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RESEARCH ARTICLE **OPEN ACCESS**

CYP2C19 Genotype and Stroke Risk Score: Implications for Clopidogrel Therapy and Recurrent Events

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Abstract:

Background and Purpose: Clopidogrel, a commonly used antiplatelet agent for stroke prevention, requires CYP2C19-mediated metabolism for efficacy. Loss-of-function alleles reduce clopidogrel's antiplatelet effect, potentially leading to treatment failure. This study aimed to determine the prevalence of CYP2C19 polymorphisms in a Thai population and the association of these polymorphisms with recurrent cardiovascular events.

Methods: This retrospective chart review included patients who presented to Bangkok Hospital, Thailand (January 2014–December 2023), for whom CYP2C19 genetic testing results were available. Patients were categorized as carriers or noncarriers of loss-of-function alleles. The Essen Stroke Risk Score (ESRS) was used to stratify patients at high risk (≥3) or low risk (<3) for recurrent stroke. The primary outcome was either recurrent ischemic stroke or myocardial infarction. Log-rank test was used to assess differences in event rates between groups.

Results: Among the 126 patients (mean age 70.45 ± 12.48 years, 74.6% male), the CYP2C19 phenotypes were distributed as follows: normal metabolizers (31%), intermediate metabolizers (48.4%), poor metabolizers (12.7%), and ultrarapid metabolizers (7.9%). All recurrent cardiovascular events occurred in the carriers. Compared to noncarriers, carriers exhibited significantly greater rates of recurrent stroke (p=0.028) and recurrent myocardial infarction (p=0.04). Recurrent stroke and myocardial infarction were significantly more frequent in carriers only within the high ESRS group.

Conclusion: Loss-of-function CYP2C19 alleles were prevalent in more than half of the studied population. Carriers demonstrated a significantly increased risk for recurrent cardiovascular events. Pretreatment CYP2C19 genotyping should be considered to prevent adverse outcomes in clopidogrel-treated patients, particularly those with high ESRS (≥3).

Keywords: Cardiovascular event, Clopidogrel, CYP2C19 polymorphisms, Ischemic stroke metabolizer, Therapy, Ischemic and hemorrhagic stroke.

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1. INTRODUCTION

Stroke is the second leading cause of death and disability worldwide [1]. Ischemic and hemorrhagic stroke subtypes differ in etiology, risk factors, treatment, and outcomes [2]. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification categorizes ischemic stroke subtypes based on underlying mechanisms [3]. Despite similarities in acute management, secondary prevention strategies for each subtype vary [4, 5]. Antiplatelet therapy, in conjunction with lifestyle modification and vascular risk factor control (*e.g.*, blood pressure, low-density lipoprotein cholesterol), is commonly prescribed for secondary stroke prevention. Aspirin is frequently utilized as an antiplatelet agent due to its affordability and accessibility [6]. However, for aspirin-intolerant patients, clopidogrel is an evidence-based alternative for secondary stroke prevention [7-9].

Clopidogrel, a prodrug, requires hepatic cytochrome P450 (CYP450), primarily CYP2C19, for its conversion into its active metabolite [10]. The two most frequent loss-of-function polymorphisms are CYP2C19*2 and CYP2C19*3 [11, 12]. The prevalence of these polymorphisms varies by race, reaching 65% in East Asian populations [13]. In Thai populations, however, prevalence estimates have ranged from 5% to 55% [14-17]. Although substantial evidence has demonstrated the impact of CYP2C19 polymorphisms on cardiovascular events after percutaneous coronary intervention [18-20] or ischemic stroke [21-23], the evidence remains insufficient to recommend routine pretreatment genotyping for CYP2C19 polymorphisms. This study aimed to determine the prevalence of CYP2C19 polymorphisms in a Thai population and assess their impact on recurrent ischemic stroke and myocardial infarction risk.

2. METHODS

2.1. Study Population

Patients who underwent CYP2C19 genotyping from January 2014 to December 2023 were included if they met the following criteria: (1) were aged older than 18 years, (2) had a diagnosis of ischemic stroke or myocardial infarction, and (3) had current or previous clopidogrel use. The exclusion criteria were (1) concurrent anticoagulant therapy and (2) stroke mechanisms other than large or small vessel disease (*e.g.*, cardioembolic, dissection, vasculitis).

