

# Presenter Disclosure Information

**Dr Bruce Campbell** MBBS BMedSc PhD FRACP FAHMS

Determining The Optimal Dose Of Tenecteplase Before Endovascular Thrombectomy (EXTEND-IA TNK Part 2): A Multicenter, Randomized, Controlled Trial

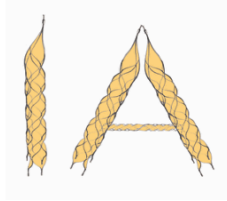
## **FINANCIAL DISCLOSURE:**

Supported by grants from the Australian Government National Health and Medical Research Council (1043242, 1035688, 1113352, 1111972), and National Heart Foundation of Australia (100782).

## **UNLABELED/UNAPPROVED USES DISCLOSURE:**

intravenous tenecteplase for ischemic stroke

# EXTEND -



# TNK II

Determining The Optimal Dose Of Tenecteplase Before Endovascular Thrombectomy

A randomized controlled trial of  
0.40mg/kg tenecteplase versus 0.25mg/kg tenecteplase  
prior to endovascular thrombectomy

Bruce Campbell

Co-PI and Medical Coordinator

Peter Mitchell

Co-PI and Head of Neurointervention

Stephen Davis and Geoffrey Donnan

Co-chairs Steering Committee

Acknowledging support from:



Australian Government

National Health and Medical Research Council

ClinicalTrials.gov NCT03340493



RMH Comprehensive Stroke Centre



# Background

- “Bridging” thrombolysis + thrombectomy remains standard of care for eligible patients with large vessel occlusion
- There are often delays to thrombectomy during inter-hospital transfers (especially from rural sites) and some endovascular procedures will fail due to poor access etc
- Enhanced IV lytic strategies therefore have potential to improve outcome

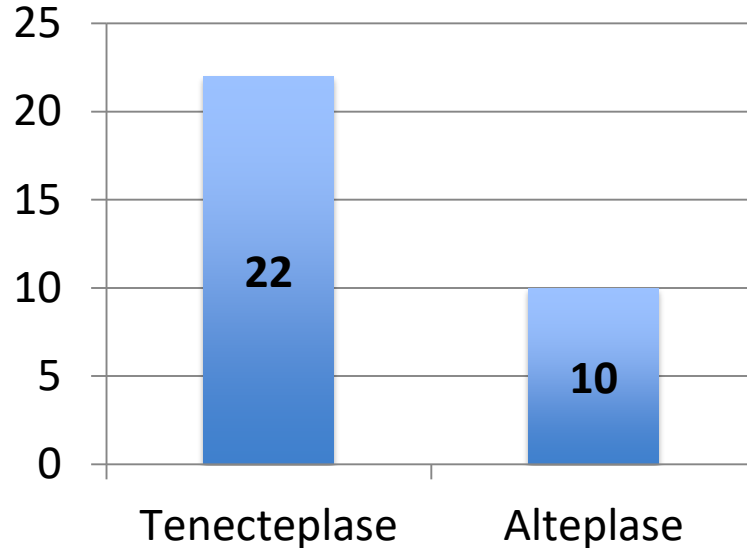


# Background

- Tenecteplase is a genetically modified tPA with greater fibrin specificity and longer half-life permitting convenient single-bolus administration
- This eliminates bolus-infusion gap that often occurs with alteplase and ensures the entire lytic dose is given without infusion interruption
- Tenecteplase is less expensive than alteplase in many countries and is the standard lytic for ST-elevation myocardial infarction
- The original EXTEND-IA TNK trial (NEJM 2018) showed improved reperfusion and clinical outcome with tenecteplase versus alteplase



## Substantial reperfusion at initial angiogram (TICI 2b/3 or no retrievable thrombus)



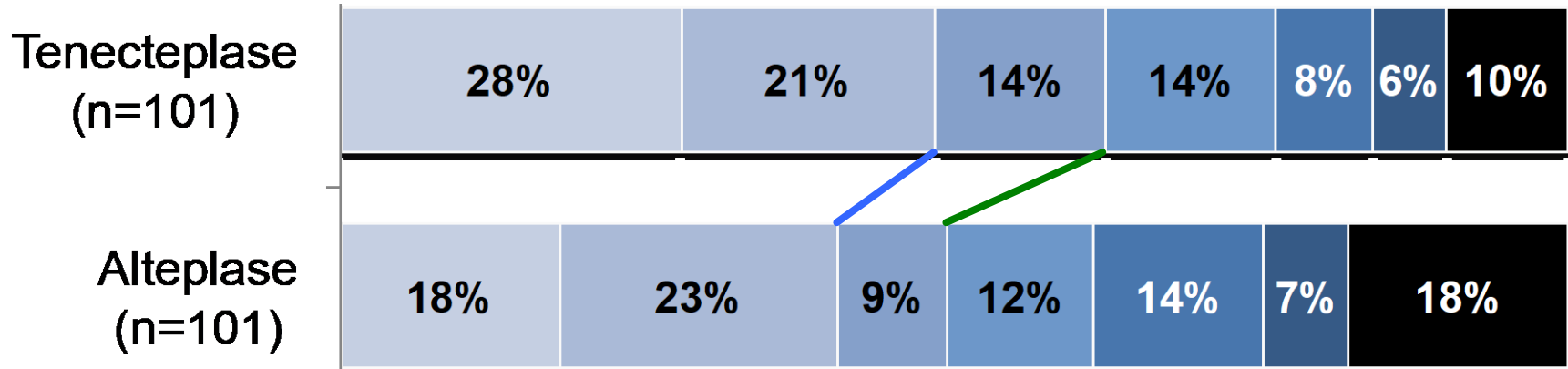
risk difference 0.12 (95%CI 0.02-0.21)  
adjusted odds ratio: 2.6 (1.1-5.9)

