SUPPLEMENTAL MATERIAL

Table S1. Alteplase trials in the latest 5 years.

Study Acronym/ Publication Year/ Location	Study Type/ Study Size (N)	Time Window/ Eligibility Criteria of Imaging	Baseline Characteristics (Intervention vs. Comparator)	Clinical Outcomes (Intervention vs. Comparator)	Recanalization/ Reperfusion Rate (Intervention vs. Comparator)	Symptomatic Intracranial Hemorrhage (Intervention vs. Comparator)	Disability and Death at 90 Days (Intervention vs. Comparator)
WAKE-UP[44] 2018 Europe	**Study type:** An investigator-initiated, multicenter, randomized, double-blind, placebo-controlled clinical trial **Study size:** 503	**Time window:** >4.5 hours **Eligibility criteria of imaging:** had a mismatch between the presence of an abnormal signal on MRI-DWI and no visible signal change on FLAIR in the region of the acute stroke; MRI to exclude intracranial hemorrhage or lesions larger than one third of the territory of the	**0.9 mg/kg alteplase (n=254) vs. placebo (n=249)** **1.age (years):** 65.3±11.2 vs. 65.2±11.9 **2.baseline NIHSS:** 37 (IQR 14.6) vs. 31 (IQR 12.4) **3. onset-to-treatment interval (hours):** 10.3 (8.1–12.0) vs. 10.4 (8.1–12.1) **4.large vessel oclussion**	***mRS 0-1 at 90 days:** 53.3% vs 41.8% (aOR, 1.61 [95%CI, 1.09-2.36]; P=0.02)		**sICH:** **ECASS II**: 7 (2.8%) vs. 3 (1.2%) , OR 2.40 (95%CI 0.60–9.53), P=0.21 **ECASS III**: 6 (2.4%) vs.1 (0.4%) , OR 6.04 (95%CI 0.72–50.87), P=0.10 **SITS-MOST**: 5 (2.0%) vs. 1 (0.4%) ,OR 4.95	**Death:** 4.1% vs1.2% (OR, 3.38 [95%CI, 0.92-12.52]; P=0.07)

		middle cerebral artery	**<u>on time-of-flight MRA:</u>** 84/249 (33.7%) vs. 84/246 (34.1%)			(95%CI 0.57 – 42.87), P=0.15 **NINDS**: 20 (8.0%) vs. 12 (4.9%), OR1.78 (95%CI 0.84 – 3.71), P=0.13 **<u>PH2</u>** (an intracerebral hemorrhage that involved more than 30% of the infarcted area with a substantial space-occupying effect or that was remote from the original infarcted area):10 (4.0%) vs. 1	

						(0.4%) ,OR 10.46 (95%CI 1.32–82.77), P= 0.03	
EXTEND[45] 2019 Australia, New Zealand, Finland, and Taiwan	**Study type:** A phase 3, investigator-initiated, multicenter, randomized, placebo-controlled trial **Study size:** 225	**Time window:** 4.5-9 hours (4.5-6 hours: 10%; 6-9 hours: 25%; wake-up stroke: 65%) **Eligibility criteria of imaging:** Infarct core: rCBF< 30% of that in normal brain regions; Critically hypo-perfused brain: Tmax>6s; Perfusion lesion-ischemic core mismatch: a ratio greater than 1.2 between the volume of	**0.9 mg/kg alteplase (n=113) vs. placebo (n=112)** **1.age (years):** 73.7±11.7 vs. 71.0±12.7 **2.baseline NIHSS:** 12.0 (8.0–17.0) vs. 10.0 (6.0–16.5) **3. onset-to-treatment interval (min):** 432 (374–488) vs. 450 (374–500) 4.**large vessel occlusion:** 78 (69.0%) vs. 81 (72.3%)	***mRS 0-1 at 90 days:** 35.4% vs 29.5% (aRR, 1.44 [95%CI, 1.01-2.06]; P=0.04) **Major neurologic improvement at 24 hours:**27/113 (23.9%) vs. 11/112 (9.8%), aRR 2.76 (95%CI 1.45–5.26)	**Reperfusion** (defined as ≥50% and ≥90% reductions at 24 hours, respectively, in the volume of the perfusion lesion in hypo-perfused brain region): 71.7% vs 52.3% (aRR, 1.35 [95%CI, 1.09-1.67]); 50.0% vs 28.4% (aRR, 1.73 [95%CI, 1.22-2.46]); **Recanalization** (defined as a score of 2 or 3 at 24 h on	**sICH within 36 hours (SITS-MOST):** 6.2% vs 0.95 (aRR, 7.22 [95%CI, 0.97-53.5]; P=0.05)	**Death:** 11.5% vs. 8.9% (aRR, 1.17 [95%CI, 0.57-2.40]; P=0.67)

		hypoperfusion and the volume of the ischemic core, an absolute difference in volume greater than 10 ml, and an ischemic-core volume of less than 70 ml.			the arterial occlusive lesion scale): 67.3% vs 39.4% (aRR, 1.68 [95%CI, 1.29-2.19])		
ECASS-4[46] 2019 Europe	**Study type:** A randomized, multicenter, double-blind, placebo-controlled phase 3 trial **Study size:** 119	**Time window:** 4.5-9 hours **Eligibility criteria of imaging:** Patients with inability for MRI with infarct core>1/3MCA territory qualitatively or >100 ml quantitatively (determined by DWI lesion on MRI) should not be enrolled.	**0.9 mg/kg alteplase (n=61) vs. placebo (n=58)** **1.baseline NIHSS:** 10.6 **3. onset-to-treatment interval (min):** Median time was 7 h 42 min	***90-day mRS distribution:** (OR, 1.200 [95%CI, 0.633-2.273]; P=0.5766) **90-day mRS 0-1:** 35.0% vs 28.6% (OR, 1.346 [95%CI, 0.613-2.954]; P= 0.4585)		**sICH (ECASS-3):** 1 vs 0	**Death:** 11.5% vs 6.8% (OR, 1.742 [95%CI, 0.414-8.598]; P= 0.5303)

		Penumbral mismatch was defined as PWI:DWI ratio of >1.2 and PWI minimum volume of at least 20 ml.					
THAWS[48] 2020 Japan	**Study type:** An investigator-initiated, multicenter, randomized, open-label, blinded-end point trial **Study size:** 131	**Time window:** >4.5 hours **Eligibility criteria of imaging:** WAKE-UP criteria: Patients underwent randomization if they showed mismatch between the presence of an abnormal signal on DWI and no marked signal change on FLAIR (negative FLAIR pattern) in the corresponding region of	**0.6 mg/kg alteplase (n=70) vs. placebo (n=561)** **1.age：** 73.2±12.4 vs. 75.8±11.9 **2.baseline NIHSS:** 7 (4–13) vs. 7 (5–12) **3. last known well-to-randomization interval (hours):** 10.2 (8.2–12.2) vs. 10.3 (7.7–11.8) **4.large vessel occlusion:** 19 (27%) vs. 22 (36%)	*** mRS 0-1 at 90 days:** 47.1% vs 48.3% (RR, 0.97 [95%CI, 0.68-1.41]; P=0.89)	**Recanalization of culprit artery on MRA at 22-36 h:** 73.7% vs 40.9% (RR, 1.80 [95%CI, 1.02-3.64]; P=0.04)	**sICH (an increase in NIHSS score by ⩾4 from baseline and PH type II on MRI at 22 to 36 h):** 1 vs 0	**Death:** 2 vs 2 (RR, 0.85 [95%CI, 0.06-12.58]; P >0.99)

		the acute stroke. Patients with clinically acute ischemic stroke and a negative FLAIR pattern who did not display an abnormal signal on DWI were also enrolled. As MRI criteria, patients were excluded with intracranial hemorrhage or large infarct with ASPECT Score of 4 or less in the territory of the middle cerebral artery, or with visual lesion volume over 50% of the anterior cerebral artery or posterior cerebral artery, more than half of the brain stem or more than half of the unilateral cerebellar hemisphere.					

WAKE-UP indicates MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion

recovery; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; MRA, Magnetic Resonance Angiography; mRS, modified Rankin Scale; aOR, adjusted odds ratio; CI, confidence interval; sICH, symptomatic intracerebral haemorrhage; ECASS, European Cooperative Acute Stroke Study; SITS-MOST, Safe implementation of treatments in stroke Monitoring Study; PH, parenchymal hematoma; NINDS, the national institute of neurological disorders and stroke rt-PA stroke study; EXTEND, Extending the time for Thrombolysis in Emergency Neurological Deficits; rCBF, Regional Cerebral Blood Flow; Tmax, time to maximum of the residual function; aRR, adjusted risk ratio; MCA, middle cerebral artery; PWI, perfusion weighted imaging; THAWS, Thrombolysis With Alteplase at 0.6 mg/kg for Stroke With Unknown Time of Onset; and ASPECT, Acute Stroke Prognosis Early CT score.

* The primary outcome in the trial.

Table S2. Clinical trials about tenecteplase

Study Acronym/ Publication Year/ Location	Study Type/ Study Size(N)	Time Window/ Eligibility Criteria of Imaging	Baseline Characteristics (Intervention vs. Comparator)	Efficacy Outcomes (Intervention vs. Comparator)	Recanalization/ Reperfusion Rate (Intervention vs. Comparator)	Symptomatic Intracranial Hemorrhage (Intervention vs. Comparator)	Disability and Death at 90 Days (Intervention vs. Comparator)
Haley et al.[34] 2005 the USA	**Study type:** A pilot, open-label, dose-escalation safety study **Study size:** 88	**Time window:** 3 hours **Eligibility criteria of imaging:** CT scan to exclude hemorrhage	**0.1 mg/kg (n=25) vs. 0.2 mg/kg (n=25) vs. 0.4 mg/kg (n=25) vs. 0.5 mg/kg (n=13) tenecteplase** **1.age (years):** 67±14 vs. 69±11 vs. 72±13 vs. 68±13 **2.baseline NIHSS:** 12 (8–17, 4–28) vs. 14 (9–20, 2–27) vs. 10 (6–15, 3–28) vs. 8 (6–15, 5–23) **3. onset-to-treatment**	**mRS 0-1 at 90 days:** 36% vs. 32% vs. 32% vs. 46% **Major neurological improvement (**an improvement of 8 points or a score of 0 on the NIHSS score at 24 hours): 36% vs. 24% vs. 16% vs. 23%		***sICH within 36 hours:**0 vs.0 vs. 0 vs. 15% **aICH within 48 hours:** 8% vs. 32% vs. 28% vs. 23%	**Death:** 12% vs. 24% vs.16% vs. 15%

			interval (min): 145 (135 – 165) vs. 150 (130 – 170) vs. 158 (121 – 168) vs.154 (135 – 161)				
Parsons MW et al[37] 2009 Australia	**Study type:** A prospective, nonrandomized, pilot study **Study size:** 50	**Time window:** 3-6 hours **Eligibility criteria of imaging:** 1) a hemispheric perfusion lesion at least 20% greater than the infarct core on baseline CTP or MRI and 2) an infarct core on CTP or MRI less than one-third of the middle cerebral artery territory	**0.1 mg/kg tenecteplase (n=15)** **vs. 0.9 mg/kg alteplase (n=35)** **1.age (years):** 73.0± 9.5 vs. 69.4±13.5，P=0.35 **2.baseline NIHSS:** 14 (13 to 17) vs. 15 (11 to 18), P=0.66 **3.onset-to-treatment interval (hours):** 3.4 ±0.4 vs. 2.3 ±0.4, P=0.001 **4.:baseline vessel**	**mRS 0-1 at 90 days:** 9/15 vs. 12/35, P=0.09 **Major neurological improvement :** (an improvement of 8 points): 10/15 vs.7/35, P=0.001	***Percent reperfusion at 24 hours:** 73.8 ± 23.3 vs. 44.4 ± 30.5, P= 0.01 ***Proportion with 24-h reperfusion >80:**9/15 vs. 7/30, P=0.02 ***Proportion with 24-h reperfusion >50：**11/15 vs.11/30, P=0.02 ***TIMI >2/complete recanalization :**	**24-hour Parenchymal hematoma (ECASS):** 0/15 vs. 4/35, P=0.30 **24-hour Hemorrhagic infarction (ECASS):** 5/15 vs. 8/35, P=0.44	

