TNK for stroke thrombolysis – TNK vs tPA within the Treatment Window

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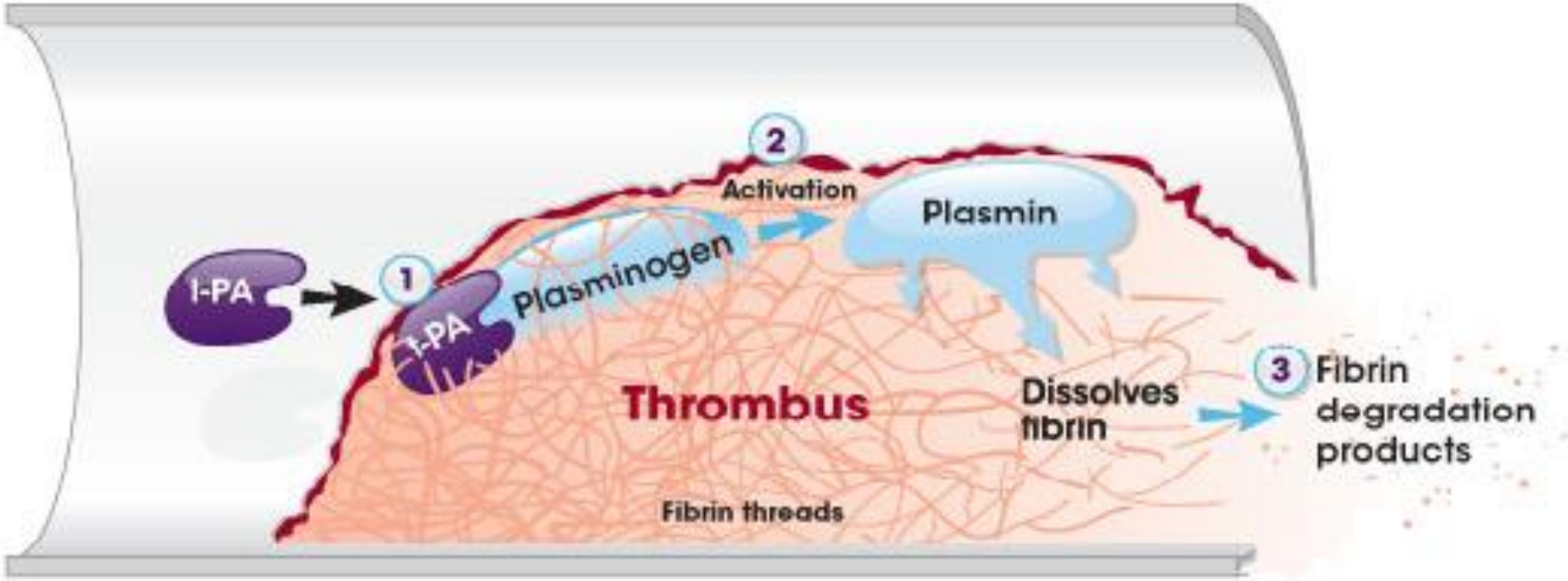
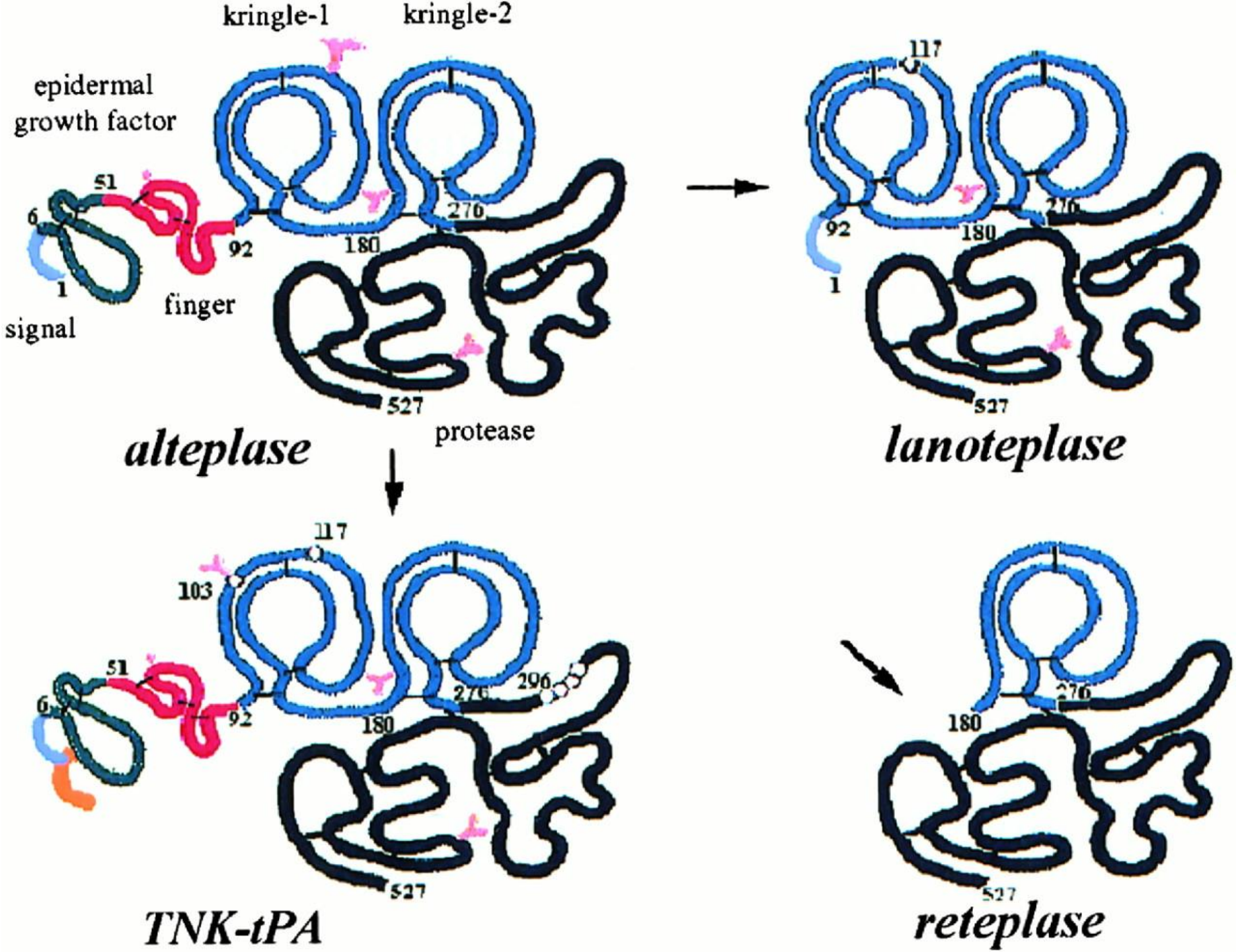
Calgary Stroke Program
Cumming School of Medicine
University of Calgary

