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ESO Expedited Recommendation on Tenecteplase for Acute Ischaemic Stroke

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Guideline Webinar- February 2, 2023

Disclosures

Disclosures of the 11 module working group members are provided in Suppl Table of the recommendation

Personal Financial Disclosures:

- Participation in advisory meetings & satellite symposia for Boehringer Ingelheim, Astra-Zeneca, Pfizer, Amgen
- Principal investigator of the Tenecteplase treatment in Ischemic Stroke (TETRIS) registry, which receives financial support from Boehringer Ingelheim
- Principal investigator of ToGiac trial supported by a research grant from Roche-Shugai

Personal Intellectual Disclosures:

- Chair of French Neurovascular Society

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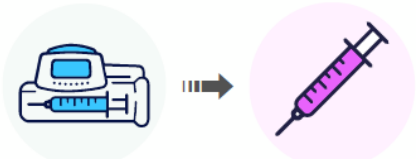
Background – Intravenous thrombolysis (IVT) in acute ischaemic stroke (AIS) patients

Tenecteplase

A genetically modified form of alteplase
- Longer half life
- Greater resistance to plasminogene activator inhibitor 1

Single bolus administration



Easier administration

Advantages in the setting of AIS

- Door to needle time
- Intra and inter-hopital transfers in patients eligible for mechanical thrombectomy (MT)

- Phase 2 trials in AIS
- Preliminary efficacy and safety data

Thiebaut AM et al, Lancet Neurol 2018; Tsivgoulis G et al, Ther Adv Neurol Disord 2021; Neumann F-J et al, Eur Heart J 2019

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Background. Intravenous thrombolysis – ESO Guidelines 2021

Berge E et al, Eur Stroke J 2021; 6: I-LXII

Recommendation *AIS <4.5h**

For patients with acute ischaemic stroke of <4.5 h duration and not eligible for thrombectomy, we suggest intravenous thrombolysis with alteplase over intravenous thrombolysis with tenecteplase.

Quality of evidence: **Low** ⊕⊕

Strength of recommendation: **Weak** ↑?

* *TNK S2B (0.25-0.40 mg/kg) ATTEST (0.25 mg/kg) NorTest (0.40mg/kg)*

Recommendation *AIS + LVO <4.5h**

For patients with acute ischaemic stroke of < 4.5 h duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom intravenous thrombolysis is considered before thrombectomy, we suggest intravenous thrombolysis with tenecteplase 0.25 mg/kg over intravenous thrombolysis with alteplase 0.9 mg/kg.

Quality of evidence: **Low** ⊕⊕

Strength of recommendation: **Weak** ↑?

* *TAAIS (0.25 mg/kg) EXTEND-IA (0.25 mg/kg)*

- 2022 : 4 published RCTs comparing IVT with tenecteplase and alteplase

AcT / TASTE A / NorTest 2A /TRACE ---- *TWIST (results presented)*

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Methodology – *GRADE approach...*

ESO Standard Operating Procedure

PICO

Population

PICO 1. Acute ischaemic stroke patients <4.5 h

PICO 2. Acute ischaemic stroke patients <4.5 h and large vessel occlusion

PICO 3. Wake-up stroke / unknown onset

Intervention (IVT)	*Comparator*
Tenecteplase 0.25 mg/kg	Current standard of care
Tenecteplase 0.40 mg/kg	Alteplase 0.9 mg/kg

Steiner T et al, Eur Stroke J 2021; 6(3): CXXII-CXXXIV

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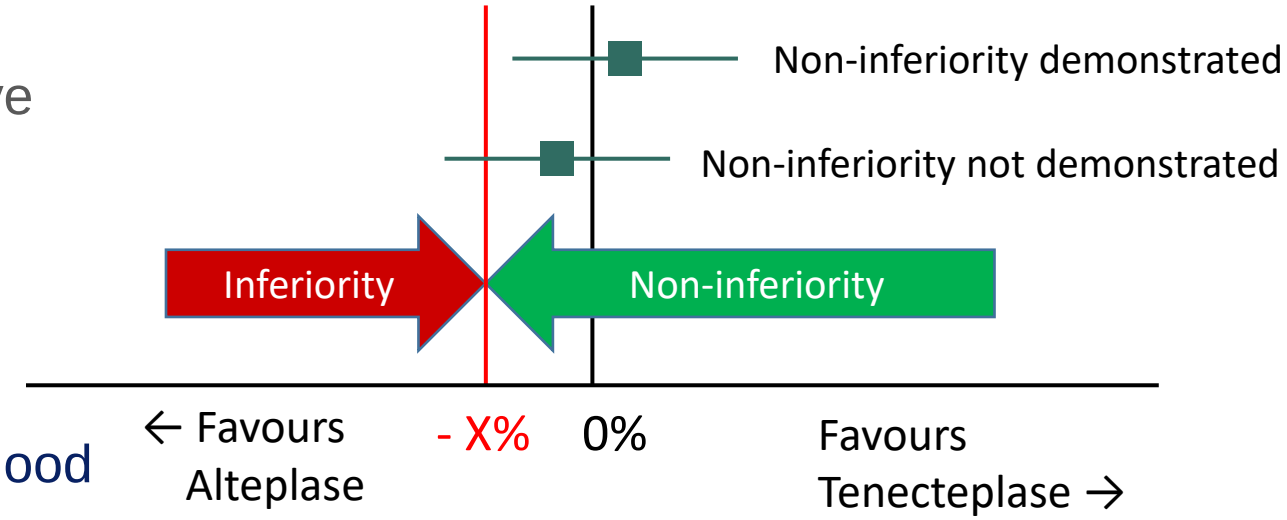
Outcomes of interest (rating of the importance - secret ballot voting)

