Thrombolysis with Tenecteplase for Minor Disabling Stroke: Secondary Analysis of the TEMPO-2 Randomized Clinical Trial

Yiran Zhang MD[1,2], Brian H Buck MD[1,2], Philip A Barber MD[3], Prof Kausik Chatterjee MD[4], Brian Clarke MRCPI[5], Philip M C Choi MBChB[6,7], Gary Hunter MD[8], Aravind Ganesh MD[3,9,10,11], Sachin M Mishra MD[1], Prof David Williams PhD[12], Prof Bruce C V Campbell PhD[13], Prof Dar Dowlatshahi MD[14,15], Prof Ken S Butcher PhD[16], Kailash Krishnan PhD[17], M Ivan Wiggam MD[18], Prof Timothy J Kleinig MD[19,20], Prof Keith W Muir MD[21], Charlotte Zerna PhD[3,22], Thalia S Field MD[23], Prof Mayank Goyal MD[3,10,24], Amy Y X Yu MD[25], Prof Christine Roffe MD[26], Prof Andrew M Demchuck MD[3,9,10,24,27], Prof Mark W Parsons PhD[28,29], Prof Rodrigo Bazan MD[30], Sandeep Ankolekar FRCP[31], James Kennedy MSc[32], Prof Bijoy K Menon MD[3,9,10,24,27], Jennifer L Mandzia MD[33], Arthur Pille MD[34], Prof Peter J Kelly MD[35], Martha Marko MD[36], Nishita Singh MD[37], Shabnam Vatanpour PhD[3], Fabrico O Lima PhD[38], Luciana Catanese PhD[39], MacKenzie Horn BSc[3], Darshan Ghia FRACP[40,41], Julia Ferrari MD[42], Prof Stefen Greisenegger MD[36], Prof Michael D Hill MD[3,9,10,24,27], Prof Shelagh B Coutts MD[3,9,10,24 *] for the TEMPO-2 Investigators†

[1] Division of Neurology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

[2] Neuroscience and Mental Health Institute, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

[3] Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[4] Countess of Chester Hospital NHS Foundation Trust, Chester, UK

[5] St George's University Hospitals, London, UK

[6] Department of Neuroscience, Box Hill Hospital, Eastern Health, Melbourne, VIC, Australia

[7] Eastern Health Clinical School, Monash University, Melbourne, VIC, Australia

[8] University of Saskatchewan, Saskatoon, SK, Canada

[9] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[10] Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[11] the O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[12] RCSI University of Medicine and Health Sciences and Beaumont Hospital, Dublin, Ireland

[13] Department of Medicine and Neurology, Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia

[14] Department of Medicine, University of Ottawa, Ottawa, ON, Canada

[15] Ottawa Hospital Research Institute, Ottawa Hospital, Ottawa, ON Canada

[16] School of Clinical Medicine, University of New South Wales, NSW, Australia

[17] Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK

[18] Royal Victoria Hospital, Belfast, UK

[19] Department of Neurology, Royal Adelaide Hospital, Adelaide, SA, Australia

[20] Department of Medicine, University of Adelaide, Adelaide, SA, Australia

[21] School of Neuroscience and Psychology, University of Glasgow, Glasgow, UK

[22] Städtisches Klinikum Dresden, Dresden, Germany

[23] Vancouver Stroke Program, Division of Neurology, University of British Columbia, Vancouver, BC, Canada

[24] Department of Radiology, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[25] Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

[26] Stroke Research, Keele University, Stoke-on-Trent, UK

[27] Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[28] Department of Neurology, Liverpool Hospital, University of New South Wales South Western Sydney Clinical School, Liverpool, NSW, Australia

[29] Ingham Institute of Applied Medical Research, Liverpool, NSW, Australia

[30] Botucatu Medical School, São Paulo State University, San Paulo, Brazil

[31] Department of Neurology, King's College Hospital London, UK

[32] Acute Multidisciplinary Imaging & Interventional Centre, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[33] Department of Clinical Neurological Sciences, Western University, London, ON, Canada

[34] Neurology Department, Hospital Moinhos de Vento, Porto Alegre, Brazil

[35] School of Medicine University College Dublin-Mater University Hospital Dublin, Dublin, Ireland

[36] Department of Neurology, Medical University of Vienna, Vienna, Austria

[37] Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

[38] Stroke Unit, Hospital Geral De Fortaleza, Fortaleza-ce, Brazil

[39] McMaster University, Population Health Research Institute, Hamilton, ON, Canada

[40] Fiona Stanley Hospital, Murdoch, WA, Australia

[41] University of Western Australia, Perth, WA, Australia

[42] Department of Neurology, St John's of God Hospital Vienna, Vienna, Austria

* Correspondence to: Prof Shelagh Coutts, Department of Clinical Neurosciences, University of Calgary, Calgary, AB T2N 2T9, Canada

Email: scoutts@ucalgary.ca

Phone: +1 (403) 944-1594

† TEMPO-2 investigators are listed in the appendix

Date of the Revision: Jul 17, 2025

Word Count (Main text): 2980 (Max 3000)

Word Count (Abstract): 347 (Max 350)

Figures & Tables: 2 Figures, 3 Tables

Running Title: TEMPO-2 Disabling Stroke

Keywords: Stroke, Intravenous Thrombolysis, Minor Disabling Stroke, Tenecteplase, Intracranial Occlusion

Key Points

Question

Did outcomes following intravenous tenecteplase for minor ischemic stroke vary based on the presence of disabling deficits?

Findings

In this secondary analysis of the TEMPO-2 trial including 884 patients with minor ischemic stroke and proven intracranial occlusion, both patients with and without disabling deficits defined according to National Institutes of Health Stroke Scale (NIHSS)-based criteria showed a neutral treatment effect from intravenous tenecteplase, with no significant effect modification.

Meaning

Current definitions of disabling stroke did not modify the neutral treatment effect of intravenous tenecteplase in patients with minor stroke and intracranial occlusion.

