

ORIGINAL RESEARCH

Sex Differences in Outcomes After Tenecteplase for Minor Stroke: A Subanalysis of the TEMPO-2 Trial

Amy Y. X. Yu , MD; Shabnam Vatanpour , PhD; Aravind Ganesh , MD; Thalia S. Field , MD; Philip A. Barber , MD; Philip M. C. Choi , MBChB; Brian Buck , MD; Timothy Kleinig , MD; Carlos A. Molina , MD; Bruce C. V. Campbell , PhD; Ramana Appireddy , MD; Keith W. Muir , MD; Michael D. Hill , MD; Shelagh B. Coutts , MD; the TEMPO-2 Investigators

BACKGROUND: In this subanalysis of the TEMPO-2 (Tenecteplase Versus Standard of Care for Minor Ischaemic Stroke With Proven Occlusion) trial, a randomized clinical trial comparing tenecteplase and nonthrombolytic control in patients with minor stroke and symptomatic intracranial occlusion, we investigated sex differences in the efficacy and safety of tenecteplase.

METHODS: We compared outcomes after tenecteplase versus control, stratified by sex. We also compared outcomes in female versus male patients treated with tenecteplase. The primary outcome was a “responder” outcome, defined as return to baseline modified Rankin Scale score at 90 days. Secondary outcomes included the Lawton Instrumental Activities of Daily Living Scale, the EuroQoL-5 Dimension, vessel recanalization, and adverse events. We used generalized linear modeling with a Poisson distribution adjusted for baseline differences to calculate adjusted risk ratios (aRR) and 95% CIs.

RESULTS: There were 884 patients in the intention-to-treat analysis (48.9% tenecteplase, 41.5% female). Among female participants, the tenecteplase group was less likely to be a responder compared with control (63.8% tenecteplase, 73.9% control, aRR, 0.87 [95% CI, 0.76–1.00]). Among male participants, the responder outcome was similar between groups (77.5% tenecteplase, 75.4% control, 1.03 [95% CI, 0.94–1.13]). Female participants randomized to tenecteplase were less likely to be responders than male counterparts (63.8% female, 77.5% male, 0.85 [95% CI, 0.75–0.96]). Early recanalization was more frequent after tenecteplase than control in both sexes.

CONCLUSIONS: Tenecteplase was not associated with better clinical outcomes over nonthrombolytic control in female or male patients with minor ischemic stroke, despite more frequent recanalization. Fewer women treated with tenecteplase returned to baseline function compared with men.

Key Words: sex ■ stroke ■ minor ischemic stroke ■ thrombolysis

See Editorial by Kim.

The TEMPO-2 (Tenecteplase Versus Standard of Care for Minor Ischaemic Stroke With Proven Occlusion) randomized clinical trial did not show superiority of tenecteplase versus standard of care treatment for

patients with minor ischemic stroke with a symptomatic intracranial occlusion.¹ In the main paper, analysis of major subgroups identified a sex-by-treatment interaction (P -interaction 0.04). There was a signal toward harm

Correspondence to: Shelagh B. Coutts, MD, C1242A, Foothills Medical Centre, 1403 29th St NW, Calgary, AB T2N 2T9, Canada. Email: scoutts@ucalgary.ca

This article was sent to Thomas S. Metkus, MD, PhD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

A complete list of the TEMPO-2 investigators can be found in the Appendix at the end of the article.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.039154>

For Sources of Funding and Disclosures, see page 12.

© 2025 The Author(s). Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](#) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

RESEARCH PERSPECTIVE

What Is New?

- In this subanalysis of the TEMPO-2 (Tenecteplase Versus Standard of Care for Minor Ischaemic Stroke With Proven Occlusion) trial, a randomized clinical trial comparing tenecteplase and nonthrombolytic standard of care in patients with minor ischemic stroke and symptomatic intracranial occlusion within 12 hours of symptom onset, we found that tenecteplase was not associated with better clinical outcomes over nonthrombolytic control in female or male patients with minor ischemic stroke.
- Female patients treated with tenecteplase were less likely to return to baseline function, as measured by the modified Rankin Scale score, compared with male patients even though there were no sex differences in early vessel recanalization, symptomatic intracerebral hemorrhage, or other adverse events.

What Question Should be Addressed Next?

- To understand reasons for differences in outcomes, future clinical trials exploring sex differences in outcomes after minor stroke should consider aiming for better sex balance in recruitment and including the evaluation of patient-reported symptoms, such as cognitive decline, sleep disturbances, mood, and fatigue, as well as patient-reported outcomes.

Nonstandard Abbreviations and Acronyms

ARAMIS	Antiplatelet versus R-tPA for Acute Mild Ischemic Stroke
IADL	instrumental activities of daily living
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
TEMPO-2	Tenecteplase Versus Standard of Care for Minor Ischaemic Stroke With Proven Occlusion

among women who received tenecteplase compared with standard of care, but this was not statistically significant (risk ratio [RR], 0.87 [95% CI, 0.76–1.00] for women and 1.03 [95% CI, 0.94–1.13] for men).

Prior studies have reported that women with stroke experience worse outcomes compared with men, including higher mortality,^{2,3} more physical disability,^{4,5} and overall lower quality of life.^{6,7} These findings can

be partially explained by the older age and higher pre-stroke disability of women with stroke, but other potential contributing factors such as differences in the safety and effectiveness of acute stroke treatments are less well understood. Data from a large European registry of patients treated with thrombolysis found no difference in symptomatic intracranial hemorrhage between women and men after thrombolysis, but women still had worse functional outcomes.⁸ However, data from routine clinical practice may be vulnerable to selection bias as women may be less likely to receive thrombolytic agents⁹ and patients with minor ischemic stroke are typically underrepresented. Finally, few data exist on sex differences in the safety and effectiveness of tenecteplase, a relatively recent addition to acute stroke therapeutic agents.

In this sex disaggregated subanalysis of the TEMPO-2 trial, we evaluated the difference in adverse events, recanalization rates, and clinical outcomes among women and men treated with tenecteplase for minor ischemic stroke.

METHODS

Data collected for the study, including deidentified individual participant data and a data dictionary defining each field in the set, can be made available to others on reasonable request and after signing appropriate data sharing agreements and approval by all the respective ethics boards and appropriate data custodians.

Data are from the TEMPO-2 study, a randomized, multicenter, phase 3 clinical trial that tested the superiority of intravenous tenecteplase (0.25 mg/kg) over nonthrombolytic standard of care in patients with minor ischemic stroke deficits and symptomatic intracranial occlusion or focal perfusion lesion within 12 hours of symptom onset. The trial protocol¹⁰ and main results¹ have been published. Briefly, eligibility criteria included adults ≥ 18 years, baseline independence (modified Rankin Scale [mRS] score ≤ 2), minor deficits (National Institutes of Health Stroke Scale [NIHSS] score ≤ 5), and no evidence of evolved infarction concordant with the acute presenting syndrome or Alberta Stroke Program Early Computed Tomography Score ≥ 7 . Patients were not eligible if there were contraindications to thrombolysis or if the treating physician judged thrombolysis was warranted as part of clinical standard of care. 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.¹¹

Between April 27, 2015 and January 19, 2024, 886 patients were enrolled across 48 sites in Australia, Austria, Brazil, Canada, Finland, Ireland, New Zealand,

Singapore, Spain, and the United Kingdom.¹ There were 432 patients (49%) assigned to tenecteplase and 454 (51%) to standard of care, which included dual antiplatelet therapy (n=263), single antiplatelet therapy (n=157), and anticoagulation (n=24). Four patients received alteplase and 2 patients did not receive treatment post randomization. Two patients withdrew consent and 2 patients were lost to follow-up.

We performed 2 parallel analyses to evaluate sex differences in outcomes. First, we compared the efficacy and safety of tenecteplase versus control, stratified by participants' sex at birth. This evaluates whether sex modified the efficacy and safety of tenecteplase. Second, we compared outcomes in female versus male patients treated with tenecteplase. This step evaluates whether female patients treated with tenecteplase experienced different clinical outcomes and adverse events compared with male patients given this treatment.

