

Effectiveness of CYP2C19 Genotype-Guided Antiplatelet Therapy Following Neurovascular Endovascular Procedures: A Prospective Non-Randomized Controlled Study

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Background: CYP2C19 loss-of-function alleles are highly prevalent in Asian populations and may reduce the effectiveness of clopidogrel. This study aimed to evaluate the efficacy and safety of CYP2C19 genotype-guided antiplatelet therapy in patients with symptomatic severe intracranial atherosclerotic stenosis undergoing neurovascular endovascular treatment (EVT).

Methods: This prospective non-randomized controlled study enrolled 175 patients who underwent neurovascular intervention. Patients in the genotype-guided group (n=100) received individualized antiplatelet therapy according to CYP2C19 genotyping results, whereas patients in the conventional therapy group (n=75) received routine dual antiplatelet therapy with aspirin and clopidogrel. Safety events, 90-day neurological outcomes, and the cumulative incidence of ischemic events within one year were compared between groups.

Results: The incidence of bleeding events did not differ significantly between the genotype-guided group and the conventional therapy group (1.0% vs 4.0%, $P>0.05$). At 90 days, a significantly higher proportion of patients achieved a favorable functional outcome (modified Rankin Scale score 0–1) in the genotype-guided group than in the conventional therapy group (84.0% vs 65.3%, $P=0.004$). At one year, the proportion of patients experiencing at least one ischemic event was significantly lower in the genotype-guided group than in the conventional therapy group (12.0% vs 26.7%, $P=0.013$). Multivariable Cox regression analysis demonstrated that patients in the conventional therapy group had a significantly higher risk of ischemic events during follow-up than those in the genotype-guided therapy group (HR: 2.723, 95% CI: 1.259–5.888, $P=0.011$). Interaction analysis suggested that treatment effects differed according to device type, with a numerically greater benefit observed in the stent subgroup, although this finding should be considered exploratory.

Conclusion: CYP2C19 genotype-guided antiplatelet therapy following neurovascular EVT was associated with improved neurological outcomes and a lower incidence of ischemic events without increasing bleeding risk. However, because ticagrelor exposure differed between treatment groups, the independent contribution of pharmacogenetic testing requires further confirmation in larger randomized studies.

Keywords: intracranial atherosclerotic severe stenosis, endovascular treatment, CYP2C19 genotyping, pharmacogenetics, antiplatelet therapy

Introduction

More than 65% of ischemic strokes in Asian populations are caused by intracranial atherosclerotic disease, which contrasts sharply with Caucasian populations.^{1,2} Endovascular treatment (EVT) has become an important therapeutic approach for severe symptomatic intracranial stenosis.³ However, despite continuous advances in endovascular devices and techniques, the risk of recurrent ischemic events after EVT remains substantial, with reported one-year event rates ranging from 4.4% to 36.2%.^{4–8} Optimizing post-procedural antiplatelet therapy therefore remains a major clinical challenge. Current guidelines

and expert consensus generally recommend dual antiplatelet therapy (DAPT) with aspirin and clopidogrel following neurovascular intervention, particularly in patients receiving intracranial stents.⁹ Clopidogrel is a prodrug whose antiplatelet activity depends on hepatic bioactivation mediated primarily by the CYP2C19 enzyme.¹⁰ The prevalence of CYP2C19 loss-of-function (LOF) alleles, including *2 and *3, is considerably higher in East Asian populations than in Western populations, affecting approximately 30–60% of individuals.¹¹ Consequently, a substantial proportion of patients may experience reduced responsiveness to clopidogrel and remain at increased risk of thromboembolic events despite standard DAPT.

Ticagrelor is a direct-acting P2Y₁₂ receptor inhibitor that does not require CYP2C19-mediated metabolic activation and therefore provides more consistent platelet inhibition in LOF allele carriers.¹⁰ In the cardiovascular field, individualized selection of P2Y₁₂ inhibitors has increasingly been adopted to optimize antiplatelet efficacy and clinical outcomes.¹² Furthermore, the CHANCE-2 trial demonstrated that ticagrelor plus aspirin significantly reduced recurrent stroke risk among CYP2C19 LOF carriers with minor stroke or transient ischemic attack compared with clopidogrel plus aspirin, without increasing severe bleeding risk.¹³ Previous neurointerventional studies have also suggested that CYP2C19 polymorphisms and clopidogrel hyporesponsiveness may be associated with thromboembolic complications after cerebral endovascular procedures and carotid artery stenting.^{14,15} These findings provide a rationale for considering genotype-guided antiplatelet therapy in neurovascular intervention.

