JoS JOURNAL OF STROKE

Journal of Stroke 2025;27(1):113-117
https://doi.org/10.5853/jos.2024.03062

Letter to the Editor

Thrombolysis in Patients With Versus Without Visible Occlusion: A Secondary Analysis From the AcT Trial

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Dear Sir:

Approximately 70% of patients who present with symptoms of acute ischemic stroke (AIS) have no visible occlusion (NVO) on intracranial computed tomography angiography (CTA).[1] These patients may either have lacunar stroke, intracranial pial arterial occlusions that are not visible on CTA, vascular stenosis resulting in hypoperfusion, spontaneous recanalization, or conditions that are stroke mimics. Owing to these different mechanisms, current data on the safety and efficacy of intravenous thrombolysis in patients with NVO is conflicting.[2,3] The aim of the current study, from the phase 3 Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke (AcT) randomized controlled trial, is to report on safety and efficacy outcomes in patients with NVO versus those with visible occlusion (VO) on baseline CTA who received thrombolysis.

This sub-study is an exploratory analysis of the AcT trial, which randomized adult patients with stroke symptoms, eligible for intravenous thrombolysis as per guidelines, to either alteplase or tenecteplase.[4,5] The trial was regulated by Health Canada and approved by research ethics boards at all participating sites. The trial used deferred consent procedures wherever approved by local research ethics boards. The current analysis included patients with interpretable baseline CT angiogram who received intravenous thrombolysis. An independent blinded imaging core lab with 4–20 years of experience read all imaging data. VO was defined as any occluded artery visualized on baseline CTA. NVO were those patients who did not have any intracranial occlusion on baseline CTA. Safety outcomes included symptomatic intracerebral hemorrhage (sICH) within 24 hours, mortality, and evidence of bleeding on follow-up imaging as per the Heidelberg Bleeding Classification described in the trial protocol[5] (Supplementary Methods). Functional outcomes included modified Rankin Scale (mRS)[6] 0–1, mRS 0–2, ordinal mRS at 90–120 days, return

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to pre-stroke function, length of stay in hospital, and EuroQol 5-Dimension 5-Level (EQ-5D-5L).

Baseline characteristics and imaging variables were described in patients with NVO as compared to VO using descriptive statistics. Categorical variables were expressed as frequencies with percentages and quantitative variables as medians with interquartile ranges or means with standard deviations as appropriate per distribution of data. Fisher's exact test and Wilcoxon rank sum test or t-test were used for categorical and continuous variables, respectively, as appropriate. Adjusted analyses were performed using mixed-effects models adjusted for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale [NIHSS] score), thrombolytic type, and stroke onset-to-needle time as fixed effect variables, and participating site as random effect variable. All analyses were considered exploratory. Statistical significance was defined as 2-tailed *P* value ≤0.05. Analyses was performed using Stata/MP version 16.0 (StataCorp., College Station, TX, USA).

Of 1,577 patients randomized in the AcT trial, 1,470 (93.2%) patients received thrombolysis within 4.5 hours, had baseline CTA available, and were included in the study (Supplementary Figure 1). Of 1,470 patients, 479 (32.6%; 247 receiving tenecteplase and 232 receiving alteplase) were in NVO group and 991 (67.4%; 509 receiving tenecteplase and 482 receiving alteplase) were in VO group. Patients in NVO group were younger (median 71 yr vs. 75 yr, *P*<0.001), presented with less severe strokes (median NIHSS 6 vs. 12, *P*<0.001), and had longer onset to needle time (median 141 min vs. 119 min, *P*<0.001) (Table 1). In VO group, 493 (49.7%) patients received endovascular treatment.

Comparing safety outcomes, rates of any intracranial hemorrhage and type II hemorrhagic infarction were significantly lower in NVO group (8.2% vs. 26.0%, adjusted relative risk [RR] 0.38, 95% confidence interval [CI], 0.26–0.55 and 2.5% vs. 11.2% adjusted RR 0.23, 95% CI, 0.12–0.42; respectively). There was no difference between groups for other hemorrhage subtypes, sICH rates, and other safety outcomes (Table 2 and Figure 1A).

