Tenecteplase: Ready for prime time?

Implications for non-TNK clinical trials

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Disclosures

Off label use of drugs

Intravenous alteplase for ischemic stroke beyond 3 hours
Intravenous tenecteplase for ischemic stroke

Financial

Modest: Genentech

The New England
Journal of Medicine

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TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

	alteplase	placebo	p
Disability-free recovery (mRS ≤ 1)	43%	27%	< .001
Symptomatic intracerebral hemorrhage	6.4%	0.6%	< .001

Can we do better?

Alteplase administration: bolus then infusion

Phase	Alteplase
Initial (free plasma)	3-5 min
Plasma Clearance	380-570 mL/min
Terminal (tissue bound)	72-144 min

Stroke Dosing
0.9 mg/kg Max 90mg
10% as 60 sec bolus
remainder as infusion over 60 minutes

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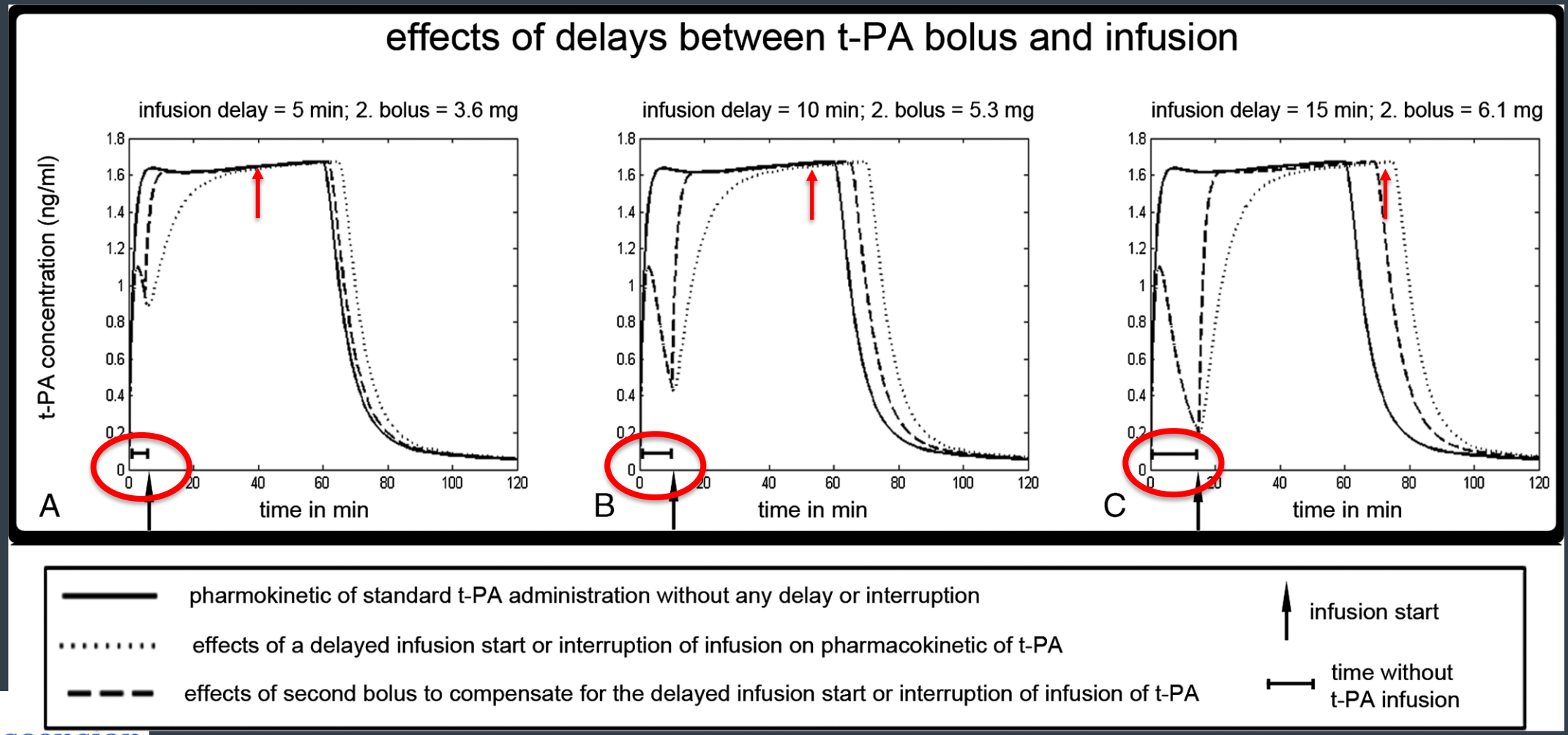
Alteplase administration: *mind the gap!*



Brodoehl et al.,Clin Neuropharm 2015;38: 85–88

Alteplase administration: *mind the gap!*

Bolus-Infusion Delays of Alteplase during Thrombolysis in Acute Ischaemic Stroke and Functional Outcome at 3 Months.

Acheampong et al. 2014, Stroke Res Treat

N=276 alteplase treated stoke
Mean bolus to infusion delay of 9 minutes

80% >= 5 minutes
22% >=12 minutes

Trend to worse mRS outcome with longer bolus to infusion delays

Search for a better thrombolytic

Single bolus injection – workflow advantages

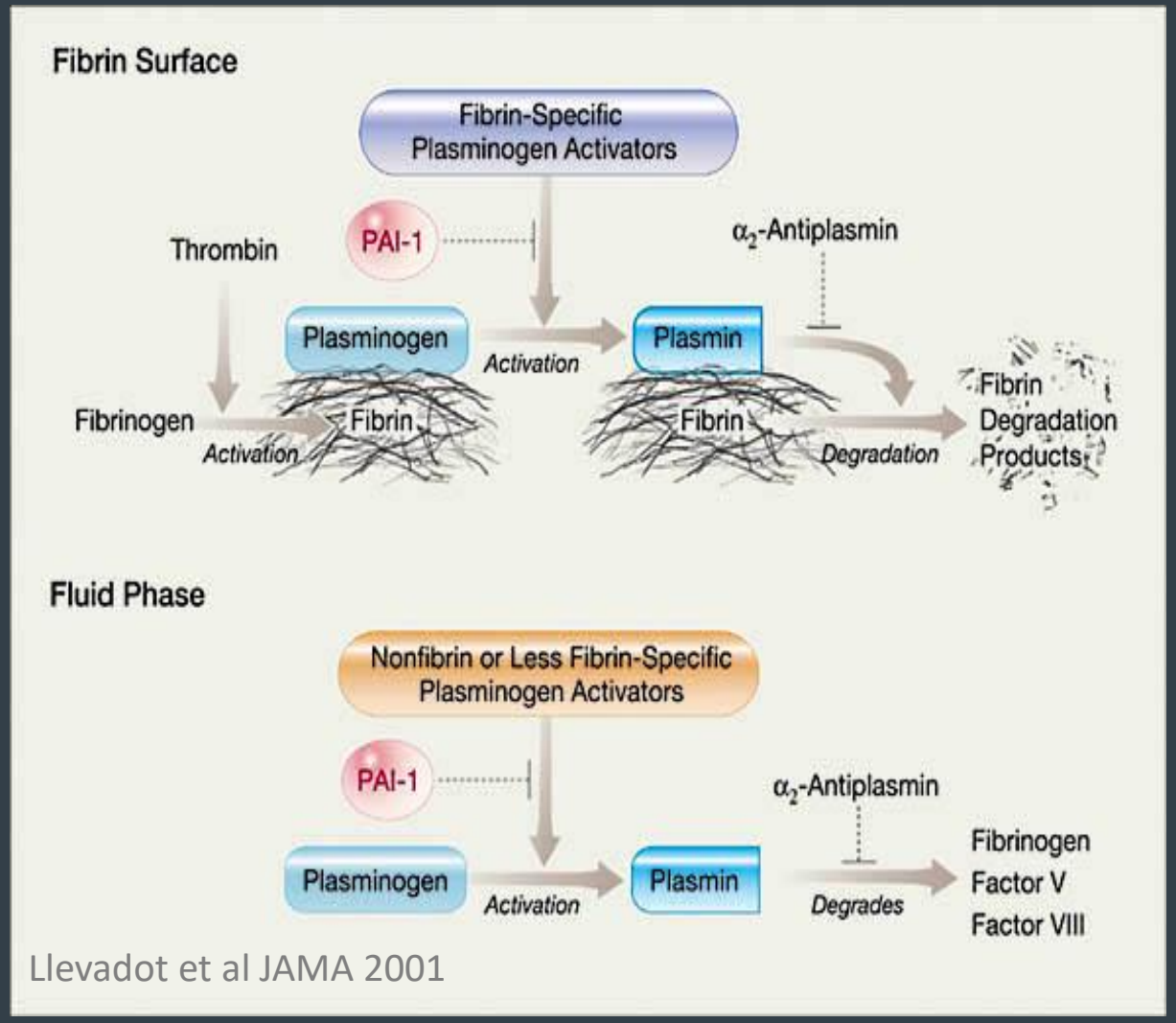
Higher rates of recanalization – better outcomes

Reduced bleeding complication – better safety

Search for a better thrombolytic

Greater
fibrin specificity
resistance to PAI-1 inhibition
conservation of fibrinogen
speed of clot lysis