However, an important distinction should be made between the benefit of genotype-guided treatment selection and the pharmacological effect of ticagrelor itself. The value of a genotype-guided strategy lies in identifying patients who are less likely to respond adequately to clopidogrel and selecting a more appropriate P2Y₁₂ inhibitor. Nevertheless, any observed clinical benefit may also reflect the intrinsically stronger and more consistent platelet inhibition provided by ticagrelor. This distinction remains insufficiently explored in the neurointerventional setting. In addition, different endovascular devices may confer distinct thrombotic risks. Intracranial stent implantation introduces a permanent metallic scaffold and may result in prolonged platelet activation and delayed endothelialization, whereas balloon angioplasty does not leave a permanent implant and may therefore have a different thrombogenic profile. These mechanistic differences provide a biological rationale for evaluating whether the effectiveness of genotype-guided antiplatelet therapy varies according to device type. Therefore, this prospective non-randomized controlled study aimed to evaluate the efficacy and safety of CYP2C19 genotype-guided antiplatelet therapy after neurovascular EVT and to explore whether its potential benefits differ according to interventional device type.

Methods

Study Population

This study was designed as a single-center, prospective, non-randomized controlled trial. The project approval number is MR-37-24-055021. The study was approved by the Ethics Review Committee of the Fifth People's Hospital of Jinan, Shandong Province (Approval No.: 23-1-05). Written informed consent was obtained from all patients or their legally authorized representatives, in accordance with the Declaration of Helsinki. Each neurointerventional physician involved in the study performed more than 40 interventional procedures annually.

Patients who underwent EVT (including stent implantation and drug-coated balloon, DCB) for symptomatic intracranial atherosclerotic severe stenosis from January 2022 to June 2024 were consecutively enrolled. Because this was a prospective non-randomized study, treatment allocation was not determined by randomization. Eligible patients were consecutively enrolled during the study period. Patients managed according to CYP2C19 genotyping results were assigned to the genotype-guided treatment group, whereas patients receiving standard dual antiplatelet therapy irrespective of genotype results were assigned to the conventional treatment group. No formal matching procedure was performed. To reduce potential confounding, baseline characteristics were compared between groups and multivariable Cox regression analyses were conducted to adjust for relevant clinical variables. Inclusion criteria: Age ≥ 18 years; Severe stenosis confirmed by digital subtraction angiography (DSA). According to the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) measurement method, severe stenosis was defined as 70–99%; Symptomatic intracranial atherosclerotic stenosis, defined as neurological deficits due to TIA or ischemic cerebral infarction diagnosed by MRI; Postoperative standard dual antiplatelet therapy (aspirin + clopidogrel/ticagrelor); Successful EVT was defined as residual stenosis $\leq 50\%$ after endovascular treatment; Signed informed

consent. CYP2C19 genotyping was offered to all eligible patients as part of routine clinical evaluation; however, treatment decisions were made according to the antiplatelet strategy selected by the treating physician and patient preference.

Exclusion criteria: Concomitant anticoagulation therapy such as atrial fibrillation; Severe hepatic or renal dysfunction; Allergy to aspirin or P2Y₁₂ inhibitors; Concomitant intracranial tumors, aneurysms, or arteriovenous malformations; Any hemorrhagic disorder within 90 days; Inability to participate in follow-up (Figure 1).

Genetic Analysis

We used nucleic acid mass spectrometry (Zhejiang Dipo Diagnostic Technology Co., Ltd., Zhejiang, China) to rapidly and efficiently detect whole blood DNA samples and identify gene variants in enrolled patients. The main genotypes included: CYP2C191, CYP2C192, CYP2C193, CYP2C1917. The workflow of nucleic acid mass spectrometry included: PCR amplification of target fragments using Shrimp Alkaline Phosphatase (PCR), followed by removal of deoxynucleotide triphosphates (dNTPs) with Shrimp Alkaline Phosphatase (SAP); subsequently, single-base extension was performed, purified, and spotted. Finally, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) was used to analyze the generated spectra, and genotypes were directly identified by peak position interpretation.

CYP2C19 Phenotype and Grouping

CYP2C19 Phenotypes Were Classified as LOF and Non-LOF

LOF included intermediate metabolizers (IM): *1/*2, *1/*3, *2/*17, *3/*17, and poor metabolizers (PM): *2/*2, *2/*3, *3/*3. Non-LOF included rapid metabolizers (RM): *1/*17 and normal metabolizers (NM): *1/*1. Genotype testing of CYP2C19 (*2, *3, *17 alleles) was performed at the Jinan Dian Pharmacogenetic Testing Center. This classification followed the recommendations of the Clinical Pharmacogenetics Implementation Consortium (CPIC).¹⁶