Table 1. Baseline characteristics of population with no visible occlusion versus with visible occlusion

Characteristic	No visible occlusion (n=479)	Visible occlusion (n=991)	*P*
Age (yr)	71 (59–81)	75 (65–84)	<0.001
Female sex	213 (44.5)	492 (49.7)	0.066
Baseline NIHSS	6 (5–10)	12 (7–19)	<0.001
Baseline NIHSS score categories			<0.001
<8	289 (60.3)	287 (29.0)	
8–15	163 (34.0)	312 (31.5)	
≥16	27 (5.6)	392 (39.6)	
Type of enrolling center			0.060
Primary stroke center	37 (7.7)	51 (5.2)	
Comprehensive stroke center	442 (92.3)	940 (94.9)	
Thrombolytic type			0.956
Alteplase	232 (48.4)	482 (48.6)	
Tenecteplase	247 (51.6)	509 (51.4)	
Workflow times (min)			
Stroke symptom onset to hospital arrival	94 (60–147)	77 (52–123)	<0.001
Stroke symptom onset to randomisation	133 (96–190)	112 (83–168)	<0.001
Stroke symptom onset to needle	141 (104–200)	119 (90–175)	<0.001
Door (hospital arrival) to needle (thrombolysis start)	133 (96–190)	112 (83–168)	<0.001
Site of occlusion			NA
Intracranial ICA	NA	129 (8.8)	
M1-MCA		223 (15.2)	
M2-MCA		299 (20.3)	
Vertebrobasilar		61 (4.2)	
Distal		254 (17.3)	
Cervical ICA		25 (1.7)	

Values are presented as median (interquartile range) or n (%).
NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; MCA, middle cerebral artery; NA, not applicable.

https://doi.org/10.5853/jos.2024.03062

Table 2. Safety and efficacy outcomes in patients with no visible occlusion versus those with visible occlusion

Outcome	No visible occlusion (n=479)	Visible occlusion (n=991)	Risk difference (95% CI)	Adjusted RR (95% CI)[§]
Safety outcomes				
Death within 90 days of randomization	38 (8.1)	189 (19.1)	-0.11 (-0.14 to -0.08)	0.67 (0.46 to 0.98)
24-h sICH*	11 (2.3)	36 (3.6)	-0.01 (-0.03 to 0.00)	1.00 (0.47 to 2.12)
Any ICH on imaging	39 (8.2)	255 (26.0)	-0.18 (-0.22 to -0.14)	0.38 (0.26 to 0.55)
Subarachnoid hemorrhage	13 (2.7)	86 (8.8)	-0.02 (-0.04 to 0.01)	0.54 (0.29 to 1.01)
Subdural hemorrhage	3 (0.6)	4 (0.4)	0.00 (-0.01 to 0.01)	3.53 (0.59 to 20.9)
Intraventricular hemorrhage	9 (1.9)	31 (3.2)	-0.01 (-0.03 to 0.01)	0.81 (0.36 to 1.82)
HI1 (scattered small petechia)[†]	6 (1.3)	35 (3.6)	-0.02 (-0.04 to -0.01)	0.44 (0.17 to 1.11)
HI2 (confluent petechiae)[†]	12 (2.5)	110 (11.2)	-0.09 (-0.11 to -0.06)	0.23 (0.12 to 0.42)
PH1 (hematoma occupying <30% of infarct with no substantive mass effect)[†]	11 (2.3)	34 (3.5)	-0.01 (-0.03 to -0.01)	0.75 (0.35 to 1.57)
PH 2 (hematoma occupying ≥30% of infarct with obvious mass effect)[†]	4 (0.8)	33 (3.4)	-0.03 (-0.04 to -0.01)	0.58 (0.19 to 1.78)
Remote PH1 (hematoma outside infarcted tissue without mass effect)[†]	3 (0.6)	11 (1.1)	0.00 (-0.01 to 0.00)	0.55 (0.14 to 2.11)
Remote PH2 (hematoma outside infarcted tissue with obvious mass effect)[†]	1 (0.2)	4 (0.4)	0.00 (-0.01 to 0.00)	0.52 (0.05 to 5.54)
Extracranial bleeding requiring blood transfusions	0 (0.0)	12 (1.2)	-0.01 (-0.02 to -0.01)	-
Orolingual angioedema	6 (1.3)	10 (1.0)	0.00 (-0.01 to 0.01)	1.22 (0.41 to 3.67)
Efficacy outcomes				
mRS score 0–1 at 90–120 days	204 (43.3)	316 (31.9)	NA	1.0 (0.8 to 1.1)
mRS score 0–2 at 90–120 days	308 (65.4)	509 (51.4)	NA	1.0 (0.9 to 1.1)
Actual mRS score at 90-120 days	2 (1–3)	2 (1–5)	NA	0.88[‡] (0.7 to 1.1)
Return to baseline function	157 (34.3)	220 (24.5)	NA	1.1 (0.9 to 1.2)
Length of hospital stay	4 (2–8)	6 (3–13)	NA	0.70 (0.67 to 0.73)
EQ-5D index	0.61 (0.37–0.76)	0.61 (0.35–0.74)	0.90 (0.73 to 1.11)	1.13 (0.90 to 1.42)
EQ-5D-VAS	75 (60–90)	75 (55–87)	0.82 (0.67 to 1.03)	0.96 (0.77 to 1.20)

