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Original Article

Dual antiplatelet therapy is associated with favorable outcome in acute minor stroke with an onset-to-door time beyond 24 h

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KEYWORDS
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Outcome

Background/Purpose: In patients with noncardioembolic acute minor ischemic stroke (AMIS), dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel within 24 h after stroke onset was more effective than aspirin alone. This study investigated the efficacy and safety of DAPT in AMIS patients with an onset-to-door time (OTDT) of more than 24 h.
Methods: This was a retrospective analysis of a prospective stroke registry from 2015 to 2021. Patients with AMIS and an OTDT within seven days were classified into the Early (≤24 h) and Late groups (>24 h) according to the time of antiplatelet administration after stroke onset.
Results: In total, 691 patients were identified. Of these, 446 (64.5%) and 245 (35.5%) patients were classified into the Early and Late groups, respectively. The rates of recurrent infarction and symptomatic intracranial hemorrhage at 90 days were similar between the single antiplatelet therapy (SAPT) and DAPT subgroups in both the Early and Late groups. More patients in the DAPT subgroup had a favorable outcome (modified Rankin scale of 0–1) at 90 days in both Early (84.2% versus 75.0%, $p = 0.016$) and Late (88.2% versus 76.9%, $p = 0.040$) groups. DAPT was independently associated with a favorable outcome in both the Early (odds ratio, 1.95; 95% CI, 1.15–3.32; $p = 0.013$) and Late (odds ratio, 2.72; 95% CI, 1.14–6.48; $p = 0.024$) groups.
Conclusion: In patients with AMIS and an OTDT of more than 24 h, DAPT was associated with a favorable outcome at 90 days.

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Introduction

Acute minor ischemic stroke (AMIS), defined as an NIH Stroke Score (NIHSS) of less than 4, accounts for 30% of acute ischemic stroke (AIS).[1,2] The risk of recurrent infarction in patients with AMIS is 3—15% in the first three months after the index event.[3—5] Dual antiplatelet therapy (DAPT) with aspirin plus clopidogrel was more effective than aspirin alone in reducing the risk of recurrent infarction in several pivotal large-scale randomized controlled trials, which only included patients with AMIS and onset to randomization time within 24 h.[3—6] Therefore, clinical practice guidelines recommend administering DAPT in patients with AMIS within 24 h after stroke onset.[7—12] However, in the real world, almost a third attend medical centers beyond 24 h after the onset of symptoms, especially patients with minor stroke.[13] Guidelines of DAPT for AMIS patients with an onset-to-door time (OTDT) beyond 24 h are currently not available.

This study investigated the efficacy and safety of DAPT with clopidogrel plus aspirin in patients with AMIS and OTDT of more than 24 h.

Materials and methods

Data source

This retrospective cohort study analyzed data from a hospital-based prospective stroke registry in a comprehensive stroke center. Between August 2015 and April 2021, patients over 18 years of age with AIS were prospectively registered. All ischemic strokes were classified into subtypes according to the criteria from the Trial of ORG 10172 in Acute Stroke Treatment study.[14] Stroke severity was assessed using the NIHSS score.

Antiplatelet therapy using SAPT or DAPT

Since 2013, the stroke center of our hospital has endorsed the use of DAPT with clopidogrel plus aspirin in AMIS patients who have met the criteria of the CHANCE trial.[4] However, using DAPT in real-world settings is individualized and not mandatory like clinical practices in trials. Regarding the dosages of antiplatelets in the registry, the stroke center required a loading dose of 300 mg of clopidogrel or aspirin to be administered to patients with AMIS naïve to clopidogrel or aspirin as soon as possible. Following the loading dose, a maintenance dose of single antiplatelet therapy (SAPT) of either 75 mg of clopidogrel or 100 mg of aspirin or both (DAPT) was administered daily. The duration of treatment was lifelong for SAPT and 21 days for DAPT. A stroke case manager monitored and audited each patient to ensure that antiplatelet treatment was adequately aligned with SAPT or DAPT strategies in both the Early and Late groups.

Patient population and study design

The inclusion criteria were: (1) patients with an initial NIHSS score of less than 4, and (2) an OTDT within 7 days (168 h). Exclusion criteria were: (1) use of thrombolytic therapy or endovascular thrombectomy for index stroke; (2) a clear indication of anticoagulation therapy (presumed cardiac source of embolus or coagulopathy); (3) contraindication to clopidogrel or aspirin; (4) use of antiplatelets other than clopidogrel or aspirin; (5) the time of antiplatelet administration more than 168 h after stroke onset; (6) active cancer; (7) a premorbid modified Rankin scale (mRS) $\geq$1; and (8) a follow-up period of less than three months.

