CYP2C19 polymorphisms in the Thai population and the clinical response to clopidogrel in patients with atherothrombotic-risk factors

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Abstract: Genetic variation in the cytochrome P450 2C19 (CYP2C19) gene has been documented gradually as the determinant conversion and variability in the antiplatelet effect of clopidogrel. The aims of this study were to determine the prevalence of clinically relevant allele variants (CYP2C19*2, CYP2C19*3, and CYP2C19*17) in a Thai study population, and finally determine whether the allele distributes and predicts metabolic phenotypes in clopidogrel treated patients. A total of 1,051 Thai patients participated in this study. Genotypes for CYP2C19 polymorphisms were detected by the microarray-based technique. Furthermore, results of genotyping and platelet aggregation in 96 cardiovascular disease patients on 75 mg clopidogrel maintenance daily dose therapy also were analyzed. Among 1,051 samples, the allele frequencies of CYP2C19 *1/*1, *1/*2, *1/*3, *2/*2, *2/*3, and *1/*17 were found in 428 (40.72%), 369 (35.10%), 72 (6.85%), 77 (7.32%), 59 (5.61%), and 45 (4.30%) of the patients, respectively. Homozygous CYP2C19 *3/*3 was found in one patient (0.10%). Therefore, 40.72% of the patients were predicted as extensive metabolizers, 41.95% as intermediate metabolizers, 13.03% as poor metabolizers, and 4.30% as ultra-rapid metabolizers. Among 96 patients, the frequency of poor metabolizers was significantly higher in the clopidogrel non-responder group than in the responder group (36.0% and 15.5%, respectively, P = 0.03). CYP2C19*1/*17 was observed in responders (n = 2; 2.8%). As a result, CYP2C19 variants were associated with clopidogrel non-responders. However, there is a need for further elucidation of the clinical importance and use of this finding to make firm and cost-effective recommendations for drug treatment in the future.

Keywords: CYP2C19 polymorphisms, Thai population, clopidogrel, responders, non-responders

Introduction
Cytochrome P450 2C19 (CYP2C19) is a major enzyme of the cytochrome P450 family, and is responsible for the metabolism of a number of therapeutic drugs. Genetic polymorphism of these drug metabolizing enzymes causes interindividual variability in the response to drugs. CYP2C19 plays an important role in many clinically important drugs and xenobiotic compounds including barbiturates, diazepam, lansoprazole, omeprazole, proguanil, propranolol, and clopidogrel.1–3

Clopidogrel is a thienopyridine derivative antiplatelet drug and an inactive prodrug, which requires transformation into an active thiol metabolite via several hepatic CYP450 enzymes for exerting its antiplatelet effects.4 Hepatic metabolizing of clopidogrel is achieved by a number of different cytochrome P450 subfamilies, including CYP2C19, CYP3A4, CYP3A5, CYP1A2, CYP2B6, and CYP2C9.
Accumulating evidence of the polymorphically expressed isoenzyme, CYP2C19, constitutes a dominant part in this process.4–10 About 24 mutant allelic variants of CYP2C19 are known, of which CYP2C19*2, CYP2C19*3, and CYP2C19*17 are the most important. CYP2C19 polymorphisms lead to a defective or nonfunctional protein, or inactive enzyme; hence, the lack of ability to metabolize clopidogrel into an active metabolite leads to a diminished response to antiplatelet effects, therapeutic failure, and possible increased risk of cardiovascular events. Furthermore, individual carriers of the CYP2C19*2 allele are at three times greater risk of stent thrombosis than non-carriers.7 This finding is consistent with the potential immediate loss of a platelet-inhibitory effect. On the other hand, individuals with homozygous and heterozygous genotypes for the wild-type CYP2C19*1 allele can metabolize drugs at a fast rate (called extensive metabolizers), which may lead to an increased risk of side effects and drug toxicity.11–15 Variability of the enzyme for CYP2C19 drug metabolism is responsible for the pronounced interindividual differences in plasma concentration and for the clinical outcome in patients receiving the recommended dose of clopidogrel. The mechanisms leading to a poor response to clopidogrel have not been understood fully and are most likely multifactorial and closely related to levels of active metabolite formation.10,16,17 Several studies suggest that the response to clopidogrel and its variability may be influenced not only by genetic variation in the genes encoding CYP2C19 enzymes, but also lack of compliance, clinical factors, pharmacokinetic variables, and the nature of coronary event.5,6,10,17–22 The poor metabolizers that predicted the metabolic phenotype were shown to represent 2%–5% of Caucasian,23 4%–8% of African,24,25 and 11%–12% of Asian populations.23,26

Up until now, no data are available on CYP2C19 polymorphism and a clopidogrel non-responder in a Thai population. Additionally, data relating to the genetic polymorphism of CYP2C19 in Thailand are very limited. The aims of this study were to determine the frequencies of clinically relevant allele variants (CYP2C19*2, CYP2C19*3, and CYP2C19*17) in a Thai study population, and finally determine whether the allele distributes in a clopidogrel non-responder population.

