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# Dual antiplatelet versus alteplase in anterior and posterior circulation minor stroke

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## ABSTRACT

**Objective** The Antiplatelet versus R-tPA for Acute Mild Ischaemic Stroke trial has demonstrated the non-inferiority of dual antiplatelet therapy (DAPT) to alteplase in minor non-disabling stroke. This prespecified secondary analysis aimed to investigate whether the treatment effects were similar across stroke territories.

**Methods** Participants were divided according to stroke territory, which were subdivided into DAPT and alteplase. An excellent functional outcome at 90 days defined as modified Rankin Scale scoring 0–1 was primary outcome. National Institutes of Health Stroke Scale (NIHSS) score change and early neurological improvement measured by a 2-point decline in NIHSS score at 24 hours were secondary outcomes. Symptomatic intracerebral haemorrhage (sICH) and bleeding events were safety outcomes. Primary analyses adjusted unbalanced baseline characteristics between treatments by multivariate logistic regression.

**Results** A total of 719 patients were included: 566 in anterior circulation stroke (ACS) and 153 in posterior circulation stroke (PCS). Primary outcome was 94.1% in DAPT and 91.7% in alteplase among ACS patients (adjusted risk difference (RD) and 95% CI, 1.5% (−1.5% to 4.6%), p=0.32), while 91.2% in DAPT and 91.8% in alteplase among PCS patients (adjusted RD and 95% CI, −2.1% (−8.5% to 4.4%), p=0.53). Compared with alteplase, DAPT was associated with lower risk of sICH (p=0.03) and bleeding events (p<0.001) in ACS, but only lower risk of bleeding events (p=0.007) in PCS. Additionally, among ACS patients, the alteplase was superior to DAPT in terms of decrease in NIHSS score at 24 hours compared with admission (adjusted geometric mean ratio and 95% CI, −0.09 (−0.16 to −0.03), p=0.005) and early neurological improvement (adjusted RD and 95% CI, −7.2% (−11.6% to −2.7%), p=0.001).

**Conclusion** Among ischaemic stroke with minor non-disabling symptoms, DAPT was similar with intravenous alteplase regarding long-term functional outcome and better safety regardless of ACS or PCS. The potential benefit of intravenous alteplase regarding early neurological improvement in patients with ACS warrants further investigation.

**Trial registration number** NCT03661411.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Up to date, no study compares the efficacy of dual antiplatelet therapy (DAPT) with intravenous alteplase in non-disabling minor ischaemic stroke attributed to different stroke territories.

### WHAT THIS STUDY ADDS

⇒ This finding proved that DAPT was similar with intravenous alteplase regarding long-term functional outcome and better safety regardless of stroke territory. Given that more symptomatic intracranial haemorrhage and early neurological improvement occurred in anterior circulation stroke (ACS), whether patients with ACS may benefit from intravenous alteplase warrants further investigation.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study might suggest that DAPT could be used in stroke with non-disabling minor neurological deficit regardless of stroke territory although patients with acute circulation stroke may benefit from intravenous alteplase regarding early neurological improvement.

## INTRODUCTION

Intravenous thrombolysis was recommended for ischaemic stroke within 4.5 hours of symptom onset by guidelines.[1–3] About half of acute ischaemic stroke have been defined as minor strokes based on the score of National Institutes of Health Stroke Scale (NIHSS) which is equal to or less than 5.[4 5] However, the evidence supporting intravenous thrombolysis for this population remained inconclusive.[6 7] Minor stroke was proven to benefit from dual antiplatelet therapy (DAPT).[8 9] The Antiplatelet versus R-tPA for Acute Mild Ischaemic Stroke trial (ARAMIS) first demonstrated DAPT is non-inferior to intravenous alteplase regarding 3-month outcomes for minor non-disabling stroke.[10]

Ischaemic stroke are divided into the anterior circulation stroke (ACS) and posterior circulation stroke (PCS) according to stroke territories.[11] PCS differs from ACS in several aspects,[12] such as risk factors, stroke mechanisms and functional outcome.[13 14] With respect to DAPT, the post hoc analysis of the CHANCE-2 has demonstrated that antiplatelet treatments showed similar efficacy in preventing stroke recurrence was similar among two stroke territories.[15] Similar to