As in the main TEMPO-2 publication, the primary outcome of this subanalysis was the responder outcome, defined as a return to baseline function as measured by the 90-day blinded mRS assessment. Thus, for a participant with a baseline mRS score of 0 to 1, a return to mRS score 0 to 1 at 90 days is a good outcome, and the participant is deemed a "responder." Similarly, a participant with baseline mRS score of 0 to 2 who returns to mRS score 0 to 2 at 90 days is a responder. Secondary clinical outcomes include percent function on Lawton Instrumental Activities of Daily Living (IADL) Scale at 90 days, NIHSS score of 0 at day 5 or on day of hospital discharge (whichever is earlier), quality of life measured at 90 days on the EuroQol-5 Dimension 5-Level score where raw scores were converted into an index using country-specific algorithms, stroke progression, stroke recurrence, all-cause mortality, intracerebral hemorrhage, and other adverse events. Whereas the Lawton IADL Scale was historically scored in a gendered manner whereby women were expected to perform more IADLs than men, we used the more equitable and granular scoring method used in the COMPASS-ND (Comprehensive Assessment of Neurodegeneration and Dementia) study,¹² whereby patients receive scores out of 23 points, with higher scores indicating greater degrees of independence. In patients with vessel occlusion on baseline computed tomography angiogram, we reported the proportion with early recanalization on the follow-up intracranial vascular imaging at 4 to 8 hours after randomization. A repeat computed tomography angiogram was not required for patients enrolled based on symptomatic perfusion defect.

Privacy and Ethics

The trial was sponsored by the University of Calgary, Alberta, Canada. The trial was regulated by Health

Canada and in the countries of each site as required. Local ethics board approval was obtained and all participants or their representative provided informed consent before enrollment.

Statistical Analysis

We analyzed the outcomes in the intention-to-treat population (n=884), defined as all patients assigned to a treatment group and who did not withdraw consent to participate. We performed complete case analyses; missing data were rare. We compared baseline characteristics using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. We used generalized linear modeling with a Poisson distribution and log link function to directly generate adjusted RR (aRR) and used Huber-Sandwich robust SE estimation to estimate 95% CI. Multivariable models were adjusted for age, baseline NIHSS score, and baseline occlusion (large vessel occlusion versus not). Given age may be an important modifier of the affect between sex and outcomes, we evaluated for a multiplicative age-by-sex interaction as well as age-by-treatment interaction (*P* interaction <0.05 indicates statistical significance). Analyses were performed using Stata Statistical Software: Release 18 (College Station, TX: StataCorp LLC).

RESULTS

Tenecteplase Versus Control, Stratified by Sex

Among the 368 female participants (51.1% tenecteplase, 48.9% control), baseline characteristics were balanced. This was expected given the computer-generated minimization algorithm for randomization accounted for sex as a key variable. Stroke characteristics were also similar between the 2 groups except for a longer onset-to-treatment time in the control compared with the tenecteplase group (Table 1). Among the 516 male participants (47.3% tenecteplase, 52.7% control), baseline patient and stroke characteristics were similar, including similar onset-to-treatment time.

Among female participants, those in the tenecteplase group were less likely to be responders than those in the control group (63.8% tenecteplase, 73.9% control, aRR, 0.87 [95% CI, 0.76–1.00], Table 2 and Table S1). In addition, a higher proportion of female participants in the tenecteplase group had any intracerebral hemorrhage on follow-up imaging compared with those in the control group (13.8% tenecteplase, 5.7% control, *P*=0.013), but few had symptomatic hemorrhage (1.1% tenecteplase, none among controls). Among male participants, the proportion of responders was similar between

Table 1. Baseline Characteristics by Treatment Arm, Stratified by Sex

	Female (N=368)			Male (N=516)		
	Tenecteplase	Control	P value	Tenecteplase	Control	P value
	No.=188 (51.1%)	No.=180 (48.9%)		No.=244 (47.3%)	No.=272 (52.7%)	
Patient characteristics						
Median age, y (IQR)	75 (64–84)	74 (65–82)	0.72	70 (60–78)	70 (59–78)	0.36
Hypertension	119 (63.3%)	106 (58.9%)	0.39	146 (59.8%)	155 (57.0%)	0.53
Past smoking	59 (31.4%)	60 (33.3%)	0.74	113 (46.3%)	116 (42.6%)	0.43
Hyperlipidemia	72 (38.3%)	70 (38.9%)	0.91	108 (44.3%)	102 (37.5%)	0.13
Diabetes	36 (19.1%)	32 (17.8%)	0.79	46 (18.9%)	54 (19.9%)	0.82
Past stroke	30 (16.0%)	29 (16.1%)	1.00	42 (17.2%)	56 (20.6%)	0.37
Atrial fibrillation	36 (19.1%)	31 (17.2%)	0.69	55 (22.5%)	47 (17.3%)	0.15
Ischaemic heart disease	20 (10.6%)	18 (10.0%)	0.87	49 (20.1%)	55 (20.2%)	1.00
Congestive heart failure	9 (4.8%)	6 (3.3%)	0.60	7 (2.9%)	12 (4.4%)	0.48
Chronic renal failure	14 (7.4%)	5 (2.8%)	0.06	8 (3.3%)	12 (4.4%)	0.65
Peripheral vascular disease	6 (3.2%)	5 (2.8%)	1.00	7 (2.9%)	10 (3.7%)	0.63
Past intracerebral hemorrhage	3 (1.6%)	0 (0.0%)	0.25	0 (0.0%)	1 (0.4%)	1.00
Prestroke modified Rankin Scale score						
0	141 (75.0%)	137 (76.1%)	0.95	195 (79.9%)	217 (79.8%)	0.67
1	25 (13.3%)	23 (12.8%)		36 (14.8%)	36 (13.2%)	
2	22 (11.7%)	20 (11.1%)		13 (5.3%)	19 (7.0%)	
Stroke characteristics						
Median baseline NIHSS (IQR)	2 (1–3)	2 (1–3)	0.55	2 (1–3)	2 (1–3)	0.75
NIHSS=0	35 (18.6%)	28 (15.6%)	0.49	39 (16.0%)	40 (14.7%)	0.71
Baseline Alberta Stroke Program Early Computed Tomography Score	10 (9–10)	10 (9–10)	0.98	10 (10–10)	10 (9–10)	0.77
Baseline occlusion (core laboratory)						
Large vessel	27 (14.4%)	26 (14.4%)	0.52	26 (10.7%)	24 (8.9%)	0.31
Medium vessel	112 (59.9%)	102 (56.7%)		123 (50.4%)	143 (53.0%)	
Vertebrobasilar	2 (1.1%)	6 (3.3%)		18 (7.4%)	19 (7.0%)	
Focal perfusion lesion	45 (24.1%)	43 (23.9%)		73 (29.9%)	84 (31.1%)	
No occlusion detected	1 (0.5%)	3 (1.7%)		4 (1.6%)	0 (0.0%)	
Hemoglobin, g/L	132 (125–142)	136 (128–143)	0.06	146 (135–155)	146 (135–156)	0.89
Glucose, mM	6 (6–8)	6 (6–7)	0.17	6 (5–7)	6 (6–8)	0.24
Creatinine, μM	72 (63–85)	72 (63–88)	0.21	89 (77–103)	89 (78–103)	0.31
Time metrics in minutes						
Onset to emergency department arrival	127 (70–330)	154 (80–336)	0.91	154 (86–335)	147 (68–338)	0.83
Onset to randomization	268 (160–450)	309 (178–454)	0.46	291 (162–436)	259 (154–435)	0.51
Onset to treatment	276 (162–461)	347 (201–510)	0.01	301 (169–450)	300 (170–485)	0.15

Large vessel: intracranial internal carotid artery, M1 segment of the middle cerebral artery. Medium vessel: M2 segment of the middle cerebral artery or distal, A2 segment of the anterior cerebral artery, or distal. Vertebrobasilar: vertebral artery, basilar artery, posterior cerebral artery, or branches. IQR indicates interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

the 2 groups (77.5% tenecteplase, 75.4% control, aRR, 1.03 [95% CI, 0.94–1.13]). However, compared with the control group, those in the tenecteplase group were more likely to achieve NIHSS score=0 at day 5 or discharge (61.4% tenecteplase, 50.6% control, $P=0.019$); yet 90-day mortality was higher (5.7% tenecteplase, 0.4% control, $P<0.001$). Among

participants enrolled with a baseline intracranial occlusion, recanalization was higher in the tenecteplase group in both sexes (40.4% female, 38.9% male) than the control group (17.9% female, 17.2% male), but this outcome was more likely to be missing among women (Table S2). The distribution of the 90-day mRS stratified by sex is shown in Figure 1. There was