Outline

- Introduction
- Current evidence for TNK in stroke
- The proposed trial
- Discussion



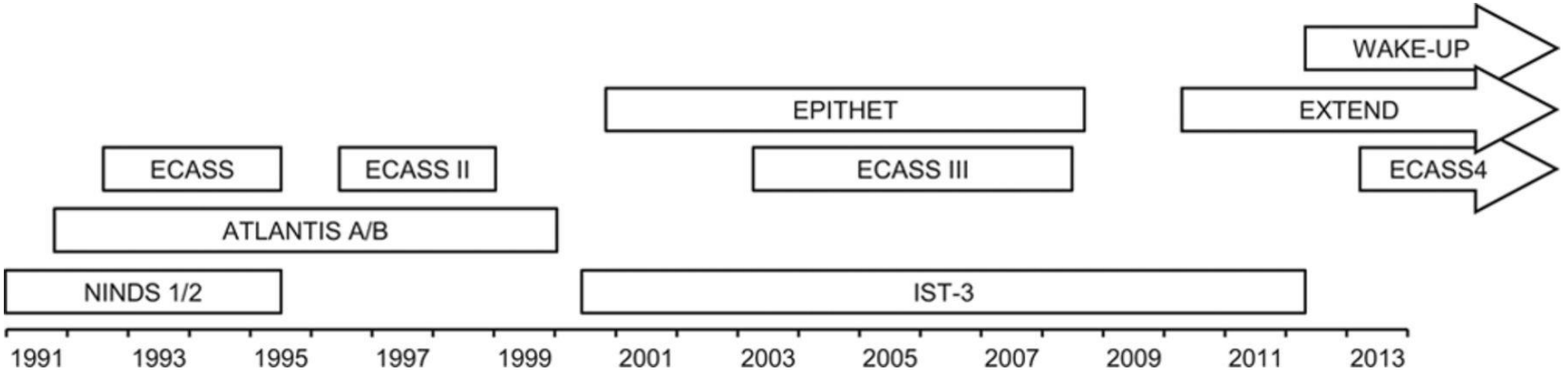
1 Recombinant t-PA (alteplase) binds to fibrin in thrombus 2 converts entrapped plasminogen to plasmin that 3 initiates local fibrinolysis.


kringle-1
kringle-2
epidermal
growth factor
51
6
92
180
276
1
finger
signal
527
protease
alteplase
117
92
180
276
1
527
lanoteplase
117
103
51
6
92
180
276
296
527
TNK-tPA
180
276
527
reteplase

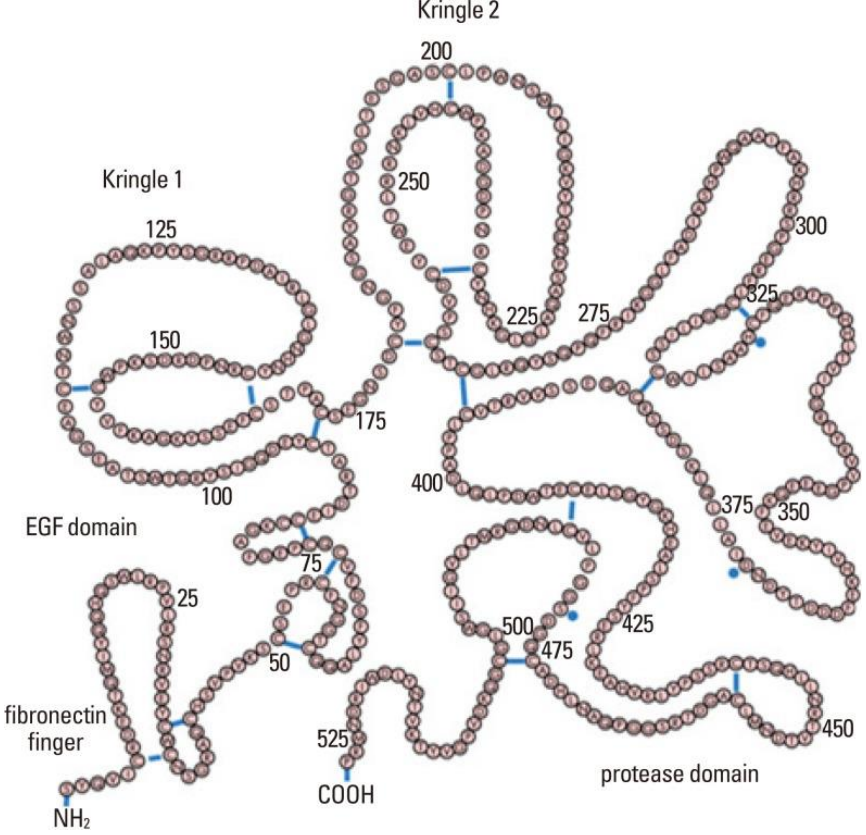
Agent	Half-life (min	Fibrin selectivity	PAI-1 inhibition
Urokinase	15	-	+++
Alteplase	4-8	++	+++
Staphylokinase	6	---	-
Monteplase	23	+/-	+++
Pamiteplase	30-47	++	+++
Lanoteplase	23-37	+	-
Reteplase	14-18	+	++
Tenecteplase	11-20	+++	-
Desmoteplase	138	+++++	?

