Ticagrelor with aspirin dual antiplatelet therapy combined with intravenous thrombolysis in patients with ischaemic stroke in China (TAPIS): a multicentre, double-blind, randomised controlled trial

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Summary

Background Evidence supporting the early addition of antiplatelet therapy to intravenous thrombolysis in patients with acute ischaemic stroke remains inconclusive. We aimed to investigate the efficacy and safety of early oral dual antiplatelet therapy (DAPT), started within 6 h of onset, as an adjunct to intravenous thrombolysis.

Methods TAPIS was a randomised, double-blind, placebo-controlled trial done in 60 hospitals across China. We enrolled patients treated with intravenous thrombolysis for ischaemic stroke, with a National Institutes of Health Stroke Scale score of 4–10. We randomly assigned (1:1) patients to receive oral aspirin plus ticagrelor (DAPT group) or corresponding placebo within 6 h of stroke onset, either before, during, or after receiving thrombolysis. Ticagrelor or placebo was continued for days 2–7 in each group, with open-label aspirin administered for days 2–90. Patients, clinicians, and investigators were masked to the group assignment. The primary efficacy outcome was an excellent functional outcome (modified Rankin Scale score 0–1) at 90 days. The primary safety outcome was symptomatic intracranial haemorrhage within 36 h. This trial was registered with ClinicalTrials.gov (NCT06316570) and is completed.

Findings Between April 3, 2024, and Sept 30, 2025, we randomly assigned 1382 patients to the early DAPT (n=690 [49·9%]) or placebo (n=692 [50·1%]) groups. The median age was 65·6 years (IQR 58·3–72·0), 991 (71·7%) were men, and 391 (28·3%) were women. At 90 days, 474 (68·7%) patients in the early DAPT group and 429 (62·0%) in the placebo group achieved excellent functional outcomes (risk ratio 1·11 [95% CI 1·03–1·20; p=0·0089). Symptomatic intracranial haemorrhage within 36 h occurred in six (0·9%) patients in the early DAPT group versus five (0·7%) in the control group (risk ratio 1·20 [95% CI 0·37–3·93; p=0.76).

Interpretation Among patients treated with intravenous thrombolysis for moderate ischaemic stroke, initiation of oral DAPT within 6 h of onset improved the likelihood of excellent functional outcomes at 90 days. Although no significant between-group difference in symptomatic intracranial haemorrhage was detected, wide CIs precluded exclusion of a small increased risk.

Funding National Natural Science Foundation of China, Capital's Funds for Health Improvement and Research, Noncommunicable Chronic Diseases-National Science and Technology Major Project, Beijing Municipal Science & Technology Commission, and the New Cornerstone Science Foundation.

Published Online May 8, 2026 https://doi.org/10.1016/S0140-6736(26)00757-9

See Online/Comment https://doi.org/10.1016/S0140-6736(26)00820-2

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Introduction

Early recanalisation of occluded arteries substantially improves the prognosis of acute ischaemic stroke. Intravenous thrombolysis is widely recommended as a standard reperfusion therapy for eligible patients with acute ischaemic stroke.[1–4] However, complete recanalisation is achieved in only 14–36% of patients treated with intravenous thrombolysis, and issues such as macrovascular reocclusion and microvascular thrombosis after initial recanalisation remain inadequately resolved.[5–7] Approximately 40–50% of patients treated with intravenous thrombolysis do not achieve excellent functional outcomes.[8,9]

Theoretically, initiating antiplatelet therapy concurrently with or soon after intravenous thrombolysis might inhibit platelet aggregation and prevent re-occlusion of recanalised vessels, and thereby improve functional outcomes. However, the clinical application of antiplatelet therapy is limited by concerns regarding the risk of symptomatic intracranial haemorrhage and uncertain therapeutic efficacy. The ARTIS trial,[10] recognised as the first large-sample randomised trial

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Research in context

Evidence before this study

We searched PubMed for randomised trials published from database inception to March 15, 2026, assessing the efficacy of antiplatelet therapy within 24 h after intravenous thrombolysis in patients with acute ischaemic stroke, using the terms "antiplatelet", "intravenous thrombolysis", and "ischaemic stroke".

Previous randomised trials have reported conflicting findings on the efficacy and safety of intravenous antiplatelet agents as adjunctive therapy to intravenous thrombolysis. The ARTIS trial, among the first large-sample randomised clinical trials assessing the efficacy of intravenous aspirin within 90 min after alteplase treatment, was prematurely terminated because of worse safety outcomes than with alteplase alone. Similarly, the MOST trial showed no clinical benefit of adjunctive intravenous eptifibatide but found increased mortality. By contrast, the ASSET-IT trial suggested that tirofiban use within 60 min after intravenous thrombolysis improved functional outcomes with an acceptable risk of symptomatic intracranial haemorrhage.

Evidence on oral antiplatelet therapy remains scarce. The EAST trial showed safety but no additional benefit of antiplatelet treatment with clopidogrel plus aspirin in patients with mild neurological deficits treated with intravenous thrombolysis. The TREND-IVT trial, designed to investigate whether patients with moderate-to-severe ischaemic stroke benefit from a single loading dose of oral aspirin adjunctive to thrombolysis, is still ongoing. To date, there is a paucity of evidence supporting early oral antiplatelet therapy for patients with stroke treated with intravenous thrombolysis, particularly those with moderate neurological severity.

Added value of this study

The TAPIS trial, a double-blind, randomised controlled trial enrolling 1382 patients with acute ischaemic stroke from 60 sites in China, suggests that in patients with acute ischaemic stroke with a National Institutes of Health Stroke Scale score of 4–10 who received thrombolysis, early initiation (within 6 h of symptom onset) of oral dual antiplatelet therapy with ticagrelor plus aspirin was associated with an improved likelihood of excellent functional outcomes (a modified Rankin Scale score of 0–1) at 90 days. Moreover, no statistically significant difference in the risk of symptomatic intracranial haemorrhage was detected between the early dual antiplatelet therapy group and the placebo control group, with wide CIs that did not rule out a modest increase in risk.