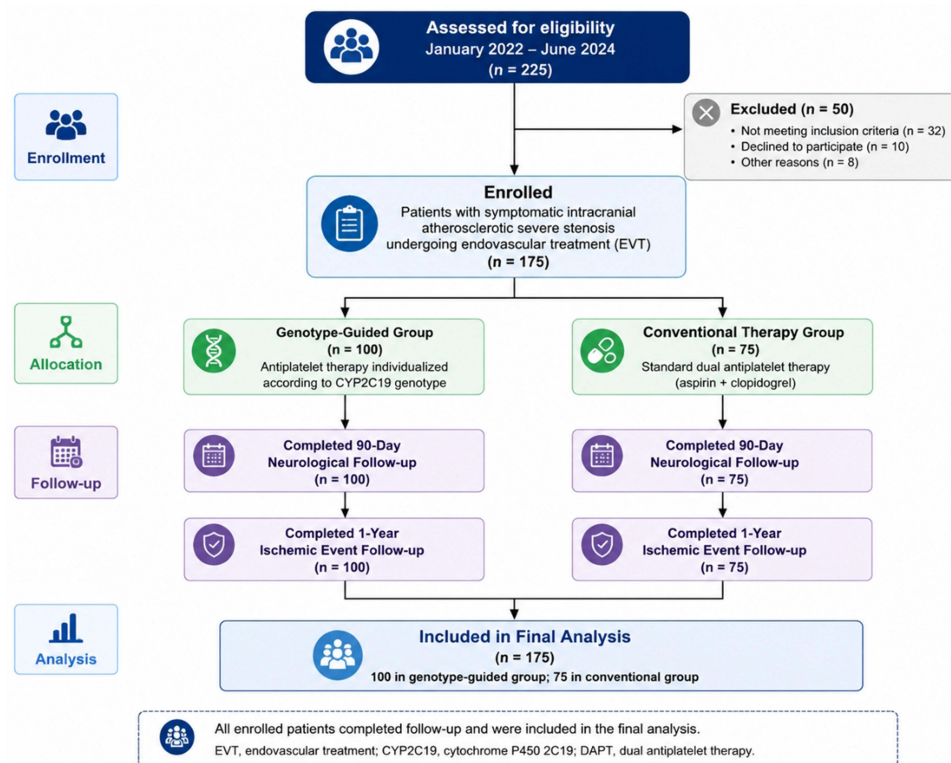


Figure 1 Flow Diagram of Patient Enrollment, Treatment Allocation, Follow-up, and Analysis.

Grouping Criteria

Experimental group (n=100): Patients with IM or PM received aspirin (100 mg once daily) plus ticagrelor (90 mg twice daily); RM or NM continued aspirin plus clopidogrel. Conventional group (n=75): Empirically treated with aspirin (100 mg once daily) plus clopidogrel (75 mg once daily).

All patients received loading doses of aspirin (300 mg) and clopidogrel (300 mg) before the interventional procedure. Genotyping results were available before or shortly after the procedure, and antiplatelet therapy was adjusted as early as clinically feasible, generally within 24 hours. Duration of DAPT was 6 months after stenting and 3 months after DCB. After completing the prescribed course, aspirin was continued lifelong. Patients with hypertension, diabetes, or hyperlipidemia received long-term management.

Outcome Measures

All patients received outpatient or inpatient follow-up at 3 months, 6 months, and 1 year. Follow-up assessments were conducted through scheduled outpatient visits whenever possible. For patients who were unable to attend in person, structured telephone interviews were performed by trained investigators. Neuroimaging examinations, including CT, MRI, or vascular imaging, were reviewed when clinically indicated to verify suspected ischemic or thrombotic events. Clinical outcome events were independently adjudicated by two neurologists who were not involved in treatment allocation. During each follow-up contact, information regarding medication use, treatment discontinuation, and adherence to prescribed antiplatelet therapy was collected. Patients were considered adherent if they reported continuous use of the prescribed antiplatelet regimen throughout the recommended treatment period. The primary ischemic events were composite adverse cerebrovascular events, including cerebrovascular-related death, ischemic stroke, TIA, and thrombotic events.

Ischemic stroke was defined as sudden onset of neurological deficits lasting more than 24 hours, with CT/MRI excluding hemorrhage or confirming ischemia. TIA was defined as transient neurological deficits resolving within 24 hours, with no acute infarction on DWI-MRI. Thrombotic events included in-stent thrombosis and target-vessel thrombosis (DCB procedures did not involve implants). Myocardial infarction was defined as elevated troponin levels with ischemic symptoms or ischemic ECG changes, or new regional wall-motion abnormalities unrelated to surgery.

Neurological function at 90 days after surgery was assessed via the modified Rankin Scale (mRS). Ischemic events such as stroke or TIA occurring during follow-up were included in the mRS outcome. Neurological outcomes were dichotomized: mRS 0–1 = good, mRS 2–6 = poor.