The patients were classified into two groups according to the time of antiplatelet administration: (1) the Early group, in which antiplatelet was administered within 24 h after stroke onset, and (2) the Late group, in which antiplatelet was administered beyond 24 h after stroke onset.

Assessment of efficacy and safety outcomes

The efficacy and safety outcomes were recorded during the 90-day follow-up period, including recurrent infarction, symptomatic intracranial hemorrhage (ICH), and mRS. A recurrent infarction or symptomatic ICH was defined by a new and persisting ($>$24 h) neurological deficit, which occurred $>$24 h after the index stroke, after a neuroimaging study. Functional outcome was measured with mRS by stroke managers with telephone questionnaires. A favorable functional outcome was an mRS of 0—1 at 90 days.

Statistical analysis

Continuous data are presented as mean values $\pm$ standard deviation (SD), and categorical data as numbers with percentages. OTDT and discrete variables, including NIHSS and mRS, are expressed as the median and interquartile range (IQR). The clinical characteristics of the Early and Late groups were compared. We used Fisher's exact test or the X^2 test to analyze categorical variables, while continuous variable analyses were performed using the Mann-Whitney U test. Binary logistic regression analyses, which included variables of traditionally presumed pivotal risk factors for an unfavorable outcome or of interest in the univariate and multivariate logistic regression analyses, were performed to explore the factors associated with a favorable outcome in the Early and Late groups separately. Adjusted odds ratios (OR) with a 95% confidence interval (CI) were calculated accordingly in the two groups. We also performed subgroup analyses using logistic regressions according to antiplatelet strategies. p values less than 0.05 were considered significant. All data were analyzed using SPSS version 22.0 for Windows.

Results

Baseline characteristics between the Early and Late groups

Of the 3659 patients with AIS between August 2015 and April 2021, we identified 691 patients who met the selection criteria (Fig. 1). Of these, 446 (64.5%) and 245 (35.5%) patients received antiplatelet within 24 (Early group) and 25–168 h (Late group) after stroke onset, respectively. In the Early and Late groups, 245 (54.9%) and 81 (33.1%) patients received DAPT, respectively. In the Late group, 47.8%, 21.2%, 14.3%, 9.0%, 6.1%, and 1.6% had an OTDT of 25–48 h, 49–72 h, 73–96 h, 97–120 h, 121–144 h, and 145–168 h, respectively (Fig. 2). That is to say, nearly 70% of patients in the Late group had an OTDT of less than 72 h.

Characteristics of the SAPT and DAPT subgroups in the Early and Late groups

In the Early group, the DAPT group had fewer patients with a history of previous stroke compared to the SAPT group (12.4% versus 22.2%, $p = 0.006$), and shorter OTDT (5 [2–12] hours versus 8 [2–19] hours, $p = 0.042$) (Table 1). Other clinical characteristics, including age, sex, history of hypertension, hyperlipidemia, diabetes, coronary heart disease, smoking, stroke subtypes, and initial NIHSS score, were similar between the SAPT and DAPT groups.

In the Late group, fewer patients in the DAPT group were of an undetermined subtype compared to the SAPT group (18.4% versus 31.4%, $p = 0.036$). Other clinical characteristics, including age, sex, history of hypertension, hyperlipidemia, diabetes, previous stroke, coronary heart disease, smoking, OTDT, and initial NIHSS score, were similar between the SAPT and DAPT groups.

Efficacy and safety outcomes in the Early and Late groups

The rates of recurrent infarction were not significantly different between the DAPT and SAPT subgroups in the Early (6.4% versus 7.1%, $p = 0.779$) and Late (2.6% versus 7.7%, $p = 0.157$) groups. Symptomatic ICH during the follow-up period and mortality at 90 days were similar between the SAPT and DAPT subgroups in both the Early and Late groups (Table 2). The mRS at 90 days in the DAPT subgroup was similar to that of the SAPT subgroup in the Early (0 (0–1) versus 1 (0–2), $p = 0.169$) and the Late (0.5 (0–1) versus 1 (0–1), $p = 0.388$) groups. Compared to the SAPT subgroup, there were more patients with a favorable