Population	Critical outcomes (score 9-7)	Critical outcomes (score 9-7)	Important outcomes (score 6-4 : AIS-AIS+LVO)	Important outcomes (score 6-4)
AIS 14 Outcomes	**mRS= 0-1 at 90 days Excellent functional outcome (8.7)** mRS = 0-2 at 90 days Good functional outcome (7.9)	Reduced disability at 90 days (7.8) sICH at 24-48 h (7.7) Mortality at 90 days (7.6)	Major neurological improvement at 24-72 h (6.2) Reperfusion at 24 h (6.2-6.3) Final infarct volume at 24 h (5.9-6.2) Quality of life metrics (5.8-5.9) Ischemic core growth within the first 24 h (5.6-5.7) Door-to-needle time (5.4-5.8) Any ICH (5.1) Onset-to-treatment time (5.0) Extracranial bleeding (4.7)	
AIS + LVO 17 Outcomes	**mRS= 0-2 at 90 days Good functional outcome (8.3)** mRS= 0-1 at 90 days Excellent functional outcome (8.2)			Recanalization after MT-24 h (mTICI) score ≥2b (6.8) Recanalization before MT-first angiographic acquisition (mTICI) score ≥2b (6.8) Needle to groin puncture time (5.6)

Choice of a pre-defined non inferiority margin (secret ballot voting)

- AIS patients : Absolute difference to achieve excellent functional outcome (mRs 0-1)
  - 3.0% (7/9)
  - To conserve at least half of the conservative alteplase effect
  - 1.3% (2/9) : secondary analysis



G Turc, Webinar 2022

- LVO patients : Absolute difference to achieve good functional outcome (mRs 0-2)
  - 1.3% (9/9)
  - Consistency with ESO Guidelines on Bridging therapy

Emberson J et al, Lancet 2014. Saver JL et al; J Neurointerv Surg 2023; Cranston JS et al, Stroke 2017; Turc G et al, Eur Stroke J 2022

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PICO 1. AIS patients of <4.5 h duration

PICO 1.1 For patients with acute ischaemic stroke of 4.5h duration, does intravenous thrombolysis with **tenecteplase 0.25mg/kg** compared with intravenous thrombolysis with alteplase lead to:

a) a **non-inferior** proportion of patients with excellent **functional outcome (mRS 0-1) at 90 days**?

b) non-inferior or better results on other efficacy outcomes (mRS shift analysis at 90 days, mRS 0-2 at 90 days…)?

c) a reduction in the risk of adverse events (mortality at 90 days, sICH…) ?

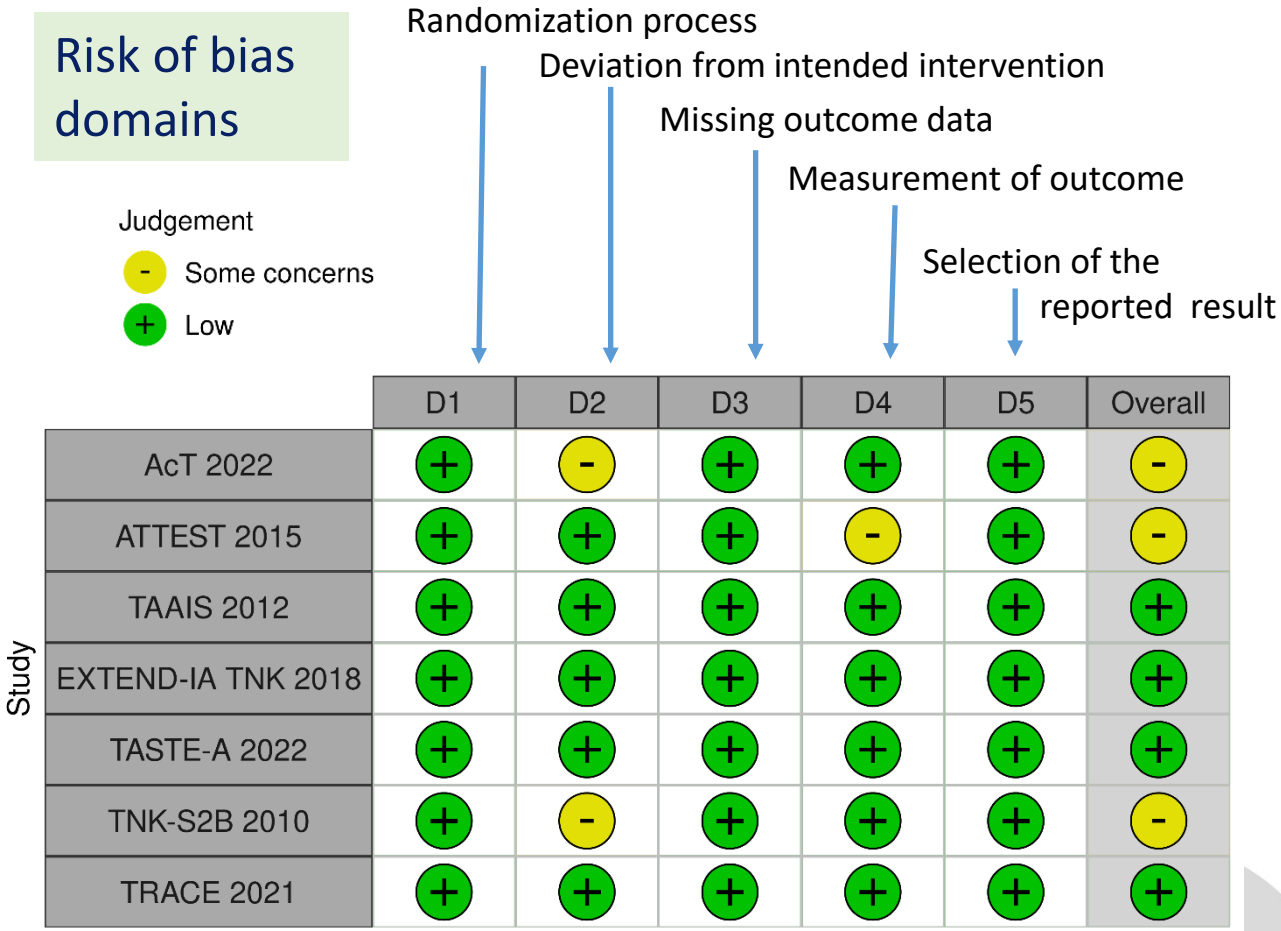
d) a reduction in key time metrics (onset-to-treatment time, door-to-needle time)?

e) an improvement in neuroimaging parameters ?