Safety events were defined according to the Bleeding Academic Research Consortium (BARC) class 2 or higher bleeding events:¹⁷ Type 2: actionable bleeding requiring non-surgical intervention, hospitalization, or physician evaluation; Type 3: 3a: hemoglobin drop 3–5 g/dL or transfusion; 3b: hemoglobin drop ≥ 5 g/dL, surgical intervention; 3c: intracranial hemorrhage; Type 4: unrelated to coronary bypass surgery; Type 5: 5a: probable fatal bleeding without documentation; 5b: definite fatal bleeding. All events were verified by at least two neurologists. Follow-up ended upon the occurrence of the first clinical event.

Data Analysis

Statistical analysis was performed using SPSS 29.0 (IBM, Armonk, New York), and figures were generated using GraphPad Prism (version 10.1.2). The Shapiro–Wilk test was used to assess normality of variable distribution. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), and compared using Student's *t*-test, one-way analysis of variance (ANOVA), the Kruskal–Wallis test, or the Mann–Whitney *U*-test as appropriate. Categorical variables were presented as frequencies and percentages, and compared using the chi-square test or Fisher's exact test. Differences in baseline characteristics and outcomes were analyzed using McNemar's test for categorical variables and the Wilcoxon signed-rank test. Kaplan–Meier curves and Log rank tests were used to compare ischemic events. Age, sex, smoking, alcohol consumption, diabetes, hypertension, postoperative residual stenosis rate, lesion length, and device type were included in univariate Cox regression analysis. Based on previous prospective research and clinical importance, age, sex, and diabetes were pre-specified prognostic factors. Variables with $P < 0.05$ in univariate analysis were included in the multivariate model to assess the independent effect of genotype-guided therapy. To examine whether the benefit of genotype-

guided therapy varied by device type, an interaction term “group × device type” was introduced into the Cox model. All probability values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics are shown in Table 1. The mean age of the 175 patients included in the study was 65.9 ± 8.37 years, of whom 119 (68.0%) were male. No significant differences were observed between the two groups in demographic data, cerebrovascular risk factors, or laboratory findings. There were no statistically significant differences in etiology ($P = 0.573$), NIHSS at admission ($P = 0.057$), or ABCD2 score ($P = 0.143$). In the experimental group, 46% of patients were IM and 16% were PM. We subsequently calculated the allele frequencies of *2 and *3 according to genotype distribution. The *2 allele frequency was 35%, and the *3 allele frequency was 4%.

Table 1 Baseline Characteristics of the Two Groups

	Experimental Group N=100	Conventional Group N=75	P
Sex: male (%)	63 (63.0)	56 (74.7)	0.102
Age [Mean (SD), year]	66.1 (8.9)	65.7 (7.8)	0.379
Etiology at admission			0.445
AIS	82 (82.0)	58 (77.3)	
TIA	18 (18.0)	17 (22.7)	
NIHSS at admission [median (IQR)]	2 (0,3)	2 (1,2.5)	0.869
ABCD2 at admission [median (IQR)]	5 (4,5)	3.5 (2,5)	0.143
Smoking (%)	37 (37.0)	23 (30.7)	0.382
Alcohol consumption (%)	25 (25.0)	16 (21.3)	0.571
Hypertension (%)	72 (72.0)	45 (60.0)	0.095
Diabetes (%)	49 (49.0)	30 (40.0)	0.236
Hyperlipidemia (%)	25 (25.0)	22 (29.3)	0.522
Coronary artery disease (%)	42 (42.0)	32 (42.7)	0.930
Peripheral vascular disease (%)	27 (27.0)	28 (37.3)	0.145
History of stroke (%)	32 (32.0)	25 (33.3)	0.852
Total cholesterol [Mean (SD), mmol/L]	4.82 (1.19)	4.49 (1.02)	0.334
Triglycerides [median (IQR), mmol/L]	1.49 (0.97,2.15)	1.35 (0.89,1.99)	0.355
HDL-C [median (IQR), mmol/L]	1.12 (0.96,1.36)	1.22 (1.02,1.55)	0.078
LDL-C [Mean (SD), mmol/L]	2.59 (0.88)	2.32 (0.74)	0.269
Location of stenosis (%)			0.631
Anterior circulation	51 (51.0)	41 (54.7)	
Posterior circulation	49 (49.0)	34 (45.3)	
Device type (%)			0.164
Stent	75 (75.0)	49 (65.3)	
Balloon	25 (25.0)	26 (34.7)	
Residual stenosis rate [median (IQR)]	0 (0,14)	0 (0,12.1)	0.288
Lesion length [median (IQR), mm]	11.0 (8.8,15.8)	10.6 (8.7,13.7)	0.171
NM	37 (37)	NA	
IM/PM	62 (62)	NA	
RM	1 (1)	NA	
*2	70 (35)	NA	
*3	8 (4)	NA	

Abbreviations: AIS, acute ischaemic stroke; TIA, transient ischaemic attack; NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; RM, rapid metabolizer; *2, CYP2C192 loss-of-function allele; *3, CYP2C193 loss-of-function allele; allele frequencies are presented as percentages of all tested alleles; NA, not available.

