

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*.

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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 $\geq 70\%$) 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 (LTA) 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 $\geq 10\%$ 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/*3), 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 ($p^2 + 2pq + q^2 = 1$), 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 <i>CYP2C19</i>	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.

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

Predicted phenotype	Genotypes	Samples (number)	Frequency (%)
Extensive metabolizer	*1/*1	428	40.72
Intermediate metabolizer	*1/*2	369	35.10
	*1/*3	72	6.85
Poor metabolizer	*2/*2	77	7.32
	*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.

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 allelic 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 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 ³ /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

Note: *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.

Table 4 Predicated 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.

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.¹⁴ 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.¹⁴ 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).²⁶ 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.^{26–34} 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.³⁵ 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,²³ 4%–8% in Africans,^{24,25} and 11%–23% in Asians.^{23,26} 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.³⁶ The results of this study showed that the prevalence of the poor metabolizers phenotype is 13.03% (n = 137 of 1,051), which is consistent with other Asian population studies.

Clopidogrel, 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.^{4–10} Pharmacological interests in *CYP2C19* polymorphic genes and clopidogrel response have been investigated extensively. The mutant allele of *CYP2C19* includes

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

Populations	Number	Alleles frequency of <i>CYP2C19</i>				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	0.56	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
Turkisks	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 based pair mutation, *CYP2C19**2; c.681G>A, *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,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 *CYP2C19* polymorphisms (*CYP2C19**2, *CYP2C19**3, and *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 study³⁸ indicated the influence of the gain-of-function allele (*CYP2C19**17) on clopidogrel efficacy. In this study, *CYP2C19**1/*17 carriers (n = 2) were observed in clopidogrel responders. However, the data on *CYP2C19**17 in clopidogrel non-responders are limited, therefore this study cannot investigate the influence of *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 *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 *CYP2C19**2 allele was quite high, whereas the prevalence of the *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 (TCELS) 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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