EXTEND - IA TNK

Extending the time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial using Tenecteplase

A randomized controlled trial of
0.25mg/kg tenecteplase versus 0.9mg/kg alteplase
prior to endovascular thrombectomy

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Background

- "Bridging" thrombolysis + thrombectomy remains standard of care for eligible patients with large vessel occlusion
- There are still delays to thrombectomy during inter-hospital transfers (especially from rural sites) and some IA procedures will fail due to poor arterial access
- Enhanced IV lytic strategies therefore have potential to improve outcome
- Tenecteplase is a genetically modified tPA with greater fibrin specificity and longer half-life permitting convenient single-bolus administration
  - tenecteplase has replaced alteplase as the standard lytic in STEMI
- Some previous studies have suggested improved reperfusion and clinical outcome with tenecteplase versus alteplase

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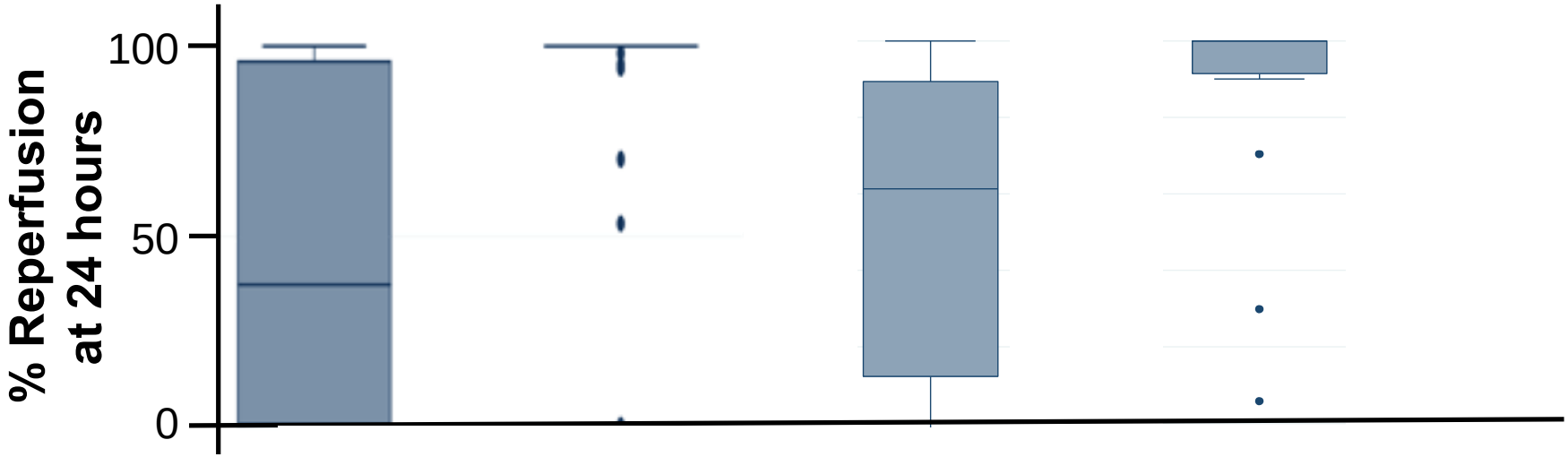
Reperfusion at 24hr