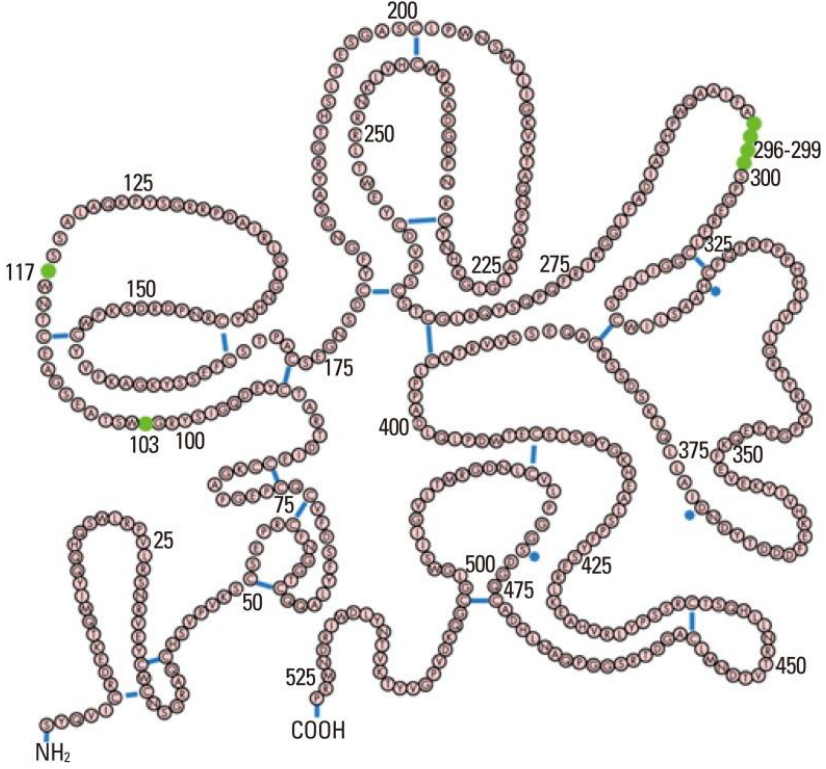

ALTEPLASE
ACTIVASE®
or intravenous use
00 mg (58 million IU)
tissue plasminogen activator
Genentech, Inc.
ALTEPLASE
ACTIVASE®
for intravenous use
50 mg (29 million IU)
a tissue plasminogen activator
Genentech, Inc.

Evolution of the tissue-type plasminogen activator trials and ongoing efforts to extend the time window beyond 4.5 hours.



Bruce C.V. Campbell et al. Stroke. 2015;46:2341-2346





Agent	Fibrin specificity	Thrombolytic potency	PAI-1 resistance	Fibrinogen depletion	PRT activity	Clearance (mL/kg/min)
TPA	++	+	−	++	++	16.1
TNK	+++	+++	++	+	+++	1.9

PAI-1 plasminogen activator inhibitor type 1, *PRT* platelet-rich thrombus

The NEW ENGLAND JOURNAL of MEDICINE

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.

