# Clopidogrel plus Aspirin versus Aspirin alone in Patients with Acute Mild-to-Moderate Stroke

# The ATAMIS Randomized Controlled Trial

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## Key Points

**Question** Is dual antiplatelet therapy superior to aspirin alone in patients with acute mild-to-moderate ischemic stroke?

**Findings** In this randomized clinical trial that included 3000 participants, early neurologic deterioration at 7 days (equal to or more than 2-point National Institutes of Health Stroke Scale score increase) occurred in 4.8% of those randomized to dual antiplatelet therapy and 6.7% of those randomized to receive aspirin alone, a difference that was statistically significant.

**Meaning** Among patients with acute mild-to-moderate ischemic stroke, dual antiplatelet therapy, compared with aspirin alone, was significantly associated with reducing early neurologic deterioration at 7 days.

## Abstract

**IMPORTANCE** Dual antiplatelet (DAPT) has been demonstrated superior to single antiplatelet in reducing recurrent stroke among patients with transient ischemic attack or minor stroke, but robust evidence for its effect in patients with mild-to-moderate ischemic stroke is lacking.

**OBJECTIVE** To evaluate whether DAPT is superior to single antiplatelet among patients with mild-to-moderate ischemic stroke (National Institutes of Health Stroke Scale [NIHSS]: 4-10).

**DESIGN, SETTING, AND PARTICIPANTS** This multicenter, open-label, blinded-endpoint, randomized clinical trial was conducted at hospitals in China from December 20, 2016, through August 9, 2022. The date of final follow-up was October 30, 2022. Of 3065 patients with ischemic stroke, 3000 patients with acute mild-to-moderate stroke within 48 hours of symptom onset were enrolled, after excluding 65 patients who did not meet eligibility criteria, or had no randomization outcome. The analysis was reported on March 12, 2023.

**INTERVENTIONS** Within 48 hours after symptom onset, patients were randomly assigned to receive clopidogrel plus aspirin (n=1541) or aspirin alone (n=1459) in a 1:1 ratio.

**MAIN OUTCOMES AND MEASURES** The primary endpoint was early neurologic deterioration at 7 days, defined as $\geq$ 2-point NIHSS score increase, but not as a result of cerebral hemorrhage, compared with baseline. We assessed the superiority of clopidogrel plus aspirin to aspirin alone based on a modified intention-to-treat (mITT) population, which included all randomized participants with at least one efficacy evaluation regardless of treatment allocation. Bleeding events were safety endpoints.

**RESULTS** Of the randomly assigned 3000 patients, 1942 (64.7%) were men, the mean (SD) age was 65.9 (10.6) years, median NHSS score at admission was 5, and 1830 (61.0%) were undetermined cause of stroke. A total of 2915 patients were included in the mITT analysis. The primary endpoint occurred in

4.8% (72/1502) in the DAPT group vs 6.7% (95/1413) in the aspirin alone group (risk difference -1.9%, 95%CI -3.6% to -0.2%, *P*=.03). Similar bleeding events were found between two groups.

**CONCLUSIONS AND RELEVANCE** Among Chinese patients with acute mild-to-moderate ischemic stroke, clopidogrel plus aspirin was superior to aspirin alone with regard to reducing early neurologic deterioration at 7 days with similar safety profile.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT02869009.

## Introduction

Reperfusion and thrombolytic therapies are effective strategies in the treatment of acute ischemic stroke (AIS).[1-2] However a subset of AIS patients are not eligible for reperfusion therapies due to a limited therapeutic window and access to endovascular care.[3] According to current guidelines, almost all AIS patients receive an antithrombotic treatment, such as antiplatelet or anticoagulant, to prevent the progression and recurrence of stroke. Antiplatelet therapy with aspirin alone is recommended in AIS patients who do not receive reperfusion therapy.[1,4] Compared with aspirin alone, dual antiplatelet with clopidogrel and aspirin was reported to be more effective for some individuals.[5] The Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) and Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA (POINT) trials confirmed that, in patients who were treated within 24 hours of symptom onset after transient ischemic attack (TIA) or minor ischemic stroke (defined as National Institutes of Health Stroke Scale [NIHSS] score $\leqq$ 3), dual antiplatelet with clopidogrel and aspirin reduced the risk of recurrent stroke compared with aspirin alone, but did not improve clinical outcome.[6-7] For patients with mild-to-moderate ischemic stroke, aspirin monotherapy is recommended by stroke guidelines,[1] however, early neurologic deterioration (END) remains a challenge to overcome in this population, given the association of END with clinical outcome.[8]

Up to 50% of END occurs within 48 hours after TIA or AIS onset.[8] The Fast assessment of stroke and transient ischemic attack to prevent early recurrence (FASTER) trial suggested some evidence for benefit of early clopidogrel and aspirin in patients at high risk of recurrent stroke.[9] Two previous studies found that in patients with acute mild-to-moderate ischemic stroke (NIHSS score $\leq$ 7 or 14) within 48 hours of symptom onset, dual antiplatelet with clopidogrel and aspirin may be superior to aspirin alone with comparable safety profile.[10,11] In theory, the intensive antithrombotic therapy such as clopidogrel and

aspirin could reduce END and improve clinical outcome if the hemorrhagic risk can be contained. Nonetheless, there is a lack of robust evidence for dual antiplatelet in this patient population.