Table 2. Adverse Events and Outcomes by Treatment Arm, Stratified by Sex

	Female (N=368)			Male (N=516)		
	Tenecteplase	Control	<i>P</i> value	Tenecteplase	Control	<i>P</i> value
	No.=188 (51.1%)	No.=180 (48.9%)		No.=244 (47.3%)	No.=272 (52.7%)	
Responder outcome	120 (63.8%)	133 (73.9%)	0.04	189 (77.5%)	205 (75.4%)	0.60
NIHSS score=0 at 5 d or discharge	103 (56.0%)	89 (50.3%)	0.29	143 (61.4%)	134 (50.6%)	0.02
IADL-Lawton-COMPASS-ND scoring algorithm	23 (17–23)	23 (19–23)	0.12	23 (22–23)	23 (21–23)	0.51
Median EQ5D-5L index (n=845)	1 (1–1)	1 (1–1)	0.13	1 (1–1)	1 (1–1)	0.19
Any serious adverse event	46 (24.5%)	39 (21.7%)	0.54	54 (22.1%)	41 (15.1%)	0.04
Stroke progression	18 (9.6%)	15 (8.3%)	0.72	17 (7.0%)	18 (6.6%)	1.00
Stroke recurrence	5 (2.7%)	6 (3.3%)	0.77	11 (4.5%)	9 (3.3%)	0.50
Symptomatic intracerebral hemorrhage	2 (1.1%)	0 (0.0%)	0.50	6 (2.5%)	2 (0.7%)	0.16
Any hemorrhage on follow-up imaging	26 (13.8%)	10 (5.7%)	0.01	36 (14.8%)	30 (11.5%)	0.29
Rescue intracerebral hemorrhage for index stroke	8 (4.3%)	5 (2.8%)	0.58	7 (2.9%)	5 (1.8%)	0.56
Death within 5 d	3 (1.6%)	0 (0.0%)	0.25	5 (2.0%)	1 (0.4%)	0.11
Death at 90 d	6 (3.2%)	4 (2.2%)	0.75	14 (5.7%)	1 (0.4%)	<0.01
Aspiration pneumonia	2 (1.1%)	1 (0.6%)	1.00	4 (1.6%)	1 (0.4%)	0.19
Atrial fibrillation	3 (1.6%)	2 (1.1%)	1.00	1 (0.4%)	1 (0.4%)	1.00
Congestive heart failure	4 (2.1%)	1 (0.6%)	0.37	1 (0.4%)	0 (0.0%)	0.47
Seizure	1 (0.5%)	2 (1.1%)	0.62	2 (0.8%)	1 (0.4%)	0.61
Urinary tract infection	0 (0.0%)	3 (1.7%)	0.12	2 (0.8%)	1 (0.4%)	0.61

Missing data: 25 patients had missing NIHSS score at 5 d or discharge, 34 patients had missing Lawton IADL score, 39 patients had missing EQ5D-5L index, and 17 patients had missing data on hemorrhage on follow-up imaging.

EQ-5D-5L indicates EuroQol-5 5-Level Dimension score; IADL-Lawton-COMPASS-ND, Lawton Instrumental Activities of Daily Living Scale (Comprehensive Assessment of Neurodegeneration and Dementia); and NIHSS, National Institutes of Health Stroke Scale.

no statistically significant modification by age; all *P*-interaction were greater than 0.05 (Table S1).

Female Versus Male Participants, Stratified by Treatment Arm

There were 432 participants assigned to tenecteplase (43.5% female, 56.5% male) and we observed several differences in baseline characteristics. Compared with male participants, women were older, less likely to have smoking history or ischemic heart disease, but more likely to have some degree of functional dependence at baseline and more likely to have a large or medium vessel occlusion versus a perfusion lesion without occlusion (Table 3). Among the 452 participants assigned to control treatment (39.8% female, 60.2% male), we observed similar sex differences in baseline characteristics as those assigned to tenecteplase.

Compared with male participants assigned to tenecteplase, the female participants were less likely to be responders (63.8% female, 77.5% male, aRR, 0.85 [95% CI, 0.75–0.96], Table 4 and Table S1). The range of the Lawton IADL scores was also lower

among female participants. However, among participants in the control group, men and women had similar responder outcomes (73.9% female, 75.4% male, aRR, 1.00 [95% CI, 0.90–1.12]). The distribution of the 90-day mRS score stratified by sex and treatment arm is shown in Figure 2. There were no sex differences in NIHSS score=0 at day 5 or discharge, the EuroQol-5 Dimension 5-Level index, intracerebral hemorrhage, any other significant adverse event, or early vascular recanalization (Table 4, Table S2). There was no statistically significant modification by age, all *P*-interaction were >0.05 (Table S1).

DISCUSSION

In this sex-stratified subanalysis of the TEMPO-2 randomized clinical trial that tested the superiority of tenecteplase versus nonthrombolytic control, we found that tenecteplase was not associated with better functional outcomes compared with control in women or men with transient ischemic attack or minor stroke, despite both sexes having higher early recanalization rates in the

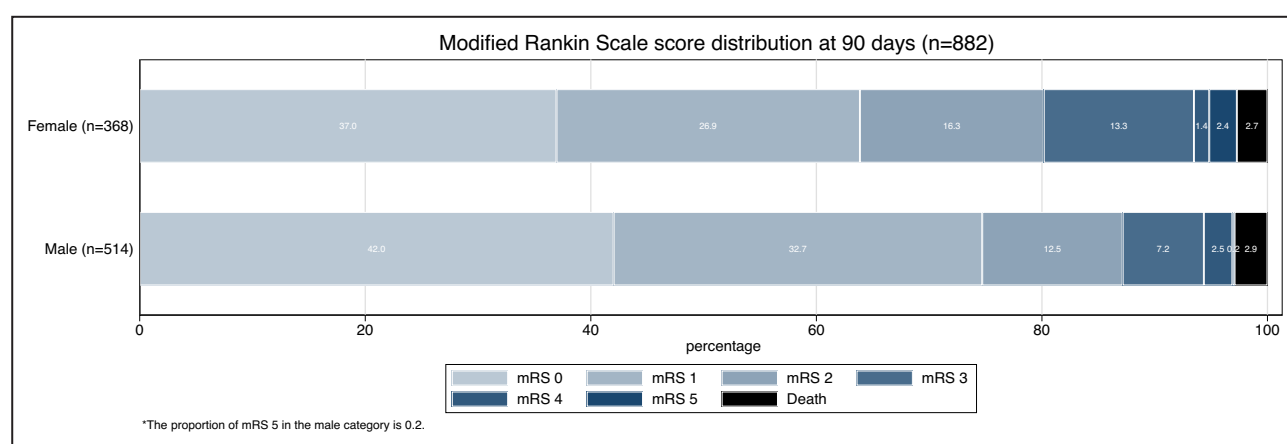


Figure 1. Horizontal stacked bar graphs of Modified Rankin Scale score at 90 days stratified by sex. mRS indicates Modified Rankin Scale.

tenecteplase group compared with control. Fewer female patients treated with tenecteplase returned to baseline function compared with those treated with control, but this difference was not statistically significant. Female patients treated with tenecteplase were more likely to have intracranial hemorrhage on follow-up imaging, but rates of symptomatic intracerebral hemorrhage and 90-day mortality was similar. Any intracranial hemorrhage has previously been shown to be associated with worse outcomes after thrombolysis, this may partly why female patients were less likely to return to baseline function.¹³ Male patients treated with tenecteplase had similar functional outcomes as those treated with control. The 90-day mortality among male patients treated with tenecteplase was higher than those treated with control, but the total number of deaths was quite small. It is not clear if this was a random variation because the burden of serious adverse events was similar between the 2 groups.

In the second comparison, we found that female patients treated with tenecteplase were less likely to meet the return-to-baseline function responder outcome compared with men treated with tenecteplase. Female patients in the tenecteplase group were more likely to have comorbidities, functional dependence, and large or medium vessel occlusions compared with the male counterparts, but the difference in outcomes persisted even after adjustment for baseline risk factors. The reason for this observation is unclear as there were no sex differences in effect as measured by early vessel recanalization among those with a baseline occlusion or harm, including intracerebral hemorrhage or other adverse events. This finding is surprising because prior sex-stratified analyses of data from patients treated with thrombolysis in population-based registries,^{14,15} cohort studies,^{16,17} and clinical trials^{18,19} have found no modification of treatment effect by sex, suggesting that thrombolysis may in fact mitigate the sex disparities in stroke outcomes. However, most of these studies did

not include patients with transient ischemic attacks and minor strokes.