non-inferiority  $p=0.002$   
superiority  $p=0.02$



# Day 90 mRS

## Modified Rankin scale



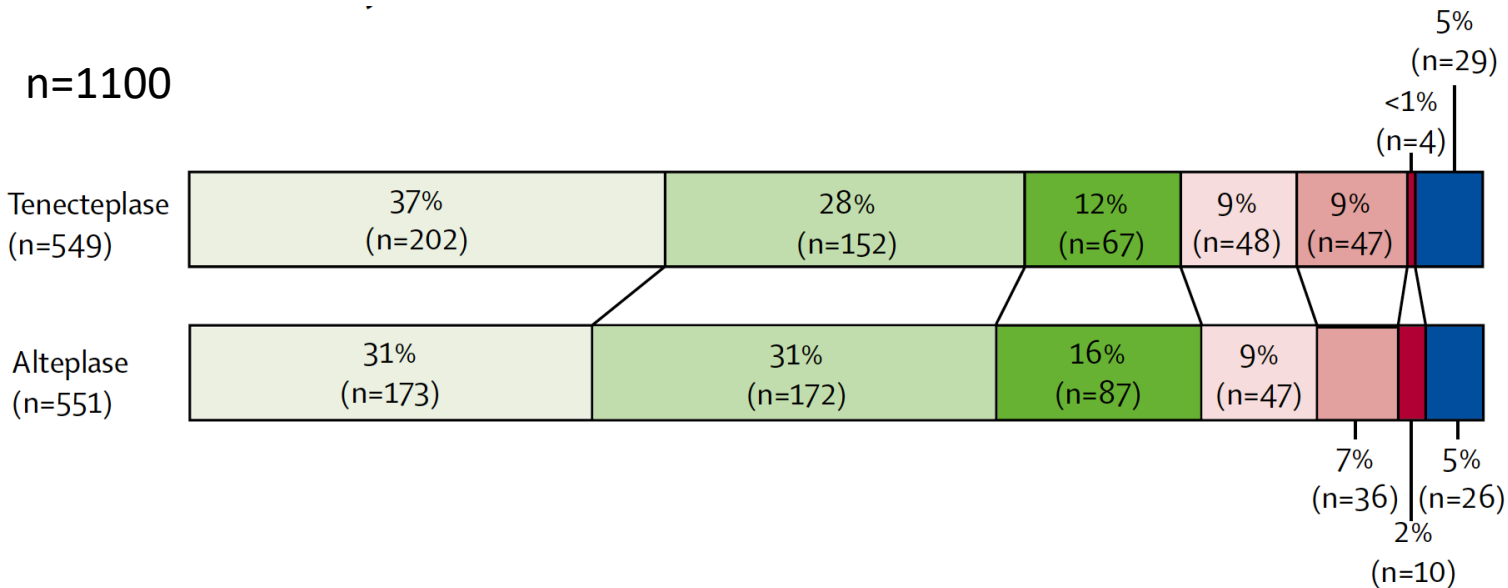
**ordinal cOR 1.7 (1.0-2.8), p=0.037 (adjusted age, NIHSS)**