Clinical Outcomes

At 1 year after EVT, the cumulative incidence of cerebrovascular death, ischemic stroke, TIA, and thrombotic events was significantly lower in the experimental group compared with the conventional group (12% vs 26.7%, $P = 0.013$) (Table 2). We then divided the 175 patients into two subgroups based on device type: stent implantation and balloon angioplasty. Kaplan–Meier curves were generated to compare the 1-year cumulative incidence of ischemic events. Kaplan–Meier analysis demonstrated a significantly lower cumulative incidence of ischemic events in the genotype-guided therapy group compared with the conventional therapy group in the overall study population (HR=0.393, 95% CI: 0.193–0.797, $P=0.008$; Figure 2A). In the stent subgroup, genotype-guided therapy showed a trend toward reduced ischemic event risk compared with conventional therapy (HR=0.405, 95% CI: 0.163–1.009, $P=0.052$; Figure 2B). In the drug-coated balloon subgroup, no statistically significant difference was observed between treatment groups (HR=0.462, 95% CI: 0.128–1.418, $P=0.164$; Figure 2C).

The subsequent univariate Cox regression confirmed this association (HR:2.565, 95% CI:1.251–5.259, $P = 0.010$, Figure 3). To evaluate whether the genotype-guided treatment strategy was an independently associated with ischemic event risk and eliminate potential confounders, we included age, sex, smoking, alcohol consumption, hypertension, diabetes, device type, residual stenosis rate, and lesion length in the multivariate Cox regression model. After adjustment for potential confounders, treatment strategy remained significantly associated with the risk of ischemic events during follow-up (HR: 2.723, 95% CI: 1.259–5.888, $P = 0.011$). Patients in the conventional treatment group had a significantly higher risk of ischemic events than those in the genotype-guided treatment group. (Figure 3).

In the Kaplan–Meier analysis, a numerically greater survival benefit was observed in stent-treated patients receiving genotype-guided therapy compared with conventional therapy. To rigorously examine this heterogeneity, we introduced an interaction term “treatment group $\times$ device type” into the model. The interaction analysis suggested a potential difference in treatment effect according to device type (P for interaction = 0.004), although the subgroup findings should be interpreted cautiously because of the limited number of events. In the stent subgroup, genotype-guided therapy showed the strongest trend toward benefit, reaching marginal significance compared with the conventional group (HR:0.405, 95% CI:0.163–1.009, $P = 0.052$). No significant benefit was observed in the DCB subgroup (HR:0.462, 95% CI:0.128–1.419, $P = 0.164$, Table 3).

Neurological recovery differed significantly between groups (16% vs 34.7%, $P = 0.004$). Among all-cause deaths in the conventional group, 4% died from severe gastrointestinal bleeding. Of the thrombotic events, two occurred within

Table 2 Comparison of Outcomes Between Groups

	Experimental Group N=100	Conventional Group N=75	P
Major ischemic events			0.013
Cerebrovascular death	0	2 (2.7)	
AIS	11 (11.0)	13 (17.3)	
TIA	1 (1.0)	2 (2.7)	
Thrombotic events	0	3 (4.0)	
90-day mRS			0.004
Good (0–1)	84 (84.0)	49 (65.3)	
Poor (2–6)	16 (16.0)	26 (34.7)	
Myocardial infarction	2 (2.0)	3 (4.0)	0.366
All-cause death	0	3 (4.0)	0.077
Safety events	1 (1.0)	3 (4.0)	0.221

Notes: Major ischemic events represent the number of patients experiencing at least one ischemic event during the 1-year follow-up period.

Abbreviations: AIS, acute ischaemic stroke; TIA, transient ischaemic attack; mRS, modified Rankin Scale.