2.2. CYP2C19 Genotype

Single nucleotide polymorphism genotyping of CYP2C19*2 (rs4244285), CYP2C19*3 (rs4986893), and CYP2C19*17 (rs12248560) was performed using TaqMan allelic discrimination assays (TaqMan; Applied Biosystems, Foster City, CA, USA) [24]. Phenotypes were classified based on genotype as ultrarapid metabolizers (*1/*17 or *17/*17), normal metabolizers (*1/*1), intermediate metabolizers (*1/*2, *1/*3, or *2/*17), or poor metabolizers (*2/*2, *3/*3, or *2/*3) [11]. “Carriers” were defined as patients possessing at least one loss-of-function allele (*2 or *3) corresponding to phenotypes classified as intermediate or poor metabolizers. “Noncarriers” were defined as patients who lacked loss-of-function alleles corresponding to phenotypes classified as normal or ultrarapid metabolizers.

2.3. Data Collection

Demographic data, medical history, laboratory test data (including CYP2C19 genotype), and medication information were extracted from electronic medical records at Bangkok Hospital, Bangkok, Thailand. Stroke- or myocardial infarction-related data, including symptom onset, clinical presentation, acute management, and medications, were collected for each event. The etiology of ischemic stroke was categorized by TOAST classification [3]. Recurrent cardiovascular events were monitored for at least 1 year after the initial event or CYP2C19 genotyping. Recurrent events were defined as a second occurrence of ischemic stroke or myocardial infarction in patients with a documented history of either event, as identified in the medical records. The Essen Stroke Risk Score (ESRS) was calculated for all patients upon hospitalization to predict one-year recurrent stroke risk or combined cardiovascular events. Patients received 1 point each for hypertension, diabetes mellitus, myocardial infarction, other cardiovascular disease (excluding myocardial infarction and atrial fibrillation), peripheral arterial disease, current smoking, and previous ischemic stroke or transient ischemic attack. Regarding age, patients received 1 point for an age between 65 and 75 years and 2 points for an age over 75 years. The total possible ESRS was 9. Patients were stratified into low-risk (ESRS 0–2) or high-risk (ESRS ≥3) categories [25]. The primary outcome was the occurrence of either recurrent ischemic stroke or myocardial infarction. The ESRS was used to further stratify both carrier and noncarrier groups into high- or low-risk categories for recurrent cardiovascular events.

2.4. Statistical Analysis

Categorical variables are presented as numbers (percentages), and continuous variables are reported as means (standard deviations) or medians (interquartile ranges). For demographic comparisons between noncarrier and carrier groups, categorical variables were analyzed using the chi-square test or Fisher’s exact test, while continuous variables were compared using the Student’s t-test or the Mann–Whitney U test, as appropriate. The log-rank test was used to assess differences in event rates between groups. Generalized linear and Cox regression models were used to adjust for potential confounders and assess the associations between CYP2C19 polymorphisms and patient outcomes. All the statistical analyses were conducted using Stata Statistical Software (release 15) and RStudio (version 2023.12.1, Build 402).

3. RESULTS

A total of 126 patients were recruited based on the inclusion criteria. The mean age was 70.45 ± 12.48 years, with a male predominance (n=94, 74.6%). The majority of participants were of Thai nationality (n=78, 61.9%), followed by Asian (n=38, 30.1%) and Western (n=10, 8%) ethnicities. The baseline characteristics, detailed in Table **1**, revealed a significant difference between CYP2C19 carriers and noncarriers only in the history of type 2 diabetes mellitus (p=0.003).

Table 1. Baseline characteristics of CYP2C19 carriers and noncarriers.

-	Carriers[a] (n=77)	Noncarriers[b] (n=49)	*p*-value[c]
Age (y)	71.42 ± 11.68	68.94 ± 13.64	0.279
Male	57 (74%)	37 (75.5%)	0.852
BMI (kg/m^2)	24.67 ± 4.26	26.23 ± 4.33	0.051
Thai nationality	47 (61%)	31 (63.3%)	0.802
Smoking	6 (7.8%)	6 (12.2%)	0.427
Alcohol	6 (7.8%)	1 (2%)	0.137
Diabetes mellitus	37 (48.1%)	14 (28.6%)	0.03*
Hypertension	59 (76.6%)	32 (65.3%)	0.167
Hypercholesterolemia	42 (54.5%)	26 (53.1%)	0.871
Coronary artery disease	50 (64.9%)	31 (63.3%)	0.849
Chronic kidney disease	14 (18.2%)	6 (12.2%)	0.374
Recurrent ischemic stroke	11 (14.3%)	1 (2%)	0.028*
Recurrent myocardial infarction	15 (19.5%)	1 (2%)	0.004*
ESRS ≥3 (high risk)	66 (85.7%)	39 (79.6%)	1.000

Note: [a] Carriers were defined as patients who possessed at least one loss-of-function allele (*2 or *3).
[b] Noncarriers were defined as patients who lacked loss-of-function alleles.
[c] *p* values correspond to the chi-square or Fisher's exact test for categorical variables and to the Student's t-test or the Mann-Whitney U test for continuous variables, as appropriate.
The data are presented as the means ± standard deviations or as numbers (%).BMI, body mass index.