			occlusion: 15/15 vs. 30/35, P=0.12		10/15 vs. 7/29, P=0.01 ***Any (TIMI >1) recanalization :** 13/15 vs.15/29, P=0.02		
TNK-S2B[38] 2010 the USA	**Study type:** A small, multicenter, randomized, double-blind, phase IIB/III controlled clinical trial **Study size:** 112	**Time window:** 3 hours **Eligibility criteria of imaging:** CT scan to exclude hemorrhage, large infarction (greater than one lobe)，subtle early signs of cerebral infarction and the dense artery sign	**0.1 mg/kg tenecteplase (n=31) vs. 0.25mg/kg tenecteplase (n=31) vs. 0.4 mg/kg tenecteplase (n=19) vs.0.9 mg/kg alteplase (n=31)** **1.age (years):** 67±19 vs. 69±15 vs. 68±16 vs. 72±16 **2.baseline NIHSS:** 8 (5–11) vs.10 (6–15) vs. 9 (5–17) vs.13 (5–17) **3. onset-to-treatment**	***mRS 0-1 at 90 days (%, 95%CI):** (45.2%, 27.3–64.0) vs. (48.4%, 30.2–66.9) vs. (36.8%, 16.3–61.6) vs. (41.9%, 24.6–60.9) **Major neurological improvement (%, 95%CI) (**an improvement of 8 points or a score of 0 on the NIHSS score at 24 hours):		***sICH within 24 hours (%, 95%CI):** (0%, 0–11.2) vs. (6.5%, 0.8–21.4) vs. (15.8%, 3.4–39.6) vs. (3.2%, 0.1–16.7)	**Death (%, 95%CI):** (6.5%, 0.8–21.4) vs. (22.6%, 9.6–41.1) vs. (15.8%, 3.4–39.6) vs. (25.8%, 11.9–44.6)

			interval (min): 145 (135 – 165) vs. 150 (130 – 170) vs. 158 (121 – 168) vs.154 (135 – 161)	(22.6%, 9.6 – 41.1) vs. (35.5%, 19.2 – 54.6) vs. (21.1%, 6.1 – 45.6) vs. (16.1%, 5.5 – 33.7)			
Australian-TNK[40] 2012 Australia	**Study type:** A randomized, open-label, blinded, phase 2B trial **Study size:** 75	**Time window:** 6 hours **Eligibility criteria of imaging:** 1.the presence of intracranial occlusion in the anterior cerebral, middle cerebral, or posterior cerebral artery.2. a hemispheric perfusion lesion on transit-time maps that was at least 20% greater than the infarct-core lesion, with a volume of at least 20 ml. The infarct-core	**0.1 mg/kg tenecteplase (n=25) vs. 0.25mg/kg tenecteplase (n=25) vs. 0.9 mg/kg alteplase (n=25)** **1.age (years):** 72±6.9 vs. 68±9.4 vs. 70±8.4 **2.baseline NIHSS:** 14.5±2.3 vs. 14.6±2.3 vs. 14.0±2.3 **3. onset-to-treatment interval (hours):** 3.1±0.9 vs. 3.0±0.7 vs. 2.7±0.8	***Improvement in NIHSS score between baseline and 24 hours:** 8.0±5.5 vs. 3.0±6.3, P<0.001 **mRS 0-1 at 90 days:**54% vs. 40%, P=0.25	***Reperfusion at 24 hours :** 79.3±28.8% vs. 55.4±38.7%, P=0.004 **Complete recanalization at 24 hours:** 8/22 (36%) vs. 28/48 (58%), P=0.09	***sICH within 24 hours:** (large parenchymal hematoma combined with a significant clinical deterioration of ⩾4 points on the NIHSS score) 4% vs. 12%, P=0.33	**mRS 5-6:** 10% vs. 28% , p=0.09 **Death:** 8% vs. 12%,P=0.68

		lesion on CT perfusion maps of cerebral blood volume less than one third the territory of the middle cerebral artery or less than one half the territory of the anterior cerebral or posterior cerebral artery.					
TEMPO-1[41] 2015 Canada	**Study type:** Multicenter, prospective, uncontrolled, 2-cohort, TNK-tPA dose-escalation, safety, and feasibility trial **Study size:** 50	**Time window:** 12 hours **Eligibility criteria of imaging:** any acute intracranial occlusion (MCA, ACA, PCA, and vertebral arteries and basilar arteries) defined by CTA; Patients can be treated within 90 min of the CT/CTA being	**0.1 mg/kg tenecteplase (n=25) vs. 0.25 mg/kg (n=25) tenecteplase** **1. age:** 72.3 (IQR 21.7) vs. 70.8 (IQR 19.9) **2. baseline NIHSS:** 3 (IQR 1) vs. 2 (IQR 1) **3. onset-to-treatment interval (min):** 212 (IQR194) vs. 206 (IQR 160)	**mRS 0-1 at 90 days:** 56% (14/25) vs. 76 % (19/25)	**Complete or partial recanalization after 4-8 hours:** 56% (13/23) vs. 61% (14/23) **Complete recanalization after 4-8 hours:** 39 % (9/23) vs. 52 % (12/23)	***sICH TEMPO-1 definition (intracranial hemorrhage with associated neurological worsening (NIHSS increase of ⩾2 points different than baseline):**	**Death:** 0 (0/25) vs. 4% (1/25)

		completed				0 (0/25) vs. 4% ; **<u>sICH NINDS definition:</u>** 0 (0/25) vs. 4 (1/25) ; **<u>sICH ECASS definition:</u>** 0 (0/25) vs. 4 (1/25) ; **<u>sICH SITS-MOST definition:</u>** 0 (0/25) vs. 0 (0/25)	

ATTEST[42] 2015 Glasgow	**Study type:** A single-centre, phase 2, prospective, randomized, open-label, blinded end-point study **Study size:** 104	**Time window:** 4.5 hours	**0.25 mg/kg tenecteplase (n = 52)** **vs. 0.9 mg/kg alteplase (n=52)** **1.age:** 71±13 vs. 71 ±12 **2. baseline NIHSS:** 12 (9–18) [2–26] vs. 11 (8–16) [3–27] **3.onset-to-treatment interval (min):** 180 (156–215) vs. 200 (160–220) **4. Large vessel occlusion:** 35/47 (74%) vs.38/49 (78%)	**mRS 0–1 at 90 days :** 13/47 (28%) vs. 10/49 (20%) , P=0.28, OR 1.8 (95%CI 0.6 to 5.5) **Early neurological improvement at 24 h (NIHSS reduction ≥8 points or 24–48 h NIHSS 0–1):** 19/47 (40%) vs. 12/49 (24%) , P=0.10, OR 2.1 (95% CI 0.9 to 5.2)	***Percentage penumbral salvaged at 24–48 h:** 68% vs. 68% (23), P=0.81, mean difference: 1.3% (95% CI –9.6 to 12.1) **Recanalisation at 24–48 h:** 21/32 (66%) vs. 26/35 (74%) , P=0.38, OR 0.6 (95%CI 0.2 to 1.8)	**sICH (ECASS II definition) :** 3/52 (6%) vs. 4/51 (8%) , P=0·59, OR 0.6 (95%CI 0.1 to 3.2) **sICH (SITS-MOST definition):** 1/52 (2%) vs. 2/51 (4%) ,P=0.50, OR 0.4 (95%CI 0.04 to 5.1)	**mRS 5-6:** 10% vs. 9% **Death:** 8/47 (17%) vs. 6/49 (12%), P= 0.51, OR 1.3 (95%CI 0.4 to –3.7)

NOR-TEST[43] 2017 Norway	**Study type:** Phase 3, multicenter, prospective，randomized, open-label, blinded endpoint, superiority trial **Study size:** 1100	**Time window:** 4.5 hours **Eligibility criteria of imaging:** off-label if mismatch between DW-MRI and FLAIR-MRI was detected	**0.4 mg/kg tenecteplase (n = 549)** **vs. 0.9 mg/kg alteplase (n=551)** **1.age:** 77 (64–79) vs. 77 (64–79) **2. baseline NIHSS:** 4 (2–7) vs. 4 (2–8) **3.onset-to-treatment interval (min):** 118.0 (79–180) vs.111 (80–174) **4. Large vessel occlusion:** 13% vs.17% 5.**patients with EVT**:3% vs.4%	***mRS 0-1 at 90 days:** 354/549 (64%) vs. 345/551 (63%) , OR 1·08, 95% CI 0·84–1·38; P = 0·52). **Major clinical improvement （NIHSS score of 0 or improvement of at least 4 points compared with baseline）at 24 h:** 229/549 (42%) vs. 214/551 (39%) , OR 1.12 (95%CI 0.89–1.43) , P=0.97		**sICH within 24-48 hours (ECASS 3):** 15/549 (3%) vs. 13/551 (2%) , OR 1.16 (95%CI 0.51–2.68) , P=0.70	**Death:** 29/549 (5%) vs. 26/551 (5%), OR 1.12 (95%CI 0.63–2.02) ,P=0.68
EXTEND-IA TNK[8]	**Study type:** Investigator-initi	**Time window:** 4.5 hours	**0.25 mg/kg tenecteplase (n = 101)**	**mRS 0-1 at 90 days:**	***Substantial reperfusion （restoration of**	**sICH within 36 hours:** (a large parenchymal	**Death:**10% vs. 18%, aOR 0.4 (95%CI

2018 Australia and New Zealand	ated, noninferiority followed by superiority, multicenter, prospective, randomized, open-label, blinded outcome trial **Study size:** 202	**Eligibility criteria of imaging:** had cerebral vascular occlusion on CT angiography of the internal carotid artery, the first segment of the middle cerebral artery, the second segment of the middle cerebral artery, or the basilar artery and if treatment to retrieve the intraarterial clot could commence (arterial puncture) within 6 hours after stroke onset (the criteria of CT-perfusion mismatch were removed on October 12, 2016)	**vs. 0.9 mg/kg alteplase (n=101)** **1.age:** 70.4±15.1 vs. 71.9±13.7 **2. baseline NIHSS:** 17 (12–22) vs. 17 (12–22) **3.onset-to-treatment interval (min):** 125 (102–156) vs. 134 (104–176)	51% vs. 43%, aOR 1.4 (95%CI 0.8–2.6) , P=0.23 **mRS 0-2 at 90 days:** 64% vs. 51%, aOR 1.8 (95%CI 1.0–3.4) , P=0.06 **Early neurologic improvement:** 71% vs. 68%, aOR 1.1 (95%CI 0.6–2.1) , P=0.70	**blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus in the target vessel）at initial angiographic assessment:** 22% vs. 10% (incidence difference, 12 percentage points; 95% CI 2 to 21; incidence ratio, 2.2; 95% CI 1.1 to 4.4; P = 0.002 for noninferiority; P = 0.03 for superiority).	hematoma (blood clot occupying >30 % of the infarct volume with mass effect) and an increase of 4 points or more in the NIHSS score) 1% vs. 1%, OR 1.0 (95% 0.1–16.2) , P=0.99	0.2–1.1), P= 0.08