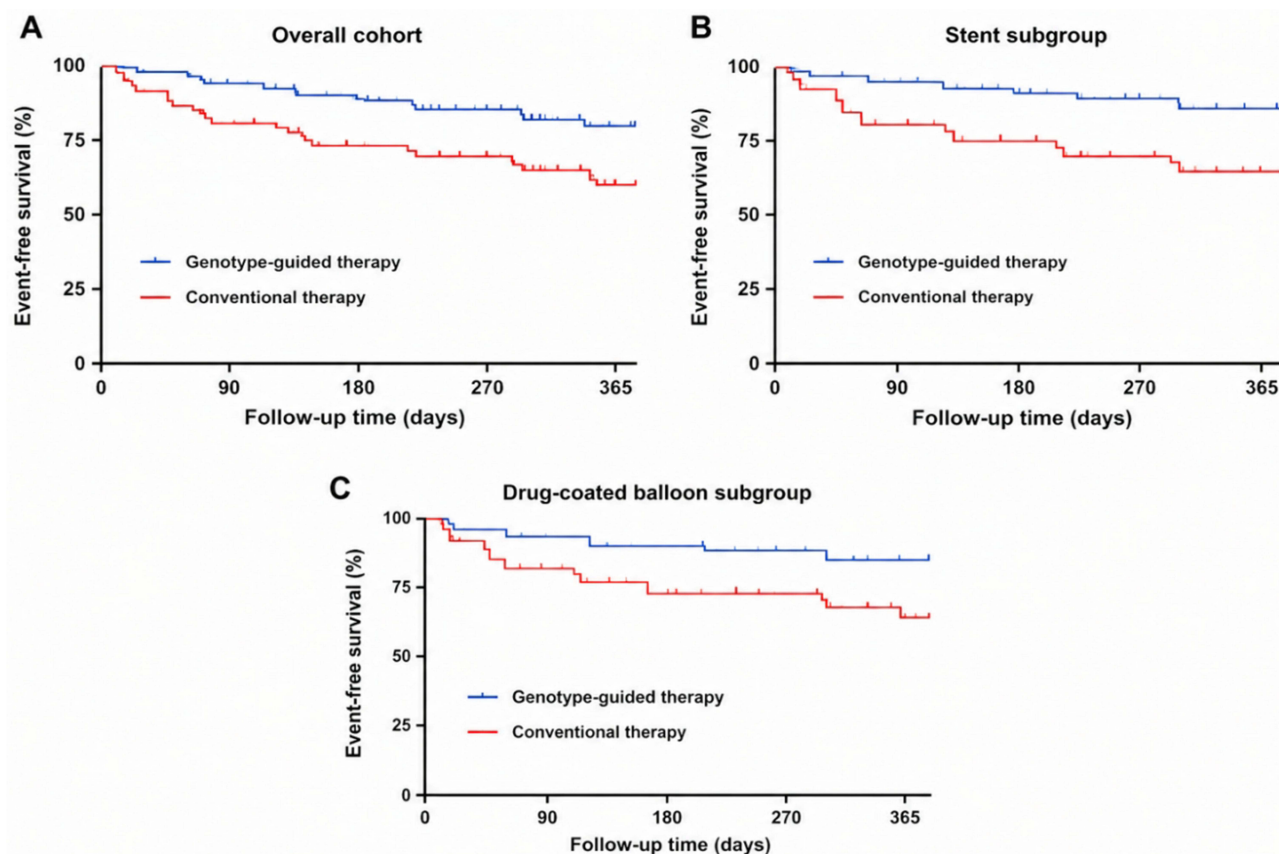


Figure 2 Kaplan–Meier curves for 1-year ischemic-event-free survival according to treatment strategy.

Notes: The primary endpoint was the occurrence of at least one ischemic event during the 1-year follow-up period, including cerebrovascular death, ischemic stroke, transient ischemic attack, or thrombotic events. **(A)** Overall study population. **(B)** Patients treated with intracranial stent implantation. **(C)** Patients treated with drug-coated balloon angioplasty. Subgroup analyses were exploratory and should be interpreted with caution because of the limited number of events.

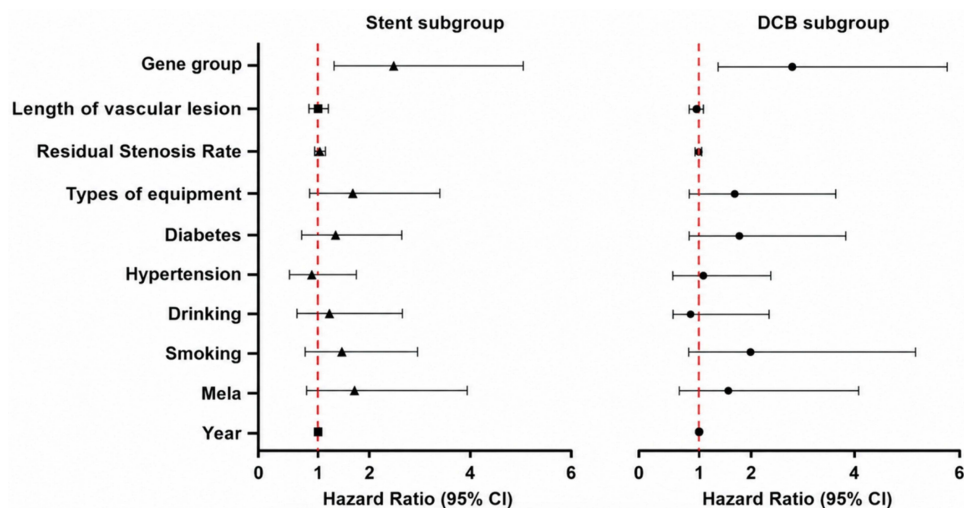


Figure 3 Forest plot of risk factors for ischemic events.