Material and methods

Study population

This study was retrospective, and a total of 1,051 unrelated samples were randomly enrolled. In order to determine the frequencies of important allelic variants of CYP2C19, the clinically relevant allele variants; CYP2C19*2 (c.681G>A; rs4244285), CYP2C19*3 (c.636G>A; rs4986893), CYP2C19*17 (g.-806C>T; rs12248560) were genotyped. Of the 1,051 samples, 96 individuals with cardiovascular diseases while receiving treatment with clopidogrel once daily for at least 14 consecutive days were obtained from a cardiology clinic, within the inclusion criteria. Patients with multiple atherothrombotic risk factors, as described, with one major risk (type 2 diabetes mellitus, diabetic nephropathy, ankle-brachial index <0.9 or asymptomatic carotid stenosis ≥70%) or two minor risks (systolic blood pressure ≥140 mmHg, primary hypercholesterolemia, male ≥45 years, or female ≥55 years) were included in this study.

Patients currently using nonsteroidal anti-inflammatory drugs, anticoagulants, aspirin or other antiplatelet drugs, or showing poor compliance with anticipated difficulty in attending follow-up visits, also were excluded. The study was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee, Ramathibodi Hospital, Mahidol University, Thailand.

Definition of clopidogrel responders and non-responders

All 96 patients received 75 mg of clopidogrel and blood samples for identifying their genotype and phenotype (adenosine diphosphate [ADP]-induced platelet aggregation) were collected during treatment. The patients were categorized into two groups (clopidogrel responders and non-responders) according to their phenotype, using platelet response as assessed by transmitted light aggregation (BLT) techniques. Optical platelet aggregometry with 5 and 10 μmol of ADP was used to measure the platelet response. Platelet rich plasma was pipetted into a cuvette, which then was incubated for 2 minutes at 37°C. ADP of 5 and 10 μmol was added into the platelet rich plasma, with the final concentration of ADP being 10 mol/mL. A control specimen was evaluated daily in the same manner as that for each test specimen in order to ensure reagent performance. The control consisted of fresh platelet rich plasma collected from a normal donor, who had not ingested aspirin or clopidogrel within the past 14 days. Therefore, clopidogrel responders were defined as patients with a platelet inhibition percentage of ≥10% pre- and post-treatment, while clopidogrel non-responders were classified as patients with a platelet inhibition percentage of <10% pre- and post-treatment.27
DNA extraction and CYP2C19 genotyping

Genomic DNA was extracted from venous blood specimens with the use of a purifier kit (QIAamp DNA Blood mini kit; Qiagen NV, Venlo, Netherlands) according to the manufacturer’s instructions. The association of genetic variants in the CYP2C19 gene encoding enzyme was tested in this study to assess the effect of CYP2C19*2 (splicing defect G681A SNP), CYP2C19*3 (stop codon G636A SNP) and CYP2C19*17 (increased enzyme activity g.-806 C>T) allelic variation in response to clopidogrel. A microarray-based technique (AmpliChip CYP450 test; Roche, Basel, Switzerland) was performed to genotype the CYP2C19 gene (*1/*2/*3). Regarding the predicted metabolic phenotypes related to CYP2C19 polymorphisms, an extensive metabolizer was defined as a patient who had a homozygous wild-type genotype (CYP2C19*1/*1) and an ultra-rapid metabolizer was defined as a patient who had a heterozygous genotype with at least one CYP2C19*17 allele (CYP2C19*1/*17 or CYP2C19*17/*17). An intermediate metabolizer was defined as a patient who had a heterozygous genotype with at least one CYP2C19*1 allele (CYP2C19*1/*2 or *1/*2), and a poor metabolizer was classified as a patient who had a homozygous (CYP2C19*2/*2 or *3/*3) or heterozygous (CYP2C19*2/*3) genotype with a mutant allele.