EXTEND-IA TNK, Part 2[47] 2020 Australia and New Zealand	**Study type:** Investigator-initiated, multicenter, randomized, open-label, blinded end point trial **Study size:** 300	**Time window:** 4.5 hours **Eligibility criteria of imaging:** cerebral vascular occlusion on CTP of the intracranial internal carotid artery, middle cerebral artery first or second segments, or basilar artery	**0.4 mg/kg tenecteplase (n = 150) vs. 0.25 mg/kg tenecteplase (n = 150)** **1.age:** 71.7±11.3 vs. 73.8±12.8 **2. baseline NIHSS:** 17 (11-21) vs.16 (9-20) **3.onset-to-treatment interval (min):** 132 (96-180) vs.133 (102-180)	**mRS 0-1 or no change:** 74/150 (49) vs. 74/150 (49) unadjusted risk difference 0.0 [95%CI −11.3 to 11.3]; Adjusted RR, 1.04 [95%CI 0.84 to 1.29], P=0.69 **mRS0-2 or no change:** 88/150 (59) vs. 84/150 (56) , unadjusted risk difference 2.7 [95%CI −8.5 to 13.9], Adjusted RR, 1.08 [95%CI 0.90 to 1.29], P=0.40	***Substantial reperfusion （restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus in the target vessel）at initial angiographic assessment:** 19.3% vs. 19.3% (unadjusted risk difference, 0.0% [95% CI−8.9% to −8.9%]; adjusted risk ratio, 1.03 [95% CI 0.66-1.61]; P = 0.89).	**sICH within 36 hours:** (large parenchymal hematoma blood clot occupying >30 % of infarct volume with mass effect and 4-point increase in NIHSS score) (7 [4.7%] versus 2 [1.3%]; unadjusted risk difference, 3.3% [95% CI−0.5% to 7.2%]).	**Death:**(26 [17%] versus 22 [15%]; unadjusted risk difference, 2.7% [95% CI −5.6% to 11.0%])

				Substantial early neurological deficit improvement: (8-point reduction in NIHSS score between baseline and day 3 or reaching NIHSS score of 0 to 1 at day 3):102/150 (68) vs. 93/150 (62),unadjusted risk difference 6.0 [95%CI−4.8 to 16.8], Adjusted RR, 1.08 [95%CI 0.91 to 1.27], P=0.39			
TRACE[49] 2022 China	**Study type:** A multicentre, prospective, randomized, open-label,	**Time window:** 3 hours **Eligibility criteria of**	**0.1 mg/kg (n=60) vs. 0.25 mg/kg (n=57) vs. 0.32 mg/kg (n=60) tenecteplase vs. 0.9 mg/kg alteplase (n=59)**	***Improvement on NIHSS of ⩾4 points or a score ⩽1 at day 14:** 38 (63.3%) vs.		**sICH at 36 hours (ECASS III):** 3 (5.0%) vs. 0 (0.0%) vs. 2 (3.3%) vs. 1	

	blinded end-point, phase II study **Study size:** 236	**imaging:** CT scan to exclude hemorrhage	**1.age (years):** 62.4 ±11.1 vs. 64.3±12.8 vs. 64.8±12.1 vs. 66.5 ±12.6 **2.baseline NIHSS:** 7.0 (5.0 – 10.0) vs. 8.0 (5.0 – 12.0) vs. 7.5 (6.0 – 12.0) vs. 8.0 (5.0 – 12.0) **3. onset-to-treatment interval (min):** 154 (56 – 195) vs. 149 (80 – 179) vs. 147 (69 – 220) vs. 153 (18 – 187)	44 (77.2%) vs. 40 (66.7%) vs. 37 (62.7%); OR 1.03 (95%CI 0.49 to 2.16) vs. OR 2.01 (95%CI 0.89 to 4.54) vs. OR 1.19 (95%CI 0.56 to 2.52) vs. ref. **mRS 0-1 at 90 days:** 33 (55.0%) vs. 35 (63.6%) vs. 36 (62.15) vs. 35 (59.3%); OR 0.84 (95%CI 0.41 to 1.73) vs. OR 1.20 (95%CI 0.56 to 2.56) vs. OR 1.12 (95%CI 0.53 to 2.36) vs. ref.		(1.7%) ,P=0.52 **Serious adverse events:** 12 (20.0%) vs. 7 (12.3%) vs. 11 (18.3%) vs. 14 (23.7%), P=0.46	
TASTE-A[50]	**Study type:**	**Time window:**	**0.25 mg/kg tenecteplase (n = 55) vs.**	**mRS0-1 or no**	***Volume of the perfusion lesion**	**sICH within 36 hours**	**mRS 5-6 at 90 days:** 8

2022 Australia	A phase 2, randomized, open-label trial **Study size:** 104	4.5 hours	**0.9 mg/kg alteplase (n = 49)** **1.age:** 76 (60 – 84) vs. 73 (61 – 80) **2. baseline NIHSS:** 8 (5 – 14) vs. 8 (5 – 17) **3.onset-to-treatment interval (min):** 97 (68 – 157) vs. 92 (66 – 31) **4.large vessel occlusion:** 27 (49%) vs. 19 (39%)	**change:** 24 (44%) vs. 22 (45%), aOR 0.95 (95%CI 0.38 to 2.39), P= 0.92 **Reduction in NIHSS between pre-treatment score and score at 24 h post treatment:** 4.5 (1 to 9) vs. 4 (2 to 8),adjusted difference 0.85 (95%CI – 1.7 to 3.4) ,P=0.51	**on CT-perfusion imaging performed on arrival at the receiving hospital , mL:** 12 (3 to 28) vs. 35 (18 to 76)，Adjusted incidence rate ratio 0.55 (95%CI 0.37 to 0.81) ,P=0.0030	(including subarachnoid hemorrhage that was associated with clinical symptoms and symptomatic intracerebral hemorrhage was adjudicated centrally by a panel and defined as parenchymal hematoma type 2 within 36h after treatment, combined with an increase from baseline in the NIHSS score of at least 4 points): 0 vs. /	(15%) vs. 10 (20%) , aOR 0.70 (95% CI 0.23 to 2.16) , P=0.54 **Death:**5 (9%) vs. 5 (10%) ,aOR1. 12 (95%CI 0.26 to 4.90), P= 0.88

CHABLIS-T **NCT04086147**[51] 2022 China	**Study type:** A prospective, multicenter, randomized, open-label, rater-blinded, randomized trial **Study size:** 86	**Time window:** 4.5-24 hours **Eligibility criteria of imaging:** Vessel occlusion or severe stenosis (ICA, MCA-M1/M2, ACA) on CTA/MRA; Multi-modal CT/MRI perfusion lesion volume (DT > 3 s) to infarct core volume ratio (rCBF<30% or DWI lesion) >1.2, absolute difference >10 ml, and ischemic core volume <70ml	**0.25 mg/kg tenecteplase (n = 43) vs. 0.32 mg/kg tenecteplase (n = 43)** **1.age (years):** 68.3 vs.67.1 **2.bridge treatment:** 39.5%	**the primary outcome: (** 1. patients without endovascular therapy obtained >50% reperfusion at 4-6 hours 2. patients with endovascular therapy: mTICI score 2b or better at initial angiogram 3. no symptomatic intracranial hemorrhage at 24-36 hours: 14 (32.6%) vs. 10 (23.3%) **mRS 0-1 at 90 days:** 12 (27.9%) vs. 21 (48.8%) **recanalization within 4-6 hours:** 18 (43.9%) vs. 18 (43.9%) **sICH (ECASS II)**: 4 (9.3%) vs. 4 (9.3%) **Parenchymal hemorrhage** **type 2**: 5 (11.6%) vs. 1 (2.3%) **90 day-mRS 5-6**:11 (25.6%) vs. 7 (16.3%)

AcT[11] 2022 Canada	**Study type:** An investigator-initiated, multicenter, parallel-group, open-label, registry-linked, randomized, controlled trial **Study size:** 1577	**Time window:** 4.5 hours	**0.25mg/kg tenecteplase (n=806) vs. 0.9 mg/kg alteplase (n=771)** **1.age (years):** 74 (63–83) vs. 73 (62–83) **2.baseline NIHSS:** 9 (6–16) vs. 10 (6–17) **3.onset-to-treatment interval (min):** 128 (93–186) vs.131 (95–188) **4.large vessel occlusion:** 196/801 (24.5%) vs. 193/757 (25.5%) **5.Endovascular thrombectomy use:** 258/806 (32.0%) vs. 248/771 (32.2%), RD –0.2 (95%CI –4.8 to 4.5)	***mRS 0-1 at 90-120 days :** 296/802 (36.9%) vs. 266/765 (34.8%) , RD2.1 (95%CI –2.6 to 6.9), meeting the pre-specified non-inferiority threshold of -5%	**eTICI score of ⩾2b on initial angiography of EVT :** 26/256 (10.2%) vs. 27/256 (10.5%), RD –0.8 (95%CI –6.3 to 4.6) **rAOL score of ⩾2b on initial angiography of EVT (post hoc):** 48/253 (19.0%) vs. 40/246 (16.3%) ,RD 2.7 (95%CI –4.0 to 9.4)	**sICH within 24 hours :** 27/800 (3.4%) vs. 24/763 (3.2%) , RD0.2 (95%CI –1.5 to 2.0) **Parenchymal hematoma type 2 (hematoma occupying ⩾30% of infarct with obvious mass effect):** 21/800 (2.6%) vs. 18/763 (2.4%) ,RD 0.3 (95%CI –1.3 to 1.8)	**mRS 5-6:**20.7% vs. 21.1% **Death:** 122/796 (15.3%) vs. 117/758 (15.4%), RD –0.1 (95%CI –3.7 to 3.5)

NOR-TEST-2[52] 2022 Norway	**Study type:** A phase 3, randomized, open-label, blinded endpoint, non-inferiority trial （The noninferiority margin was 3%） **Study size:** 204	**Time window:** 4.5 hours **Eligibility criteria of imaging:** Patients with signs or symptoms on awakening or an unknown onset of stroke signs or symptoms were included if an MRI showed a mismatch between diffusion-weighted imaging and fluid attenuated inversion recovery	**0.4mg/kg tenecteplase (n=100) vs. 0.9 mg/kg alteplase (n=104)** **1.age (years):** 75 (65–83) vs. 72 (58–78) **2.baseline NIHSS:** 11.5 (8–17) vs. 11 (8–17.5) **3.onset-to-treatment interval (min):** 92.5 (74–143) vs. 99 (73–143) **4.large vessel occlusion:** 57% vs. 56.7% **5.Endovascular thrombectomy use:** 34.0% vs. 40.8%	***mRS 0-1 at 90 days :** 31/96 (32%) vs. 52/101 (51%); unadjusted OR 0.45 [95% CI 0.25–0.80]; p=0.0064) **Major neurological improvement （a reduction in NIHSS score of at least 4 points） at 24 h：** 53/91 (58%) vs. 73/98 (74%) , unadjusted OR 0.48 (95% CI 0.26 to 0.88)，P=0.018		**sICH within 24-48 hours :（ECASS 3）** 6/100 (6%) vs. 1/104 (1%) , unadjusted OR 6.57 (95%CI 0.78 to 55.62), P=0.061 **Parenchymal hematoma type 2 :** 8/100 (8%) vs. 1/104 (1%), P=0.017	**mRS 5-6:**17/96 (18%) vs. 6/101 (6%) , unadjusted OR 3.41 (95%CI 1.28 to 9.05),P=0.010 **Death:** 15/96 (16%) vs. 5/101 (5%) ,unadjusted OR 3.56 (95% CI 1.24 to 10.21), P=0.013

TWIST[53] 2022 77 hospitals in ten countries (Denmark, Estonia, Finland, Latvia, Lithuania, New Zealand, Norway, Sweden, Switzerland and the UK)	**Study type:** An investigator-initiated, multicenter, open-label, randomized controlled trial **Study size:** 578	**Time window:** 4.5 hours of awakening **Eligibility criteria of imaging:** non-contrast CT to exclude intracranial hemorrhage or infarct comprising hypoattenuation in more than a third of the middle cerebral artery territory	**0.25 mg/kg tenecteplase (n = 288) vs. control (no thrombolysis) (n = 290)** **1.age:** 73.9 (66.4 – 80.8) vs. 73.3 (65.8 – 82.0) **2. baseline NIHSS:** 6 (5 – 11) vs. 6 (5 – 10) **3.endovascular treatment:** 18 (6%) vs.42 (14%) **4.large vessel occlusion:** 69/231 (30%) vs. 83/226 (37%)	***Functional improvement in the** **mRS at 90 days:** OR 1.18 (95%CI 0.89 – 1.58), P=0.26 **mRS 0-1 at 90 days:** 130 (45%) vs. 111 (38%) , OR 1.33 (95%CI 0.95 – 1.85)		**sICH (SITS-MOST):** 6 (2%) vs. 3 (1%) , OR 2.04 (95%CI 0.50 – 8.22) **sICH (IST-3):** 12 (4%) vs. 8 (3%) , OR 1.53 (95%CI 0.62 – 3.81) **Parenchymal hemorrhage type 2:** 7 (2%) vs. 5 (2%), OR 1.42 (95%CI 0.45 – 4.53)	**Death:**28 (10%) vs. 23 (8%) , HR 1.29 (95%CI 0.74 – 2.26) **Serious adverse events:** 82 vs. 70