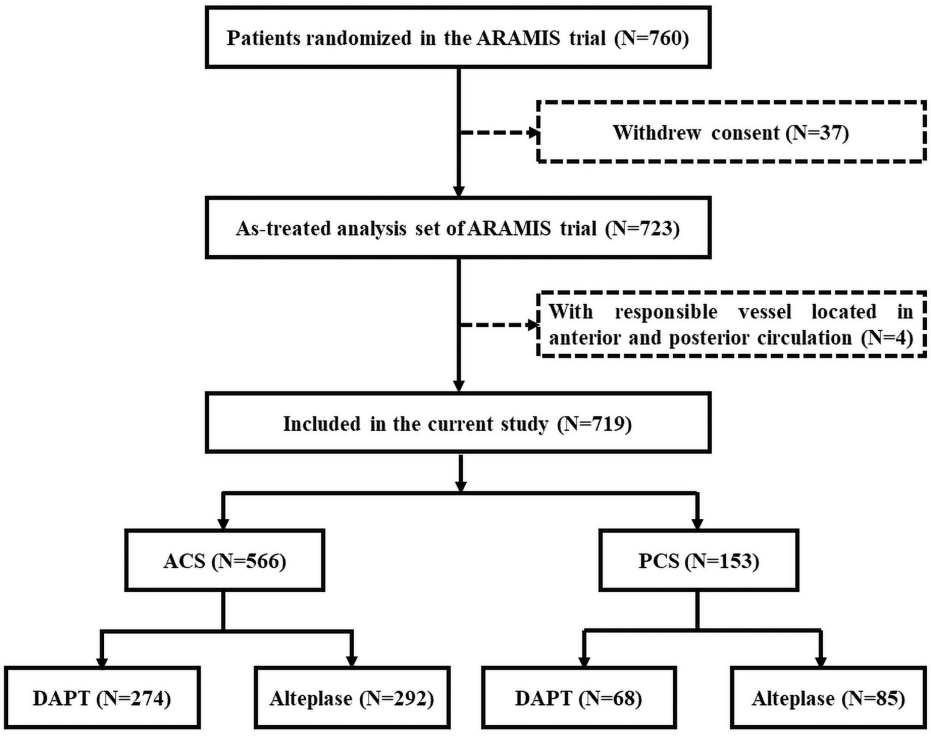


**Figure 1** Flow chart. ACS, anterior circulation stroke; ARAMIS, the Antiplatelet versus R-tPA for Acute Mild Ischaemic Stroke trial; DAPT, dual antiplatelet therapy; PCS, posterior circulation stroke.

the finding in DAPT, post-thrombolytic outcomes were also found similar between two stroke territories,[16] but the safety profile was better among patients with PCS.[17] However, in the stroke with large vessel occlusion, intravenous thrombolysis showed different efficacies among two stroke territories.[18] Although the efficacy of two treatments has been respectively investigated between two stroke territories, no study compared DAPT and intravenous alteplase in either stroke subtype until now.

According to the context, we conducted this prespecified secondary analysis of the ARAMIS to compare DAPT versus intravenous thrombolysis with alteplase in different stroke territories to investigate whether stroke territories affected the similar treatment effect.

## METHODS

### Study design and population

The secondary analysis was performed according to the guidelines of observational study. As described in the protocol,[19] ARAMIS was a multicentre randomised clinical trial assessing whether DAPT was non-inferior to intravenous alteplase for treating minor stroke presenting non-disabling symptoms. The trial included participants who were acute ischaemic stroke with NIHSS scores at randomisation equal to or less than 5 (≤1-point in single item) and presenting within 4.5 hours of symptoms onset, and excluded those showed prestroke modified Rankin Scale (mRS) scores ≥2, experienced intracerebral haemorrhage or need anticoagulation treatment. Given a higher crossover rate of 20.4% in ARAMIS, patients included in this analysis were from the as-treated analysis set, which divided patients into DAPT or intravenous alteplase based on the study agent they actually received. Those diagnosed with both ACS and PCS were excluded from the current study.

### Procedures

Screened participants were classified into two stroke territories according to the infarct location of responsible vessel judged by clinical symptoms at admission and imaging data during hospitalisation: ACS (anterior cerebral artery, middle cerebral artery or internal carotid artery) and PCS (posterior cerebral artery, vertebral artery or basilar artery). Based on the agents actually used, participants with ACS or PCS were further classified into DAPT group treated with clopidogrel and aspirin for 12±2 days, and alteplase group treated with intravenous alteplase with a dose of 0.9 mg/kg and followed by standard antiplatelet therapy beginning at 24 hours after intravenous thrombolysis for 12±2 days. Detail of treatment procedure was reported in our previous study.[10] Investigators collected data of clinical characteristics at randomisation, neurological status at admission and 24 hours after randomisation, and 90-day follow-up data, which were recorded in a web-based system.