Two recent randomized trials (PRISMS²⁰ [Potential of rtPA (Recombinant Tissue Plasminogen Activator) for Ischemic Strokes With Mild Symptoms] and ARAMIS²¹ [Antiplatelet vs R-tPA for Acute Mild Ischemic Stroke]) and a recent systematic review and meta-analysis²² found no benefit of thrombolysis over best medical therapy in patients with minor ischemic stroke, but these studies did not mandate the presence of symptomatic occlusion or perfusion defect. Without confirmed vascular abnormality or ischemia, the benefit and risks of thrombolysis could be diluted by nonstroke mimics, which could vary by sex. A sex-stratified subanalysis of NOR-TEST (Norwegian Tenecteplase Stroke Trial), a randomized controlled trial comparing tenecteplase (0.4 mg/kg) to alteplase that largely enrolled patients with minor strokes, found that enrollment for a mimic was more common among women (21% mimic among women, 15% among men).²³ Over 90% of patients enrolled in PRISMS had a 90-day mRS score of 0 to 2 and 13% of patients had a final diagnosis of stroke mimic.²⁰ In ARAMIS, >95% of patients had a 90-day mRS score of 0 to 2, but the proportion of mimics was not reported.²¹ A sex-stratified subanalysis of ARAMIS did not identify any modification of the overall effect of thrombolysis by sex.²⁴ In TEMPO-2, only 80% of female and 87% of male participants had a 90-day mRS score of 0 to 2 and about 1 in 4 patients did not return to their baseline function (64% female, 78% male) despite thrombolysis. These outcomes challenge the notion that strokes with low NIHSS scores are “minor.” Instead, minor stroke is a heterogenous entity where the presence of vascular occlusion or perfusion defect heralds a worse outcome. Future studies on the acute treatment of this population should include information on imaging evidence of acute ischemia such as vessel occlusion or perfusion defect.

Table 3. Baseline Characteristics by Sex, Stratified by Treatment Arm

	Tenecteplase (N=432)			Control (N=452)		
	Female	Male	P value	Female	Male	P value
	No.=188 (43.5%)	No.=244 (56.5%)		No.=180 (39.8%)	No.=272 (60.2%)	
Patient characteristics						
Median age, y (IQR)	75 (64–84)	70 (60–78)	<0.01	74 (65–82)	70 (59–78)	<0.01
Hypertension	119 (63.3%)	146 (59.8%)	0.49	106 (58.9%)	155 (57.0%)	0.70
Past smoking	59 (31.4%)	113 (46.3%)	<0.01	60 (33.3%)	116 (42.6%)	0.05
Hyperlipidemia	72 (38.3%)	108 (44.3%)	0.24	70 (38.9%)	102 (37.5%)	0.77
Diabetes	36 (19.1%)	46 (18.9%)	1.00	32 (17.8%)	54 (19.9%)	0.63
Past stroke	30 (16.0%)	42 (17.2%)	0.80	29 (16.1%)	56 (20.6%)	0.27
Atrial fibrillation	36 (19.1%)	55 (22.5%)	0.41	31 (17.2%)	47 (17.3%)	1.00
Ischemic heart disease	20 (10.6%)	49 (20.1%)	<0.01	18 (10.0%)	55 (20.2%)	<0.01
Congestive heart failure	9 (4.8%)	7 (2.9%)	0.32	6 (3.3%)	12 (4.4%)	0.63
Chronic renal failure	14 (7.4%)	8 (3.3%)	0.08	5 (2.8%)	12 (4.4%)	0.45
Peripheral vascular disease	6 (3.2%)	7 (2.9%)	1.00	5 (2.8%)	10 (3.7%)	0.79
Past intracerebral hemorrhage	3 (1.6%)	0 (0.0%)	0.08	0 (0.0%)	1 (0.4%)	1.00
Prestroke modified Rankin Scale score						
0	141 (75.0%)	195 (79.9%)		137 (76.1%)	217 (79.8%)	0.33
1	25 (13.3%)	36 (14.8%)		23 (12.8%)	36 (13.2%)	
2	22 (11.7%)	13 (5.3%)	0.06	20 (11.1%)	19 (7.0%)	
Stroke characteristics						
Median baseline National Institutes of Health Stroke Scale score (IQR)	2 (1–3)	2 (1–3)	0.54	2 (1–3)	2 (1–3)	0.76
NIHSS=0	35 (18.6%)	39 (16.0%)	0.52	28 (15.6%)	40 (14.7%)	0.89
Baseline Alberta Stroke Program Early Computed Tomography Score	10 (9–10)	10 (10–10)	0.84	10 (9–10)	10 (9–10)	0.97
Baseline occlusion (core laboratory)						
Large vessel	27 (14.4%)	26 (10.7%)	<0.01	26 (14.4%)	24 (8.9%)	0.01
Medium vessel	112 (59.9%)	123 (50.4%)		102 (56.7%)	143 (53.0%)	
Vertebrobasilar	2 (1.1%)	18 (7.4%)		6 (3.3%)	19 (7.0%)	
Focal perfusion lesion	45 (24.1%)	73 (29.9%)		43 (23.9%)	84 (31.1%)	
No occlusion detected	1 (0.5%)	4 (1.6%)		3 (1.7%)	0 (0.0%)	
Hemoglobin, g/L	132 (125–142)	146 (135–155)	<0.01	136 (128–143)	146 (135–156)	<0.01
Glucose, mM	6 (6–8)	6 (5–7)	0.73	6 (6–7)	6 (6–8)	0.03
Creatinine, μM	72 (63–85)	89 (77–103)	<0.01	72 (63–88)	89 (78–103)	<0.01
Time metrics in minutes						
Onset to emergency department arrival, min	127 (70–330)	154 (86–335)	0.76	154 (80–336)	147 (68–338)	0.99
Onset to randomization, min	268 (160–450)	291 (162–436)	0.94	309 (178–454)	259 (154–435)	0.18
Onset to treatment, min	276 (162–461)	301 (169–450)	0.88	347 (201–510)	300 (170–485)	0.32

IQR indicates interquartile range. Large vessel: intracranial internal carotid artery, M1 segment of the middle cerebral artery. Medium vessel: M2 segment of the middle cerebral artery or distal, A2 segment of the anterior cerebral artery or distal. Vertebrobasilar: vertebral artery, basilar artery, posterior cerebral artery, or branches.

Table 4. Adverse Events and Outcomes by Sex, Stratified by Treatment Arm

	Tenecteplase (N=432)			Control (N=452)		
	Female	Male	P value	Female	Male	P value
	No.=188 (43.5%)	No.=244 (56.5%)		No.=180 (39.8%)	No.=272 (60.2%)	
Responder	120 (63.8%)	189 (77.5%)	<0.01	133 (73.9%)	205 (75.4%)	0.74
NIHSS score=0 at 5 d or discharge	103 (56.0%)	143 (61.4%)	0.27	89 (50.3%)	134 (50.6%)	1.00
IADL-Lawton-COMPASS_ND scoring algorithm	23 (17–23)	23 (22–23)	<0.01	23 (19–23)	23 (21–23)	0.14
Median EQ5D-5L index (n=845)	1 (1–1)	1 (1–1)	0.12	1 (1–1)	1 (1–1)	0.11
Any serious adverse event	46 (24.5%)	54 (22.1%)	0.57	39 (21.7%)	41 (15.1%)	0.08
Stroke progression	18 (9.6%)	17 (7.0%)	0.38	15 (8.3%)	18 (6.6%)	0.58
Stroke recurrence	5 (2.7%)	11 (4.5%)	0.44	6 (3.3%)	9 (3.3%)	1.00
Symptomatic intracerebral hemorrhage	1 (0.5%)	5 (2.0%)	0.47	0 (0.0%)	2 (0.7%)	0.52
Any hemorrhage on follow-up imaging	26 (13.8%)	36 (14.8%)	0.89	10 (5.7%)	30 (11.5%)	0.06
Rescue endovascular thrombectomy for index stroke	8 (4.3%)	7 (2.9%)	0.44	5 (2.8%)	5 (1.8%)	0.53
Death within 5 d	3 (1.6%)	5 (2.0%)	1.00	0 (0.0%)	1 (0.4%)	1.00
Death at 90d	6 (3.2%)	14 (5.7%)	0.25	4 (2.2%)	1 (0.4%)	0.09
Aspiration pneumonia	2 (1.1%)	4 (1.6%)	0.70	1 (0.6%)	1 (0.4%)	1.00
Atrial fibrillation	3 (1.6%)	1 (0.4%)	0.32	2 (1.1%)	1 (0.4%)	0.57
Congestive heart failure	4 (2.1%)	1 (0.4%)	0.17	1 (0.6%)	0 (0.0%)	0.40
Seizure	1 (0.5%)	2 (0.8%)	1.00	2 (1.1%)	1 (0.4%)	0.57
Urinary tract infection	0 (0.0%)	2 (0.8%)	0.51	3 (1.7%)	1 (0.4%)	0.31

Missing data: 25 patients had missing NIHSS at 5 d or discharge, 34 patients had missing Lawton IADL, 39 patients had missing EQ5D-5L index, and 17 patients had missing data on hemorrhage on follow-up imaging.