TRACE-2[12] 2023 China	**Study type:** A phase 3, multicenter, prospective, open-label, blinded-endpoint , randomized controlled, non-inferiority trial **Study size:** 1417	**Time window:** 4.5 hours	**0.25mg/kg tenecteplase (n=710) vs. 0.9 mg/kg alteplase (n=707)** **1.age (years):** 67 (58–73) vs. 65 (58–72) **2.baseline NIHSS:** 7 (5–10) vs. 7 (6–10) **3.onset-to-treatment interval (min):** 180 (135–222) vs. 178.5 (135–230) **4.bridging thrombectomy:** 27 (4%) vs. 24 (3%)	***mRS 0-1 at 90 days :** 439/705 (62%) vs. 405/696 (58%); RR 1.07 (95%CI 0.98 to 1.16), the lower limit of the RR' s 95% CI was greater than the non-inferiority margin of 0.937 **Improvement on NIHSS of ≥4 points or a score ≤1 at 24 h：** 342/690 (50%) vs. 345/698 (49%) , RR 0.97 (95%CI 0.88 to 1.08), P= 0.58		**sICH** **within 36 hours :（ECASS 3）** 15 (2%) vs.13 (2%) , RR 1.18 (95%CI 0.56–2.50) , P=0.72 **Parenchymal hematoma 2 within 36 hours** **(SITS-MOST):** 10 (1%) vs. 3 (<1%), RR 3.73 (95%CI 0.99–14.13) , P=0.053	**Death:** 46 (7%) vs. 35 (5%) , RR 1.31 (95%CI 0.86–2.01), P=0.22 **Serious adverse events:**116 (16%) vs.107 (15%) , RR 1.10 (95%CI 0.87–1.41), P=0.55
TIMELESS **NCT0378567**	**Study type:** A phase III,	**Time window:** 4.5-24 hours	**0.25mg/kg tenecteplase (n=228)**	***Ordinal mRS score :**	**complete recanalization at 24 hours post**	**sICH** **within 36**	**Death:** 19.7% vs.

8[54] 2023 the USA and Canada	prospective, double-blind, randomized, placebo-controlled trial **Study size:** 458	**Eligibility criteria of imaging:** ICA or M1, M2 occlusion (carotid occlusions can be cervical or intracranial, with or without tandem MCA lesions) by MRA/CTA. AND target mismatch profile on CTP/ MR perfusion (ischemic core volume <70 mL, mismatch ratio is >=1.8 and mismatch volume is >= 15 mL)	**vs. placebo (n=230)** **1.age (years):** 72 vs. 73 **2.baseline NIHSS:** 12 vs. 12 **3.bridging thrombectomy:** 77.2% vs. 77.4%	cOR 1.13 (95%CI 0.82-1.57); P=0.45 **mRS 0-1 at 90 days：** 32.3% vs. 26.6% **mRS 0-2 at 90 days：** 46% vs. 42.4%,OR 1.18 (95%CI 0.80-1.74)	**randomization：** 76.7% vs. 63.9%,OR 1.89 (95%CI 1.21-2.95)	**hours (≥ 4-point clinical worsening of the NIHSS score , attributed to any ICH on imaging):** 3.2% vs. 2.3% **Parenchymal hematoma 2:** 3.7% vs. 2.8%	18.2% **Serious adverse events:**41.7% vs. 47.7%
ATTEST-2 **NCT02814409** [13] WSO 2023 the United	**Study type:** A phase 3, randomized, open-label, parallel	**Time window:** 4.5 hours	**0.25 mg/kg tenecteplase (n=885) vs. 0.9 mg/kg alteplase (n=891)**	***90-day mRS score distribution:** acOR 1.07 (95%CI 0.90-1.27); Non-inferiority	**Endovascular thrombectomy undertaken：** 11.6% vs. 13.2%, OR 0.82 (95%CI 0.60-1.13), P=0.223;	**sICH (SITS-MOST) :** 20/885 (2.3%) vs. 15/891 (1.7%) , OR 1.37(95%CI	**mRS 5-6:** 95/885 (10.7%) vs. 111/891 (12.5%)

Kingdom	assignment trial **Study size:** 1776		**1.age (years):** 70.5±12.5 vs. 70.4±13.4 **2.baseline NIHSS:** 7.0 (5.0–13.0) vs. 7.0 (5.0–12.0) **3.onset-to-treatment interval (min):** 143.0 (115.0–189.0) vs. 147.0 (113.0–185.0) **4.imaging CT/CTA/CTP:** 81%/16%/4% vs. 81%/16%/3% **5.Endovascular thrombectomy use:** 11.6% vs. 13.2%	P<0.0001; Superiority P=0.456 **mRS 0-1 at 90 days：** RD 1.99 (-2.77-6.75); OR 1.05 (0.85-1.30) Non-inferiority P=0.002; Superiority P=0.415 **mRS 0-2 at 90 days：** RD 3.41 (-1.14-7.95); OR 1.15 (0.91-1.45) Superiority P=0.143	mTICI 2b: 36.3% vs. 33.6%; mTICI 3:50.0% vs. 53.4%	0.69 to 2.69) , P=0.368 **sICH (ECASS-3) :** 29/885 (3.3%) vs. 21/891 (2.4%) , OR 1.44(95%CI 0.81 to 2.56) , P=0.212 **Parenchymal hematoma type 2 :** 37/885 (4.3%) vs. 27/891 (3.1%) , OR 1.43(95%CI 0.86 to 2.38) , P=0.171	**Death:** 68/885 (7.7%) vs. 75/891 (8.4%) , OR 0.96 (95%CI 0.69 to 1.33) , P=0.797

CT indicates Computed Tomography; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; sICH, symptomatic Intracerebral Haemorrhage; aICH, asymptomatic intracranial hemorrhage; CTP, Computed Tomography Perfusion; MRI, Magnetic Resonance Imaging; TIMI, Thrombolysis In Myocardial Infarction; ECASS, The European Cooperative Acute Stroke

Study; TNK-S2B, Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke; CI, confidence interval; TEMPO-1, TNK-tPA Evaluation for Minor Ischemic Stroke With Proven Occlusion; TNK-tPA,Tenecteplase; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; CTA, Computed Tomography Angiography; IQR, interquartile range; NINDS, TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY; SITS-MOST, Safe implementation of treatments in stroke Monitoring Study; ATTEST, Alteplase Tenecteplase Trial Evaluation for Stroke Thrombolysis; NOR-TEST, Norwegian Tenecteplase Stroke Trial; DW-MRI, diffusion-weighted Magnetic Resonance Imaging; FLAIR-MRI, fluid-attenuated inversion Recovery- Magnetic Resonance Imaging; EVT, Endovascular Thrombectomy; EXTEND-IA TNK, Tenecteplase Versus Alteplase Before Thrombectomy for Ischemic Stroke; RR, risk ratio; LVO, Large Vessel Occlusion; TRACE,Tenecteplase versus alteplase in acute ischemic cerebrovascular events; rhTNK-tPA, Recombinant Human TNK Tissue-type Plasminogen Activator for Injection; OR, odds ratio; TASTE-A, Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit-A; CHABLIS-T, Chinese Acute Tissue-Based Imaging Selection for Lysis In Stroke-Tenecteplase; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; MRA, magnetic resonance angiography; DT, delay time; rCBF, Regional Cerebral Blood Flow; DWI, Diffusion Weighted Imaging; mTICI: modified Thrombolysis in Cerebral Infarction Score; TWIST, Tenecteplase in Wake-Up Ischemic Stroke Trial; IST-3, Stroke Association phase of the Third International Stroke Trial; HR, Hazard Ratio; AcT, Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada; RD, risk difference; eTICI, extended thrombolysis in cerebral ischemia; EVT, Endovascular thrombectomy; rAOL, revised Arterial Occlusive Lesion score; NOR-TEST, Norwegian Tenecteplase Stroke Trial; TIMELESS, Tenecteplase in Stroke Patients Between 4.5 and 24 Hours; ESOC, European Stroke Organization Conference; ICA, internal carotid artery and WSC, World Stroke Congress.

* The primary outcome in the trial.

Table S3. Observational studies about alteplase and tenecteplase.

Study Acronym/ Publication Year/ Location	Study Type/ Study Size(N)	Time Window/ Eligibility Criteria of Imaging	Baseline Characteristics (Intervention vs. Comparator)	Effectiveness Outcomes (Intervention vs. Comparator)	Recanalization/ Reperfusion Rate (Intervention vs. Comparator)	Symptomatic Intracranial Hemorrhage (Intervention vs. Comparator)	Disability and Death at 90 Days (Intervention vs. Comparator)
SITS-MOST[78] 2007 14 European countries	**Study type:** A prospective, open, multicenter, multinational, observational monitoring study **Study size:** 6483	**Time window:** 3 hours **Eligibility criteria of imaging:** CT scan to exclude severe stroke	**0.9 mg/kg alteplase** **1.age (years):** 68 (59–75) **2.baseline NIHSS:** 12 (8–17) **3. onset-to-treatment interval (min) :**140 (115–165)	**independence (mRS 0–2) at 3 months:** 54.8% (3362/6136; 95% CI 53.5–56.0)		***sICH**（local or remote parenchymal hemorrhage type 2 on the 22–36 h post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 h, or leading to death）**:**	***Death within 90 days:** 11.3% (701/6218; 95% CI 10.5–12.1)

						7.3% (468/6438; 95% CI 6.7 – 7.9)	
SITS-ISTR[79] 2008 650 centers in Europe, Asia, and Australia	**Study type:** A prospective, multinational, internet-based register for patients given this drug after acute ischemic stroke	**Time window:** 3-4.5 hours vs. 3 hours	**0.9 mg/kg alteplase 3 – 4.5h (n=664) vs. Within 3h (n=11 865)** **1.age (years):** 65(55-73) vs. 68(58-74), p<0.0001 **2.baseline NIHSS:** 11 (7 – 16) vs. 12 (8 – 17), p<0.0001 **3. onset-to-treatment interval (min) :**195 (187 – 210) vs. 140 (115 – 165), p<0.0001	**Excellent recovery at 3 months (mRS 0 – 1):** 219/541 (40.5%; 36.3 – 44.8) vs. 4084/10231 (39.9%; 39.0 – 40.1) (OR 1.01 [95%CI 0.93 – .10] ,P=0.79); **Independence (mRS 0 – 2) at 3 months:** 314/541 (58.0%; 53.8 – 62.2) vs 5756/10231 (56.3%; 55.3 – 57.2) (aOR 0.93 [95%CI 0.84 – 1.03], P=0.18)		***sICH** （ISITS-MOST definition）**:** 14/649 (2.2%) vs. 183/11681 (1.6%), OR 1.18 (95%CI 0.89 – 1.55) , P=0.24 **sICH** （ECASS II definition）**:** 34/636 (5.3%) vs. 553/11505 (4.8%).OR 1.06 (95%CI 0.89 – 1.26) ,P=0.54 **sICH** （NINDS definition）**:** 52/647 (8.0%) vs. 846/11646 (7.3%),	***Death within 90 days:** 70/551 (12.7%) vs. 1263/10368 (12.2%), OR 1.02 (95%CI 0.90 – 1.17), P= 0.72