Abstract

Importance

Outcomes following intravenous thrombolysis for minor ischemic stroke may vary based on the presence of disabling deficits.

Objective

To determine whether intravenous tenecteplase improves outcomes according to National Institutes of Health Stroke Scale score (NIHSS)-based definitions of pre-treatment disabling deficits.

Design

Secondary analysis of the tenecteplase versus standard of care for minor ischemic stroke with proven occlusion (TEMPO-2) trial, conducted between April 27, 2015 and January 19, 2024. Patients were followed up for 90 days.

Setting

Conducted across 48 sites globally.

Participants

Among 886 enrolled patients with minor ischemic stroke (NIHSS 0-5) and proven intracranial occlusion within 12 h of onset, 2 withdrew consent and 884 were included in the secondary analysis. Patients were divided into having non-disabling versus disabling syndromes at presentation as per the TREAT Task Force consensus. Other established definitions of disabling stroke from ARAMIS and NINDS were explored.

Interventions

Intravenous tenecteplase (0.25 mg/kg) vs non-thrombolytic standard of care.

Main Outcomes and Measures

The primary outcome was a return to baseline modified Rankin scale at 90 days.

Results

Among 884 patients (369 women [41.7%], median age [IQR] 72 [61-80]), 100 (11.3%) had disabling and 784 (88.7%) had non-disabling deficits. Patients with disabling deficits had higher baseline NIHSS scores (median [IQR], 4 [3-5] vs 2 [1-3]), later presentations (288 [153-412] min vs 133 [70-310] min) and longer onset to treatment time (411 [307-560] min vs 278 [170-462] min). In the disabling group, the primary outcome following tenecteplase, compared with standard of care, occurred in 29 [54.7%] vs 32 [68.1%] (adjusted risk ratio [aRR], 0.81; 95% CI, 0.60-1.10). This neutral treatment effect was consistent in patients without disabling deficits (280 [73.9%] vs 306 [75.6%]; aRR, 0.98; 95% CI, 0.91-1.07; *P* for interaction .32).

Conclusions and Relevance

Current definitions of disabling symptoms based on NIHSS score at baseline did not modify the neutral treatment effect of intravenous tenecteplase in patients with minor stroke and intracranial occlusion. Together with converging evidence comparing intravenous thrombolysis to non-thrombolytic standard of care, this analysis suggests the need to re-evaluate thrombolysis in minor disabling stroke

Trial Registration

ClinicalTrials.gov Identifier: NCT02398656

Introduction

In acute ischemic stroke, minor deficits at presentation, defined as a National Institutes of Health Stroke Scale (NIHSS) score of ≤5, are common and by 90 days will leave one third of these patients disabled and/or dead.[1,2] However, evidence in support of acute revascularization with intravenous thrombolysis in these patients has remained inconclusive and heterogeneous.

Evidence for treating minor stroke with disabling deficits is indirect and comes from the pivotal pooled meta-analysis of nine randomized trials comparing alteplase versus placebo or open control.[3] Subsequently, trials were designed specifically to evaluate thrombolysis in minor ischemic stroke without disabling deficits. The Potential of Rt-PA for Ischemic Strokes with Mild Symptoms (PRISMS) trial was halted prematurely but showed no benefit of intravenous alteplase over aspirin among patients with minor nondisabling stroke presenting within 3 hours after onset;[4] the Antiplatelet vs R-tPA for Acute Mild Ischemic Stroke (ARAMIS) trial demonstrated non-inferiority of aspirin plus clopidogrel over intravenous alteplase initiated within 4·5 hours.[5] The tenet that alteplase treatment is beneficial in minor stroke based on disability is reflected in multiple current guidelines.[6–9] For example, in the American Heart Association/American Stroke Association (AHA/ASA) guidelines, for minor but disabling stroke, intravenous thrombolysis is recommended within 3 hours (Class I, B-R) or considered as a reasonable option within 3 to 4.5 hours (Class Ib, B-NR), whereas for non-disabling minor stroke, intravenous alteplase is not indicated (0-3 h: Class III No Benefit, B-R; 3-4.5h, Class III No Benefit, C-LD).[7]

The tenecteplase versus standard of care for minor ischemic stroke with proven occlusion (TEMPO-2) trial tested a novel imaging-based approach to select minor stroke patients for intravenous thrombolysis with tenecteplase up to 12 hours.[10] Patients were required to have an intracranial occlusion or perfusion abnormality consistent with an occlusion. These criteria were based on prospective cohort study data showing that these imaging features predicted a particularly high risk for early neurological deterioration and poor functional outcome.[11,12] The implication was that such patients could potentially benefit from thrombolysis. While the TEMPO-2 trial demonstrated no benefit from treatment with intravenous tenecteplase over non-thrombolytic standard of care, the neutral results could have stemmed from the heterogeneous mix of patients regarding the presence of disabling deficits. TEMPO-2 did not specify a definition of disabling deficits, instead, following the same principle as current guidelines, leaving the determination to the treating clinicians, excluding patients who were already eligible for intravenous thrombolysis under standard-of-care.

The aim of this secondary analysis of the TEMPO-2 trial was to determine if a more objective definition of disabling symptoms based on the NIHSS score could identify a subgroup of mild stroke patients with proven occlusion that benefit from thrombolysis with tenecteplase up to 12 hours from onset.