Table 2. Frequency of CYP2C19 genotypes and corresponding metabolizer phenotypes.

CYP2C19 Metabolizer Phenotype	Genotypes	Frequency (%) (N=126)
Normal (31%)	1*/1*	39 (31%)
Intermediate (48.4%)	1*/2*	58 (46%)
-	1*/3*	1 (0.8%)
-	2*/17*	2 (1.6%)
Poor (12.7%)	2*/2*	9 (7.1%)
-	2*/3*	7 (5.6%)
Ultrarapid (7.9%)	1*/17*	9 (7.1%)
-	17*/17*	1 (0.8%)

Note: The data are presented as numbers (%).

Table 3. Distribution of CYP2C19 metabolizer phenotypes by nationality.

CYP2C19 Metabolizers Phenotype	Thai (n=78)	Asian (n=38)	Western (n=10)
Normal	30 (38.5%)	4 (10.5%)	5 (50%)
Intermediate	38 (48.7%)	22 (57.9%)	1 (10%)
Poor	9 (11.5%)	6 (15.8%)	1 (10%)
Ultrarapid	1 (1.3%)	6 (15.8%)	3 (30%)

Note: The data are presented as numbers (%).

The overall distribution of CYP2C19 phenotypes was as follows: 39 normal metabolizers (31%), 61 intermediate metabolizers (48.4%), 16 poor metabolizers (12.7%), and 10 ultrarapid metabolizers (7.9%). Within the Thai subpopulation, these distributions were 30 (38.5%), 38 (48.7%), 9 (11.5%), and 1 (1.3%), respectively. Tables **2** and **3** provide further details on the phenotype frequencies. The reasons for checking CYP2C19 phenotype in our patients were as follows: 1. Before prescribing clopidogrel in 65 patients (51.6%), 2. Had recurrent cardiovascular events when taking clopidogrel in 28 patients (22.2%), 3. Clopidogrel was prescribed by a previous physician but CYP2C19 phenotype was never checked in 33 patients (26.2%). None of the patients taking clopidogrel were on medications known to affect its metabolism (*e.g.*, omeprazole, esomeprazole, fluconazole, fluoxetine, rifampicin, or phenytoin). Additionally, none were using medications that could cause cardiovascular events, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antipsychotics, or triptans.

As of December 2023, 64 patients (50.8%) were alive, 11 (8.7%) had died, and 51 (40.5%) were lost to follow-up. Of the 11 deceased patients, 2 died from recurrent ischemic stroke, with both exhibiting the intermediate metabolizer CYP2C19 phenotype.

Clopidogrel was prescribed for secondary prevention in 109 patients (86.5%) due to previous ischemic stroke (n=28, 22.2%) or coronary artery disease (n=81, 64.3%), while 17 patients (13.5%) received clopidogrel for acute treatment. The dosage of clopidogrel for acute treatment was a 300 mg loading dose, followed by 75 mg once daily. For secondary prevention, the dosage was 75 mg once daily. Among clopidogrel users, recurrent stroke occurred in 12 patients (9.5%), and recurrent myocardial infarction was experienced by 16 patients (12.7%), all exhibiting intermediate or poor CYP2C19 metabolism phenotypes. Among the 12 patients with recurrent stroke, 5 were prescribed clopidogrel following myocardial infarction, and 7 were prescribed it following ischemic stroke. Among the 16 patients with recurrent myocardial infarction, 14 had been prescribed clopidogrel after myocardial infarction, and 2 after ischemic stroke. For all patients who had recurrent ischemic stroke, their etiology is small vessel disease. The duration between the first dose of clopidogrel and the onset of a cardiovascular event was available to calculate in 41 patients. The median time from starting clopidogrel to either recurrent stroke or myocardial infarction was 817 days (range 324–1871). For recurrent stroke alone, the median time was 1284 days (range 476–1871), while for recurrent myocardial infarction alone, the median time was 533 days (range 236–2275). A statistically significant difference was observed between carriers and noncarriers for recurrent stroke (p=0.028) and myocardial infarction (p=0.004), as detailed in Table **1**. Notably, carriers demonstrated a significantly increased risk of recurrent myocardial infarction (odds ratio [OR] 29.89, 95% confidence interval [CI] 2.29–390.73, p=0.01) but not of recurrent stroke (OR 4.54, 95% CI 0.50–41.53, p=0.18). In a subgroup analysis of patients who were not lost to follow-up, 75 patients (59.5%) remained. Recurrent stroke occurred in 7 patients (9.3%), including 6 carriers (4 alive, 2 deceased) and 1 noncarrier (alive). Recurrent myocardial infarction occurred in 12 carriers (16%), all of whom were alive. A statistically significant difference was observed between carriers and noncarriers for recurrent myocardial infarction (p=0.006) but not recurrent ischemic stroke (p=0.413).

