

Research Article

ONE-YEAR CLINICAL AND IMAGING OUTCOMES OF CYP2C19 PHENOTYPE-GUIDED ANTIPLATELET THERAPY IN PATIENTS WITH ISCHEMIC STROKE AND INTRACRANIAL ARTERIAL STENOSIS OR OCCLUSION

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ABSTRACT

Objective: To describe 12-month clinical and imaging outcomes and explore the association between CYP2C19 metabolizer phenotype and functional outcome in patients with ischemic stroke and intracranial arterial stenosis or occlusion treated using a phenotype-guided antiplatelet strategy. **Methods:** This single-center observational cohort study with 12-month follow-up included 194 patients treated at S.I.S Can Tho International General Hospital between March 2024 and August 2026. CYP2C19 *2 and CYP2C19 *3 were genotyped from peripheral blood using Realgene qualitative IVD kits on a SaCycler-96 real-time PCR system, and patients were classified as normal, intermediate, or poor metabolizers. Antiplatelet treatment comprised aspirin combined with clopidogrel or ticagrelor according to the study protocol. Outcomes included all-cause mortality, recurrent ischemic stroke, modified Rankin Scale (mRS), and follow-up MRI/MRA findings. Imaging analyses were restricted to the 90 patients with repeat imaging. **Results:** Mean age was 62.06 ± 11.50 years and 67.0% were men. Normal, intermediate, and poor metabolizers accounted for 47.9%, 43.8%, and 8.2%, respectively. At 12 months, 90 patients underwent repeat imaging, 75 had clinical follow-up without repeat imaging, 13 were lost to follow-up, and 16 (8.2%) died. Among the 90 patients with complete clinical and imaging reassessment, 52 (57.8%) had mRS 0–1 and 2 (2.2%) had recurrent ischemic stroke. The proportions with mRS 0–1 were 84.4%, 37.8%, and 0.0% across normal, intermediate, and poor metabolizers, respectively ($p < 0.001$). Follow-up MRI/MRA showed no residual stenosis in 78 (86.7%), severe stenosis in 2 (2.2%), and persistent occlusion in 10 (11.1%). Bleeding outcomes were not systematically available and therefore could not be reliably evaluated. **Conclusion:** CYP2C19 metabolizer phenotype was significantly associated with 12-month functional outcome in the 90-patient reassessed subgroup in unadjusted analysis. However, the observational design, incomplete follow-up, lack of multivariable adjustment, and sparse recurrent events preclude causal inference or direct comparison of antiplatelet regimens. Larger prospective studies with standardized treatment and complete efficacy and safety ascertainment are warranted.

Keywords: ischemic stroke; CYP2C19; clopidogrel; ticagrelor; intracranial arterial stenosis; magnetic resonance angiography; modified Rankin Scale.

INTRODUCTION

Short-term dual antiplatelet therapy with aspirin and clopidogrel has been established for selected patients with minor ischemic stroke or high-risk transient ischemic attack, particularly through the CHANCE and POINT trials [11,12]. Clopidogrel is a prodrug that requires bio activation partly through CYP2C19. Loss-of-function alleles, particularly CYP2C19 *2 and CYP2C19 *3, reduce formation of the active metabolite and may attenuate platelet inhibition. In the pharmacogenetic analysis of CHANCE, the benefit of clopidogrel plus aspirin for recurrent stroke prevention was concentrated among patients who did not carry CYP2C19 loss-of-function alleles [1]. The 2022 CPIC guideline likewise recognizes CYP2C19 phenotype as clinically relevant when clopidogrel is considered for selected neurovascular indications [2].

CHANCE-2 demonstrated a modest reduction in 90-day stroke with ticagrelor plus aspirin compared with clopidogrel plus aspirin among CYP2C19 loss-of-function carriers, although total bleeding was more frequent with ticagrelor [3]. A post hoc analysis in patients with intracranial arterial stenosis did not demonstrate a clearly different treatment effect between the two regimens [4]. Meta-analyses and observational studies have further supported an association between CYP2C19 loss-of-function alleles and adverse ischemic outcomes during clopidogrel therapy [5-7].