Methods

Study Population

This was an exploratory secondary analysis of the TEMPO-2 trial (NCT02398656). TEMPO-2 was a multicenter, prospective, open-label randomized clinical trial with blinded outcome assessment, testing the superiority of intravenous tenecteplase (0.25 mg/kg) over non-thrombolytic standard of care in patients with minor ischemic stroke and symptomatic intracranial occlusion or focal perfusion abnormality within 12 hours of symptom onset. The trial design and results were reported previously.[10,13] The trial protocol (Supplement 1) was approved by local ethics boards and written informed consent was obtained from patients or their representatives. The statistical analysis plan for the main trial is available in the supplement of the main trial publication.[10]

Briefly, the trial enrolled 886 patients at 48 sites across Australia, Austria, Brazil, Canada, Finland, Ireland, New Zealand, Singapore, Spain and the United Kingdom between April 27, 2015 and January 19, 2024. Patients were eligible if they were ≥ 18 years of age, independent at baseline [modified Rankin Score (mRS) ≤2], presenting within 12 hours with minor deficits (NIHSS ≤5), had either direct or indirect imaging evidence of an intracranial occlusion relevant to the presenting symptoms, and an Alberta Stroke Program Early CT score (ASPECTS) of ≥7. Patients were excluded if intravenous thrombolysis was indicated as standard of care. At most trial sites, this meant that patients with disabling minor deficits were only enrolled beyond 4.5 hours. The study protocol did not include any prespecified criteria for defining disability. Enrolled patients were randomized 1:1 to receive intravenous tenecteplase at a dose of 0.25

mg/kg versus non-thrombolytic standard of care (control). The rest of care was the same in each group. Randomization in the trial was completed by a computer-generated minimization algorithm to ensure balance on key variables, including age, sex assigned at birth, baseline NIHSS score, and time from symptom onset to randomization. The trial was stopped early for futility after a planned interim analysis that showed no benefit and possible harm from treatment with intravenous tenecteplase.

Definition of Disabling vs Non-disabling Stroke

Patients were retrospectively categorized as having disabling or non-disabling deficits based on NIHSS subscores using criteria derived from previous groups that have investigated minor stroke.[5,14,15] The PRISMS definition was not included as it required information from the patient/family regarding the impact of the stroke deficits on activities of daily living.[4] A summary of all the definitions of disabling minor stroke used in the study is shown in Table 1 and Supplement 2. The Re-examining Acute Eligibility for Thrombolysis (TREAT) Task Force definition provides a standardized, expert-endorsed framework that is widely used in the literature and was selected as the primary definition of disabling stroke in the current analysis.[5,16–19]

Outcomes

The primary outcome for this secondary analysis was a responder as measured by the mRS, defined using a sliding dichotomy approach, as follows: mRS 0-1 at 90 days if the pre-morbid mRS was 0 or 1, or mRS 0-2 at 90 days if the pre-morbid mRS was 2. Secondary clinical

outcomes included return to exact baseline mRS or better, excellent outcome (mRS 0-1) at 90 days, functional independence (mRS 0-2) at 90 days, mRS score at 90 days, and NIHSS at day 5 or on the day of hospital discharge (whichever is earlier). Key safety outcomes were 90-day all-cause mortality and symptomatic intracranial hemorrhage (sICH) within 24h of randomization defined as any new intracranial hemorrhage (ICH: intracerebral, subarachnoid, interventricular, or subdural hemorrhage) associated with clinical evidence of neurological worsening (an increase in NIHSS of 2 or more from the baseline). All events were reported by certified investigators blinded to the treatment assignment.

Statistical Analysis

The statistical analysis plan was finalized prior to conducting the analysis. We analyzed the intention-to-treat population, which included 884 patients from 886 randomized, after excluding two early withdrawals of consent (eFigure 1 in Supplement 2). Patient characteristics were compared between treatment arms using descriptive statistics in the disabling group and non-disabling group. Categorical variables were expressed as frequencies and percentages, and quantitative non-normally distributed variables as medians and IQRs. Adjusted analyses for binary outcomes were conducted using generalized linear modelling with a Poisson distribution, log link function and robust (Huber-Sandwich) standard error estimation. Mortality was analyzed using a Cox regression model. The ordinal mRS score was intended to be analyzed with a multivariable proportional odds model. However, the proportional odds assumption was not met and mRS score was assessed with quantile regression. Adjustments were made a priori for age, sex, time from onset to randomization and baseline NIHSS score (these variables were all

included in the randomized minimization algorithm). Effect size estimates were reported as adjusted risk ratios (aRRs), adjusted hazard ratios, or adjusted differences of medians with 95% confidence intervals (cIs). Effect modification of the presence of disabling deficits on the relationship between treatment arm and outcomes was assessed using 2-way multiplicative interaction terms (treatment x disabling deficit) in the multivariable models. Missing data in this secondary analysis were handled in accordance with the methodology outlined in the main trial publication.[10] A two-sided *P* <.05 was considered statistically significant. All analyses were performed with STATA (Version 18).

Results

Among the 884 patients, 100 (11.3%) and 784 (88.7%) were identified to have disabling and non-disabling deficits, respectively, according to the TREAT Task Force consensus (eFigure 1 in Supplement 2). Compared to patients with non-disabling deficits, those with disabling deficits had higher baseline NIHSS scores (median [IQR], 4 [3-5] vs 2 [1-3]), different distribution of occlusion sites (less frequent LVO but more frequent focal perfusion deficit), presented later to the emergency room after symptom onset (median [IQR], 288 [153-412] min vs 133 [70-310] min) and had a longer onset to treatment time (median [IQR], 411 [307-560] min vs 278 [170-462] min) (Table 2).

Fifty-three (53.0%) and 379 (48.3%) patients received tenecteplase in the disabling deficit group and non-disabling deficit group, respectively. There were no significant differences in baseline characteristics between treatment arms in both groups (eTable 1 in Supplement 2).