Values are presented as n (%) or median (interquartile range), unless otherwise indicated.
sICH, symptomatic intracerebral hemorrhage; ICH, intracranial hemorrhage; HI1, hemorrhagic infarction type 1; HI2, hemorrhagic infarction type 2; PH1, parenchymal hematoma type 1; PH2, parenchymal hematoma type 2; mRS, modified Rankin Scale; EQ-5D Index, EuroQol-5 Dimensions Index; EQ-5D-VAS, EuroQol-5 Dimensions Visual Analog Scale; CI, confidence interval; RR, relative risk; -, not computable; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale.
*Defined as any intracerebral hemorrhage that was temporally related to or directly responsible for decline in patient's clinical status; [†]Subclassification based on Heidelberg Bleeding Classification; [‡]Common odds ratio; [§]Mixed effects Poisson regression model adjusting for age, sex, stroke severity (NIHSS), thrombolytic type and onset to needle time as fixed effects and participating site as random effects.

Patients in NVO group had significantly lower mortality (8.1% vs. 19.1%, adjusted RR 0.67, 95% CI, 0.46–0.98). Comparing efficacy outcomes, patients in NVO group had significantly shorter hospital stay (4 vs. 6 days; adjusted RR 0.70, 95% CI, 0.67–0.73). Rates of excellent functional outcome (mRS 0–1), functional independence (mRS 0–2), and return to baseline function at 90 days were similar between two groups in unadjusted and adjusted analyses (Table 2 and Figure 1B). Baseline characteristics, safety outcomes, and efficacy outcomes of tenecteplase and alteplase groups are provided in the Supplementary Tables 1-3 and Supplementary Figures 2 and 3. There were no differences in any outcomes between alteplase and tenecteplase arms in the NVO group.

In this exploratory analysis from the AcT trial, patients in the NVO group, compared to those in the VO group, had lower mortality rates. The group also had numerically lower rates of sICH and higher rates of excellent functional outcomes, although this did not reach significance. These results are also similar when compared to overall trial results.[7] Consistent with previous studies,[3,8] the current study shows that thrombolysis, either with alteplase or tenecteplase, is safe in patients with AIS symptoms with NVO compared to those with VO. This can be due to several reasons. First, some of the patients may have had lacunar strokes, which potentially have better outcomes.[9] Second, a mi-