**mRS 0-2 or no change from BL 65% vs 52%, p=0.06**

**mRS 0-1 or no change from BL 52% vs 43%, p=0.23**

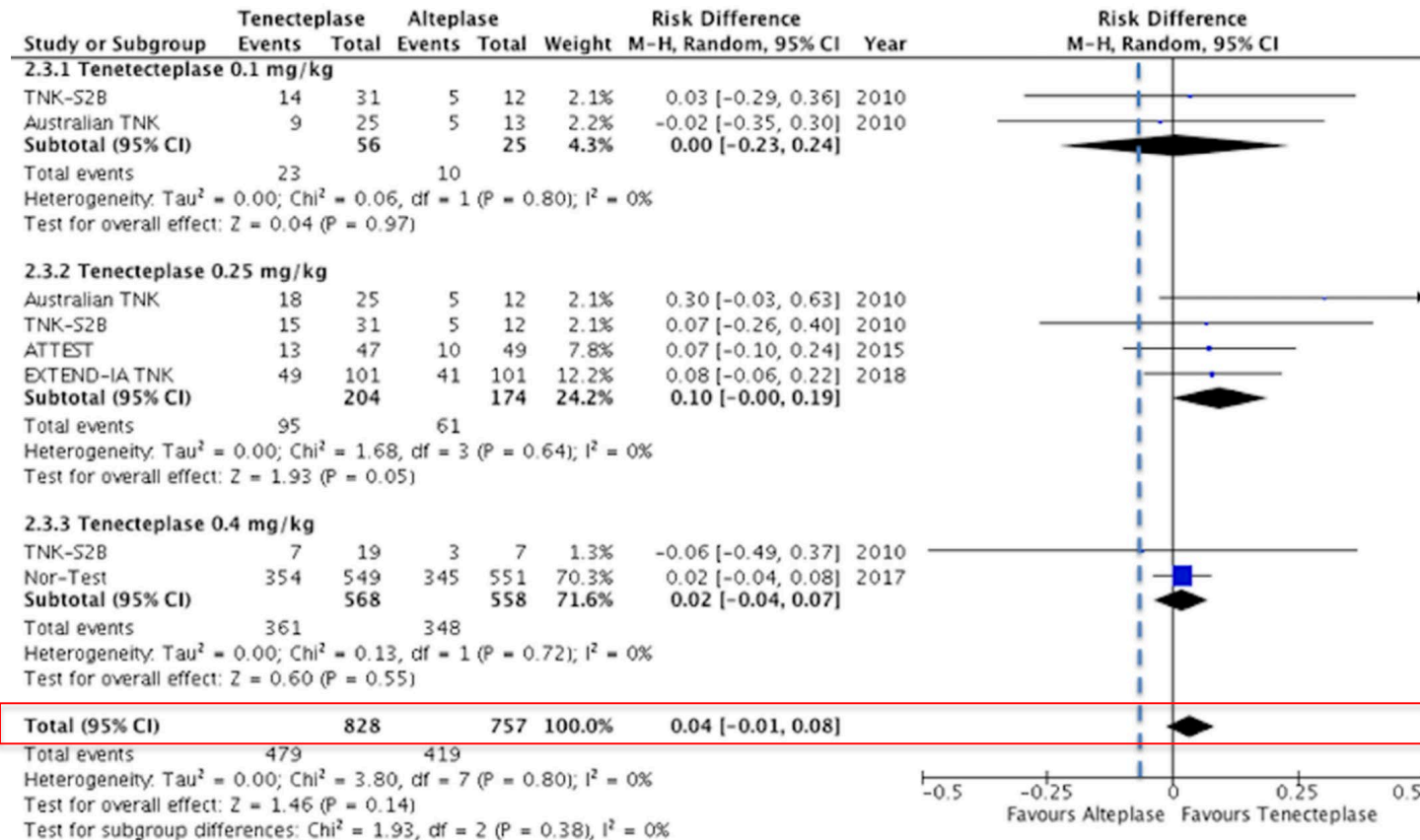


# NOR-TEST



- 0.40mg/kg TNK appeared similar to alteplase (not a formal non-inferiority study)
- no significant difference in symptomatic ICH BUT
- very mild stroke population (median NIHSS 4, 75% had NIHSS 0-7)
- 17% mimics

# Non-inferiority Meta-analysis



Overall for mRS 0-1 outcome the lower 95% CI bound of -1% fell within all of the assessed noninferiority margins of -6.5%, -5%, and -1.3%, meeting all criteria for declaration of noninferiority



# 2019 AHA Guidelines

## 3.6. Other IV Fibrinolytics and Sonothrombolysis

3.6. Other IV Fibrinolytics and Sonothrombolysis	COR	LOE
<p><b>1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.</b></p> <p>IV tenecteplase (0.25 mg/kg bolus, maximum 25 mg) was compared with IV alteplase (usual dose of 0.9 mg/kg over 60 minutes, maximum 90 mg) in the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke).<sup>178</sup> This multicenter trial randomized 202 patients without previous severe disability and with documented occlusion of the internal carotid artery, proximal MCA (M1 or M2 segments), or basilar arteries presenting within 4.5 hours of symptom onset to receive 1 of these 2 fibrinolytic agents. Primary end point was reperfusion of &gt;50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The trial was designed to test for noninferiority and, if noninferiority proven, for superiority. Secondary outcomes included the mRS score at 90 days. Median NIHSS score was 17. The primary end point was achieved by 22% of patients treated with tenecteplase versus 10% of those treated with alteplase (<math>P=0.002</math> for noninferiority and 0.03 for superiority). In an analysis of secondary end points, tenecteplase resulted in better functional outcomes at 90 days on the basis of the ordinal shift analysis of the mRS score (common OR [cOR], 1.7 [95% CI, 1.0–2.8]; <math>P=0.04</math>) but less robustly for the proportion who achieved an mRS score of 0 to 1 (<math>P=0.23</math>) or 0 to 2 (<math>P=0.06</math>). sICH rates were 1% in both groups.</p>	IIb	B-R
<p><b>2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.</b></p> <p>IV tenecteplase has been compared with IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase.<sup>179–182</sup> In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion.<sup>182</sup> Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.</p>	IIb	B-R