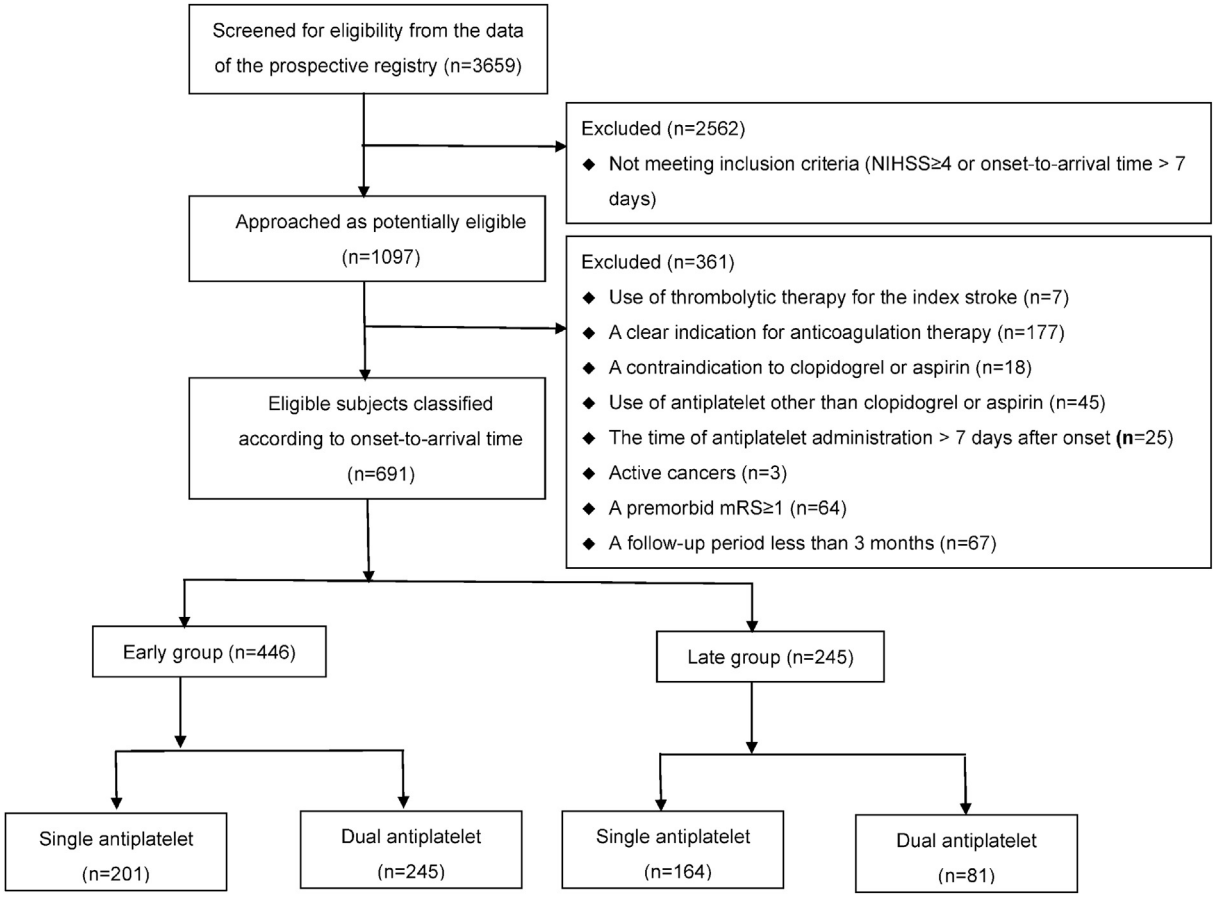
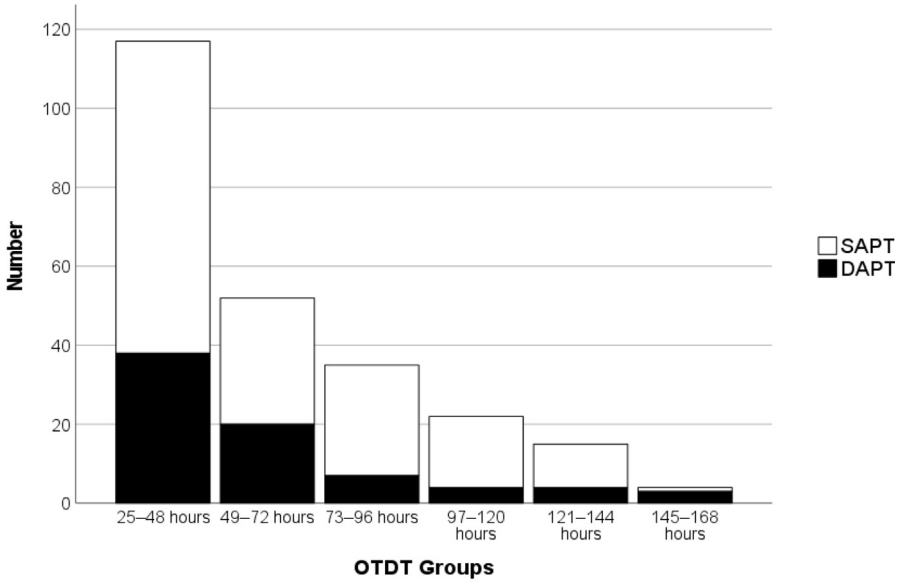


Figure 1 Flow diagram of the patient inclusion, exclusion, and antiplatelet strategies for the Early (≤24 h) and Late (>24 h) groups, stratified according to the onset–to–door time.