The overall responder rate in the disabling group was significantly lower than the non-disabling group (61 of 100 [61.0%] vs 586 of 784 [74.7%], eTable 2 in Supplement 2). In the disabling group, 55% (29 of 53) in the tenecteplase arm and 68% (32 of 47) in the control arm achieved the primary outcome (mRS responder analysis: adjusted risk ratio [aRR], 0.81; 95% CI, 0.60–1.10), while in the non-disabling group, 73.9% (280 of 379) in the tenecteplase arm and 75.6% (306 of 405) in the control arm were responders. Rates of excellent outcomes and functional independence were also not different between treatment arms in both groups stratified by disabling deficits at presentation. Other secondary outcomes are shown in Table 3 and Figure 1. There were numerically more patients treated with tenecteplase compared to those treated with standard of care displaying a NIHSS of 0 at day 5 or discharge in both groups and this difference was statistically significant in the non-disabling group (tenecteplase, 226 of 379 [59.9%]; control, 210 of 405 [51.9%]; aRR, 1.15; 95% CI, 1.02–1.30). No evidence of treatment effect heterogeneity was found between disabling and non-disabling groups on all primary and secondary outcomes.

There were more patients with symptomatic ICH at 24 hours in the tenecteplase treated patients in both the disabling and non-disabling groups although these differences were not significant. Symptomatic ICH occurred in 3 patients (6%) treated with tenecteplase and 0 patient (0%) treated with standard of care in the disabling group, and 5 patients (1.3%) treated with tenecteplase and 2 patients (0.5%) treated with standard of care in the non-disabling group (aRR 2.79; 95% CI, 0.58–13.42). The risk of any hemorrhage was significantly higher with

tenecteplase in the disabling group (tenecteplase, 11 of 53 [21%]; control, 1 of 47 [2%]; aRR, 9.79; 95% CI, 1.15–83.29), but not in the non-disabling group (tenecteplase, 51 of 379 [13.5%]; control, 39 of 405 [10.0%]; aRR, 1.37; 95% CI, 0.93-2.02), with borderline evidence of interaction between disabling vs non-disabling stroke and active treatment arm (*P* for interaction = .049).

Applying different criteria for disability from the ARAMIS trial, modified ARAMIS definition and the NINDS trial, we identified 140 (15.8%), 506 (57.2%) and 773 (87.4%) patients with disabling deficits, respectively. Baseline characteristics were balanced between treatment arms within disabling and non-disabling deficits groups regardless of definitions applied (eTable 3-5 in Supplement 2). Results regarding efficacy and safety were similar across all definitions of disability tested (eTable 6-8 and eFigure 2-4 in Supplement 2).

Discussion

In this secondary analysis of the subgroup of minor stroke patients with disabling deficits in the TEMPO-2 trial, no benefit was noted from treatment with intravenous tenecteplase at a dose of 0.25 mg/kg compared to non-thrombolytic standard of care. The neutral effect of tenecteplase was seen across multiple NIHSS-subscore based definitions of acute neurological disability in minor stroke. In addition, there was a suggestion of an increased rate of intracranial hemorrhage, with more hemorrhages observed on follow-up imaging in the disabling group treated with thrombolysis.

The present study aligns with other recent minor stroke trials showing that intravenous thrombolysis is not superior to the current medical standard of care. This neutral result is consistent across trials with different imaging selection criteria and thrombolytic agents in the intervention arm (Figure 2). PRISMS and ARAMIS included only individuals with minor stroke and non-disabling deficits. While definitions of non-disabling stroke differed, both trials failed to show a benefit of thrombolysis over antiplatelet therapy.[4,5] The Prourokinase for Mild Ischemic Cerebrovascular Events (PUMICE) trial studied prourokinase among minor ischemic stroke patients within 4.5 hours of onset, without eligibility criteria based on whether symptoms were disabling. The majority of patients (88.8%) included in the trial had non-disabling deficits based on the TREAT Task Force consensus, and, again, no benefit over standard of care was observed.[16] Similarly, the subgroup of TEMPO-2 patients with deficits classified as disabling was small (11.3% in TEMPO-2 vs 11.2% in PUMICE using the same TREAT Task Force criteria). As with PUMICE, the current analysis did not suggest any heterogeneity in thrombolytic treatment outcomes in minor stroke patients regardless of whether baseline deficits were classified as disabling or non-disabling using the NIHSS subscore.

In TEMPO-2 there were no pre-specified eligibility criteria around the presence of disabling deficits; however, the trial included an imaging requirement for visible or inferred vessel occlusion that was intended to select minor stroke patients at higher risk of progression and poor functional outcome.[10] Applying the TREAT Task Force and ARAMIS criteria respectively to TEMPO-2 patients, 11.3% and 15.8% were classified as having disabling deficits. As both criteria focus on cortical symptoms and set a high threshold for disability, the present study also tested

the less stringent criteria modified from ARAMIS, which classified 57.2% of trial patients as having disabling deficits; still, no benefit from intravenous tenecteplase was observed. All of these criteria rely on the NIHSS score, a tool designed to assess neurological deficit rather than disability. However, it provides an objective, deficit-based measure that could replace the unsatisfactory subjectivity of determining what constitutes a potentially disabling condition. Judging whether a neurological deficit is disabling necessarily involves consideration of patient-specific social, occupational and economic factors, making it intrinsically unsuited to the acute setting. Explicitly moving away from defining "disabling" using clinical judgement and moving toward standardized severity of neurological deficit could be advantageous.

A potential explanation for the discrepancy between recent studies and the pivotal individual patient data meta-analysis from older studies by Emberson and colleagues, which shaped current practice, lies in the evolution of recognized standards of care over the past decade. Nearly all trials included in the Emberson meta-analysis were double-blinded, used a placebo as the control arm, and restricted the administration of anti-thrombotic agents within the first 24 hours.[3] The exception is IST-3, which was open-label and commenced after evidence for acute aspirin became available,[20,21] thereby allowing for an antiplatelet control arm. This contrasts with the more contemporary trials, where immediate aspirin was used as the control arm in PRISMS,[4] and dual antiplatelet therapy was used in ARAMIS and a predominant proportion of patients in TEMPO-2 (57%) and PUMICE (91%).[5,10,16] The absence of potent early treatment in the control arms of the meta-analysis likely contributed to the marginal benefit observed for intravenous thrombolysis. By contrast, contemporary open-label trials using early antiplatelet

therapy as the control arm may have mitigated the relative advantage of intravenous thrombolysis.