Implications of all the available evidence

The TAPIS trial showed benefits of ticagrelor–aspirin dual antiplatelet therapy within 6 h of onset on functional outcomes in patients with acute ischaemic stroke who received thrombolysis, providing high-quality evidence that might inform clinical decision-making regarding early adjunctive oral antiplatelet therapy in this population.

comparing early addition of intravenous aspirin to intravenous thrombolysis versus intravenous thrombolysis alone, was prematurely terminated because of an excess rate of symptomatic intracranial haemorrhage and a lack of significant clinical benefits. Similarly, the MOST trial[11] showed that adjunctive intravenous eptifibatide failed to reduce post-stroke disability and was associated with increased mortality. By contrast, the ASSET-IT trial[12] showed the efficacy of tirofiban, another type of glycoprotein IIb/IIIa inhibitor, as an adjunct to intravenous thrombolysis, despite a modest increase in the risk of symptomatic intracranial haemorrhage.

Given the inconclusive evidence, the 2026 American Heart Association/American Stroke Association guideline did not support very early use of intravenous aspirin in conjunction with alteplase,[3] and substantial controversy remains regarding early oral antiplatelet therapy in patients with ischaemic stroke who undergo intravenous thrombolysis. The Early Antiplatelet for Minor Stroke following Thrombolysis (EAST) trial[13] confirmed the safety and feasibility of oral dual antiplatelet therapy (DAPT) within 6 h after intravenous thrombolysis in patients with minor stroke, and highlighted the need for an optimised DAPT strategy in patients with moderate-to-severe ischaemic stroke. In the Ticagrelor with Aspirin Dual Antiplatelet Therapy Combined with Intravenous Thrombolysis in Patients with Ischaemic Stroke (TAPIS) trial, we tested the hypothesis that initiation of oral DAPT with ticagrelor plus aspirin within 6 h of symptom onset would improve functional outcomes in patients with acute ischaemic stroke receiving intravenous thrombolysis.

Methods

Study design

TAPIS was a multicentre, randomised, double-blind, parallel-group, placebo-controlled trial done at 60 sites in China and designed to assess the efficacy and safety of early add-on oral DAPT with ticagrelor plus aspirin started within 6 h of ischaemic stroke onset in patients treated with intravenous thrombolysis. The trial was approved by the ethics committees of Beijing Tiantan Hospital (KY2023-200-03) and each participating site. Written informed consent was obtained from the participants or their legally authorised representatives before enrolment. The trial was done in compliance with the Declaration of Helsinki. The trial rationale, design, and methods have been previously published.[14] The full details of committee compositions and participating sites are available in appendix 1 (pp 2–7) and the protocol, including statistical analysis plan, is provided in appendix 2. This trial was reported in accordance with the CONSORT 2025 statements.

Participants

Eligible participants were aged 18–80 years, diagnosed with acute ischaemic stroke, had a National Institutes of Health Stroke Scale (NIHSS) score of 4–10 (range 0–42, with higher scores indicating greater stroke severity before intravenous thrombolysis, with at least one point on any NIHSS limb motor subitem),[15] and had received or intended to receive intravenous thrombolysis with alteplase (0·9 mg/kg, maximum dose 90 mg) or tenecteplase (0·25 mg/kg, maximum dose 25 mg) within 4·5 h of symptom onset (appendix 1 pp 8–9). Randomisation was required to be completed within 6 h of stroke onset (defined as the last-seen-well time). Key exclusion criteria were planned endovascular therapy, pre-existing disability with a score of 2 or higher on the modified Rankin Scale (mRS; ranging from 0 [no symptoms] to 6 [death]),[16] receipt of any antiplatelet therapy after symptom onset, pre-existing atrial fibrillation, or use of anticoagulants. Those with previous antiplatelet use, with new-onset atrial fibrillation, or with unplanned endovascular therapy after randomisation were not excluded and remained in the analyses. Patient sex was indicated from their identity card, recorded as male or female.

Randomisation and masking

The randomisation sequence, in accordance with which the trial medications were packaged, was generated centrally by an independent statistician using a site-stratified, blocked-randomisation method with a fixed size of four. Once a patient was deemed eligible and written informed consent was obtained, the patient was immediately randomly assigned (1:1) to either the early DAPT intervention group or the double placebo control group within 6 h of onset. The trial agents and placebos were identical in size, shape, colour, taste, and appearance; thus, although the randomisation method was publicly available, complete masking of the patient and all trial personnel, as well as strict allocation concealment, were maintained throughout the entire trial.

Procedures

The initial doses of trial medications were administered orally at the time of randomisation within 6 h of symptom onset, before, during, or after intravenous thrombolysis. Patients in the early DAPT group received a loading dose of 180 mg ticagrelor (90 mg/tablet, two tablets) plus 100 mg aspirin (100 mg/tablet, one tablet) on day 1, followed by 90 mg ticagrelor twice daily for days 2–7. Patients in the placebo group received two tablets of ticagrelor placebo and one tablet of aspirin placebo on day 1, followed by matching ticagrelor placebo for days 2–7. All patients in both groups received open-label aspirin 100 mg daily for days 2–90.

Standard care in accordance with the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischaemic Stroke was permitted.[17,18] Rescue antiplatelet therapy, including but not limited to tirofiban, was permitted in cases of neurological deterioration meeting the following prespecified criteria: an increase in NIHSS score of 4 points or more from the lowest post-randomisation value or a return to the neurological status before intravenous thrombolysis, occurring between day 1 and day 7. Otherwise, the use of any other off-protocol antiplatelet agents within 7 days after randomisation was strictly prohibited (appendix 1 pp 10–11).

The steering committee designed and oversaw the conduct of the trial. An independent clinical event adjudication committee, whose members were masked to treatment allocation, adjudicated the mRS score through audio or video recording, as well as symptomatic intracranial haemorrhage through neuroimaging. The progress of the trial was monitored by an independent data and safety monitoring board (DSMB) to safeguard the wellbeing of patients.