*** No ICA occlusion in TNK study and no data on 1st 1-2hr reperfusion rates**

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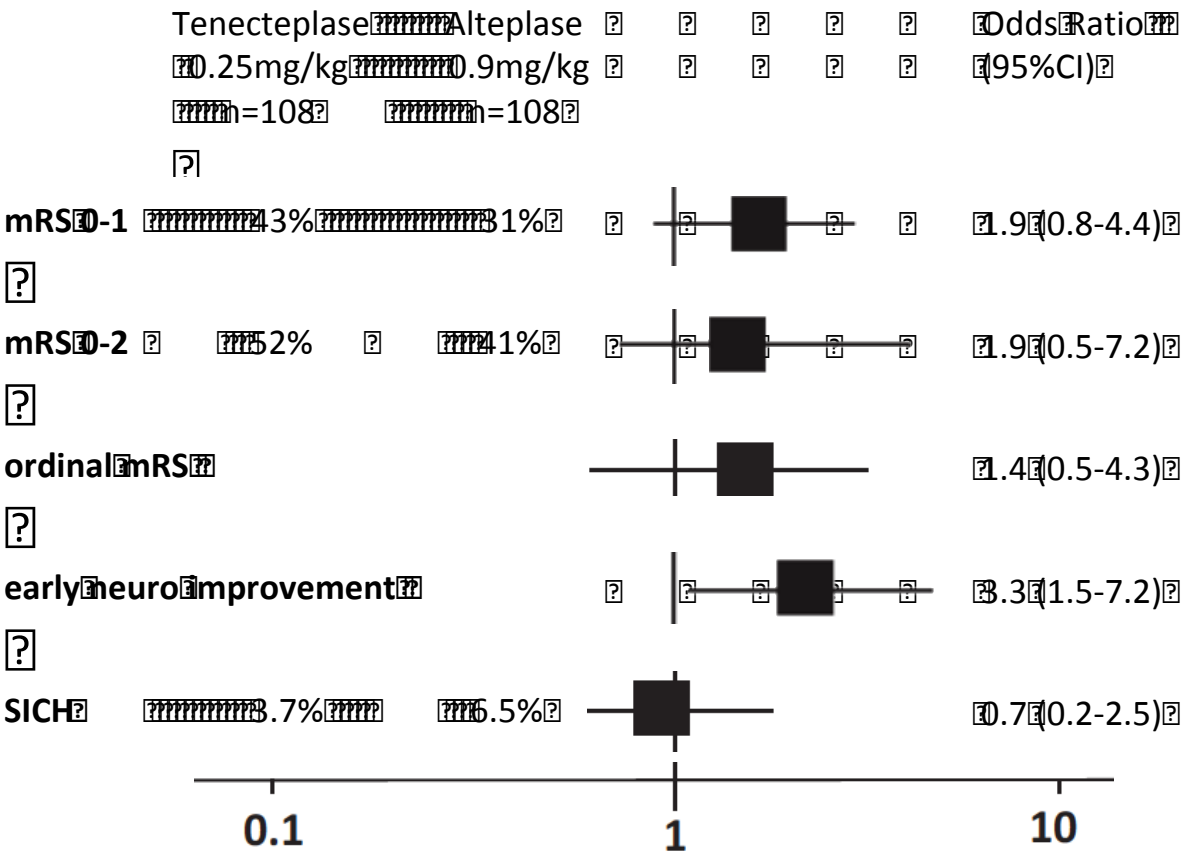
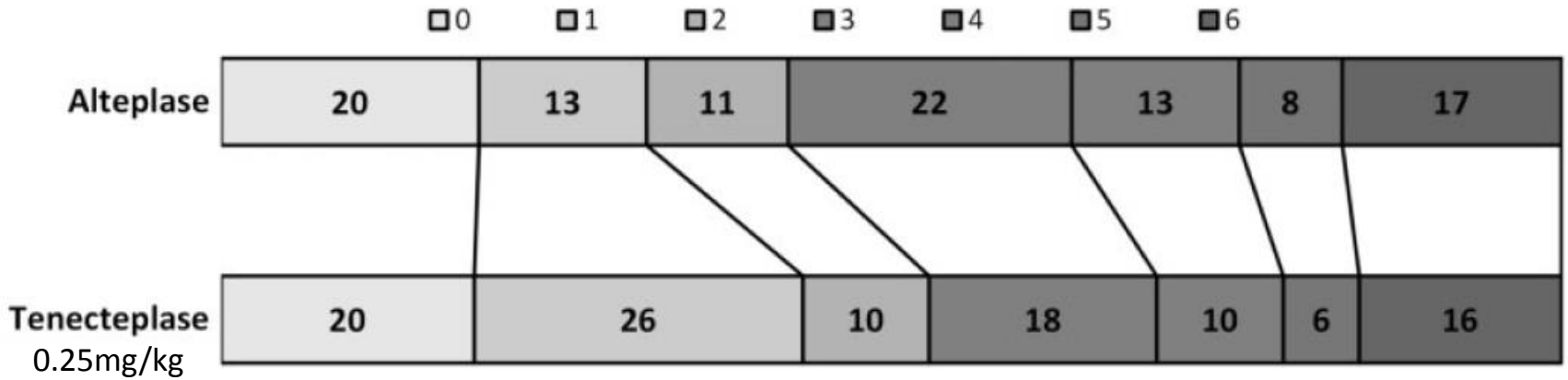
Individual patient data meta-analysis