Reduced
plasma clearance



Llevadot et al JAMA 2001

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Tenecteplase

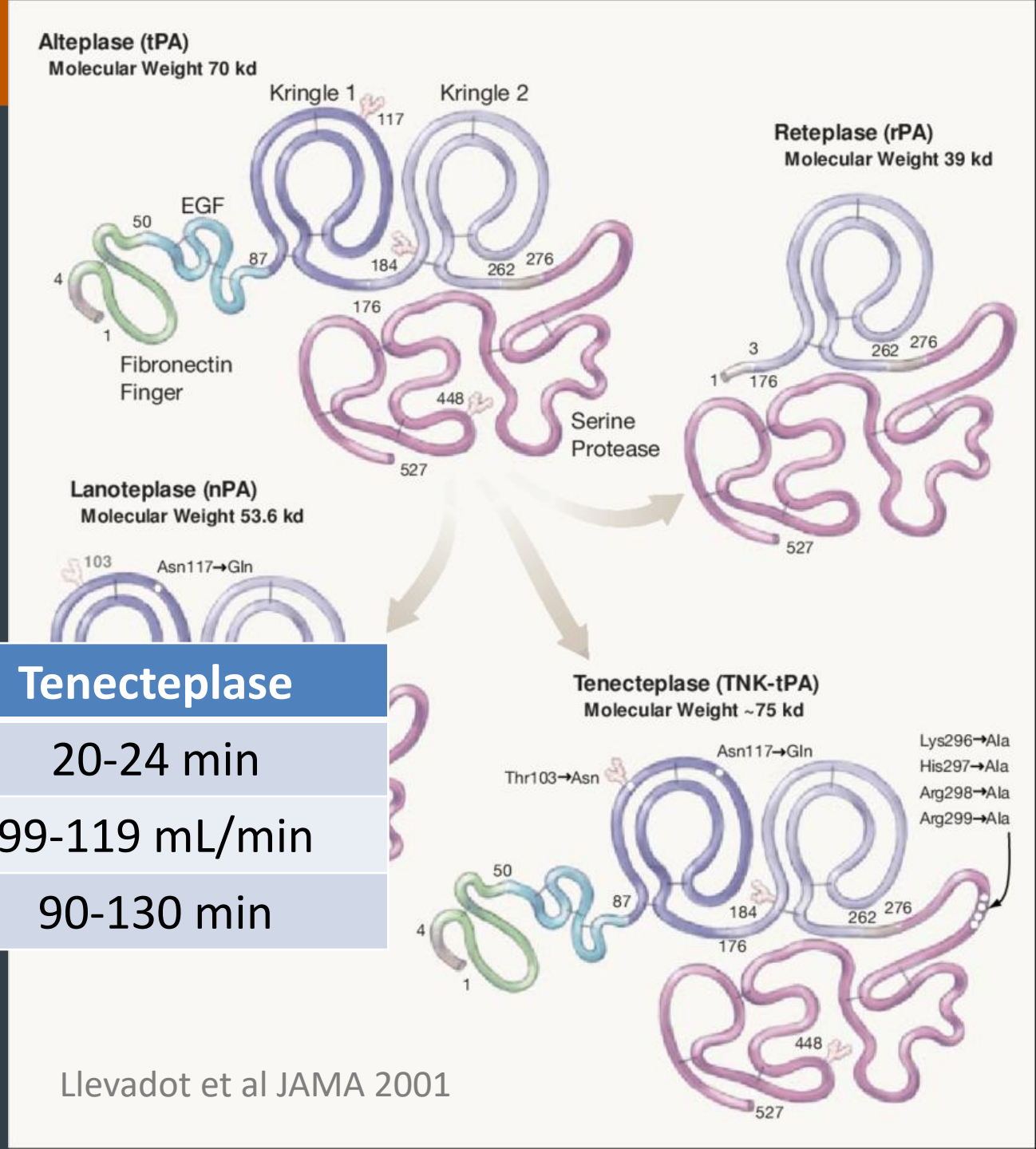
TNK-tpa

T103N

N117Q

KHRR (296-299)AAAA

Phase	Alteplase	Tenecteplase
Initial (free plasma)	3-5 min	20-24 min
Plasma Clearance	380-570 mL/min	99-119 mL/min
Terminal (tissue bound)	72-144 min	90-130 min



Llevadot et al JAMA 2001

Ascension

Tenecteplase

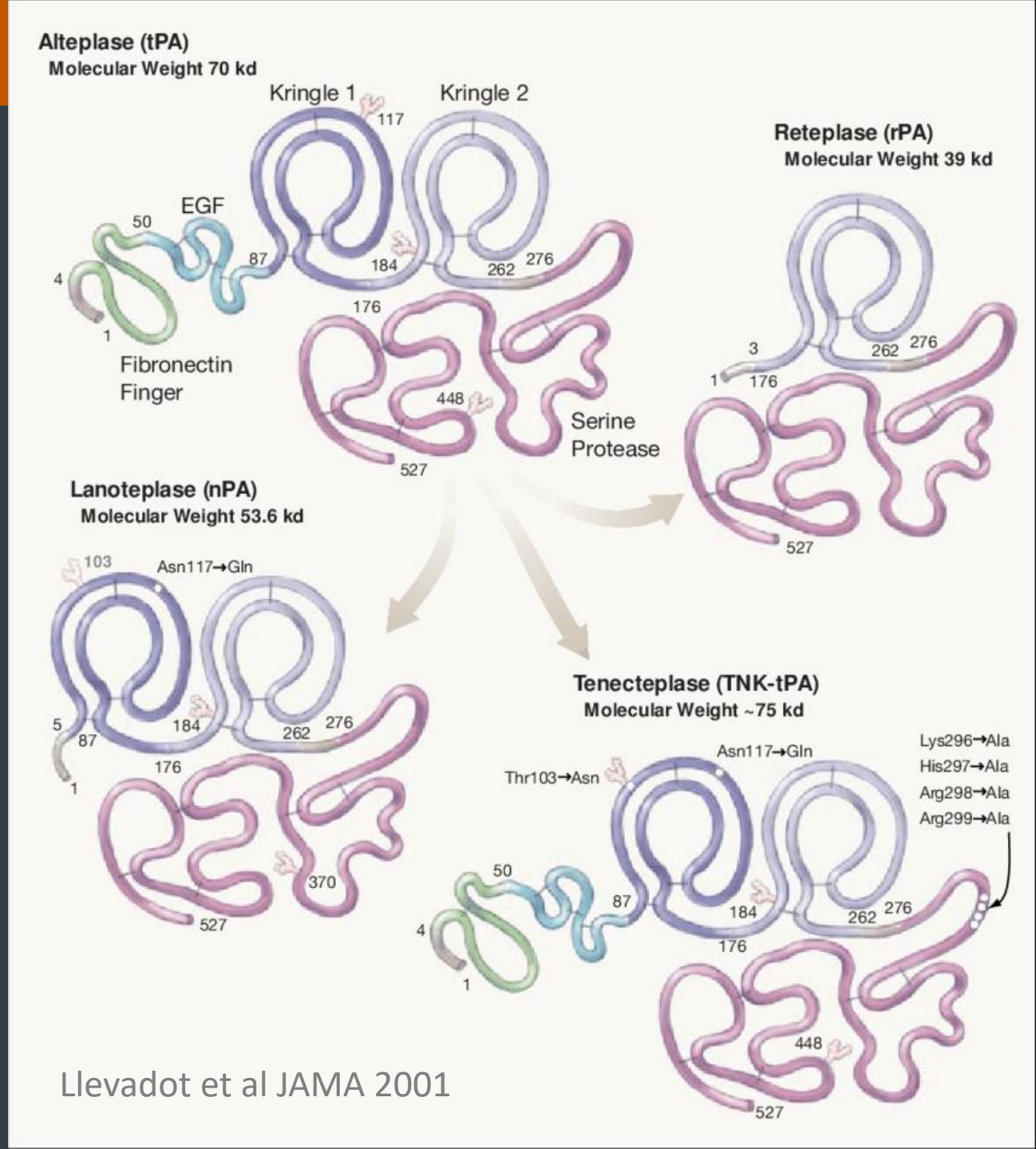
TNK-tpa

T103N

N117Q

KHRR (296-299)AAAA

14-fold greater fibrin specificity
10-fold greater conservation of fibrinogen
80-fold increased resistance to PAI-1
more rapid thrombolysis



Llevadot et al JAMA 2001

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ASSENT-2 (1999)

- Alteplase vs Tenecteplase in STEMI; ~8500 per group
- Equivalent 30-day morality
- 0.9% ICH both groups
- Fewer non-CNS bleeding events (26% to 29%)
- No difference in recanalization or reinfarction
- FDA approved in 2000 at 0.5 mg/kg to 50 mg maximum

Van der Werf et al Lancet 1999

Alteplase vs Tenecteplase randomized trials 2010-2019

Stroke *Stroke*. 2010;41:707-711.

Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke

Results of a Prematurely Terminated Randomized Clinical Trial

E. Clarke Haley, Jr, MD; John L.P. Thompson, PhD; James C. Grotta, MD; Patrick D. Lyden, MD; Thomas G. Hemmen, MD; Devin L. Brown, MD, MS; Christopher Fanale, MD; Richard Libman, MD; Thomas G. Kwiatkowski, MD; Rafael H. Llinas, MD; Steven R. Levine, MD; Karen C. Johnston, MD, MSc; Richard Buchsbaum; Gilberto Levy, MD, MS; Bruce Levin, PhD; for the Tenecteplase in Stroke Investigators

Background and Purpose—Intravenous alteplase (rtPA) remains the only approved treatment for acute ischemic stroke, but its use remains limited. In a previous pilot dose-escalation study, intravenous tenecteplase showed promise as a potentially safer alternative. Therefore, a Phase IIB clinical trial was begun to (1) choose a best dose of tenecteplase to carry forward; and (2) to provide evidence for either promise or futility of further testing of tenecteplase versus rtPA. If promise was established, then the trial would continue as a Phase III efficacy trial comparing the selected tenecteplase dose to standard rtPA.

