, 15%)	Poor (n=61, 24%)	Good (n=57, 22%)	Poor (n=101, 39%)	
Age (years)	61.0±11.1	57.8±11.2	57.1±10.9	63.8±9.5	63.0±11.4	0.005*
Female (sex)	74 (29)	1 (3)	2 (3)	23 (40)	48 (48)	0.001*
Hypertension	137 (54)	10 (27)	34 (56)	35 (61)	58 (57)	0.006*
Diabetes mellitus	63 (25)	7 (19)	17 (28)	14 (25)	25 (25)	0.802
Hypercholesterolemia	61 (24)	7 (19)	14 (23)	15 (26)	25 (25)	0.859
Ischemic heart disease	7 (3)	1 (3)	1 (2)	2 (4)	3 (3)	0.935
Hemoglobin (g/dL)	13.9±1.7	14.5±1.6	14.5±1.5	13.6±1.5	13.5±1.7	0.001*
Hematocrit (%)	40.9±4.5	42.6±4.3	42.6±4.2	40.0±4.2	39.8±4.4	0.001*
Platelet count (10^3/mm^3)	237.0±55.2	233.0±39.7	246.0±54.8	237.0±57.3	233.0±59.1	0.470
Stroke classification						0.293
LAA	52 (20)	4 (11)	17 (28)	11 (19)	20 (20)	
Lacune	136 (53)	22 (59)	32 (52)	26 (46)	56 (55)	
SUDn	68 (27)	11 (30)	12 (20)	20 (35)	25 (25)	
Use of antihypertensive at any follow-up visit	166 (65)	17 (46)	38 (62)	42 (74)	69 (68)	0.037*
Use of statin at any follow-up visit	224 (88)	33 (89)	47 (77)	52 (91)	92 (91)	0.064

Data are number (% of total participants) or mean±standard deviation.
LAA, large artery atherosclerosis; SUDn, stroke of undetermined etiology.
*Significant p is marked.

The results of the VerifyNow P2Y12 assay among the groups are presented in **Table 2**. PRU was significantly lower and % INH was higher in the current smoking group than in the nonsmoking group (p<0.001). The same results were also observed in the good genotype group when compared with the poor genotype group (p<0.001). Smoking status adjusted partial correlation analysis showed that CYP2C19 polymorphisms were related to PRU and % INH in patients with non-cardiogenic ischemic stroke who underwent clopidogrel treatment (r=0.371, p<0.0001). CYP2C19 polymorphisms adjusted partial correlation analysis demonstrated that smoking status was related to PRU and % INH as well (r=0.197, p=0.002). Among the groups, significant lower PRU and higher % INH was demonstrated in current smoking with good genotype group. However, there was no difference in PRU and % INH between current smoking with poor genotype group and nonsmoking with good genotype group, suggesting that clopidogrel activity was concurrently related to CYP2C19 polymorphisms and smoking status (**Figure 1**).

DISCUSSION

In this study, we investigated the relationship between VerifyNow P2Y12 assay with regard to CYP2C19 polymorphisms and smoking status in patients with non-cardiogenic ischemic stroke. There was no significant difference in PRU and % INH between current smoking with poor genotype group and nonsmoking with good genotype group. Our study clearly showed

Table 2. Clopidogrel PRU and % INH according to smoking status and CYP2C19 genotyping

Genotype	Total (n=256)	Current smoking (n=98)		Nonsmoking (n=158)		p value
		Good	Poor	Good	Poor	
2 weeks						
PRU	215.0±77.0	163.0±68.9	215.0±60.6	185.0±74.8	248.0±74.6	0.001*
% INH	32.0±21.0	43.0±22.6	33.0±14.1	40.0±21.9	23.0±19.3	0.001*
12 weeks						
PRU	226.0±67.0	195.0±61.1	216.0±43.9	209.0±75.6	249.0±69.0	0.001*
% INH	28.0±17.2	39.0±15.7	27.0±14.7	34.0±20.1	24.0±15.5	0.001*

CYP2C19, cytochrome P450 2C19; % INH, percent inhibition; PRU, P2Y12 reaction unit.
*Significant p is marked.