Data analysis

Genotyping and allele frequencies were calculated by counting. Expected genotype frequencies were calculated using the Hardy-Weinberg equation from allele frequencies (p² + 2pq + q² = 1), where p was the frequency of the CYP2C19*1 allele and q was the combined allele frequency of CYP2C19*2, CYP2C19*3, and CYP2C19*17. Hardy-Weinberg equilibrium and linkage disequilibrium analyses were performed with the Haploview version 4.0 software (Broad Institute of MIT and Harvard, Cambridge, MA, USA). The chi-square test was performed for comparative analysis of the allelic and genotypic frequencies for CYP2C19 polymorphisms, and predicted metabolic phenotype frequency, according to clopidogrel response. All other statistical analyses were carried out with the level of significance set at P < 0.05.

Results

Allelic and genotype frequencies for CYP2C19 in Thai population

CYP2C19 polymorphisms (*1, *2, *3, and *17) genotypes were available for 1,051 subjects. The relative prevalence of allele frequencies among the patients is summarized in Tables 1 and 2. Of the 1,051 subjects included in this study, the frequency of alleles CYP2C19*1, *2, *3, and *17 was 0.63, 0.27, 0.06, and 0.04, respectively. In addition, 428 subjects (40.72%) were homozygous for the *1/*1 genotype. Heterozygous genotypes were identified in 369 patients carrying CYP2C19*1 with the *2 (*1/*2, 35.10%) allele, and 72 with *3 (*1/*3, 6.85%). Homozygous genotypes for the lost-function alleles, CYP2C19 *2/*2 and *2/*3, were made up 7.32% (n = 77) and 5.61% (n = 59) of the sample population, respectively. Only one patient was found to be homozygous for the CYP2C19 *3/*3 allele (0.01%). In the present study, 45 (4.3%) samples were CYP2C19*1/*17, and none was homozygous (*17/*17). No subject was found to be CYP2C19*2/*17 or CYP2C19*3/*17.

Effect of the metabolizer phenotype on the response of clopidogrel

The study population included females (71.9%) and males (28.1%), with an average age of 65 ± 9.8 years. The ratio of previous smokers to non-smokers was 1.3. The prevalence of factors that are associated with high risk in cardiovascular disease was 86.3%, 89.5%, and 29.5% for hypertension, dyslipidemia, and diabetes, respectively. Patients in this study were undergoing treatment with additional medications, including statins (78.9%) and angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs; 46.3%). The patient demographics and clinical characteristics of age, gender, sex, comorbidity, and laboratory results were found to be statistically insignificant across the groups. However, cholesterol levels were significantly higher in the clopidogrel non-responders (P = 0.023). The patient demographics and clinical characteristics are summarized in Table 3.

The 96 patients receiving clopidogrel were categorized into two groups, ie, clopidogrel responders (n = 71; 73.96%) and clopidogrel non-responders (n = 25; 26.04%), according to their phenotype, and the platelet response

| Table 1 | Allele frequency of CYP2C19 polymorphisms (*1, *2, *3, and *17) of 1,051 unrelated samples |
|---------|------------------------------------------|
| Alleles of CYP2C19 | Allele (number) | Frequency |
| *1 (Wild type) | 1,318 | 0.63 |
| *2 (c. 681G>A) | 568 | 0.27 |
| *3 (c. 636G>A) | 126 | 0.06 |
| *17 (g.-806C>T) | 90 | 0.04 |
| Total number | 2,102 | 1.00 |

Abbreviation: CYP2C19, cytochrome P450 2C19.
was assessed by LTA techniques. Data relating to the number of cohort patients are summarized in Table 4. The predicted phenotypes of extensive metabolizers, intermediate metabolizers, poor metabolizers, and ultra-rapid metabolizers in the clopidogrel responders group were 32 (45.1%), 26 (36.6%), 11 (15.5%), and 2 (2.8%), respectively, whereas, the predicted phenotypes in the clopidogrel non-responders were extensive metabolizers (n = 9; 36.0%), intermediate metabolizers (n = 7; 28.0%), and poor metabolizers (n = 9; 36.0%). The proportion of extensive metabolizers was significantly higher in the responders group than in the non-responders group. However, no significant difference was observed in the frequency (45.1% and 36.0%, respectively, P = 0.304). Remarkably, the frequency of the poor metabolizers phenotype in the non-responders group was significantly higher than in the responders group, (36.0% and 15.5%, respectively, P = 0.03). In addition, two patients (2.8%) who were heterozygous for the *17 allele variant (CYP2C19 *1/*17) were observed in the clopidogrel responders group.