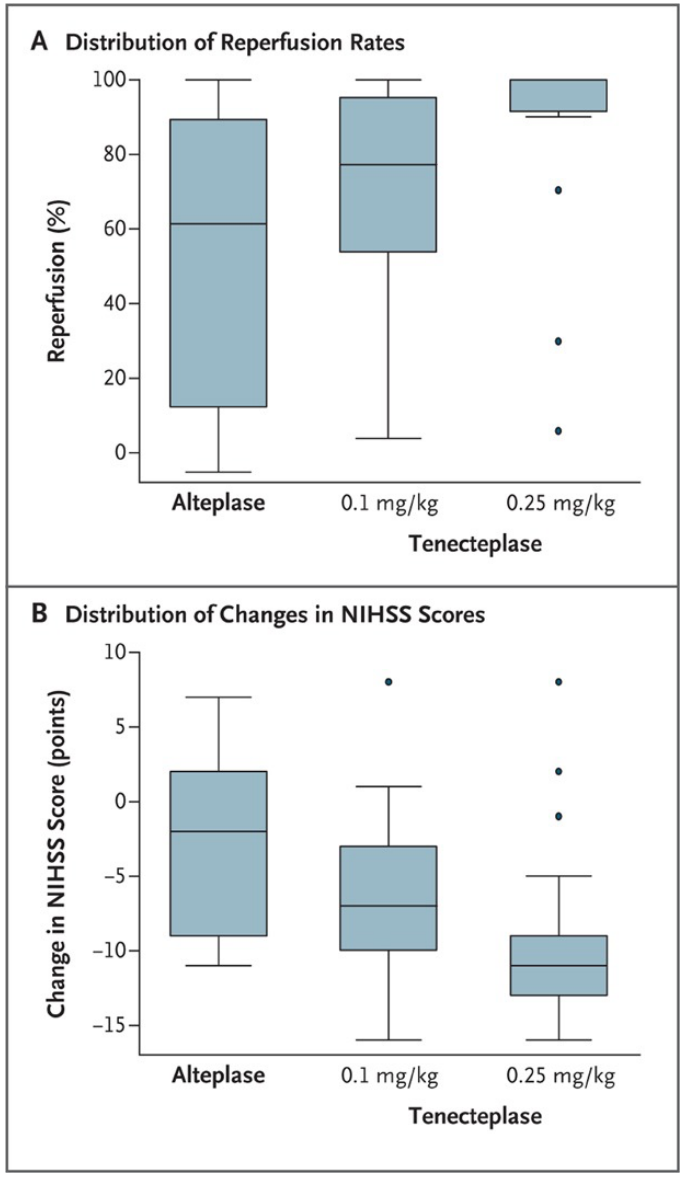


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Table 2. Study Outcomes in the Alteplase and Pooled Tenecteplase Groups.*

Outcome	Alteplase (N=25)	Tenecteplase (N=50)	P Value
Secondary imaging safety outcome			
Large parenchymal hematoma — no. (%)	4 (16)	2 (4)	0.09
Any parenchymal hematoma — no. (%)	5 (20)	3 (6)	0.11
Symptomatic intracranial hematoma — no. (%)§	3 (12)	2 (4)	0.33

International Journal of Stroke WSO

Tenecteplase versus alteplase in stroke thrombolysis: An individual patient data meta-analysis of randomized controlled trials

Xuya Huang[1], Rachael MacIsaac[2], John LP Thompson[3], Bruce Levin[3], Richard Buchsbaum[3], E Clarke Haley Jr[4], Christopher Levi[5], Bruce Campbell[6], Christopher Bladin[7], Mark Parsons[5] and Keith W Muir[1]