0.25mg/kg for large vessel occlusion

0.40mg/kg for mild stroke without large vessel occlusion



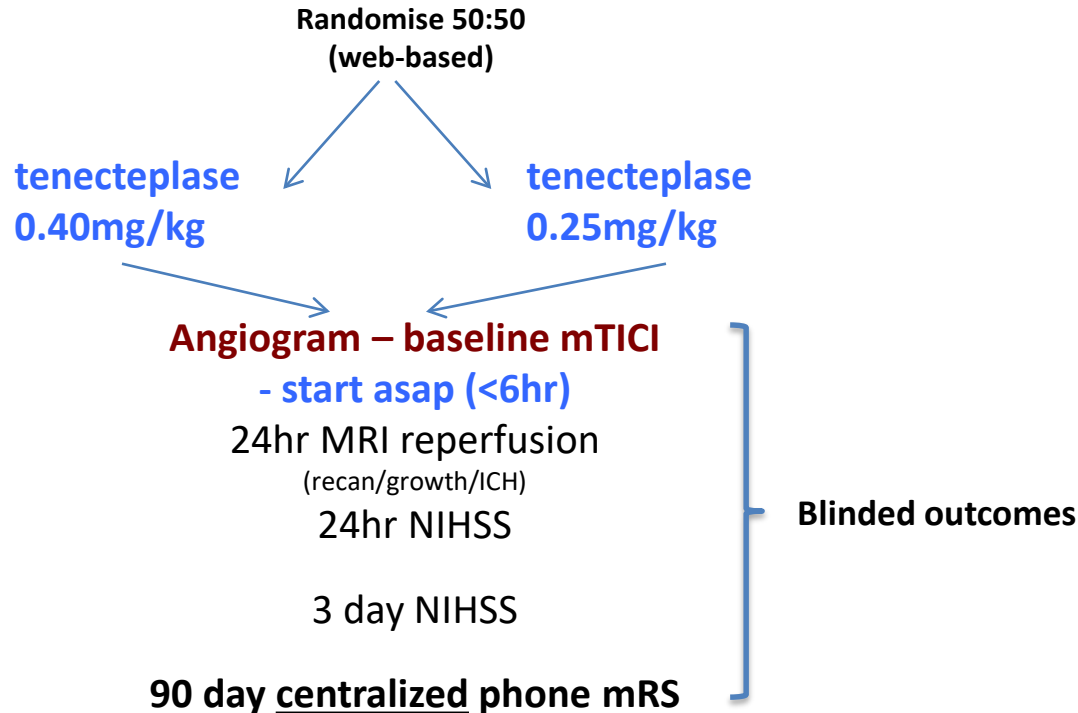
# Aim and Hypothesis

- Aim: to determine the optimal dose of tenecteplase for stroke
  - 0.40mg/kg vs 0.25mg/kg
  - those with large vessel occlusion, largest clot burden, more likely to benefit from increased dose
  - would only increase from 0.25mg/kg to 0.40mg/kg if higher dose superior → superiority (not non-inferiority) design
- Hypothesis: that 0.40mg/kg tenecteplase would be more effective than 0.25mg/kg tenecteplase in establishing reperfusion prior to endovascular thrombectomy when administered within 4.5h of onset of symptoms



**TRIAL DESIGN** – PROBE superiority design  
(n=300-656 – interim sample size recalculation final n=300)

**“LVO” patients eligible for thrombolysis**



27 centers in Australia  
and 1 in New Zealand  
(including rural telemedicine  
and 1 Mobile Stroke Unit)

Abbreviated 1 page consent  
form or deferral of consent  
for emergency treatment