Note: ▲ Univariate Cox regression; ● Multivariate Cox regression.

stents and one at the distal segment of a balloon-dilated vessel. The experimental group had lower rates of myocardial infarction (2% vs 4%, $P = 0.336$), all-cause death (0 vs 4%, $P = 0.077$), and safety events (1% vs 4%, $P = 0.221$), although none reached statistical significance (Table 2).

Table 3 Subgroup Analysis and Interaction Effects Across Device Types

Subgroup	Experimental Group	Conventional Group	HR, 95% CI	P value	Interaction P value
Stent	8/75 (10.7%)	11/49 (22.4%)	0.405, 0.163–1.009	0.052	0.004
Balloon	4/25 (16%)	9/26 (34.6%)	0.462, 0.128–1.418	0.164	
Overall interaction					

Abbreviations: HR, hazard ratio; CI, confidence interval.

Discussion

This study investigated the efficacy of CYP2C19 genotype-guided antiplatelet therapy after EVT in a prospective, non-randomized controlled trial. The genotype-guided strategy was associated with improved neurological recovery and a lower incidence of ischemic events without increasing bleeding risk. However, the observed clinical benefit should be interpreted cautiously. In the genotype-guided group, intermediate and poor metabolizers received ticagrelor, whereas all patients in the conventional group received clopidogrel. Therefore, part of the observed benefit may have resulted from the greater and more consistent antiplatelet effect of ticagrelor itself rather than the pharmacogenetic testing strategy alone. We found that the experimental group did not show an increased risk of moderate-to-severe bleeding (1% vs 4.0%, $P=0.221$). At 90 days postoperatively, patients in the experimental group demonstrated significantly improved neurological recovery (16% vs 34.7%, $P=0.004$). Compared with conventional DAPT therapy, genotype-guided antiplatelet treatment significantly reduced the proportion of patients experiencing at least one ischemic event within 1 year after EVT (12.0% vs 26.7%, $P=0.013$). Multivariate COX regression analysis indicated that conventional therapy was a prognostic risk factor after EVT. Kaplan–Meier analysis demonstrated a significantly lower cumulative incidence of ischemic events in the genotype-guided therapy group in the overall cohort. Interaction analysis further suggested that the treatment effect differed according to device type (P for interaction = 0.004).

Among the 175 patients in this study, the frequencies of CYP2C19*2 and *3 were 35% and 4%, respectively, consistent with previous reports in East Asian populations.^{18,19} The observed clinical benefit may be attributable to both the genotype-guided treatment strategy and the pharmacological differences between ticagrelor and clopidogrel. Because CYP2C19 loss-of-function carriers in the genotype-guided group were preferentially treated with ticagrelor, the present study cannot fully separate the effect of pharmacogenetic-guided treatment selection from the intrinsic antiplatelet superiority of ticagrelor in this patient population. Studies exploring the relationship between CYP2C19 polymorphisms and postoperative outcomes after EVT showed that *2 and *3 significantly influenced postoperative outcomes among clopidogrel users, and ticagrelor was recommended as an alternative.^{20,21} One study reported that in LOF allele carriers, clopidogrel combined with aspirin did not reduce 90-day stroke risk compared with aspirin monotherapy (9.4% vs 10.8%; HR:0.93, 95% CI:0.69–1.26, $p=0.64$),²² while non-LOF carriers experienced a significant risk reduction (6.7% vs 12.4%; HR:0.51; 95% CI:0.35–0.75; $p<0.01$).²¹ Another study using genotyping to assess clopidogrel treatment found that compared with normal metabolizers, IM or PM patients receiving clopidogrel had more than double the risk of vascular events (HR:2.16, 95% CI:1.31–3.56, $p=0.003$).²³ Our study observed a significant reduction in ischemic events in the experimental group compared with the conventional group ($P=0.013$), and Kaplan–Meier analysis ($P=0.008$) together with multivariate COX regression ($P=0.011$) demonstrated a sustained survival advantage throughout the follow-up period. Overall, we found that clopidogrel failed to provide strong platelet inhibition for IM or PM patients, consistent with a meta-analysis including seven studies showing that LOF patients had increased thromboembolic complications after neurointerventional procedures.¹⁴ In this study, thrombotic events occurred in only three cases, and although the number was too small for definitive conclusions, all occurred in the conventional group.