In this context, we conducted the Antiplatelet Therapy in Acute Mild-to-Moderate Ischemic Stroke (ATAMIS) trial to determine whether dual antiplatelet with clopidogrel and aspirin would be superior to aspirin alone in patients with acute mild-to-moderate ischemic stroke (NIHSS 4 to 10) presenting within 48 hours of symptom onset.

## Methods

### Study Design

ATAMIS was a multicenter, open-label, blinded-endpoint, randomized trial to assess the efficacy and safety of clopidogrel plus aspirin in patients with mild-to-moderate ischemic stroke within 48 hours of symptom onset. The study protocol is available in Supplement 1 and the statistical analysis plan in Supplement 2. The trial was conducted at 66 sites (Supplement 3) in China. Details of the study design and rationale have been published.[12] The trial protocol was approved by the regulatory and Ethics Committee of the General Hospital of Northern Theatre Command and other participating hospitals. An independent data monitoring committee monitored the progress of the trial every 6 months. Signed informed consent was obtained from patients or their legally authorized representative. The ATAMIS trial was registered at clinicialtrials.gov (NCT02869009).

### Participants

Eligible patients were adults 18 years or older with AIS at the time of randomization (baseline NIHSS scores of 4 to 10; range from 0 to 42, with higher scores indicating greater stroke severity), who had been functioning independently (modified Rankin Scale [mRS] scores ≤ 1; range from 0 [no symptoms] to 6 [death]) before a stroke, and were enrolled up to 48 hours after the onset of stroke symptoms (time last

seen was well). Head computed tomography or magnetic resonance imaging was performed on admission to identify patients with ischemic stroke. If a patient met eligibility criteria for intravenous thrombolysis (IVT) or endovascular therapy (EVT), then they received this as standard of care, and were excluded from the trial. Other exclusion criteria were as follows: had a clear indication for anticoagulation, had a history of intracerebral hemorrhage, was planned for carotid revascularization, had gastrointestinal or urinary tract bleeding in the last 3 months, and had an allergy to clopidogrel and/or aspirin. A full list of inclusion and exclusion criteria are in the study protocol.

**Randomization and Masking**

Eligible patients were randomly assigned to either the clopidogrel plus aspirin group or the aspirin alone group with the simple randomization (1:1) method, through a computer-generated random sequence that was centrally administered via a password-protected web-based program at http://atamis.medsci.cn (Shanghai Meisi Medical Technology Co., Ltd). The study team members were unblinded to the treatment allocation.

**Procedures**

Patients were randomly assigned to the clopidogrel plus aspirin group (300 mg loading dose of clopidogrel plus aspirin 100 mg, followed by clopidogrel 75 mg/d and aspirin 100 mg/d from day 2 to day 14, and followed by clopidogrel 75 mg/d or aspirin 100 mg/d from day 15 to day 90) or the aspirin alone group (100 to 300 mg aspirin from day 1 to day 14, followed by aspirin 100 mg/d from day 15 to day 90).[10] All patients received guideline-based stroke care for vascular risk factor control, including statin if eligible.[1] Details of the study procedure are in the supplement (Supplement 3).

The NIHSS was used to assess the neurologic status at baseline, 7 days, and 14 days after randomization. A detailed flowchart of the assessment schedule is provided in the study protocol. Data

on demographic and clinical characteristics were obtained at randomization. Follow-up data were collected at 7 days, 14 days (or at hospital discharge if earlier), and 90 days after randomization. Remote and on-site quality control monitoring and data verification were conducted throughout the study.

**Outcomes**

The primary endpoint was the presence of END at 7 days, defined as an equal or greater than 2-point increase in the NIHSS score, while excluding cerebral hemorrhage, hypoglycemia, cardiac complications, fever or infection, compared with baseline.[11] The primary endpoint was modified from the original definition (more than or equal to 1 point increase in NIHSS, compared with baseline at 14 days) and published definition (≥4 point increase in the NIHSS score in 48 hours)[12] to the current definition prior to analysis. The modification rationale was explained in detail in Supplement 1 (Details of Change in Protocol).

The secondary endpoints were excellent functional outcome at 90 days, defined as a mRS score of 0 to 1; a shift in the distribution of the mRS score at 90 days; change in NIHSS score compared with baseline at 14 days; the occurrence of new ischemic or hemorrhagic stroke[13] within 90 days, and the occurrence of other vascular events (pulmonary embolism, peripheral vascular, or cardiovascular event) or death within 90 days.

Any bleeding event and adverse event that occurred during the study period was recorded. The prespecified adverse event outcomes were mucocutaneous hemorrhage, organ hemorrhage, intracranial hemorrhage according to the Heidelberg bleeding classification within 14 days and severe adverse events.