Evidence from prior randomized controlled trials demonstrates that early aspirin significantly reduced the risk of recurrent stroke,[22] and dual antiplatelet therapy with aspirin and clopidogrel further improves outcomes, with a reported relative reduction of 30% in major ischemic events.[23] Moreover, the relatively short half-life of thrombolytics and the gap during the initial 24 hours when anti-thrombotic drugs could not be co-administered, may contribute to a reduced overall benefit of thrombolysis compared to DAPT, particularly for minor strokes due to atherosclerosis, where the platelet-rich thrombi may be less amenable to thrombolytics.[24] Indeed, the ARAMIS trial, primarily composed of non-cardioembolic stroke patients, demonstrated that compared with intravenous thrombolysis, dual antiplatelet significantly reduced occurrences of early neurological deterioration within the first 24 hours by almost 50%. Supporting this, a recent observational study using propensity score matching found that intravenous thrombolysis was effective when compared with aspirin alone but not with dual treatment in patients with minor ischemic stroke and large vessel occlusion.[19] These summative findings suggest that dual antiplatelet therapy may provide benefits comparable to intravenous thrombolysis in treating minor ischemic stroke.

Our study has several limitations. First, multiple definitions have been proposed for disability in minor stroke with no clear standard. These definitions result in anywhere from 11.3% to 87.4% of trial patients classified as having disabling deficits. However, our study suggests that there is

no treatment benefit in either group, regardless of the definition used. Some alternative definitions (e.g. PRISMS) requiring individualized decisions, depend on information from the patient or family that was not captured in the trial and, therefore could not be tested. Secondly, the outcome measure may not have been sensitive enough to capture functional disability in minor stroke; e.g., there were no cognitive assessments available. Many patients with excellent functional outcomes on the mRS report continued impairment in other domains.[25] Future studies could incorporate scales better tailored to detect deficits in the minor stroke population.[26] Thirdly, stratification by disabling deficits was not performed at enrollment, and patients with disabling strokes and minor symptoms may have been differentially excluded from the trial in the early time window due to current guidelines. This analysis, however, provides a potential rationale for revisiting the utility of IV thrombolysis in patients with minor but disabling symptoms. Finally, this is a post-hoc secondary analysis that was not powered to detect group differences and interactions regarding the safety and efficacy outcomes. The results should be considered exploratory and hypothesis-generating.

Conclusion

In this secondary analysis of the TEMPO-2 randomized trial comparing the safety and efficacy of tenecteplase vs standard of care in patients with minor stroke due to proven intracranial arterial occlusion, the presence of disabling symptoms based on NIHSS score at baseline did not modify the neutral treatment effect of tenecteplase. Together with converging evidence comparing

intravenous thrombolysis to non-thrombolytic standard of care, this analysis suggests the need to re-evaluate thrombolysis in minor disabling stroke.

Author Contributions

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

Concept and design: Zhang, Buck, Hill, Coutts.

Acquisition, analysis, or interpretation of data: Zhang, Buck, Hill, Vatanpour, Coutts.

Drafting of the manuscript: Zhang, Buck, Hill, Coutts.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Hill, Vatanpour.

Obtained funding: Coutts, Hill, Muir.

Administrative, technical, or material support: Coutts, Hill, Kennedy.

Supervision: Coutts, Hill.

Conflict of Interest Disclosures

Dr Barber holds an international patent related to perfusion imaging. Dr Ganesh reports speaker fees from Alexion, Biogen, and Servier Canada; an advisory role for Eisai; and stock options for SnapDx and Collavidence. Dr Williams is the Co-principal Investigator for Health Research Board of Ireland Collaborative Doctoral Award. Dr Wiggam reports payment for participation in advisory panels from Boehringer Ingelheim. Dr Muir reports grant funding from the British Heart Foundation (BHF), National Institute for Health and Care Research, and the Stroke Association; consultancy fees from Boehringer Ingelheim; lecture fees from Boehringer

Ingelheim, Brainomix, and IschaemaView; payment for participation in advisory boards from Boehringer Ingelheim. Dr Field reports lecture fees from AstraZeneca; payment for expert testimony from Canadian medical Protective Agency and plaintiff; payment for participation in advisory boards from Bayer, HLS Therapeutics, AstraZeneca, and Novartis; and advisory board memberships with DESTINE HEALTH and Vancouver General Hospital/UBC Hospital Foundation. Dr Goyal reports grant funding from Medtronic and Cerenovus; consulting fees from Philips, MicroVention, Penumbra, Medtronic, Stryker, and Mentice; and stock options for Circle Neurovascular. Dr Yu reports grant funding from the Canadian Institute of Health Research (CIHR), Heart and Stroke Foundation of Canada (HSFC), Physician Services Incorporated, and Government of Canada, and an unpaid associate editor role for Canadian Journal of Neurological Sciences. Dr Demchuck reports consulting fees from Hoffman LaRoche; lecture fees from Boehringer Ingelheim; a patent related to stroke imaging with Circle CVI; stock options in Circle CVI; and serves as Chair of the Board of Directors for Canadian Stroke Consortium. Dr Parsons reports consulting fees from Hoffman LaRoche. Dr Mandzia received payment from the CIHR grant for study patient enrolment. Dr Marko reports honoraria from Boehringer Ingelheim. Dr Lima reports speaker fees from Boehringer Ingelheim and travel support from AstraZeneca and Boehringer Ingelheim. Dr Catanese reports grant funding from Servier. Dr Ferrari received honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Bayer, BMS, Daiichi Sankyo, Novartis, and Pfizer. Dr Hill reports grant funding from the CIHR, HSFC, Alberta Innovates, and study drug from Boehringer Ingelheim; grants from NoNo and Medtronic; consulting fees from Sun Pharma Brainsgate; a DSMB member role on many stroke clinical trials; and stock options from Circle and Basking Biosciences. Dr Coutts received grant funding from the CIHR, HSFC, and

the BHF to complete the TEMPO-2 study. Boehringer Ingelheim provided off-the-shelf study drug (tenecteplase) for the study. No other disclosures were reported.