Following CYP2C19 genotyping, 52 patients (41.3%) with intermediate or poor metabolizer phenotypes were switched from clopidogrel to alternative antiplatelet therapies before any recurrent cardiovascular events. However, 13 patients (10.3%) continued clopidogrel despite their CYP2C19 status (12 intermediate, 1 poor). Of these, 6 were lost to follow-up, while the remaining 7 were monitored for a median of 396 days (range 308–1046) without experiencing further cardiovascular events by the end of December 2023.

Using the ESRS, 105 patients (83.3%) were classified as at high risk for recurrent stroke (ESRS ≥3). Stratifying patients based on both carrier status and the ESRS into 4 groups revealed that recurrent stroke and myocardial infarction were significantly elevated only in carriers in the high-risk subgroup (p=0.048 and p=0.006, respectively). Within the high-risk subgroup, carriers maintained a significantly increased risk of recurrent myocardial infarction (OR 29.14, 95% CI 2.01–422.0, p=0.013) but not of recurrent stroke (OR 4.18, 95% CI 0.43–41.16, p=0.22). Table **4** displays information categorized into 4 groups (low-risk, high-risk, carrier, and noncarrier).

Subgroup analysis focusing on intermediate metabolizers revealed a persistent, significant increase in recurrent stroke and myocardial infarction compared to noncarriers (p=0.04 and p=0.021, respectively). This significance was predominantly driven by patients with a high risk for recurrent stroke (ESRS ≥3).

Table 4. Baseline characteristics of patients stratified by ESRS and CYP2C19 carrier status.

Variables	Low Risk (ESRS <3, n=21)			High Risk (ESRS ≥3, n=105)		
-	Carriers[a] (n=11)	Noncarriers[b] (n=10)	*p* value[c]	Carriers[a] (n=66)	Noncarriers[b] (n=39)	*p* value[c]
Age	65.1 (9.8)	56.1 (14.8)	0.204	72.5 (11.7)	71.1 (12.4)	0.623
Sex (male)	6 (54.5)	5 (50)	0.637	51 (77.3)	32 (82.1)	0.897
Smoking	0	0	–	6 (9.1)	6 (14.3)	0.442
Alcohol	0	0	–	6 (9.1)	1 (2.4)	0.117
Diabetes mellitus	0	0	–	37 (56.1)	14 (3.3)	0.021*
Hypertension	5 (45.4)	1 (14.3)	0.316	54 (81.8)	31 (73.8)	0.322
Hypercholesterolemia	3 (27.3)	2 (28.6)	1.000	39 (59.1)	24 (57.1)	0.841
Coronary artery disease	3 (27.3)	5 (71.4)	0.145	47 (71.2)	26 (61.9)	0.314
Chronic kidney disease	3 (27.3)	0	0.245	11 (16.7)	6 (14.3)	0.74
Recurrent ischemic stroke	1 (9.1)	0	1.000	10 (15.2)	1 (2.4)	0.048*
Recurrent myocardial infarction	1 (9.1)	0	1.000	14 (21.2)	1 (2.4)	0.006*

Note: [a] Carriers were defined as patients who possessed at least one loss-of-function allele (*2 or *3).

[b] Noncarriers were defined as patients who lacked loss-of-function alleles.

[c] *p* values correspond to the chi-square or Fisher's exact test for categorical variables and to Student's t-test or the Mann–Whitney U test for continuous variables, as appropriate.

The data are presented as the means ± standard deviations or as numbers (%).BMI, body mass index.

4. DISCUSSION

Recent years have seen substantial advancements in acute stroke management aimed at reducing the global stroke burden. Despite the expanded time frame for reperfusion therapies such as intravenous recombinant tissue plasminogen activator and mechanical thrombectomy, a significant proportion of stroke patients remain ineligible and require antiplatelet therapy [4]. While aspirin alone was historically the mainstay for acute ischemic stroke [26, 27], the therapeutic landscape has evolved with emerging evidence supporting alternative antiplatelet agents. Although data on the use of clopidogrel for acute stroke treatment is limited, the medication is considered a first-line agent for secondary prevention [28]. Dual antiplatelet therapy, which combines aspirin with either clopidogrel or ticagrelor, has demonstrated superiority over aspirin alone in reducing recurrent stroke and mortality in patients with minor acute ischemic stroke or high-risk transient ischemic attack [29].

In secondary stroke prevention, along with controlling vascular risk factors, various antiplatelet options are available. These options include single or dual therapies, each with specific indications for different patient subgroups [7-9, 30-33].