Outcomes

The primary efficacy outcome was an excellent functional outcome at 90 days, defined as a score of 0 or 1 on the mRS.[16] Secondary efficacy outcomes were functional independence at 90 days, which was characterised by a score of 0–2 on the mRS; an ordinal distribution of scores on the mRS at 90 days (shift towards lower disability); neurological improvement at 7 days defined as a decrease of 4 points or more in NIHSS score from baseline; quality of life at 90 days assessed by the EQ-5D 5-level questionnaire (EQ-5D-5L; range from –0·391 to 1, with higher scores indicating better quality of life) and the EQ-5D visual analogue scale (EQ-5D-VAS; range from 0 to 100, with higher scores indicating better quality of life); [19] independence in activities of daily living at 90 days defined as a Barthel Index score of 95–100 points (ranging from 0 to 100, with higher scores indicating greater independence function);[20] and recurrent ischaemic stroke within 90 days after randomisation.

The primary safety outcome was symptomatic intracranial haemorrhage within 36 h, defined by the European Cooperative Acute Stroke Study III criteria as the presence of any apparently extravascular blood in the brain or within the cranium associated with an increase in NIHSS score of at least 4 points or death, where the haemorrhage was identified as the predominant cause of neurological deterioration.[9] Secondary safety outcomes were symptomatic intracranial haemorrhage within 7 days; symptomatic intracranial haemorrhage with parenchymal haematoma type 2 within 36 h and 7 days defined by the SITS-MOST criteria; [21] any bleeding events within 90 days according to the GUSTO criteria;[22] and all investigator-reported adverse events and serious adverse events within 90 days.

Statistical analysis

We calculated that 1380 patients (690 in each group) would yield approximately 90% power to detect a

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See **Online** for appendices 1 and 2

9% absolute difference in the proportion of patients with excellent functional outcomes at 90 days after randomisation between treatment groups, assuming the proportion in the control group to be 60% and the overall dropout rate to be 10%.[8] The significance threshold for the final analysis was set at 0·048 with the O'Brien–Fleming α-spending function, accounting for a single interim analysis of the primary efficacy outcome when 60% of patients completed the trial. However, the independent DSMB only reviewed overall incidences of safety endpoints in the interim analysis. Given that 1238 participants had been enrolled by that time, the independent DSMB recommended cancelling the efficacy interim analysis and proceeding with full recruitment and follow-up, and the final significance threshold was reset to 0·05.

The primary efficacy analyses were done in the intention-to-treat population, defined as all randomly assigned patients who completed at least one assessment on the mRS within 90 days after randomisation. We did further supportive efficacy analyses in the per-protocol population. The per-protocol population included participants who completed study treatment without protocol violations, excluding those with failure to comply with inclusion/exclusion criteria, discontinuation of trial treatment, use of prohibited concomitant medications, and loss to 90-day follow-up visit. The safety population included all patients who received at least one dose of trial drug and for whom safety was assessed. Missing primary outcomes were imputed with the last observation carry-forward estimation, with 60-day, 30-day, or 7-day mRS scores used in descending order of data availability. Moreover, deceased patients were analysed using an NIHSS score of 42, an EQ-5D-5L score of –0·391, an EQ-5D-VAS score of 0, and a Barthel Index of 0.

We did unadjusted analyses for both efficacy and safety outcomes. For the primary outcome analysis, effects of early DAPT compared with those of placebo were reported as risk ratios (RRs) with 95% CIs using generalised linear models with a log link and binomial error distribution, along with binary secondary efficacy and safety outcomes. The distribution of scores on the mRS at 90 days was analysed with ordinal logistic regression after verification of the proportional-odds assumption using the score test, with the treatment effect presented as a common odds ratio (OR) with a 95% CI. The median difference (95% CI) of EQ-5D-5L and EQ-5D-VAS scores at 90 days (modelled as continuous variables) was calculated using the Hodges–Lehmann estimation. The Cox proportional hazards model was used to estimate the hazard ratio of the relative time to recurrent ischaemic stroke by treatment assignment, with no violations of the proportional hazard assumption observed.

We did subgroup analyses on the primary outcome on the basis of age (<65 years *vs* ≥65 years), sex, time from onset to randomisation (<240 min *vs* ≥240 min, by median), NIHSS score before intravenous thrombolysis (<6 *vs* ≥6, by median), TOAST classification, thrombolytic agent, history of ischaemic stroke, hypertension, type 2 diabetes, and timing of randomisation. We did two prespecified sensitivity analyses to test the robustness of primary findings. First, the adjusted scores on the mRS were applied, under which scenario any patient receiving prespecified rescue antiplatelet therapy was assigned a score of 5 on their subsequent visits, unless death had occurred. The number of patients who received rescue therapy was further listed by treatment group. Second, we used a mixed-effects model with a random intercept for pooled study sites to account for potential site-level clustering. Before unmasking of treatment groups, sites with fewer than 20 participants were pooled within the same geographical region, ensuring that the pooled sites were of adequate size for statistical analysis. We did additional sensitivity analyses for the primary outcome excluding patients who received off-protocol antiplatelet agents for reasons other than rescue therapy, and imputing missing data using worst-case imputation and multiple imputation.

Secondary outcome analyses and subgroup analyses were not adjusted for multiple comparisons and should not be interpreted as definitive evidence of treatment