**Inclusion criteria:**

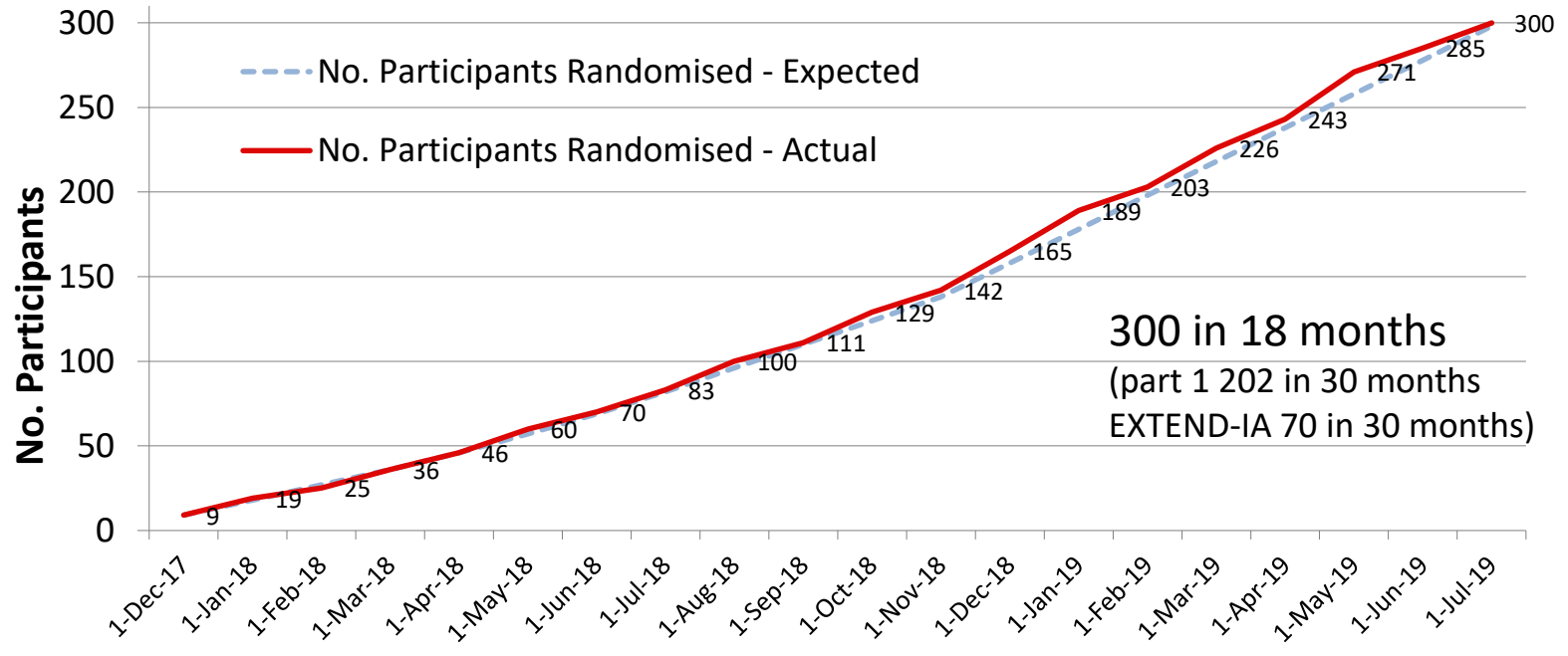
- Age  $\geq 18$  years (no upper limit), No NIHSS restrictions
- Ischemic stroke eligible for intravenous thrombolysis within 4.5 hours of stroke onset
- Imaging
  - Major vessel occlusion – **ICA, M1, M2 or basilar** amenable to clot retrieval
  - no maximum core volume (but CTP performed)
- Informed consent obtained from patient or legal representative or emergency treatment with consent to continue in some jurisdictions

**Exclusion criteria:**

- Severe premorbid disability (mRS $\geq 4$ )
- Contra-indication to imaging with contrast agents
- Rapid neurological recovery (investigator's discretion) prior to randomization.