EQ-5D-5L indicates EuroQol-5 Dimension score; IADL-Lawton-COMPASS-ND, Lawton Instrumental Activities of Daily Living Scale (Comprehensive Assessment of Neurodegeneration and Dementia); and NIHSS, National Institutes of Health Stroke Scale.

There are several limitations in the current study. Like other acute clinical trials in the minor stroke population, such as PRISMS (46% female), ARAMIS (31% female), NOR-TEST (40% female), TEMPO-2 also had an underenrollment of female participants (41.5% female), which could have made this analysis underpowered to detect differences in outcomes. Early recanalization status was measurable only in patients who were enrolled based on the presence of intracranial occlusion (n=628, 70.8%) and among these,

protocol deviations with missing 4- to 8-hour computed tomography angiograms were more common in female versus male participants. Finally, identifying clinically relevant outcomes that are meaningful to patients in a minor stroke trial is challenging. Although the mRS is the most widely used measure of stroke outcome, its responsiveness to change for minor stroke may be limited and its subjective nature may lead to sex or gender biases that have not yet been formally evaluated.²⁵ The responder outcome was designed to

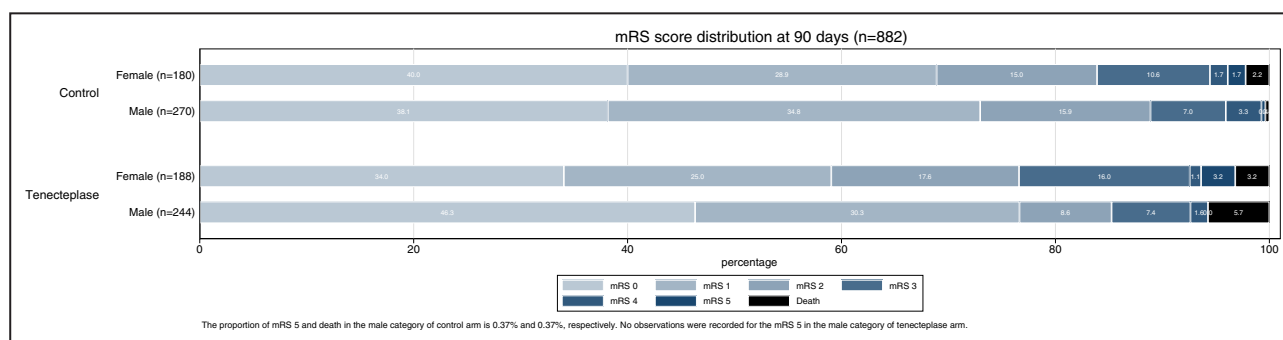


Figure 2. Horizontal stacked bar graphs of Modified Rankin Scale score at 90 days stratified by sex and treatment. mRS indicates Modified Rankin Scale.

take into account that patients in this population likely already have disability at baseline and we evaluated several patient-reported outcome measures, including the Lawton IADL and EuroQol-5 Dimension, but perhaps more data on cognition, sleep disturbances, mood, fatigue, and other symptoms could shed light on why female patients are not returning to baseline function despite similar adverse events and most imaging outcomes.^{26,27}

CONCLUSIONS

We showed that tenecteplase was not associated with better clinical outcomes over medical management in female or male patients with minor ischemic stroke. Tenecteplase was associated with higher revascularization compared with control, but fewer women returned to baseline function compared with men in the treatment arm.

APPENDIX: TEMPO-2 STUDY GROUP INVESTIGATORS CENTRAL AND BY SITE

Central

Calgary Image Processing and Analysis Centre: Marina Salluzzi, Nicole Blenkin, Ashley Dueck
 Contracts and Finances: Craig Doram, Qiao Zhang
 Site Monitors: Carol Kenney, Charlotte Zerna, Karla Ryckborst, Shelly Bohn
 Safety Review Committee: P Barber, T Field, D Dowlatsahi
 Data Safety Monitoring Board: Robert Hard (Chair), David Kent, Renee Martin and William Whiteley
 Website and Video: Quinten Collier
 Clinical Research Unit: Frances Taylor, B. Cord Lethebe
 By Enrolling Sites:
Foothills Medical Centre, University of Calgary, Calgary, AB
 Site principal investigator [PI]: PA Barber
 Primary Study Coordinators: C Kenney, A Jambula, K Sage, K Ryckborst, L Toussaint, S Save, J Lee, N Laham
 Other Site Investigators: A A Sultan, A Moussaddy, A Deepak, A Sitaram, A Y X Yu, A M Demchuk, A Locky, A Micielli, A Wadhwa, A Ganesh, B Arabambi, B K Menon, B Graham, C Tham, C Zerna, C Bogiatzi, D Doshi, D Chakraborty, D Kim, D Vasquez, D Singh, D Tse, E Harrison, E Smith, E Teleg, E Klourfeld, G Klein, I A Sebastian, J Evans, J Hegedus, J Kromm, K Lin, K Ignacio, K Ghavami, M Ismail, M Moores, M A Panzini, M Marko, M Boyko, M D Hill, M A Almekhlafi, N Newcommon, N Maraj, N Singh, O Imoukhuede, O Volny, P Stys, P Barber, P Couillard, P Ojha, P

Eswaradass, R Joundi, R Appireddy, R Singh, R M Asuncion, R T Muir, S Dey, S Mansoor, S Wasyliv, S Nagendra, S Hu, S Althubait, S Chen, S Bal, S Van Gaal, S Peters, S Ray, S Chaturvedi, S Subramaniam, V Fu

Vancouver General Hospital, Vancouver, BC

Site PI: T S Field

Primary Study Coordinators: K Villaluna, G Maclean, P King-Azote, C Ma

Other Site Investigators: A Plecash, C Murphy, D Tse, J Gorman, K Ghavami (Also listed under Calgary), L Wilson, L Zhou, O Benavente, P Teal, S Yip, S Mann, S Van Gaal(also listed under Calgary)

Ottawa Hospital Research Institute, Ottawa, ON

Site PI: D Dowlatsahi

Primary Study Coordinators: B Dewar, M Demetroff, R Shamloul, R Beardshaw, S Roberts

Other Site Investigators: D Blaquiére, G Stotts, M Shamy, O Berezhnyakova, R Fahed, W Alesefir

Enfant-Jésus Hospital, Centre Hospitalier Universitaire de Québec, Quebec City, QC

Site PI: M C Camden

Primary Study Coordinator: Suzy Lavoie, A Hache, K Collard

Other Site Investigators: A Mackey, S Gosselin-Lefebvre, S Verreault

London Health Sciences Centre, University Hospital, London, ON

Site PI: J Mandzia

Primary Study Coordinators: B Beauchamp, L Lambourn

Other Site Investigators: A Khaw, L Mai, L Sposato, M Bres Bullrich, R Azarpazhooh, S Fridman

Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON

Site PI: A Y X Yu

Primary Study Coordinators: A Kapoor, A Southwell, E Bardi, I Fatakdawala, M Kamra, K Lopes, N Popel, V Norouzi

Other Site Investigators: A Liu, AM Liddy, B Ghoari, C Hawkes, C A Enriquez, D J Gladstone, H A Manosalva Alzate, H Khosravani, J J Hopyan, K Sivakumar, M Son, M I Boulos, M A Hamind, R H Swartz, R Murphy, S Reiter, T Fitzpatrick, V Bhandari
Victoria General Hospital, Victoria, BC

Site PI: A Penn

Primary Study Coordinators: J Good, M Penn, M Naylor, S Frost

Toronto Western Hospital, University Health Network, University of Toronto, Toronto, ON

Site PI: L Casaubon

Primary Study Coordinators: A Cayley, F Akthar, J Williams, L Kalman, L Crellin, R Wiegner, S Singh, T Stewart, W To, S Singh