7 RCTs: AIS of <4.5 h duration - IV Tenecteplase 0.25mg/kg VS Alteplase

Trials	N	Design
Act (2022), Phase 3-Canada	**1600**	**AIS<4.5h Non inferiority : -5%**
ATTEST (2015) Phase 2b/3-UK	**104**	**AIS <4.5h**
TAAIS (2012) Phase 2b- Australia	**75**	**AIS<6H Vessel occlusion-mismatch CT >20%, Tenecteplase 0.10 and 0.25mg/kg, no MT**
EXTEND-IA (2018) Phase 2-Australia	**202**	**AIS with LVO eligible to MT**
TNK-2S (2010) Phase 2b/3-USA	**112**	**AIS<3h Tenecteplase 0.10 vs 0.25 vs 0.40 mg/kg**
TASTE A (2022) Phase 2-Australia	**104**	**AIS<4.5h, MSU**
TRACE (2021) Phase 2-China	**236**	**AIS<3h Tenecteplase 0.10 vs 0.25 VS 0.40 mg/kg**

Quality of evidence



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PICO 1.1 AIS of <4.5 h duration- IV Tenecteplase 0.25mg/kg

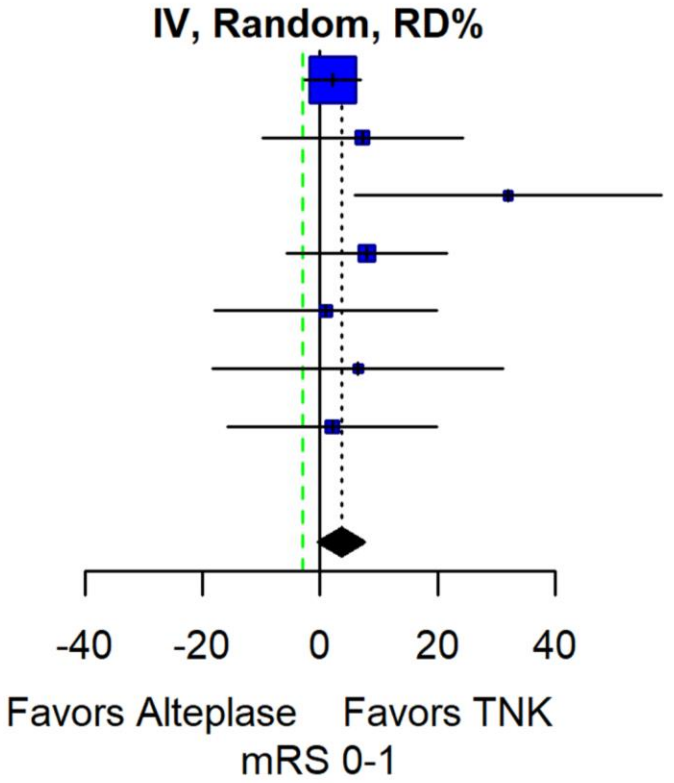
Excellent functional outcome (mRS 0-1 at 90 days)

Non inferiority margin = -3% *(-1.3%)*

	TNK		Alteplase			
Study	**Events**	**Total**	**Events**	**Total**	**Weight**	**RD% [95% CI]**
AcT 2022	296	802	266	765	71.3%	2.14 [-2.61, 6.88]
ATTEST 2015	13	47	10	49	5.5%	7.25 [-9.80, 24.31]
TAAIS 2012	18	25	10	25	2.4%	32.00 [5.95, 58.05]
EXTEND-IA TNK 2018	49	101	41	101	8.6%	7.92 [-5.74, 21.59]
TASTE-A 2022	23	55	20	49	4.5%	1.00 [-17.95, 19.96]
TNK-S2B 2010	15	31	13	31	2.6%	6.45 [-18.27, 31.17]
TRACE 2021	35	57	35	59	5.1%	2.08 [-15.72, 19.88]
Total (95% CI)		**1118**		**1079**	**100.0%**	**3.68 [-0.32, 7.69]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 5.64$, df = 6 (P = 0.46); $I^2 = 0\%$

Test for overall effect: Z = 1.80 (P = 0.07)



Unadj. RD = 3.68 % (95%CI=-0.32% to 7.69%)

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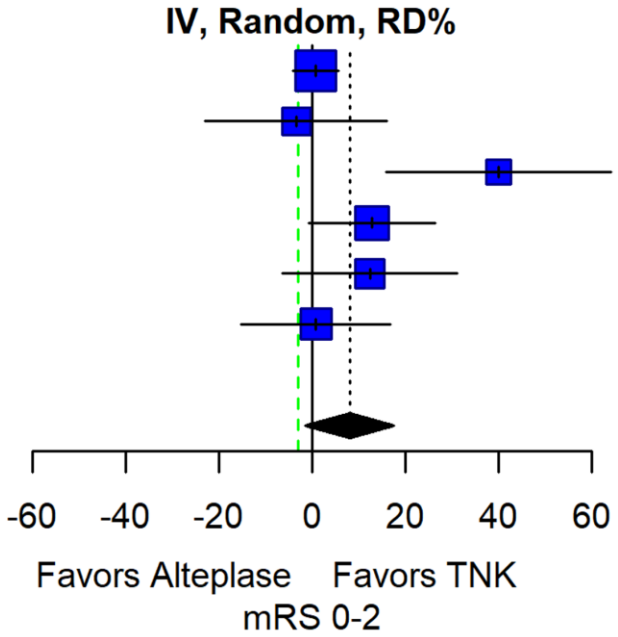
PICO 1.1 AIS of <4.5 h duration - IV Tenecteplase 0.25mg/kg

Good functional outcome (mRS 0-2 at 90 days)

Study	TNK Events	TNK Total	Alteplase Events	Alteplase Total	Weight	RD% [95% CI]
AcT 2022	452	802	425	765	27.8%	0.80 [-4.11, 5.72]
ATTEST 2015	17	47	19	48	13.3%	-3.41 [-22.91, 16.08]
TAAIS 2012	21	25	11	25	10.2%	40.00 [15.81, 64.19]
EXTEND-IA TNK 2018	64	101	51	101	18.7%	12.87 [-0.67, 26.41]
TASTE-A 2022	36	55	26	49	13.8%	12.39 [-6.40, 31.19]
TRACE 2021	42	57	43	59	16.2%	0.80 [-15.30, 16.91]
Total (95% CI)		**1087**		**1047**	**100.0%**	**8.11 [-1.41, 17.62]**

Heterogeneity: $Tau^2 = 0.008$; $Chi^2 = 13.19$, df = 5 (P = 0.02); $I^2 = 62\%$

Test for overall effect: Z = 1.67 (P = 0.10)