The follow-up NIHSS scores were evaluated by a certified neurologist, who was blinded to the treatment allocation. Final follow-up was performed at 90 days in person or, if an in-person visit was not possible, a structured interview for telephone assessment (Supplement 3) was performed by a trained and

certified staff member in each center who was unaware of the randomized treatment assignment. A training course was held for all investigators at each center to ensure the validity and reproducibility of the evaluation. Only certified investigators were eligible to evaluate the NIHSS or mRS score. Central adjudication of clinical outcomes and adverse events was performed by assessors who were unaware of treatment allocation or patient clinical details. If there was disagreement between the local and central assessors, a consensus was reached by discussion. The local assessor retained control of the NIHSS and final mRS score following discussion.

**Sample Size Calculation**

Power calculations were based on the estimated treatment effects with a binary assessment of END at 7 days. Based on our previous study[10] reporting 6% END (defined as an increase in $\geq$ 2 NIHSS points compared with baseline at 14 days) in patients receiving aspirin monotherapy with similar characteristics to this current trial, we assumed a 7.5% rate of END (defined as $\geq$ 2 NIHSS point increase compared with baseline at 7 days) in the aspirin alone group in this trial, and that clopidogrel plus aspirin would result in a 35% reduction of END compared with aspirin alone, namely to 4.88% in the clopidogrel plus aspirin group. A sample size of 2638 (1319 per group) was estimated to provide more than 80% power (using a two-sided $\alpha = 0.05$) to detect the 2.62% lower rate of END in the clopidogrel plus aspirin group. Assuming a 12% loss to follow-up, the total sample size was 2998. Therefore, this study was planned to include 3000 participants (1500 participants per group). The sample size calculation was also revised (see Details of Change in Protocol, Supplement 1).

**Statistical analysis**

Statistical analyses were performed on the modified intention-to-treat (mITT) population, which included all randomized participants with at least one valid post-baseline efficacy evaluation.

Generalized linear models (GLMs) were performed for the analyses of the primary outcome of 7-day END and secondary outcomes of excellent functional outcome at 90 days. The treatment effects for the above outcomes were presented as risk differences (RD) and risk ratio (RR) with their 95% confidence intervals (CIs). In sensitivity analyses, missing values in the primary outcome were imputed using the last observation carried forward method, the worst-case scenario, and best-case scenario approaches. No interim analyses were performed in this study.

The 90-day mRS score was compared using ordinal logistic regression with treatment effect presented as odds ratio (OR) with 95% CI. The odds proportionality assumption for treatment was assessed by a likelihood ratio test. A GLM was used to compare changes in log (NIHSS score+1) between admission and 14 days, and a geometric mean ratio with 95% CI was calculated between the two groups. Time-to-event outcomes of new ischemic or hemorrhagic stroke within 90 days, and other vascular or death events were compared using Cox regression models, and the corresponding treatment effects were presented as hazard ratios (HR) with 95% CI. The hazard proportionality assumption was tested by introducing an interaction between time and treatment in the Cox model.

The primary analyses of the primary and secondary outcomes were unadjusted. Covariate adjusted GLM analyses were performed for all outcomes, adjusting for seven prespecified prognostic factors: age, sex, history of diabetes, history of hypertension, NIHSS score at randomization, time from symptom onset to antiplatelet treatment, and stroke etiology. The degree of responsible vessel stenosis and location of responsible vessel were planned in the covariate adjusted analyses but were excluded due to a skewed distribution or a large proportion of missing values. The missing values of baseline variables in the covariate adjusted analyses were imputed using simple imputation methods based on their sample distributions. For example, for a continuous variable, missing values were imputed from random values

generated from a normal distribution with mean and standard deviation with a pre-specified seed calculated from the available sample.

Subgroup analysis of the primary outcome was performed using GLM on nine prespecified subgroups (age [< 65 years or ≥ 65 years], sex [female or male], history of diabetes, history of hypertension, NIHSS score at randomization [< 7 or ≥ 7], time from symptom onset to antiplatelet therapy [<24 hours or ≥ 24 hours], stroke etiology, degree of responsible vessel stenosis (≤50% vs. >50%) measured by CTA or MRA according to the WASID method of measurement,[14] and location of responsible vessel (anterior circulation vs. posterior circulation vs. anterior and posterior circulation). Assessment of the homogeneity of the treatment effect by a subgroup variable was conducted using a GLM with the treatment, subgroup variable, and their interaction term as independent variables, and the P value for the interaction term was presented. In addition, per-protocol analyses for primary and secondary outcomes were performed on patients who received complete intervention as specified in the protocol. Detailed statistical analyses are described in the statistical analysis plan (Supplement 2).

A 2-sided P value of less than .05 was considered statistically significant. Because of the potential for a type I error due to multiple comparisons, findings for secondary outcome analyses should be interpreted as exploratory. SPSS software (version 23) and R software (version 4.1.0) were used for the statistical analyses.