	25–48 hours, N=117	49–72 hours, N=52	73–96 hours, N=35	97–120 hours, N=22	121–144 hours, N=15	145–168 hours, N=4	Total, N=245
SAPT, n (%)	79 (67.5)	32 (61.5)	28 (80.0)	18 (81.8)	11 (73.3)	1 (25.0)	169 (69.0)
DAPT, n (%)	38 (32.5)	20 (38.5)	7 (20.0)	4 (18.2)	4 (26.7)	3 (75.0)	76 (31.0)

Figure 2 Distribution of patients according to the OTDT in the Late group. Abbreviations: DAPT, dual antiplatelet therapy; OTDT, onset-to-door time.

Table 1 Comparison between groups classified according to antiplatelet strategies in Early and Late Groups.

Clinical characteristics	Early group (n = 446)			Late group (n = 245)		
	SAPT (n = 212)	DAPT (n = 234)	*p*	SAPT (n = 169)	DAPT (n = 76)	*p*
Age, years	66.2 (14.2)	65.3 (12.6)	0.516	65.7 (13.0)	63.4 (13.4)	0.162
Male sex	159 (75.0)	165 (70.5)	0.288	117 (69.2)	56 (73.7)	0.479
Hypertension	176 (83.0)	185 (79.1)	0.288	136 (80.5)	59 (77.6)	0.610
Hyperlipidemia	131 (61.8)	161 (68.8)	0.120	129 (76.3)	60 (78.9)	0.652
Diabetes	81 (38.2)	84 (35.9)	0.614	78 (46.2)	32 (42.1)	0.556
Previous stroke	47 (22.2)	29 (12.4)	0.006	22 (13.0)	14 (18.4)	0.269
Coronary heart disease	3 (1.4)	1 (0.4)	0.350	0 (0.0)	0 (0.0)	n.a[a]
CKD stage ≥3[b]	62 (29.2)	64 (27.4)	0.675	70 (41.4)	24 (31.6)	0.157
Smoking history	108 (50.9)	110 (43.2)	0.100	80 (47.3)	32 (42.1)	0.447
Onset-to-door time, hours	8 (2—19)	5 (2—12)	0.042	54 (48—96)	49 (38—72)	0.220
Stroke subtypes						
LAA	48 (22.6)	56 (23.9)	0.748	55 (32.5)	31 (40.8)	0.211
LAC	88 (41.5)	106 (45.3)	0.420	61 (36.1)	31 (40.8)	0.483
Undetermined	76 (35.8)	72 (30.8)	0.255	53 (31.4)	14 (18.4)	0.036
Initial NIHSS	2 (1—2)	2 (1—3)	0.872	2 (1—3)	2 (1—3)	0.439
Antiplatelet strategies						
Single aspirin	153 (76.1)	0 (0.0)		141 (83.4)	0 (0.0)	
Single clopidogrel	48 (23.9)	0 (0.0)		23 (16.6)	0 (0.0)	
Dual antiplatelets	0 (0.0)	245 (100.0)		0 (0.0)	81 (100.0)	

Abbreviations: CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; LAA, large artery atherosclerosis; LAC, lacunar; n.a, nonapplicable; NIHSS, National Institutes of Health Stroke Scale; SAPT, single antiplatelet therapy.

[a] Statistical analyses could not be carried out due to measures of variables being zero.

[b] CKD stage ≥3 was defined by glomerular filtration rate estimated to be < 60 ml/min by Cockcroft—Gault equation.

Table 2 Outcomes between Early and Late groups, and subgroups of SAPT and DAPT.

Outcome[a]	Early group				Late group			
	Total (n = 446)	SAPT (n = 201)	DAPT (n = 245)	*p*	Total (n = 245)	SAPT (n = 164)	DAPT (n = 81)	*p*
Recurrent infarction	30 (6.7)	15 (7.1)	15 (6.4)	0.779	15 (6.1)	13 (7.7)	2 (2.6)	0.157
Symptomatic ICH	1 (0.2)	1 (0.5)	0 (0.0)	0.475	1 (0.4)	1 (0.6)	0 (0.0)	>0.99
mRS at 90 days	1 (0–1)	1 (0–2)	0 (0–1)	0.169	1 (0–1)	1 (0–1)	1 (0–1)	0.388
Mortality at 90 days	2 (0.4)	1 (0.5)	1 (0.4)	>0.99	0 (0.0)	0 (0.0)	0 (0.0)	n.a[b]
Favorable outcome at 90 days	365 (79.8)	159 (75.0)	197 (84.2)	0.016	197 (80.4)	130 (76.9)	67 (88.2)	0.04

Abbreviations: DAPT, dual antiplatelet therapy; ICH, intracranial hemorrhage; mRS, modified Rankin scale; n.a, nonapplicable; SAPT, single antiplatelet therapy.
[a] The outcomes are categorical variables and expressed as n (%).
[b] Statistical analyses could not be carried out due to measures of variables being zero.