Methods—The trial began as a small, multicenter, randomized, double-blind, controlled clinical trial comparing 0.1, 0.25, and 0.4 mg/kg tenecteplase with standard 0.9 mg/kg rtPA in patients with acute stroke within 3 hours of onset. An adaptive sequential design used an early (24-hour) assessment of major neurological improvement balanced against occurrence of symptomatic intracranial hemorrhage to choose a "best" dose of tenecteplase to carry forward. Once a "best" dose was established, the trial was to continue until at least 100 pairs of the selected tenecteplase dose versus standard rtPA could be compared by 3-month outcome using the modified Rankin Scale in an interim analysis. Decision

Stroke *Stroke*. 2010;41:707-711.

Dose finding study

Randomized, double-blind

< 3hr

0.1, 0.25, 0.4 mg/kg TNK vs ALT

N (TNK) = 81

Composite Outcome at 24 hr

0.4mg/kg dose discarded as inferior

Phase … Stroke … ial

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Thomas C … man, MD;
Karen … , PhD;

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Methods—T… …ng 0.1, 0.25, and 0.4 … …f onset. An adaptive … …nced against occurren… …ard. Once a "best" do… …dose versus standard rtPA could be compared by 3-month outcome using the modified Rankin Scale in an interim analysis. Decision

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ORIGINAL ARTICLE

A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke

Mark Parsons, M.D., Neil Spratt, M.D., Andrew Bivard, B.Sc., Bruce Campbell, M.D., Kong Chung, M.D., Ferdinand Miteff, M.D., Bill O'Brien, M.D., Christopher Bladin, M.D., Patrick McElduff, Ph.D., Chris Allen, M.D., Grant Bateman, M.D., Geoffrey Donnan, M.D., Stephen Davis, M.D., and Christopher Levi, M.D.

Phase 2

Randomized

< 6hr; LVO with penumbra by CTA/CTP

0.1, 0.25 mg/kg TNK vs ALT

N (TNK) = 50

Reperfusion and clinical improvement at 24 hr

Combined TNK superior to ALT

Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study

Xuya Huang, Bharath Kumar Cheripelli, Suzanne M Lloyd, Dheeraj Kalladka, Fiona Catherine Moreton, Aslam Siddiqui, Ian Ford, Keith W Muir

Lancet Neurol 2015; 14: 368–76

Published Online
February 26, 2015
http://dx.doi.org/10.1016/S1474-4422(15)70017-7

See Comment page 343

Institute of Neuroscience and

Summary

Background In most countries, alteplase given within 4·5 h of onset is the only approved medical treatment for acute ischaemic stroke. The newer thrombolytic drug tenecteplase has been investigated in one randomised trial up to 3 h after stroke and in another trial up to 6 h after stroke in patients selected by advanced neuroimaging. In the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST), we aimed to assess the efficacy and safety of tenecteplase versus alteplase within 4·5 h of stroke onset in a population not selected on the basis of advanced neuroimaging, and to use imaging biomarkers to inform the design of a definitive phase 3 clinical trial.

Phase 2

Randomized, PROBE

< 4.5 hr; with penumbra by CTA/CTP

0.25mg/kg TNK vs ALT

N (TNK) = 52

Penumbral Salvage at 24-48 hr

No differences

Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial

Nicola Logallo, Vojtech Novotny, Jörg Assmus, Christopher E Kvistad, Lars Alteheld, Ole Morten Rønning, Bente Thommessen, Karl-Friedrich Amthor, Hege Ihle-Hansen, Martin Kurz, Håkon Tobro, Kamaljit Kaur, Magdalena Stankiewicz, Maria Carlsson, Åse Morsund, Titto Idicula, Anne Hege Aamodt, Christian Lund, Halvor Næss, Ulrike Waje-Andreassen, Lars Thomassen

Summary

Background Tenecteplase is a newer thrombolytic agent with some pharmacological advantages over alteplase. Previous phase 2 trials of tenecteplase in acute ischaemic stroke have shown promising results. We aimed to investigate the safety and efficacy of tenecteplase versus alteplase in patients with acute stroke who were eligible for intravenous thrombolysis.

Methods This phase 3, randomised, open-label, blinded endpoint, superiority trial was done in 13 stroke units in Norway. We enrolled adults with suspected acute ischaemic stroke who were eligible for thrombolysis and admitted within 4·5 h of symptom onset or within 4·5 h of awakening with symptoms, or who were eligible for bridging therapy before thrombectomy. Patients were randomly assigned (1:1) to receive intravenous tenecteplase 0·4 mg/kg (to a maximum of 40 mg) or alteplase 0·9 mg/kg (to a maximum of 90 mg), via a block randomisation schedule stratified by centre of inclusion. Patients were not informed of treatment allocation; treating physicians were aware of treatment allocation but those assessing the primary and secondary endpoints were not. The primary outcome was excellent functional outcome defined as modified Rankin Scale (mRS) score 0–1 at 3 months. The primary analysis was an unadjusted and non-stratified intention-to-treat analysis with last observation carried forward for imputation of missing data. This study is registered with ClinicalTrials.gov, number NCT01949948.

Findings Between Sept 1, 2012, and Sept 30, 2016, 1107 patients met the inclusion criteria and seven patients were excluded because informed consent was withdrawn or eligibility for thrombolytic treatment was reconsidered. 1100 patients were randomly assigned to the tenecteplase (n=549) or alteplase (n=551) groups. The median age of participants was 77 years (IQR 64–79) and the median National Institutes of Health Stroke Scale score at baseline

Lancet Neurol 2017; 16: 781–88

Published Online
August 2, 2017
http://dx.doi.org/10.1016/S1474-4422(17)30253-3

See Comment page 762

Department of Neurology, Centre for Neurovascular Diseases (N Logallo PhD, V Novotny MD, C E Kvistad PhD, Prof H Næss PhD, U Waje-Andreassen PhD, Prof L Thomassen PhD) **and Centre for Clinical Research** (J Assmus PhD), **Haukeland University Hospital, Bergen, Norway; Department of Clinical Medicine, University of Bergen, Bergen, Norway** (N Logallo, V Novotny, C E Kvistad, Prof M Kurz PhD, U Waje-Andreassen, Prof L Thomassen); **Department of Neurology, Oslo University**

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Prof L Thomassen); Department
of Neurology, Oslo University

Phase 3

Randomized, PROBE

< 4.5 hr (+ Wake-up), all eligible for thrombolytic

0.4 mg/kg TNK vs ALT

N (TNK) = 549

mRS at 3 months

No differences mRS or sICH

Tenecteplase versus alteplase for management of acute isch ope

Phase 3

Randomized, PROBE

< 4.5 hr (+ Wake-up), all eligible for thrombolytic

0.4 mg/kg TNK vs ALT

Median NIHSS 4

Severe (NIHSS ≥ 15) subgroup higher mortality in TNK group

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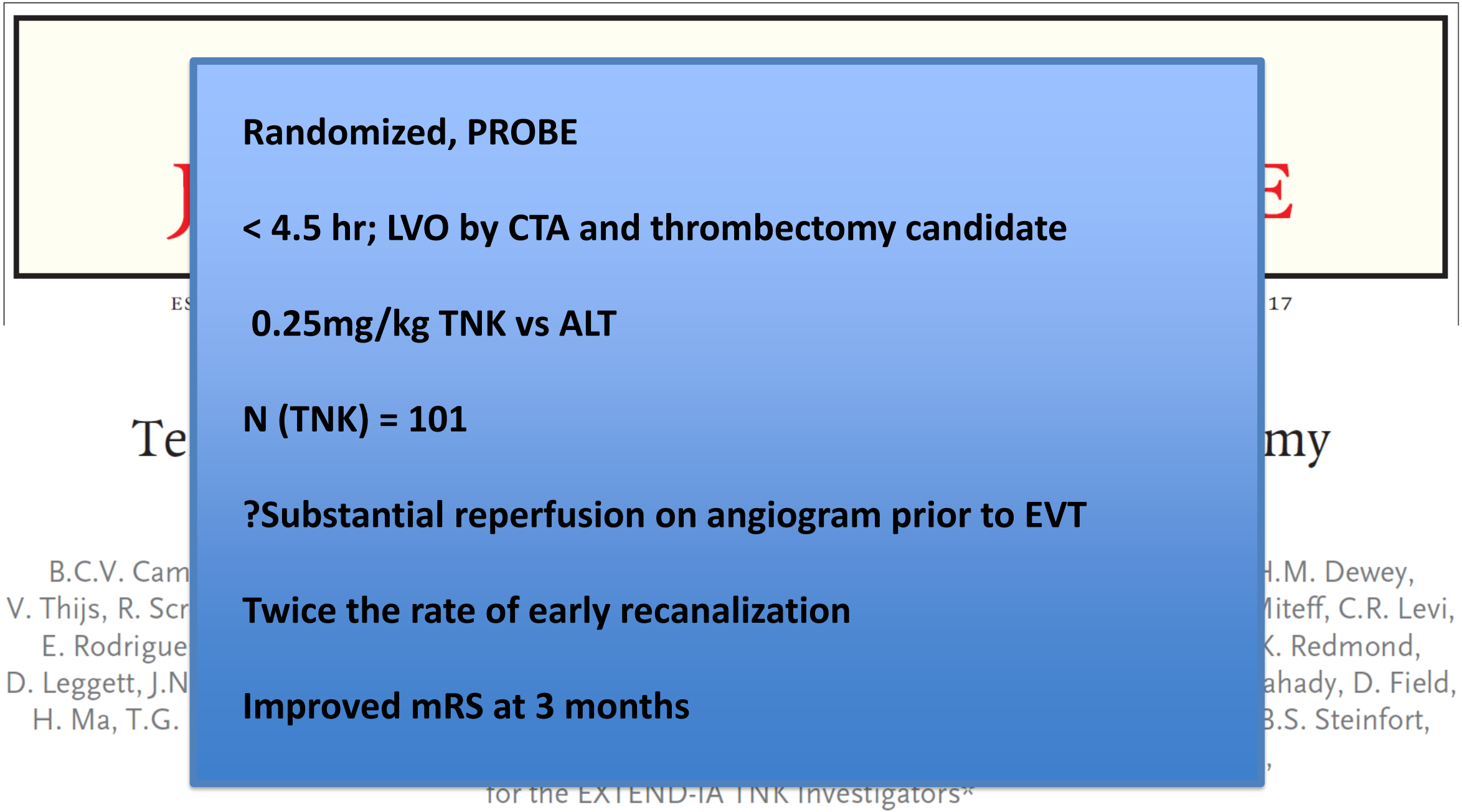
Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