### Outcomes

The outcomes of the current study are parallel with the ARAMIS trial.[10] We used 90-day excellent functional

**Table 1** Baseline characteristics compared between treatments in ACS and PCS

| | ACS | | | PCS | | |
|---|---|---|---|---|---|---|
| | DAPT (N=274) | Alteplase (N=292) | P value | DAPT (N=68) | Alteplase (N=85) | P value |
| Age, years | 65 (58–73) | 63 (56–70) | 0.17 | 65 (54–71) | 63 (56–70) | 0.35 |
| Sex (female) | 92 (33.6) | 82 (28.1) | 0.16 | 19 (27.9) | 30 (35.3) | 0.33 |
| Current smoker | 84 (30.7) | 121 (41.4) | 0.02* | 14 (20.6) | 22 (25.9) | 0.63 |
| Current drinker† | 38 (13.9) | 57 (19.5) | 0.16 | 12 (17.6) | 9 (10.6) | 0.25 |
| Comorbidities‡ | | | | | | |
| Hypertension | 153 (55.8) | 136 (46.6) | 0.03* | 41 (60.3) | 48 (56.5) | 0.63 |
| Diabetes | 70 (25.5) | 79 (27.1) | 0.68 | 16 (23.5) | 22 (25.9) | 0.74 |
| Previous stroke§ | 66 (24.1) | 59 (20.2) | 0.27 | 17 (25.0) | 17 (20.0) | 0.46 |
| Previous transient ischaemic attack | 3 (1.1) | 1 (0.3) | 0.29 | 1 (1.5) | 1 (1.2) | 0.87 |
| Atrial fibrillation | 1 (0.4) | 0 (0.0) | 0.30 | 0 (0.0) | 1 (1.2) | 0.37 |
| Blood pressure at randomisation, mm Hg | | | | | | |
| Systolic | 148 (135–160) | 153 (139–165) | 0.06 | 151 (139–163) | 153 (140–169) | 0.65 |
| Diastolic | 87 (80–95) | 88 (80–95) | 0.78 | 88 (82–93) | 90 (80–97) | 0.46 |
| FBG at randomisation, mmol/L | 6.19 (5.37–8.14) | 6.49 (5.42–8.19) | 0.40 | 6.17 (5.53–7.81) | 6.26 (5.39–9.03) | 0.94 |
| NIHSS score at randomisation¶ | 2 (1–3) | 2 (1–3) | <0.01* | 2 (1–3) | 2 (1–3) | 0.09 |
| Estimated premorbid function (mRS score)** | | | | | | |
| 0 | 196 (71.5) | 217 (74.3) | 0.46 | 50 (73.5) | 70 (82.4) | 0.19 |
| 1 | 78 (28.5) | 75 (25.7) | | 18 (26.5) | 15 (17.6) | |
| Time from onset to treatment, min | 191 (140–239) | 170 (125–213) | <0.01* | 185 (139–230) | 163 (122–219) | 0.48 |
| Duration of hospitalisation¶ | 8 (6–10) | 8 (6–10) | 0.73 | 9 (7–12) | 8 (7–11) | 0.54 |
| Presumed stroke cause†† | | | | | | |
| Large artery atherosclerosis | 32 (11.7) | 44 (15.1) | 0.56 | 12 (17.6) | 13 (15.3) | 0.48 |
| Cardioembolic | 1 (0.4) | 0 (0.0) | | 0 (0.0) | 1 (1.2) | |
| Small artery occlusion | 59 (21.5) | 66 (22.7) | | 14 (20.6) | 25 (29.4) | |
| Other determined cause | 2 (0.7) | 3 (1.0) | | 0 (0.0) | 0 (0.0) | |
| Undetermined cause | 180 (65.7) | 178 (61.2) | | 42 (61.8) | 46 (54.1) | |
| Large vessel occlusion | 10 (3.6) | 19 (6.5) | 0.12 | 3 (4.4) | 4 (4.7) | 0.93 |