Other Site Investigators: A Pikula, C Jaigobin, F Carpani, F Silver, H Janssen, J Schaafsma, K Sivakumar (Also

listed under Sunnybrook), M del Campo, M Alskaini, P Rajendram
University of Alberta Hospital, Edmonton, AB
 Site PI: B Buck
 Primary Study Coordinators: P Fairall, B Granfield, D Crawford, J Jabs, L White, L Sivakumar, L Piquette, T Nguyen
 Other Site Investigators: A Nomani, A Wagner, A Alrohim, A Butt, A D'Souza, B Gajurel, C Vekhande, H Kamble, H Kalashyan, K Butcher, M Lloret, M Benguzzi, N Arsalan, N Ishaque, R Ashayeriahmadabad, R Samiento, S Mishra, S Hosseini, S Kazi, S Das, T Sugumar
St. Michael's Hospital, Toronto, ON
 Site PI: A Zafar and D Selchen (also listed in SM as PI)
 Primary Study Coordinators: P Kostyrko
 Other Site Investigators: A Muccilli, G Saposnik
Medical University of Vienna, General Hospital, Vienna, Austria
 Site PI: S Greisenegger
 Primary Study Coordinators: K Werner, S Wieszmuellner
 Other Site Investigators: A Langer, A Gisold, H Zach, M Marko, P Rommer, S Macher, S Blechinger, W Marik, W Series
St. John's of God Hospital, Vienna, Austria
 Site PI: J Ferrari
 Primary Study Coordinators: M Baumgartinger
 Other Site Investigators: S Krebs
Hamilton Health Sciences Centre, Hamilton, ON
 Site PI: L Catanese
 Primary Study Coordinators: C Vandervelde, K Ratnayake, S McMillan
 Other Site Investigators: A Katsanos, A Shoamanesh, D J Sahlas
Royal Columbian Hospital, New Westminster, BC
 Site PI: G Medvedev
 Primary Study Coordinators: V Naidoo, V Todorov
 Other Site Investigators: H Toma, J Brar, J Lee, M Horton, S Chen
Red Deer Regional Centre Hospital, Red Deer, AB
 Site PI: O Imoukhuede
 Primary Study Coordinators: E Shand
Kingston General Hospital, Kingston, ON
 Site PI: R Appireddy
 Primary Study Coordinators: S Weatherb
 Other Site Investigators: A Jin, B Durafourt, S Jalini
Royal University Hospital, Saskatoon, SK
 Site PI: G Hunter
 Primary Study Coordinators: A Gardner, C Tyson, E Junk, K Foster, K Bolt, N Sylvain, S Maley
 Other Site Investigators: B Graham, L Urroz, L Peeling, M Kelly, R Whelan, S Wasyliv, R Cooley
McGill University Health Centre, Montreal, QC
 Site PI: A Moussaddy and J Teitelbaum (also listed as PI in SM)

Primary Study Coordinators: A Boutayeb, A Moore, E Cole, L Waxman, N Ben-Amor, R Sanchez, S Khalil
 Other Site Investigators: A Nehme, C Legault, D Tampieri, E Ehrensperger, L Vieira, M Cortes, M Angle, M Hannouche, M Badawy
Helsinki University Hospital, Helsinki, Finland
 Site PI: D Strbian
 Primary Study Coordinators: J Koski, S Eirola, T Ivanoff, A Erakanto, L Kupari
 Other Site Investigators: G Sibolt, J Panula, L Tomppo, M Tiainen, M Ahlstrom, N Martinez Majander, O Suomalainen, S Raty
John Hunter Hospital, New South Wales, Australia
 Site PI: C Levi and N Spratt
 Primary Study Coordinators: E Kerr, J Allen, L P Kaauwai, L Belevski, M Russell, S Ormond
 Other Site Investigators: A Chew, A Loiselle, A Royan, B Hughes, C Garcia Esperon, E Pepper, F Miteff, J He, M Lycett, M Min, N Murray, N Pavey, R Starling de Barros, S Gangadharan, S Dunkerton, S Waller, T Canento Sanchez, T Wellings
Fiona Stanley hospital, Murdoch, Western Australia, University of Western Australia, Perth, Western Australia
 Site PI: D Ghia
 Primary Study Coordinators: G Edmonds, K A Whittaker, M Ewing, P Lee, R Singkang
Royal Melbourne Hospital, Parkville, Australia
 Site PI: B Campbell
 Primary Study Coordinators: A McDonald, C Shin, D Jackson, J Tsoleridis, L Fisicchia, N Parsons, N Shenoy, S Smith
 Other Site Investigators: A Sharobeam, A Balabanski, A Park, A Dos Santos, C Williams, D Pavlin-Premri, E Rodrigues, F Alemseged, F Ng, H Zhao, J Beharry, J L Ng, J Williamson, J Z W Wong, K Li, M K Kwan, M Parsons, M Valente, N Yassi, R Cooley, V Yogendrakumar
Box Hill Hospital, Box Hill, Australia
 Site PI: P Choi
 Primary Study Coordinators: B McNamara, C Buchanan, C McCarthy, G Thomas, K Stephens, M F Chung, M Tang, N Pachani, N Stuart, R Lee, T Frost, T Busch, M Chung
 Other Site Investigators: A Menon, B Borojevic, C M Linton, E P Callaly, G Garcia, H Dewey, J Liu, J Chen, J Wong, K Nowak, K To, N S Lizak, O Bhalala, P Park, P Tan, R Martins, R Cody, R Forbes, S K Chen, S Tu, S Ooi, Y L Dang, Z Ling
Royal Adelaide Hospital, Adelaide, Australia
 Site PI: T Kleinig
 Primary Study Coordinators: J Cranefield, R Drew
 Other Site Investigators: A Tan, C Kurunawai, J Harvey, J J Mahadevan, L Cagi, L Palanikumar, N Chia, R Goh, S El-Masri
Gold Coast University Hospital, Gold Coast, Australia
 Site PI: P Bailey, S Mishra

Primary Study Coordinators: B Urbi, C Rapier, H Berrill, H McEvoy, R Dunning, S Kuriakose, T Chad, V Sapaen

Other Site Investigators: A Sabet, D Shah, D Yeow, K Lilley, K Ward, M Mozhy Mahizhnan, M Tan

Mater Misericordiae University Hospital, Dublin, Ireland

Site PI: Peter Kelly

Primary Study Coordinators: C Lynch, S Coveney, K Tobin

Other Site Investigators: J McCabe, M Marnane, S Murphy

Beaumont Hospital, Dublin, Ireland

Site PI: D Williams

Primary Study Coordinators: M Large

Other Site Investigators: B Moynihan, K Boyle

Hospital Universitari Vall d'Hebronq, Barcelona, Spain

Site PI: C Molina

Primary Study Coordinators: E Sanjuan, M Sanchis, O Pancorbo, V Sala, L Garcia

Other Site Investigators: A Garcia-Tornel, J Juega, J Pagola, K Santana, M Requena, M Muchada, M Olive, M Rubiera, M Deck, N Rodriguez, P J Lozano, S Boned

Clinic University Hospital Valladolid, Valladolid, Spain

Site PI: J F Arenillas

Primary Study Coordinators: B Gomez, F J Reyes Munoz

Other Site Investigators: A S Gomez, A C Sanz, E C Garcia, G Penacoba, M E Ramos, M de Lera Alfonso

Hospital Universitari Doctor Josep Trueta, Girona, Spain

Site PI: J Leal

Primary Study Coordinators: A Feliu, L Pardo, P Ramirez

Other Site Investigators: A Murillo, D Lopez Dominguez, J Rodriguez, M Terceno Izaga, M Reina, S B Viturro, U Bojaryn, V A Vera Monge, Y Silva Blas

National Neuroscience Institute, Tan Tock Seng Hospital, Novena, Singapore

Site PI: C Tham

Primary Study Coordinators: R Siew, S J Agustin

Other Site Investigators: C Seet, T Tianming

Christchurch Hospital, Christchurch, New Zealand

Site PI: T Y H Wu

Primary Study Coordinators: A d'Emden

Other Site Investigators: None listed

Queen Elizabeth University Hospital, Glasgow, Scotland

Site PI: K Muir

Primary Study Coordinators: A Murray, A Welch, K Hatherley, N Day, W Smith, E MacRae, S Mitchell

Other Site Investigators: A Sitaram, A Mahmood, J Elliot, S Neilson, V Biswas, C Brown

University College London Hospital, London, England

Site PI: R Simister

Primary Study Coordinators: A Lewis, A Ashton, A Black, A Robinson, A Williams, A Banaras, C Cahoy, G Raingold, M Marinescu, N Atang, N Bason, N Francia, R Muhammad, S Obarey, S Feerick, Y C Lee

Other Site Investigators: D Werring, R Perry

John Radcliffe Hospital, Oxford, England

Site PI: J Kennedy

Primary Study Coordinators: J Joseph, J Benjamin, L Quinn, M Jhoots, R Teal

Other Site Investigators: G Ford, G Harston, H Bains, I Gbinigie, P Mathieson, R Irons, U Schulz

St. George's University Hospital (Foundation Trust), London, England

Site PI: B Clarke

Primary Study Coordinators: C H Sim, E Hayter, K Kennedy, L Binnie, N Priestley, R Williams, R Ghatala, S Stratton

Other Site Investigators: None listed

Countess of Chester Hospital, Chester, England

Site PI: K Chatterjee

Primary Study Coordinators: A Davies, H Duffy, J Roberts, J Homer, K Roberts, K Dodd, K Cawley, M Martin, S Leason, S Cotgreave, T Taylor