## Results

### Trial Population

Between December 20, 2016, and August 9, 2022, 3005 patients were enrolled, and 3000 were randomly assigned to the clopidogrel plus aspirin group (1541 patients) or the aspirin alone group (1459 patients)

after excluding 5 patients due to randomization error. A total of 85 (2.8%) patients were further excluded (63 withdrew consent due to the patient's decision, 13 for duplicate randomization, and 9 were lost to follow-up). Finally, the mITT population included 2915 patients (1502 in the clopidogrel plus aspirin group and 1413 in the aspirin alone group) (Figure 1 and eFigure 1 in Supplement 3). The procedure was completed according to the protocol for 2763 patients (1433 in the clopidogrel plus aspirin group and 1330 in the aspirin alone group), and the results were included in the per-protocol analysis. The reasons for the incomplete procedures are provided in Figure 1. The trial was completed in October 2022.

The treatment groups were well balanced with respect to baseline patient characteristics in the mITT population (Table 1) and per-protocol analysis (eTable 1 in Supplement 3). In the clopidogrel plus aspirin group, 1433 of 1502 patients (95.4%) underwent the complete procedure of clopidogrel plus aspirin treatment at a mean of 19.1 hours from symptom onset to antiplatelet treatment. The remaining 69 patients did not complete clopidogrel plus aspirin treatment. In the aspirin alone group, 1330 of 1413 patients (94.1%) underwent the complete procedure of aspirin treatment at a mean of 19.8 hours from symptom onset to antiplatelet treatment. The remaining 83 patients did not complete aspirin treatment.

**Primary Outcome**

For the primary outcome, the proportion of patients with END at 7 days was 4.8% (72/1502) in the clopidogrel plus aspirin group and 6.7% (95/1413) in the aspirin alone group. In the mITT population, the risk of having END showed significant difference between the clopidogrel plus aspirin and aspirin alone groups (unadjusted RD -1.9%; 95% CI -3.6% to -0.2%; *P*=.03; RR 0.71; 95% CI 0.53 to 0.96; *P*=.03; Table 2). Given that there were 85 dropout patients, sensitivity analyses were performed and similar RD results were observed (eTable 2 in Supplement 3). The difference in the risks of having a primary outcome remained significant after adjustment for prespecified prognostic variables (RD -1.9%;

95% CI -3.6% to -0.2%; *P*=.03; RR 0.71; 95% CI 0.53 to 0.96; *P*=.03; Table 2). The per-protocol analysis yielded similar results (unadjusted RD -1.8%; 95% CI -3.5% to -0.2%; *P*=.03; RR 0.69; 95% CI 0.50 to 0.96; *P*=.03; adjusted RD -1.8%; 95% CI -3.5% to -0.2%; *P*=.03; RR 0.69; 95% CI 0.50 to 0.96; *P*=.03; eTable 3 in Supplement 3).

**Secondary Outcomes**

For the secondary outcomes, no differences were observed in both the unadjusted and adjusted analyses, including the risks of having new ischemic or hemorrhagic stroke within 90 days, change in NIHSS score compared with randomization at 14 days, mRS improvement at 90 days (Figure 2), and other vascular or death events within 90 days (Table 2). In the per-protocol analysis, similar results were obtained in both unadjusted and adjusted per-protocol analyses (eFigure 2 and eTable 3 in Supplement 3).

Prespecified subgroup analysis showed no evidence of effect modification in the risks of having a primary outcome between the clopidogrel plus aspirin and aspirin alone groups by age, sex, history of diabetes, history of hypertension, NIHSS score at randomization, stroke etiology, degree of responsible vessel stenosis, and location of responsible vessel, with the exception of time from the onset of symptoms to antiplatelet treatment (< vs > 24 hours) (Figure 3). The results of the per-protocol analysis were similar to those of the mITT population for the primary outcome (eFigure 3 in Supplement 3).

**Adverse Events**

Analyses of adverse events were based on the safety population which consisted of all randomized patients who received at least one dose of study drug. There were no differences in adverse events including mucocutaneous hemorrhage, organ hemorrhage, intracranial hemorrhage, adverse events, and severe adverse events between the two groups (Table 2).

## Discussion

To our knowledge, this is the first large-scale, multicenter, randomized trial to investigate the effect of dual antiplatelet treatment in patients with mild-to-moderate ischemic stroke who are not eligible for IVT or EVT presenting within 48 hours of symptom onset. We found that dual antiplatelet therapy with clopidogrel and aspirin reduced the likelihood of END at 7 days by 1.9%, as compared with aspirin alone. Dual antiplatelet with clopidogrel and aspirin, as compared with aspirin alone, was not associated with an increased incidence of bleeding events.

Previous studies focused on the role of clopidogrel plus aspirin in the secondary prevention of AIS or high-risk TIA.[6-7,15-16] Both the CHANCE and POINT trials evaluated the role of dual antiplatelet in patients with minor stroke or TIA as characterized by NIHSS $\leq$3. The ARAMIS trial evaluated the role of dual antiplatelet therapy compared to intravenous thrombolysis in patients with nondisabling stroke.[17] However there was a lack of evidence for its use in patients with mild to moderate stroke (patients presenting with NIHSS 4-10), as well as lack of data on its effect on early neurologic function. In the ATAMIS trial, dual antiplatelet with clopidogrel plus aspirin was identified with appropriate power to significantly reduce the incidence of END in patients with mild-to-moderate ischemic stroke. Different from previous trials,[6-7,17] the target population in ATAMIS was patients with mild-to-moderate neurologic deficit (NIHSS scoring 4 to 10). Additionally, the primary endpoint in ATAMIS was END at 7 days, which was different from the occurrence of stroke or ischemic vascular events within 90 days in the CHANCE and POINT trials.[6-7] Given the association of neurologic deterioration after mild-to-moderate ischemic stroke with poor outcome,[18-19] END was selected as the primary endpoint in this trial as a deterioration in 2 points or greater, which can be a clinically meaningful event to the patient. As there were logistical challenges to consistently capture the initial primary endpoint at 48 hours from