The data was shown with median (IQR) or number (percentage).
*P value<0.05.
†Defined as consuming alcohol at least once a week within 1 year prior to the onset of the disease.
‡The comorbidities were based on the patient or family report.
§Previous stroke included ischaemic and haemorrhagic stroke.
¶NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficit.
**Scores on the mRS of functional disability range from 0 (no symptoms) to 6 (death).
††The presumed stroke aetiology was classified according to the Trial of Org10172 in Acute Stroke Treatment (TOAST) using clinical findings, brain imaging, and laboratory test results. Other causes included non-atherosclerotic vasculopathies, hypercoagulable states and haematological disorder.
ACS, anterior circulation stroke; DAPT, dual antiplatelet therapy; FBG, fasting blood glucose; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PCS, posterior circulation stroke.

outcome (scoring 0–1 on the mRS) as the primary outcome. Additionally, we investigated several secondary outcomes including 90-day favourable functional outcome (scoring 0–2 on the mRS); a shift in 90-day mRS score distribution; occurrence of early neurological deterioration (increasing ≥2 points on the 24-hour NIHSS score); occurrence of early neurological improvement (decreasing ≥2 points on the 24-hour NIHSS score); changes in 24-hour NIHSS score; occurrence of 90-day stroke or other vascular events and 90-day mortality. For

**Table 2** Outcomes compared between treatments

| Outcomes | Groups | No.(%) of events or median difference | | Unadjusted | | Adjusted* | | $P_{int}$† value |
|---|---|---|---|---|---|---|---|---|
| | | DAPT | Alteplase | Treatment difference (95% CI) | P value | Treatment difference (95% CI) | P value | |
| Primary outcome | | | | | | | | |
| mRS 0–1 at 90 days‡ § | ACS | 256/272 (94.1) | 266/290 (91.7) | 2.4 (–1.8 to 6.6) | 0.27 | 1.8 (–1.2 to 4.9) | 0.23 | 0.56 |
| | PCS | 62/68 (91.2) | 78/85 (91.8) | –0.6 (–9.5 to 8.3) | 0.90 | –2.8 (–9.0 to 3.5) | 0.39 | |
| Secondary outcomes | | | | | | | | |
| mRS 0–2 at 90 days‡ § | ACS | 261/272 (96.0) | 277/290 (95.5) | 0.4 (–2.9 to 3.8) | 0.80 | 0.4 (–2.1 to 2.9) | 0.75 | 0.97 |
| | PCS | 62/68 (95.6) | 81/85 (95.3) | 0.3 (–6.3 to 6.9) | 0.93 | –0.8 (–5.4 to 3.9) | 0.75 | |
| mRS distribution at 90 days‡¶ | ACS | NA | NA | 1.12 (0.77 to 1.62) | 0.55 | 1.10 (0.85 to 1.42) | 0.49 | 0.48 |
| | PCS | NA | NA | 0.78 (0.36 to 1.65) | 0.51 | 0.65 (0.38 to 1.09) | 0.10 | |
| Early neurological deterioration within 24 hours** | ACS | 13/274 (4.7) | 23/292 (7.9) | –3.1 (–7.1 to 0.9) | 0.12 | –2.7 (–5.4 to 0.1) | 0.06 | 0.79 |
| | PCS | 4/68 (5.9) | 9/85 (10.6) | –4.7 (–13.3 to 3.9) | 0.28 | –4.9 (–10.9 to 1.2) | 0.11 | |
| Early neurological improvement within 24 hours‡‡ | ACS | 37/274 (13.5) | 70/292 (24.0) | –10.5 (–16.8 to -4.1) | <0.01†† | –7.0 (–11.3 to -2.7) | <0.01†† | 0.71 |
| | PCS | 10/68 (14.7) | 19/85 (22.4) | –7.6 (–19.9 to 4.6) | 0.22 | –2.7 (–11.1 to 5.6) | 0.52 | |
| Change in NIHSS score at 24 hours§§ | ACS | 0.00 (–0.41 to 0.00) | 0.00 (–0.69 to 0.00) | –0.10 (–0.19 to –0.01) | 0.03†† | –0.08 (–0.15 to –0.02) | 0.01†† | 0.71 |
| | PCS | 0.00 (–0.38 to 0.00) | 0.00 (–0.69 to 0.00) | –0.06 (–0.21 to 0.08) | 0.40 | –0.06 (–0.16 to 0.05) | 0.28 | |
| Stroke or other vascular events within 90 days¶¶ | ACS | 1/272 (0.4) | 1/290 (0.3) | 1.06 (0.07 to 16.96) | 0.97 | 1.35 (0.08 to 23.84) | 0.84 | 0.94 |
| | PCS | 0/68 (0.0) | 1/85 (1.2) | 0.02 (0.00 to NA) | 0.63 | 0.00 (0.00 to NA) | 0.98 | |
| All-cause death at 90 days§ | ACS | 2/272 (0.7) | 1/290 (0.3) | 0.4 (–0.8 to 1.6) | 0.53 | 0.3 (–0.5 to 1.2) | 0.42 | 0.99 |
| | PCS | 0/68 (0.0) | 2/85 (2.4) | –2.4 (NA to NA) | 0.20 | –2.5 (NA to NA) | 0.05 | |
| Safety outcomes | | | | | | | | |
| sICH§ *** | ACS | 0/274 (0.0) | 3/292 (1.0) | –1.0 (NA to NA) | 0.09 | –1.1 (NA to NA) | <0.01†† | 0.99 |
| | PCS | 0/68 (0.0) | 1/85 (1.2) | –1.2 (NA to NA) | 0.37 | –1.3 (NA to NA) | 0.16 | |
| Bleeding events§††† | ACS | 1/274 (0.4) | 16/292 (5.5) | –5.1 (–7.8 to –2.4) | <0.01†† | –5.3 (–7.2 to –3.3) | <0.01†† | 0.51 |
| | PCS | 1/68 (1.5) | 7/85 (8.2) | –6.8 (–13.3 to –0.3) | 0.04†† | –3.7 (–7.9 to –0.5) | 0.03†† | |

