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*Research Article*

# Effect of Dual- versus Single-Antiplatelet Therapy on Early Neurological Deterioration in Minor Stroke of Undetermined Cause

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*Background.* There is insufficient evidence about the suitability of dual-antiplatelet therapy (DAPT) for different stroke subtypes. We aimed to determine the relationship between DAPT and early neurological deterioration (END) in patients with minor stroke of undetermined cause. *Methods.* We retrospectively collected data on patients with minor stroke treated with aspirin alone or in combination with clopidogrel and aspirin. Efficacy was the incidence of END defined as the National Institutes of Health Stroke Scale score increase of $\geq 2$ within 7 days after admission. Safety was defined as the rate of any bleeding event. These were investigated in subtypes including the stroke of undetermined cause (SUC), large artery atherosclerosis (LAA), cardioembolism (CE), and small artery occlusion (SAO). *Results.* 442 patients were assigned to the SUC ($n = 91$), LAA ($n = 157$), CE ($n = 30$), and SAO ($n = 164$) groups. The incidences of END were not significantly different between patients treated with dual- versus single-antiplatelet therapy in any stroke subtypes: LAA, 17.6% vs. 12.1% ($P = 0.348$); CE, 0% vs. 20.0% ($P = 0.224$); SAO, 8.8% vs. 2.4% ($P = 0.093$); and SUC, 13.6% vs. 2.1% ($P = 0.053$). Multivariable analysis showed that after adjusting for confounding factors, DAPT was the independent factor associated with END (odds ratio 13.39, 95% confidence interval (1.16-154.81), $P = 0.038$) in the SUC group, rather than the LAA, CE, and SAO groups. *Conclusion.* Combined clopidogrel and aspirin is a risk factor for the rate of END only in minor stroke patients with the SUC subtype. This suggests that cryptogenic stroke may not be suitable for DAPT in the acute phase.

## 1. Introduction

The efficacy and safety of dual-antiplatelet therapy (DAPT) combining aspirin and clopidogrel have been strongly demonstrated in patients with transient ischemic attack (TIA) and minor acute ischemic stroke (AIS) [1, 2]. Subsequently, the treatment regimen of ticagrelor combined with aspirin has been also found to reduce stroke recurrence rates, but it increases the risk of severe bleeding [3]. Moreover, the application of DAPT in patients with ischemic cerebrovascular events has been confirmed to be safe and effective, at least in the two acute situations mentioned above [4]. However, it is also important to note that DAPT may cause early neurologic deterioration (END) due to certain reasons such as cerebral hemorrhage.

END is defined as a worsening of neurological severity within the first few days after the onset of AIS, with an incidence ranging from 10% to 30% [5–7]. Based on the results of the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) and Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trials, the current guideline recommends that patients with minor stroke or high risk of TIA start DAPT for 21 days after clinical onset [8]. However, early DAPT may increase the risk of END, with hemorrhage and ischemic infarct growth being the most common causes of END [9]. Meanwhile, DAPT can improve the long-term prognosis of patients with AIS [10]. This suggests that the potential benefit of DAPT in improving long-term outcomes may not be offset by the possibility of increased END. However,

it should be noted that different stroke subtypes have different pathogenesis, and the pathogenesis of stroke of undetermined cause (SUC) is currently believed to be mainly caused by embolism [11], which is completely different from the pathogenesis of large artery atherosclerosis (LAA) and small artery occlusion (SAO). Therefore, it is worth investigating whether DAPT is appropriate for minor SUC.

In summary, the aim of this retrospective study was to examine the variation in the incidence of END among patients with minor stroke of different stroke subtypes, particularly in SUC, who received dual- versus single-antiplatelet therapy. In addition, we also paid attention to whether there were differences in the occurrence of cerebral hemorrhage among stroke patients of different subtypes treated with dual- versus single-antiplatelet therapy.

## 2. Methods

### 2.1. Subjects.
We retrospectively enrolled patients from the Department of Neurology at the First Affiliated Hospital of Jinan University from January 2008 and December 2016. Patients that met the following criteria were included: aged ≥40 years, hospital admission within 24 hours of onset, having a score of 3 or lower on the National Institutes of Health Stroke Scale (NIHSS), diagnosis of an AIS confirmed by computed tomography or magnetic resonance imaging [1, 2], and aspirin only or aspirin plus clopidogrel at admission. Prior to the CHANCE trials, there was no consensus regarding the use of DAPT for minor stroke, and this was therefore dependent on the experience of the clinician. After the publication of the CHANCE trials, neurologists were more likely to use DAPT for 21 days in minor stroke. Thus, in the absence of intracerebral hemorrhage, DAPT (aspirin 100 mg plus clopidogrel 75 mg) lasted from 7 days to 21 days.