						OR 1.06 (95%CI 0.91 – 1.22), P= 0.46	
A. Belkouch, et al.[80] 2015 Morocco	**Study type:** An open prospective study **Study size:** 13	**Time window:** 4.5 hours **Eligibility criteria of imaging:** CT/MRI scan to exclude hemorrhage	**0.4 mg/kg tenecteplase** **1.age (years):** 63±15 **2.baseline NIHSS:** 14.3 (range:±7) **3. onset-to-treatment interval :** 3h 30 min (±35min)	***Early neurological recovery(NIHSS reduction ⩾ 4 at 24 h):**77%		**sICH （NINDS）:** 1/13	**Death:** 0/13
M. George, et al.[81] 2021 India	**Study type:** A single center, retrospective, comparative study **Study size:** 90	**Time window:** 4.5 hours **Eligibility criteria of imaging:** No intracranial bleed in NCCT; ASPECTS score ⩾7	**0.2 mg/kg tenecteplase (n=61) vs. 0.9 mg/kg alteplase (n=29)** **1.age (years):** 64.3 ± 11.3 vs 63.2 ± 12.01, P=0.67 **2.baseline NIHSS:** 8(IQR 5,12) vs 8(IQR 4.5,12), P=0.34 **3. referred for**	***mRS scores 0-2 at 90 days** 83.6% (51/61) vs 79.3% (23/29), P= 0.62 **Immediate favorable outcome (NIHSS reduction >4 at 24 h):** 70.4%	**Recanalization of LVO:** 0 vs. 6.8% (6/29), P=0.06	**sICH within 7 days (ECASS II):** 9.8% (6/61) vs 17.2% (5/29), P = 0.36	**Death during hospital stay :** 1.6% (1/61) vs 6.8% (2/29)

			mechanical **thrombectomy :**1.6%vs. 3.4%	(43/61) vs 51.7% (15/29), p= 0.08			
K. Mahawish, et al.[76] 2021 New Zealand	**Study type:** Extracting data from a mandatory national stroke registry **Study size:** 838	**Time window:** 4.5 hours	**0.25 mg/kg tenecteplase (n=283) vs. 0.9 mg/kg alteplase (n=555)** **1.age (years):**71.8 ±14.3 vs 71.9±14.9, P=0.96 **2.baseline NIHSS:** 8 (5–16) vs 8 (5–15), P=0. 95 **3.thrombectomy:** 46 (16.3) vs 33 (5.95), P<0.001	***shift analysis of mRS:** adjusted odds ratio, 1.60 [95% CI, 1.15–2.22] **mRS scores 0-2 at 90 days** 63.6% (147/231) vs. 60.0% (282/478), aOR 2.17 [95% CI 1.31–3.59]		**sICH：** 1.8% (5/283) vs 3.4% (19/555), aOR 0.46 [95% CI 0.13–1.64]	**Death** **at day7 :** 7.4% (21/283) vs 11.2% (62/555), aOR 0.46 [95% CI 0.21–0.99]
K. Psychogios, et al.[71] 2021 Greece	**Study type:** Extracting data from a mandatory national stroke registry	**Time window:** 4.5 hours **Eligibility criteria of imaging:** LVO	**0.25 mg/kg tenecteplase (n=283) vs. 0.9 mg/kg alteplase (n=555)** **1.age (years):** 69 (51–78) vs 70 (63–77), P=0.471	**mRS scores 0-2 at 90 days** 57.9% vs 48.7%, p=0.512 **Major neurological improvement at**		**sICH（SITS）：** 15.8% vs 5.1%, P=0.318	**Death** **at 90** **days:** 10.5% vs 17.9%, p=0.703

	Study size: 838	(ICA/MCA-M1/MCA-M2/ BA) confirmed by CTA/MRA/TCD	**2.baseline NIHSS:** 8 19 (12–23) vs 16 (10–20), P=0.340 **3. onset to treatment time (min):**165 (105–230) vs 165 (130–220), P=0.486 **4.poximal occlusion:**89.5% vs 74.3%, P=0.182	**24h (NIHSS score decrease ⩾8 points):** 64.2% vs 33.3%, p=0.046			
K.C. S. Zhong, et al.[75] 2021 New Zealand Psychogios, et al. 2021 Greece	**Study type:** A retrospective analysis of consecutive patients thrombolyzed with intravenous tenecteplase **Study size:** 419	**Time window:** 4.5 hours **Eligibility criteria of imaging:** Routine CT angiogram to exclude hemorrhage	**0.25 mg/kg tenecteplase (n=165) vs. 0.9 mg/kg alteplase (n=254)** **1.age (years):** 75 (64–84) vs 74 (62–83), p=0.50 **2.baseline NIHSS:** 8 (5–14) vs. 10 (5–17), P=0.17 **3. onset to treatment time（min）:**130 (97–	**mRS scores 0-2 at 90 days** 61% (100/164) vs 57% (140/244), P=0.47		**sICH**（NIHSS increase of ⩾4 with associated with parenchymal hemorrhage type 2 or subarachnoid hemorrhage on repeat imaging within 48 hours）： 1.8% (3/165) vs 2.7% (7/254), P=0.75	

			183) vs 129 (100 – 175), P=0.72 **4.large vessel occlusion:**53% (87/165) vs 46% (118/254), P= 0.21 **5.Endovascular thrombectomy**：37% (61/165) vs 24% (61/254), P=0.004				
A. Estella, et al.[73] 2022 Spain	**Study type:** A retrospective multicenter cohort study **Study size:** 100	**Time window:** according to clinical practice guidelines **Eligibility criteria of imaging:** MCA-M1/MCA-M2/ICA/ BA on CT/MRI	**0.25 mg/kg tenecteplase (n=20) vs. 0.9 mg/kg alteplase (n=80)** **1.age (years):** 73 (69 – 78.5) vs 74.5 (66 – 81.75), P=0.766 **2.baseline NIHSS:** 19.5 (14.75 – 22) vs 13.5 (9 – 20), P=0.021 **3. onset to treatment time ⩽ 3 h:** 16 (80) vs 59	***mRS scores 0-1 at 90 days** 35% vs 58.8%, P=0.38 ***Neurological improvement (NIHSS at 24h = 0 or reduction ⩾ 4：** 30% vs 55%, P= 0.008	***Successful recanalization (mTICI 2b-3)：** 75% vs 83.8% (OR 0.58; [95% CI 0.18 – 1.88]; P = 0.56)	**sICH（ECASS）：** 30% vs 15.2%, P=0.12	**Death at 90 days:** 20% vs 17.5%, P=0.79

			(73.8), P=0.564				
A. Teivane, et al.[72] 2022 Latvia	**Study type:** A retrospective observational single-center non-randomized study **Study size:** 184	**Time window:** 4.5 hours **Eligibility criteria of imaging:** LVO (ICA/MCA-M1/MCA-M2/ BA) confirmed by CTA/MRA/TCD	**0.25 mg/kg tenecteplase (n=45) vs. 0.9 mg/kg alteplase (n=139)** **1.age (years):** 68.4 ±13.5 vs 73.0±11.4, P=0.14 **2.baseline NIHSS:** 14 (4–26) vs 15 (2–31), P=0.52	**mRS scores 0-2 at 90 days** 56.7% vs 39.6%, OR 0.50 [95% CI 0.24–1.06]	**Successful recanalization (mTICI 2b-3)：** 93.4% (42/45) vs 81.3% (113/139), P = 0.07	**Hemorrhagic imbibition within 24 hours** 33.3% (15/45) vs 28.1% (39/139), P = 0.50	**Death at 90 days:** 13.5% vs 15.3%, P = 0.79

			3. onset to thrombectomy time (min）: 165 vs 180, P=0.32 **4.EVT：** Anterior: 31 (88.6%) vs 113 (89%); Posterior: 4 (11.4%) vs 14 (11%); p=0.95				
S. J. Warach, et al.[82] 2022 The USA	**Study type:** A prospective registry-based observational, sequential cohort **Study size:** 588	**Time window:** 4.5 hours	**0.25 mg/kg tenecteplase (n=234) vs. alteplase (n=354)** **1.age (years)**:68 (57–77) vs 67 (55–79), P=0.61 **2.baseline NIHSS:** 8 (4–13) vs 8 (4–15), P=0.32 **3. onset to treatment time (min）:** 148 (107–202) vs 139 (103–197), P=0.24 **4.EVT：** 54 (24%) vs 77 (22%), P=0.65	**mRS scores 0-1 at 90 days** 60 (48) vs 78 (41), aOR 1.26 (95%CI [0.79, 2.02], P=0.34		**sICH：** 1.7% vs 2.8%, P=0.55	**All-cause death during hospitalization：** 3.8% vs 6.2%, P=0.29

CERTAIN[74] 2023 New Zealand, Australia, and the USA	**Study type:** A retrospective observational study **Study size:** 9238	**Time window:** within 4.5 hours or wake-up stroke or beyond 4.5 hours with CT or MRI **Eligibility criteria of imaging:** according to local operating procedures at each center	**0.25 mg/kg tenecteplase (n=1925) vs. 0.9 mg/kg alteplase (n=7313)** **1.age (years):** 73 (61-81) vs 70 (58-80), P<0.001 **2.baseline NIHSS:** 9 (5-17) vs 7 (4-14), P<0.001 **3. onset to thrombectomy time (min）:** 141 (100-198) vs 136 (98-189), P=0.002 **4.LVO:**923 (48%) vs 1827 (25%), P<0.001 **4.EVT**：744 (38%) vs 1474 (20), P<0.001	**mRS scores 0-1 at 90 days** 704 (45%) vs 2179 (40%), OR 1.57 [95% CI, 1.16-2.12], P=0.003 **mRS scores 0-2 at 90 days** 858 (55%) vs 2815 (52%), OR 1.44 [95% CI, 1.00-2.09], P= 0.05	**Successful endovascular reperfusion** 1694 (88%) vs 6655 (91%), P=0.09	***sICH** (clinical worsening of at least 4 points on the NIHSS, attributed to parenchymal hematoma, subarachnoid, or intraventricular hemorrhage)**:**35 (1.8%) vs 264 (3.6%), aOR 0.42 [95% CI, 0.30-0.58], P<0.001	**Death** **at 90** **days:** 227 (14%) vs 635 (11%), P=0.001

Tenecteplase; SITS-MOST indicates Safe implementation of treatments in stroke Monitoring Study; CT, Computed Tomography; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; sICH, symptomatic Intracerebral Hemorrhage; CI, confidence interval; SITS-ISTR, Safe Implementation of Treatments in Stroke, a prospective internet-based audit of the International Stroke Thrombolysis Registry; ECASS, The European Cooperative Acute Stroke Study; aOR, adjusted odds ratio; NINDS, TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY; MRI, Magnetic Resonance Imaging; NCCT, Non-contrast Computed Tomography; ASPECT, Acute Stroke Prognosis Early CT score; IQR, interquartile range; LVO, large vessel occlusion; ICA, internal carotid artery; MCA, middle cerebral artery; CTA, Computed Tomography Angiography; MRA, magnetic resonance angiography; TCD, Transcranial Doppler; mTICI: modified Thrombolysis in Cerebral Infarction Score; BA, basilar artery; EVT, Endovascular Thrombectomy; and CERTAIN,

The Comparative Effectiveness of Routine Tenecteplase vs Alteplase in Acute Ischemic Stroke.

* The primary outcome in the trial.

Table S4. Ongoing tenecteplase trials and registries globally.