International Journal of Stroke
2016, Vol. 11(5) 534–543

DOI: 10.1177/1747493016641112
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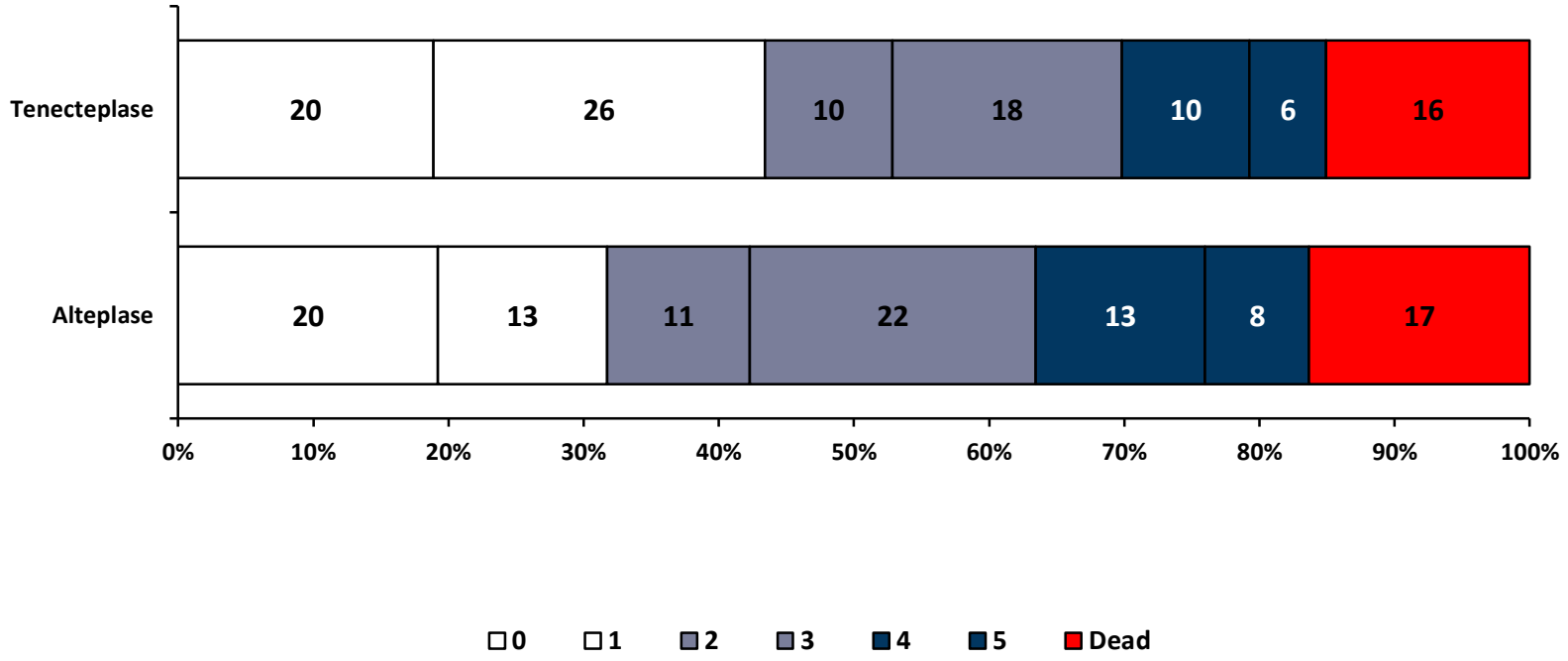
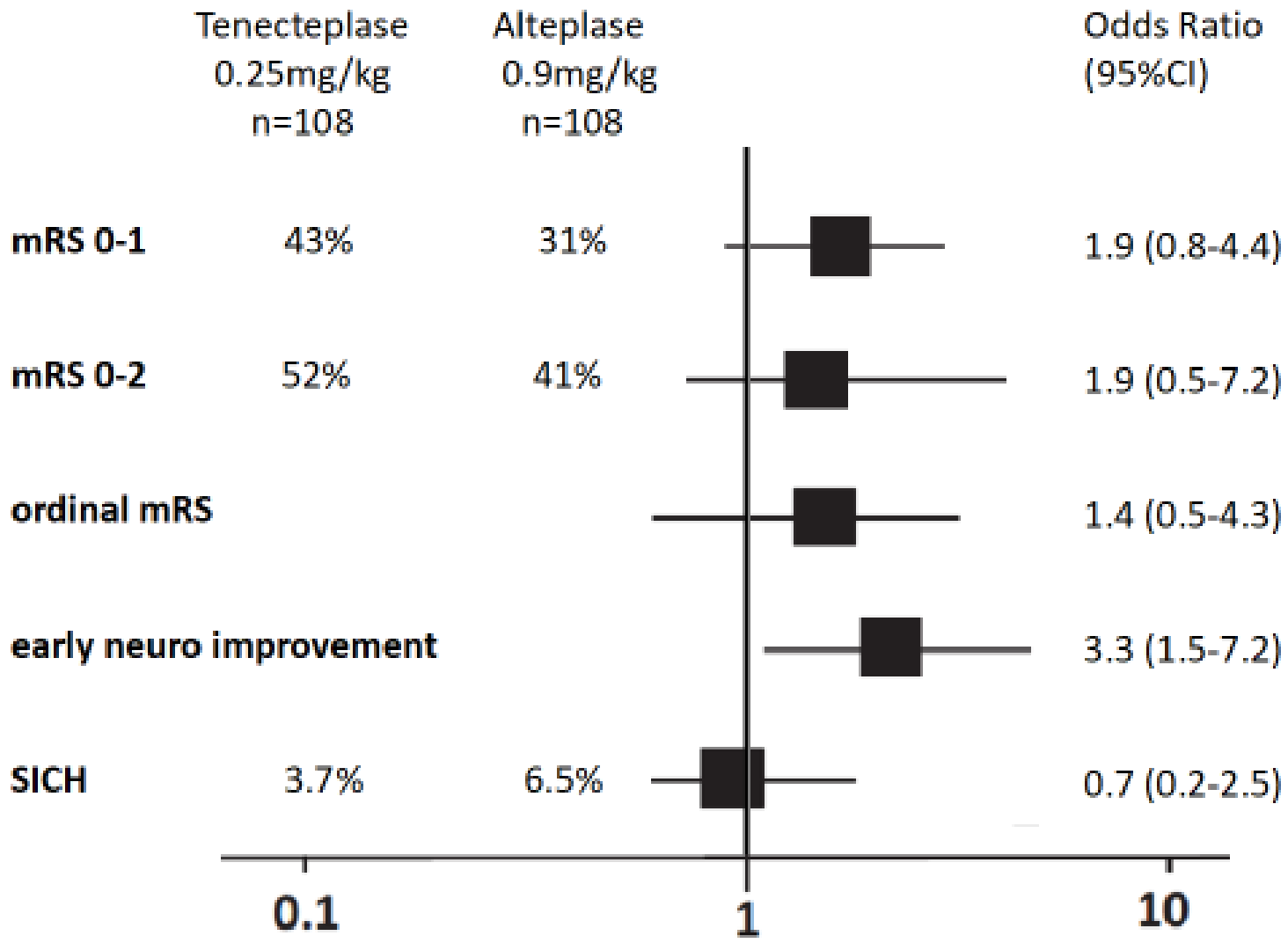


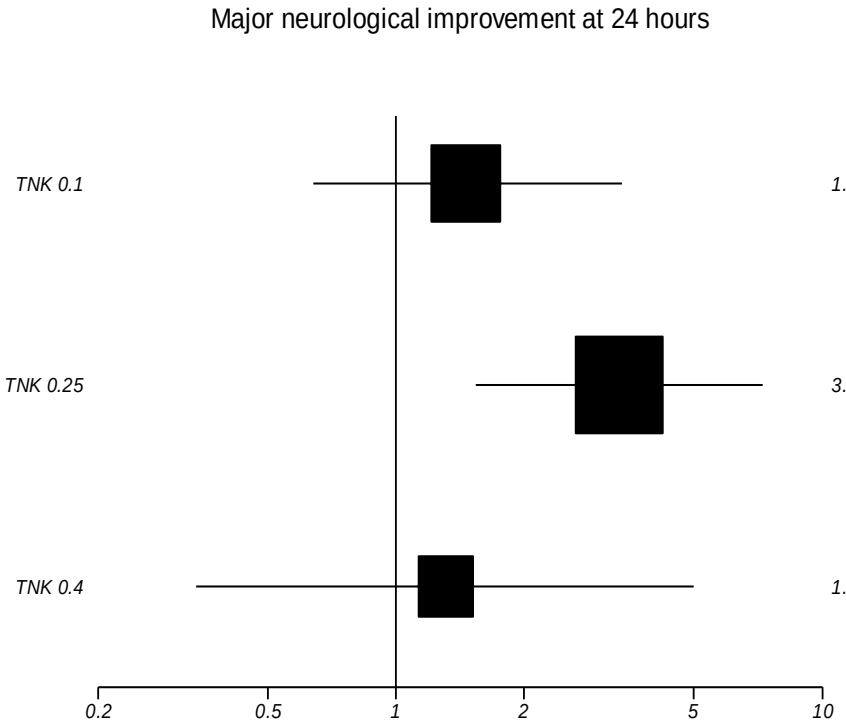
Modified Rankin Scale (mRS) score distribution in all patients randomised in RCTs comparing tenecteplase 0.25mg/kg and alteplase.