Unadj. RD = 8.11 % (95%CI=-1.41% to 17.69%)

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PICO 1.1 AIS of <4.5 h duration - IV Tenecteplase 0.25mg/kg

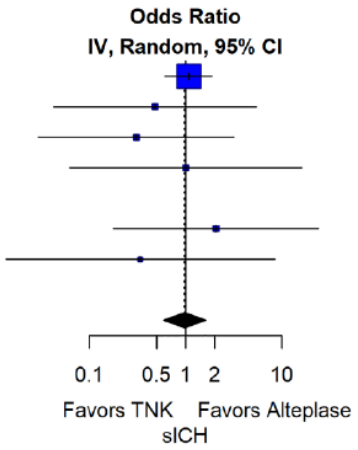
Safety data

Symptomatic intracranial haemorrhage (study definition)

Study	TNK Events	TNK Total	Alteplase Events	Alteplase Total	Weight	Odds Ratio IV, Random, 95% CI
AcT 2022	27	800	24	763	81.1%	1.08 [0.61, 1.88]
ATTEST 2015	1	52	2	51	4.3%	0.48 [0.04, 5.47]
TAAIS 2012	1	25	3	25	4.6%	0.31 [0.03, 3.16]
EXTEND-IA TNK 2018	1	101	1	101	3.3%	1.00 [0.06, 16.21]
TASTE-A 2022	0	55	0	49	0.0%	
TNK-S2B 2010	2	31	1	31	4.2%	2.07 [0.18, 24.07]
TRACE 2021	0	57	1	59	2.4%	0.34 [0.01, 8.50]
Total (95% CI)		**1121**		**1079**	**100.0%**	**0.98 [0.59, 1.62]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.17$, df = 5 (P = 0.83); $I^2 = 0\%$

Test for overall effect: Z = -0.09 (P = 0.93)



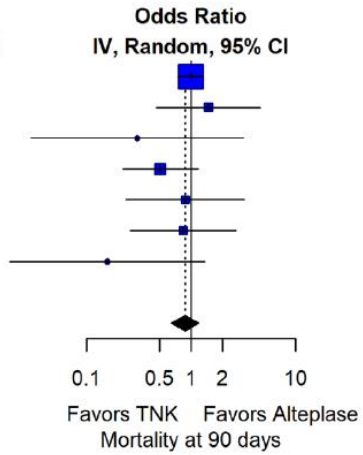
Unadj. OR = 0.98 (95%CI=0.59 to 1.62)

All cause mortality at 3 months

Study	TNK Events	TNK Total	Alteplase Events	Alteplase Total	Weight	Odds Ratio IV, Random, 95% CI
AcT 2022	122	796	117	763	65.4%	1.00 [0.76, 1.32]
ATTEST 2015	8	47	6	49	6.8%	1.47 [0.47, 4.61]
TAAIS 2012	1	25	3	25	1.7%	0.31 [0.03, 3.16]
EXTEND-IA TNK 2018	10	101	18	101	12.4%	0.51 [0.22, 1.16]
TASTE-A 2022	5	55	5	49	5.3%	0.88 [0.24, 3.24]
TNK-S2B 2010	7	31	8	31	6.5%	0.84 [0.26, 2.69]
TRACE 2021	1	57	6	59	2.0%	0.16 [0.02, 1.35]
Total (95% CI)		**1112**		**1077**	**100.0%**	**0.88 [0.65, 1.19]**

Heterogeneity: $Tau^2 = 0.017$; $Chi^2 = 6.45$, df = 6 (P = 0.37); $I^2 = 7\%$

Test for overall effect: Z = -0.86 (P = 0.39)



Unadj. OR = 0.88 (95%CI=0.65 to 1.19)

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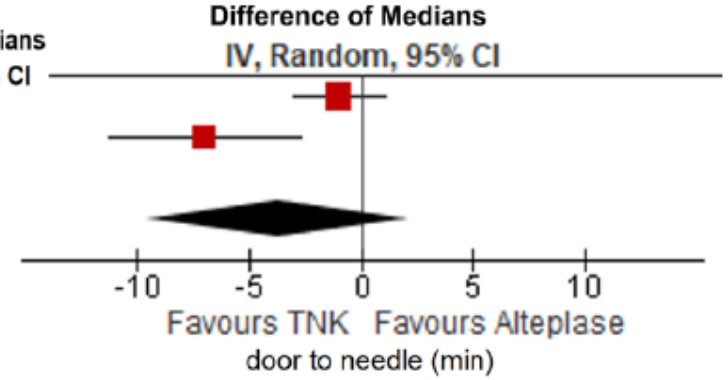
PICO 1.1 AIS of <4.5 h duration - IV Tenecteplase 0.25mg/kg

Door-to-needle time (mn)

Study	TNK Median	TNK IQR	TNK Total	Alteplase Median	Alteplase IQR	Alteplase Total	Weight	Difference of Medians IV, Random, 95% CI
AcT 2022	36	27 - 49	802	37	29 – 52	756	55.2%	-1.0 (-3.1, 1.1)
TASTE-A 2022	30	25 – 38	54	37	32 – 43	49	44.8%	-7.0 (-11.3,-2.7)
Total (95% CI)							**100.0%**	-3.7 [-9.5, 2.2]

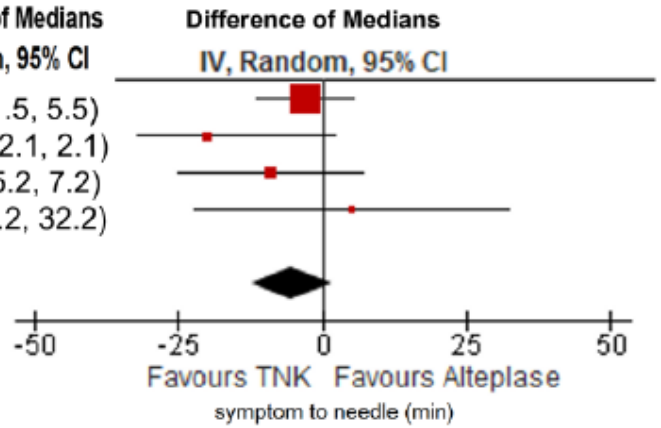
Heterogeneity: Tau² = 15.03; Chi² = 6.06, df = 1 (P = 0.01); I² = 83%
Test for overall effect: Z = 1.24 (P = 0.22)