### Discussion

The Thai population is one of the most heterogeneous in the world. In order to determine the distribution of CYP2C19 polymorphisms in a Thai study population, the clinically relevant allele variants (CYP2C19*2, splicing defect G681A; CYP2C19*3, stop codon G636A; and CYP2C19*17, C806T) were genotyped in 1,051 subjects. To the best of our

### Table 2 Genotype frequency of CYP2C19 polymorphisms (*1, *2, *3, and *17) of 1,051 unrelated samples

| Genotypes   | Samples (number) | Frequency (%) |
|-------------|------------------|---------------|
| Extensive metabolizer *1/*1 | 428 | 40.72 |
| Intermediate metabolizer *1/*2 | 369 | 35.10 |
| Poor metabolizer *2/*2 | 77 | 6.85 |
| *2/*3 | 59 | 5.61 |
| *3/*3 | 1 | 0.10 |
| Ultra-rapid metabolizer *1/*17 | 45 | 4.30 |
| Total | 1,051 | 100.00 |

**Abbreviation:** CYP2C19, cytochrome P450 2C19.

### Table 3 Patient demographics and clinical characteristics of the studied patients treated with clopidogrel

| Demographic and clinical data | Responder (n = 71) | Non-responder* (n = 25) | Total (n = 96) | P-value |
|-------------------------------|-------------------|-------------------------|---------------|---------|
| Age (mean ± SD)               | 65 ± 10.1         | 64 ± 8.8                | 65 ± 9.8      | 0.412   |
| Gender                        |                   |                         |               |         |
| Male (n; %)                   | 22 (31)           | 5 (20)                  | 27 (28.1)     | 0.340   |
| Female (n; %)                 | 49 (69)           | 20 (80)                 | 68 (71.9)     |         |
| Smoking                       |                   |                         |               |         |
| Quit (n; %)                   | 19 (26.8)         | 3 (12.5)                | 22 (23.2)     | 0.152   |
| Never smoke (n; %)            | 52 (73.2)         | 21 (87.5)               | 73 (76.8)     |         |
| Co-morbidity (n; %)           |                   |                         |               |         |
| Hypertension                  | 61 (85.9)         | 21 (87.5)               | 82 (86.3)     | 0.845   |
| Dyslipidemia                  | 65 (91.5)         | 20 (83.3)               | 85 (89.5)     | 0.257   |
| Diabetes                      | 21 (29.6)         | 7 (29.2)                | 28 (29.5)     | 0.834   |
| Current use of Statin (n; %)  | 58 (81.7)         | 17 (70.8)               | 75 (78.9)     | 0.259   |
| Current use of ACEI/ARB (n; %)| 33 (46.5)         | 11 (45.8)               | 44 (46.3)     | 0.956   |
| Body mass index (mean ± SD)   | 25.4 ± 4.5        | 26.9 ± 4.3              | 25.8 ± 4.4    | 0.147   |
| SBP (mmHg) (mean ± SD)        | 134 ± 14.8        | 128 ± 13.7              | 132 ± 14.6    | 0.127   |
| DBP (mmHg) (mean ± SD)        | 74 ± 10.1         | 75 ± 10.3               | 74 ± 10.1     | 0.586   |
| Laboratory results (mean ± SD)|                   |                         |               |         |
| Hematocrit (mg%)              | 39.3 ± 3.9        | 38.6 ± 3.4              | 39.2 ± 3.8    | 0.447   |
| Platelet count 10^9/mm^3       | 273 ± 65.8        | 275 ± 67.1              | 273 ± 65.7    | 0.878   |
| FBS (mg/dl)                   | 108 ± 22.5        | 104 ± 26.6              | 107 ± 23.6    | 0.427   |
| Creatinine (mg/dl)            | 0.92 ± 0.24       | 0.85 ± 0.19             | 0.90 ± 0.23   | 0.146   |
| Triglyceride (mg/dl)          | 141 ± 87          | 126 ± 41.6              | 137 ± 78.0    | 0.408   |
| Cholesterol (mg/dl)           | 186 ± 39.3        | 208 ± 39.3              | 191 ± 40.2    | 0.023   |
| LDL (mg/dl)                   | 109 ± 33.8        | 123 ± 35.9              | 113 ± 34.7    | 0.083   |
| Total protein (g/L)           | 79 ± 5.1          | 78 ± 4.6                | 78 ± 4.9      | 0.635   |
| Albumin (g/L)                 | 41 ± 3.2          | 40 ± 2.8                | 41 ± 3.1      | 0.444   |