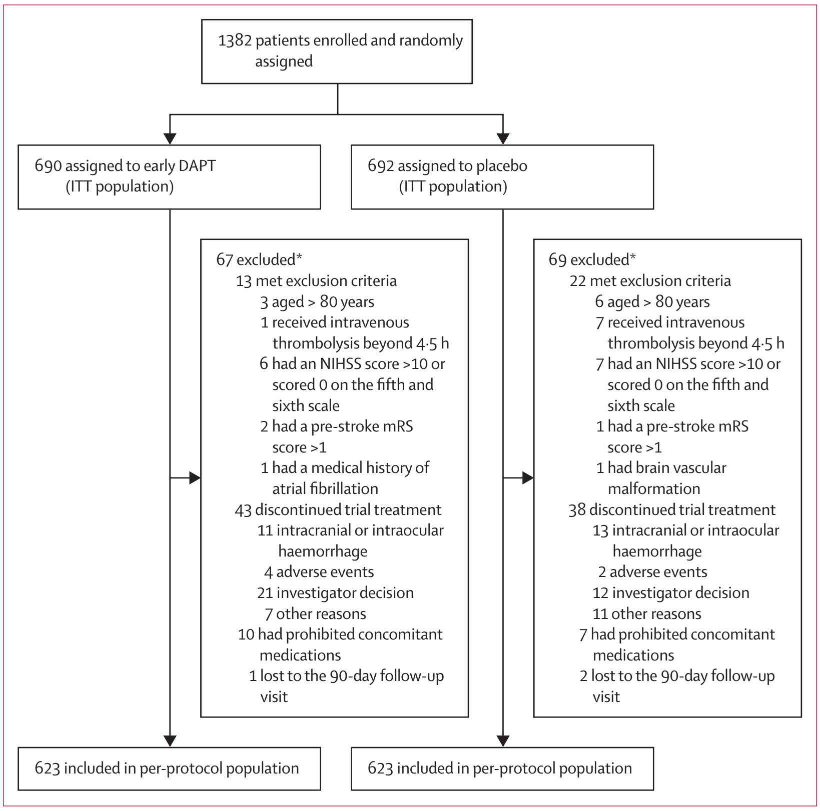

***Figure 1:* Trial profile**
DAPT=dual antiplatelet therapy. ITT=intention to treat. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *A single reason was recorded in screening logs. Some patients might have had multiple reasons for exclusion.

effects. All statistical analyses were done using SAS (version 9.4).

This trial was registered at ClinicalTrials.gov, NCT06316570.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 3, 2024, and Sept 30, 2025, we randomly assigned 1382 patients, with 690 (49·9%) assigned to the early DAPT group and 692 (50·1%) assigned to the placebo group (figure 1) No screening logs were kept. All patients received at least one dose of trial medication and underwent at least one assessment on the mRS within 90 days after randomisation and were thus included in both the intention-to-treat and safety analysis population. The last patient was followed up on Dec 29, 2025, and three (0·2%) did not complete the 90-day follow-up. There were 67 (9·7%) participants in the early DAPT group and 69 (9·7%) participants in the placebo group with protocol violations; these were excluded from the per-protocol analysis.

Baseline demographics and clinical characteristics were well balanced between the two treatment groups (table 1). The median age of the patients was 65·6 years (IQR 58·3–72·0), 991 (71·7%) were men, and 391 (28·3%) were women. The two most common causes of stroke were large-artery atherosclerosis (n=569 [41·2%]) and small-artery occlusion (n=736 [53·3%]). The median time from onset to randomisation was 240 min (IQR 172–297). In the early DAPT group, 113 (16·4%) participants were randomly assigned before, 92 (13·3%) during, and 485 (70·3%) after intravenous thrombolysis. In the placebo group, 107 (15·5%) participants were randomly assigned before, 86 (12·4%) during, and 499 (72·1%) after intravenous thrombolysis. 168 (24·3%) patients in the early DAPT group and 165 (23·8%) patients in the placebo group had a medical history of ischaemic stroke, and the median NIHSS scores before intravenous thrombolysis were 6 (IQR 5–7) in the early DAPT group and 6 (6–8) in the placebo group. The concomitant medications administered during the treatment period are summarised in appendix 1 (pp 12–15). Endovascular therapy was done in 14 (2·0%) patients in the early DAPT group and in 22 (3·2%) patients in the placebo group. 23 (3·3%) participants in the early DAPT and 38 (5·5%) in the placebo group received anticoagulants. 62 (9·0%) patients in the early DAPT group and 97 (14·0%) patients in the placebo group received additional antiplatelet therapy within 7 days after randomisation, including both rescue therapy (50 [7·2%] in the early DAPT group *vs* 81 [11·7%] in the placebo group) and off-protocol antiplatelet use for other indications (appendix 1 pp 12, 23). Despite no restrictions being placed on the type of antiplatelet agent used for rescue therapy in this study, all patients requiring rescue treatment received tirofiban in our study.

	Early DAPT (n=690)	Placebo (n=692)
Age, years	65·1 (57·9–71·9)	66·1 (59·0–72·1)
Sex		
Male	495 (71·7%)	496 (71·7%)
Female	195 (28·3%)	196 (28·3%)
BMI, kg/m²	23·7 (21·9–26·0)	24·1 (22·0–26·6)
Blood pressure, mm Hg		
Systolic	153 (140–166)	153 (140–166)
Diastolic	87 (78–96)	87 (80–96)
Current smoking	237 (34·3%)	238 (34·4%)
Current drinking	121 (17·5%)	99 (14·3%)
Previous antiplatelet therapy*	72 (10·4%)	60 (8·7%)
Medical history		
Ischaemic stroke	168 (24·3%)	165 (23·8%)
Ischaemic heart disease	77 (11·2%)	84 (12·1%)
Type 2 diabetes	159 (23·0%)	159 (23·0%)
Hypertension	420 (60·9%)	412 (59·5%)
mRS score before stroke onset		
0	625 (90·6%)	631 (91·2%)
1	63 (9·1%)	60 (8·7%)
2	2 (0·3%)	1 (0·1%)
NIHSS score before intravenous thrombolysis	6 (5–7)	6 (6–8)
Thrombolytic agents		
Alteplase	340 (49·3%)	321 (46·4%)
Tenecteplase	350 (50·7%)	371 (53·6%)
TOAST classification		
Large-artery atherosclerosis	284 (41·2%)	285 (41·2%)
Cardioembolic	5 (0·7%)	5 (0·7%)
Small-artery occlusion	370 (53·6%)	366 (52·9%)
Other determined cause	13 (1·9%)	10 (1·4%)
Undetermined cause	18 (2·6%)	26 (3·8%)
Time from onset to randomisation, min†	240 (172–292)	240 (171–300)
Time from onset to intravenous thrombolysis initiation, min	156 (112–210)	155 (110–209)
Time from intravenous thrombolysis initiation to randomisation, min	65 (16–112)	66 (17–111)
Timing of randomisation		
Before intravenous thrombolysis	113 (16·4%)	107 (15·5%)
During intravenous thrombolysis	92 (13·3%)	86 (12·4%)
After intravenous thrombolysis	485 (70·3%)	499 (72·1%)

Data are n (%) or median (IQR). Percentages might not total 100 because of rounding. DAPT=dual antiplatelet therapy. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *Previous antiplatelet therapy within 1 month before this onset. †The first dose of study medication was administered at the time of randomisation; therefore, time from onset to randomisation equals time from onset to study drug administration.