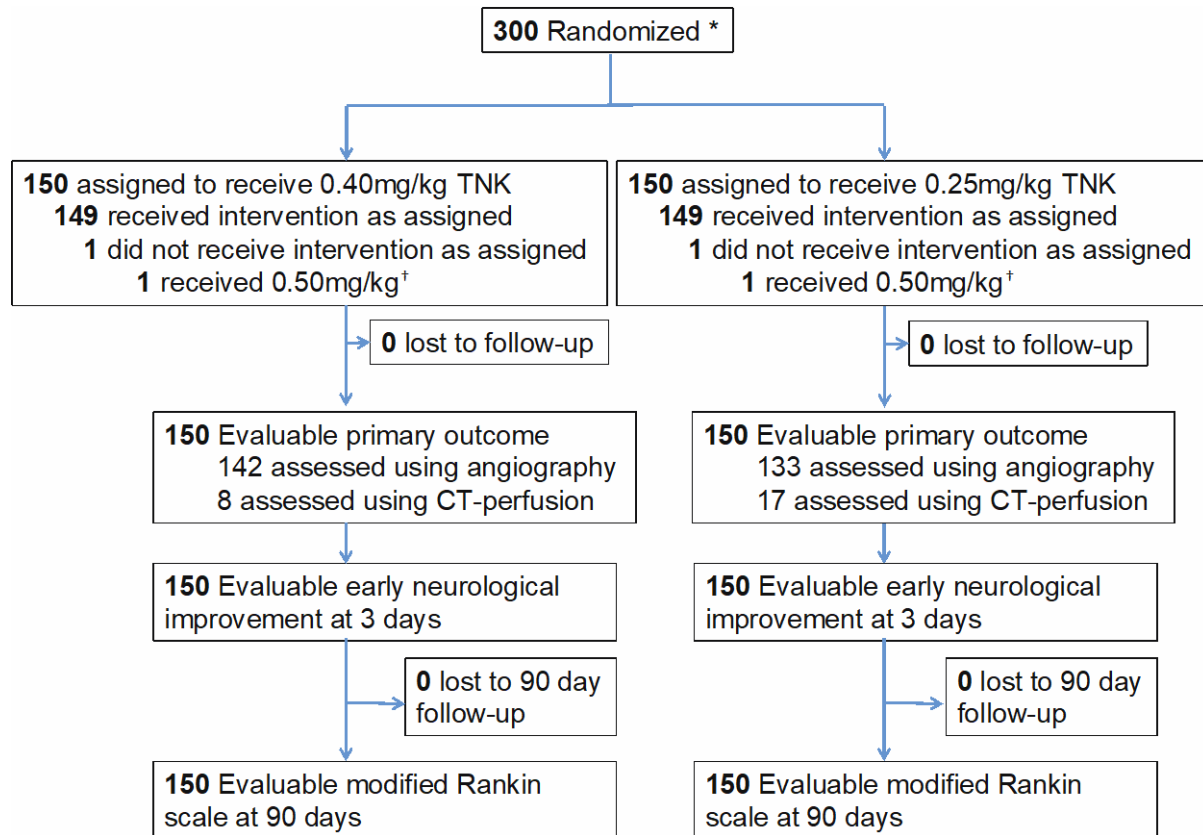


## EXTEND-IA TNK II Recruitment



# CONSORT trial profile

EXTEND - IA TNK II



\* The number of patients assessed for eligibility is unknown as screening logs were not maintained.)

† One patient in each group received the 0.50mg/kg tenecteplase dose recommended for myocardial infarction. Neither patient achieved reperfusion at the time of the initial angiogram and neither developed hemorrhagic transformation



**Australia: Royal Adelaide Hospital** (40) T.J. Kleinig, R. Scroop, J. Taylor, C. Kurunawai, E. Cheong, A. Balabanski, M. Waters, J. Harvey, L. Cagi, N. Chia, A. Khoo, R. Drew, J. Cranefield; **Royal Melbourne Hospital** (27) and **Melbourne Mobile Stroke Unit** (26) B.C.V. Campbell, P.J. Mitchell, S.M. Davis, G.A. Donnan, M.W. Parsons, N. Yassi, B. Yan, R.J. Dowling, S. Bush, T.J. Oxley, T.Y. Wu, D. Shah, H. Zhao, C. Williams, E. Rodrigues, P. Salvaris, F. Alemseged, F.C. Ng, A. Balabanski, A. dos Santos, J-L Ng, S. Coote, C. Beltrame, E. Mackey, K. Lagma, A. McDonald, D. Jackson, J Tsoleridis, L. Pesavento; **Austin Hospital** (25) V. Thijs, M. Simpson, M. Brooks, H. Asadi, A. Jhamb, A. Brodtmann, F.C. Ng, A. Warwick, B. Coulton, D. Young; **Princess Alexandra Hospital** (23) D. Shah, H. Brown, K. Redmond, D. Leggett, J. Whitley, C. Bendall; **Western Hospital** (18) T. Wijeratne, H. Tu, E. Mackey, S. Celestino, E. Low; **Gold Coast University Hospital** (15) P. Bailey, H. Rice, L. de Villiers, A. Sabet, S. Mishra, B. Urbi; **Box Hill Hospital** (14) H.M. Dewey, P.M.C. Choi, T. Frost, J. Chen, S.K. Chen, M.Y.Tang, K. Nowak, R. Martins, C. Senanayake, C.H. Yam, D. Barber, F.M. Bridge, J.Z.W. Wong, G. Thomas, J. Liu, N. Pachani, R. Lee; **Ballarat Base Hospital** (12) T Kraemer, R Sahathevan, C Hair; **Royal North Shore Hospital** (11) M. Krause, T.J. Harrington, B. Steinfort, K. Faulder, S. Day. **Liverpool Hospital** (10) D. Cordato, A.J. McDougall, C. Cappelen-Smith, J. Wenderoth, A. Cheung, N. Manning, **Lyell McEwin Hospital** (8) D. Field, A. Moey, M.J. Waters, V. Maxwell; **Monash Medical Centre** (5) H. Ma, T. Phan, S. Singhal, B Clissold, J. Ly, W. Chong, R.V. Chandra, L-A. Slater, H. Asadi; **Gosford Hospital** (5) B. O'Brien, J. Evans, D. Alchin; **University Hospital Geelong** (5) B Clissold, P. Talman, C. Shaw, A. Malhotra, R Makonahalli; **John Hunter Hospital** (5) F. Miteff, N. Spratt, C. Garcia-Esperon, L. Kaauwai; **Southwest Healthcare Warrnambool** (4) A. Clissold, P. Groot; **Alfred Hospital** (4) G. Cloud, A. Madan, C. Chung, A. Moore; **Northeast Health Wangaratta** (4) L. Bolitho, R. Krones, N. Bilkhu, H. Haines; **Albury Base Hospital** (3) F. Eversheim, L. Bonavia, **Goulburn Valley Base Hospital Shepparton** (3) A. Bhattacharya; **Bendigo Base Hospital** (3) R.D. Smith, E. Ray, T. Coupland; **Latrobe Regional Health Traralgon** (2) A. Wright; **Campbelltown Hospital** (2) A. Mamun; **Royal Prince Alfred Hospital** (1) J. Worthington, T. Ang, S. Winters, D. Brunacci, K. Tastula; **Royal Brisbane and Women's Hospital** (1) A.A. Wong, C. Muller, A. Coulthard, J. Clouston, K. Mitchell, K. Mahady; **Bankstown-Lidcombe Hospital** (1) F. O'Rourke, Y. Liu, Y-M Kuang, A. Wu; **Victorian Stroke Telemedicine service (Ambulance Victoria)** Karen Smith, Michael Stephenson, Emily Andrew, Christopher Bladin, Matthew Lightermoet, Matthew Lee-Archer, Felix C Ng, Marion Simpson,