*Adjusted for participating centres and covariates compared between DAPT and alteplase treatments with p value<0.1 in each group in table 1.
†P value for interaction was calculated by adjusting covariates compared between ACS and PCS group with p value<0.1 in table 1.
‡mRS scores ranged from 0 to 6.
§Calculated using generalised linear model and presented by risk difference.
¶Calculated using ordinal regression analysis and presented by OR.
**Early neurological deterioration was defined as an increase between baseline and 24 hours of 2 on the NIHSS score, but not as a result of cerebral haemorrhage.
††P value<0.05.
‡‡Early neurological improvement was defined as a decrease between baseline and 24 hours of 2 on the NIHSS score.
§§NIHSS scores range from 0 to 42. Log (NIHSS+1) was analysed using generalised linear model and presented by geometric mean ratio.
¶¶Calculated using Cox regression model and presented by HR.
***Symptomatic intracranial haemorrhage was defined as any evidence of bleeding on head CT associated with neurological deterioration (NIHSS ≥4 point increase).
†††Bleeding events included symptomatic and asymptomatic intracerebral haemorrhage and gingival bleeding during the ARAMIS trial.
ACS, anterior circulation stroke; DAPT, dual antiplatelet therapy; mRS, modified Rankin Scale; N/A, not applicable; NHSS, National Institute of Health Stroke Scale; PCS, posterior circulation stroke; sICH, symptomatic intracranial haemorrhage.