**Notes:** *Only gender, genotype, and phenotype were available for one non-responder.

**Abbreviations:** ACEI/ARB, angiotensin-converting-enzyme inhibitor/angiotensin receptor blockers; DBP, diastolic blood pressure; FBS, fasting blood sugar; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.
knowledge, this is the first study to report the allele frequency of the CYP2C19*17 allelic variant in the Thai population. The highest native allele frequency was for CYP2C19*1 (0.63), followed by CYP2C19*2 (0.26), CYP2C19*3 (0.06), and CYP2C19*17 (0.04). All genotype distributions were in Hardy-Weinberg equilibrium. This result was similar to that in a previous study in northeast Thailand. The prevalence of subjects with the gain-of-function allele (CYP2C19*1/*17) in the studied population was 4.3%.

There was no difference in frequency of the CYP2C19*2 allelic variants among Asians in this study, but there was a difference in Caucasians. In this study, CYP2C19*3 was detected in only one case. The allele frequency of CYP2C19*3 in this study was no different from that in previous reports on the Thai population. The frequency of CYP2C19*3 defective alleles was only 0.06, which is lower than that of 0.12 in Japanese and Korean subjects (Table 5). Higher frequency of the defective alleles (CYP2C19*2 and *3) in these ethnic populations may explain their higher prevalence of poor metabolizers when compared to other Asian populations. Although CYP2C19*3 is Asian specific, and extremely rare or totally absent in Caucasians, this mutant allele appears to account for the remaining defective alleles in Asians. Our results could be very beneficial in the strategic planning of the clinical implementation of pharmacogenetic testing in Thailand and the region around it.

For the implementation of pharmacogenetic testing in daily clinical practice, it is relevant to translate CYP2C19 genotypes into predicted phenotypes. According to the results of this study, predicted phenotypes could be classified into four categories: extensive metabolizers (CYP2C19*1/*1), intermediate metabolizers (CYP2C19*1/*2 or *1/*3), poor metabolizers (CYP2C19*2/*2 or *3/*3 or *2/*3), and ultra-rapid metabolizers (CYP2C19*1/*17). The most common mutated allele is CYP2C19*2, which accounts for 75%–83% of poor metabolizers’ phenotypes. The CYP2C19 genetic polymorphism shows inter-ethnic differences in the distribution of poor metabolizer traits. The prevalence of poor metabolizers is estimated to be 2%–5% in Caucasians, 4%–8% in Africans, and 11%–23% in Asians. In addition, several independent studies have shown a much higher prevalence of poor metabolizers in the Asian population, of up to 18%–23% in Japanese, 15%–17% in Chinese, and 12%–16% in Koreans. The results of this study showed that the prevalence of the poor metabolizer phenotype is 13.03% (n = 137 of 1,051), which is consistent with other Asian population studies.

Clopigogrel, a prodrug, is a thienopyridine that inhibits ADP-induced platelet aggregation. CYP2C19 is involved in the two steps that contribute to its change into an active metabolite. Pharmacological interests in CYP2C19 polymorphic genes and clopidogrel response have been investigated extensively. The mutant allele of CYP2C19 includes

### Table 4 Predicted phenotypes of 96 subjects according to clopidogrel response

| Predicted phenotypes          | Responders n = 71 (%) | Non-responders n = 25 (%) | P-value* |
|-------------------------------|-----------------------|---------------------------|----------|
| Extensive metabolizer         | 32 (45.1)             | 9 (36.0)                  | 0.304    |
| Intermediate metabolizer      | 26 (36.6)             | 7 (28.0)                  | 0.435    |
| Poor metabolizer              | 11 (15.5)             | 9 (36.0)                  | 0.030    |
| Ultra-rapid metabolizer       | 2 (2.8)               | 0 (0.00)                  | –        |

Note: *P*-values were determined by a chi-square test.