Adjusted for age, NIHSS, onset to treatment time and trial

Huang et al IJS 2016

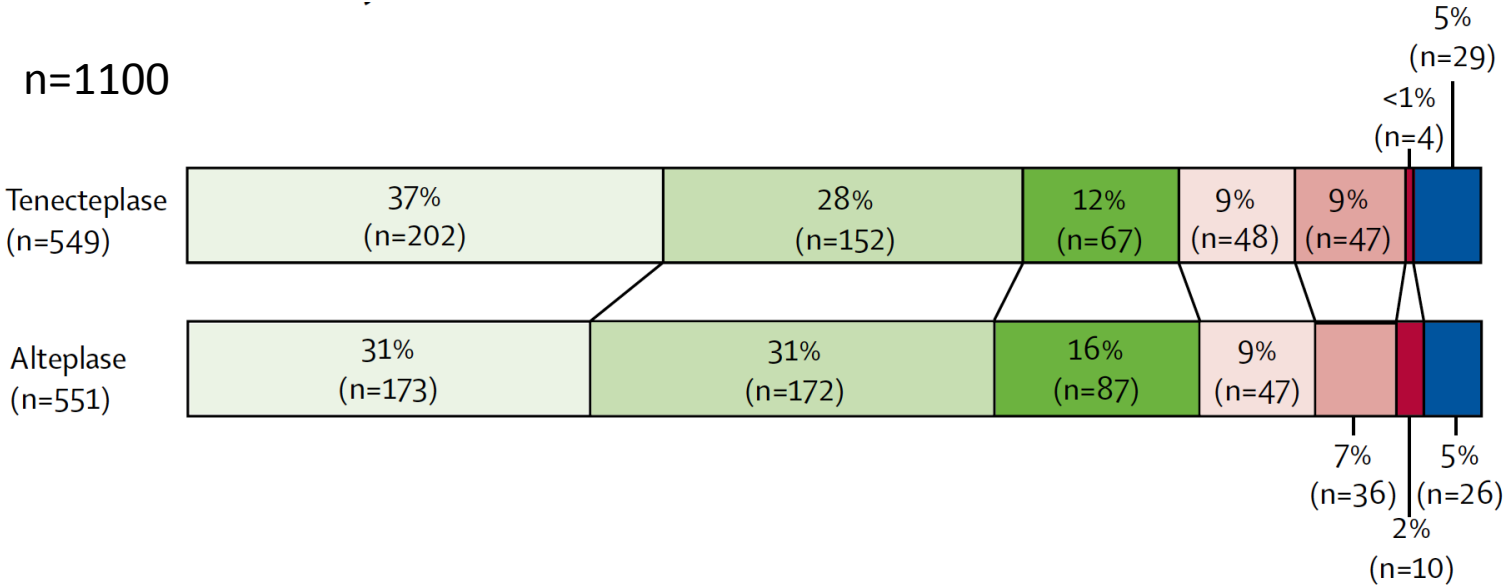
Individual patient data meta-analysis



(ordinal analysis trend but not statistically significant for superiority)
OR 1.4 (0.5-4.3)

Huang et al IJS 2016

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, 15% large vessel occlusion

Logallo Lancet Neurol 2017

EXTEND-IA TNK HYPOTHESIS:
That tenecteplase is non-inferior to alteplase in achieving reperfusion at initial angiogram, when administered within 4.5 hours of ischaemic stroke onset, in patients planned to undergo endovascular therapy

TRIAL DESIGN

– investigator initiated, PROBE non-inferiority design,
  - non-inferiority margin 2.3% (50% of the lower 95%CI for proportion of substantial reperfusion in ESCAPE, EXTEND-IA & SWIFT PRIME 7.5% (95%CI 4.6-11.5%)
– test superiority if non-inferiority demonstrated
– interim sample size recalculation* at n=100 (range 120-276) – final sample n=202