Funding/Support

Dr Zhang was supported by a PhD scholarship awarded by the China Scholarship Council. The TEMPO-2 trial was funded by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Canada and the British Heart Foundation.

Role of the Funder/Sponsor

The funders of the study had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information

The TEMPO-2 investigators appear in Supplement 3.

Meeting Presentation

This work was presented at the 2025 International Stroke Conference, February 5, 2024; Los Angeles, California.

Data sharing Statement

Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, can be made available to others upon reasonable request and after signing appropriate data sharing agreements. Please send data access requests to scoutts@ucalgary.ca. Such requests must be approved by all the respective ethics boards and appropriate data custodians.

Additional Contributions

We thank all investigators for their efforts in conducting the TEMPO-2 trial.

References

1. Smith EE, Fonarow GC, Reeves MJ, et al. Outcomes in Mild or Rapidly Improving Stroke Not Treated With Intravenous Recombinant Tissue-Type Plasminogen Activator: Findings From Get With The Guidelines–Stroke. *Stroke*. 2011;42(11):3110-3115. doi:10.1161/STROKEAHA.111.613208

2. Guerrero WR, Savitz SI. Mild acute ischaemic stroke—the case for thrombolytic therapy. *Nat Rev Neurol*. 2013;9(11):653-656. doi:10.1038/nrneurol.2013.174

3. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *The Lancet*. 2014;384(9958):1929-1935. doi:10.1016/S0140-6736(14)60584-5

4. Khatri P, Kleindorfer DO, Devlin T, et al. Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits: The PRISMS Randomized Clinical Trial. *JAMA*. 2018;320(2):156. doi:10.1001/jama.2018.8496

5. Chen HS, Cui Y, Zhou ZH, et al. Dual Antiplatelet Therapy vs Alteplase for Patients With Minor Nondisabling Acute Ischemic Stroke: The ARAMIS Randomized Clinical Trial. *JAMA*. 2023;329(24):2135. doi:10.1001/jama.2023.7827

6. Stroke Foundation. Australian and New Zealand Living Clinical Guidelines for Stroke Management. Accessed March 21, 2025. https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management

7. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12). doi:10.1161/STR.0000000000000211

8. Heran M, Lindsay P, Gubitz G, et al. Canadian stroke best practice recommendations: acute stroke management, 7th edition practice guidelines update, 2022. *Can J Neurol Sci J Can Sci Neurol*. 2024;51(1):1-31. doi:10.1017/cjn.2022.344

9. Berge E, Whiteley W, Audebert H, et al. European stroke organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021;6(1):I-LXII. doi:10.1177/2396987321989865

10. Coutts SB, Ankolekar S, Appireddy R, et al. Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion (TEMPO-2): a randomised, open label, phase 3 superiority trial. *The Lancet*. 2024;403(10444):2597-2605. doi:10.1016/S0140-6736(24)00921-8

11. Heldner MR, Jung S, Zubler C, et al. Outcome of patients with occlusions of the internal carotid artery or the main stem of the middle cerebral artery with NIHSS score of less than 5: comparison between thrombolysed and non-thrombolysed patients. *J Neurol Neurosurg Psychiatry*. 2015;86(7):755-760. doi:10.1136/jnnp-2014-308401

12. Kim JT, Park MS, Chang J, Lee JS, Choi KH, Cho KH. Proximal Arterial Occlusion in Acute Ischemic Stroke with Low NIHSS Scores Should Not Be Considered as Mild Stroke. Baron JC, ed. *PLoS ONE*. 2013;8(8):e70996. doi:10.1371/journal.pone.0070996

13. Singh N, Kenney CC, Butcher KS, et al. A Randomized Controlled Trial of Tenecteplase Versus Standard of Care for Minor Ischemic Stroke with Proven Occlusion (TEMPO-2): Rational and design of a multicenter, randomized open-label clinical trial. *Int J Stroke*. 2024;19(7):817-822. doi:10.1177/17474930241253702

14. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue Plasminogen Activator for Acute Ischemic Stroke. *N Engl J Med*. 1995;333(24):1581-1588. doi:10.1056/NEJM199512143332401

15. Levine SR, Khatri P, Broderick JP, et al. Review, Historical Context, and Clarifications of the NINDS rt-PA Stroke Trials Exclusion Criteria: Part 1: Rapidly Improving Stroke Symptoms. *Stroke*. 2013;44(9):2500-2505. doi:10.1161/STROKEAHA.113.000878

16. Xiong Y, Meng X, Jin A, et al. Prourokinase vs Standard Care for Patients With Mild Ischemic Stroke: The PUMICE Randomized Clinical Trial. *JAMA Neurol*. 2025;82(3):258. doi:10.1001/jamaneurol.2024.4688

17. Cao X, Luo J, Xu B, et al. Best medical management versus intravenous thrombolysis for mild non-disabling ischemic stroke: A prospective noninferiority registry study. *J Neurol Sci*. 2023;451:120706. doi:10.1016/j.jns.2023.120706

18. Choi JC, Jang MU, Kang K, et al. Comparative Effectiveness of Standard Care With IV Thrombolysis Versus Without IV Thrombolysis for Mild Ischemic Stroke. *J Am Heart Assoc*. 2015;4(1):e001306. doi:10.1161/JAHA.114.001306

19. Duan C, Xiong Y, Gu H, et al. Intravenous thrombolysis versus antiplatelet therapy in minor stroke patients with large vessel occlusion. *CNS Neurosci Ther*. 2023;29(6):1615-1623. doi:10.1111/cns.14124

20. International Stroke Trial Collaborative Group. The international stroke trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet Lond Engl*. 1997;349(9065):1569-1581. doi:10.1016/S0140-6736(97)04011-7