Ongoing Trial/ NCT Number/ Status	Registry Title	Aim of Study/ Study Type	Sponsor/ PI	Centers/ Sample Size/ Time Course	Inclusion Criteria	Intervention/ Comparator	Primary Outcome
Clinical Trials							
TEMPO-2 NCT02398656 Recruiting	A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion	**Study type** multicenter, prospective randomized open label, blinded-endpoint (PROBE) controlled trial	**Sponsor** University of Calgary **PI** Dr. Michael Hill, University of Calgary	**Centers** 50 **Sample size** 1274 **Time course** 2015/04-2024/12	18 years of age or older；Onset (last-seen-well) time to treatment time ≤ 12 hours；TIA or minor stroke defined as a baseline NIHSS ≤ 5 at the time of randomization；Any acute intracranial occlusion or near occlusion (TICI 0 or 1) (MCA, ACA, PCA, VB territories) defined by non-invasive acute imaging (CTA or MRA) that is neurologically relevant to the presenting	Tenecteplase (0.25mg/kg) given as a single, intravenous bolus vs. standard of care based antiplatelet treatment	mRS0-1/mRS 0-2

					symptoms and signs. Multiphase CTA or CT perfusion are required for this study；Pre-stroke mRS ≤2；Patients can be treated within 90 minutes of the first slice of CT or MRI.		
ORIGINAL NCT04915729 Active, Not Recruiting	A Study in Chinese Patients to Compare How Tenecteplase and Alteplase Given After a Stroke Improve Recovering of Physical Activity	**Study aim** to compare how tenecteplase and alteplase improve peoples' recovering of physical activity. **Study type** Phase III Multi-center, PROBE, Active-controlled Parallel Group Trial	**Sponsor** Boehringer Ingelheim	**Sample size** 1400 **Time course** 2021/06-2023/07	Age ≥18 years old Diagnosis of ischemic stroke with a measurable neurological deficit on NIHSS (0< NIHSS ≤25); if NIHSS <4, patients have to be with at least a measurable deficit on motor power (upper or lower limbs ≥1) Stroke symptoms should have been present for at least 30 minutes without significant improvement prior to randomization Thrombolytic therapy can be initiated within 4.5	Tenecteplase vs. alteplase	mRS 0-1 at 90 days

					Hour(s) (h) of AIS onset Patients with premorbid mRS 0 or 1		
NOR-TEST 2, part B NCT03854500 Recruiting	The Norwegian Tenecteplase Stroke Trial 2	**Study aim** To compare efficacy and safety of tenecteplase 0.4 mg/kg (single bolus) vs. alteplase 0.9 mg/kg within 4.5 hours after awakening with stroke symptoms, and as bridging therapy within 4.5 hours before thrombectomy **Study type** PROBE trial	**Sponsor** Haukeland University Hospital **PI** Christopher Kvistad, MD PhD	**Sample size** 201 **Time course** 2019/10-2023/09	**General inclusion criteria** 18 years or older; baseline NIHSS>5; All stroke sub-types and vascular distributions are eligible; Treatment <4½ hours after stroke onset or after awakening with symptoms. **Specific sub-set inclusion criteria** Wake-Up Stroke: FLAIR-DWI mismatch on MRI as judged by the (neuro-) radiologist or neurologist.;	Tenecteplase 0.25 mg/kg single bolus intravenously vs. Alteplase 0.9 mg/kg as 10% bolus + 90% infusion/60 minutes intravenously Other Name: Actilyse	favorable functional outcome (mRS 0-1) at 90 days

					Thrombectomy: Occlusion of intracerebral artery technically accessible for endovascular embolectomy as defined by local treatment protocols.		
CHABLIS-T II NCT04516993 Recruiting	CHinese Acute Tissue-Based Imaging Selection for Lysis In Stroke -Tenecteplase II	**Study aim** To explore the efficacy and safety of tenecteplase for acute ischemic stroke patients (onset time 4.5-24h) of large vessel occlusion using early combined CT/MR imaging outcomes **Study type** Prospective, Multicenter, Open,	**Sponsor** Huashan Hospital **PI** Qiang Dong, Huashan Hospital	**Sample size** 224 **Time course** 2021/09-2022-01	Anterior circulation acute ischemic stroke；Time from onset to treatment 4.5h-24h；Patient's age is >= 18 years，<= 80；Pre-stroke mRS score of <= 2；Clinically significant acute neurologic deficit (Baseline NIHSS scale >= 6); Vessel occlusion or severe stenosis (ICA, MCA-M1/M2, ACA) on CTA/MRA; Multimodal CT/MRI: perfusion lesion volume (DT > 3 s) to	Intravenous (IV) tenecteplase 0.25 mg/kg (single bolus; maximum dose 25 mg) vs. The best treatment selected by local doctors(Aspirin, Recombinant Tissue Plasminogen Activator,	Without endovascular therapy: >50% reperfusion on CTP at 4-6 hours；With endovascular therapy: mTICI score 2b or better at initial angiogram after thrombolysis before endovascular therapy；No sICH at 24-36 hours

		End-point Blinded, Stratified Block Randomized, Parallel Positive Controlled Clinical Trial			infarct core volume ratio (rCBF<30% or DWI imaging lesion) >1.2, absolute difference >10 ml, and ischemic core volume <70ml	Urokinase, Thrombectomy)	
RESILIENT (EXTEND-IV) NCT05199662 Recruiting	Randomization to Extend Stroke Intravenous ThromboLysis In Evolving Non-Large Vessel Occlusion With TNK	**Study aim** To examine whether treatment with intravenous TNK is superior to placebo in patients who suffer a non-large vessel occlusion ischemic stroke within 4.5-12 hours from time last seen well **Study type** phase III, Prospective, multi-center, randomized,	**Sponsor** Hospital Moinhos de Vento **PIs** Gisele Sampaio Silva, MD, MPH, PhD (Universidade Federal de São Paulo); Raul G Nogueira,	**Centers** At least 6 **Sample size** 642 **Time course** 2022/01-2024/05	Acute ischemic stroke where patient is ineligible for IV thrombolytic treatment with Alteplase due to onset >4.5 hours and is ineligible for endovascular treatment under standard of care due to absence of proximal arterial occlusion (e.g. intracranial ICA, MCA-M1 and dominant M2 segments, and vertebrobasilar arteries); Pre-mRS ≤2;Evidence of a disabling deficit including significant aphasia, neglect,	Intravenous thrombolysis with Tenecteplase at a dose of 0.25 mg/Kg (maximum 25mg, administered as a bolus over 5 seconds) vs. Placebo administered as a single bolus injection over 5 seconds	Distribution of the mRS scores at 90 days (shift analysis)

		controlled, double blinded trial	MD (Emory University); Sheila CO Martins, MD, PhD (Hospital Moinhos de Vento)		hemianopsia, or hemiparesis and/or baseline NIHSS score ≥4 points; Age ≥18 years; The presence of a Target Mismatch defined as:a. Ischemic Core < 50cc) (defined on NCCT/CTP* or DWI-MRI),b.. Mismatch Volume (TMax >6sec lesion - Core volume lesion) >10cc c. Mismatch Ratio >1.4.;Patient treatable within 4.5-12 hours of symptom onset.		
ETERNAL-LVO NCT04454788	Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients With Large Vessel	**Study type** PROBE design.	**Sponsor** University of Melbourne **PI** Bruce	**Centers** At least 7 **Sample size** 740	present with AIS with onset (or the time they last known to be well) within 24 hours; ≥18 years old; Premorbid mRS <3; Presence of a vessel occlusion on CTA or MRA (LVO will be	0.25mg/kg tenecteplase vs. no intravenous thrombolytic treatment or intravenous 0.9mg/kg	mRS 0-1 (no disability) or return to baseline mRS (if baseline premorbid mRS =2) at 90 days

Recruiting	Occlusion		Campbell, University of Melbourne	**Time course** 2020/08-2025/12	defined as 'potentially retrievable' thrombus atnICA, MCA M1、M2 or isolated/tandem occlusion of the extracranial ICA.); Presence of 'target mismatch' on automated CTP or diffusion-perfusion MRI software defined as an ischemic core of <70mL, penumbra of >20mL and an ischemic core to perfusion lesion ratio of >1.8	alteplase	

POST-ETERNAL NCT05105633 Recruiting	Extending the Time Window for Tenecteplase by Recanalization of Basilar Artery Occlusion in Posterior Circulation Stroke	**Study aim** to test the hypothesis that the thrombolytic tenecteplase (TNK, 0.25mg/kg) ± mechanical thrombectomy administered within 24 hours after symptoms onset, is superior to current best practice (alteplase, rtPA, 0.9mg/kg or standard care/no lysis ± mechanical thrombectomy) in achieving excellent functional outcome (mRS 0-1) or return to the premorbid modified Rankin Scale at 90 days in patients with acute ischemic stroke due	**Sponsor** University of Melbourne **PI** Bruce Campbell (University of Melbourne); Fana Alemseged (University of Melbourne)	**Centers** At least 11 **Sample size** 688 **Time course** 2021/11-1022/12	presenting with posterior circulation ischemic stroke symptoms due to partial or complete basilar artery occlusion within 24 hours from symptom onset (or clinical deterioration/coma) or the time the patient was last known to be well; ≥18 years old; Presence of basilar artery occlusion, proven by CTA or MRA; Premorbid mRS ≤3	tenecteplase 0.25mg/kg before undergoing mechanical thrombectomy vs. no intravenous thrombolytic treatment or intravenous alteplase 0.9mg/kg	mRS 0-1 or return to baseline mRS at 90 days

		to basilar artery occlusion **Study type** Multi-Arm Multi-Stage (MAMS), multiregional, multicenter, PROBE, controlled seamless phase 2b/3 trial					
TRACE III NCT05141305 Recruiting	Teneteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events-III	**Study aim** To investigate the safety and efficacy of rhTNK-tPA (0.25mg/kg, max 25mg) versus standard medical treatment in acute ischemic stroke due to large vessel occlusion between	**Sponsor** Beijing Tiantan Hospital **PI** Yongjun Wang, Beijing Tiantan Hospital	**Sample size** 516 **Time course** 2022/03-2023/12	Age ≥18 years; symptom onset between 4.5 to 24 hours prior to enrollment; including wake-up stroke and unwitnessed stroke, onset time refers to 'last normal time'; Pre-stroke mRS score≤1; Baseline NIHSS 6-25 (both included);	tenecteplase (0.25 mg/kg, Max 25 mg) vs. standard medical treatment （Aspirin combined with clopidogrel, aspirin alone, or clopidogrel alone）	excellent functional outcome defined as an mRS score ≤ 1 at 90 days

		4.5-24 hours of symptom onset (including wake-up stroke and unwitnessed stroke) **Study type** PROBE design			Neuroimaging: Internal carotid artery, middle cerebral artery M1 or M2 occlusion confirmed by CTA/MRA, and target mismatch profile on CTP or MRI_PWI including ischemic core volume <70 mL, mismatch ratio≥1.8 and mismatch volume≥15 mL demonstrated by iStroke		
DIRECT-TNK NCT05199194 Recruiting	Randomization to Endovascular Treatment Alone or Preceded by Systemic Thrombolysis With Tenecteplase in Ischemic Stroke	**Study type** phase III randomized, multi-center, double-blinded, placebo-controlled clinical trial	**Sponsor** Hospital Moinhos de Vento **PIs** Octavio M Pontes-Neto, MD, PhD（Hospital de	**Smple size** 530 **Time course** 2022/04-2022	pre-mRS ≤ 1；Baseline NIHSS ≥ 6；Age ≥ 18 and =< 85 years；Occlusion (TICI 0-1) of the proximal MCA segments (M1 or M2) suitable for endovascular treatment, as evidenced by CTA, MRA, or angiogram, with or without concomitant cervical carotid stenosis；Patient	Intravenous thrombolysis with tenecteplase 0.25mg/kg vs. Intravenous administration of placebo, matching the volume of tenecteplase 0.25mg/kg	Distribution of 90-day mRS scores (shift analysis).