Table 3 The association between risk factors and favorable outcome by univariate and multivariate logistic regression analyses of the Early and Late groups.

	Early group				Late group			
	Univariate model		Multivariate model[a]		Univariate model		Multivariate model[a]	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Age, years	0.95 (0.93–0.97)	<0.001	0.96 (0.94–0.98)	<0.001	0.93 (0.91–0.96)	<0.001	0.94 (0.91–0.97)	<0.001
OTDT, hours	0.99 (0.96–1.02)	0.370	1.00 (0.97–1.04)	0.839	1.00 (0.99–1.01)	0.800	1.00 (0.99–1.01)	0.879
Hypertension	0.74 (0.40–1.38)	0.345	0.90 (0.45–1.82)	0.773	0.61 (0.26–1.46)	0.268	1.01 (0.38–2.68)	0.990
Hyperlipidemia	1.35 (0.84–2.16)	0.223	0.94 (0.55–1.62)	0.834	1.73 (0.86–3.49)	0.125	0.98 (0.43–2.24)	0.969
Diabetes	0.96 (0.60–1.55)	0.863	1.04 (0.61–1.78)	0.895	1.31 (0.69–2.49)	0.410	1.40 (0.68–2.88)	0.368
Previous stroke	0.65 (0.37–1.16)	0.145	0.69 (0.36–1.32)	0.260	0.42 (0.19–0.91)	0.028	0.37 (0.15–0.90)	0.028
Smoking history	2.29 (1.40–3.75)	0.001	2.51 (1.45–4.36)	0.001	1.37 (0.72–2.60)	0.343	1.17 (0.55–2.46)	0.686
LAA subtype	0.53 (0.32–0.87)	0.013	0.47 (0.27–0.84)	0.011	0.46 (0.24–0.87)	0.017	0.42 (0.20–0.87)	0.019
Initial NIHSS	0.52 (0.40–0.67)	<0.001	0.49 (0.38–0.65)	<0.001	0.65 (0.47–0.91)	0.012	0.61 (0.42–0.88)	0.009
DAPT	1.22 (1.04–1.42)	0.014	1.95 (1.15–3.32)	0.013	1.23 (0.96–1.57)	0.099	2.72 (1.14–6.48)	0.024

Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; OTDT, onset–to–door time.
[a] The multivariate model included all variables in the univariate model.

outcome at 90 days in the DAPT subgroup in both the Early (84.2% versus 75.0%, $p = 0.016$) and the Late (88.2% versus 76.9%, $p = 0.040$) groups.

Factors associated with a favorable outcome

In the Early group, univariate analysis showed that older age (OR, 0.95; 95% CI, 0.93–0.97; $p < 0.001$), LAA subtype (OR, 0.53; 95% CI, 0.32–0.83; $p = 0.013$), and a higher initial NIHSS score (OR, 0.52; 95% CI, 0.40–0.67; $p < 0.001$) were less likely to be associated with a favorable outcome at 90 days (Table 3). Conversely, the history of smoking (OR, 2.29; 95% CI, 1.40–3.75; $p = 0.001$) and DAPT (OR, 1.22; 95% CI, 1.04–1.42; $p = 0.014$) were associated with a favorable outcome at 90 days. Multivariate analyses showed that older age (OR, 0.96; 95% CI, 0.94–0.98; $p < 0.001$), LAA subtype (OR, 0.47; 95% CI, 0.27–0.84; $p = 0.011$), and a higher initial NIHSS score (OR, 0.49; 95% CI, 0.38–0.65; $p < 0.001$) were less likely to be associated with a favorable outcome at 90 days. In contrast, history of smoking (OR, 2.51; 95% CI, 1.45–4.36; $p = 0.001$) and DAPT (OR, 1.95; 95% CI, 1.15–3.32; $p = 0.013$) were associated with a favorable outcome at 90 days.