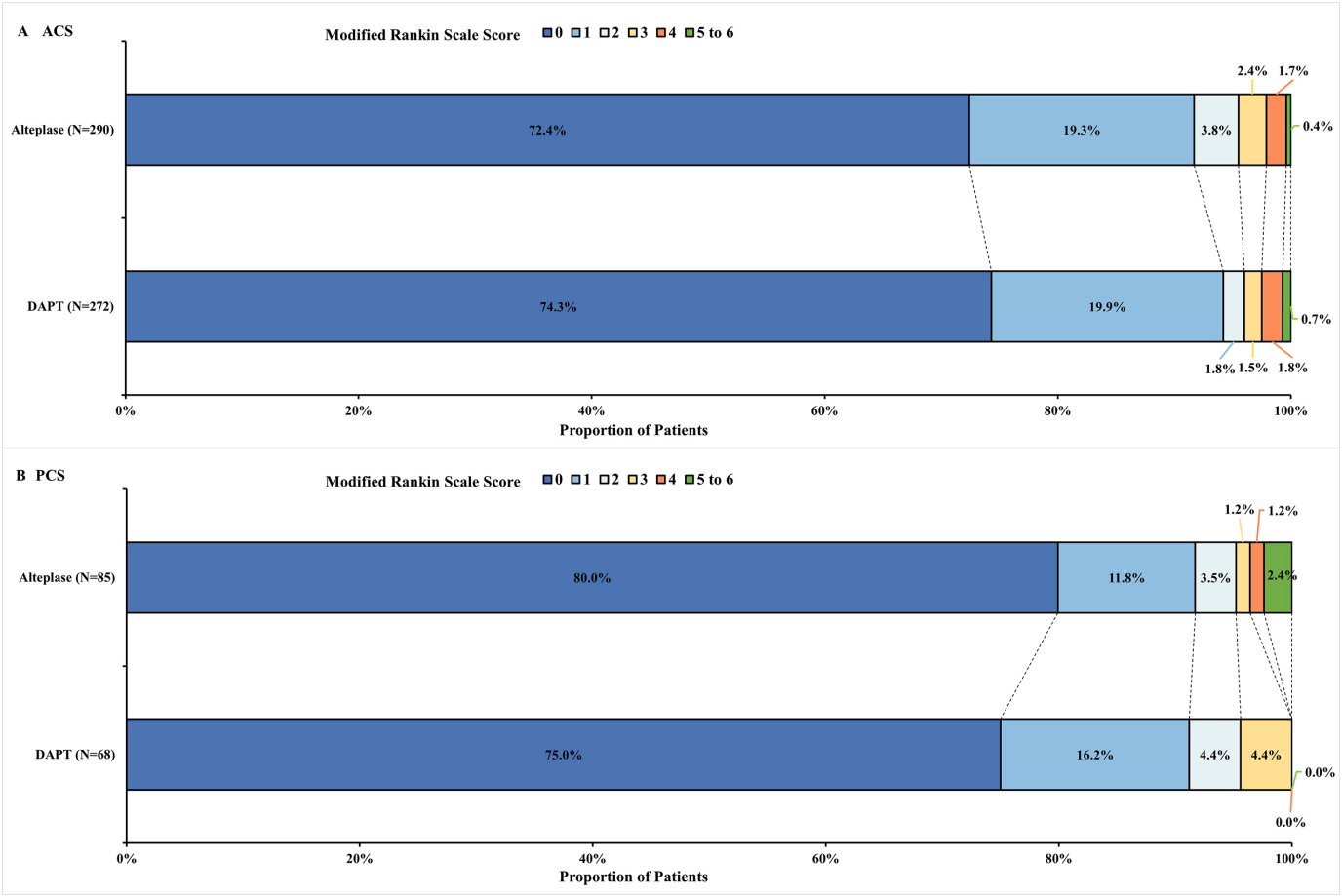


**Figure 2** Distribution of modified Rankin Scale score at 90 days. Scores ranged from 0 to 6. 0=no symptoms, 1=symptoms without clinically significant disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability and 6=death. ACS, anterior circulation stroke; DAPT, dual antiplatelet therapy; PCS, posterior circulation stroke.

safety, we investigated symptomatic intracranial haemorrhage (sICH, defined as increasing ≥4 points on the NIHSS score resulted from bleeding on head CT[20]) and any bleeding events during the trial. Considering the open-label and blind endpoint design in the trial, imaging assessment and NIHSS score were evaluated by investigators who were unblinded to therapy assignment, but vascular events and mRS score at 90-day follow-up were evaluated by trained investigators blinded to any clinical details including therapy assignment.

## Statistical analysis

In ARAMIS,[10] baseline characteristics of participants between full analysis and as-treated analysis sets were similar, which addressed potential selection bias. Furthermore, adjusted analyses were primary in the current study as an imbalance between treatments after dividing according to stroke territories.

In the current study, a median (IQR) was used to describe continuous variables with non-normal distributions and a frequency (percentage) was used for categorical variables. Furthermore, the absolute number (percentage) or median difference were calculated for outcomes. The treatment-outcome relationship was detected in each subgroup separately. Using generalised linear models with binomial distributions and identity link functions, GMRs were generated for change in NIHSS score at 24 hours and risk difference (RD) for outcomes such as excellent functional outcomes, favourable functional outcomes, early neurological deterioration, early neurological improvement, mortality, sICH and bleeding events. Using the ordinal regression model, ORs were generated for distribution of 90-day mRS score. Using the Cox regression model, HRs were generated for stroke or other vascular events. A two-sided 95% CI and p value were also provided. The assessment of interactions between treatment effects and stroke territories were performed by each model with the independent variables including treatments, stroke territories and the interaction terms, and the $p_{int}$ values were reported. In treatment effect or interaction analyses, the centres and patients' characteristics compared between treatments or stroke territories and presenting p<0.1 were adjusted, respectively.