304 randomization, this was changed to the 7-day time interval from randomization to optimize completeness
305 in reporting of the primary endpoint (Details of Change in Protocol). The trial was also unique with
306 regards to the short duration of dual antiplatelet treatment (10-14 days). Although a longer duration of
307 dual antiplatelet therapy has been shown to be protective from subsequent ischemic stroke, the higher
308 risk of major hemorrhage over time cannot be ignored.[7] As subgroup analysis of the CHANCE trial found
309 that the optimal duration of dual antiplatelet may be 14 days,[18] this shorter duration of dual antiplatelet
310 therapy was used in ATAMIS in contrast to the CHANCE and POINT trials (14 days vs 21 days and 90
311 days, respectively).[6-7] In addition, a significant interaction for time of onset (< vs ≥ 24 hours) with
312 obvious reduction of END was identified for dual antiplatelet therapy in the early onset group, which
313 suggests that earlier intensive antiplatelet treatment may have a greater effect in reducing the occurrence
314 of END. Collectively, the dual antiplatelet therapy of clopidogrel and aspirin with 14 days was proven to
315 improve early neurologic function in mild-to-moderate ischemic stroke in this trial.
316 In this trial, with respect to 90-day functional outcome, we did not find that dual antiplatelet therapy
317 improved functional outcome compared with aspirin alone, although a high probability of excellent
318 functional outcome was found in the clopidogrel plus aspirin group. Given the signal of benefit from
319 antiplatelet therapy in the RESCUE BT2 trial in patients with large artery atherosclerosis,[19] we inferred
320 the lack of improved functional outcome with dual antiplatelet therapy in ATAMIS may be attributed to
321 the relatively mild neurological deficits in the enrolled patients (median NIHSS 5 in ATAMIS vs median
322 NIHSS 9 in RESCUE-BT2). This proposal was supported by the CHANCE and POINT trials wherein
323 dual antiplatelet therapy had no effect on 90-day functional outcome.[6-7] For other secondary endpoints,
324 there was no difference in change in NIHSS score at 14 days, the incidence of new stroke and other
325 vascular events or all-cause death within 90 days between two groups, which was different from the

CHANCE and POINT trials.[6-7] This inconsistency may be due to lack of statistical power in the secondary endpoints and the shorter duration of dual antiplatelet treatment in ATAMIS.

For adverse events, similar rates of symptomatic intracranial hemorrhage were observed between the clopidogrel plus aspirin group and the aspirin alone group, which was consistent with a prior study.[7] In this trial, the rate of bleeding events was 0.7%, which was comparable to the 1.6% bleeding rate in the ARAMIS trial. However, the 0.7% bleeding rate in ATAMIS was lower than the 2.3% bleeding event rate in the CHANCE trial, despite ATAMIS patients presenting with a higher severity of disease compared to CHANCE.[6] This lower bleeding rate may be due to the shorter duration of dual antiplatelet therapy in the present study, which was comparable to a recent study involving mild-to-moderate ischemic stroke patients.[20] Collectively, the current results suggest the safety and feasibility of dual antiplatelet therapy in this population.

**Limitations**

We acknowledge this study has limitations. First, the imbalance in sample size (1541 versus 1459) between groups occurred due to the use of a simple randomization method, which may have reduced the statistical power of the study. Second, due to the open-label design, the present study did not conceal the assigned treatment from the participants and physicians. However, the blinded-endpoint assessments were used to reduce measurement bias and ensure that the primary endpoint was measured objectively. Third, more patients with mild neurologic deficit (67.4%, NIHSS scoring 4 to 5) were enrolled in this trial, which may have weakened the statistical power in the analysis of moderate severity stroke patients. Fourth, patients receiving thrombolysis and endovascular treatment were excluded, which would limit the generalization of this finding. Fifth, the duration of DAPT treatment was 14 days, and we do not know the ideal duration of treatment. Moreover, considering that approximately 30% of our patient

population had a history of a prior stroke, the utilization of prior antiplatelet therapy was low in our study with approximately 4% reporting prior use. This discrepancy may be related to patient compliance with antiplatelet therapy or differences in long term secondary stroke prevention strategies in this patient population. Sixth, a NIHSS change of 2 points at 7 days may not have been an optimal definition of END in this trial, which may have been affected by neurological fluctuation. Finally, further confirmation of these findings in a non-Chinese population would be of interest, given potential differences in body mass, comorbidities, secondary stroke prevention strategies, and etiology of AIS patients across different ethnic populations.