Patients that met the following criteria were excluded: a history of contraindications to aspirin or clopidogrel, definite indications for anticoagulation (e.g., atrial fibrillation or artificial heart valves), and a history of intracranial hemorrhage; patients who had undergone or plan to undergo thrombectomy were excluded as well. Stroke etiologies were classified according to the TOAST criteria by a registered neurologist (X.F.X.). Only patients with AIS diagnosed with LAA, cardioembolism (CE), SAO, and SUC at discharge were included in the analysis. The enrolled CE patients had no evidence of cardiogenic factors at the time of admission and were given either dual or single antiplatelet. After the diagnosis has been confirmed, the patients were treated by anticoagulation. The institutional review board of the First Affiliated Hospital of Jinan University approved this study protocol (ethical approval reference number: KY-2022-183).

### 2.2. Clinical Assessment.
Baseline data on stroke-related risk factors were collected including age, gender, history of hypertension, diabetes mellitus, valvular heart disease, active cancer, and the presence of smoking and drinking, and blood pressure, admission NIHSS score, onset-to-door time, and topography of infarcts were reviewed. Active cancer was defined as newly diagnosed cancer undergoing treatment or confirmed by pathological biopsy during hospitalization.

Laboratory findings on glucose, hyperlipidemia, and platelet count were also collected.

### 2.3. Efficacy and Safety of DAPT.
In this study, we used END to assess the efficacy of DAPT. END was defined as an increase in NIHSS score of 2 points or more within 7 days after onset. We assessed the safety of DAPT by using the presence or absence of hemorrhage. Referring to a previous study, hemorrhage was classified as mild, moderate, or severe [1]. Mild hemorrhage was defined as a bleeding event that did not require transfusion or that did not alter hemodynamics. Moderate hemorrhage was defined as bleeding that required transfusion but did not result in hemodynamic changes that required intervention. Severe hemorrhage was defined as symptomatic intracranial hemorrhage or severe extracranial hemorrhage.

### 2.4. Statistical Analysis.
All analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Numerical variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) when appropriate. Categorical variables between subgroups were analyzed using the chi-square test, while numerical data were compared using the Mann-Whitney $U$ rank-sum test in the baseline data. The chi-square test was used to compare the incidence of END and hemorrhage in the presence of DAPT for each TOAST subtype. Multivariable regression analysis was used to determine the potential independent parameters related to END in each TOAST subtype. Variables defined as $P < 0.1$ in univariate analysis are imported into multivariable analysis. A $P$ value $< 0.05$ was statistically significant.

## 3. Results

### 3.1. Baseline Results.
Between January 2008 and December 2016, a total of 442 patients with minor AIS met the inclusion criteria. Table 1 shows the clinical baseline data based on stroke subtypes. In total, 157 (36%), 30 (7%), 164 (37%), and 91 (20%) patients were diagnosed with AIS due to LAA, CE, SAO, and SUC, respectively. Patients in the CE group were older, had a higher proportion of valvular heart disease and atrial fibrillation, and had a shorter onset-to-door time than those in the other three stroke subgroups ($P$ – all $< 0.05$).

### 3.2. Efficacy and Safety of DAPT in Each TOAST Subtype.
After seven days of stroke onset, 43 (10%) of the 422 patients showed END, with 29 (12%) patients in the DAPT group and 14 (7%) patients in the aspirin group ($P = 0.033$). We then assessed whether the impact of DAPT on END differed among TOAST subtypes. As shown in Table 2, the addition of clopidogrel to aspirin did not prevent END in these stroke subtypes ($P = 0.348$ in the LAA, 0.224 in the CE, and 0.093 in the SAO group), while DAPT may increase the incidence of END in the SUC group ($P = 0.053$). DAPT did not increase the risk of hemorrhage compared with single-antiplatelet therapy in all stroke subtypes ($P$ – all $> 0.05$).