Table 1: **Baseline characteristics**

	Early DAPT (n=690)	Placebo (n=692)	Effect size (95% CI)*	p value
Primary efficacy outcome				
mRS score 0–1 at 90 days	474/690 (68·7%)	429/692 (62·0%)	1·11 (1·03–1·20)	0·0089
Secondary efficacy outcomes				
mRS score 0–2 at 90 days	550/690 (79·7%)	517/692 (74·7%)	1·07 (1·01–1·13)	0·027
Ordinal mRS score at 90 days†	..	..	1·24 (1·02–1·50)	0·029
0	222/690 (32·2%)	204/692 (29·5%)	..	..
1	252/690 (36·5%)	225/692 (32·5%)	..	..
2	76/690 (11·0%)	88/692 (12·7%)	..	..
3	87/690 (12·6%)	106/692 (15·3%)	..	..
4	23/690 (3·3%)	38/692 (5·5%)	..	..
5	11/690 (1·6%)	8/692 (1·2%)	..	..
6	19/690 (2·8%)	23/692 (3·3%)	..	..
NIHSS score decreasing by ≥4 points at 7 days from baseline	400/690 (58·0%)	377/692 (54·5%)	1·06 (0·97–1·17)	0·19
EQ-5D-VAS score at 90 days‡	90 (78–95)	88 (70–95)	1·00 (0·00–2·00)	0·024
EQ-5D-5L score at 90 days‡	1·0 (0·9–1·0)	1·0 (0·8–1·0)	0·00 (0·00–0·00)	0·056
Barthel Index 95–100 at 90 days§	553/689 (80·3%)	514/690 (74·5%)	1·08 (1·02–1·14)	0·011
Recurrence of ischaemic stroke within 90 days¶	27/690 (3·9%)	24/692 (3·5%)	1·17 (0·67–2·05)	0·57
Safety outcomes				
Symptomatic intracranial haemorrhage within 36 h‖	6/690 (0·9%)	5/692 (0·7%)	1·20 (0·37–3·93)	0·76
Symptomatic intracranial haemorrhage within 7 days‖	7/690 (1·0%)	6/692 (0·9%)	1·17 (0·39–3·47)	0·78
Symptomatic intracranial haemorrhage with parenchymal haematoma type 2 within 36 h**	6/690 (0·9%)	5/692 (0·7%)	1·20 (0·37–3·93)	0·76
Symptomatic intracranial haemorrhage with parenchymal haematoma type 2 within 7 days**	6/690 (0·9%)	6/692 (0·9%)	1·00 (0·32–3·10)	>0·99
Any bleeding within 90 days††	50/690 (7·2%)	42/692 (6·1%)	1·19 (0·80–1·78)	0·38
Minor	37/690 (5·4%)	33/692 (4·8%)	..	..
Moderate	2/690 (0·3%)	0/692 (0·0%)	..	..
Severe or life-threatening	11/690 (1·6%)	9/692 (1·3%)	..	..
Adverse events within 90 days	109/690 (15·8%)	103/692 (14·9%)	1·06 (0·83–1·36)	0·64
Serious adverse events within 90 days	48/690 (7·0%)	48/692 (6·9%)	1·00 (0·68–1·48)	0·99

Data are n/N (%) or median (IQR), unless otherwise indicated. DAPT=dual antiplatelet therapy. EQ-5D-5L=EuroQoL Group 5-Dimension 5-Level Self-Report Questionnaire. EQ-5D-VAS=EQ-5D Visual Analogue Scale. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *The effect size is a risk ratio unless otherwise indicated. The widths of CIs for difference or risks for secondary outcomes were not adjusted for multiple comparisons, so no conclusions can be drawn from these data. †The common odds ratio (95% CI) is provided for ordinal score on the mRS at 90 days. ‡The median difference (95% CI) is provided for EQ-5D-VAS and EQ-5D-5L scores at 90 days. Data on the EQ-5D-VAS and EQ-5D-5L scores at 90 days were missing for three patients (one in the early DAPT group and two in the placebo group). §Data on the Barthel Index at 90 days were missing for three patients (one in the early DAPT group and two in the placebo group). ¶The hazard ratio (95% CI) is provided for recurrence of ischaemic stroke within 90 days. ‖Symptomatic intracranial haemorrhage was defined according to the ECASS-III criteria. **Symptomatic intracranial haemorrhage with parenchymal hematoma type 2 was defined by the SITS-MOST criteria. ††A bleeding event was defined according to the GUSTO criteria.

Table 2: **Efficacy and safety outcomes in the intention-to-treat population**

For the primary outcome, excellent functional outcomes (scores of 0 or 1 on the mRS) at 90 days were reported for 474 (68·7%) of 690 patients in the early DAPT group and 429 (62·0%) of 692 patients in the placebo group in the intention-to-treat population (RR 1·11 [95% CI 1·03–1·20]; p=0·0089; table 2).

Regarding secondary outcomes, 550 (79·7%) patients in the early DAPT group and 517 (74·7%) patients in the placebo group had an mRS score of 0–2 at 90 days (RR 1·07 [95% CI 1·01–1·13]; p=0·027). The ordinal distribution of scores on the mRS at 90 days is shown in figure 2. The common OR (95% CI) of early DAPT compared with placebo for a favourable shift towards lower disability on the mRS at 90 days was 1·24 (95% CI 1·02–1·50]; p=0·029), with the odds proportionality assumption satisfied (p=0·44). 553 (80·3%) patients in the early DAPT group and 514 (74·5%) patients in the placebo group had a Barthel index of 95–100 at 90 days (RR 1·08 [1·02–1·14]; p=0·011). All other secondary efficacy outcomes are reported in table 2. The results of the per-protocol analysis were consistent with those of the intention-to-treat analysis, with an RR of 1·10 (1·02–1·19; p=0·016) for the primary efficacy outcome (appendix 1 pp 16–19, 31).