The present study represents the 12-month pharma cogenetic follow-up analysis of the same research cohort whose baseline clinical and intracranial vascular imaging characteristics were analyzed separately. The objective was to describe 12-month clinical and imaging outcomes and to explore the association between CYP2C19 metabolizer phenotype and functional outcome in patients with ischemic stroke and intracranial arterial stenosis or occlusion managed with a phenotype-guided antiplatelet strategy.

MATERIALS AND METHODS

Study Design and Participants

This was a single-center observational cohort study with 12-month follow-up conducted at S.I.S Can Tho International General Hospital, Can Tho, Vietnam. Patients were enrolled between March 2024 and August 2026. The cohort comprised 194 patients with ischemic stroke and intracranial large-artery stenosis or occlusion documented by neurovascular imaging. All 194 patients underwent both 3-T MRI/MRA and digital subtraction angiography (DSA) during the index clinical evaluation.

Patients were eligible if they had ischemic stroke with an intracranial large-artery stenosis or occlusion recorded in the study database and underwent CYP2C19 testing. Patients were excluded if they had a potential cardiac source of embolism, including atrial fibrillation or valvular heart disease; lacunar ischemic stroke; no identifiable

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intracranial arterial lesion on neuroimaging; isolated thrombotic occlusion with complete recanalization and no residual intracranial arterial stenosis; or severe stroke with a Glasgow Coma Scale score <8 at admission that precluded adequate follow-up.

The present analysis focused on *CYP2C19* phenotype, antiplatelet treatment strategy, and 12-month outcomes. Baseline clinical and imaging characteristics from this cohort were analyzed separately; therefore, only baseline variables necessary to interpret the longitudinal analysis are summarized here.

***CYP2C19* Genotyping and Phenotype Classification**

Peripheral venous blood was collected for *CYP2C19* genotyping. Genomic DNA was extracted from whole blood using the Gene JET Genomic DNA Purification Kit (Thermo Scientific). *CYP2C19* *2 (G681A; rs4244285) and *CYP2C19* *3 (G636A; rs4986893) were determined using Realgene (Italy) qualitative IVD genotyping kits on a SaCycler-96 real-time PCR system, according to the manufacturer's instructions and the laboratory protocol of the parent study.

Phenotype classification was based on the two tested loss-of-function alleles. Patients without a detected *CYP2C19* *2 or *3 loss-of-function allele were classified as normal metabolizers; those carrying one tested loss-of-function allele were classified as intermediate metabolizers; and those carrying two tested loss-of-function alleles were classified as poor metabolizers. Because only *CYP2C19* *2 and *3 were tested, these phenotype assignments should be interpreted within the scope of the alleles assessed rather than as comprehensive star-allele profiling [2].

Antiplatelet Treatment Strategy

Antiplatelet treatment was selected after *CYP2C19* genotyping according to the prespecified parent-study protocol. The protocol used aspirin 81 mg once daily plus clopidogrel 75 mg once daily for patients assigned to the clopidogrel-based strategy. Patients assigned to the ticagrelor-based strategy received aspirin 81 mg once daily plus ticagrelor 90 mg twice daily. At 3 months or earlier if bleeding occurred, aspirin was discontinued and the assigned P2Y₁₂ inhibitor was continued as monotherapy (clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily). Treatment was followed for 12 months. Because allocation was phenotype-guided rather than randomized, the present analysis was not designed as a head-to-head comparative-effectiveness trial of ticagrelor versus clopidogrel.

Clinical, Laboratory, and Imaging Follow-up

Patients were followed for 12 months after the index ischemic stroke. The study protocol included reassessment at 3 months or earlier if bleeding occurred and continued clinical follow-up through 1 year. Follow-up information included survival status, recurrent ischemic stroke, functional status assessed using the modified Rankin Scale (mRS), LDL-C, HbA1c, and available neurovascular imaging findings. Repeat 3-T MRI/MRA was obtained at approximately 12 months in patients who returned for imaging reassessment.