### 3.3. Risk Factors Associated with END.
The baseline characteristics based on the presence of END in stroke subtypes

TABLE 1: Demographic and baseline characteristics.

| Variable | LAA ($n = 157$) | CE ($n = 30$) | SAO ($n = 164$) | SUC ($n = 91$) | P value |
|---|---|---|---|---|---|
| Age (y) | 65.7 ± 13.7 | 70.8 ± 14.9 | 63.5 ± 11.6 | 63.1 ± 13.3 | 0.016 |
| Women | 45 (28.7%) | 13 (43.3%) | 61 (37.2%) | 28 (30.8%) | 0.234 |
| Prestroke vascular risk factors | | | | | |
| Hypertension | 104 (66.2%) | 19 (63.3%) | 120 (73.2%) | 59 (64.8%) | 0.399 |
| Diabetes mellitus | 33 (21.0%) | 8 (26.7%) | 56 (29.9%) | 19 (20.9%) | 0.438 |
| Valvular heart disease | 0 (0%) | 2 (6.7%) | 0 (0%) | 0 (0%) | 0.003 |
| Atrial fibrillation | 0 (0%) | 14 (46.7%) | 1 (0.6%) | 0 (0%) | <0.001 |
| Active cancer | 2 (1.3%) | 0 (0%) | 2 (1.2%) | 1 (1.1%) | 0.944 |
| Current smoking | 64 (40.8%) | 13 (43.3%) | 52 (31.7%) | 31 (34.1%) | 0.297 |
| Current drinking | 26 (16.6%) | 1 (3.3%) | 20 (12.2%) | 16 (17.6%) | 0.156 |
| Clinical findings | | | | | |
| SBP at baseline (mm Hg) | 158.6 ± 26.2 | 150.5 ± 25.7 | 158.8 ± 22.7 | 153.1 ± 25.8 | 0.126 |
| DBP at baseline (mm Hg) | 85.9 ± 14.7 | 84.3 ± 18.3 | 86.9 ± 15.4 | 85.6 ± 16.1 | 0.819 |
| Admission NIHSS score | 2 (2-3) | 2 (1-3) | 2 (1-3) | 2 (1-3) | 0.352 |
| Onset-to-door time (hour) | 10.0 (5.0-17.0) | 5.5 (3.0-10.2) | 12.0 (6.0-21.0) | 12.0 (5.0-22.0) | 0.012 |
| Topography of infarcts | | | | | <0.001 |
| Cortical infarct | 53 (33.8%) | 8 (26.7%) | 0 (0%) | 37 (40.7%) | |
| Subcortical infarct | 86 (54.8%) | 3 (10.0%) | 164 (100.0%) | 13 (14.3%) | |
| Both types of infarcts | 18 (11.4%) | 19 (63.3%) | 0 (0%) | 41 (45.0%) | |
| Laboratory findings | | | | | |
| Glucose (mmol/L) | 6.6 ± 2.8 | 7.2 ± 4.0 | 6.6 ± 2.5 | 5.9 ± 1.9 | 0.076 |
| Hyperlipidemia | 52 (33.1%) | 4 (13.3%) | 56 (34.1%) | 29 (31.9%) | 0.154 |
| Platelet count $\geq 200 \times 10^9$/L | 113 (72.0%) | 22 (73.3%) | 133 (81.1%) | 60 (65.9%) | 0.052 |

Values are expressed as mean ± SD, median (interquartile range), or frequency (%). SBP: systolic blood pressure; DBP: diastolic blood pressure; NIHSS: National Institutes of Health Stroke Scale; LAA: large artery atherosclerosis; CE: cardioembolism; SAO: small artery occlusion; SUC: stroke of undetermined cause.

TABLE 2: Safety and efficacy of dual-antiplatelet therapy in patients with different stroke types.

| Outcomes | LAA SAT ($n = 66$) | LAA DAPT ($n = 91$) | P value | CE SAT ($n = 15$) | CE DAPT ($n = 15$) | P value | SAO SAT ($n = 84$) | SAO DAPT ($n = 80$) | P value | SUC SAT ($n = 47$) | SUC DAPT ($n = 44$) | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Efficacy | | | | | | | | | | | | |
| END | 8 (12.1%) | 16 (17.6%) | 0.348 | 3 (20.0%) | 0 (0%) | 0.224 | 2 (2.4%) | 7 (8.8%) | 0.093 | 1 (2.1%) | 6 (13.6%) | 0.053 |
| Safety | | | | | | | | | | | | |
| Hemorrhage | | | 0.696 | | | NA | | | 0.236 | | | 1.000 |
| Severe | 0 (0%) | 0 (0%) | | 0 (0%) | 0 (0%) | | 0 (0%) | 0 (0%) | | 0 (0%) | 0 (0%) | |
| Moderate | 0 (0%) | 0 (0%) | | 0 (0%) | 0 (0%) | | 0 (0%) | 0 (0%) | | 0 (0%) | 0 (0%) | |
| Mild | 3 (4.5%) | 3 (3.3%) | | 0 (0%) | 0 (0%) | | 0 (0%) | 2 (2.5%) | | 1 (2.1%) | 1 (2.2%) | |