https://doi.org/10.36011/cpp.2019.1.e8

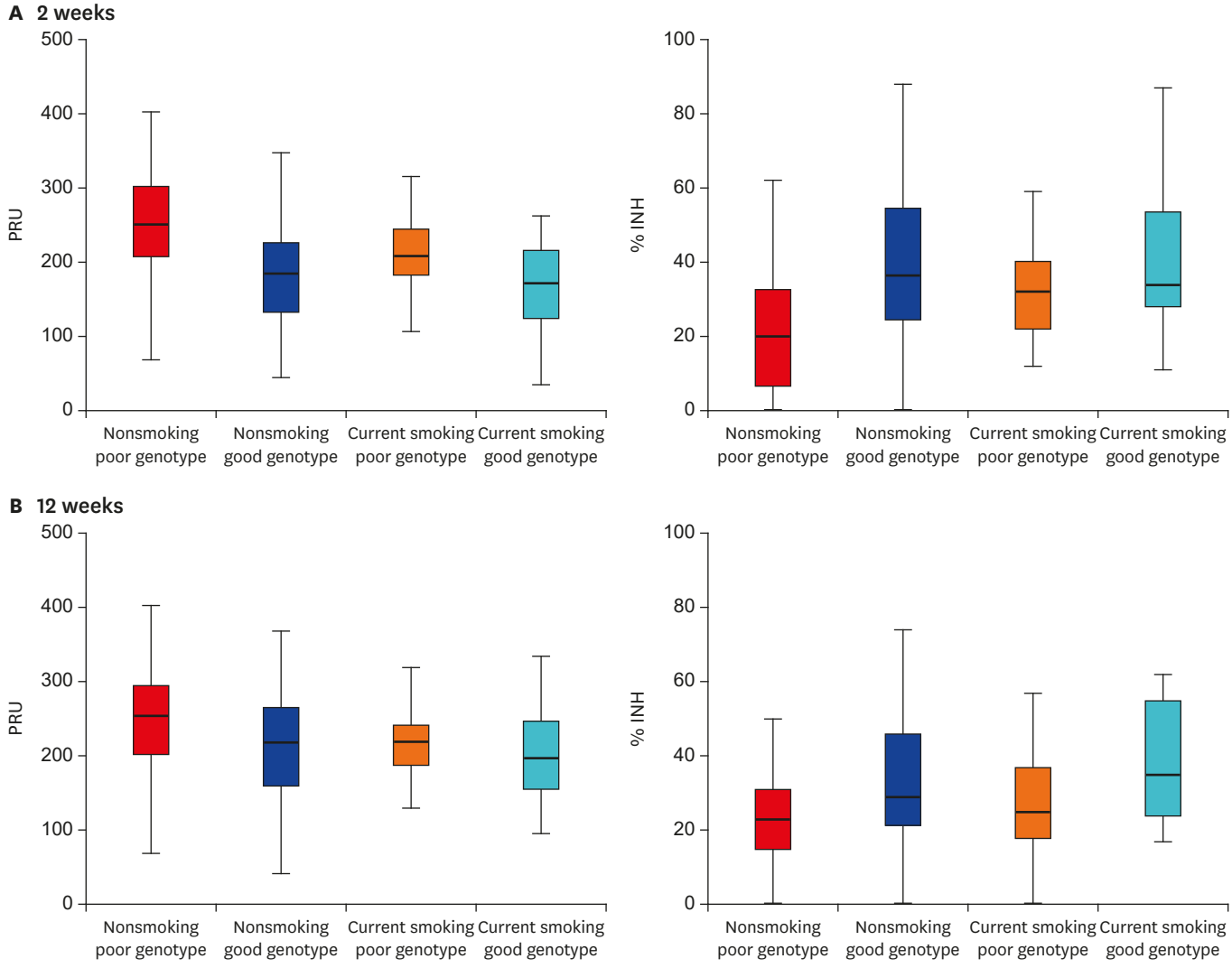
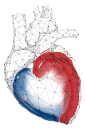


Figure 1. Clopidogrel PRU and % INH according to smoking status and CYP2C19 genotyping. Among the groups, significant lower PRU and higher % INH is demonstrated in current smoking with good genotype group. However, there are no difference in PRU and % INH between current smoking with poor genotype group and nonsmoking with good genotype group, suggesting that clopidogrel activity is concurrently related to CYP2C19 polymorphisms and smoking status. CYP2C19, cytochrome P450 2C19; % INH, percent inhibition; PRU, P2Y12 reaction unit.

that responsiveness to the platelet P2Y12 receptor antagonist clopidogrel was related to both CYP2C19 polymorphisms and smoking status. Smoking status modified the results of VerifyNow P2Y12 assay according to the CYP2C19 polymorphisms.