*Mehta and Pocock Stat Med 2011

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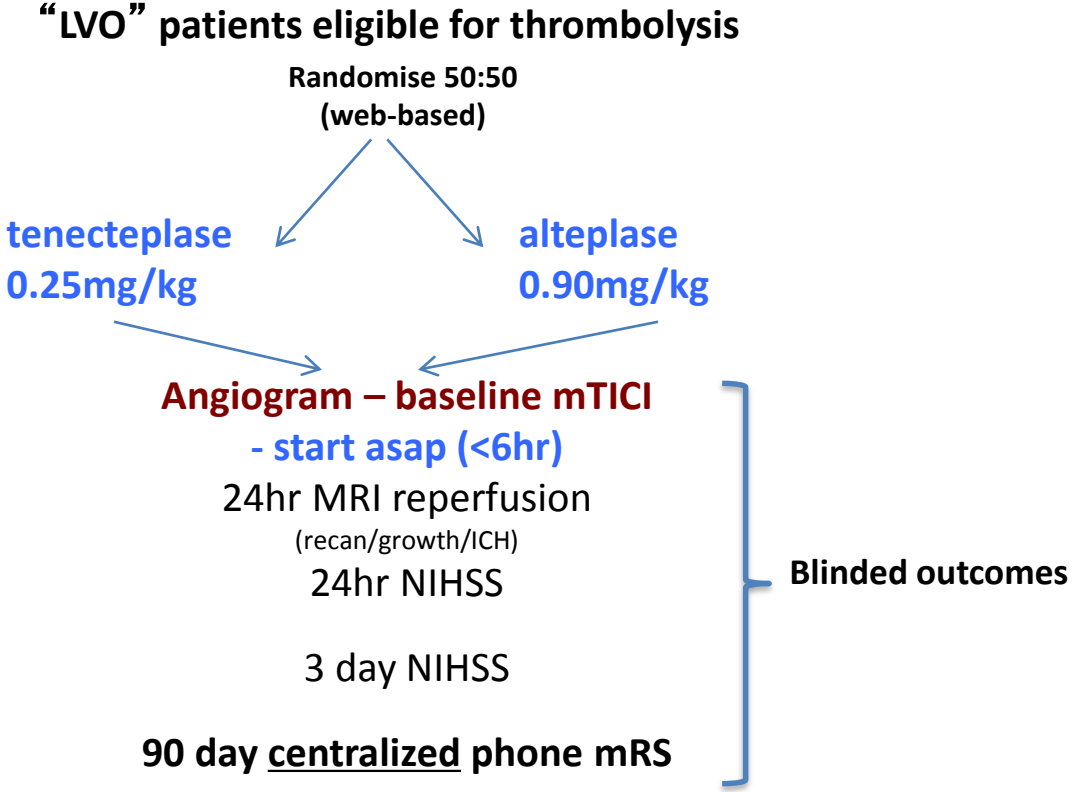

13 centers in Australia and New Zealand (including 3 "spoke" sites)

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

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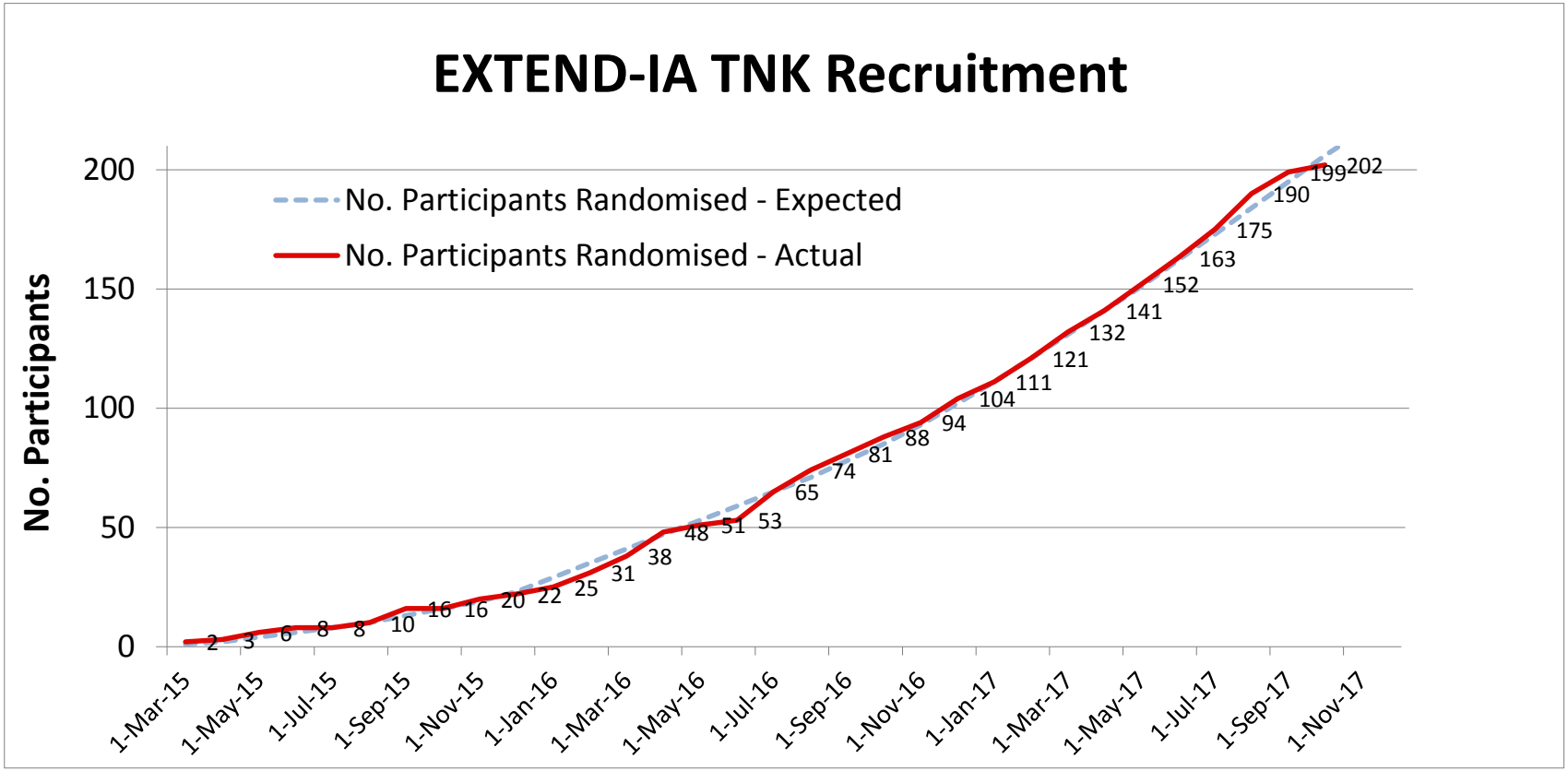
Inclusion criteria:

- Age ≥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 (removed after ~80 patients enrolled but CTP performed)
- Able to commence intra-arterial therapy within 6 hours of onset
- Informed consent obtained from patient or legal representative
  or deferral for emergency treatment in some jurisdictions

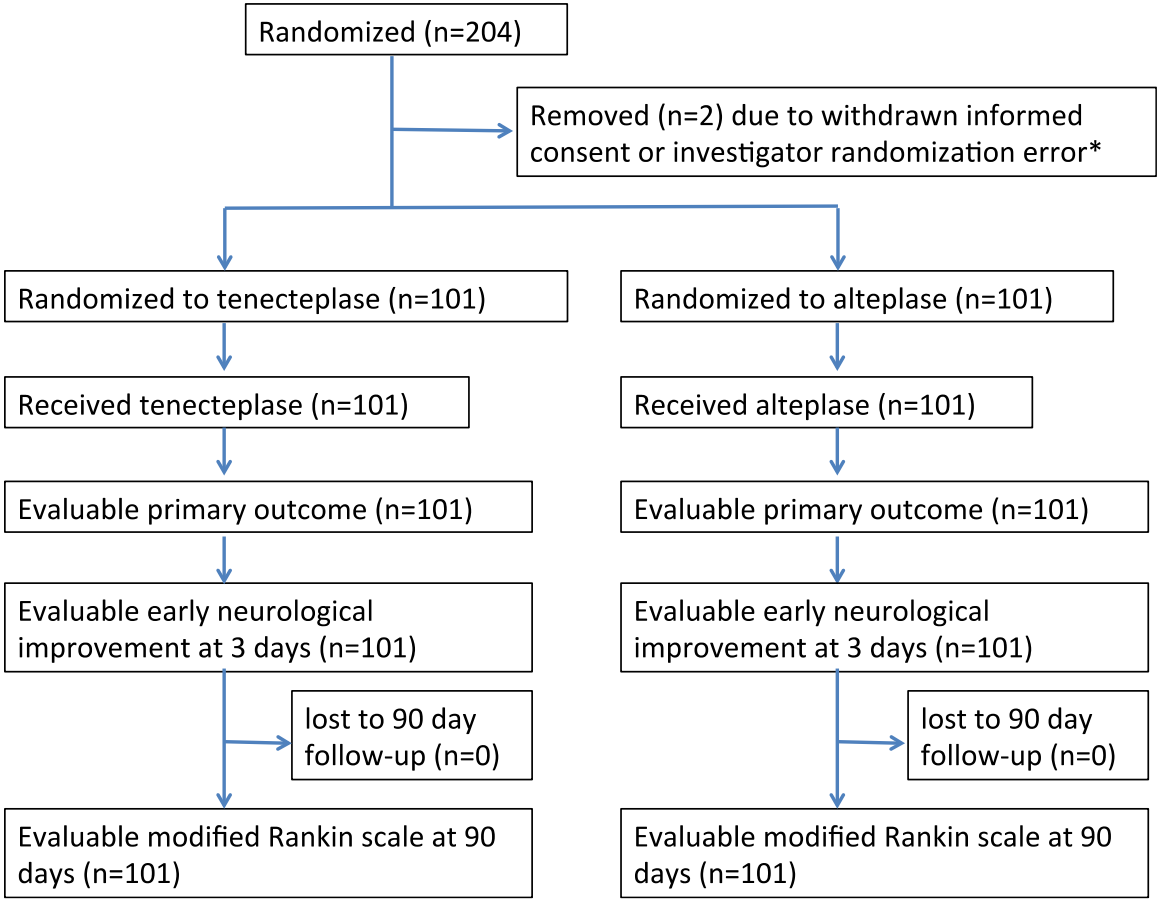
Exclusion criteria:

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


EXTEND-IA TNK Recruitment
No. Participants
200
150
100
50
0
No. Participants Randomised - Expected
No. Participants Randomised - Actual
2
3
6
8
8
10
16
16
20
22
25
31
38
48
51
53
65
74
81
88
94
104
111
121
132
141
152
163
175
190
199
202
1-Mar-15
1-May-15
1-Jul-15
1-Sep-15
1-Nov-15
1-Jan-16
1-Mar-16
1-May-16
1-Jul-16
1-Sep-16
1-Nov-16
1-Jan-17
1-Mar-17
1-May-17
1-Jul-17
1-Sep-17
1-Nov-17

CONSORT trial profile

EXTEND - IA TNK



intention to treat population same as per protocol population

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Demographics

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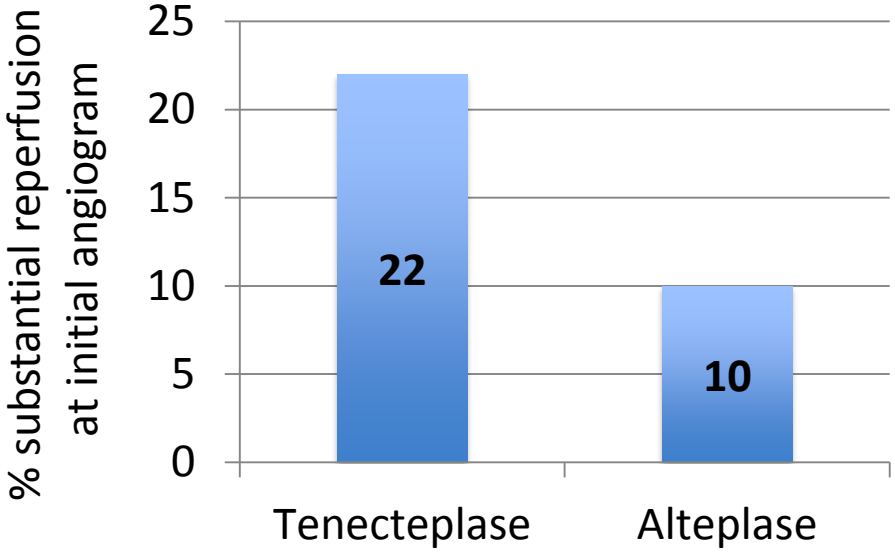
Patient Characteristics	Tenecteplase	Alteplase
Number	101	101
Age – yr: Mean (SD)	70.4 (15.1)	71.9 (13.7)
Male sex – no. (%)	58 (58%)	52 (52%)
NIHSS score: Median (IQR)	17 (12-22)	17 (12-22)
Onset to Lysis – min Median (IQR)	125 (102-156)	134 (104-176)
Lysis to puncture – min Median (IQR)	43 (25-57)	42 (30-63)
Site of vessel occlusion (%)		
Internal carotid artery (ICA)	24%	24%
Basilar artery	3%	3%
First segment of middle cerebral artery (M1)	59%	60%
Second segment of middle cerebral artery (M2)	15%	14%