Symptom onset-to needle time (mn)

Study	TNK Median	TNK IQR	TNK Total	Alteplase Median	Alteplase IQR	Alteplase Total	Weight	Difference of Medians IV, Random, 95% CI
AcT 2022	128	93 - 186	802	131	95 – 188	765	66.0%	-3.0 (-11.5, 5.5)
ATTEST 2015	180	156 - 215	47	200	160 – 220	49	9.6%	-20.0 (-42.1, 2.1)
EXTEND-IA TNK 2	125	102 - 156	101	134	104 – 176	101	18.0%	-9.0 (-25.2, 7.2)
TASTE-A 2022	97	68 – 157	55	92	66 – 131	49	6.3%	5.0 (-22.2, 32.2)
Total (95% CI)							**100.0%**	-5.2 [-12.1, 1.7]

Heterogeneity: Tau² = 0.00; Chi² = 2.73, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)



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Evidence-based Recommendation

PICO1.1 Patients with AIS of <4.5 h duration

For patients with acute ischaemic stroke of <4.5 hrs duration who are eligible for intravenous thrombolysis, tenecteplase 0.25 mg/kg can be used as a safe and effective alternative to alteplase 0.9 mg/kg.

Quality of evidence: **Moderate** ⊕⊕⊕

Strength of recommendation: Strong ↑↑

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Expert Consensus Statement

PICO1.1 Patients with AIS of <4.5 h duration

All MWG members suggest favouring tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg for patients with acute ischaemic stroke of <4.5 hrs duration in light of safety and efficacy data and because tenecteplase can be administered with a single bolus rather than a 1-hr infusion.

Voting: 9/9 members

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PICO 1 AIS patients of <4.5h duration

PICO 1.2 For patients with acute ischaemic stroke of <4.5hr duration, does intravenous thrombolysis with tenecteplase 0.40 mg/kg compared with intravenous thrombolysis with alteplase 0.90 mg/kg lead to:

a) a non-inferior proportion of patients with excellent **functional outcome (mRS 0-1) at 90 days**?

b) non-inferior or better results on other efficacy outcomes (mRS shift analysis at 90 days, mRS 0-2 at 90 days…)?

c) a reduction in the risk of adverse events (mortality at 90 days, sICH…) ?

d) a reduction in key time metrics (onset-to-treatment time, door-to-needle time)?

e) an improvement in neuroimaging parameters ?

PICO 1.2 AIS of <4.5 h duration- IV Tenecteplase 0.40mg/kg

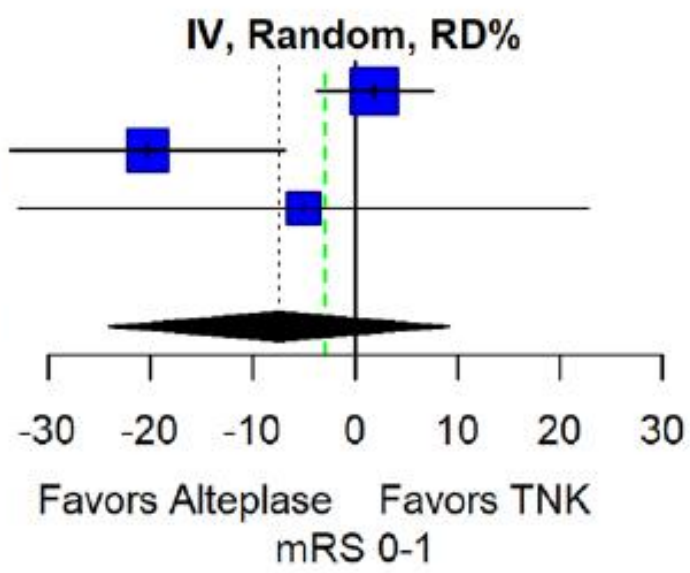
Excellent functional outcome (mRS 0-1 at 90 days)

Non inferiority margin = -3%

Study	TNK Events	TNK Total	Alteplase Events	Alteplase Total	Weight	RD% [95% CI]
NOR-TEST 2017	354	549	345	551	44.0%	1.87 [-3.82, 7.55]
NOR-TEST 2A 2022	29	96	51	101	35.7%	-20.29 [-33.68, -6.89]
TNK-S2B 2010	7	19	13	31	20.3%	-5.09 [-32.88, 22.69]
Total (95% CI)		**664**		**683**	**100.0%**	**-7.45 [-24.13, 9.22]**

Heterogeneity: $Tau^2 = 0.016$; $Chi^2 = 8.96$, df = 2 (P = 0.01); $I^2 = 78\%$

Test for overall effect: Z = -0.88 (P = 0.38)



Unadj. RD -7.45 % (95%CI= -24.13% to 9.22%)

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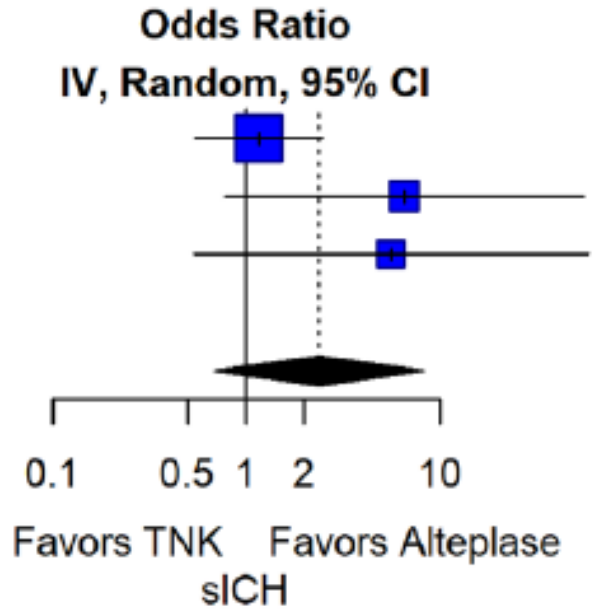
PICO 1.2 AIS of <4.5 h duration- IV Tenecteplase 0.40mg/kg

Symptomatic intracranial haemorrhage (study definition)

	TNK		Alteplase			Odds Ratio
Study	**Events**	**Total**	**Events**	**Total**	**Weight**	**IV, Random, 95% CI**
NOR-TEST 2017	15	549	13	551	56.9%	1.16 [0.55, 2.47]
NOR-TEST 2A 2022	6	100	1	104	23.0%	6.57 [0.78, 55.62]
TNK-S2B 2010	3	19	1	31	20.2%	5.62 [0.54, 58.58]
Total (95% CI)		**668**		**686**	**100.0%**	**2.38 [0.69, 8.23]**

Heterogeneity: $Tau^2 = 0.557$; $Chi^2 = 3.48$, df = 2 (P = 0.18); $I^2 = 43\%$

Test for overall effect: Z = 1.37 (P = 0.17)



Unadj. OR = 2.38 (95%CI= 0.69 to 8.23)

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Evidence-based Recommendation

PICO1.2 AIS of <4.5 duration time window

For patients with acute ischaemic stroke of <4.5 hrs duration who are eligible for intravenous thrombolysis, we recommend against using tenecteplase at a dose of 0.40 mg/kg.