SAT: single-antiplatelet therapy; DAPT: dual-antiplatelet therapy; LAA: large artery atherosclerosis; CE: cardioembolism; SAO: small artery occlusion; SUC: stroke of undetermined cause; END: early neurological deterioration.

are shown in Table 3. The diastolic blood pressure at baseline differed significantly between the END and no-END groups in the SUC subgroup ($P = 0.011$). There were no clinical features associated with END in the LAA, CE, and SAO groups. We then conducted a multivariable regression analysis to explore the independent factors related to the END in the LAA, CE, SAO, and SUC groups (Table 3). Parameters associated with END with $P < 0.1$ were involved in the analysis. DAPT was the only risk factor related to the END in the SUC group (OR = 13.39, 95% CI = 1.16 − 154.81, $P = 0.038$). No associated independent risk factors were found in the LAA, CE, and SAO groups.

TABLE 3: Multivariable logistic regression of END in patients with different stroke types.

| Variable | LAA OR (95% CI)* | P value* | LAA OR (95% CI)† | P value† | CE OR (95% CI)* | P value* | CE OR (95% CI)† | P value† | SAO OR (95% CI)* | P value* | SAO OR (95% CI)† | P value† | SUC OR (95% CI)* | P value* | SUC OR (95% CI)† | P value† |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 1.02 (0.98-1.05) | 0.327 | | | 1.02 (0.93-1.13) | 0.638 | | | 0.96 (0.91-1.02) | 0.180 | | | 0.98 (0.92-1.04) | 0.451 | | |
| Women | 2.00 (0.81-4.91) | 0.131 | | | 0.62 (0.05-7.75) | 0.714 | | | 1.37 (0.36-5.33) | 0.645 | | | 1.77 (0.37-8.49) | 0.475 | | |
| Hypertension | 1.28 (0.49-3.32) | 0.606 | | | ... | ... | | | 0.72 (0.17-3.01) | 0.652 | | | 1.39 (0.25-7.59) | 0.705 | | |
| Diabetes mellitus | 0.99 (0.34-2.88) | 0.981 | | | ... | ... | | | ... | ... | | | 0.61 (0.07-5.41) | 0.658 | | |
| Current smoking | 0.55 (0.21-1.41) | 0.214 | | | 2.91 (0.23-36.16) | 0.406 | | | 1.08 (0.26-4.51) | 0.914 | | | 0.76 (0.14-4.15) | 0.750 | | |
| Current drinking | 0.19 (0.02-1.46) | 0.110 | | | ... | ... | | | 0.89 (0.11-7.56) | 0.919 | | | 2.00 (0.35-11.36) | 0.434 | | |
| SBP at baseline | 1.02 (1.00-1.03) | 0.054 | 1.01 (0.99-1.03) | 0.082 | 1.02 (0.97-1.06) | 0.515 | | | 1.00 (0.97-1.03) | 0.969 | | | 1.03 (1.00-1.06) | 0.051 | 1.02 (0.98-1.07) | 0.272 |
| DBP at baseline | 1.00 (0.97-1.03) | 0.790 | | | 1.07 (0.99-1.14) | 0.084 | 1.07 (0.99-1.14) | 0.084 | 1.02 (0.97-1.06) | 0.437 | | | 1.06 (1.01-1.10) | 0.011 | 1.04 (0.98-1.10) | 0.169 |
| Admission NIHSS score | 1.32 (0.73-2.40) | 0.363 | | | 4.49 (0.58-34.94) | 0.151 | | | 0.95 (0.41-2.21) | 0.910 | | | 0.72 (0.29-1.81) | 0.486 | | |
| Onset-to-door time | 0.98 (0.92-1.04) | 0.535 | | | 0.58 (0.26-1.31) | 0.194 | | | 1.04 (0.95-1.13) | 0.438 | | | 1.04 (0.95-1.15) | 0.380 | | |
| Topography of infarcts | | | | | | | | | | | | | | | | |
| Cortical infarct | Reference | | | | Reference | | | | | | | | Reference | | | |
| Subcortical infarct | 0.63 (0.14-2.86) | 0.558 | | | 2.57 (0.14-47.01) | 0.524 | | | ... | ... | | | 1.72 (0.27-10.91) | 0.564 | | |
| Both types of infarcts | 1.05 (0.27-4.11) | 0.936 | | | 9.01 (0.39-206.52) | 0.169 | | | ... | ... | | | 3.54 (0.44-28.12) | 0.230 | | |
| Glucose | 1.12 (0.98-1.27) | 0.096 | 1.10 (0.96-1.25) | 0.157 | 0.98 (0.71-1.36) | 0.925 | | | 0.96 (0.71-1.31) | 0.812 | | | 1.23 (0.91-1.67) | 0.177 | | |
| Hyperlipidemia | 1.55 (0.63-3.77) | 0.336 | | | 4.00 (0.27-58.56) | 0.311 | | | 1.58 (0.41-6.15) | 0.506 | | | 0.84 (0.15-4.63) | 0.846 | | |
| Platelet count ≥200 × 10⁹/L | 0.59 (0.24-1.48) | 0.265 | | | ... | ... | | | 0.81 (0.16-4.08) | 0.794 | | | 1.32 (0.24-7.22) | 0.750 | | |
| DAPT | 1.55 (0.62-3.86) | 0.350 | | | ... | ... | | | 3.93 (0.79-19.53) | 0.094 | 3.93 (0.79-19.53) | 0.094 | 7.26 (0.83-62.99) | 0.072 | 13.39 (1.16-154.81) | 0.038 |