**New Zealand: Christchurch Hospital** (23) T.Y. Wu, J.N. Fink, J. Beharry, W. Collicutt, A. Laing, M Krauss, J. Eagle.

- Chief co-ordinator – Amy McDonald
- CRO: Neuroscience Trials Australia – Michele Sallaberger
- DSMB: B. Snow (Chair), J. Kolbe, R. Stark, J. King, R. Macdonnell, J. Attia, C. D'Este (Independent Statistician)
- iSchemaView (RAPID) – G Albers, R Bammer
- Patients and families



# Demographics

EXTEND - IA TNK II

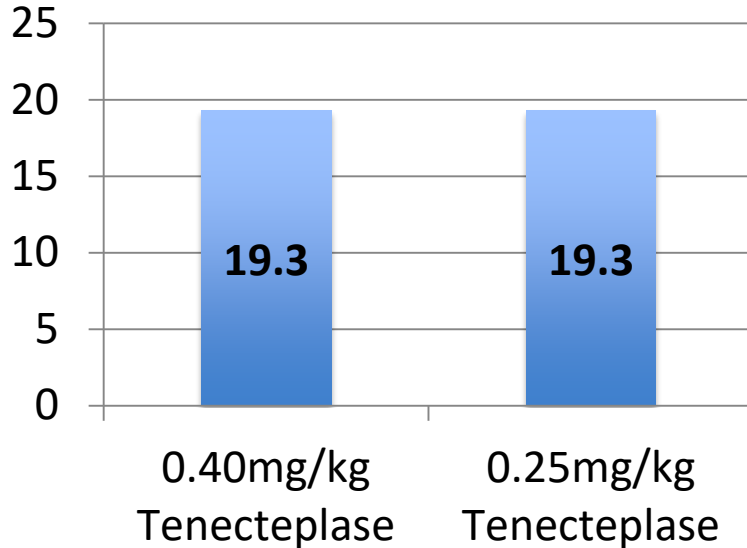
Patient Characteristics	0.40mg/kg Tenecteplase	0.25mg/kg Tenecteplase
Number	150	150
Age – yr: Mean (SD)	71.7 (11.3)	73.8 (12.8)
Male sex – no. (%)	77/150 (51%)	82/150 (55%)
NIHSS score: Median (IQR)	17 (11-21)	16 (9-20)
Onset to Lysis – min Median (IQR)	132 (96-180)	133 (102-180)
Lysis to puncture – min Median (IQR)	45 (26-86)	48 (25-90)
<b>Site of vessel occlusion (%)</b>		
Internal carotid artery (ICA)	24%	20%
Basilar artery	5%	4%
First segment of middle cerebral artery (M1)	50%	53%
Second segment of middle cerebral artery (M2)	21%	23%



# Primary outcome



## Substantial reperfusion at initial angiogram (TICI 2b/3 or no retrievable thrombus)



unadjusted risk difference 0.0% (95%CI -8.9 to 8.9%)  
adjusted risk ratio: 1.03 (95%CI 0.66 to 1.61), p=0.89

very similar to tenecteplase group in EXTEND-IA TNK  
(22% had no retrievable thrombus by time of angiogram)