In the conventional group, three cases of moderate-to-severe bleeding were confirmed; all were related to gastrointestinal bleeding, and subsequent genetic testing revealed no UM. A retrospective study reported that after percutaneous neurointerventional procedures, UM patients exhibited a higher bleeding risk.¹⁵ Given the limited sample size of this study, further investigation is required. Another randomized controlled trial found that ticagrelor combined with aspirin did not increase bleeding risk compared with clopidogrel plus aspirin, consistent with our findings. Neurological function assessed by mRS showed better recovery in the experimental group, consistent with results from a single-blind trial.^{24,25}

From the perspective of device type, interaction analysis suggested that treatment effects may differ between stent implantation and drug-coated balloon procedures. Although a larger numerical risk reduction was observed in the stent subgroup, the result did not reach conventional statistical significance ($P=0.052$) and should therefore be considered exploratory. This observation is biologically plausible because stents, as permanent implants, create an environment with prolonged platelet activation and a potentially higher thrombotic burden. Under these conditions, differences in antiplatelet responsiveness may have a greater clinical impact. Therefore, CYP2C19-guided antiplatelet selection may be particularly relevant in patients receiving stent implantation.^{26,27} However, these findings require confirmation in larger studies with adequate statistical power. Avoiding clopidogrel resistance via genotyping allows ticagrelor to provide strong and consistent platelet inhibition, which was most evident in our study. From a practical perspective, implementation of CYP2C19 genotyping in neurointerventional practice is becoming increasingly feasible because testing can now be completed within a relatively short time frame and at a modest cost in many centers. Early identification of CYP2C19 loss-of-function carriers may facilitate individualized antiplatelet selection before or shortly after EVT, potentially reducing thromboembolic complications in high-risk patients. Nevertheless, the cost-effectiveness of routine pharmacogenetic testing in neurovascular intervention remains uncertain and may vary across healthcare systems. Future prospective studies should evaluate not only clinical outcomes but also economic impact and optimal timing of genotyping in relation to the procedure. Compared with stents, DCB avoids permanent implants, reduces chronic inflammation, and lowers long-term thrombotic risk.²⁸ However, antiproliferative drugs such as paclitaxel, while preventing restenosis, may delay functional endothelial healing, creating a surface prone to platelet adhesion and activation during the mid-to-late postoperative period, thereby potentially increasing thrombotic risk.²⁹ As drug effects diminish, the vessel achieves near-complete endothelialization, and the thrombosis risk window is relatively short. This mechanism helps explain why genotype-guided therapy still trends toward benefit in the DCB subgroup, although its absolute value is less pronounced than in the stent subgroup. From another angle, the relatively lower thrombogenic burden associated with DCB procedures may provide a rationale for future studies investigating de-escalation antiplatelet strategies in selected patients at high bleeding risk. However, the present study was not designed to evaluate DAPT duration, and therefore no conclusions regarding de-escalation strategies can be drawn from our findings.

Limitations

Our study has several limitations. First, this was a single-center study. All enrolled patients were Han Chinese from northern China, which may introduce selection bias. Multi-center studies with larger sample sizes are required to validate our findings. Second, no formal sample size calculation was performed before study initiation. Although 175 patients were enrolled, the absolute number of ischemic events was relatively small, particularly within individual device subgroups. Consequently, the statistical power for exploratory subgroup and interaction analyses may have been limited. The observed trend toward benefit in the stent subgroup did not reach conventional statistical significance, which may partly reflect insufficient sample size rather than the absence of a true treatment effect. Therefore, subgroup findings should be interpreted cautiously and regarded as hypothesis-generating until confirmed in larger adequately powered studies. Third, an important source of potential confounding should be acknowledged. The genotype-guided group did not simply undergo pharmacogenetic testing; rather, intermediate and poor metabolizers were switched to ticagrelor, whereas patients in the conventional group uniformly received clopidogrel. Consequently, the observed reduction in ischemic events may partly reflect the stronger antiplatelet efficacy of ticagrelor rather than the effect of genotyping alone. Fourth, although genotype results were available before or shortly after EVT and antiplatelet therapy was adjusted within 24 hours whenever feasible, all patients initially received a clopidogrel loading dose before the procedure. Consequently, some CYP2C19 loss-of-function carriers may have experienced suboptimal platelet inhibition during the peri-procedural period before treatment adjustment. This could have influenced the risk of early thrombotic events and may have attenuated the potential benefit of genotype-guided therapy. Because platelet function testing was not routinely performed during this early phase, the impact of this temporary exposure to clopidogrel cannot be fully quantified and warrants further investigation.

Conclusion

In patients undergoing EVT, CYP2C19 genotype-guided dual antiplatelet therapy was associated with improved neurological outcomes at 90 days and a lower incidence of ischemic events during 1-year follow-up without increasing bleeding risk. Interaction analysis suggested that treatment effects may vary according to device type; however, these subgroup findings should be considered exploratory and interpreted with caution. Given the non-randomized design and the potential confounding effect of differential ticagrelor exposure between groups, the independent contribution of pharmacogenetic-guided treatment selection requires further confirmation in larger multicenter randomized studies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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