Other Site Investigators: A Nallasivan, S Haider, T Chakraborty, T Webster

Charring Cross Hospital, London, England

Site PI: O Halse

Primary Study Coordinators: A Gil, B Martin, B Joseph, C Cabrera, D Jose, J Man, J Aquino, L Sebastian, M Osterdahl, M Kwan, M Matthew, N Ike, P Bello, P Wilding, R Fuentes, R Shah, S Mashate, T Patel, U Nwanguma, V Dave

Other Site Investigators: A El-Masry, A Ali Sheikh, A C Dawson, A Haber, A Lee, A O'Sullivan, B Drumm, C O'Hare, D Roberts, D Kallacka, E Taylor, E Rounis, F Vonberg, I H Jenkins, J Blagojevic, J George, J Kwan, M Saeed, M Evans, M Haji-Coll, M Tsuda, M Sayed, N Thanbirajah, N Winterkron, O Raha, O Vittay, R Karim, R C Smail, S Gauhar, S Kalam, S Elmamoun, S Malani, S Pralhad Kelavkar, S Jamil, S Auger, T Matar, V Biswas

University Hospital of North Midlands, Stoke, England

Site PI: C Roffe

Primary Study Coordinators: J Hiden, R Varquez

Other Site Investigators: P Ferdinand, R Sanyal

Royal Victoria Hospital, Belfast, Ireland

Site PI: I Wiggam

Primary Study Coordinators: B Smith, C Okechukwu, E Fox, E Collins, K Courtney, S Tauro

Other Site Investigators: C Patterson, D McShane, E Kerr, G Roberts, J McIlmoyle, K McGuire, P Fearon, P Gordon

Birmingham City Hospital, Birmingham, England

Site PI: M Willmot

Primary Study Coordinators: K Isaacs, K Lucas, L Smith, L Dews, M Bates, S Lawrence, S Heeley, V Patel, Y M Chin

Other Site Investigators: D Sims, E Littleton, J Khaira, K Nadar

King's College Hospital, London, England

Site PI: S Ankolekar

Primary Study Coordinators: A Kieliszkowska, B Sari, C Domingos Belo, E Smith, E Y Manolo, J Aeron-Thomas, M Doheny, M Garcia Pardo, M Recaman, M C Tibajia, M Aissa, S Bayhonian, S Conway

Other Site Investigators: A Bhalla, A Engineer, D Nouvakis, E Theochari, F Boyle, J Teo, J King-Robson, K Y Law, L Sztriha, M Ismail, M Benger, M Farag, O Williams, R Alsukhni, S Heller, S Meenakshisundaram, T Yu, V Patel, Y Mah

Cambridge University Hospital, Cambridge, England

Site PI: G Zachariah

Primary Study Coordinators: A McGovern, A Iqbal, D Day, J Mitchell-Douglas, J Francis, P Punjabivaryani

Other Site Investigators: J Anonuevo Reyes, M Pauls, M Anonuevo Reyes

Nottingham City Hospital, Nottingham, England

Site PI: K Krishnan

Primary Study Coordinators: A Buch, A Hedstrom, C Hutchinson, C Kirkland, G Wilkes, J Newham, L Fleming

Porto Alegre Hospital, Porto Alegre, Brazil

Site PI: S Martins

Primary Study Coordinators: N Fleck

Other Site Investigators: A Franca, A Pille, B Chwal, C Oldoni, G Mantovani, G Noll, L Zanella, M Soma, T Secchi, W Borelli

Hospital de Clinicas de Ribeirão Preto, Ribeirão Preto, Brazil

Site PI: O Marques Pontes Neto

Primary Study Coordinators: B P Rimoli, G H da Cunha Silva, L A Machado Galvao Mondin, R Barbosa Cerantola

Other Site Investigators: A K Imthon, A S Esaki, A L A de Albuquerque, A M Pazini, C E Massote Fontanini, C F Matinez Rubio, C Milani, D T dos Santos, F A Dias, F F A Alves, G G Riccioppa Rodrigues, K Santos Ferreira, M A Pena Pereira, M B Morillos, M Camilo, O C Vincenzi, R R de Cruz

Hospital de Clinicas de Botucatu, Botucatu, Brazil

Site PI: R Bazan

Primary Study Coordinators: B Pegorer Santos, F Winckler, J T De Souza, L A M Bonome, N C Ferreira

Other Site Investigators: D F Barbosa dos Santos, G P Modolo, J C dos Santos Moreira, R S Teodoro, V A Cury Silva

Hospital Geral de Fortaleza, Fortaleza, Brazil

Site PI: F O Lima and A B Cruz Guedes de Morais (two PIs listed—not sure of order or second name)

Primary Study Coordinators: J Vieira

Other Site Investigators: G Mendes, J P de Queiroz

ARTICLE INFORMATION

Received October 13, 2024; accepted February 4, 2025.

Affiliations

Department of Medicine (Neurology), University of Toronto, Sunnybrook Health Sciences Centre, Toronto, ON, Canada (A.Y.Y.); Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, AB, Canada (S.V., A.G., P.A.B., M.D.H., S.B.C.); Vancouver Stroke Program, Division of Neurology, University of British Columbia, Vancouver, BC, Canada (T.S.F.); Department of Neuroscience, Box Hill Hospital, Eastern Health, Melbourne, Australia (P.M.C.); Australia and Eastern Health Clinical School, Monash University, Melbourne, Australia (P.M.C.); Department of Medicine, Division of Neurology, University of Alberta, Edmonton, AB, Canada (B.B.); Department of Neurology, Royal Adelaide Hospital, Adelaide, SA, Australia (T.K.); Department of Medicine, University of Adelaide, Adelaide, SA, Australia (T.K.); Vall d'Hebron Stroke Center, Hospital Vall d'Hebron, Barcelona, Spain (C.A.M.); Department of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia (B.C.C.); Division of Neurology, Department of Medicine, Queen's University, Kingston, ON, Canada (R.A.); and School of Neuroscience & Psychology, University of Glasgow, UK (K.W.M.).

Sources of Funding

Funding for the TEMPO-2 trial is from grants from Heart and Stroke Foundation of Canada, Canadian Institutes of Health Research, and the British Heart Foundation (CS/18/5/34081). Intravenous tenecteplase is a standard off-the-shelf drug and was paid for by Boehringer Ingelheim, who had no role in the trial design or conduct, data analysis, or article preparation.

Disclosures

Amy Y. X. Yu holds a Tier 2 Canada Research Chair in Data-driven design of stroke systems and has received operating grant funding from the Heart and Stroke Foundation of Canada and the Canadian Institutes of Health Research. Aravind Ganesh reports a grant from Microvention and speaker fees from Alexion, Biogen and Servier Canada. Aravind Ganesh holds stock options for SnapDx Inc and Collavidence Inc. Thalia S. Field reports advisory board participation for AstraZeneca, Bayer, HLS Therapeutics, and Novartis and speaker's bureau for AstraZeneca. She is on the boards of Destine Health and the Vancouver General Hospital/UBC Hospital Foundation and has served as an expert witness. Keith W. Muir reports funding from the British Heart Foundation (CS/18/5/34081) for this study. Michael D. Hill reports grant funding from Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, Alberta Innovates, and study drug from Boehringer-Ingelheim. He also reports grants from NoNo and Medtronic. He has had consulting fees from Sun Pharma Brainsgate Inc. Shelagh B. Coutts reports grant funding from Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, and the British Heart Foundation to complete the TEMPO-2 study. Boehringer Ingelheim provides the study drug (tenecteplase) for the study.