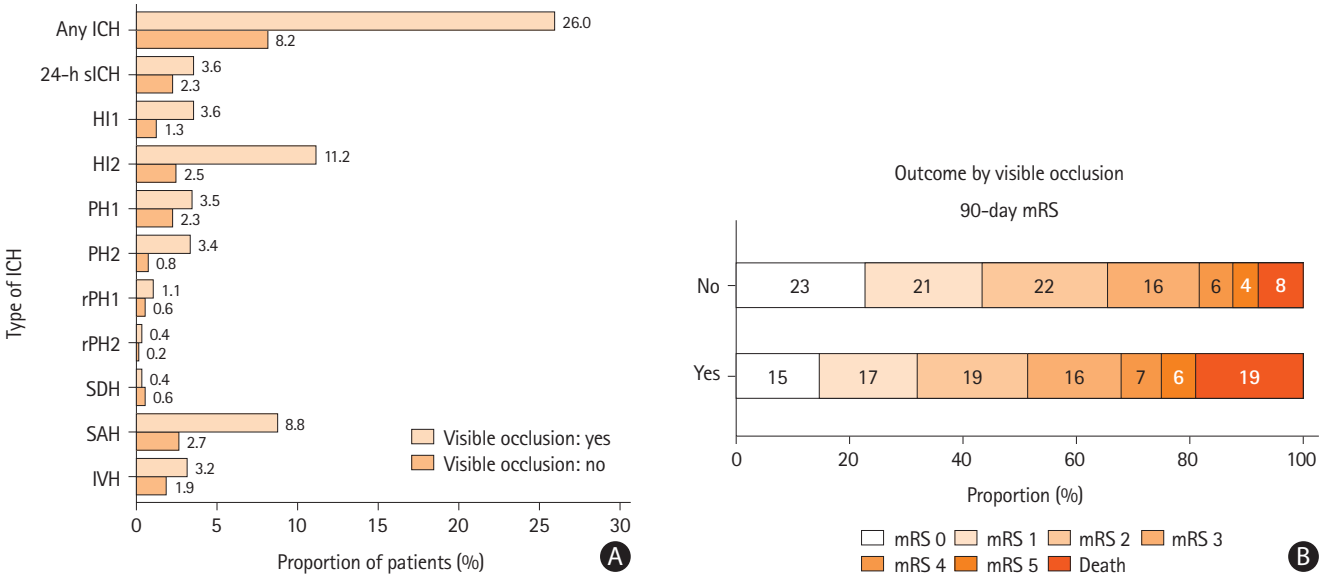

Figure 1. Hemorrhage rates and functional outcomes in patients with no visible occlusion versus those with visible occlusion. (A) Hemorrhage rates as per Heidelberg classification by visible occlusion status (yes/no). (B) Outcome by visible occlusion status (yes/no). ICH, intracranial hemorrhage; sICH, symptomatic intracerebral hemorrhage; HI1, hemorrhagic Infarction type 1; HI2, hemorrhagic Infarction type 2; PH1, parenchymal hematoma type 1; PH2, parenchymal hematoma type 2; rPH1, remote parenchymal hematoma type 1; rPH2, remote parenchymal hematoma type 2; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale.

nority of patients in the NVO group may have recanalized prior to any imaging. Lastly, some of the patients in the NVO group may have been stroke mimics who have better outcomes and lower rates of ICH compared to those with AIS.[10]

Patients in the NVO group had longer onset-to-needle and even door-to-needle times as compared to the VO group. This may be due to the challenge that accompanies clinical decision-making for these AIS patients for different reasons. Firstly, patients in the NVO group might have presented with less severe symptoms, which could lead to a delayed recognition of stroke or a lower urgency to initiate treatment. Additionally, the diagnostic processes for no vessel occlusion strokes may require more comprehensive evaluation, potentially extending the time to thrombolysis.

The fact that patients with NVO have good safety outcomes with thrombolysis is especially relevant for clinical decision-making regarding whether a patient presenting with stroke-like symptoms and NVO should receive thrombolysis. While thrombolysis is well-established to be effective for AIS, fewer patients receive thrombolysis than are eligible. The results from the present study are encouraging in that they propose that it is safe to do so and may help with rapid decision-making in the future.

One limitation of our study is that we did not analyze the number of patients that had an infarct on follow-up imaging. AcT was a pragmatic trial with most enrolled patients having a follow-up CT (51.4%), instead of magnetic resonance imaging, which may not be sensitive enough to detect small strokes and differentiate mimics. Second, we cannot comment on the efficacy of thrombolysis versus no thrombolysis with this data. Third, we do not have data on stroke etiology, which can potentially affect outcomes due to varying recurrent stroke risk. Lastly, this is an exploratory analysis, thus limiting the conclusions.

This *post hoc* subgroup analysis of the AcT trial suggests that intravenous thrombolysis is safe in patients with suspected ischemic stroke presenting within 4.5 hours from symptom onset with NVO on baseline imaging.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.03062.