**Conclusions**

Among patients with acute mild-to-moderate ischemic stroke who are not eligible for IVT or EVT, treatment with clopidogrel plus aspirin was superior to aspirin alone with regard to reducing END at 7 days with comparable safety profile. Given a lack of improvement of 90-day clinical outcome and the benefit of earlier dual antiplatelet treatment observed in this study, future clinical trials focusing on patients with mild-to-moderate stroke presenting within 24 hours of symptom onset are needed.

## Author Contributions

HSC had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: HSC.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: HSC, TNN.

Statistical analysis: YC and DLW.

Administrative, technical, or material support: All authors.

Supervision: HSC.

## Competing interest declaration

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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## Group Information

The principal investigators from each participating center in ATAMIS trial are listed in Supplement 4.

## Data Sharing Statement

See Supplement 5.


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**Figure Legends**

**Figure 1 Trial Profile.**

Abbreviations: NIHSS = National Institutes of Health Stroke Scale. TIA = transient ischemic attack. mRS = modified Rankin Scale. IVT = intravenous thrombolysis. * The baseline characteristics of dropout patients from the modified intention-to-treat population are shown in Table S4 in Supplement 3.

**Figure 2 Distribution of Modified Rankin Scale Scores at 90 Days by Assigned Treatment.**

The raw distribution of scores is shown. 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. The odds ratio was 1.10 (95% CI, 0.96-1.25), and the P value was 0.19; the adjusted odds ratio was 1.10 (95% CI, 0.96-1.26), and the P value was 0.18.

**Figure 3 Risk Difference for the Primary Outcome According to Prespecified Subgroups.**

The primary outcome was early neurological deterioration at 7 days. For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events) and horizontal lines represent the 95% CI. NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficits. For the NIHSS score, subgroups were dichotomized according to the median value.
Abbreviations: CI = confidence interval. NIHSS = National Institutes of Health Stroke Scale.

**Table 1. Baseline Characteristics of the Patients.**

| Baseline characteristics | Clopidogrel plus aspirin group (n=1502) | Aspirin alone group (n=1413) |
|---|---|---|
| Age, mean ± SD, y | 65.7 ± 10.3 | 66.1 ± 10.8 |
| ＜65 | 669 (44.5) | 622 (44.0) |
| ≥ 65 | 833 (55.5) | 791 (56.0) |
| Sex, No. (%) | | |
| Male | 972 (64.7) | 923 (65.3) |
| Female | 530 (35.3) | 490 (34.7) |
| Body-mass index, mean ± SD, kg/m$^2$ | 23.7 ± 2.6 | 23.9 ± 2.7 |
| ＜30 | 1478/1501 (98.5) | 1382/1412 (97.9) |
| ≥ 30 | 23/1501 (1.5) | 30/1412 (2.1) |
| Current smoker, No./total (%) | 503/1489 (33.8) | 464/1403 (33.1) |
| Current drinker, No./total (%) [a] | 301/1489 (20.2) | 289/1402 (20.6) |
| Comorbidities, No./total (%) [b] | | |
| Hypertension | 931 (62.0) | 879 (62.2) |
| Diabetes | 401 (26.7) | 341 (24.1) |
| Previous ischemic stroke [c] | 482/1491 (32.3) | 457/1409 (32.4) |
| Myocardial infarction | 242/1487 (16.3) | 201/1402 (14.3) |
| Atrial fibrillation | 19/1486 (1.3) | 16/1398 (1.1) |
| Hyperlipidemia | 19/1464 (1.3) | 19/1387 (1.4) |
| Previous transient ischemic attack | 7/1493 (0.5) | 5/1401 (0.4) |
| Time from onset to randomization, mean ± SD, h | 19.1 ± 13.1 | 19.8 ± 14.5 |
| ＜24 h | 902 (60.1) | 855 (60.5) |
| ≥ 24 h | 600 (39.9) | 558 (39.5) |
| Blood pressure at randomization | | |
| Systolic blood pressure, mean ± SD, mm Hg | 154.4 ± 21.6 | 154.3 ± 21.9 |
| Systolic blood pressure > 140 mm Hg, No. (%) | 1006 (67.0) | 959 (67.9) |
| Diastolic blood pressure, mean ± SD, mm Hg | 89.6 ± 12.6 | 89.4 ± 12.5 |
| Diastolic blood pressure > 90 mm Hg, No. (%) | 561 (37.4) | 486 (34.4) |
| Blood glucose, mean ± SD, mg/dL | 130.7 ± 59.3 | 129.8 ± 59.8 |
| Blood glucose > 126 mg/dL, No. (%) | 444/1329 (33.4) | 416/1247 (33.4) |
| NIHSS score at randomization, median (IQR) [d] | 5 (4-6) | 5 (4-6) |
| ＜7, No. (%) | 1244 (82.8) | 1153 (81.6) |
| ≥ 7, No. (%) | 258 (17.2) | 260 (18.4) |
| Estimated premorbid function (mRS), No. (%) [e] | | |
| No symptoms (score 0) | 1056 (70.3) | 1016 (71.9) |
| Symptoms without any disability (score 1) | 443 (29.5) | 396 (28.0) |
| Mild disability (score 2) | 3 (0.2) | 1 (0.1) |
| Presumed stroke cause, No./total (%) [f] | | |
| Undetermined cause | 917/1499 (61.2) | 855/1410 (60.6) |
| Small-artery occlusion | 454/1499 (30.3) | 444/1410 (31.5) |