			Clínicas da Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo）； Sheila CO Martins, MD, PhD（Hospital Moinhos de Vento）； Raul G Nogueira, MD（Emory University）		randomized within 4.5 hours of symptom onset.（Symptoms onset is defined as the point in time the patient was last seen well. Treatment start is defined as groin puncture, max 90 minutes after randomization.）		

BRIDGE-TNK NCT04733742 Recruiting	Endovascular Treatment With Versus Without Intravenous rhTNK-tPA in Stroke	**Study aim** to investigate whether intravenous rhTNK-tPA prior to endovascular treatment can improve 90-day functional outcome of stroke patients with large vessel occlusion who are thrombolysis-eligible within 4.5 hours of symptom onset **Study type** phase2/3 Multicenter, Randomized Controlled Trial	**Sponsor** Xinqiao Hospital of Chongqing **PIs** Qingwu Yang, MD (Neurology, Xinqiao Hospital of the Army Medical University) ; Raul G Nogueira, MD (Marcus Stroke & Neuroscience Center, Grady Memorial	**Centers** At least 5 **Sample size** 498 **Time course** 2022/05-2026/03	Aged 18 years or older; AIS confirmed by clinical symptoms or imaging examination; MCA-M1 or -M2, basilar artery, or PCA-P1 occlusion proved by CTA/MRA; Eligible for intravenous thrombolysis with TNK-tPA; Time from stroke onset to randomization within 4.25 hours	intravenous t enecteplase bridging with endovascular treatment vs. endovascular treatment alone	mRS score at 90 days

			Hospital, Emory University, Atlanta, USA)； Jeffrey L Saver, MD (Neurology, University of California, Los Angeles, USA)； Wenjie Zi, MD (Neurology, Xinqiao Hospital of the Army Medical University)				

3T Stroke-III NCT05745259 Recruiting	Thrombolysis Treated by TNK-tPA in Acute Ischemic Stroke Patients: a Multi-center, Block Randomized, Positive Drug Parallel Control and Non-inferior Phase Ⅲ Trial	**Study type** PROBE design	**Sponsor** Beijing Tiantan Hospital **PIs** Yongjun Wang, Beijing Tiantan Hospital	**Centers** 63 **Sample size** 1630 **Time course** 2022/10-2024/03	Age ≥18 years old; AIS within 4.5h; mRS before onset was ≤1 points; Baseline NIHSS (at the time of randomization) should be > 5 and ≤25 points; Informed consent from the patient or surrogate.	0.9 mg/kg alteplase vs. 0.25 mg/kg tenecteplase	Proportion of subjects with mRS scores of (0-1) at 90±7 days
NCT05626972 Recruiting	Tenecteplase Compared to Alteplase for Patients With Large Vesel Oclusion Suspicion Before Thrombectomy	**Study aim:** To determine the safety and efficacy of TNK (0.25mh/kg) compared to tPA (0.9 mg/kg) in patients with Large Vessel Occlusion (LVO) suspicion, candidates for thrombectomy, in	**Sponsor** Hospital Universitari Vall d'Hebron Research Institute	**Center** Hospital Universitari Vall d'Hebron **Sample size** 500 **Time course** 2022/05-2024	Patients eligible to undergo intravenous thrombolysis (tPA or TNK) within 4.5 hours after the onset of ischemic stroke;Suspicion of Cerebral vascular occlusion on brain imaging;Age >18 years	0.9 mg/kg alteplase vs. 0.25 mg/kg tenecteplase before endovascular therapy (EVT)	1. Shift analysis of the mRS score at 3 months 2. Mortality at 3 months 3. sICH and neurological deterioration within 24-36 hours

		both Mothership and Drip-and-Ship scenarios. **Study type** PROBE		/05	old; A new focal disabling neurologic deficit consistent with acute cerebral ischemia;Informed consent obtained from subject or acceptable subject surrogate		
ATTIS NCT05604638 Not yet recruiting	Early Administration of Tirofiban in Patients Treated With Tenecteplase for Acute Ischemic Stroke	**Study aim** to assess the safety and efficacy of early administration of tirofiban in patients treated with tenecteplase for acute ischemic stroke **Study type** randomized, placebo-controlled clinical trial	**Sponsor** Second Affiliated Hospital of Guangxi Medical University **PI** Jian Zhang, MD, Second Affiliated Hospital of	**Sample size** 600 **Time course** 2023/03-2025/12	Age 18-80 years; Ischemic stroke with measurable deficit on NIHSS; Treatment within 4.5 hours of stroke onset; Pre-mRS score: 0-1;	a continuous intravenous infusion of tirofiban at a rate of 0.1 μg/kg per minute for 26.5 h after start of 0.25mg/kg tenecteplase treatment within 90 min vs. a continuous	functional independence(mRS0-2) at 90 dys； Mortality at 90 days

			Guangxi Medical University			intravenous infusion of Placebo at a rate of 0.1 μg/kg per minute for 26.5 h after start of 0.25mg/kg tenecteplase treatment within 90 min	

INSIST-TNK NCT04201964 Recruiting	Improving Neuroprotective Strategy for Ischemic Stroke With Poor Recanalization After Thrombectomy by Intra-arterial TNK	**Study aim** to explore the proportion of sufficient recanalization (2b/3) after intra-arterial tenecteplase administration in patients undergoing thrombectomy with insufficient recanalization (1/2a) **Study type** a Prospective, Single Arm, Pilot Study	**Sponsor** Hui-Sheng Chen **PI** Hui-Sheng Chen, General Hospital of Shenyang Military Region	**Sample size** 30 **Time course** 2019/12-2022/12	Age ≥18 years; Patients who presented with acute ischemic stroke and a large vessel occlusion in the anterior circulation and met the criteria of mechanical thrombectomy; insufficient perfusion (mTICI 1/2a) after endovascular treatment;	Intra-arterial administration of tenecteplase (0.2-0.4 mg/min) immediately after thrombectomy device pass for 30-40 minutes	sufficient recanalization is defined as TICI 2b-3

INSIST- IT NCT05657457 Recruiting	Improving Neurological Outcome for Acute Basilar Artery Occlusion With Sufficient Recanalization After Thrombectomy by Intra-arterial Tenecteplase	**Study aim** to explore the efficacy and safety of intra-arterial tenecteplase in acute BAO patients with successful reperfusion after EVT **Study type** a Prospective, Randomized, Open-label, Blinded-end Point, Multicenter Trial	**Sponsor** General Hospital of Shenyang Military Region **PI** Hui-Sheng Chen, General Hospital of Shenyang Military Region	**Sample size** 228 **Time course** 2023/03-2025/03	Age ≥ 18;Patients with BAO who received EVT within 24 hours of estimated time of stroke onset as per BASICS trial definition; NIHSS≥ 6 before EVT; Successful recanalization (mTICI 2b-3) after EVT;PC-ASPECTS ≥ 6 on CT; Absence of parenchymal hematoma on CT images done in the angio suite immediately after the procedure; mRS score before stroke onset ≤ 3; Signed informed consent by patient or their legally authorized representative	Intra-arterial administration of tenecteplase vs. control group	mRS 0-3 at 90 days
ALLY NCT05172934	Adjunctive Intra-arterial Tenecteplase Following Mechanical	**Study aim** to assess the feasibility of IA TNK following standard of	**Sponsor** ProMedica Health System	**Centers** Single	Age 18-85; Anterior circulation ischemic stroke symptoms with confirmed	intra-arterial Tenecteplase after achieving mTICI 2b or	any ICH and neurologic worsening of at least 4 points on the NIHSS according to the ECASS-II criteria,

Not yet recruiting	Thrombectomy Pilot Trial	care mechanical thrombectomy (MT) in patients with AIS **Study type** Phase 2, prospective, single center, non-randomized, pilot study	**PI** Syed F Zaidi, MD (ProMedica Health System)	**Sample size** 20 **Time course** 2022/01-2023/06	occlusion (ICA, M1, or M2) on angiogram and mechanical thrombectomy initiated within 24 hours since last known well a. Patients treated less than 6 hours since last known well with ASPECTS >6. b. Patients treated beyond 6 hours since last known well, CT or MRI perfusion scan showing favorable mismatch profile (Target mismatch profile on CT perfusion or MRI (ischemic core volume is <70ml, mismatch ratio is >1.8 and mismatch volume is >15ml); Post-mechanical thrombectomy with ≤5 device passes and mTICI grade 2b or 2c with	2c reperfusion with standard of care MT	within 24 hours of treatment with IA TNK

					persistent occlusion(s) in terminal branches not amenable to MT		
TECNO NCT05499832 Not yet recruiting	Safety and Efficacy of Intra-arterial Tenecteplase for Noncomplete Reperfusion of Intracranial Occlusions	**Study aim** To evaluate if additional administration of intra-arterial tenectep lase improves reperfusion in patients with incomplete mechanical thrombectomy **Study type** PROBE, proof-of-concept trial	**Sponsor** University Hospital Inselspital, Berne **PI** Urs Fischer, PhD (NCTU)	**Centers** 20 **Sample size** 156 **Time course** 2022/09-2025 /10	Age ≥18 years; Patient had an initial large vessel occlusion in the anterior circulation defined as intracranial ICA, M1 or M2;. Patient has undergone endovascular stroke treatment; Onset to randomization no later than < 345 minutes after symptom-onset/last-seen well.; Incomplete reperfusion defined as 1. For ICA/M1: TICI2b/2c (50-99%) reperfusion after endovascular treatment without mechanically amendable target-occlusion (as per definition by the	intra-arterial administratio n of 3 mg tenecteplase using a standard approved microcatheter .vs. Best Medical Treatment (standard of care)	Early reperfusion of the residual intracranial occlusion(s) within 25 minutes; Late reperfusion of the residual intracranial occlusion(s) at 24 hours ±6 hours

					interventionalist). 1. For M2: TICI2a/2b/2c (1-99%) reperfusion after endovascular treatment without mechanically amendable target-occlusion (as per definition by the interventionalist). 3.ICA/M1/M2 with TICI3 reperfusion (MCA territory) but emboli to the ACA territory without mechanically amendable target-occlusion (as per definition by the interventionalist).; Signs of early ischemic changes of non-contrast CT-ASPECTS ≥5 (for DWI-ASPECTS ≥ 4, for DWI-ASECTS: a region must have diffusion abnormality in 20% or		

					more of its volume to be considered DWI-ASPECTS positive)		
BRETIS-TNK II NCT05657444 Recruiting	Intra-arterial Tenecteplase During First Thrombectomy Attempt for Acute Stroke	**Study aim** To determine the efficacy and safety of intra-arterial TNK administration during EVT in AIS-LVO patients **Study type** a Prospective, Randomized, Adaptive Enrichment, Open-label, Blinded End Point, Multi-center Study	**Sponsor** General Hospital of Shenyang Military Region **PI** Hui-Sheng Chen, General Hospital of Shenyang Military Region	**Center** General Hospital of Northern Theater Command **Sample size** 372 **Time course** 2023/03-2025/05	Age ≥18 years; Stroke patient with LVO (ICA, M1 or M2 of MCA, BA, or intracranial segment of VA) who meets criteria for endovascular treatment within 24 hours of stroke onset; The mRS score before onset ≤ 2;ASPECTS 6 or greater on CT; Signed informed consent.	intra-arterial tenecteplase during endovascular treatment vs. control group	mRS0-2 at 90 days

RESCUE-TNK NCT05657470 Recruiting	Rescue Thrombolysis for Medium Vessel Occlusion	**Study aim:** To explore the safety and efficacy of intra-arterial TNK in patients with MeVO. **Study type** A Prospective, Randomized, Open-label, Blinded End Point, and Multicenter Trial	**Sponsor** General Hospital of Shenyang Military Region **PI** Hui-Sheng Chen, General Hospital of Shenyang Military Region	**Center** General Hospital of Northern Theater Command **Sample size** 80 **Time course** 2023/03-2025/03	Age ≥18 years; Medium vessel occlusion (MeVO), referring to M2-3 of MCA; A1-3 of ACA; P1-3 of PCA; PICA, AICA or SCA (including primary, distal embolism in the same region after thrombectomy or concurrent embolism in other regions);Within 24 hours from symptom onset; Signed informed consent by patient or patient's legally authorized representative.	intra-arterial tenecteplase during endovascular treatment vs. control group	proportion of patients with successful MeVO recanalization (defined as the expanded treatment in cerebral ischemia (eTICI) score 2b67-3 in the territory of the target occluded MeVO artery)