Given its role as a cornerstone of secondary stroke prevention, the efficacy of clopidogrel is paramount. In addition to drug interactions with proton pump inhibitors or CYP2C19 inhibitors, genetic polymorphisms in the CYP2C19 gene are a significant contributor to antiplatelet resistance and subsequent recurrent stroke [34]. This polymorphism categorizes individuals into ultrarapid, normal, intermediate, and poor metabolizers. Patients classified as intermediate or poor metabolizers exhibit significantly lower levels of the active clopidogrel metabolite, resulting in reduced platelet inhibition [35].

In our study, the prevalence of CYP2C19 carriers was 61.1% overall and 60.2% in the Thai population, consistent with previous literature [16]. Although recurrent ischemic stroke was significantly more frequent in carriers than in noncarriers (14.3% *vs*. 2.0%, p=0.028), the OR did not reach statistical significance (OR 4.54, 95% CI 0.50–41.53, p=0.18) due to the limited sample size. The prevalence of CYP2C19*17 alleles in our study was very high (15.8%) compared to previous studies, which found only 0.5-4% in Asian populations [11]. This result may be influenced by selection bias, as our study included only patients with available *CYP2C19* test results, rather than all patients taking clopidogrel. This could have led to an overestimation of the prevalence.

The high loss-to-follow-up rate (40%) was addressed by utilizing the ESRS to identify high-risk patients (ESRS ≥3) instead of assuming that they all have recurrent events. In this subgroup, carriers exhibited a greater rate of recurrent stroke than noncarriers did (p=0.048), although the odds ratio remained statistically nonsignificant (OR 4.18, 95% CI 0.43–41.16, p=0.22).

Conversely, the incidence of recurrent myocardial infarction was significantly greater in carriers than in noncarriers, with a statistically significant OR observed both with and without ESRS subgrouping. Even after subgrouping to only patients who were not lost to follow-up, the remaining 75 patients (59.5%), there is still a statis-tically significant difference between carrier and noncarriers in recurrent myocardial infarction. However, the OR could not be calculated due to mismatched observed and expected event rates (the Hosmer-Lemeshow test indicated that the model did not fit the data, $p < 0.05$).

Aside from the limited sample size, the lack of statistical significance in recurrent ischemic stroke may be attributed to the silent or mild nature of 8%–30% of strokes, resulting in underdiagnosis [36]. Conversely, myocardial infarction typically presents with more overt symptoms, with chest pain occurring in 80%–90% of cases, facilitating detection [37].

Recent studies corroborate our findings of a higher rate of recurrent cardiovascular events in intermediate or poor metabolizers than in noncarriers [38-41]. However, our results diverge from previous research when stratified by the ESRS. A prior study revealed no benefit of ticagrelor over clopidogrel in reducing recurrent stroke among high-risk carriers (ESRS ≥3) but a significant reduction in low-risk patients (ESRS <3) [42]. In our study, we found that clopidogrel failed to secondary prevention of cardiovascular events among high-risk carriers (ESRS ≥3). The discrepancy in the findings may be attributable to the limitations of the prior study. Notably, that research constituted a post hoc analysis of the CHANCE-2 trial and exclusively included Chinese individuals who are known for having a higher incidence of intracranial stenosis. These factors warrant consideration when interpreting the contrasting findings regarding the interaction between CYP2C19 status, the ESRS, and the treatment effect.

The majority of research examining the relationship between CYP2C19 genotype and clopidogrel response has focused on myocardial infarction patients undergoing percutaneous coronary intervention. No randomized controlled trials have demonstrated that routine genetic testing improves clinical outcomes. This lack of definitive evidence extends to ischemic stroke patients, with limited studies and no randomized trials investigating this relationship [43]. Due to the uncertain role of genetic testing, current guidelines for preventing recurrent cardiovascular events do not recommend routine CYP2C19 pharmacogenetic screening prior to clopidogrel initiation [5, 44].

5. STUDY LIMITATIONS

Our study has several limitations. First, the sample size was small compared to that of previous studies [15, 16]. This limited sample size may be due to the lack of recommendations for CYP2C19 testing prior to clopidogrel initiation and the retrospective design precluding genetic testing during recruitment. Second, the high loss-to-follow-up rate (40%) was likely influenced by two factors. These factors included patients seeking care at other hospitals under Thailand's Universal Coverage Scheme (a government health insurance program) after emergency management at our hospital and the inclusion of foreign patients (38%). Third, 50% of patients who were prescribed clopidogrel underwent CYP2C19 evaluation within the same

episode. If the results (typically available within 3 days) identified loss-of-function alleles, the antiplatelet therapy was promptly changed (41.3% of patients), which potentially reduced the incidence of recurrent ischemic stroke and myocardial infarction. Finally, our study included only patients with available CYP2C19 genotype data, and due to the retrospective nature of the study, this may have introduced selection bias that affected the outcomes and also imbalance in genetic polymorphism distribution.