Brain MRI was performed using a 3-T Siemens MAGNETOM Lumina system. The index MRI protocol included diffusion-weighted imaging, apparent diffusion coefficient mapping, fluid-attenuated inversion recovery imaging, and three-dimensional time-of-flight magnetic resonance angiography. At 12 months, 90 patients underwent repeat MRI/MRA, 75 had clinical follow-up without repeat imaging, 13 were lost to follow-up, and 16 had died. Imaging analyses were therefore restricted to the 90 patients with repeat neuro imaging.

Outcomes

The primary outcome was functional status at 12 months, assessed using the mRS. Favorable functional outcome was defined as mRS 0–1 and unfavorable functional outcome as mRS ≥2. In the available analytical dataset, mRS by *CYP2C19* phenotype was reported for the 90 patients with complete clinical and imaging reassessment; therefore, this analysis may be affected by selection bias and should be interpreted as exploratory.

Secondary clinical outcomes were recurrent ischemic stroke and all-cause mortality during the 12-month follow-up. Exploratory outcomes included changes in intracranial arterial status on follow-up MRI/MRA and changes in LDL-C and HbA1c among patients with paired measurements. Bleeding outcomes were not systematically available and were not treated as an evaluable safety endpoint.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Differences in categorical outcomes across *CYP2C19* metabolizer groups were evaluated using the chi-square test or Fisher's exact test, as appropriate. Changes in LDL-C and HbA1c between baseline and 12 months were summarized descriptively because patient-level paired data required for formal paired statistical testing were unavailable in the analytical dataset; therefore, no statistical significance was inferred for these changes. Because recurrent ischemic stroke events were sparse and the poor-metabolizer subgroup was small, no regression analysis was performed for recurrent stroke. The association between *CYP2C19* metabolizer phenotype and 12-month functional outcome was evaluated using an unadjusted categorical comparison; no multivariable-adjusted model was available. All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. Analyses were performed using SPSS version 21.0.

Ethical Considerations

The study was conducted as part of a research project approved by the Ethics Committee for Biomedical Research of S.I.S Can Tho International General Hospital (Approval No. 2113/QĐ-S.I.S, September 25, 2023). All study procedures were conducted in accordance with the approved research protocol. Participant information was kept confidential and used solely for research purposes.

RESULTS

Baseline Characteristics

The study included 194 patients with a mean age of 62.06 ± 11.50 years (range, 24–95 years); 130 (67.0%) were men. Normal, intermediate, and poor *CYP2C19* metabolizer phenotypes were identified in 93 (47.9%), 85 (43.8%), and 16 (8.2%) patients, respectively. Overall, 101 patients (52.1%) were intermediate or poor metabolizers. Baseline lesion severity comprised severe stenosis (70–99%) in 49 patients (25.3%) and complete occlusion in 145 (74.7%).

Table 1. Baseline characteristics relevant to the 12-month pharmacogenetic analysis.

Characteristic	Value
Age, years, mean $\pm$ SD (range)	62.06 $\pm$ 11.50 (24–95)
Male sex	130 (67.0%)
NIHSS ≤ 5	64 (33.0%)
NIHSS 6–15	109 (56.2%)
NIHSS >15	21 (10.8%)
Severe stenosis (70–99%)	49 (25.3%)
Complete occlusion	145 (74.7%)
CYP2C19 normal metabolizer	93 (47.9%)
CYP2C19 intermediate metabolizer	85 (43.8%)
CYP2C19 poor metabolizer	16 (8.2%)

Data are n (%) unless otherwise indicated. NIHSS, National Institutes of Health Stroke Scale.

Follow-up Status at 12 Months

Of the 194 patients, 90 (46.4%) underwent repeat MRI/MRA, 75 (38.7%) had clinical follow-up without repeat imaging, 13 (6.7%) were lost to follow-up, and 16 (8.2%) died during the first year.