Funding statement

None

Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: NS, AZS. Study design: NS. Methodology: NS, BM. Data collection: NS, AZS. Investigation: NS, BM, KI, CK,

FB, AA, AT, BHB, LC, GH,DD, MS, AZ, TSF, RA, AW, TS, RS, MA, AD. Statistical analysis: NS, TS, AZS. Writing—original draft: AZS. Writing—review & editing: all authors. Funding acquisition: NS, BM. Approval of final manuscript: all authors.

Acknowledgments

We would like to acknowledge all the patients who took part in the AcT Trial.

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Received: July 30, 2024
Revised: September 24, 2024
Accepted: October 7, 2024

Supplementary Methods

Definitions

- Visible occlusion (VO): any occluded artery visualized on baseline computed tomography angiography (CTA) including all large vessel occlusions (intracranial internal carotid artery [ICA] occlusion, M1 segment of the middle cerebral artery [MCA], or functional M1 occlusion of the MCA) and occlusions in the cervical ICA, vertebrobasilar system, M2 segment, and more distal vessels such as the M3/M4 segments of the MCA, the posterior cerebral artery, and anterior cerebral artery.
- No visible occlusion (NVO): those patients who did not have any intracranial occlusion on initial CTA.
- Symptomatic intracerebral hemorrhage (sICH): any ICH that was temporally related to and directly responsible for a worsening of a patient's neurological condition and in the investigator's opinion was the most important factor for the neurological worsening.

Heidelberg Bleeding Classification[1]

- Hemorrhagic infarction type 1 (HI1): scattered small petechia, no mass effect
- Hemorrhagic infarction type 2 (HI2): confluent petechia, no mass effect
- Parenchymal hematoma type 1 (PH1): hematoma within infarcted tissue, occupying less than 30%, no substantive mass effect
- Parenchymal hematoma type 2 (PH2): hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
- Remote parenchymal hematoma type 1 (rPH1): hematoma outside the infarcted tissue with no substantive mass effect
- Remote parenchymal hematoma type 2 (rPH2): hematoma outside the infarcted tissue, with obvious mass effect
- Intraventricular hemorrhage (IVH)
- Subarachnoid hemorrhage (SAH)
- Subdural hemorrhage (SDH)

Supplementary Reference

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Supplementary Table 1. Baseline characteristics of population with no visible occlusion that received tenecteplase versus alteplase

Characteristic	Tenecteplase (n=247)	Alteplase (n=232)
Age (yr)	71 (59–82)	71 (59–80)
Female sex	110 (44.5)	103 (44.4)
Baseline NIHSS	7 (5–10)	6 (4–9)
Baseline NIHSS score categories		
<8	143 (57.9)	146 (62.9)
8–15	87 (35.2)	76 (32.8)
≥16	17 (6.9)	10 (4.3)
Type of enrolling center		
Primary stroke center	23 (9.3)	14 (6.01)
Comprehensive stroke center	224 (90.7)	218 (93.9)
Workflow times (min)		
Stroke symptom onset to hospital arrival	94 (60–152)	95 (60–142)
Stroke symptom onset to needle	137 (103–208)	144 (108–192)
Stroke symptom onset to randomisation	132 (96–202)	138 (99–184)
Door (hospital arrival) to needle (thrombolysis start)	38 (29–51)	40 (32–55)

Values are presented as median (interquartile range) or n (%).
NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; MCA, middle cerebral artery; NA, not applicable.

Supplementary Table 2. Safety outcomes in patients who received tenecteplase vs. alteplase in no visible occlusion subgroup