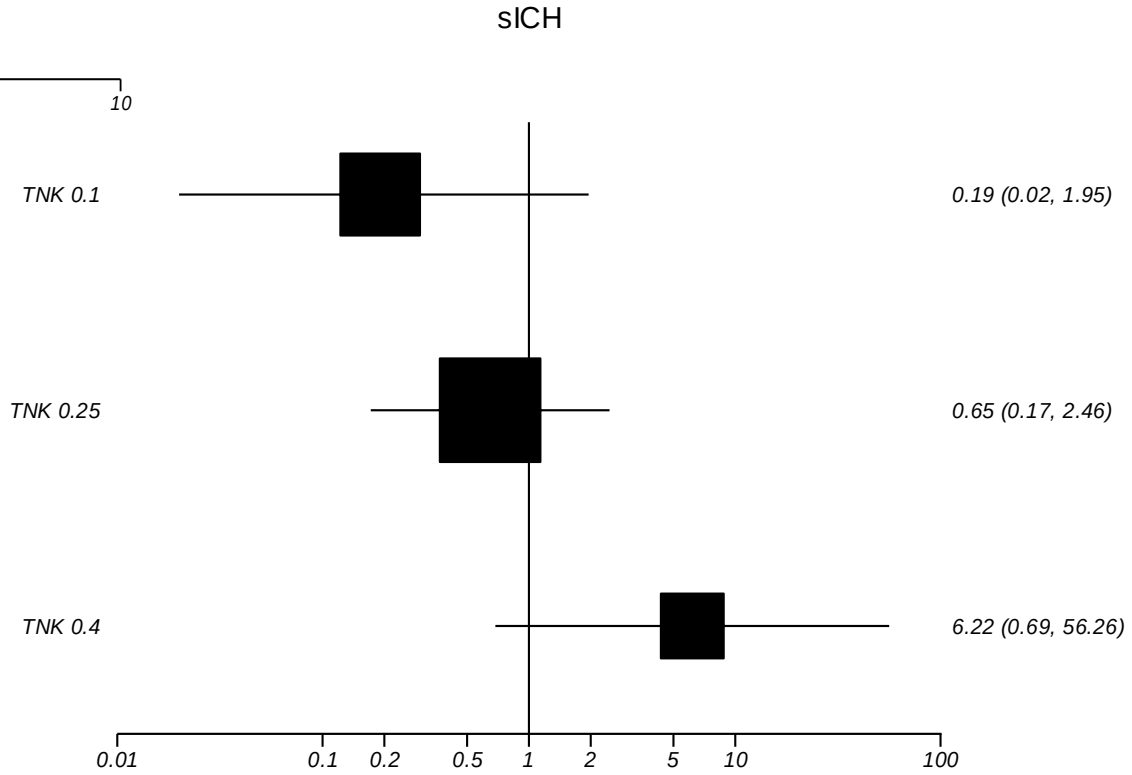
Individual patient data meta-analysis



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

Huang et al IJS 2016


Major neurological improvement at 24 hours
TNK 0.1
1.46 (0.64, 3.39)
TNK 0.25
3.34 (1.54, 7.24)
TNK 0.4
1.31 (0.34, 5.00)
0.2
0.5
1
2
5
10


sICH
TNK 0.1
0.19 (0.02, 1.95)
TNK 0.25
0.65 (0.17, 2.46)
TNK 0.4
6.22 (0.69, 56.26)
0.01
0.1
0.2
0.5
1
2
5
10
100

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 26, 2018 VOL. 378 NO. 17

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*

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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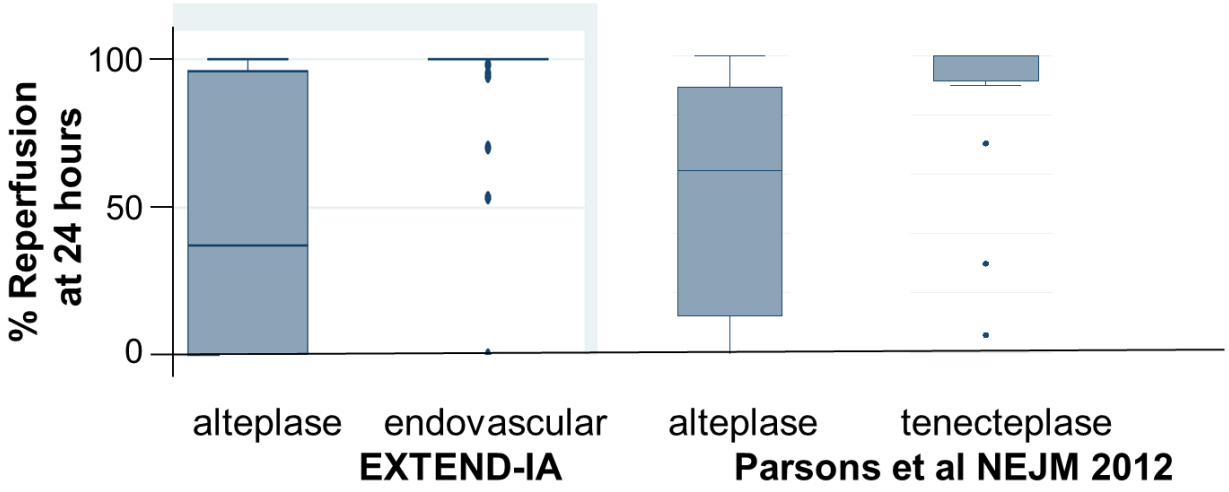
EXTEND - IA TNK