Despite these limitations, our study has notable strengths. Few studies have investigated the association between CYP2C19 polymorphisms and recurrent ischemic stroke risk in clopidogrel users. Moreover, we demonstrated a heightened risk of recurrent ischemic stroke in carriers with a high ESRS value (≥3). This novel finding suggests that CYP2C19 screening may be warranted in this high-risk subgroup, a concept not previously explored in the literature.

CONCLUSION

The prevalence of carriers of CYP2C19 loss-of-function alleles exceeds 50% in the population and substantially impacts clinical outcomes when clopidogrel is used. Carriers exhibit a markedly greater incidence of recurrent ischemic stroke and myocardial infarction, particularly among high-risk patients identified by the ESRS. Therefore, screening for the CYP2C19 phenotype should be considered before prescribing clopidogrel to patients with a high ESRS. There are high loss-to-follow-up rates in our patients with many limitations from study design, making interpretation of our findings need to be cautious. Given our study's small sample size and retrospective design, larger prospective cohort studies are necessary to further evaluate the impact of CYP2C19 loss-of-function alleles on clinical outcomes.

AUTHOR'S CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: T.Y., P.B.: Data collection; C.D.: Draft manuscript. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

CI	=	Confidence interval
ESRS	=	Essen Stroke Risk Score
OR	=	Odds ratio

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Bangkok Hospital Institutional Review Board, Bangkok, Thailand (COA 2023-41).

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Written informed consent was waived by the review board due to the retrospective and anonymity-preserving nature of the chart review.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Feigin VL, Stark BA, Johnson CO, *et al*. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol 2021; 20(10): 795-820. http://dx.doi.org/10.1016/S1474-4422(21)00252-0 PMID: 34487721

[2] Caplan LR. Intracranial branch atheromatous disease. Neurology 1989; 39(9): 1246-50. http://dx.doi.org/10.1212/WNL.39.9.1246 PMID: 2671793

[3] Adams HP Jr, Bendixen BH, Kappelle LJ, *et al*. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24(1): 35-41. http://dx.doi.org/10.1161/01.STR.24.1.35 PMID: 7678184

[4] Powers WJ, Rabinstein AA, Ackerson T, *et al*. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019; 50(12): e344-418. http://dx.doi.org/10.1161/STR.0000000000000211 PMID: 31662037

[5] Kleindorfer DO, Towfighi A, Chaturvedi S, *et al*. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke 2021; 52(7): e364-467. http://dx.doi.org/10.1161/STR.0000000000000375 PMID: 34024117

[6] Guzik A, Bushnell C. Stroke Epidemiology and Risk Factor Management. Continuum (Minneap Minn) 2017; 23(1): 15-39. http://dx.doi.org/10.1212/CON.0000000000000416 PMID: 28157742

[7] A randomised, blinded, trial of clopidogrel *versus* aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348(9038): 1329-39. http://dx.doi.org/10.1016/S0140-6736(96)09457-3 PMID: 8918275

[8] Sacco RL, Diener HC, Yusuf S, *et al*. Aspirin and extended-release dipyridamole *versus* clopidogrel for recurrent stroke. N Engl J Med 2008; 359(12): 1238-51.