Outcome	Tenecteplase (n=247)	Alteplase (n=232)	Unadjusted risk difference (95% CI)	Adjusted RR (95% CI)
Death within 90 days of randomization	19 (7.8)	19 (8.4)	-0.01 (-0.06 to 0.04)	0.86 (0.45 to 1.65)
24-h sICH*	6 (2.4)	5 (2.1)	0.00 (-0.02 to 0.03)	1.19 (0.36 to 3.93)
Any ICH on imaging	20 (8.1)	19 (8.3)	0.00 (-0.05 to 0.04)	0.93 (0.49 to 1.76)
Subarachnoid hemorrhage	6 (2.4)	7 (3.1)	-0.01 (-0.04 to 0.02)	0.79 (0.26 to 2.37)
Subdural hemorrhage	0 (0)	3 (1.3)	-	-
Intraventricular hemorrhage	6 (2.4)	3 (1.3)	-0.01 (-0.01 to 0.04)	1.87 (0.47 to 7.48)
HI1 (scattered small petechia)†	2 (0.9)	4 (1.6)	-0.01 (-0.01 to 0.03)	1.66 (0.30 to 9.31)
HI2 (confluent petechia)†	6 (2.4)	6 (2.6)	0.00 (-0.03 to 0.03)	0.95 (0.30 to 2.95)
PH1 (hematoma occupying <30% of infarct with no substantive mass effect)†	7 (2.8)	4 (1.8)	-0.01 (-0.02 to 0.04)	1.64 (0.48 to 5.61)
PH2 (hematoma occupying <30% of infarct with obvious mass effect)†	2 (0.8)	2 (0.9)	0.00 (-0.02 to 0.02)	0.73 (0.08 to 6.37)
rPH1 (hematoma outside infarcted tissue without mass effect)†	2 (0.8)	1 (0.4)	0.00 (-0.01 to 0.01)	2.55 (0.18 to 36.37)
rPH2 (hematoma outside infarcted tissue with obvious mass effect)†	0 (0)	1 (0.4)	0.00 (-0.01 to 0.00)	-
Extracranial bleeding requiring blood transfusions	0 (0)	0 (0)	-	-
Orolingual angioedema	3 (1.2)	3 (1.3)	0.00 (-0.02 to 0.02)	0.99 (0.20 to 5.03)

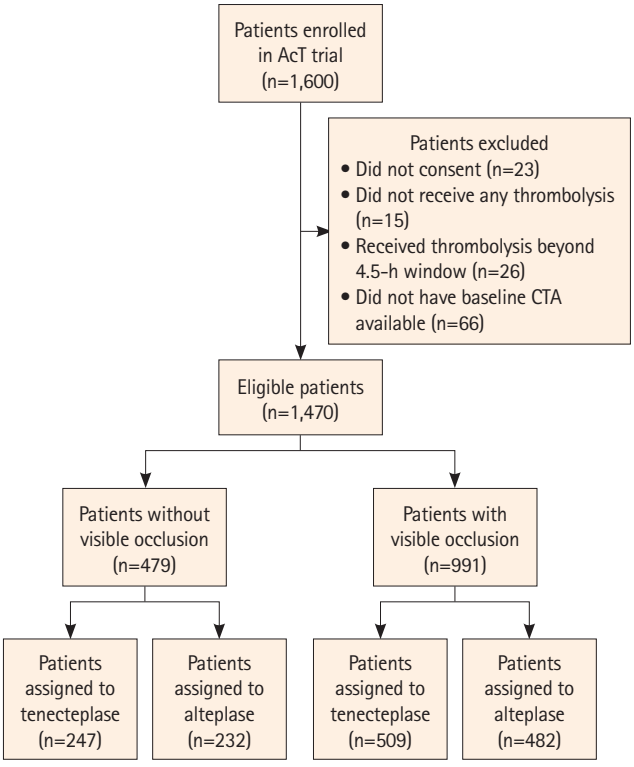
Values are presented as n (%), unless otherwise indicated.
sICH, symptomatic intracerebral hemorrhage; ICH, intracranial hemorrhage; HI1, hemorrhagic infarction type 1; HI2, hemorrhagic infarction type 2; PH1, parenchymal hematoma type 1; PH2, parenchymal hematoma type 2; CI, confidence interval; RR, relative risk; -, not computable; NA, not applicable.
*Defined as any intracerebral hemorrhage that was temporally related to or directly responsible for decline in patient's clinical status; †Subclassification based on Heidelberg Bleeding Classification.