Quality of evidence: Low ⊕⊕

Strength of recommendation: Strong against intervention ↓↓

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PICO 1 AIS patients of < 4.5 h duration

PICO 1.3 In patients with acute ischaemic stroke of <4.5hr duration **with prehospital management with a mobile stroke unit** does intravenous thrombolysis with tenecteplase 0.25 mg/kg compared with intravenous thrombolysis with alteplase 0.90 mg/kg lead to:

a) a non-inferior proportion of patients with excellent **functional outcome (mRS 0-1) at 90 days**?

b) non-inferior or better results on other efficacy outcomes (mRS 0-2 at 90 days…)?

c) a reduction in the risk of adverse events (mortality at 90 days, sICH…) ?

d) a reduction in key time metrics (onset-to-treatment time, door-to-needle time)?

e) an improvement in neuroimaging parameters ?

TASTE A (2022) **Phase 2-** **Australia**	**N= 104**	**AIS <4.5h** **MSU**	**Tenecteplase VS Alteplase** **Reduction of the volume of the post treatment perfusion lesion** **Greater ultra-early clinical recovery** **Faster initiation**

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Evidence-based Recommendation

PICO 1.3 AIS of <4.5 h duration with Mobile Stroke Unit

For patients with acute ischaemic stroke of <4.5hr duration with prehospital management with a mobile stroke unit who are eligible for intravenous thrombolysis, we suggest tenecteplase 0.25 mg/kg over alteplase 0.90 mg/kg to increase the rate of early reperfusion and to shorten the time from imaging to treatment initiation.

Quality of evidence: Low ⨁⨁

Strength of recommendation: Weak ↑

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PICO 2 AIS patients of <4.5 h duration and Large Vessel Occlusion

PICO 2 For large vessel occlusion acute ischaemic stroke patients of <4.5hr duration does intravenous thrombolysis with tenecteplase 0.25 mg/kg compared with intravenous thrombolysis with alteplase 0.90 mg/kg lead to:

a) a **non-inferior** proportion of patients with **good functional outcome (mRS scores of 0-2)** at 90 days?

b) non-inferior or better results on other efficacy outcomes (mRS shift analysis at 90 days, mRS 0-1 at 90 days…)?

c) a reduction in the risk of adverse events (mortality at 90 days, sICH..)?

d) a reduction in key time metrics (onset-to-treatment time, door-to-needle time)?

e) an improvement in neuroimaging parameters (recanalization at 24h or at the end of mechanical thrombectomy, recanalization before mechanical thrombectomy at first angiographic acquisition or averted mechanical thrombectomy…)?

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PICO 2 AIS of <4.5 h duration +LVO- IV Tenecteplase 0.25mg/kg

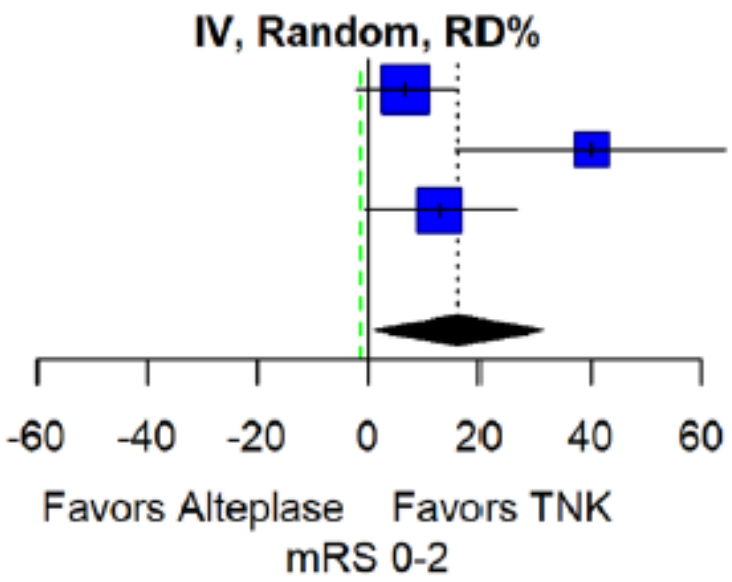
Good functional outcome (mRS 0-2 at 90 days)

Study	TNK Events	TNK Total	Alteplase Events	Alteplase Total	Weight	RD% [95% CI]
AcT 2022	63	196	49	193	42.6%	6.75 [-2.22, 15.72]
TAAIS 2012	21	25	11	25	21.7%	40.00 [15.81, 64.19]
EXTEND-IA TNK 2018	64	101	51	101	35.6%	12.87 [-0.67, 26.41]
Total (95% CI)		**322**		**319**	**100.0%**	**16.15 [1.21, 31.09]**

Heterogeneity: $Tau^2 = 0.012$; $Chi^2 = 6.45$, df = 2 (P = 0.04); $I^2 = 69\%$

Test for overall effect: Z = 2.12 (P = 0.03)

Non inferiority margin = -1.3%



Unadj. RD 16.15 % (95%CI= 1.21 to 31.09%)