In the Late group, univariate analysis showed that older age (OR, 0.93; 95% CI, 0.91–0.96; $p < 0.001$), previous stroke (OR, 0.42; 95% CI, 0.19–0.91; $p = 0.028$), LAA subtype (OR, 0.46; 95% CI, 0.24–0.87; $p = 0.017$), and higher initial NIHSS score (OR, 0.65; 95% CI, 0.47–0.91; $p = 0.012$) were less likely to be associated with a favorable outcome at 90 days (Table 3). DAPT was not associated with a favorable outcome at 90 days (OR, 1.23; 95% CI, 0.96–1.57; $p = 0.099$) in the univariate analysis. Multivariate analyses showed that older age (OR, 0.94; 95% CI, 0.91–0.97; $p < 0.001$), previous stroke (OR, 0.37; 95% CI, 0.15–0.90; $p = 0.028$), LAA subtype (OR, 0.42; 95% CI, 0.20–0.87; $p = 0.019$), and a higher initial NIHSS score (OR, 0.61; 95% CI, 0.42–0.88; $p = 0.009$) were less likely to be associated with a favorable outcome at 90 days. In contrast, DAPT was associated with a favorable outcome at 90 days (OR, 2.72; 95% CI, 1.14–6.48; $p = 0.024$). In contrast to the Early group, smoking history was not associated with a favorable outcome at 90 days in both univariate and multivariate models in the Late group.

Subgroup analyses of DAPT and the favorable outcome

Figs. 3 and 4 showed the results of subgroup analyses of the Early and Late groups, respectively. In the Early group, although DAPT was significantly associated with a favorable outcome at 90 days in patients who were older than 60 years (OR, 1.85; 95% CI, 1.08−3.16; $p = 0.025$), male (OR, 1.90; 95% CI, 1.06−3.41; $p = 0.030$), with hypertension (OR, 1.83; 95% CI, 1.09−3.06; $p = 0.022$), with diabetes (OR, 2.63; 95% CI, 1.19−5.84; $p = 0.017$), without previous stroke (OR, 1.74; 95% CI, 1.03−2.94; $p = 0.039$), without

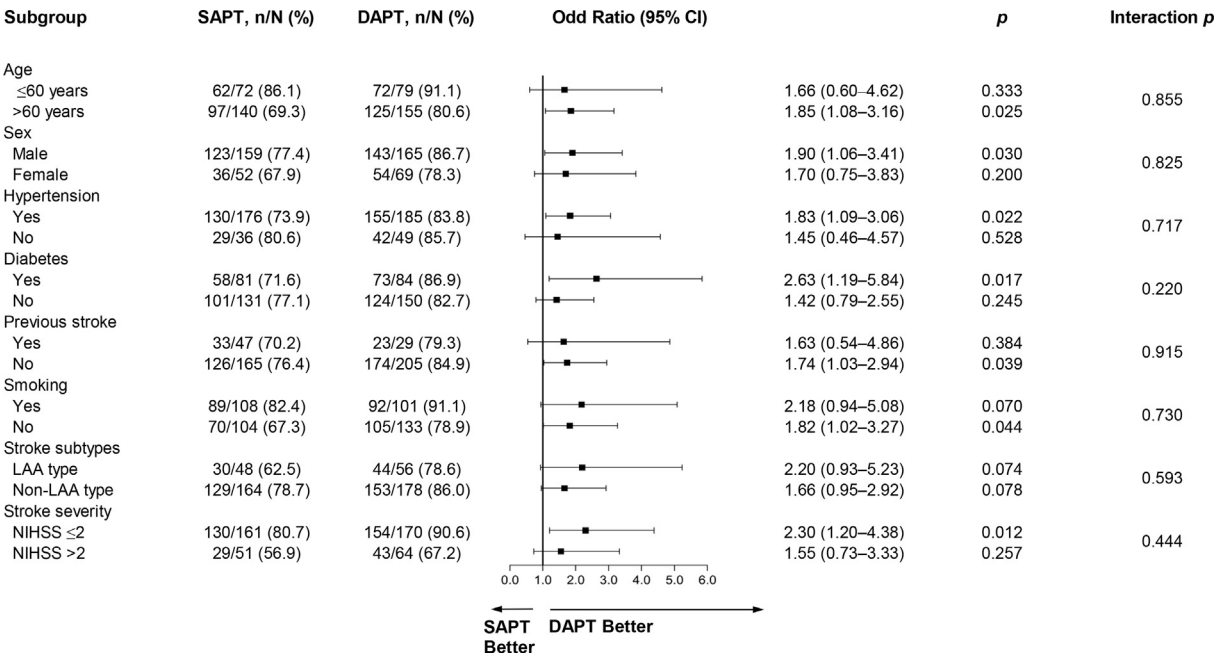


Figure 3 Subgroup analyses of the association between DAPT and a favorable outcome at 90 days of the Early group. Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SAPT, single antiplatelet therapy.