SAT: single-antiplatelet therapy; DAPT: dual-antiplatelet therapy; SBP: systolic blood pressure; DBP: diastolic blood pressure; NIHSS: National Institutes of Health Stroke Scale; LAA: large artery atherosclerosis; CE: cardioembolism; SAO: small artery occlusion; SUC: stroke of undetermined cause; END: early neurological deterioration. *P values are calculated by univariate regression analysis. †P values are calculated by multivariable regression analysis.

## 4. Discussion

In the present study, we provided compelling evidence that the combination of clopidogrel and aspirin increased the rate of END in minor AIS patients with the SUC subtype, which was also an indirect evidence that cryptogenic stroke may be due to an embolic mechanism. We found that DAPT did not significantly increase END in patients with minor LAA and SAO, which was also another favorable evidence for the application of DAPT in acute noncardioembolic minor stroke. Thus, our study data supported the use of single-antiplatelet therapy as a more reasonable approach for patients with minor SUC before the etiology was identified.

POINT and CHANCE trails confirm that DAPT can reduce the incidence of subsequent stroke for mild stroke or high-risk TIA [1, 2]. The pathogenesis differs among the subtypes of stroke, and the two randomized controlled studies do not further determine whether the DAPT is effective for all subtypes. Therefore, we hypothesized that the efficacy of DAPT might vary by TOAST subtypes. LAA is formed mainly by lipid accumulation and inflammation in the great arteries, and the growth of the lesion will progressively narrow the vascular spaces, ultimately causing ischemia and hypoxia in the brain tissue [12]. CE is attributed to cardiac-derived thrombi, and anticoagulation is the mainstay of current recommendations. Recent studies suggest that SAO is due to vascular endothelial dysfunction and blood-brain barrier disruption as a result of hypertension, oxidative stress, aging, and other risk factors [13]. In the SUC subtype, there are many causes of stroke, including paroxysmal atrial fibrillation, atrial cardiopathy, patent foramen ovale, heart failure, and occult malignancy [14]. In the interest of better diagnosis and treatment of cryptogenic stroke, clinicians have developed the concept of embolic strokes of undetermined source (ESUS) to study differences in anticoagulant or antiplatelet therapy [15]. However, randomized controlled trials found that rivaroxaban or dabigatran is not superior to aspirin in preventing recurrence after ESUS [16, 17], which suggests that there is no significant difference between anticoagulation and antiplatelet therapy in ESUS. It is also unknown whether DAPT is superior to monotherapy in reducing recurrent stroke in cryptogenic mild stroke patients. Our findings showed that DAPT increased neurologic deterioration in minor AIS patients with the SUC subtype, suggesting that monotherapy may be a better option than either anticoagulation or DAPT for the SUC subtype.