Table 2. Follow-up status at 12 months.

Follow-up status	n	%
Repeat MRI/MRA	90	46.4
Clinical follow-up without repeat imaging	75	38.7
Lost to follow-up	13	6.7
Death	16	8.2
Total	194	100.0

Laboratory and Imaging Findings in the 90-Patient Imaging Subgroup

Among the 90 patients with paired assessments, mean LDL-C decreased from 2.76 ± 0.80 mmol/L at baseline to 1.98 ± 0.60 mmol/L at 12 months, while mean HbA1c decreased from $6.30 \pm 1.48\%$ to $6.05 \pm 0.71\%$. Because paired test statistics were not available in the analytical summary, statistical significance was not inferred.

Table 3. Laboratory and vascular imaging findings in the 90 patients with repeat imaging.

Measure	Baseline	12 months
LDL-C, mmol/L	2.76 ± 0.80	1.98 ± 0.60
HbA1c, %	6.30 ± 1.48	6.05 ± 0.71
No residual stenosis	0 (0.0)	78 (86.7)
Severe stenosis	26 (28.9)	2 (2.2)
Complete occlusion	64 (71.1)	10 (11.1)

Imaging changes cannot be attributed solely to antiplatelet therapy because the study had no concurrent control group and some patients may have undergone endovascular intervention.

Recurrent Stroke and Functional Outcome

Among the 90 patients with complete clinical and imaging reassessment, 2 (2.2%) experienced recurrent ischemic stroke. One recurrence occurred in a normal metabolizer and one in an

intermediate metabolizer; no recurrence was recorded among the eight poor metabolizers. The event count was too small for meaningful between-group risk comparison.

Table 4. Recurrent ischemic stroke and functional outcome by CYP2C19 metabolizer phenotype in the 90-patient reassessed subgroup.

Outcome	Normal (n=45)	Intermediate (n=37)	Poor (n=8)	Total (n=90)	p
Recurrent ischemic stroke	1 (2.2)	1 (2.7)	0 (0.0)	2 (2.2)	—
mRS 0–1	38 (84.4)	14 (37.8)	0 (0.0)	52 (57.8)	<0.001
mRS ≥ 2	7 (15.6)	23 (62.2)	8 (100.0)	38 (42.2)	—

Overall, 52 of 90 patients (57.8%) achieved mRS 0–1. The proportion with favorable functional outcome differed across the three phenotype groups ($p < 0.001$). Because no adjusted multivariable model was available, this finding should not be interpreted as an independent effect of CYP2C19 phenotype.

Mortality

Sixteen of 194 patients (8.2%) died during the first year, with all recorded deaths occurring between 1 and 6 months after the index stroke. Mortality was descriptively highest among intermediate metabolizers, but the small number of events and lack of adjusted analysis preclude inference of a phenotype-related mortality difference.

Table 5. All-cause mortality within 12 months by CYP2C19 metabolizer phenotype.

Phenotype	Patients	Deaths	Mortality, %
Normal	93	5	5.4
Intermediate	85	10	11.8
Poor	16	1	6.3
Total	194	16	8.2

DISCUSSION

This study yielded three principal observations. First, 52.1% of the cohort had an intermediate or poor CYP2C19 metabolizer phenotype based on CYP2C19 *2 and *3 testing. Second, among the 90 patients with complete clinical and imaging reassessment, functional outcome differed across metabolizer groups, whereas recurrent ischemic stroke was uncommon. Third, vascular imaging findings and mean LDL-C and HbA1c values improved descriptively over 12 months, but the available data do not establish an independent effect of phenotype-guided antiplatelet selection.

The frequency of reduced-metabolism phenotypes is consistent with the clinical relevance of CYP2C19 loss-of-function alleles in Asian populations. CHANCE pharmacogenetic data showed that the benefit of clopidogrel plus aspirin was greater among non carriers of loss-of-function alleles [1], while CPIC guidance recognizes reduced active-metabolite formation and diminished platelet inhibition in intermediate and poor metabolizers [2]. Data from Vietnamese and other East Asian populations also support the relatively high prevalence of CYP2C19 loss-of-function alleles [8,9].