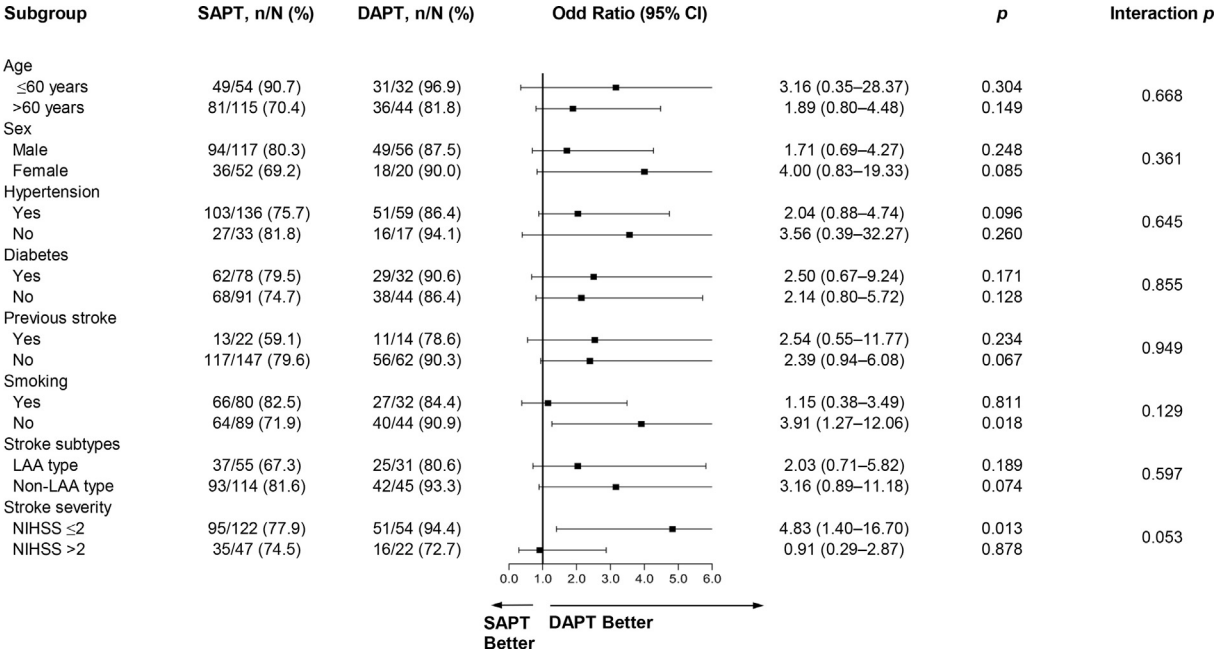


Figure 4 Subgroup analyses of the association between DAPT and a favorable outcome at 90 days of the Late group. Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; LAA, large artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SAPT, single antiplatelet therapy.

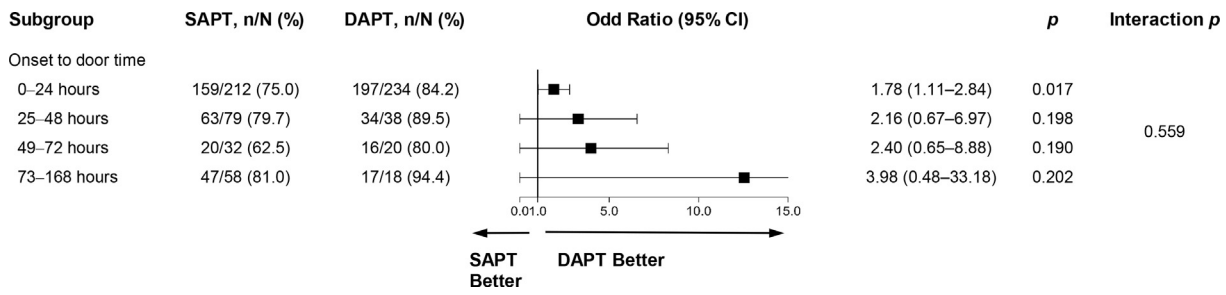


Figure 5 Efficacy of DAPT on functional outcomes at 90 days according to the OTDT groups. Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; OTDT, onset-to-door time; SAPT, single antiplatelet therapy.

smoking history (OR, 1.82; 95% CI, 1.02–3.27; p = 0.044), or with an initial NIHSS score ≤2 (OR, 2.30; 95% CI, 1.20–4.38; $p = 0.012$), there was no significant interaction between each of the paired subgroups.

In the Late group, DAPT was significantly associated with a favorable outcomes at 90 days in patients without smoking history (OR, 3.91; 95% CI, 1.27–12.06; $p = 0.018$) and with an initial NIHSS ≤2 (OR, 4.83; 95% CI, 1.40–16.70; $p = 0.013$). There was no significant interaction between each of the paired subgroups in the Late group either.

We further analyzed the efficacy of DAPT on functional outcomes at 90 days according to the OTDT groups (Fig. 5). Analysis showed DAPT was significantly associated with a favorable outcome at 90 days in the 0–24 h group (OR, 1.78; 95% CI, 1.11–2.84; $p = 0.017$). Although the efficacy of DAPT on a favorable outcome at 90 days was not significant in other OTDT groups, there was no significant interaction among OTDT groups (interaction $p = 0.559$).