21. Chen Z, CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet Lond Engl*. 1997;349(9066):1641-1649. doi:10.1016/s0140-6736(97)04010-5

22. Chen Z, Sandercock P, Pan H, et al. Indications for Early Aspirin Use in Acute Ischemic Stroke: A Combined Analysis of 40 000 Randomized Patients From the Chinese Acute Stroke Trial and the International Stroke Trial. *Stroke*. 2000;31(6):1240-1249. doi:10.1161/01.STR.31.6.1240

23. Pan Y, Elm JJ, Li H, et al. Outcomes Associated With Clopidogrel-Aspirin Use in Minor Stroke or Transient Ischemic Attack: A Pooled Analysis of Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trials. *JAMA Neurol*. 2019;76(12):1466. doi:10.1001/jamaneurol.2019.2531

24. Molina CA, Montaner J, Arenillas JF, Ribo M, Rubiera M, Alvarez-Sabín J. Differential pattern of tissue plasminogen activator–induced proximal middle cerebral artery recanalization among stroke subtypes. *Stroke*. 2004;35(2):486-490. doi:10.1161/01.str.0000110219.67054.bf

25. Kapoor A, Lanctôt KL, Bayley M, et al. "Good Outcome" Isn't Good Enough: Cognitive Impairment, Depressive Symptoms, and Social Restrictions in Physically Recovered Stroke Patients. *Stroke*. 2017;48(6):1688-1690. doi:10.1161/STROKEAHA.117.016728

26. Goyal M, Ganesh A, Bosshart SL, et al. COSMOS: interrater and intrarater reliability study of a novel outcome measure. *Stroke*. 2025;56(7):1958-1964. doi:10.1161/strokeaha.125.049454

27. Adams HP, Brott TG, Furlan AJ, et al. Guidelines for Thrombolytic Therapy for Acute Stroke: A Supplement to the Guidelines for the Management of Patients With Acute Ischemic Stroke: A Statement for Healthcare Professionals From a Special Writing Group of the Stroke Council, American Heart Association. *Circulation*. 1996;94(5):1167-1174. doi:10.1161/01.CIR.94.5.1167

28. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Recombinant Tissue Plasminogen Activator for Minor Strokes: The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Experience. *Ann Emerg Med*. 2005;46(3):243-252. doi:10.1016/j.annemergmed.2005.02.013

Table 1. Summary of definitions of minor disabling stroke used in the study

	Non-disabling Stroke[a]	Disabling Stroke[a]		
	NINDS[27,28]	**TREAT Task Force**[15]	**ARAMIS**[5]	**Modified ARAMIS**
1. LOC	0		any item >0	any item >0
2. Best Gaze	0			
3. Visual	0	≥2	>1	>0
4. Facial Palsy	isolated			
5-6. Motor	0	any item ≥2	any item >1	any item > 0
7. Ataxia	isolated			
9. Sensory	isolated			
10. Best Language	0	≥2	>1	>0
11. Dysarthria	isolated			
12. Extinction	0	≥2	>1	>0

Abbreviations: LOC, level of consciousness; NINDS, National Institute of Neurological Disorders and Stroke rt-PA Stroke; TREAT Task Force, The REexamining Acute Eligibility for Thrombolysis Task Force; ARAMIS, Antiplatelet vs R-tPA for Acute Mild Ischemic Stroke.

[a] Each definition combines all individual criteria using 'OR'.

570 **Table 2.** Patient Characteristics Stratified by Disabling Deficits at Presentation According to the
571 TREAT Task Force Consensus[15]

	Disabling Deficits (N=100)	Non-disabling Deficits (N=784)
Tenecteplase arm	53 (53.0%)	379 (48.3%)
Demographics		
Age, median (IQR), y	73 (64-82)	72 (61-80)
Female, No. (%)	46 (46.0%)	323 (41.1%)
Clinical Presentation, median (IQR)		
NIHSS score at baseline	4 (3-5)	2 (1-3)
mRS score at baseline	0 (0-1)	0 (0-0)
Hemoglobin, g/dL[a]	13.7 (12.8-15.0)	14.1 (13.1-15.1)
Glucose, mg/dL[b]	108 (108-144)	108 (108-126)
Creatinine, mg/dL[c]	0.87 (0.76-1.04)	0.94 (0.79-1.12)
Medical History, No. (%)		
Hypertension	61 (61.0%)	465 (59.3%)
Past smoking	29 (29.0%)	319 (40.7%)
Hyperlipidemia	40 (40.0%)	312 (39.8%)
Diabetes mellitus	19 (19.0%)	149 (19.0%)
Past stroke	19 (19.0%)	138 (17.6%)
Atrial fibrillation	18 (18.0%)	151 (19.3%)
Ischemic heart disease	16 (16.0%)	126 (16.1%)
Congestive heart failure	6 (6.0%)	28 (3.6%)
Chronic renal failure	3 (3.0%)	36 (4.6%)
Peripheral vascular disease	6 (6.0%)	22 (2.8%)
Past ICH	1 (1.0%)	3 (0.4%)
Imaging Characteristics		
Occlusion site at baseline, No. (%)		
LVO[d]	4 (4.0%)	99 (12.7%)
MeVO[e]	58 (58.0%)	422 (54.0%)
Vertebrobasilar circulation[f]	0 (0.0%)	45 (5.8%)
Focal perfusion deficit	37 (37.0%)	208 (26.6%)
No occlusion detected	1 (1.0%)	7 (0.9%)
ASPECTS baseline, median (IQR)	10 (9-10)	10 (10-10)
Time Metrics		
onset to randomization time, median (IQR), min	400 (298-524)	256 (156-427)
onset to hospital arrival time, median (IQR), min	288 (153-412)	133 (70-310)
onset to treatment time, median (IQR), min	411 (307-560)	278 (170-462)
≤ 4.5h, No. (%)	20 (20.0%)	381 (48.6%)
> 4.5h, No. (%)	80 (80.0%)	403 (51.4%)