Primary outcome

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



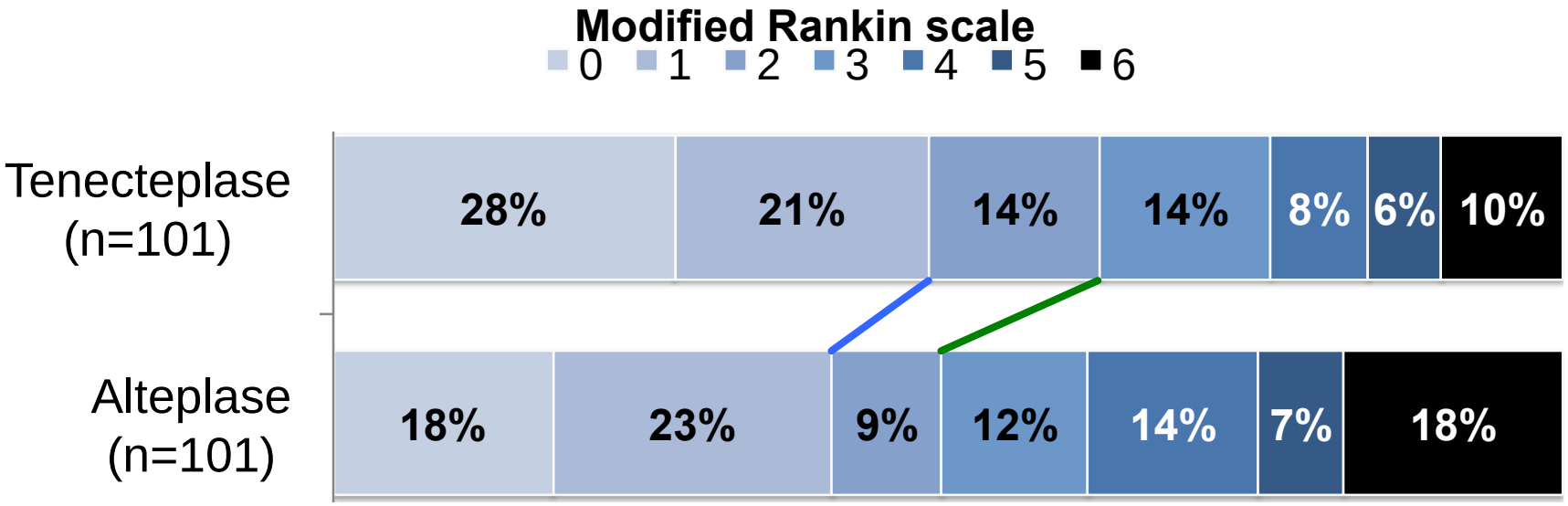
risk difference 0.12 (95%CI 0.02-0.21)
adjusted odds ratio: 2.6 (95%CI 1.1-5.9)

non-inferiority p=0.002
superiority p=0.02

very similar to EXTEND-IA – 4/35 (11%) had no retrievable thrombus by time of angiogram (longer lysis to puncture median 83min)