Supplemental Material

Tables S1–S2

REFERENCES

1. Coutts SB, Ankolekar S, Appireddy R, Arenillas JF, Assis Z, Bailey P, Barber PA, Bazan R, Buck BH, Butcher KS, et al. Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion (TEMPO-2): a randomised, open label, phase 3 superiority trial. *Lancet*. 2024;403:2597–2605. doi: [10.1016/s0140-6736\(24\)00921-8](https://doi.org/10.1016/s0140-6736(24)00921-8)
2. Eriksson M, Glader EL, Norrving B, Terent A, Stegmayr B. Sex differences in stroke care and outcome in the Swedish national quality register for stroke care. *Stroke*. 2009;40:909–914. doi: [10.1161/strokeaha.108.517581](https://doi.org/10.1161/strokeaha.108.517581)
3. Yu AYY, Austin PC, Rashid M, Fang J, Porter J, Vyas MV, Smith EE, Joundi RA, Edwards JD, Reeves MJ, et al. Sex differences in intensity of care and outcomes after acute ischemic stroke across the age continuum. *Neurology*. 2023;100:e163–e171. doi: [10.1212/wnl.0000000000201372](https://doi.org/10.1212/wnl.0000000000201372)

4. Renoux C, Coulombe J, Li L, Ganesh A, Silver L, Rothwell PM. Confounding by pre-morbid functional status in studies of apparent sex differences in severity and outcome of stroke. *Stroke*. 2017;48:2731–2738. doi: [10.1161/strokeaha.117.018187](https://doi.org/10.1161/strokeaha.117.018187)
5. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac DA, Sturm J, Heeley E, Otahal P, Vemmos K, Anderson C, et al. Factors contributing to sex differences in functional outcomes and participation after stroke. *Neurology*. 2018;90:e1945–e1953. doi: [10.1212/wnl.0000000000005602](https://doi.org/10.1212/wnl.0000000000005602)
6. Bushnell CD, Reeves MJ, Zhao X, Pan W, Prvu-Bettger J, Zimmer L, Olson D, Peterson E. Sex differences in quality of life after ischemic stroke. *Neurology*. 2014;82:922–931. doi: [10.1212/wnl.0000000000000208](https://doi.org/10.1212/wnl.0000000000000208)
7. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac DA, Sturm J, Heeley E, Otahal P, Rothwell P, Anderson CS, et al. Sex differences in long-term quality of life among survivors after stroke in the INSTRUCT. *Stroke*. 2019;50:2299–2306. doi: [10.1161/strokeaha.118.024437](https://doi.org/10.1161/strokeaha.118.024437)
8. Spaander FH, Zinkstok SM, Baharoglu IM, Gensicke H, Polymeris A, Traenka C, Hametner C, Ringleb P, Curtze S, Martinez-Majander N, et al. Sex differences and functional outcome after intravenous thrombolysis. *Stroke*. 2017;48:699–703. doi: [10.1161/strokeaha.116.014739](https://doi.org/10.1161/strokeaha.116.014739)
9. Reeves M, Bhatt A, Jajou P, Brown M, Lisabeth L. Sex differences in the use of intravenous rt-PA thrombolysis treatment for acute ischemic stroke: a meta-analysis. *Stroke*. 2009;40:1743–1749. doi: [10.1161/strokeaha.108.543181](https://doi.org/10.1161/strokeaha.108.543181)
10. Singh N, Kenney CC, Butcher KS, Buck B, Barber PA, Field TS, Choi PM, Yu AY, Kleinig T, Appireddy R, 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;19:817–822. doi: [10.1177/17474930241253702](https://doi.org/10.1177/17474930241253702)
11. Zhao W, Hill MD, Palesch Y. Minimal sufficient balance—a new strategy to balance baseline covariates and preserve randomness of treatment allocation. *Stat Methods Med Res*. 2015;24:989–1002. doi: [10.1177/0962280212436447](https://doi.org/10.1177/0962280212436447)
12. Chertkow H, Borrie M, Whitehead V, Black SE, Feldman HH, Gauthier S, Hogan DB, Masellis M, McGilton K, Rockwood K, et al. The comprehensive assessment of neurodegeneration and dementia: Canadian cohort study. *Can J Neurol Sci*. 2019;46:499–511. doi: [10.1017/cjn.2019.27](https://doi.org/10.1017/cjn.2019.27)
13. Tang G, Cao Z, Luo Y, Wu S, Sun X. Prognosis associated with asymptomatic intracranial hemorrhage after acute ischemic stroke: a systematic review and meta-analysis. *J Neurol*. 2022;269:3470–3481. doi: [10.1007/s00415-022-11046-6](https://doi.org/10.1007/s00415-022-11046-6)
14. Shobha N, Sylaja PN, Kapral MK, Fang J, Hill MD. Differences in stroke outcome based on sex. *Neurology*. 2010;74:767–771. doi: [10.1212/WNL.0b013e3181d5275c](https://doi.org/10.1212/WNL.0b013e3181d5275c)
15. Bonkhoff AK, Karch A, Weber R, Wellmann J, Berger K. Female stroke: sex differences in acute treatment and early outcomes of acute ischemic stroke. *Stroke*. 2021;52:406–415. doi: [10.1161/strokeaha.120.032850](https://doi.org/10.1161/strokeaha.120.032850)
16. Kent DM, Buchan AM, Hill MD. The gender effect in stroke thrombolysis: of CASES, controls, and treatment-effect modification. *Neurology*. 2008;71:1080–1083. doi: [10.1212/01.wnl.0000316191.84334.bd](https://doi.org/10.1212/01.wnl.0000316191.84334.bd)
17. Vincis E, Prandin G, Furlanis G, Scali I, Buoite Stella A, Cillotto T, Lugnan C, Caruso P, Naccarato M, Manganotti P. Sex differences in wake-up stroke patients characteristics and outcomes. *Neurol Sci*. 2024;45:4871–4879. doi: [10.1007/s10072-024-07597-3](https://doi.org/10.1007/s10072-024-07597-3)
18. Hill MD, Kent DM, Hinchey J, Rowley H, Buchan AM, Wechsler LR, Higashida RT, Fischbein NJ, Dillon WP, Gent M, et al. Sex-based differences in the effect of intra-arterial treatment of stroke: analysis of the PROACT-2 study. *Stroke*. 2006;37:2322–2325. doi: [10.1161/01.Str.0000237060.21472.47](https://doi.org/10.1161/01.Str.0000237060.21472.47)
19. Kim DJ, Singh N, Catanese L, Yu AYX, Demchuk AM, Lloret-Villas MI, Deschaintre Y, Coutts SB, Khosravani H, Appireddy R, et al. Sex-based analysis of workflow and outcomes in acute ischemic stroke patients treated with alteplase versus Tenecteplase. *Stroke*. 2024;55:288–295. doi: [10.1161/strokeaha.123.045320](https://doi.org/10.1161/strokeaha.123.045320)
20. Khatri P, Kleindorfer DO, Devlin T, Sawyer RN Jr, Starr M, Mejilla J, Broderick J, Chatterjee A, Jauch EC, Levine SR, 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;320:156–166. doi: [10.1001/jama.2018.8496](https://doi.org/10.1001/jama.2018.8496)
21. Chen HS, Cui Y, Zhou ZH, Zhang H, Wang LX, Wang WZ, Shen LY, Guo LY, Wang EQ, Wang RX, et al. Dual antiplatelet therapy vs alteplase for patients with minor nondisabling acute ischemic stroke: the ARAMIS randomized clinical trial. *JAMA*. 2023;329:2135–2144. doi: [10.1001/jama.2023.7827](https://doi.org/10.1001/jama.2023.7827)
22. Zhang Y, Lv T, Nguyen TN, Wu S, Li Z, Bai X, Chen D, Zhao C, Lin W, Chen S, et al. Intravenous alteplase versus best medical therapy for patients with minor stroke: a systematic review and meta-analysis. *Stroke*. 2024;55:883–892. doi: [10.1161/strokeaha.123.045495](https://doi.org/10.1161/strokeaha.123.045495)
23. Ihle-Hansen H, Sandset EC, Ihle-Hansen H, Hagberg G, Thommessen B, Rønning OM, Kvistad CE, Novotny V, Naess H, Waje-Andreassen U, et al. Sex differences in the Norwegian Tenecteplase trial (NOR-TEST). *Eur J Neurol*. 2022;29:609–614. doi: [10.1111/ene.15126](https://doi.org/10.1111/ene.15126)
24. Qu HL, Sun XY, He C, Chen HS. Sex differences in the dual antiplatelet therapy versus alteplase for patients with minor nondisabling acute ischemic stroke: a secondary analysis of the ARAMIS study. *CNS Drugs*. 2024;38:649–659. doi: [10.1007/s40263-024-01096-x](https://doi.org/10.1007/s40263-024-01096-x)
25. Broderick JP, Adeoye O, Elm J. Evolution of the modified Rankin scale and its use in future stroke trials. *Stroke*. 2017;48:2007–2012. doi: [10.1161/strokeaha.117.017866](https://doi.org/10.1161/strokeaha.117.017866)
26. Ospel JM, Ganesh A, Goyal M. Pragmatic outcomes for stroke research. *Lancet Neurol*. 2024;23:860–862. doi: [10.1016/s1474-4422\(24\)00316-8](https://doi.org/10.1016/s1474-4422(24)00316-8)
27. Oliveira LC, Ponciano A, Tuozzo C, Viswanathan A, Rost NS, Etherton MR. Poststroke disability: association between sex and patient-reported outcomes. *Stroke*. 2023;54:345–353. doi: [10.1161/strokeaha.122.041502](https://doi.org/10.1161/strokeaha.122.041502)