No significant between-group difference was detected in the risk of symptomatic intracranial haemorrhage (table 2). Specifically, the primary safety outcome of symptomatic intracranial haemorrhage within 36 h, as defined by the ECASS-III criteria, occurred in six (0·9%) patients in the early DAPT group and five (0·7%) patients in the control group (RR 1·20 [95% CI 0·37–3·93]; p=0·76). 50 (7·2%) patients in the early DAPT group and 42 (6·1%) in the placebo group had any bleeding according to the GUSTO criteria (RR 1·19 [0·80–1·78]; p=0·38). Adverse events within 90 days were reported in 109 (15·8%) patients in the early DAPT group and 103 (14·9%) patients in the placebo group; serious adverse events were reported in 48 (7·0%) patients in the early DAPT group and 48 (6·9%) in the placebo group (RR 1·00 [0·68–1·48]; p=0·99; appendix 1 pp 20–22).

In subgroup analyses, we found no evidence for effect modification (figure 3). 50 (7·2%) patients in the early DAPT group and 81 (11·7%) patients in the placebo group received rescue antiplatelet therapy within 7 days after randomisation. The results of sensitivity analyses done using mRS scores adjusted by rescue therapy use were consistent with the primary findings for excellent functional outcomes at 90 days (RR 1·15 [95% CI 1·06–1·25]; p=0·0008; appendix 1 pp 23–24). Furthermore, multivariable analyses that incorporated a mixed-effects term for pooled study sites yielded a similar RR of 1·11 (1·02–1·19; p=0·010) for the primary efficacy outcome (appendix 1 pp 25–29). Findings from additional sensitivity analyses were also consistent with the primary results (appendix 1 pp 30).

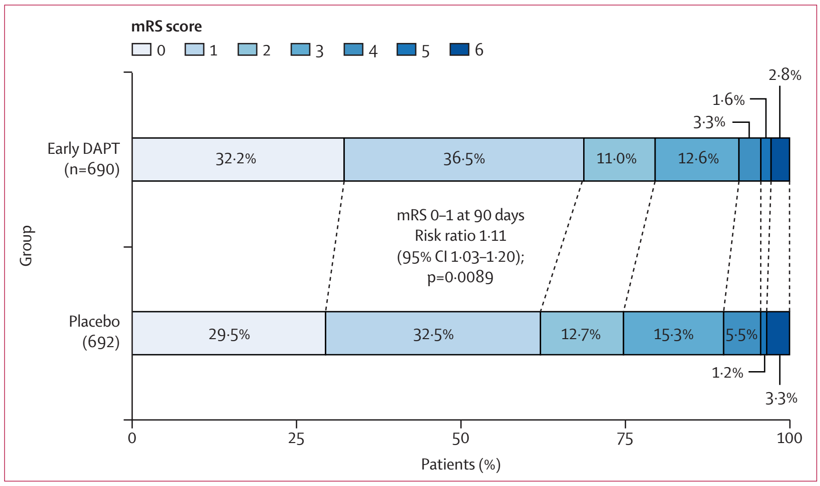

Figure 2: **Distribution of mRS scores at 90 days in the intention-to-treat population**
DAPT=dual antiplatelet therapy. mRS=modified Rankin Scale. Percentages might not amount to 100% because of rounding.

Discussion

In this trial of patients with acute ischaemic stroke who underwent intravenous thrombolysis within the conventional therapeutic time window of 4·5 h, a greater percentage of patients in the early DAPT group, who received oral ticagrelor plus aspirin within 6 h of symptom onset (before, during, or after intravenous thrombolysis), had an excellent functional outcome (defined as a score of 0 or 1 on the mRS) at 90 days than those in the placebo group (68·7% *vs* 62·0%). Symptomatic intracranial haemorrhage within 36 h was rare in both treatment groups, although the wide CIs necessitate cautious interpretation regarding a potential modest increased risk.

Although several studies before the TAPIS trial explored the efficacy and safety of antiplatelet agents as early adjunctive therapy for intravenous thrombolysis, findings regarding early initiation of antiplatelet therapy remain unclear.[10–12,23] By contrast with the ARTIS trial and the MOST trial, which did not show efficacy of intravenous aspirin and eptifibatide as adjunctive therapy to intravenous thrombolysis,[10,11] the ASSET-IT trial showed that early tirofiban administration within 1 h after intravenous thrombolysis completion was associated with improved functional outcome at 90 days among patients with moderate stroke deficits who might have less injured tissue at risk for haemorrhagic transformation than those with more severe stroke.[12]

Compared with intravenous agents, oral antiplatelet agents offer superior administration convenience in most clinical settings; however, most previous clinical trials have focused on injectable antiplatelet agents and evidence on early oral antiplatelet therapy in this setting is rather scare. The EAST trial, done in patients with minor ischaemic stroke, first showed that early oral administration of clopidogrel plus aspirin following intravenous thrombolysis was safe but failed to improve excellent functional outcomes at 90 days. In addition to the ceiling effect attributable to mild baseline neurological deficits (median NIHSS score of 3),[24] we hypothesised that the chosen DAPT strategy might also contribute to the neutral findings observed in the EAST trial. The high prevalence of *CYP2C19* loss-of-function alleles among Asian patients partially attenuated the antiplatelet efficacy of clopidogrel used in the EAST trial.[25] Moreover, the single loading dose of clopidogrel plus aspirin administered within 6 h after intravenous thrombolysis might also have been insufficient to enhance long-term functional outcomes.