| | | |
|---|---|---|
| Large-artery atherosclerosis | 119/1499 (7.9) | 106/1410 (7.5) |
| Other determined cause | 7/1499 (0.5) | 4/1410 (0.3) |
| Cardioembolic | 2/1499 (0.1) | 2/1410 (0.1) |
| Location of responsible vessel, No./total (%) [g] | | |
| Anterior circulation infarction | 910/1317 (69.1) | 870/1190 (73.1) |
| Posterior circulation infarction | 371/1317 (28.2) | 280/1190 (23.5) |
| Anterior and posterior circulation infarction | 36/1317 (2.7) | 40/1190 (3.4) |
| Degree of responsible vessel stenosis, No./total (%) [g] | | |
| Mild (< 50%) | 249/410 (60.8) | 268/412 (65.1) |
| Moderate (50%-69%) | 81/410 (19.8) | 53/412 (12.9) |
| Severe (70%-99%) | 54/410 (13.2) | 66/412 (15.0) |
| Occlusion (100%) | 26/410 (6.3) | 55/412 (7.0) |
| Previous antiplatelet therapy, No./total (%) | 61/1502 (4.1) | 50/1413 (3.6) |
| Taking aspirin before randomization | 58/1502 (3.9) | 49/1413 (3.5) |
| Taking clopidogrel before randomization | 3/1502 (0.2) | 1/1413 (0.1) |
| Previous lipid-lowering therapy, No./total (%) | 12/1502 (0.2) | 16/1413 (1.1) |
| Time to hospital discharge, mean ± SD, d | 11.4 ± 3.5 | 11.3 ± 3.5 |

Abbreviations: IQR = interquartile range. NIHSS = National Institutes of Health Stroke Scale. mRS = modified Rankin Scale. SD = standard deviation.

[a] Currently drinks alcohol means consuming alcohol at least once a week within one year prior to the onset of stroke.

[b] Comorbidities are based on family or patient report.

[c] Prior ischemic stroke referred only to patients with premorbid mRS ≤ 1.

[d] Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficit. A median NIHSS of 5 means mild-to-moderate neurologic deficit.

[e] Scores on the modified Rankin Scale (mRS) of functional disability range from 0 (no symptoms) to 6 (death).

[f] The presumed stroke cause was classified according to the "Trial of ORG 10172 in Acute Stroke Treatment (TOAST)" using clinical findings, brain imaging, and laboratory tests. Other causes included nonatherosclerotic vasculopathies, hypercoagulable states, and hematologic disorder.

[g] The degree of stenosis was determined by cerebral vessel examination. The diagnosis was based on the clinician's interpretation of the clinical features and examination results at the time of discharge from the hospital.