Discussion

Our study showed that although the rates of recurrent infarction were not significantly different between the SAPT and DAPT subgroups in both the Early and Late groups, there were more patients with a favorable outcome at 90 days in patients with DAPT in both the Early and Late groups. Patients with AMIS and an OTDT of more than 24 h may still benefit from DAPT.

Large pivotal randomized controlled trials of DAPT only included patients with early arrival time within 24 h after stroke onset.[3–5,15] However, a model-based approach of the POINT trial suggests that the benefit of DAPT in reducing ischemic events was greatest when clopidogrel plus aspirin therapy was started within 12 h, but was still maintained when DAPT was started within 72 h after stroke onset.[16] Another model-based approach of the THALES trial suggests the risk reduction of ischemic stroke was greatest when DAPT of ticagrelor plus aspirin was initiated within 24 h, but remained significant even when DAPT was started 48 h after stroke onset.[17] The efficacy of DAPT in AIS patients with an OTDT beyond 24 h has been reported in other studies.[18,19] However, the results were contradictory, possibly due to not loading 300 mg of clopidogrel and the wide range of NIHSS scores (0–19) in one study with negative results.[19] In our study, the NIHSS scores of the patients were all <4, and we administered a loading dose of 300 mg of clopidogrel to those who were naïve to clopidogrel. Our study provides evidence from real-world practice, consistent with model-based analyses of the POINT and THALES trials,[16,17] showing that AMIS patients with delayed arrival time beyond 24 h may still benefit from DAPT.

The association between the favorable outcome and DAPT in our study is consistent with the results of the CHANCE and POINT trials.[20,21] The CHANCE trial showed that clopidogrel plus aspirin appeared to reduce recurrent disabling strokes and the risk of poor functional outcomes at 90 days compared to aspirin alone.[20] In the POINT trial, although the overall cohort did not show a significant difference in disability at 90 days between the DAPT and aspirin alone groups, DAPT was associated with a reduction in disability attributed to index stroke at randomization.[21] Antiplatelets may reduce processes other than thrombosis, such as vasoconstriction and smooth muscle proliferation following the index stroke.[22] In our study, although the rates of recurrent stroke were not significantly different between the SAPT and DAPT subgroups, the DAPT subgroup still had significantly more patients with a favorable outcome at 90 days than the SAPT subgroup in both the Early and Late groups.

In current global guidelines,[7–12] starting DAPT in AMIS patients with an OTDT beyond 24 h is not routinely recommended. Therefore, it is reasonable that fewer patients in the Late group received DAPT. The time interval between the stroke onset and hospital arrival is a major barrier to receiving acute treatment in AIS. Nearly one–third of patients with AMIS in our hospital had an OTDT of more than 24 h, of which only one–third received DAPT. In contrast, half of the patients with AMIS and an OTDT within 24 h received DAPT. Mild stroke itself is an independent factor of delayed arrival to the hospital.[13,23] Our experience indicates the need to strengthen public education about early stroke treatment and consider DAPT in patients with AMIS, even with delayed arrival.

Although the subgroup analysis of favorable outcomes at 90 days did not show significant interaction between the smoking history and DAPT, smoking history was associated with a favorable outcome at 90 days in patients with DAPT in the Early group but not in the Late group. This finding is consistent with the "smoking paradox" observed in other studies.[24,25] In the Early group in our study, 65.7% of patients who received clopidogrel–based antiplatelet treatment had a median OTDT of 5 (2–12) hours. Because the mean half-life of CYP1A2 activity induced by smoking was 38.6 h,[26] the influence of smoking on clopidogrel

metabolism could still be significant in the Early group but not in the Late group.

Our study had several limitations. First, this was a real-world cohort study with a limited number of patients, which could not allow powerful analyses by propensity score matching, so we could not avoid selection bias in real-world practice. Second, the family or patients might not have recognized new minor or transient ischemic events during the follow—up period. Third, the stroke managers who measured the mRS were not blinded to the type of antiplatelet treatment, so we could not rule out a possible measurement bias. Fourth, because this study was retrospective, we were unable to avoid the possible recall bias of self—reported data, such as transient neurological symptoms or drug compliance, from the family or observers. Furthermore, it was challenging to correctly assess the exact timing of recurrent stroke.

In conclusion, our study showed that DAPT was significantly associated with a favorable outcome at 90 days in patients with AMIS and an OTDT not only within but also beyond 24 h. DAPT may be considered in patients with AMIS and an OTDT beyond 24 h. Further randomized controlled trials or large—scale registries of DAPT in AMIS patients with delayed hospital arrival are necessary.

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Declaration of competing interest

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