https://doi.org/10.5853/jos.2024.03062

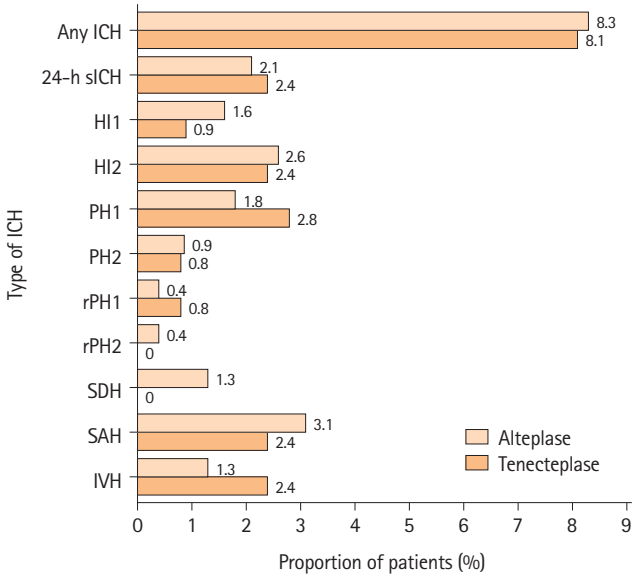
Supplementary Table 3. Efficacy outcomes in patients who received tenecteplase vs. alteplase in no visible occlusion subgroup

	Tenecteplase (n=235)	Alteplase (n=223)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
mRS score 0–1 at 90–120 days (n=471)	106 (43.4)	98 (43.2)	1.0 (0.8 to 1.2)	1.04 (0.83 to 1.30)
mRS score 0–2 at 90–120 days (n=471)	159 (65.2)	149 (65.6)	1.0 (0.9 to 1.1)	1.01 (0.90 to 1.14)
Actual mRS score at 90-120 days (n=471)	3 (2–4)	3 (2–4)	1.0 (0.7 to 1.4)*	0.95 (0.69 to 1.32)
Return to baseline function (n=458)	77 (32.8)	80 (35.9)	0.9 (0.7 to 1.2)	0.94 (0.73 to 1.22)
Length of hospital stay (n=461)	4 (2–9)	4 (2–7)	-0.32 (-2.29 to 1.65)†	1.02 (0.95 to 1.09)

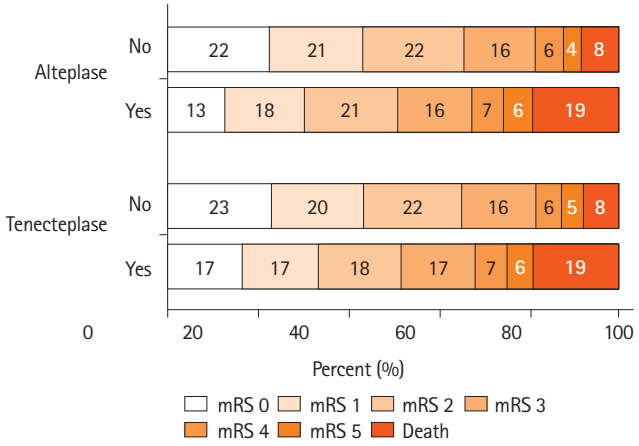
Values are presented as n (%) or median (interquartile range), unless otherwise indicated.
mRS, modified Rankin Scale; CI, confidence interval; RR, relative risk.
*Common odds ratio; †Coefficient.



Supplementary Figure 1. Flowchart of participants included in analysis. CTA, computed tomography angiography.



Supplementary Figure 2. Hemorrhage rates as per Heidelberg Bleeding Classification in patients with no visible occlusion by thrombolytic type (alteplase vs. tenecteplase). ICH, any intracranial hemorrhage; sICH, symptomatic intracerebral hemorrhage; HI1, hemorrhagic infarction type 1; HI2, hemorrhagic infarction type 2; PH1, parenchymal hematoma type 1; PH2, parenchymal hematoma type 2; rPH1, remote parenchymal hematoma type 1; rPH2, remote parenchymal hematoma type 2; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage.



Supplementary Figure 3. Outcome by visible occlusion status and thrombolytic type. Horizontal stacked bar graphs show the outcome distribution for modified Rankin Scale (mRS) at 90–120 days by visible occlusion and thrombolytic type. Bars are labeled with proportions.

https://doi.org/10.5853/jos.2024.03062