### Table 5 Ethnic variation of CYP2C19 (*1, *2, *3, and *17) in the present study and publications

| Populations          | Number | Alleles frequency of CYP2C19 | Reference |
|----------------------|--------|-----------------------------|-----------|
|                      |        | *1 | *2 | *3 | *17 |
| Thais                | 1,051  | 0.63 | 0.27 | 0.06 | 0.04 | Present study |
| Thais (North East)   | 774    | 0.68 | 0.29 | 0.03 | –   | 14         |
| Chinese-Dai          | 193    | 0.66 | 0.30 | 0.03 | –   | 27         |
| Chinese-Han          | 101    | 0.36 | 0.37 | 0.07 | –   | 28         |
| Malaysian            | 54     | 0.72 | 0.23 | 0.05 | –   | 29         |
| Filipinos            | 52     | 0.54 | 0.40 | 0.08 | –   | 23         |
| North Indians        | 200    | 0.70 | 0.30 | 0.00 | –   | 30         |
| Japanese             | 186    | 0.59 | 0.29 | 0.12 | –   | 26         |
| Koreans              | 103    | 0.67 | 0.21 | 0.12 | –   | 26         |
| Turksiks             | 404    | 0.88 | 0.12 | 0.00 | –   | 31         |
| Saudi Arabians       | 97     | 0.85 | 0.15 | 0.00 | –   | 23,32      |
| European-Americans   | 105    | 0.87 | 0.13 | 0.00 | –   | 23,32      |
| African-Americans    | 108    | 0.75 | 0.25 | 0.00 | –   | 23,32      |
| Iranian              | 200    | 0.86 | 0.14 | 0.00 | –   | 33         |

Abbreviation: CYP2C19, cytochrome P450 2C19.
the single base pair mutation, \textit{CYP2C19}*2; c.681G>A, \textit{CYP2C19}*3; c.636G>A, which leads to a defective and non-functional protein, causing poor ability to metabolize clopidogrel into an active metabolite and reduce antiplatelet efficacy, as compared with the wild type population. The clinical Pharmacogenetics Implementation Consortium (CPIC), the National Institutes of Health’s Pharmacogenomics Research Network,\textsuperscript{37} has established the guidelines for initiating clopidogrel therapy based on predicted metabolizing phenotypes. An alternative regimen (prasugrel) was recommended for poor metabolizers.

Additionally, we assessed the impact of \textit{CYP2C19} polymorphisms (\textit{CYP2C19}*2, \textit{CYP2C19}*3, and \textit{CYP2C19}*17) on ADP-induced platelet aggregation. Based on the data from this study, the frequency of this common mutated allele in Thai clopidogrel non-responders was 36% (9 of 25 subjects), which is relatively similar to that in other Asian populations. Interestingly, this study found that the poor metabolizers, predicted metabolic phenotype was significantly higher in clopidogrel non-responders (36.0%) than in responders (15.5%). A previous study\textsuperscript{18} indicated the influence of the gain-of-function allele (\textit{CYP2C19}*17) on clopidogrel efficacy. In this study, \textit{CYP2C19}*1/*17 carriers (n = 2) were observed in clopidogrel responders. However, the data on \textit{CYP2C19}*17 in clopidogrel non-responders are limited, therefore this study cannot investigated the influence of \textit{CYP2C19}*17 on ADP-induced platelet aggregation.

Nevertheless, the present study has several limitations. First, we did not include all genetic polymorphisms that could affect the pharmacokinetics and pharmacodynamics of clopidogrel. Second, the plasma concentration of active clopidogrel metabolite was not measured in the study subjects. Therefore, the \textit{CYP2C19} polymorphisms, association with the pharmacokinetics aspect could not be investigated. Finally, the main limitation is the study’s limited sample size to evaluate the clinical outcome of clopidogrel-treated patients.

In conclusion, this study indicates that in the Thai population tested, the prevalence of the \textit{CYP2C19}*2 allele was quite high, whereas the prevalence of the \textit{CYP2C19}*17 allele was relatively low. Remarkably, we observed a significant effect of loss-of-function alleles on platelet response to clopidogrel-treated patients. It is important clinically to be able to identify those individuals who are likely to have altered pharmacokinetics for clopidogrel in order to select a suitable dosage, which results in improved efficacy and safety of drug therapy. The clinical benefit of this study as well as economic cost-effectiveness remains to be proven by properly well-powered randomized trials.

Acknowledgments

This study was supported by a grant from the Thailand Center of Excellent Life Science (TECLS) and Department of Pathology, Ramathibodi Hospital, Mahidol University, Thailand.

Disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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