B.C.V. Campbell, P.J. Mitchell, L. Churilov, N. Yassi, T.J. Kleinig, R.J. Dowling, B. Yan, S.J. Bush, H.M. Dewey, V. Thijs, R. Scroop, M. Simpson, M. Brooks, H. Asadi, T.Y. Wu, D.G. Shah, T. Wijeratne, T. Ang, F. Miteff, C.R. Levi, E. Rodrigues, H. Zhao, P. Salvaris, C. Garcia-Esperon, P. Bailey, H. Rice, L. de Villiers, H. Brown, K. Redmond, D. Leggett, J.N. Fink, W. Collecutt, A.A. Wong, C. Muller, A. Coulthard, K. Mitchell, J. Clouston, K. Mahady, D. Field, H. Ma, T.G. Phan, W. Chong, R.V. Chandra, L.-A. Slater, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Steinfort, C.F. Bladin, G. Sharma, P.M. Desmond, M.W. Parsons, G.A. Donnan, and S.M. Davis, for the EXTEND-IA TNK Investigators*



Randomized, PROBE

< 4.5 hr; LVO by CTA and thrombectomy candidate

0.25mg/kg TNK vs ALT

N (TNK) = 101

?Substantial reperfusion on angiogram prior to EVT

Twice the rate of early recanalization

Improved mRS at 3 months

Table 2. Outcomes.

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
Primary efficacy outcome				
Substantial reperfusion at initial angiographic assessment — no. (%)*	22 (22)	10 (10)		
Difference — percentage points			12 (2–21)	0.002
Adjusted incidence ratio			2.2 (1.1–4.4)	0.03
Adjusted odds ratio			2.6 (1.1–5.9)	0.02
Secondary outcomes				
Score on the modified Rankin scale at 90 days†				

Campbell BCV et al. N Engl J Med 2018;378:1573-1582

Tenecteplase as Stroke Thrombolytic

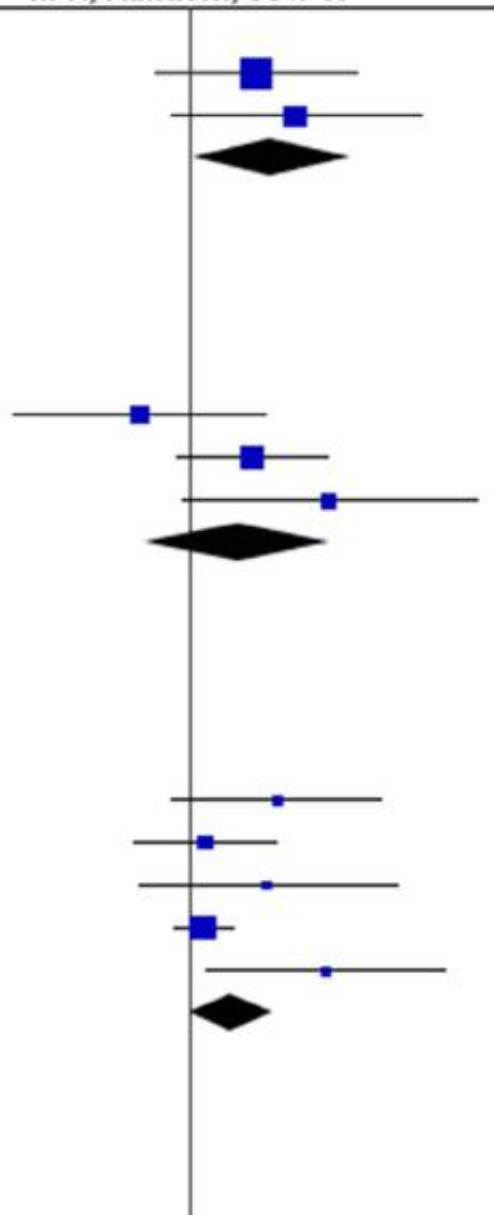
meta-analyses

Non-inferiority and possible superiority of tenecteplase v alteplase in the treatment of acute ischemic stroke

Kheiri et al., *Journal of Thrombosis and Thrombolysis* (2018)

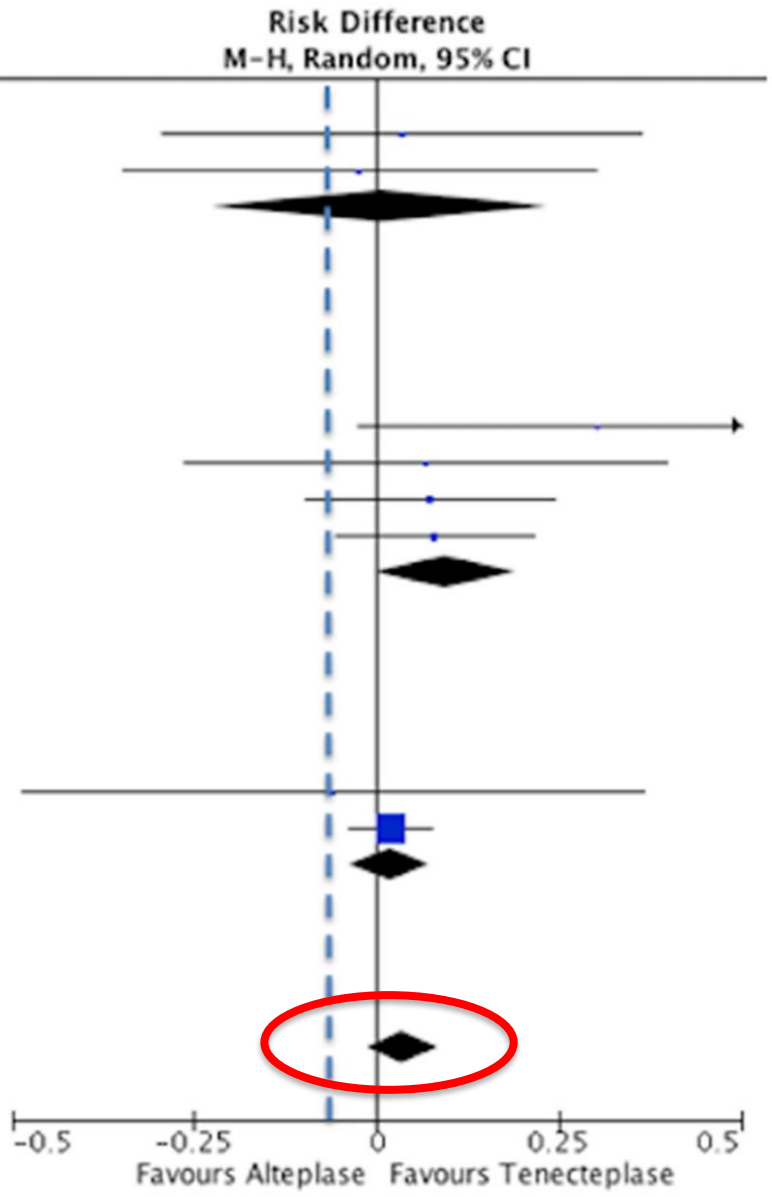
Burgos and Saver, *Stroke* (2019)

Study or Subgroup	Tenecteplase Events	Total	Alteplase Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Complete recanalization						
EXTEND-IA TNK 2018	16	97	10	99	60.3%	1.76 [0.75, 4.09]
Parsons 2012	28	48	8	22	39.7%	2.45 [0.87, 6.94]
Subtotal (95% CI)		**145**		**121**	**100.0%**	**2.01 [1.04, 3.87]**
Total events	44		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						
1.1.2 Complete/partial recanalization						
ATTEST 2015	21	32	26	35	29.6%	0.66 [0.23, 1.89]
EXTEND-IA TNK 2018	33	97	23	99	45.9%	1.70 [0.91, 3.19]
Parsons 2012	42	48	15	22	24.4%	3.27 [0.95, 11.28]
Subtotal (95% CI)		**177**		**156**	**100.0%**	**1.51 [0.70, 3.26]**
Total events	96		64			
Heterogeneity: Tau² = 0.23; Chi² = 4.00, df = 2 (P = 0.14); I² = 50%						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.1.3 Early neurological improvement						
ATTEST 2015	19	47	12	49	12.7%	2.09 [0.87, 5.01]
EXTEND-IA TNK 2018	72	101	69	101	21.7%	1.15 [0.63, 2.10]
Haley 2010	22	81	5	31	9.1%	1.94 [0.66, 5.68]
NOR-TEST 2017	229	549	214	551	46.3%	1.13 [0.89, 1.43]
Parsons 2012	32	50	9	25	10.2%	3.16 [1.16, 8.59]
Subtotal (95% CI)		**828**		**757**	**100.0%**	**1.43 [1.01, 2.03]**
Total events	374		309			
Heterogeneity: Tau² = 0.05; Chi² = 6.06, df = 4 (P = 0.19); I² = 34%						
Test for overall effect: Z = 1.99 (P = 0.05)						