ATTENTION IA NCT05684172 Recruiting	Trial of Intra-arterial Tenecteplase Following Successful Endovascular Thrombectomy on Safety and Efficacy in Patients With Large Vessel Occlusion of Posterior Circulation - a Multicenter Randomized Clinical Trial	**Study aim:** To assess the effect of EVT in addition to intra-arterial tenecteplase compared to EVT alone, in patients with large vessel occlusion of posterior circulation, on functional and safety outcomes **Study type** A multicenter, parallel group, randomized clinical trial of EVT with IA-TNK versus EVT	**Sponsor** The First Affiliated Hospital of University of Science and Technology of China	**Sample size** 208 **Time course** 2023/01-2025/03	AIS patients with symptomatic intracranial LVO in the intracranial VA, BA, or the P1 segment of the PCA; Treated with EVT resulting in an eTICI score 2b50/3 at end of the procedure; Age of 18 years or older; NIHSS score on admission≥6; Posterior Circulation ASPECTS ≥ 6 on CT/CTA-Source Images/MRI-DWI; Time from estimated time of BAO to randomization<24 hours; Written informed consent.	endovascular thrombectomy+intra-arterial tenecteplase vs.endovascular thrombectomy	mRS 0-1 at 90 (± 14 days) after procedure
ANGEL-TNK NCT05624190	Intra-arterial Recombinant Human Tenecteplase Tissue-type	**Study aim:** To evaluate whether intra-arterial (IA) rhTNK-tPA thrombolysis can	**Sponsor** Beijing Tiantan Hospital	**Sample size** 256	**Clinical Inclusion Criteria:** Age >18 years; NIHSS ≥2;	The administration of tenecteplase will be	mRS 0-1 at 90±7 days after randomization

Recruiting	Plasminogen Activator rhTNK-tPA) Thrombolysis for Acute Large Vessel Occlusion After Successful Mechanical Thrombectomy Recanalization	improve neurological outcomes in acute large vessel occlusion patients after successful mechanical thrombectomy (MT) recanalization between 4.5- 24 hours from symptom onset **Study type** PROBE design	**PI** Zhongrong Miao, Beijing Tiantan Hospital	**Time course** 2022/12-2023/12	Onset of symptoms to baseline CT imaging time: 4.5 to 24 hours, including wake-up stroke and unwitnessed stroke; Time of onset of symptoms is defined as "last known well" (LKW); Pre-stroke mRS score 0-1; Signed informed consent from patient or their health care proxy. **Neuroimaging Inclusion Criteria:** CTA/MRA proven intracranial artery occlusion: ICA、M1 of MCA、dominant M2 of MCA; ASPECTS ≥6 on NCCT scan or DWI MRI; CT perfusion or MR perfusion: ischemic	infused constant and slowly over 15min (0.125 mg/kg, Max 12.5mg) through a microcatheter vs. Best Medical Management	

					infarct core <70ml, mismatch ratio≥1.2, mismatch volume ≥15ml; Treated with MT resulting in an eTICI score 2b50-3 at end of the procedure.		
EXTEND-AGNES TNK NCT05892510 Not yet Recruiting	Post-thrombectomy Intra-arterial Tenecteplase for Acute manaGement of Non-retrievable Thrombus and No-reflow in Emergent Stroke	**Study aim:** To test intra-arterial tenecteplase at the completion of thrombectomy versus best practice in participants with anterior circulation LVO receiving mechanical thrombectomy within 24 hours of symptoms onset. **Study type** Multicenter, prospective,	**Sponsor** University of Melbourne	**Centers** 12 **Sample size** 462 **Time course** 2023/09-2027/11	Adult participants presenting with ischemic stroke with arterial LVO on CT/MR Angiogram of the ICA or MCA-M1or M2 committed to thrombectomy using standard criteria within 24 hours of onset: ① For 0-6 hours of symptom onset: Presence of arterial occlusion as defined above and ASPECTS≥3 on NCCT ②For 6-24 hours of symptom onset: Additional imaging criteria on CTP or MRI perfusion	Intra-arterial 0.062mg/kg tenecteplase injection at the completion of thrombectomy vs. placebo	1. Early Neurological Improvement (defined as NIHSS reduction>4) within 24-36 hours (Phase 2b) 2. mRS 0-2 at 90 days (phase3)

		Multi-arm Multi-stage (MAMS) seamless phase 2b/3 interventional randomized placebo-controlled double-blinded parallel-assignment (2 arms with 1:1 randomization) efficacy and safety trial			of core volume <100ml. Qualifying CT/MR within 4hrs of randomization (repeat CT for transferred participants required if >4hr)；Pre-stroke mRS score of ≤2 (mild pre-existing disability permitted；Local legal requirements for consent have been satisfied.		
Registry Studies							
INTACT-China NCT04588337 Recruiting	INtravenous TNK for Acute ischemic sTroke in China	**Study aim** to evaluate the efficacy and safety of rhTNK-tPA in Chinese patients with ischemic stroke in a prospective, multicenter registration study	**Sponsor** General Hospital of Shenyang Military Region **PI** Hui-Sheng	**Sample size** 1000 **Time course** 2022/01-2022/12	Age ≥18; The time from onset to treatment was less than 4.5 hours; Ischemic stroke confirmed by head CT or MRI; There are measurable neurological deficits;	tenecteplase	excellent prognosis (mRS 0-1) at 90 ± 7 days

		Study type Prospective, Multi-center, Registry Study	Chen, General Hospital of Shenyang Military Region		First onset or previous onset without obvious sequelae (Mrs ≤1 score) ;		
TETRIS NCT05534360 Not yet recruiting	Tenecteplase Treatment in Ischemic Stroke Registry	**Study aim** to provide routine clinical care data on the use of tenecteplase for IVT for both AIS with and without LVO, in order to further characterize the safety and efficacy of tenecteplase for AIS; to use the registry which combines clinical and radiological data to explore other aspects related to AIS management in this	**Sponsor** Assistance Publique - Hôpitaux de Paris **PI** Sonia Alamowitch, MD; Gaspard Gerschenfeld, MD, PhD	**Sample size** 5000 **Time course** 2022/09-2028/03	Age 18 and older; Confirmed acute arterial ischemic stroke on brain imaging (CT or MRI) within 270 minutes of symptoms onset or with perfusion CT or MRI criteria for an extended treatment window or wake-up strokes; Intravenous thrombolysis with tenecteplase	intravenous thrombolysis with tenecteplase.	90-day mRS

		cohort. **Study type** multicenter ambispective observational study					
TREAT NCT05724342 recruiting	Tenecteplase REperfusion in Acute Ischemic sTroke Registry	**Study aim** to establish tenecteplase thrombolysis database and to investigate the effectiveness and safety of rhTNK-tPA in acute ischemic stroke patients. related to AIS management in this cohort. **Study type**	**Sponsor** Beijing Tiantan Hospital **PI** Yunyun Xiong, MD, PhD Beijing Tiantan Hospital	**Sample size** 1600 **Time course** 2023/02-2024/12	Older than 18 years; Diagnosed as AIS； Time intervals ≤ 4.5 hours from stroke onset to thrombolysis with TNK(Perfusion imaging completed including CTA+CTP or MRA+PWI+DWI before thrombolysis if the time intervals from stroke onset to thrombolysis was ≥4.5 hours)； Thrombolysis with rhTNK-tPA and derivatives.	intravenous thrombolysis with tenecteplase.	mRS 0-1 at 90 days

		multicenter prospective, observational study					

TNK indicates Tenecteplase; PI, primary investigator; TEMPO-2, A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion; tPA, Tissue-type Plasminogen Activator for Injection; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in cerebral ischemia; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; VB, vertebral artery; CTA, Computed Tomography Angiography; MRA, magnetic resonance angiography; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; mRS, Modified Rankin Score; ORIGINAL, A Study in Chinese Patients to Compare How Tenecteplase and Alteplase Given After a Stroke Improve Recovering of Physical Activity; AIS, acute ischemic stroke; NOR-TEST, Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway; FLAIR-DWI, fluid-attenuated inversion Recovery-Diffusion Weighted Imaging; CHABLIS-T, Chinese Acute Tissue-Based Imaging Selection for Lysis In Stroke-Tenecteplase; ICA, internal carotid artery; DT, delay time; rCBF, Regional Cerebral Blood Flow; DWI, diffusion-weighted imaging; CTP, computed tomography perfusion; mTICI, modified Thrombolysis in Cerebral Infarction Score; sICH, Symptomatic Intracerebral Hemorrhage; RESILIENT (EXTEND-IV), Randomization to Extend Stroke Intravenous ThromboLysis In Evolving Non-Large Vessel Occlusion With TNK; NCCT, Non-Contrast Computed Tomography; DWI-MRI, Diffusion Weighted Imaging- Magnetic Resonance Imaging; TMax, time to maximum of the residual function; ETERNAL-LVO, Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients With Large Vessel Occlusion; POST-ETERNA, Extending the Time Window for Tenecteplase by Recanalization of Basilar Artery Occlusion in Posterior Circulation Stroke; TRACEIII, Teneteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events-III; MRI_PWI, Magnetic Resonance Imaging-perfusion weighted imaging; DIRECT-TNK, Randomization to Endovascular Treatment Alone or Preceded by Systemic Thrombolysis With Tenecteplase in Ischemic Stroke; BRIDGE-TNK, Endovascular Treatment With Versus Without Intravenous rhTNK-tPA in Stroke; rhTNK-tPA, Recombinant Human TNK Tissue-type Plasminogen Activator for Injection; PCA, posterior cerebral artery; 3T StrokeI:Thrombolysis Treated With TNK-tPA in Acute Ischemic Stroke Patients; ATTIS, Alteplase versus tenecteplase for thrombolysis after ischaemic stroke; INSIST-TNK, Improving Neuroprotective Strategy for Ischemic Stroke With Poor Recanalization After Thrombectomy by Intra-arterial TNK; INSIST-IT, Improving Neurological Outcome for Acute Basilar Artery Occlusion With Sufficient Recanalization After Thrombectomy by Intraarterial Tenecteplase; BAO, Basilar Artery Occlusion; BASICS, Basilar Artery International Cooperation Study; PC-ASPECTS, Posterior Circulation Acute Stroke Prognosis Early CT score; ALLY, Adjunctive Intra-arterial Tenecteplase Following Mechanical Thrombectomy Pilot Trial; IA, intraarterial; ECASS, European Cooperative Acute Stroke Study ;TECNO, Safety and Efficacy of Intra-arterial Tenecteplase for Noncomplete Reperfusion of Intracranial Occlusions; BRETIS-TNK, Intra-arterial Tenecteplase During First Thrombectomy Attempt for Acute Stroke;BA, basilar artery; VA, vertebral artery; RESCUE-TNK, Rescue Thrombolysis for Medium Vessel Occlusion;MeVO:Medium vessel occlusions; PICA, posterior inferior cerebellar artery; AICA, anterior inferior cerebellar artery; SCA, superior cerebellar artery; eTICI, extended thrombolysis in cerebral ischemia; ATTENTION IA, Intra-arterial TNK Following Endovascular Thrombectomy in Patients With Large Vessel Occlusion of Posterior Circulation; ANGEL-TNK, Intra-arterial Recombinant Human TNK Tissue-type Plasminogen Activator (rhTNK-tPA) Thrombolysis for Acute Large Vascular Occlusion After Successful Mechanical

Thrombectomy Recanalization; EXTEND-AGNES, Post-thrombectomy Intra-arterial Tenecteplase for Acute manaGement of Non-retrievable Thrombus and No-reflow in Emergent Stroke; INTACT-China, INtravenous TNK for Acute isChemicsTroke in China; TETRIS, Tenecteplase Treatment in Ischemic Stroke Registry and TREAT, Tenecteplase REperfusion in Acute Ischemic sTroke Registry.