Reperfusion at 24hr

(Intention to treat)



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

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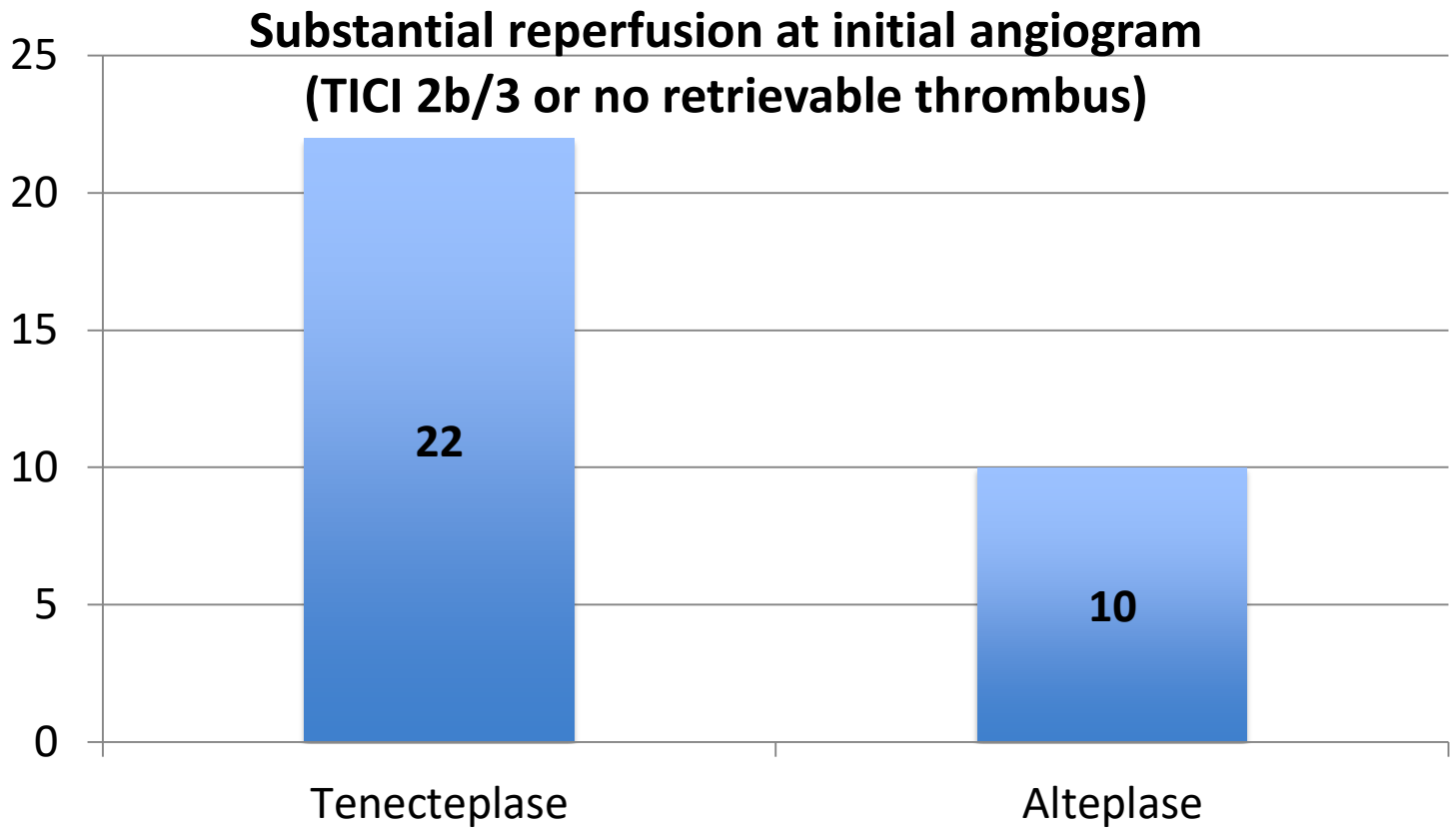
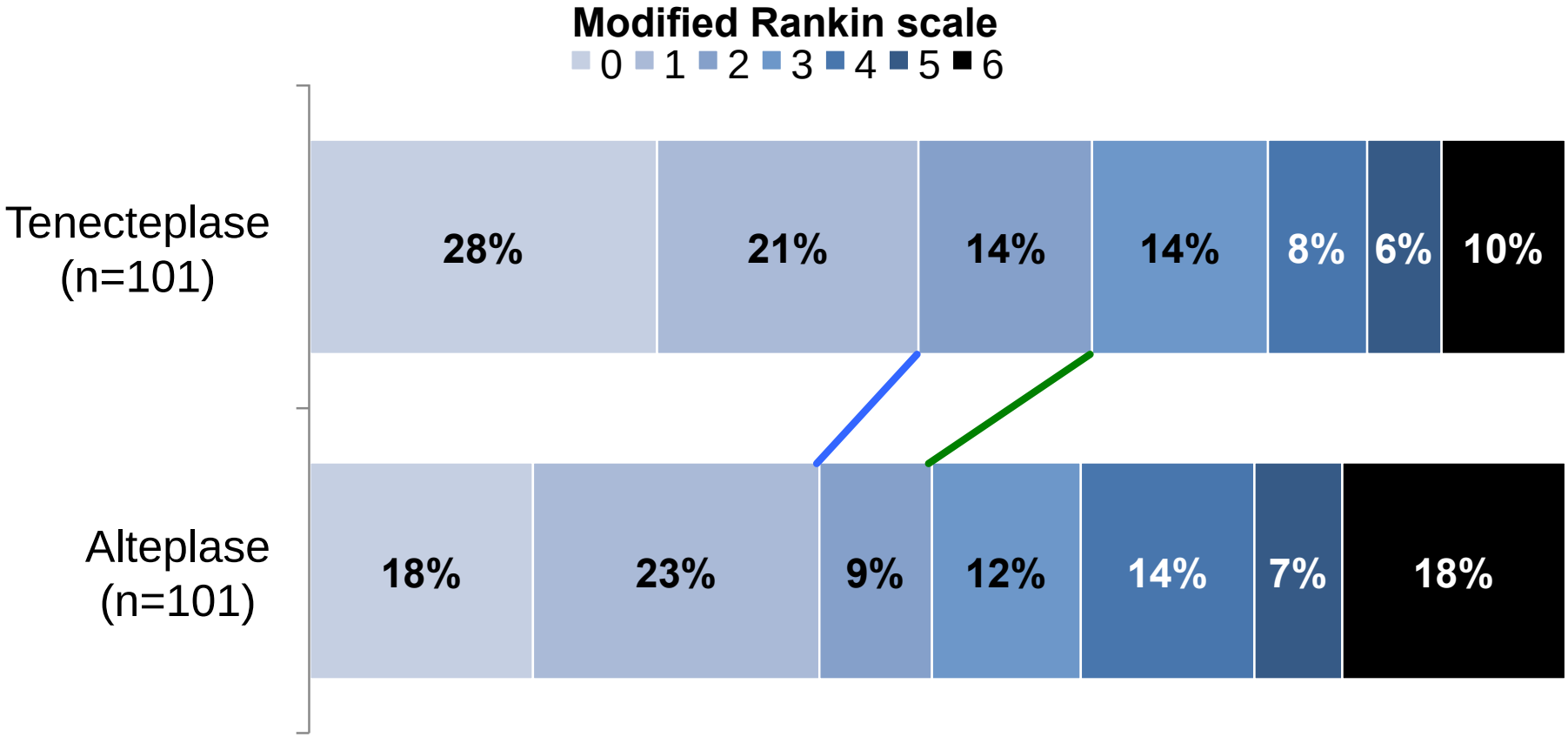