Non-inferior 3 month mRS 0-1

Study or Subgroup	Tenecteplase Events	Tenecteplase Total	Alteplase Events	Alteplase Total	Weight	Risk Difference M-H, Random, 95% CI	Year
2.3.1 Tenetecteplase 0.1 mg/kg							
TNK-S2B	14	31	5	12	2.1%	0.03 [-0.29, 0.36]	2010
Australian TNK	9	25	5	13	2.2%	-0.02 [-0.35, 0.30]	2010
Subtotal (95% CI)		**56**		**25**	**4.3%**	**0.00 [-0.23, 0.24]**	
Total events	23		10				
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%							
Test for overall effect: Z = 0.04 (P = 0.97)							
2.3.2 Tenecteplase 0.25 mg/kg							
Australian TNK	18	25	5	12	2.1%	0.30 [-0.03, 0.63]	2010
TNK-S2B	15	31	5	12	2.1%	0.07 [-0.26, 0.40]	2010
ATTEST	13	47	10	49	7.8%	0.07 [-0.10, 0.24]	2015
EXTEND-IA TNK	49	101	41	101	12.2%	0.08 [-0.06, 0.22]	2018
Subtotal (95% CI)		**204**		**174**	**24.2%**	**0.10 [-0.00, 0.19]**	
Total events	95		61				
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 3 (P = 0.64); I² = 0%							
Test for overall effect: Z = 1.93 (P = 0.05)							
2.3.3 Tenecteplase 0.4 mg/kg							
TNK-S2B	7	19	3	7	1.3%	-0.06 [-0.49, 0.37]	2010
Nor-Test	354	549	345	551	70.3%	0.02 [-0.04, 0.08]	2017
Subtotal (95% CI)		**568**		**558**	**71.6%**	**0.02 [-0.04, 0.07]**	
Total events	361		348				
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%							
Test for overall effect: Z = 0.60 (P = 0.55)							
Total (95% CI)		**828**		**757**	**100.0%**	**0.04 [-0.01, 0.08]**	
Total events	479		419				
Heterogeneity: Tau² = 0.00; Chi² = 3.80, df = 7 (P = 0.80); I² = 0%							
Test for overall effect: Z = 1.46 (P = 0.14)							
Test for subgroup differences: Chi² = 1.93, df = 2 (P = 0.38), I² = 0%							



Tenecteplase practical advantages over alteplase

Shorter time to prepare

Shorter time to administer (5-10 seconds versus 1 hour)

Does not require that a second, dedicated IV line be inserted and maintained

Does not require an IV infusion pump

Shorter time to initiate interfacility transfer after IV lytic administration*

Lower cost per dose

Tenecteplase As Stroke Thrombolytic

Transitioning to Local Standard of Care at Ascension Seton

Ascension Texas – Ascension Seton Stroke Service. 10 hospitals (2 CSC, 2 PSC)

Unchanged lytic eligibility criteria and post treatment monitoring

early drug preparation not permitted for tenecteplase

Nursing and physician education

Electronic medical record revision of ordersets and monitoring tools

Network ‘Go-Live’ September 17, 2019

Quarterly oversight review of cumulative outcome and safety data

Ascension

Prospective Observational Cohort Study of Tenecteplase Versus Alteplase in Routine Clinical Practice

Purpose To compare workflow metrics clinical outcomes of IV tenecteplase as standard of care lytic with that of alteplase

Data Source Local Stroke Registry (REDCap). 2 years of alteplase prior to switch to tenecteplase compared to first 15 months of tenecteplase

Hypotheses
Reduced door-to-needle and door-in-door-out times (higher rate of hitting target times)
Noninferior favorable outcome (discharge to home with independent ambulation)
Noninferior unfavorable outcome (sICH, in-hospital mortality or discharge to hospice)

Ascension

Baseline Characteristics

	Alteplase	Tenecteplase
N	354	234
Age (median, IQR)	67 (55-79)	68 (57-77)
NIHSS (median, IQR)	8 (4-15)	8 (4-13)
% men	52%	62%
% EVT after lytic	22%	24%

Door to Needle time

no exclusions

	Alteplase	Tenecteplase	
N	354	234	
Minutes (median, IQR)	57 (43-75)	51 (38-80)	P=0.140
% <= 45 min	**29%**	**41%**	P=0.006

aOR 1.76 (1.24, 2.52), *P*=.002

Door to Needle time

GWTG defined

	Alteplase	Tenecteplase	
N	203	135	
Minutes (median, IQR)	48 (39-59)	42 (35-53)	P=0.012
% <= 45 min	**41%**	**56%**	P=0.011

Interfacility Transfer Time After Lytic

	Alteplase	Tenecteplase	
N	65	43	
Minutes (median)	135	113	P=0.054
% <= 90 Min	**14%**	**37%**	P=0.010

OR = 3.69 (1.47, 9.7), *P*=.006

Interfacility Transfer Time *no Lytic*

	Alteplase Era	Tenecteplase Era
N	278	205
Minutes (median)	158.5	165
% <= 90 Min	**22%**	**18%**

Interfacility Transfer Time After Lytic

for EVT

	Alteplase	Tenecteplase	
N	13	16	
Minutes (median)	108	83	P=0.06
% <= 90 Min	**15%**	**62%**	P=0.03

Interfacility Transfer Time *no Lytic*

for EVT

	Alteplase Era	Tenecteplase Era
N	20	18
Minutes (median)	100.5	86.5
% <= 90 Min	**40%**	**61%**

NS

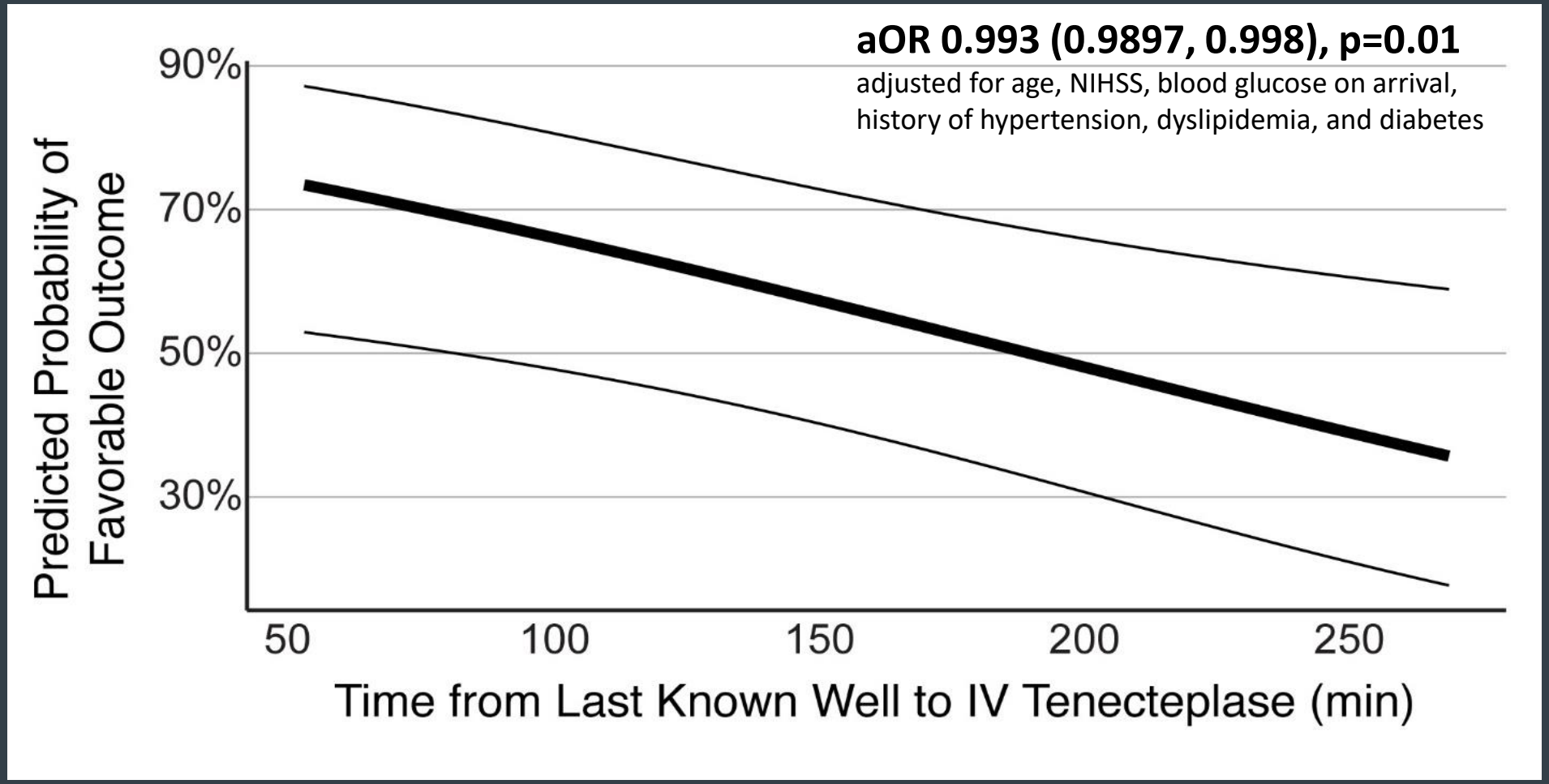
Favorable Outcome at Discharge

	Alteplase	Tenecteplase
N	354	234
Independent ambulation	43%	48%
Discharge to home	52%	52%
Discharge to home AND Independent Ambulation	**39%**	**44%**

aOR 1.26 (0.89, 1.80) within 6.5% non-inferiority margin

Favorable Outcome at Discharge

declines with onset to treatment time



Unfavorable Outcomes

	Alteplase	Tenecteplase
N	354	234
Any PH, IVH, or SAH by 36 hours	7.9%	7.7%
Symptomatic ICH	2.8 %	1.7%
In Hospital Mortality	6.2%	4.3%
Mortality OR Hospice	10.5%	6.8%
Death, Hospice, OR sxICH	**11.9%**	**7.7%**

aOR 0.77 (0.42, 1.37) *not* within 1% non-inferiority margin

Net Favorable Outcomes

NET FAVORABLE OUTCOME	Alteplase	Tenecteplase
Favorable minus Unfavorable Outcomes	27%	37%