**Table 2. Efficacy and Safety Outcomes.**

| | Group, No. (%) | | Unadjusted | | | Adjusted [a] | | |
|---|---|---|---|---|---|---|---|---|
| | **Clopidogrel + aspirin group (n=1502)** | **aspirin alone group (n=1413)** | **Treatment Effect Metric** | **Treatment Difference (95% CI)** | ***P* value** | **Treatment Effect Metric** | **Treatment Difference (95% CI)** | ***P* value** |
| **Primary outcome** | | | | | | | | |
| Early neurologic deterioration within 7 d [b, c] | 72 /1502(4.8) | 95/1413 (6.7) | Risk difference | -1.9 (-3.6 to -0.2) | .03 | Risk difference | -1.9 (-3.6 to -0.2) | .03 |
| | | | Risk ratio | 0.71 (0.53 to 0.96) | .03 | Risk ratio | 0.71 (0.53 to 0.96) | .03 |
| **Secondary outcomes** | | | | | | | | |
| mRS score of 0 to 1 within 90 d [c, d] | 1130/1470 (76.9) | 1015/1361 (74.6) | Risk difference | 2.4 (-0.8 to 5.6) | .14 | Risk difference | 2.4 (-0.8 to 5.5) | .14 |
| | | | Risk ratio | 1.10 (0.97 to 1.26) | .16 | Risk ratio | 1.10 (0.97 to 1.26) | .16 |
| mRS score distribution at 90 d [d, e] | | | Odds ratio | 1.10 (0.96 to 1.25) | .19 | Odds ratio | 1.10 (0.96 to 1.26) | .18 |
| Change in NIHSS score at 14 d from baseline, median (IQR) [f] | -0.56 (-0.99 to -0.22) | -0.51 (-1.10 to -0.22) | Geometric mean ratio | 0.00 (-0.05 to 0.04) | .87 | Geometric mean ratio | 0.00 (-0.05 to 0.04) | .89 |
| New stroke within 90 days [g] | 12/1470 (0.8) | 13/1361 (1.0) | Hazard ratio | 0.86 (0.39 to 1.87) | .70 | Hazard ratio | 0.84 (0.39 to 1.85) | .67 |
| Ischemic stroke | 11/1470 (0.7) | 11/1361 (0.8) | | | | | | |
| Hemorrhage stroke | 1/1470 (0.1) | 2/1361 (0.1) | | | | | | |
| Other vascular events or death within 90 d [g] | 16/1470 (1.1) | 12/1361 (0.9) | Hazard ratio | 1.24 (0.59 to 2.61) | .58 | Hazard ratio | 1.24 (0.59 to 2.63) | .57 |
| All-cause death | 16/1471 (1.1) | 12/1361 (0.9) | | | | | | |
| Other vascular events | 0/1471 (0.0) | 3/1361 (0.2) | | | | | | |
| **Safety outcomes** [c] | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Mucocutaneous hemorrhage | 3/1521 (0.2) | 1/1442 (0.1) | Risk difference | 0.1 (-0.1 to 0.4) | .37 | Risk difference | 0.1 (-0.3 to 0.5) | .38 |
| | | | Risk ratio | 2.84 (0.30 to 27.31) | .37 | Risk ratio | 2.78 (0.29 to 26.73) | .38 |
| Organ hemorrhage | 4/1521 (0.3) | 4/1442 (0.3) | Risk difference | 0.0 (-0.4 to 0.4) | .94 | Risk difference | 0.0 (-0.4 to 0.4) | .92 |
| | | | Risk ratio | 0.95 (0.24 to 3.78) | .94 | Risk ratio | 0.93 (0.23 to 3.71) | .92 |
| Intracranial hemorrhage [h] | 1/1521 (0.1) | 2/1442 (0.1) | Risk difference | -0.1 (-0.3 to 0.2) | .54 | Risk difference | -0.1 (-0.3 to 0.2) | .55 |
| | | | Risk ratio | 0.47 (0.04 to 5.22) | .54 | Risk ratio | 0.48 (0.04 to 5.31) | .55 |
| Symptomatic intracranial hemorrhage | 1/1521 (0.1) | 1/1442 (0.1) | | | | | | |
| Asymptomatic intracranial hemorrhage | 0 (0.0) | 1/1442 (0.1) | | | | | | |
| Any bleeding events | 10/1521 (0.7) | 14/1442 (1.0) | Risk difference | -0.3 (-1.0 to 0.3) | .35 | Risk difference | -0.3 (-1.0 to 0.3) | .34 |
| | | | Risk ratio | 0.68 (0.30 to 1.52) | .35 | Risk ratio | 0.67 (0.30 to 1.51) | .34 |
| Adverse events | 132/1521 (8.7) | 138/1442 (9.6) | Risk difference | -0.9 (-3.0 to 1.2) | .40 | Risk difference | -0.9 (-3.0 to 1.2) | .40 |
| | | | Risk ratio | 0.91 (0.72 to 1.14) | .40 | Risk ratio | 0.91 (0.72 to 1.14) | .40 |
| Serious adverse events | 8/1521 (0.5) | 5/1442 (0.3) | Risk difference | 0.2 (-0.3 to 0.7) | .47 | Risk difference | 0.2 (-0.3 to 0.7) | .47 |
| | | | Risk ratio | 1.52 (0.50 to 4.63) | .46 | Risk ratio | 1.50 (0.49 to 4.59) | .47 |

Abbreviations: CI = confidence interval; mRS = modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR = interquartile range.

[a] Adjusted for prespecified prognostic variables (age, sex, NIHSS score at randomization, time from the onset of symptoms to antiplatelet therapy, stroke etiology, history of diabetes and history of hypertension).

[b] Early neurologic deterioration was defined as an increase between baseline and 7 days of ≥ 2 on the NIHSS score, but not as a result of cerebral hemorrhage.

[c] Calculated using a generalized linear model.

[d] mRS scores range 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.

[e] A shift in measures of function according to the full range of scores on the mRS at 90 days was analyzed by ordinal logistic regression and, the P values for the likelihood ratio test 0.20 in the unadjusted analysis and 0.27 in the adjusted analysis.

[f] NIHSS scores range 0–42, with higher scores indicating greater stroke severity. The log (NIHSS+1) was analyzed using a generalized linear model.

[g] Calculated using Cox regression model.

[h] Intracranial hemorrhage will be diagnosed and classified according to the Heidelberg Bleeding Classification. Symptomatic intracranial hemorrhage was defined as new intracranial hemorrhage detected by brain imaging associated with any of the item below: (1) ≥4 points total NIHSS at the time of diagnosis compared to immediately before worsening. Note that a 4 point change is not compared with the baseline admission NIHSS score but instead to the immediate predeterioration neurologic status. (2) ≥2 point in one NIHSS category. (3) Leading to intubation/hemicraniectomy/EVD placement or other major medical/surgical intervention. (4) Absence of alternative explanation for deterioration. A total of three patients were diagnosed with ICH. One patient had asymptomatic intracranial hemorrhage with no NIHSS score change. The other two symptomatic intracranial hemorrhages occurred at Day 11 and Day 87, respectively