572 Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale;
573 ICH, intracranial hemorrhage; ASPECTS, Alberta Stroke Program Early CT score.
574 [a] To convert hemoglobin to g/L, multiply values by 10.
575 [b] To convert glucose to mmol/L, multiple values by 0.0555.
576 [c] To convert creatinine to µmol/L, multiple values by 88.4.
577 [d] Large vessel occlusion: Intracranial internal carotid artery, M1 segment of the middle
578 cerebral artery.
579 [e] Medium vessel occlusion: M2 segment of the middle cerebral artery or distal, A2 segment of
580 the anterior cerebral artery or distal.
581 [f] Intracranial vertebral artery, basilar artery or branches, posterior cerebral artery.
582

583 **Table 3.** Outcomes Stratified by Treatment Arms and Disabling Deficits at Presentation according to the TREAT Task Force Consensus[15]

	Disabling Deficits (N=100)			Non-disabling Deficits (N=784)			*P* value for interaction
	Control	Tenecteplase	aRR (95% CI)[a]	Control	Tenecteplase	aRR (95% CI)[a]	
N	47 (47.0%)	53 (53.0%)		405 (51.7%)	379 (48.3%)		
Primary Outcome							
Responder	32 (68.1%)	29 (54.7%)	0.81 (0.60,1.10)	306 (75.6%)	280 (73.9%)	0.98 (0.91,1.07)	.32
Secondary Outcomes							
mRS 0-1 at 90 days	29 (61.7%)	25 (47.2%)	0.78 (0.55,1.11)	292 (72.5%)	273 (72.0%)	1.00 (0.92,1.09)	.22
mRS 0-2 at 90 days	39 (83.0%)	37 (69.8%)	0.85 (0.69,1.06)	352 (87.3%)	315 (83.1%)	0.96 (0.90,1.01)	.49
Median (IQR) mRS score at 90 days[b]	1 (0-2)	2 (0-3)	0.33 (-0.34, 1.00)	1 (0-2)	1 (0-2)	0.11(-0.08, 0.29)	.44
mRS return to baseline	20 (42.6%)	23 (43.4%)	0.99 (0.64,1.54)	202 (49.9%)	189 (49.9%)	1.00 (0.87,1.15)	.91
NIHSS of 0 at D5 or DC	16 (34.0%)	21 (42.0%)	1.25 (0.75,2.09)	210 (51.9%)	226 (59.9%)	1.15 (1.02,1.30)	.91
Safety Outcomes							
Death within 5 days[c]	0 (0.0%)	3 (5.7%)	NA	1 (0.2%)	5 (1.3%)	5.89 (0.68, 50.76)	NA
Death within 90 days[c]	1 (2.1%)	5 (9.4%)	2.00 (0.19, 21.33)	4 (1.0%)	15 (4.0%)	4.12 (1.37, 12.41)	.72
Stroke progression	1 (2.1%)	5 (9.4%)	7.01 (0.41,120.11)	32 (7.9%)	30 (7.9%)	1.00 (0.62,1.60)	.17
Stroke recurrence	1 (2.1%)	0 (0.0%)	NA	14 (3.5%)	16 (4.2%)	1.22 (0.60,2.47)	NA
Rescue EVT for index stroke	0 (0.0%)	1 (1.9%)	NA	10 (2.5%)	14 (3.7%)	1.46 (0.65,3.24)	NA
Symptomatic ICH 24h	0 (0.0%)	3 (5.7%)	NA	2 (0.5%)	5 (1.3%)	2.79 (0.58,13.42)	NA
Any hemorrhage on FU scan	1 (2.1%)	11 (20.8%)	9.79 (1.15,83.29)	39 (10.0%)	51 (13.5%)	1.37 (0.93,2.02)	.049

584 Data are No. (%), unless otherwise indicated. Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; mRS, modified Rankin
585 Scale; NIHSS, National Institutes of Health Stroke Scale; DC, discharge; NA, not applicable; EVT, endovascular therapy; ICH,
586 intracranial hemorrhage; FU, follow-up.
587 [a] Adjusted for age, sex at birth, baseline NIHSS score and onset to treatment time.
588 [b] Adjusted difference of medians.
589 [c] Adjusted hazard ratios
590

Figure 1. Ninety-day Modified Rankin Scale Distribution Stratified by Baseline Disabling Deficits According to the TREAT Task Force Consensus[15]

The modified Rankin Scale (mRS) score ranges from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

Figure 2. Summary of Studies Evaluating Intravenous Thrombolysis in Minor Ischemic Stroke

Lytic indicates thrombolytic; tPA, alteplase; TNK, tenecteplase; Pro-UK, prourokinase; ASA, aspirin; DAPT, dual antiplatelet therapy; IVT, intravenous thrombolysis.

[a] Except for IST-3, all included trials in the individual patient data meta-analysis were double-blinded, placebo-controlled, and required patients to have some sort of neurologic deficit, but not minor symptoms. The initial 244 patients enrolled in the pilot phase of IST-3 were randomized in a double-blinded, placebo-controlled design, where, similar to the aforementioned trials, both treatment arms were to avoid antiplatelet or anticoagulant therapy for 24h. The main phase of IST-3, however, was open-label; control group patients in this phase were to initiate aspirin immediately. Patients with mild deficits were potentially eligible in the IST-3 trial but only when both the enrolling physician and the patient (or surrogate) had personal equipoise regarding benefit. Of the 6756 patients, these 666 represent the 10% of participants with low NIHSS score (NIHSS 0-4) included in the pooled analysis.

[b] Defined by the PRISMS trial criteria.

[c] In the full analysis set of the ARAMIS trial, 86 of 369 (23%) patients randomized to the DAPT arm crossed over to the alteplase group.

[d] Defined by the ARAMIS trial criteria.

[e] Defined by the TREAT Task Force Consensus.