Additionally, sensitivity analyses were performed to address the bias from imbalanced sample sizes between groups and the selection bias from the population analysed. To reduce the unbalanced sample size between ACS and PCS, propensity score matching analysis was

conducted. The propensity scores for patients' characteristics compared between stroke territories and presenting p<0.1 will be estimated by logistic multivariate regression, and then patients were matched according to the propensity scores by the nearest-neighbour matching strategy without replacement, tolerance of 0.01 and a ratio of 1:1. In addition, the relationship between treatment effects and outcome was respectively examined across subgroups within full, per-protocol and as-treated analysis sets with second adjusted model (including prespecified covariates in the ARAMIS trial and imbalanced covariates between treatments) and inverse probability of treatment weighting (IPTW) method, respectively. Definition of full analysis, per-protocol analysis and as-treated analysis sets were provided in online supplemental material.

Statistical significance was determined by two-sided p values less than 0.05. Analyses were conducted using IBM SPSS software and the propensity score matching was performed with R software.

## RESULTS

### Study participants

After excluding 4 patients with infarct located at anterior and posterior circulation from the ARAMIS trial, a total of 719 patients were included in the current study, including 566 in the ACS subgroup (274 patients used DAPT and 292 patients used alteplase) and 153 in the PCS subgroup (68 patients used DAPT and 85 patients used alteplase, figure 1). Between stroke subtypes, the proportion of current smokers was significantly different (36.2% in the ACS subgroup vs 23.5% in the PCS subgroup, online supplemental table 1). More current smokers, less previous hypertension, milder neurological deficits and shorter stroke onset to treatment time were found in the alteplase group of the ACS subgroup, while only milder neurological deficits in the alteplase group of the PCS subgroup. Detailed baseline characteristics of patients were shown in table 1.

### Study outcomes

Results of comparison between DAPT and alteplase were shown in table 2 and figure 2. There was no significant difference in proportions of excellent functional outcome at 90 days between treatments in ACS subgroup (94.1% vs 91.7%; adjusted RD, 1.8%; 95% CI −1.2% to 4.9%; p=0.23) and PCS subgroup (91.2% vs 91.8%; adjusted RD, −2.8%; 95% CI −9.0% to 3.5%; p=0.39). Additionally, there was no interaction between treatment effects and stroke subtypes (adjusted $p_{int}$=0.56).

Compared with baseline, more early neurological improvement (24.0% vs 13.5%; adjusted RD and 95% CI, −7.0% (−11.3% to −2.7%), p<0.01) and decrease in NIHSS score at 24 hours (adjusted GMR and 95% CI, −0.08 (−0.15 to −0.02), p=0.01) were found in ACS patients who received alteplase, but not in the PCS patients. For the other secondary outcomes, neither significant differences between treatments nor significant interaction between stroke subtypes were found (table 2).

For the safety outcomes, DAPT was associated with fewer sICH (0.0% vs 1.0%; adjusted RD, −1.1%; p<0.01) and bleeding events (0.4% vs 5.5%; adjusted RD and 95% CI, −5.3% (−7.2% to −3.3%), p<0.01) in ASC patients. In the PCS patients, DAPT was significantly associated with fewer bleeding events (1.5% vs 8.2%; adjusted RD and 95% CI, −3.7% (−7.9% to −0.5%), p=0.03).

### Sensitivity analysis

The baseline characteristics of population before and after propensity score matching were shown in online supplemental table 2, respectively. The results of primary outcome from the adjusted model in different populations including propensity score matching, full analysis and per-protocol analysis sets, as well as the primary adjusted model by IPTW method and the secondary adjusted model for as-treated analysis set, were consistent with those from the primary analyses. The results of sensitivity analysis were shown in online supplemental table 3.

## DISCUSSION

The current analysis assessed whether DAPT and intravenous alteplase were effective in different stroke territories based on the ARAMIS trial. We found DAPT was similar to intravenous alteplase regarding 3-month functional outcomes in neither ACS nor PCS. Intravenous alteplase was associated with higher likelihood of early neurological improvement and more decrease in 24-hour NIHSS score compared with DAPT in only patients with ACS. DAPT was associated with fewer bleeding events and sICH than intravenous alteplase in ACS, and just lower risk of bleeding events in PCS.