By contrast, in our trial, we used a different DAPT regimen comprising ticagrelor and aspirin. Unlike clopidogrel, ticagrelor directly blocks platelet $P2Y_{12}$ receptors without the need for metabolic activation, theoretically conferring more potent inhibition of platelet aggregation. Furthermore, the DAPT duration in the TAPIS trial was set to 7 days to balance the ischaemic benefit against the risk of haemorrhage.[26] Eligible patients in our trial had an NIHSS score of 4–10 (with a median score of 6 in the randomly assigned participants); we further excluded patients with a history of atrial fibrillation because such patients would typically be managed with anticoagulation therapy. These eligibility criteria contributed to a substantially lower proportion of patients with cardioembolic stroke than the general stroke population, who were at increased risk of symptomatic intracranial haemorrhage. Therefore, although no post-intravenous thrombolysis imaging was requested before the initiation of DAPT, symptomatic intracranial haemorrhage events were rare in our trial.

	Early DAPT group	Placebo group	Risk ratio (95%CI)	$p_{interaction}$
Age (years)				
<65	261/342 (76·3%)	209/321 (65·1%)	1·17 (1·06–1·29)	0·11
≥65	213/348 (61·2%)	220/371 (59·3%)	1·03 (0·92–1·16)	
Sex				
Female	134/195 (68·7%)	113/196 (57·7%)	1·19 (1·02–1·39)	0·26
Male	340/495 (68·7%)	316/496 (63·7%)	1·08 (0·99–1·18)	
Time from onset to randomisation (min)				
<240	239/332 (72·0%)	227/335 (67·8%)	1·06 (0·96–1·17)	0·26
≥240	235/358 (65·6%)	202/357 (56·6%)	1·16 (1·03–1·31)	
NIHSS score before intravenous thrombolysis				
<6	133/174 (76·4%)	115/163 (70·6%)	1·08 (0·95–1·23)	0·74
≥6	341/516 (66·1%)	314/529 (59·4%)	1·11 (1·01–1·22)	
TOAST classification				
Large-artery atherosclerosis	185/284 (65·1%)	168/285 (58·9%)	1·11 (0·97–1·26)	0·84
Small-artery occlusion	268/370 (72·4%)	237/366 (64·8%)	1·12 (1·01–1·23)	
Others	21/36 (58·3%)	24/41 (58·5%)	1·00 (0·68–1·45)	
Thrombolytic agent				
Alteplase	233/340 (68·5%)	195/321 (60·7%)	1·13 (1·01–1·26)	0·68
Tenecteplase	241/350 (68·9%)	234/371 (63·1%)	1·09 (0·98–1·21)	
History of ischaemic stroke				
No	372/522 (71·3%)	339/527 (64·3%)	1·11 (1·02–1·20)	0·96
Yes	102/168 (60·7%)	90/165 (54·5%)	1·11 (0·93–1·34)	
Type 2 diabetes				
No	376/531 (70·8%)	340/533 (63·8%)	1·11 (1·02–1·21)	0·94
Yes	98/159 (61·6%)	89/159 (56·0%)	1·10 (0·92–1·32)	
Hypertension				
No	191/270 (70·7%)	189/280 (67·5%)	1·05 (0·94–1·17)	0·21
Yes	283/420 (67·4%)	240/412 (58·3%)	1·16 (1·04–1·29)	
Timing of randomisation				
Before intravenous thrombolysis	80/113 (70·8%)	77/107 (72·0%)	0·98 (0·83–1·16)	0·33
During intravenous thrombolysis	63/92 (68·5%)	53/86 (61·6%)	1·11 (0·89–1·38)	
After intravenous thrombolysis	331/485 (68·2%)	299/499 (59·9%)	1·14 (1·04–1·25)	
Overall	**474/690 (68·7%)**	**429/692 (62·0%)**	**1·11 (1·03–1·20)**	

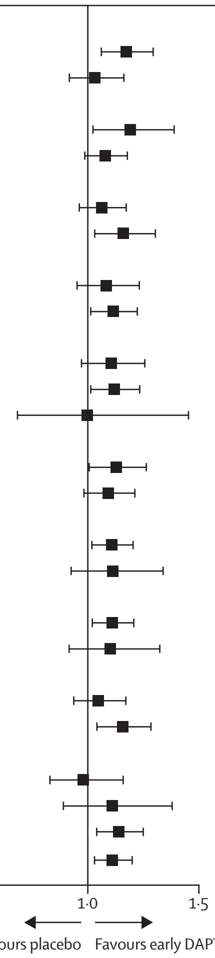

Figure 3: **Subgroup analysis of the primary efficacy outcome in the intention-to-treat population**
Data are n/N (%), unless otherwise indicated. Comparisons are unadjusted for multiplicity. Effect sizes are shown by prespecified subgroups. DAPT=dual antiplatelet therapy. NIHSS=National Institutes of Health Stroke Scale.

Collectively, the moderate severity of ischaemic stroke of the target population and the moderate duration of oral DAPT with ticagrelor and aspirin might have contributed to the positive findings in the TAPIS trial. Nevertheless, these findings should be interpreted within the context of previous trials showing neutral or negative results, given the interstudy heterogeneity probably reflects variations in patient enrolment criteria, stroke pathophysiology, and therapeutic protocols. For example, the neutral or negative results of previous trials might be explained, at least in part, by differences in stroke severity. The patients with higher median NIHSS scores in the ARTIS trial and the MOST trial might have contributed to an increased risk of haemorrhagic transformation, potentially offsetting benefits from early antiplatelet therapy. Conversely, a ceiling effect in the EAST trial enrolling patients with mild stroke might have obscured the ability to detect a treatment benefit. By contrast, the ASSET-IT trial, which showed benefit with early tirofiban, enrolled patients with moderate stroke deficits. Similarly, the TAPIS trial also targeted patients with moderate neurological severity. Taken together, there might be a range of stroke severity where early adjunctive antiplatelet therapy provides the greatest net benefit. Moreover, although the antiplatelet effects of ticagrelor and aspirin provide a biological rationale for preventing post-thrombolysis re-occlusion, we did not perform systematic vascular imaging after thrombolysis and could not directly assess whether the improved functional outcomes were mediated by reduced re-occlusion. Thus, the positive finding in TAPIS should not be viewed as definitive proof of treatment benefit across all settings but rather as a contribution to the evolving evidence base. The ongoing TREND-IVT trial (NCT06548971) might further clarify whether patients with moderate-to-severe ischaemic stroke receiving intravenous thrombolysis could benefit from a single loading dose of oral aspirin, an issue not addressed in the present trial.