P=0.02

Hospital Costs per Encounter

Table 1. Hospital Cost Breakdown: Tenecteplase vs Alteplase

	ALT, N = 354	TNK, N = 234	p-value
Diagnostic	16 (16, 127)	32 (16, 127)	0.4
Imaging	723 (507, 1,031)	834 (533, 1,143)	0.044
Lab	224 (142, 487)	259 (164, 512)	0.035
Pharmacy	9,288 (8,657, 11,751)	6,997 (6,460, 7,972)	<0.001
Service Line	117 (105, 236)	120 (105, 242)	0.7
Supplies Devices	6 (0, 702)	12 (0, 2,758)	0.2
Ancillary Services	446 (235, 773)	514 (295, 882)	0.036
Room Board	3,110 (2,107, 5,009)	3,110 (2,107, 4,665)	0.5
Operative Services	0 (0, 983)	0 (0, 1,247)	0.3

Hospital Costs by Thrombolytic Type Used	Alteplase	Tenecteplase	Savings per case with TNK
Overall Hospital Cost per Encounter	$15,841	$13,382	$2,459 P< 0.001

Approximate $450,000 savings in hospital costs annually at Ascension Texas Hospitals

Ascension Texas Tenecteplase 15 months' experience

Limitations

Single Stroke Network

Non-randomized

Not blinded

Sequential Samples
(temporal trends in quality improvement may contribute)

Ascension

Ascension Texas Tenecteplase 15 months' experience

Statistically significant:

- Reduction in time from ED arrival to treatment
- Increased % cases treated within 45 minutes of arrival
- Reduced transfer times (DIDO)
- Reduced time to EVT when transferred after lytic
- Non-inferior favorable clinical outcomes at discharge

Fewer unfavorable outcomes at discharge

Pharmacy cost savings over one year ~$450,000

Our results are comparable to published NZ experience

Ascension

Experience in Clinical Practice

Stroke

Stroke. 2021;52:1087–1090. DOI: 10.1161/STROKEAHA.120.030859

BRIEF REPORT

Routine Use of Tenecteplase for Thrombolysis in Acute Ischemic Stroke

Cathy S. Zhong, MBChB*; James Beharry, MBChB*; Daniel Salazar, MD; Kelly Smith, BN; Stephen Withington, MBChB; Bruce C.V. Campbell, MBBS, PhD; Duncan Wilson, MRCP, PhD; Campbell Le Heron, MBChB, PhD; Deborah Mason, MBChB; Roderick Duncan, MD, PhD; Jon Reimers, MBBS; Frances Mein-Smith, MBChB; William K. Diprose, MBChB; P. Alan Barber, MBChB, PhD; Annemarei Ranta, MD, PhD; John N. Fink, MBChB; Teddy Y. Wu, MBChB, PhD

BACKGROUND AND PURPOSE: In ischemic stroke, intravenous tenecteplase is noninferior to alteplase in selected patients and has some practical advantages. Several stroke centers in New Zealand changed to routine off-label intravenous tenecteplase due to improved early recanalization in large vessel occlusion, inconsistent access to thrombectomy within stroke networks, and for consistency in treatment protocols between patients with and without large vessel occlusion. We report the feasibility and safety outcomes in tenecteplase-treated patients.

Stroke

KEAHA.120.030859

BRIEF REPORT

Routine Us sis in Acute Ische

Cathy S. Zhong, MBChB*; J , MBChB;
Bruce C.V. Campbell, MBB ason, MBChB;
Roderick Duncan, MD, PhD; J
P. Alan Barber, MBChB, PhD;

BACKGROUND AND PURPOSE: I ed patients and has some practical advantag us tenecteplase due to improved early recan troke networks, and for consistency in treatr rt the feasibility and safety outcomes in tene

Table. Demographics, Stroke Reperfusion Metrics, and Outcome

	Tenecteplase (n=165)	Alteplase (n=254)	*P* value
Male	93 (56%)	152 (60%)	0.48
Age, y	75 (64–84)	74 (62–83)	0.50
Onset-to-needle time, min	130 (97–183)	129 (100–175)	0.72
Door-to-needle time, min	47 (33–69)	48 (33–66)	0.93
Baseline NIHSS	8 (5–14)	10 (5–17)*	0.17
Large vessel occlusion	87 (53%)	118(46%)	0.21
Endovascular thrombectomy	61 (37%)	61 (24%)	0.004
Angioedema	4 (2.4% [95% CI, 0.7%–6.2%])	1 (0.4% [95% CI, 0.01%–2.2%])	0.08†
Symptomatic intracerebral hemorrhage	3 (1.8% [95% CI, 0.4%–5.3%])	7 (2.7% [95% CI, 1.1%–5.7%])	0.75†
90-day functional Independence‡	100 (61%)	140 (57%)	0.47

Stroke

Stroke. 2021;52:00–00. DOI: 10.1161/STROKEAHA.121.035931

BRIEF REPORT

Switching to Tenecteplase for Stroke Thrombolysis

Real-World Experience and Outcomes in a Regional Stroke Network

Karim Mahawish, MBChB; John Gommans, MBChB; Timothy Kleinig, PhD; Bhavesh Lallu, MBChB; Alicia Tyson, BNurs PGdip; Annemarei Ranta, MD, PhD

BACKGROUND AND PURPOSE: Due to practical advantages, increasing trial safety data, recent Australian Guideline endorsement and local population needs we switched to tenecteplase for stroke thrombolysis from alteplase. We describe our change process and real-world outcome data.

METHODS: Mixed-methods including stakeholder engagement, preimplementation and postimplementation surveys, and assessment of patient treatment rates, metrics, and clinical outcomes preimplementation and postimplementation adjusting

Stroke. 2021;52:00–00. DOI: 10.1161/STROKEAHA.121.035931

Table 2. Patient Outcomes

	Tenecteplase	Alteplase		aOR
	N=283	N=555	OR	Model 1*
Death by day 7	21/283 (7.4%)	62/555 (11.2%)	0.64 (0.38–1.07)	0.46 (0.21–0.99)
sICH	5/283 (1.8%)	19/555 (3.4%)	0.51 (0.19–1.39)	0.46 (0.13–1.64)
Angioedema	2/283 (0.71%)	4/551 (0.72%)	0.98 (0.178–5.39)	1.40 (0.59–33.59)
3-month mRS score (0–2)§	147/231 (63.6%)	282/478 (60.0%)	1.24 (0.90–1.71)	2.17 (1.31–3.59)
3-month mRS (shift analysis)§			1.23 (0.93–1.63)	1.60 (1.15–2.22)

Table 3. Time Metrics Across Multiple Time Points (Medians [IQR])

Year group	Tenecteplase	Alteplase		*P* value
Door-to-needle time				
Tenecteplase vs alteplase all prior years	53 (38–73.5)	61 (45–86)		0.0002
Tenecteplase vs alteplase 2019	53 (38–73.5)	63.5 (48–95)		0.01
Alteplase 2018 vs 2019		60 (43–82)	63.5 (48–95)	0.052
Needle-to-groin time				
Tenecteplase vs alteplase all prior years	159 (124.5–258.5)	200 (174–255)		0.69

Comparative Effectiveness Of Routine Tenecteplase Thrombolysis In Acute Stroke Compared With Alteplase An International

CERTAIN Collaboration

Multinational pooling of patient level data

Hospitals or networks that use tenecteplase as stroke thrombolytic

Include alteplase cases from sources

Assess workflow and clinical outcomes of tenecteplase in large samples

First Project: symptomatic ICH (sICH)

Baseline Features, Total Sample

	Alteplase N=7313	Tenecteplase N=1925	P-value
Age (median years, IQR)	70 (58, 80)	73 (61, 81)	<0.001
Male (n, %)	3755 (51%)	1034 (55%)	0.007
NIHSS (median, IQR)	7 (4, 14)	9 (5, 17)	<0.001
Onset to needle (median minutes, IQR)	137 (98, 194)	160 (107, 246)	<0.001
Large vessel occlusion (n, %)	1745 (24%)	918 (48%)	<0.001
Systolic blood pressure (median mmHg, IQR)	153 (133, 176)	150 (130, 171)	<0.001
Glucose (median mmol/L, IQR)	6.6 (5.7, 8.5)	6.7 (5.7, 8.4)	0.365
Thrombectomy (n, %)	1465 (20%)	739 (38%)	<0.001

Tenecteplase group has greater baseline predictors of sICH

Rate of sICH, Total Sample

	Alteplase N=7313	Tenecteplase N=1925	P-value
sICH (n, %)	264 (3.6%)	35 (1.8%)	<0.001

CERTAIN ISC 2022

Logistic regression, Total sample

	Odds ratio (95% CI)	P-value	N
sICH unadjusted	0.49 (0.35, 0.71)	<0.001	9238
sICH adjusted*	0.42 (0.29, 0.61)	<0.001	8726

Alteplase is reference category vs tenecteplase

*Adjusted for age, sex, NIHSS, onset-to-needle time, thrombectomy

Rate of sICH, *no mechanical thrombectomy*

	Alteplase N=5848	Tenecteplase N=1186	P-value
sICH (n, %)	175 (3.0%)	17 (1.4%)	0.003

CERTAIN ISC 2022

Logistic regression, *no mechanical thrombectomy*

	Odds ratio (95% CI)	P-value	N
sICH unadjusted	**0.47 (0.29, 0.78)**	**0.003**	**7034**
sICH adjusted*	**0.46 (0.28, 0.77)**	**0.003**	**6628**