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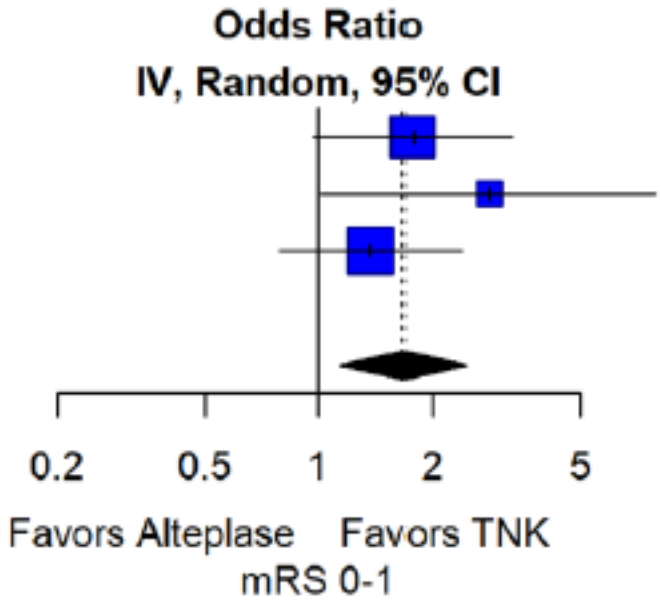
PICO 2 AIS of <4.5 h duration +LVO- IV Tenecteplase 0.25mg/kg

Excellent functional outcome (mRS 0-1 at 90 days)

Study	TNK Events	TNK Total	Alteplase Events	Alteplase Total	Weight	Odds Ratio IV, Random, 95% CI
AcT 2022	32	196	19	193	39.5%	1.79 [0.97, 3.28]
ATTEST 2015 & TAAIS 2012	18	37	8	32	13.7%	2.84 [1.02, 7.94]
EXTEND-IA TNK 2018	49	101	41	101	46.8%	1.38 [0.79, 2.41]
Total (95% CI)		**334**		**326**	**100.0%**	**1.69 [1.15, 2.47]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.53$, df = 2 (P = 0.47); $I^2 = 0\%$

Test for overall effect: Z = 2.69 (P < 0.01)



Unadj. OR = 1.69 (95%CI=1.15 to 2.47)

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PICO 2 AIS of <4.5 h duration + LVO - IV Tenecteplase 0.25mg/kg

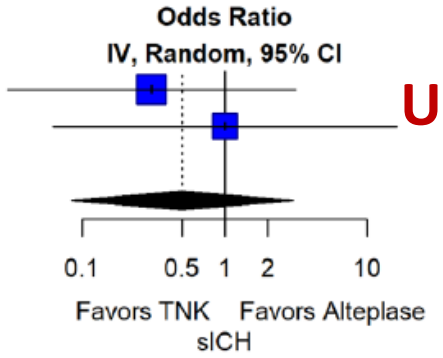
Safety data

Symptomatic intracranial haemorrhage

Study	TNK Events	TNK Total	Alteplase Events	Alteplase Total	Weight	Odds Ratio IV, Random, 95% CI
TAAIS 2012	1	25	3	25	58.7%	0.31 [0.03, 3.16]
EXTEND-IA TNK 2018	1	101	1	101	41.3%	1.00 [0.06, 16.21]
Total (95% CI)		**126**		**126**	**100.0%**	**0.50 [0.08, 2.99]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.41$, df = 1 (P = 0.52); $I^2 = 0\%$

Test for overall effect: Z = -0.76 (P = 0.45)



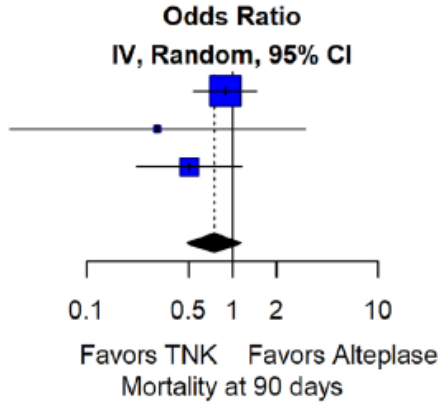
Unadj. OR = 0.50 (95%CI= 0.085 to 2.99)

All cause mortality at 3 months

Study	TNK Events	TNK Total	Alteplase Events	Alteplase Total	Weight	Odds Ratio IV, Random, 95% CI
AcT 2022	38	196	41	193	71.4%	0.89 [0.54, 1.46]
TAAIS 2012	1	25	3	25	3.2%	0.31 [0.03, 3.16]
EXTEND-IA TNK 2018	10	101	18	101	25.4%	0.51 [0.22, 1.16]
Total (95% CI)		**322**		**319**	**100.0%**	**0.75 [0.49, 1.13]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.90$, df = 2 (P = 0.39); $I^2 = 0\%$

Test for overall effect: Z = -1.37 (P = 0.17)



Unadj. OR = 0.75 (95%CI= 0.49 to 1.13)

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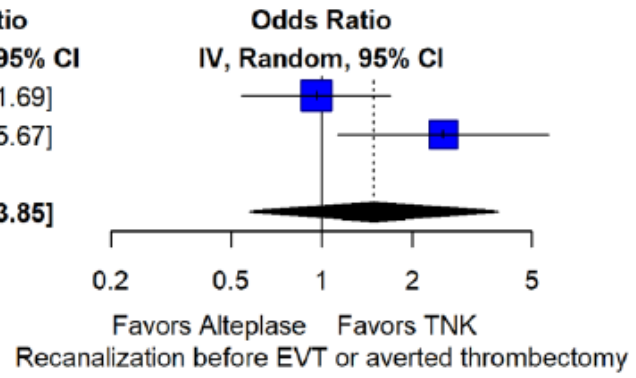
PICO 2 AIS of <4.5 h duration + LVO- IV Tenecteplase 0.25mg/kg

Recanalisation (mTICI≥2b) before Mechanical thrombectomy

Study	TNK Events	TNK Total	Alteplase Events	Alteplase Total	Weight	Odds Ratio IV, Random, 95% CI
AcT 2022	26	256	27	256	54.5%	0.96 [0.54, 1.69]
EXTEND-IA TNK 2018	22	101	10	101	45.5%	2.53 [1.13, 5.67]
Total (95% CI)		**357**		**357**	**100.0%**	**1.49 [0.58, 3.85]**

Heterogeneity: $Tau^2 = 0.346$; $Chi^2 = 3.73$, df = 1 (P = 0.05); $I^2 = 73\%$

Test for overall effect: Z = 0.83 (P = 0.41)