CHANCE-2 provided randomized evidence that ticagrelor plus aspirin modestly reduced 90-day stroke compared with clopidogrel plus aspirin among CYP2C19 loss-of-function carriers, at the cost of more

total bleeding [3]. However, the post hoc analysis among patients with intracranial arterial stenosis did not demonstrate a clearly different treatment effect [4]. Because all patients in the present cohort had intracranial stenosis or occlusion and treatment allocation was not randomized, our findings should not be interpreted as a direct comparison of ticagrelor and clopidogrel.

The marked unadjusted difference in mRS across metabolizer groups warrants cautious interpretation. Functional recovery after ischemic stroke is influenced by age, baseline NIHSS, infarct location and volume, collateral circulation, reperfusion or endovascular treatment, complications, rehabilitation, and comorbidity. These factors were not comprehensively adjusted in the present analysis. In addition, phenotype-specific mRS data were available only in the 90-patient subgroup with complete clinical and imaging reassessment, creating potential selection bias. The observed association therefore requires confirmation in a larger cohort with complete clinical follow-up and multivariable adjustment.

Only two recurrent ischemic strokes were recorded in the 90-patient reassessed subgroup. This event count is insufficient to exclude clinically meaningful differences between metabolizer groups. Recent observational and meta-analytic evidence has continued to associate *CYP2C19* loss-of-function status with adverse ischemic outcomes among clopidogrel-treated patients [5-7,10]. Differences between those reports and the low recurrence observed here may reflect sample size, event ascertainment, phenotype-guided treatment selection, and incomplete follow-up.

At 12 months, 86.7% of the imaging subgroup had no residual stenosis recorded on MRI/MRA. This change should not be attributed solely to antiplatelet therapy because MRA and DSA differ in luminal assessment, spontaneous recanalization may occur, intensive risk-factor management may contribute, and some patients may have undergone endovascular intervention. Similarly, the observed reductions in LDL-C and HbA1c were descriptive because paired statistical testing and detailed lipid-lowering or glucose-lowering treatment data were unavailable.

All-cause mortality was 8.2% during the first year. The available dataset does not support a causal relationship between *CYP2C19* phenotype and mortality. Importantly, bleeding outcomes were not systematically collected; therefore, this study cannot assess or compare the safety of ticagrelor-aspirin and clopidogrel-aspirin regimens.

The strengths of this study include real-world Vietnamese data, *CYP2C19* testing, 12-month clinical follow-up, and 3-T neurovascular imaging. Limitations include the single-center observational design, nonrandom treatment selection, lack of detailed patient-level information on treatment adherence and treatment switching during follow-up, absence of a concurrent control group, repeat imaging in only 46.4% of the cohort, sparse recurrent events, a small poor-metabolizer subgroup, lack of adjusted multivariable analysis, incomplete bleeding ascertainment, and phenotype classification based only on *CYP2C19* *2 and *3. These limitations preclude causal inference and direct comparative-effectiveness conclusions.

CONCLUSION

Among 194 patients with ischemic stroke and intracranial arterial stenosis or occlusion, 52.1% had an intermediate or poor *CYP2C19* metabolizer phenotype based on *CYP2C19* *2 and *3 testing. Sixteen patients (8.2%) died within 12 months. Among the 90 patients with complete clinical and imaging reassessment, 52 (57.8%) achieved

mRS 0–1, 2 (2.2%) had recurrent ischemic stroke, and 78 (86.7%) had no residual stenosis recorded on follow-up MRI/MRA. Functional outcome differed across *CYP2C19* phenotype groups, but the observational design, incomplete follow-up, and lack of multivariable adjustment do not permit causal attribution to phenotype or treatment regimen. Larger prospective multicenter studies with standardized genotype-guided treatment, complete efficacy and safety ascertainment, and adjusted analyses are needed.

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