Factors associated with clopidogrel response variability include clinical and genetic variables.[10)12)] The clinical factors consist of age, smoking, inflammation, diabetes, high body mass index, renal failure, and heart failure. Previous studies have shown that the various platelet function test systems detect different aspects of platelet activation and may be affected by different factors to a variable degree.[12)] Of these test systems, VerifyNow P2Y12 assay is a whole blood point-of-care test. Similar to light transmission aggregometry, the VerifyNow P2Y12 assay registers the increase of light transmittance through the sample after addition of ADP and converts this increase into the extent of platelet aggregation.[13)] The advantages of this assay include full automation, good reproducibility, use of whole blood, and small blood volume requirement.[10)] While a meta-analysis showed that the

https://doi.org/10.36011/cpp.2019.1.e8



VerifyNow P2Y12 assay is a useful tool for predicting cardiovascular events in patients treated with clopidogrel, altering antiplatelet therapy based on VerifyNow P2Y12 assay has not been shown to improve vascular outcomes in patients with coronary artery disease (CAD).[14][15] There is also little evidence from VerifyNow P2Y12 assay in relation to CYP2C19 polymorphisms that CR is more clinically informative at predicting recurrent vascular events during follow-up after ischemic stroke.[9] Owing to the diverse etiology of ischemic stroke, data on ex vivo platelet function test from CAD patients cannot be extrapolated to those with ischemic stroke. Regarding cigarette smoking, several studies have shown enhanced pharmacodynamics effect of the platelet P2Y12 receptor antagonist clopidogrel in smokers, a phenomenon known as the "smoker's paradox."[16] It has been postulated that smoking is an inducer of clopidogrel metabolism by inducing CYP1A2 activity, resulting in low platelet aggregation with clopidogrel treatment.[5][17] A meta-analysis demonstrated that current smokers have increased platelet inhibition and lower aggregation in response to clopidogrel than that in nonsmokers.[16] However, smoking is an important independent risk factor for recurrent stroke.[18][19] Our study revealed that although there was no significant difference between smokers and nonsmokers, current smokers had a higher number of major vascular events (10.2% vs. 3.4%, p=0.402). Rather than encourage smoking, it is important to recognize nonsmokers as a greater risk of having a poor antiplatelet response from the clopidogrel treatment. We believe that it is reasonable to recommend patients with ischemic stroke to stop cigarette smoking.

The strengths of this study are the long-term follow-up and good medication adherence among the patients. The median duration of follow-up was 3.0 years and the patients had >80% medication adherence during the trial. VerifyNow P2Y12 assay was performed on the same patients 2 and 12 weeks after study enrollment. It may have the potential to provide more clinically meaningful information than that from a traditional cross-sectional single test. There are several limitations to this study, the first and most important of which is that the sample size for this subgroup analysis was small and was not determined a priori. During the trial, a total of 13 (5%) patients had recurrent stroke: 10 (77%) experienced an ischemic stroke and 3 (23%) experienced an intracerebral hemorrhage. There was no significant reduction in the risk of recurrent stroke or a major vascular event among the groups (p>0.358). Second, clopidogrel response may be affected by several clinical factors. Owing to the small number of vascular outcomes, we could not evaluate clinical factors associated with clopidogrel response variability. Finally, this study enrolled only Korean patients, limiting the generalizability of our findings to other geographic regions. These limitations should be considered during the interpretation of our data.

In conclusion, our study showed that responsiveness to the platelet P2Y12 receptor antagonist clopidogrel was related to both CYP2C19 polymorphisms and smoking status. Regarding secondary stroke prevention, patients who were current smokers and had a poor genotype for clopidogrel metabolism may benefit from clopidogrel treatment similar to that in patients who were nonsmokers and had a good genotype. Further larger clinical trials are essential to establish whether current smoking may have a significant role in patients who had stroke and are undergoing clopidogrel treatment.

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https://doi.org/10.36011/cpp.2019.1.e8

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