Secondary outcomes

Day 90 mRS

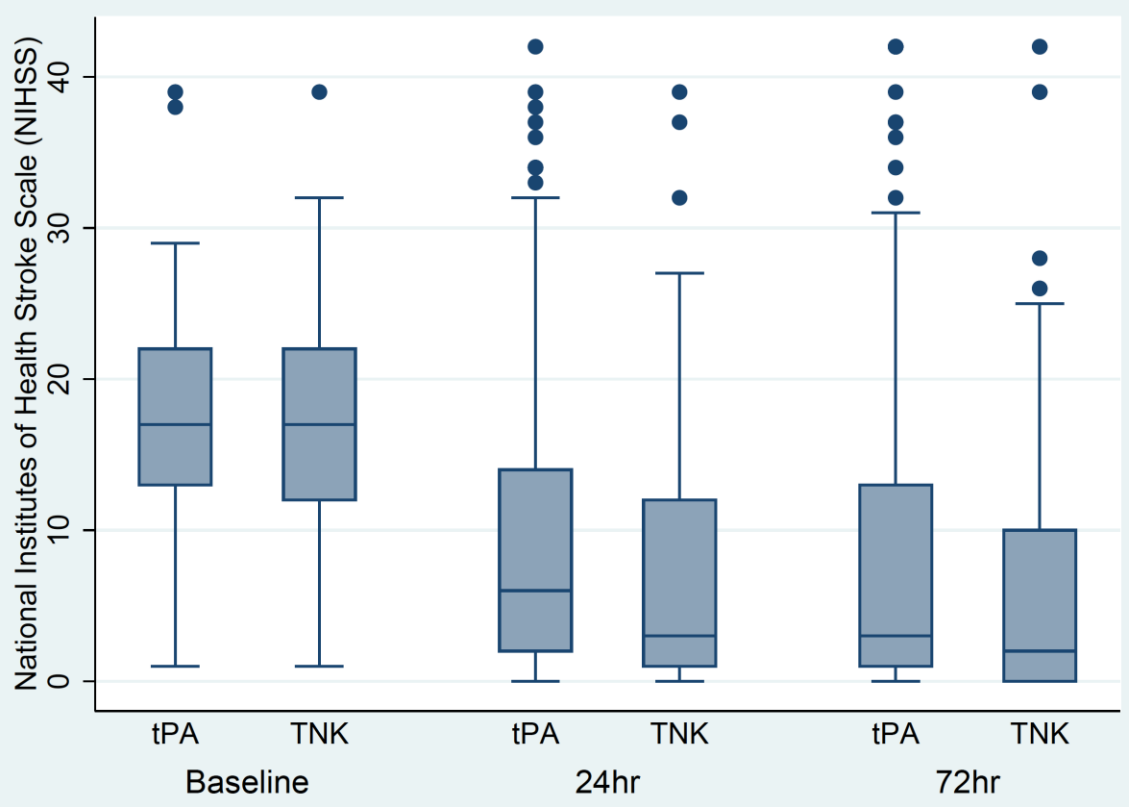


Ordinal cOR 1.7 (95%CI 1.0-2.8), p=0.037 (adjusted age, NIHSS)

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

Early neurological recovery



Reduction of ≥8 NIHSS points or reaching 0-1 by day 3

72% tenecteplase
vs 69% alteplase p=0.66

Safety outcomes

Outcome	Tenecteplase	Alteplase	OR (95%CI)	p value
Death	10/101 (10%)	18/101 (18%)	0.44 (0.18-1.1)	0.08
SICH *	1/101 (1%)	1/101 (1%)	1.0 (0.062-16.2)	0.99
PH §	6/101 (6%)	5/101 (5%)	1.2 (0.36-4.1)	0.76

** pre-specified SITS definition = PH2 + ≥4 point increase NIHSS*

§ *PH = parenchymal hematoma*

Limitations

- Results apply to ischemic stroke patients with large vessel occlusion who are eligible for thrombolysis.
  - ~13% of all ischemic stroke patients but contribute disproportionately to the disability burden

- We studied 0.25mg/kg tenecteplase based on previous data that demonstrated improved outcomes compared with 0.10mg/kg dosing.
  - The NOR-TEST results reported during the recruitment phase of EXTEND-IA TNK suggest that 0.40mg/kg TNK deserves further study

Conclusions

- Compared to alteplase 0.9mg/kg, **tenecteplase 0.25mg/kg** led to:
  - More frequent reperfusion at initial angiogram
    - NNT 9.1 to avoid thrombectomy procedure
  - Improved functional outcomes
  - No safety concerns
- Convenience of single bolus
  - fast, avoids transporting patients with infusion
- Reduced cost
  - drug cheaper, fewer endovascular devices required
    - US wholesale $5861.87 per 50 mg TNK
      vs $8800.36 per 100 mg alteplase

Implications

- Tenecteplase is an attractive alternative to alteplase prior to endovascular thrombectomy
- TASTE (Parsons/Levi) and ATTEST-2 (Muir) trials are ongoing testing 0.25mg/kg TNK vs alteplase in non-endovascular patients
- EXTEND-IA TNK part 2 underway comparing 0.40mg/kg vs 0.25mg/kg tenecteplase prior to endovascular thrombectomy NCT03340493

Acknowledgements

EXTEND - IA TNK

- Recruiting Sites

Australia: Royal Melbourne Hospital (56) B.C.V. Campbell, P.J. Mitchell, S.M. Davis, B. Yan, R.J. Dowling, S. Bush, N. Yassi, A. McDonald; Royal Adelaide Hospital (33) T.J. Kleinig, R. Scroop, J. Taylor, R. Drew, J. Cranefield; Box Hill Hospital (24) H.M. Dewey, C.F. Bladin, P.S. Loh, P.M. Choi, Z. Ross, G. Thomas; Austin Hospital (21) V. Thijs, M. Simpson, M. Brooks, B. Coulton, D. Young; Western Hospital (20) T. Wijeratne, H. Tu, S. Celestino, E. Low; Gold Coast University Hospital (16) P. Bailey, H. Rice, L. de Villiers, B. Urbi; John Hunter Hospital (10) F. Miteff, M.W. Parsons, C.R. Levi, L. Kaauwai; Princess Alexandra Hospital (5) D. Shah, H. Brown, K. Redmond, D. Leggett; Royal Brisbane and Women's Hospital (4) A.A. Wong, A. Coulthard; Monash Medical Centre (4) H. Ma, T. Phan, W. Chong, R.V. Chandra, L-A. Slater, K. Wong; Lyell McEwin Hospital (4) D. Field, V. Maxwell; Royal North Shore Hospital (2) M. Krause, T.J. Harrington, B. Steinfort, K. Faulder, S. Day.
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- Patients and families

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