 www.thelancet.com Published online May 8, 2026 https://doi.org/10.1016/S0140-6736(26)00757-9

The high proportion of male patients included in our trial was consistent with the epidemiological profile of ischaemic stroke in China.[8,27,28] Although subgroup analyses suggested a numerically larger treatment benefit in female than in male patients, no significant interaction was observed. Likewise, interaction tests for other prespecified subgroups were also not statistically significant, with CIs for effect estimates crossing unity in several subgroups. Because the subgroup analyses were exploratory, unadjusted for multiple comparisons, and limited by small sample sizes in some subgroups, these findings should be interpreted cautiously. Further studies specifically powered to assess treatment effects in key subpopulations are warranted to confirm the consistency of early DAPT benefits.

In addition to better functional outcomes defined by the mRS, we also observed suggestive improvements in independence in activities of daily living and EQ-5D-VAS score at 90 days, whereas no significant differences were observed in other secondary efficacy endpoints. These findings suggest the potentially increased efficacy of early DAPT on the overall subjective quality of life, although these findings should be interpreted as hypothesis-generating rather than as definitive evidence of treatment effects. Notably, although death was recorded as part of safety outcomes, this outcome was not assessed as a separate secondary efficacy outcome in our trial, given the low mortality among patients with mild-to-moderate stroke, which provided insufficient statistical power to draw firm conclusions. Moreover, a somewhat large proportion of patients received antiplatelet agents (including rescue antiplatelet therapy), anticoagulants, or endovascular therapy in the placebo group, which to some extent attenuated the efficacy of early DAPT with ticagrelor and aspirin because the placebo group might receive more active intervention for neurological deterioration than the early DAPT group. Nonetheless, the benefits of early antiplatelet therapy were still significant despite this treatment imbalance, and further benefits were observed in the prespecified sensitivity analyses using the modified functional outcomes adjusted for rescue antiplatelet therapy use.

The TAPIS trial has several limitations. First, this study was done exclusively in China, where approximately 60% of patients carry *CYP2C19* loss-of-function alleles, which might have contributed to the benefits from early DAPT with ticagrelor and aspirin. Moreover, the distribution of stroke mechanisms in our trial, predominantly large-artery atherosclerosis and small-artery occlusion, reflects the high burden of intracranial atherosclerotic disease in east Asian populations and might partially account for the observed treatment benefit, given that DAPT is especially effective against platelet-mediated thrombosis in atherosclerotic disease. Our findings therefore cannot necessarily be generalised to populations with a higher proportion of cardioembolic stroke or to patients with acute ischaemic stroke of other racial backgrounds with distinct genetic profiles. Additionally, some important subpopulations were excluded, such as those with more severe stroke, and those who planned to receive endovascular therapy. Further confirmatory clinical trials across diverse settings are warranted to validate the generalisability of these findings. Moreover, the rate of protocol violation in our trial was approximately 10%, which might introduce potential bias. Although the consistency between the per-protocol analyses and the intention-to-treat analyses indicated minimal effect, the presence of protocol violation still should be considered when interpreting the results.

In this trial involving Chinese patients with moderate stroke deficits (NIHSS score of 4–10) who were treated with intravenous thrombolysis within 4·5 h of symptom onset and who were not scheduled to receive endovascular therapy, early initiation of oral DAPT with ticagrelor plus aspirin within 6 h of onset was associated with an increased incidence of excellent functional outcomes at 90 days. The overall risk of symptomatic intracranial haemorrhage was low in each treatment group, although cautious interpretation is warranted because of limited statistical precision.

Contributors

YW and AW proposed the study conception and study design. PMB and GT supervised the study design. AW, XX, YT, FZ, and XH prepared the first draft of the report. PMB, GT, and YW provided essential revisions, and all coauthors reviewed and revised the Article. YT, FZ, XH, JW, YS, FC, YB, YH, WJ, JHa, JHe, HY, SC, WW, YL, HD, CY, ZS, LL, and YC were involved in trial conduct, patient management, and data collection. XX, JL, and XZ supported data management, prepared the statistical analysis plan, and conducted statistical analyses. YW, AW, XX, YT, FZ, and XH accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and the corresponding authors (YW and AW) had the final responsibility to submit the publication.

Declaration of interests

YW reports grants from the National Natural Science Foundation of China, the Noncommunicable Chronic Diseases-National Science and Technology Major Project, the Beijing Municipal Science & Technology Commission, and the New Cornerstone Science Foundation. AW reports a grant from the Capital's Funds for Health Improvement and Research. PMB reports grants or contracts from the National Institute for Health and Care Research Health Technology Assessment programme and the British Heart Foundation; consulting fees from CoMind and DiaMedica; stock or stock options in CoMind and DiaMedica; membership of the data safety monitoring board for the AVERT Dose and ECS'T-2 trials; serving as co-chair of the Industry Roundtable at the World Stroke Organization; and receipt of device support from Phagenesis for the PhEAST trial. All other authors declare no competing interests.

Data sharing

De-identified individual participant data can be available on reasonable request to the corresponding authors YW or AW and after signing appropriate data sharing agreements. Such requests must be approved by the respective ethics boards and appropriate data custodians.

Acknowledgments

This trial was supported by grants from the National Natural Science Foundation of China (82425101), the Capital's Funds for Health Improvement and Research (CFH2024-2-2045), the Noncommunicable Chronic Diseases-National Science and Technology Major Project (2023ZD0504800, 2023ZD0504801, 2023ZD0504802, 2023ZD0504803, and 2023ZD0504804), the Beijing Municipal Science & Technology

Commission (Z231100004823036), and the New Cornerstone Science Foundation. We sincerely acknowledge the CSPC Pharmaceutical Group, which provided aspirin, ticagrelor, and their placebo at no cost and with no restrictions. We also thank all the patients and their relatives who participated in the TAPIS study.

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