Alteplase is reference category vs tenecteplase

*Adjusted for age, sex, NIHSS, onset-to-needle time

Baseline Features, *mechanical thrombectomy*

	Alteplase N=1465	Tenecteplase N=739	P-value
Age (median years, IQR)	70 (58, 80)	73 (62, 81)	<0.001
Male (n, %)	733 (50%)	408 (57%)	0.005
NIHSS (median, IQR)	15 (8, 21)	16 (9, 21)	0.229
Onset to needle (median minutes, IQR)	144 (97, 233)	199 (126, 304)	<0.001
Systolic blood pressure (median mmHg, IQR)	145 (120, 167)	145 (120, 166)	0.749
Glucose (median mmol/L, IQR)	6.7 (5.8, 8.5)	6.7 (5.8, 8.3)	0.570

Tenecteplase group has greater baseline predictors of sICH

Rate of sICH, *mechanical thrombectomy*

	Alteplase N=1465	Tenecteplase N=739	P-value
sICH (n, %)	89 (5.9%)	18 (2.4%)	<0.001

CERTAIN ISC 2022

Logistic regression: *mechanical thrombectomy*

	Odds ratio (95% CI)	P-value	N
sICH unadjusted	**0.39 (0.23, 0.65)**	**<0.001**	**2204**
sICH adjusted*	**0.40 (0.24, 0.68)**	**0.001**	**2098**

Alteplase is reference category vs tenecteplase

*Adjusted for age, sex, NIHSS, onset-to-needle time

Limitations

- Non-randomized
- Unblinded
- Variability in definition and recording of registry source data

Strengths

- Large sample
- Multinational, multicenter
- Rates of sICH agree with those from randomized trials; results unlikely due to bias

Conclusions

- Incidence of symptomatic ICH in stroke patients treated with tenecteplase was half that of patients treated with alteplase
  - Overall and for both EVT and non-EVT subgroups
- Statistically significant differences that were not previously observed in smaller samples
- Supports tenecteplase safety in clinical practice, relative to alteplase

CERTAIN ISC 2022

Alteplase vs Tenecteplase randomized trials

2022

Which Dose?

JAMA | Original Investigation

Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke
The EXTEND-IA TNK Part 2 Randomized Clinical Trial

Bruce C. V. Campbell, PhD; Peter J. Mitchell, MMed; Leonid Churilov, PhD; Nawaf Yassi, PhD; Timothy J. Kleinig, PhD; Richard J. Dowling, MBBS; Bernard Yan, DMedSci; Steven J. Bush, MBBS; Vincent Thijs, PhD; Rebecca Scroop, MBBS; Marion Simpson, MBBS; Mark Brooks, MBBS; Hamed Asadi, MBBS; Teddy Y. Wu, PhD; Darshan G. Shah, MBBS; Tissa Wijeratne, MD; Henry Zhao, MBBS; Fana Alemseged, MD; Felix Ng, MBBS; Peter Bailey, MD; Henry Rice, MBBS; Laetitia de Villiers, MBBS; Helen M. Dewey, PhD; Philip M. C. Choi, MBChB; Helen Brown, MB BCh BAO; Kendal Redmond, MBBS; David Leggett, MBBS; John N. Fink, MBChB; Wayne Collecutt, MBBS; Thomas Kraemer, MD; Martin Krause, MD; Dennis Cordato, PhD; Deborah Field, MBBS; Henry Ma, PhD; Bill O'Brien, MBBS; Benjamin Clissold, MBBS; Ferdinand Miteff, MBBS; Anna Clissold, MBBS; Geoffrey C. Cloud, MBBS; Leslie E. Bolitho, MBBS; Luke Bonavia, MBBS; Arup Bhattacharya, MBBS; Alistair Wright, MBBS; Abul Mamun, MBBS; Fintan O'Rourke, MBBS; John Worthington, MBBS; Andrew A. Wong, PhD; Christopher R. Levi, MBBS; Christopher F. Bladin, MD; Gagan Sharma, MCA; Patricia M. Desmond, MD; Mark W. Parsons, PhD; Geoffrey A. Donnan, MD; Stephen M. Davis, MD; for the EXTEND-IA TNK Part 2 investigators

IMPORTANCE Intravenous thrombolysis with tenecteplase improves reperfusion prior to endovascular thrombectomy for ischemic stroke compared with alteplase.

OBJECTIVE To determine whether 0.40 mg/kg of tenecteplase safely improves reperfusion before endovascular thrombectomy vs 0.25 mg/kg of tenecteplase in patients with large vessel occlusion ischemic stroke.

Visual Abstract

Supplemental content

JAMA | Original Investigation

Effect of I…ntravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombe… c Stroke
The EXTE…

Bruce C. V. Campbe…vling, MBBS;
Bernard Yan, DMed…BBS;
Hamed Asadi, MBB…lix Ng, MBBS;
Peter Bailey, MD; H…Ch BAO;
Kendal Redmond, M…e, MD;
Dennis Cordato, Ph…Anna Clissold, MBBS;
Geoffrey C. Cloud, M…nun, MBBS;
Fintan O'Rourke, M…gan Sharma, MCA;
Patricia M. Desmon…vestigators

IMPORTANCE
endovascular…

OBJECTIVE To…
before endov…
vessel occlusion ischemic stroke.

…bstract

…ental content

Randomized

LVO by CTA and thrombectomy candidate

TNK dose comparison: 0.25 vs 0.4 mg/kg

N (TNK) = 150 each group

? Substantial reperfusion on angiogram prior to EVT

No difference on reperfusion, sICH or mRS

No advantage to doses higher than 0.25 mg/kg

Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): a phase 3, randomised, open-label, blinded endpoint, non-inferiority trial

Christopher Elnan Kvistad, Halvor Næss, Bernt H Helleberg, Titto Idicula, Guri Hagberg, Linn Marie Nordby, Kristian N Jenssen, Håkon Tobro, Dag M Rörholt, Kamaljit Kaur, Agnethe Eltoft, Kristin Evensen, Judit Haasz, Guruparan Singaravel, Annette Fromm, Lars Thomassen

Summary

Background Tenecteplase is a modified tissue plasminogen activator with pharmacological and practical advantages over alteplase—which is currently the only approved thrombolytic drug for ischaemic stroke. The NOR-TEST trial showed that 0·4 mg/kg tenecteplase had an efficacy and safety profile similar to that of a standard dose (0·9 mg/kg) of alteplase, albeit in a patient population with a high prevalence of minor stroke. The aim of NOR-TEST 2 was to establish the non-inferiority of tenecteplase 0·4 mg/kg to alteplase 0·9 mg/kg for patients with moderate or severe ischaemic stroke.

Methods This phase 3, randomised, open-label, blinded endpoint, non-inferiority trial was performed at 11 hospitals with stroke units in Norway. Patients with suspected acute ischaemic stroke with a National Institutes of Health Stroke Scale score of 6 or more who were eligible for thrombolysis and admitted within 4·5 h of symptom onset were consecutively included. Random assignment, done by a computer with a block size of 4 and with allocations placed into opaque envelopes to be opened consecutively, was 1:1 between intravenous tenecteplase (0·4 mg/kg) or standard dose alteplase (0·9 mg/kg). Doctors and nurses providing acute care were not masked to treatment, but primary outcome assessment at 3 months was masked. The primary outcome was favourable functional outcome defined as a

Lancet Neurol 2022

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See Online/Comment
https://doi.org/10.1016/S1474-4422(22)00172-7

Department of Neurology (C E Kvistad PhD, Prof H Næss PhD, A Fromm MD PhD, Prof L Thomassen PhD) and Department of Radiology (J Haasz PhD, G Singaravel MD), Haukeland University Hospital,

Tenecteplase versus alteplase for the management of acute ischaemic s randomise trial

Christopher Elnan Kvistad
Dag M Rörholt, Kamaljit K

Summary

Background Tenectep alteplase—which is c that 0·4 mg/kg tenec albeit in a patient po non-inferiority of ten

Methods This phase with stroke units in Stroke Scale score of consecutively includ into opaque envelop dose alteplase (0·9 outcome assessment at 3 months was masked. The primary outcome was favourable functional outcome defined as a

Phase 3. 0.4 mg/kg TNK vs ALT

Randomized, Open, Non-inferiority

< 4.5 hr: NIHSS > 5

Terminated early for Safety

N = 100 (TNK), 104 (ALT)

Symptomatic ICH and Mortality greater for 0.4 mg/kg TNK

57% were LVOs

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Department of Neurology (C E Kvistad PhD, Prof H Næss PhD, A Fromm MD PhD, Prof L Thomassen PhD) and Department of Radiology (J Haasz PhD, G Singaravel MD), Haukeland University Hospital,

Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial

*Andrew Bivard, Henry Zhao, Leonid Churilov, Bruce C V Campbell, Skye Coote, Nawaf Yassi, Bernard Yan, Michael Valente, Angelos Sharobeam, Anna H Balabanski, Angela Dos Santos, Jo Lyn Ng, Vignan Yogendrakumar, Felix Ng, Francesca Langenberg, Damien Easton, Alex Warwick, Elizabeth Mackey, Amy MacDonald BN, Gagan Sharma, Michael Stephenson, Karen Smith, David Anderson, Philip Choi, Vincent Thijs, Henry Ma, Geoffrey C Cloud, Tissa Wijeratne, Liudmyla Olenko, Dominic Italiano, Stephen M Davis, Geoffrey A Donnan, Mark W Parsons, on behalf of the TASTE-A collaborators**

Summary

Background Mobile stroke units (MSUs) equipped with a CT scanner reduce time to thrombolytic treatment and improve patient outcomes. We tested the hypothesis that tenecteplase administered in an MSU would result in superior reperfusion at hospital arrival, when compared with alteplase.