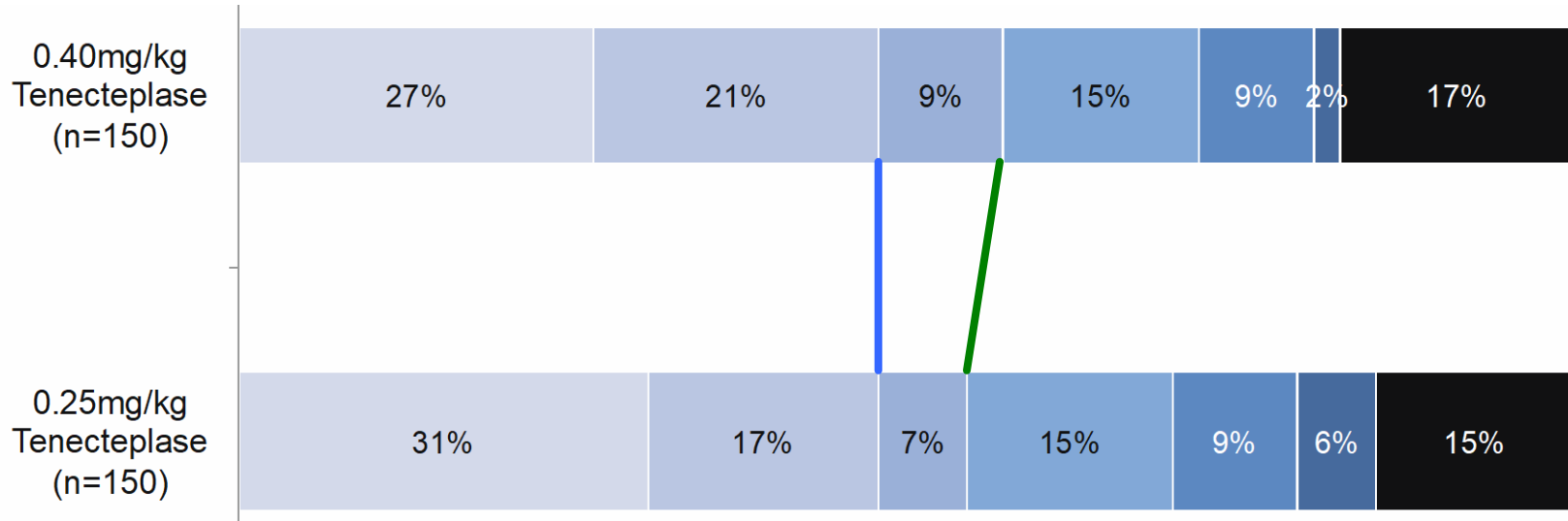


# Secondary outcomes



## Day 90 mRS

## Modified Rankin scale



**Ordinal genOR 0.96 (0.74-1.24), p=0.73 (adjusted age, NIHSS)**

**mRS 0-1 or no change from BL 49% vs 49%, p=0.69**

**mRS 0-2 or no change from BL 59% vs 56%, p=0.40**



# Safety outcomes

Outcome	0.40mg/kg Tenecteplase	0.25mg/kg Tenecteplase	RR (95%CI)	p value
Death	26/150 (17%)	22/150 (15%)	1.27 (0.77-2.11)	0.35
SICH *	7/150 (4.7%)	2/150 (1.3%)	3.5 (0.74-16.62)	0.12
PH §	4/150 (2.7%)	6/150 (4.0%)	0.67 (0.19-2.32)	0.52

\* pre-specified SITS definition = PH2 +  $\geq 4$  point increase NIHSS or symptomatic SAH  
 NB 4/7 SICH in 0.40mg/kg group a/w intraprocedural wire perforation

§ PH = parenchymal hematoma



# Limitations

- Results apply to ischemic stroke patients with large vessel occlusion who are eligible for thrombolysis.
  - unlikely that non-LVO patients would require higher dose
  - use of the reperfusion outcome (biological efficacy) complements functional outcomes which suffer random variation due to unrelated factors
- Adaptive sample size re-estimation deemed that even n=656 would not have power to detect a 15% effect
  - the minimal clinically important difference in reperfusion based on expert opinion is 3-5%\* - would require 2400-6400 patients for 80% power

\* Lin & Saver Stroke 2019, 50(12):3519-3526



# Conclusions

- Compared to tenecteplase 0.25mg/kg, **tenecteplase 0.40mg/kg** prior to endovascular thrombectomy
  - did not improve cerebral reperfusion or functional outcomes
  - numerically more symptomatic ICH (but 4/7 in 0.40mg/kg group were a/w wire perforations and PH not increased)
- There was no advantage of increasing dose to 0.40mg/kg
  - however, window of safety if inadvertently overestimate weight
- 0.25mg/kg tenecteplase is likely the most appropriate dose for stroke



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

Available online now at [jama.com](https://www.jama.com)

DOI: 10.1001/jama.2020.1511