Two randomized controlled trials show that early initiation of DAPT reduces stroke recurrence in noncardiac minor stroke, whereas our study was the first to find that DAPT may increase END in SUC stroke. The finding that aspirin plus cilostazol does not increase END in SUC stroke is not consistent with our study [18]. This may be because the safety profile of cilostazol is higher than that of clopidogrel [19]. In addition, the previous study was within 48 hours of onset, whereas our study was within 24 hours. Patients are more likely to have a progressive stroke early, so stroke progression from 24 to 48 hours after admission was not included, which may have affected the results. Besides, the underlying mechanism is related to thromboembolism, and antiplatelet therapy may

be effective [20, 21]. However, the embolic source in SUC stroke may be cardiac, carcinogenic, or otherwise. Compared with other stroke subtypes, patients with SUC have the lowest incidence of END [22]. Increased D-dimer levels are a risk factor for END in cancer-positive patients with SUC stroke [23]. The cancer-positive patients with SUC stroke present poor outcomes, including 42% END and 38% bleeding complications despite anticoagulation [24]. In addition, two prospective studies fail to demonstrate the superiority of direct oral anticoagulation over aspirin in patients with ESUS [16, 17]. Similarly, according to our results, antiplatelet monotherapy may be superior to DAPT to reduce the risk of bleeding.

Several studies have explored specific subtypes to compensate for the limitations of POINT and CHANCE trials to perform subgroup analyses. Clopidogrel and aspirin may be associated with a lower risk of recurrent stroke and death in the first year after stroke compared with aspirin alone in patients with AIS with symptomatic LAA, mainly due to a reduction in all-cause mortality [25]. Our results showed that DAPT did not increase the risk of END, further indicating that the use of DAPT was safe and effective in minor LAA stroke, which is consistent with a previous study [18]. A retrospective study demonstrates that DAPT is associated with a reduced risk of END in lacunar stroke [26]. Moreover, DAPT can improve outcomes after END in lacunar strokes in which the infarct region is located in the internal or basal ganglia [5]. In this study, DAPT did not decrease the risk of END in minor SAO stroke. This may be because some of the patients in the previous study had an NIHSS score of more than 3, greater dosage, and ethnic differences.

The safety of dual-antiplatelet therapy has been a major concern for clinicians. POINT and CHANCE trails indicate that DAPT for 7 days does not increase the risk of hemorrhage. Our study further showed that the use of DAPT does not increase any risk of bleeding in different stroke subtypes. Compared with antiplatelet therapy alone, DAPT is not related to an increased risk of hemorrhage in patients with nonminor ischemic stroke [27]. Thus, all of the above studies have shown that DAPT is safe.

Our study still had some limitations. Firstly, it is a retrospective, single-center clinical study, which means that our data reliability and representativeness are not as good as prospective, multicenter studies. Our hospital has established a cerebrovascular disease database and assigned some dedicated individuals to fill in the database, which can minimize these shortcomings as much as possible. Secondly, after calculating the sample size through power analysis and sample size (PASS) software, we found that to achieve a 10% change in the preassumed END incidence rate, at least 263 cases are needed in each group. This also led to the observation that dual-antiplatelet therapy in the SUC group did not result in a significant difference in the incidence rate of END ($P = 0.053$). Therefore, a larger sample size may be recommended for future studies. Lastly, we excluded other antiplatelet drugs such as clopidogrel and ticagrelor, which may limit the generalizability of our study conclusions. In the future, dual-antiplatelet combinations recommended by guidelines can be included in research and compared to evaluate the differences in the incidence of END among different combinations.

## 5. Conclusions

Our study findings suggest that DAPT with clopidogrel and aspirin increases the rate of short-term neurological worsening in minor AIS patients with the SUC subtype, rather than LAA, CE, and SAO. Thus, clinicians taking early DAPT may be more cautious in strokes of unknown cause.

## Data Availability

The raw data used for this study can be provided by the corresponding author upon a reasonable request.

## Ethical Approval

The institutional review board of the First Affiliated Hospital of Jinan University approved this study protocol (protocol code KY-2022-183; date of approval: 27 Oct 2022).

## Consent

Due to the retrospective nature of the study and the anonymity of the data, informed consent was waived.

## Conflicts of Interest

The authors report no conflict of interest.

## Authors' Contributions

Bingdong Xu, Xiufeng Xin, Anding Xu, and Yusheng Zhang designed this study. Bingdong Xu and Xiufeng Xin collected and analyzed the data. Anding Xu and Yusheng Zhang checked and confirmed the results of the data analysis. Bingdong Xu and Yan Ding drafted the manuscript, and all other authors critically reviewed it. All authors approved the final version of the manuscript. Bingdong Xu and Xiufeng Xin contributed equally to this work.

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