Methods The TASTE-A trial is a phase 2, randomised, open-label trial at the Melbourne MSU and five tertiary hospitals in Melbourne, VIC, Australia. Patients (aged ≥18 years) with ischaemic stroke who were eligible for thrombolytic treatment were randomly allocated in the MSU to receive, within 4·5 h of symptom onset, either standard-of-care alteplase (0·9 mg/kg [maximum 90 mg], administered intravenously with 10% as a bolus over 1 min and 90% as an infusion over 1 h), or the investigational product tenecteplase (0·25 mg/kg [maximum 25 mg], administered as an intravenous bolus over 10 s), before being transported to hospital for ongoing care. The primary outcome was the volume of the perfusion lesion on arrival at hospital, assessed by CT-perfusion imaging. Secondary safety outcomes were modified Rankin Scale (mRS) score of 5 or 6 at 90 days, symptomatic intracerebral haemorrhage and any haemorrhage within 36 h, and death at 90 days. Assessors were masked to treatment allocation. Analysis was by intention to treat. The trial was registered with ClinicalTrials.gov, NCT04071613, and is completed.

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*TASTE-A collaborators listed at the end of the Article

Department of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia (A Bivard PhD

Comparison of tenecteplase with alteplase for the early tre… Mobile S… open-lab…

Andrew Bivard, Her…
Anna H Balabanski…
Elizabeth Mackey, A…
Geoffrey C Cloud, Ti…
TASTE-A collaborat…

Phase 2 Mobile Stroke Unit

Randomized, Open

< 4.5 hr; 0.25 mg/kg TNK vs ALT

N = 55 (TNK), 49 (ALT)

Volume of Perfusion Lesion (CTP) on hospital arrival

Smaller perfusion volume with TNK

Quicker door-to-needle

Summary

Background Mo… improve patien… superior reperf…

Methods The TA… in Melbourne, … treatment were… alteplase (0·9 m… infusion over 1… intravenous bol… volume of the p… were modified … haemorrhage within 36 h, and death at 90 days. Assessors were masked to treatment allocation. Analysis was by intention to treat. The trial was registered with ClinicalTrials.gov, NCT04071613, and is completed

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e Online/Comment
ttps://doi.org/10.1016/
474-4422(22)00172-7

ASTE-A collaborators listed at
e end of the Article

epartment of Medicine and
eurology, Melbourne Brain
ntre at the Royal Melbourne
Hospital, University of
Melbourne, Parkville, VIC,
Australia (A Bivard PhD

Design

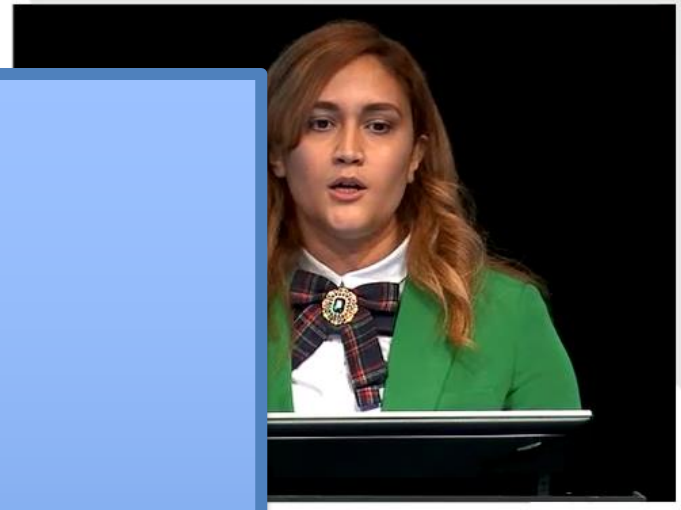
- Prospective randomised open trial with blinded endpoint assessment
- Target sample size: 600 patients
- Inclusion criteria:
  - Wake-up stroke with limb weakness and NIHSS score ≥ 3, or aphasia
  - Possible to treat within 4.5 hours of awakening
- Main exclusion criteria:
  - Intracranial hemorrhage
  - Infarct size >1/3 of the middle cerebral artery territory
  - NIHSS score >25 or NIHSS consciousness score >2
  - mRS ≥ 3

Melinda B. Roaldsen

UNIVERSITETSSYKEHUSET NORD-NORGE
UNIVERSITY HOSPITAL OF NORTH NORWAY

TWIST (TENECTEPLASE IN WAKE-UP ISCHAEMIC STROKE TRIAL)

- Prospectiv
- Target san
- Inclusion
  - Wake-u
  - Possible
- Main exclu
  - Intracra
  - Infarct s
  - NIHSS s
  - mRS ≥ 3



aldsen

Phase 3 Wake-up Stroke

Randomized, PROBE

< 4.5 hr from awakening

0.25 mg/kg TNK (N=288) vs standard care (N=290)

Imaging Screen Non-contrast CT

mRS at 3 month 45% (TNK) vs 38% (ns)

More EVT in control arm

Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial

Bijoy K Menon, Brian H Buck, Nishita Singh, Yan Deschaintre, Mohammed A Almekhlafi, Shelagh B Coutts, Sibi Thirunavukkarasu, Houman Khosravani, Ramana Appireddy, Francois Moreau, Gord Gubitz, Aleksander Tkach, Luciana Catanese, Dar Dowlatshahi, George Medvedev, Jennifer Mandzia, Aleksandra Pikula, Jai Shankar, Heather Williams, Thalia S Field, Alejandro Manosalva, Muzaffar Siddiqui, Atif Zafar, Oje Imoukhuede, Gary Hunter, Andrew M Demchuk, Sachin Mishra, Laura C Gioia, Shirin Jalini, Caroline Cayer, Stephen Phillips, Elsadig Elamin, Ashkan Shoamanesh, Suresh Subramaniam, Mahesh Kate, Gregory Jacquin, Marie-Christine Camden, Faysal Benali, Ibrahim Alhabli, Fouzi Bala, MacKenzie Horn, Grant Stotts, Michael D Hill, David J Gladstone, Alexandre Poppe, Arshia Sehgal, Qiao Zhang, Brendan Cord Lethebe, Craig Doram, Ayoola Ademola, Michel Shamy, Carol Kenney, Tolulope T Sajobi, Richard H Swartz, for the AcT Trial Investigators

Summary

Background Intravenous thrombolysis with alteplase bolus followed by infusion is a global standard of care for patients with acute ischaemic stroke. We aimed to determine whether tenecteplase given as a single bolus might increase reperfusion compared with this standard of care.

Methods In this multicentre, open-label, parallel-group, registry-linked, randomised, controlled trial (AcT), patients were enrolled from 22 primary and comprehensive stroke centres across Canada. Patients were eligible for inclusion if they were aged 18 years or older, with a diagnosis of ischaemic stroke causing disabling neurological deficit

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See Online/Comment https://doi.org/10.1016/S0140-6736(22)01107-2

Intravenous tenecteplase compared with alteplase for acute ischaemi
open-lab
non-infe

Bijoy K Menon, Brian
Houman Khosravani
Jennifer Mandzia, Al
Oje Imoukhuede, Ga
Ashkan Shoamanesh
MacKenzie Horn, Gra
Ayoola Ademola, Mi

Phase 3. 0.25 mg/kg TNK vs ALT

Randomized, Open, Registry-based, Non-inferiority

< 4.5 hr. Thrombolytic Eligible

N = 771 (TNK), 806 (ALT)

Non-inferiority demonstrated

No differences in sICH

Outcomes trend better in LVO with TNK

Summary

Background Intr
patients with ac
increase reperfu

Methods In this
were enrolled fr
if they were aged 18 years or older, with a diagnosis of ischaemic stroke causing disabling neurological deficit

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Intravenous tenecteplase compared with alteplase for acute ischaemi
open-lab
non-infe

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Phase 3. 0.25 mg/kg TNK vs ALT

Randomized, Open, Registry-based, Non-inferiority

< 4.5 hr. Thrombolytic Eligible

N = 771 (TNK), 806 (ALT)

Non-inferiority demonstrated

Weighted tiered dosing (10kg increments): >0.25mg/kg)

94% in CSCs

Summary

Background Intr
patients with ac
increase reperfu

Methods In this
were enrolled fr
if they were aged 18 years or older, with a diagnosis of ischaemic stroke causing disabling neurological deficit

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On going Phase 3 RCTs with tenecteplase vs alteplase <4.5 hours

Trial	Outcome	Target population	N
ATTEST-2	Superiority, mRS shift	Not EVT eligible	1870
TASTE-2	Superiority, mRS 0-1	LVO; favorable perfusion pattern	1024
TRACE-II	Non-inferiority, mRS 0-1	Not EVT eligible	1430

Other clinical trials with tenecteplase

Trial	Time window	Control arm	Target population	N
TEMPO-2	12	SOC	minor stroke with proven occlusion	1274
BRIDGE-TNK	4.5	no lytic	LVO	542
DIRECT-TNK	4.5	placebo	Mechanical thrombectomy	530
RESILIENT	4.5-12	placebo	Non-LVO	642
TIMELESS	> 4.5 < 24	placebo	LVO with penumbra	456
ETERNAL	< 24	SOC	Anterior Circ LVO with penumbra	740
POST-ETERNAL	< 24	SOC	Basilar artery occlusion	688

Tenecteplase as stroke Thrombolytic (as of July 2022)

Data supports tenecteplase as a thrombolytic option

Data indicates at least non-inferiority to alteplase

Possible superiority in early recanalization, safety, 90-day mRS, but confirmation required

Implications for non-TNK clinical trials

- Regulatory: Off-label of thrombolytic use in FDA regulated trials seeking new indication for a drug or device in addition to lytic.

- Design: Trial could limit to one drug but that has recruitment rate and generalizability issues. Currently ~ 20% lytic cases in US are with TNK

- Statistics: If ALT and TNK have different effects – sICH, recanalization rates – how does that affect trial planning, assumptions of effect size for the non-lytic intervention being tested? Stratify randomization sufficient?