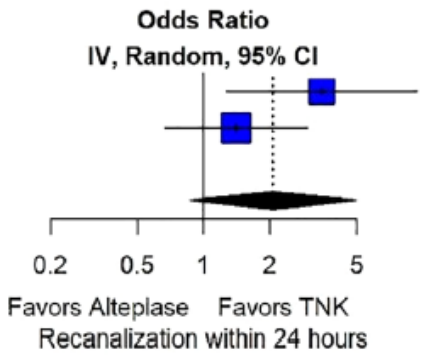
Unadj. OR = 1.49
(95%CI= 0.58 to 3.85)

Recanalisation (mTICI≥2b) at the end of MT or within 24h

Study	TNK Events	TNK Total	Alteplase Events	Alteplase Total	Weight	Odds Ratio IV, Random, 95% CI
ATTEST 2015 & TAAIS 2012	26	37	13	32	43.2%	3.45 [1.27; 9.37]
EXTEND-IA TNK 2018	83	97	80	99	56.8%	1.41 [0.66; 3.00]
Total (95% CI)		**134**		**131**	**100.0%**	**2.07 [0.87; 4.96]**

Heterogeneity: $Tau^2 = 0.1990$; $Chi^2 = 1.98$, df = 1 (P = 0.16); $I^2 = 49\%$

Test for overall effect: Z = 1.64 (P = 0.10)



Unadj. OR = 2.07
(95%CI= 0.87 to 4.96)

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Evidence-based Recommendation

PICO 2. AIS of <4.5 h duration -LVO

For patients with large vessel occlusion acute ischaemic stroke of <4.5 hr duration who are eligible for intravenous thrombolysis, we recommend tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg. Intravenous thrombolysis should not delay mechanical thrombectomy.

Quality of evidence: Moderate ⊕⊕⊕

Strength of recommendation: Strong ↑↑

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Expert Consensus Statement

PICO 2. AIS of <4.5 h duration -LVO

For patients with large vessel occlusion acute ischaemic stroke of <4.5 hr duration who are eligible for intravenous thrombolysis and are directly admitted to a thrombectomy-capable center, all MWG members suggest IVT with tenecteplase 0.25 mg/kg over skipping IVT. For patients with large vessel occlusion acute ischaemic stroke of <4.5 hr duration who are eligible for intravenous thrombolysis and are admitted to a center without mechanical thrombectomy capability, all MWG members suggest IVT with tenecteplase 0.25mg/kg followed by rapid transfer to a thrombectomy-capable center.

Voting: 9/9 members

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PICO Question

PICO 3. Wake-up stroke/unknown onset

PICO 3.1 For patients with acute ischaemic stroke on awakening from sleep or acute ischemic stroke of unknown onset and who are eligible for intravenous thrombolysis, does intravenous thrombolysis with tenecteplase 0.25 mg/kg **compared with no intravenous thrombolysis** lead to:

a) a non-inferior proportion of patients with **excellent functional outcome (mRS scores of 0-1)** at 90 days?

b) non-inferior or better results on other efficacy outcomes (mRS 0-2 at 90 days…)?

c) a reduction in the risk of adverse events (mortality at 90 days, sICH…)?

d) a reduction in key time metrics (onset-to-treatment time, door-to-needle time)?

e) an improvement in neuroimaging parameters?

TWIST (2022-23) **Phase 3-**	**N= 578**	**Within 4.5h from awakening** **Patient selection : Non contrast CT**	**Tenecteplase VS No thrombolyis : no difference** **Shift analysis of mRS : Primary endpoint** **Mortality** **sICH**

EUROPEAN STROKE ORGANISATION

Evidence-based Recommendation

PICO 3 Wake –up/unkown onset

For patients with acute ischaemic stroke on awakening from sleep or acute ischaemic stroke of unknown onset who are selected with no brain imaging other than plain CT, we recommend against intravenous thrombolysis with tenecteplase 0.25 mg/kg outside the context of a clinical trial.

Quality of evidence: Low ⊕⊕

Strength of recommendation: Strong against intervention ↓↓

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PICO Question

PICO 3. Wake-up stroke/unknown onset

PICO 3.2 For patients with acute ischaemic stroke on awakening from sleep or acute ischemic stroke of unknown onset and who are eligible for intravenous thrombolysis, does intravenous thrombolysis with tenecteplase 0.25 mg/kg or 0.40 mg/kg compared **with intravenous thrombolysis with alteplase 0.90 mg/kg** lead to:

a) a non-inferior proportion of patients with excellent functional outcome (mRS scores of 0-1) at 90 days?

b) non-inferior or better results on other efficacy outcomes (mRS 0-2 at 90 days…)?

c) a reduction in the risk of adverse events (mortality at 90 days, sICH…)?

d) a reduction in key time metrics (onset-to-treatment time, door-to-needle time)?

e) an improvement in neuroimaging parameters ?

ESO
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Evidence-based Recommendation

For patients with acute ischaemic stroke on awakening from sleep or acute ischemic stroke of unknown onset and who are eligible for intravenous thrombolysis, there is continued uncertainty over the potential benefits and harms of tenecteplase compared with alteplase.

Quality of evidence: Very low ⊕

Strength of recommendation: -

Expert Consensus Statement

All MWG members suggest that tenecteplase 0.25 mg/kg could be a reasonable alternative to alteplase 0.9 mg/kg for patients with acute ischaemic stroke on awakening from sleep or acute ischemic stroke of unknown onset and who are eligible for intravenous thrombolysis after selection with advanced imaging (FLAIR-DWI mismatch or perfusion mismatch as outlined in the 2021 ESO Guidelines on IVT).

Berge E et al, Eur Stroke J 2021; 6: I-LXII

Voting: 9/9 members

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Conclusion

- Take Home Message

  Patients with AIS of < 4.5 h duration who are eligible for IVT

- Tenecteplase 0.25mg/kg can be used as safe and effective alternative to alteplase:

  moderate evidence, strong recommendation

- Expert consensus statement : WGM suggest tenecteplase over alteplase

  Patient with AIS of < 4.5h duration and LVO who are eligible for IVT

- Tenecteplase 0.25mg/kg is recommended over alteplase

- ESO-2021 recommendation on IVT upgraded

  Evidence : Low=> Moderate // Strength of recommendation : Weak=> Strong

- Tenecteplase shortage in Europe – Appropriate packaging

- European Medicines Agency approval ?

- Perspectives : the next frontiers for tenecteplase in stroke

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