In the current study, the ratio of PCS to ACS (21.3%) was similar with that (21.1%) in a real-world registry study from China.[21] In the current study, we find similar efficacy between DAPT and intravenous alteplase in patients with ACS or PCS. Similarly, previous studies demonstrated the efficacy of either DAPT or intravenous alteplase was similar between two stroke subtypes.[14–17] In the patients with large vessel occlusion, the efficacy of intravenous alteplase differed between two stroke subtypes.[18] However, we could not compare the efficacy of two treatments in this population as the lower proportion of large vessel occlusion (36/477) in the ARAMIS trial.[10] As shown in ARAMIS,[10] DAPT led to lower risk of early neurological deterioration compared with intravenous alteplase. Thus, it was worth exploring the different effects of two treatments on the early neurological function. Interestingly, we found that patients with ACS may benefit from intravenous alteplase regarding improved neurological function at early stages. The early neurological improvement may be attributed to early recanalisation after intravenous thrombolysis.[22] Previous study found that more early recanalisation occurred in patients with middle cerebral artery occlusion compared with basilar artery occlusion,[23]

which indicated intravenous thrombolysis was easy to achieve recanalisation in ACS. Additionally, compared with PCS subgroup, there were more current smokers in the ACS subgroup. Smoking was previously reported as an independent predictor of recanalisation and reperfusion following intravenous thrombolysis.[24] The early benefit in patients with ACS may also be attributed to the better response to evaluation of neurological deficits by NIHSS score in ACS compared with PCS,[12] because improvement in the early neurological function did not result in better 3-month functional outcome in this study. Considering the continuous antithrombotic effect of DAPT and its important role in preventing the early neurological deterioration,[10 25] we interpreted that the benefit from intravenous alteplase in early neurological improvement may be balanced by DAPT. This also may result from the higher rates of excellent functional outcomes which limited the opportunity to show superiority to others. Collectively, the findings in the current study indicated efficacy of DAPT and intravenous alteplase was similar in either ACS or PCS regarding the 3-month functional outcome, but different regarding to early neurological function.

For the safety outcomes, similar to the results from the ARAMIS trial,[10] DAPT showed better safety profiles in both ACS and PCS subgroups. Additionally, the findings were consistent with that from a registry study, which showed intravenous alteplase was associated with increased risk of sICH.[26] Intravenous alteplase showed significant higher risk of sICH than DAPT in the ACS subgroup, whereas the long-term functional outcomes were similar between treatment groups in this population. As well as the higher likelihood of improvement in early neurological function, this may be attributed to ceiling effect of good prognosis in minor stroke. Whether intravenous alteplase should be used in patients with ACS warrants investigation by balancing the risk of bleeding and benefit of early neurological function.

Several limitations were presented in the current analysis. First, relatively smaller sample size in PCS resulted in unbalanced sample size between stroke territories would affect statistical power. Although we address the unbalanced sample size by performing propensity score matching, the statistical power will further decrease in each stroke territory by smaller sample size after matching. Thus, this finding warrants invalidation in trials with balanced and adequate sample size. Second, there was a lack of evaluation for post-thrombolytic recanalisation as we inferred the early neurological improvement in ACS may be attributed to more recanalisation in this population. Third, almost 20.4% of enrolled patients crossover to alternative treatment in the ARAMIS trial. The sensitivity analysis in full analysis and per-protocol analysis sets showed consistent result with the primary analysis, which reduced potential selected bias. Furthermore, as atrial fibrillation was associated with END and poor long-term functional outcomes in patients with minor stroke,[27] few patients with atrial fibrillation were included in the trial may limit the generalisability of the findings. Fourth, although we found that intravenous alteplase contributed to improvement in early neurological function in ACS, it did not lead to better long-term functional outcomes. Fifth, considering the NIHSS scores could not really reflect the severity of neurological deficit in PCS, the early-phase outcome based on NIHSS score would limit the interpretation. Finally, it is important to interpret these findings with caution due to the unblinded assessment of NIHSS score at follow-up and the exploratory nature of post hoc analysis.

## CONCLUSION

Among acute minor ischaemic stroke presenting non-disabling symptoms, DAPT was similar to intravenous thrombolysis with alteplase across ACS and PCS patients regarding long-term functional outcome and safety profile. The potential benefit of intravenous alteplase regarding improvement in early neurological function following ACS warrants further investigation.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by Ethics Committee of General Hospital of Northern Theater Command and conducted according to the Declaration of Helsinki. Informed consents were signed by participants or their legally authorised representatives.

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**Data availability statement** Data are available upon reasonable request.



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