http://dx.doi.org/10.1056/NEJMoa0805002 PMID: 18753638
[9] Toyoda K, Uchiyama S, Yamaguchi T, *et al*. Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischaemic stroke in Japan: a multicentre, open-label, randomised controlled trial. Lancet Neurol 2019; 18(6): 539-48. http://dx.doi.org/10.1016/S1474-4422(19)30148-6 PMID: 31122494
[10] Hagihara K, Kazui M, Kurihara A, *et al*. A possible mechanism for the differences in efficiency and variability of active metabolite formation from thienopyridine antiplatelet agents, prasugrel and clopidogrel. Drug Metab Dispos 2009; 37(11): 2145-52. http://dx.doi.org/10.1124/dmd.109.028498 PMID: 19704027
[11] Scott SA, Sangkuhl K, Gardner EE, *et al*. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. Clin Pharmacol Ther 2011; 90(2): 328-32. http://dx.doi.org/10.1038/clpt.2011.132 PMID: 21716271
[12] Hulot JS, Bura A, Villard E, *et al*. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood 2006; 108(7): 2244-7. http://dx.doi.org/10.1182/blood-2006-04-013052 PMID: 16772608
[13] Levine GN, Jeong YH, Goto S, *et al*. World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Nat Rev Cardiol 2014; 11(10): 597-606. http://dx.doi.org/10.1038/nrcardio.2014.104 PMID: 25154978
[14] Tassaneeyakul W, Tawalee A, Tassaneeyakul W, *et al*. Analysis of the CYP2C19 polymorphism in a North-eastern Thai population. Pharmacogenetics 2002; 12(3): 221-5. http://dx.doi.org/10.1097/00008571-200204000-00006 PMID: 11927837
[15] Tassaneeyakul W, Mahatthanatrakul W, Niwatananun K, *et al*. CYP2C19 genetic polymorphism in Thai, Burmese and Karen populations. Drug Metab Pharmacokinet 2006; 21(4): 286-90. http://dx.doi.org/10.2133/dmpk.21.286 PMID: 16946555
[16] Sukasem C, Tunthong R, Chamnanphol M, *et al*. *CYP2C19* polymorphisms in the Thai population and the clinical response to clopidogrel in patients with atherothrombotic-risk factors. Pharm Genomics Pers Med 2013; 6: 85-91. http://dx.doi.org/10.2147/PGPM.S42332 PMID: 24019752
[17] Sukprasong R, Chuwongwattana S, Koomdee N, *et al*. Allele frequencies of single nucleotide polymorphisms of clinically important drug-metabolizing enzymes CYP2C9, CYP2C19, and CYP3A4 in a Thai population. Sci Rep 2021; 11(1): 12343. http://dx.doi.org/10.1038/s41598-021-90969-y PMID: 34117307
[18] Cavallari LH, Lee CR, Beitelshees AL, *et al*. Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. JACC Cardiovasc Interv 2018; 11(2): 181-91. http://dx.doi.org/10.1016/j.jcin.2017.07.022 PMID: 29102571
[19] Pereira NL, Rihal C, Lennon R, *et al*. Effect of CYP2C19 Genotype on Ischemic Outcomes During Oral P2Y12 Inhibitor Therapy. JACC Cardiovasc Interv 2021; 14(7): 739-50. http://dx.doi.org/10.1016/j.jcin.2021.01.024 PMID: 33744207
[20] Sun H, Qu Q, Chen ZF, *et al*. Impact of *CYP2C19* Variants on Clinical Efficacy of Clopidogrel and 1-Year Clinical Outcomes in Coronary Heart Patients Undergoing Percutaneous Coronary Intervention. Front Pharmacol 2016; 7: 453. http://dx.doi.org/10.3389/fphar.2016.00453 PMID: 27932982
[21] Wang Y, Zhao X, Lin J, *et al*. Association Between *CYP2C19* Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack. JAMA 2016; 316(1): 70-8. http://dx.doi.org/10.1001/jama.2016.8662 PMID: 27348249
[22] Meschia JF, Walton RL, Farrugia LP, *et al*. Efficacy of Clopidogrel for Prevention of Stroke Based on *CYP2C19* Allele Status in the POINT Trial. Stroke 2020; 51(7): 2058-65. http://dx.doi.org/10.1161/STROKEAHA.119.028713 PMID: 32568642
[23] Li C, Jia W, Li J, Li F, Ma J, Zhou L. Association with CYP2C19 polymorphisms and Clopidogrel in treatment of elderly stroke patients. BMC Neurol 2021; 21(1): 104. http://dx.doi.org/10.1186/s12883-021-02127-6 PMID: 33685396
[24] Zhang L, Cui G, Li Z, Wang H, Ding H, Wang DW. Comparison of high-resolution melting analysis, TaqMan Allelic discrimination assay, and sanger sequencing for Clopidogrel efficacy genotyping in routine molecular diagnostics. J Mol Diagn 2013; 15(5): 600-6. http://dx.doi.org/10.1016/j.jmoldx.2013.04.005 PMID: 23810503
[25] Weimar C, Diener HC, Alberts MJ, *et al*. The Essen stroke risk score predicts recurrent cardiovascular events: a validation within the REduction of Atherothrombosis for Continued Health (REACH) registry. Stroke 2009; 40(2): 350-4. http://dx.doi.org/10.1161/STROKEAHA.108.521419 PMID: 19023098
[26] Chen Z-M. CAST: randomised placebo-controlled trial of early aspirin use in 20 000 patients with acute ischaemic stroke. Lancet 1997; 349(9066): 1641-9. http://dx.doi.org/10.1016/S0140-6736(97)04010-5 PMID: 9186381
[27] The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. Lancet 1997; 349(9065): 1569-81. http://dx.doi.org/10.1016/S0140-6736(97)04011-7 PMID: 9174558
[28] Greving JP, Diener HC, Reitsma JB, *et al*. Antiplatelet Therapy After Noncardioembolic Stroke. Stroke 2019; 50(7): 1812-8. http://dx.doi.org/10.1161/STROKEAHA.118.024497 PMID: 31177983
[29] Lun R, Dhaliwal S, Zitikyte G, Roy DC, Hutton B, Dowlatshahi D. Comparison of Ticagrelor *vs* Clopidogrel in Addition to Aspirin in Patients With Minor Ischemic Stroke and Transient Ischemic Attack. JAMA Neurol 2022; 79(2): 141-8. http://dx.doi.org/10.1001/jamaneurol.2021.4514 PMID: 34870698
[30] Collaboration AT. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324(7329): 71-86. http://dx.doi.org/10.1136/bmj.324.7329.71 PMID: 11786451
[31] Verro P, Gorelick PB, Nguyen D. Aspirin plus dipyridamole *versus* aspirin for prevention of vascular events after stroke or TIA: a meta-analysis. Stroke 2008; 39(4): 1358-63. http://dx.doi.org/10.1161/STROKEAHA.107.496281 PMID: 18323511
[32] Shinohara Y, Katayama Y, Uchiyama S, *et al*. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. Lancet Neurol 2010; 9(10): 959-68. http://dx.doi.org/10.1016/S1474-4422(10)70198-8 PMID: 20833591
[33] Derdeyn CP, Chimowitz MI, Lynn MJ, *et al*. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet 2014; 383(9914): 333-41. http://dx.doi.org/10.1016/S0140-6736(13)62038-3 PMID: 24168957
[34] Krishnan K, Nguyen TN, Appleton JP, *et al*. Antiplatelet resistance: A review of concepts, mechanisms, and implications for management in acute ischemic stroke and transient ischemic attack. Stroke Vasc Intervent Neurol 2023; 3(3): e000576. http://dx.doi.org/10.1161/SVIN.122.000576
[35] Klein MD, Williams AK, Lee CR, Stouffer GA. Clinical Utility of CYP2C19 Genotyping to guide antiplatelet therapy in patients with an acute coronary syndrome or undergoing percutaneous coronary intervention. Arterioscler Thromb Vasc Biol 2019; 39(4): 647-52. http://dx.doi.org/10.1161/ATVBAHA.118.311963 PMID: 30760018
[36] Smith EE, Saposnik G, Biessels GJ, *et al*. Prevention of Stroke in Patients With Silent Cerebrovascular Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2017; 48(2): e44-71. http://dx.doi.org/10.1161/STR.0000000000000116 PMID:

27980126
[37] Björck L, Nielsen S, Jernberg T, Zverkova-Sandström T, Giang KW, Rosengren A. Absence of chest pain and long-term mortality in patients with acute myocardial infarction. Open Heart 2018; 5(2): e000909. http://dx.doi.org/10.1136/openhrt-2018-000909 PMID: 30564376
[38] Wang Y, Meng X, Wang A, *et al*. Ticagrelor *versus* Clopidogrel in *CYP2C19* Loss-of-Function Carriers with Stroke or TIA. N Engl J Med 2021; 385(27): 2520-30. http://dx.doi.org/10.1056/NEJMoa2111749 PMID: 34708996
[39] Xie X, Johnston SC, Wang A, *et al*. Association of *CYP2C19* Loss-of-Function Metabolizer Status With Stroke Risk Among Chinese Patients Treated With Ticagrelor-Aspirin *vs* Clopidogrel-Aspirin. JAMA Netw Open 2023; 6(6): e2317037. http://dx.doi.org/10.1001/jamanetworkopen.2023.17037 PMID: 37279000
[40] Mega JL, Simon T, Collet JP, *et al*. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA 2010; 304(16): 1821-30. http://dx.doi.org/10.1001/jama.2010.1543 PMID: 20978260
[41] Pan Y, Chen W, Xu Y, *et al*. Genetic Polymorphisms and Clopidogrel Efficacy for Acute Ischemic Stroke or Transient Ischemic Attack. Circulation 2017; 135(1): 21-33. http://dx.doi.org/10.1161/CIRCULATIONAHA.116.024913 PMID: 27806998
[42] Wang A, Meng X, Tian X, *et al*. Ticagrelor Aspirin *vs* Clopidogrel Aspirin in *CYP2C19* Loss-of-Function Carriers With Minor Stroke or TIA Stratified by Risk Profile. Neurology 2023; 100(5): e497-504. http://dx.doi.org/10.1212/WNL.0000000000201454 PMID: 36535779
[43] Lee CR, Luzum JA, Sangkuhl K, *et al*. Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update. Clin Pharmacol Ther 2022; 112(5): 959-67. http://dx.doi.org/10.1002/cpt.2526 PMID: 35034351
[44] Lawton JS, Tamis-Holland JE, Bangalore S, *et al*. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022; 145(3): e18-e114. http://dx.doi.org/10.1161/CIR.0000000000001038 PMID: 34882435