Adjusted odds ratio: 2.6 (95%ci 1.1-5.9)

Non-inferiority p=0.002
Superiority p=0.02

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=0.06

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

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

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

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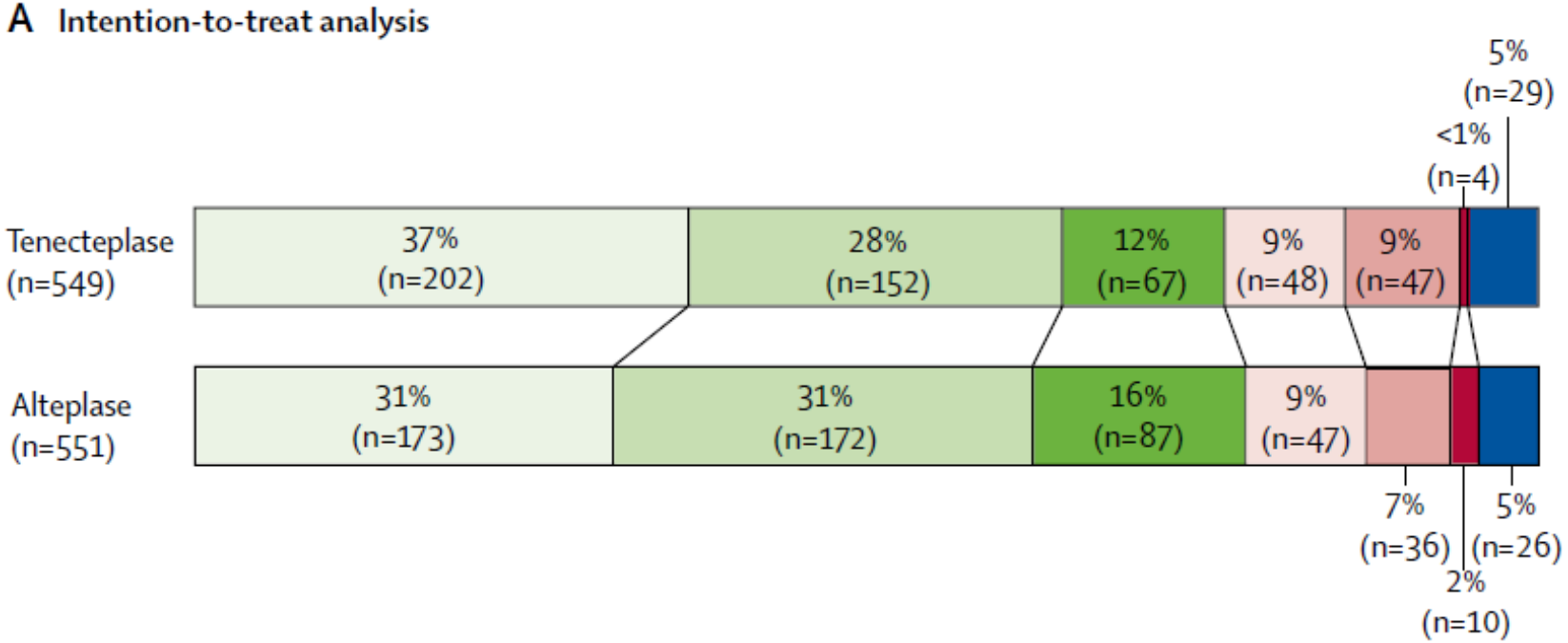

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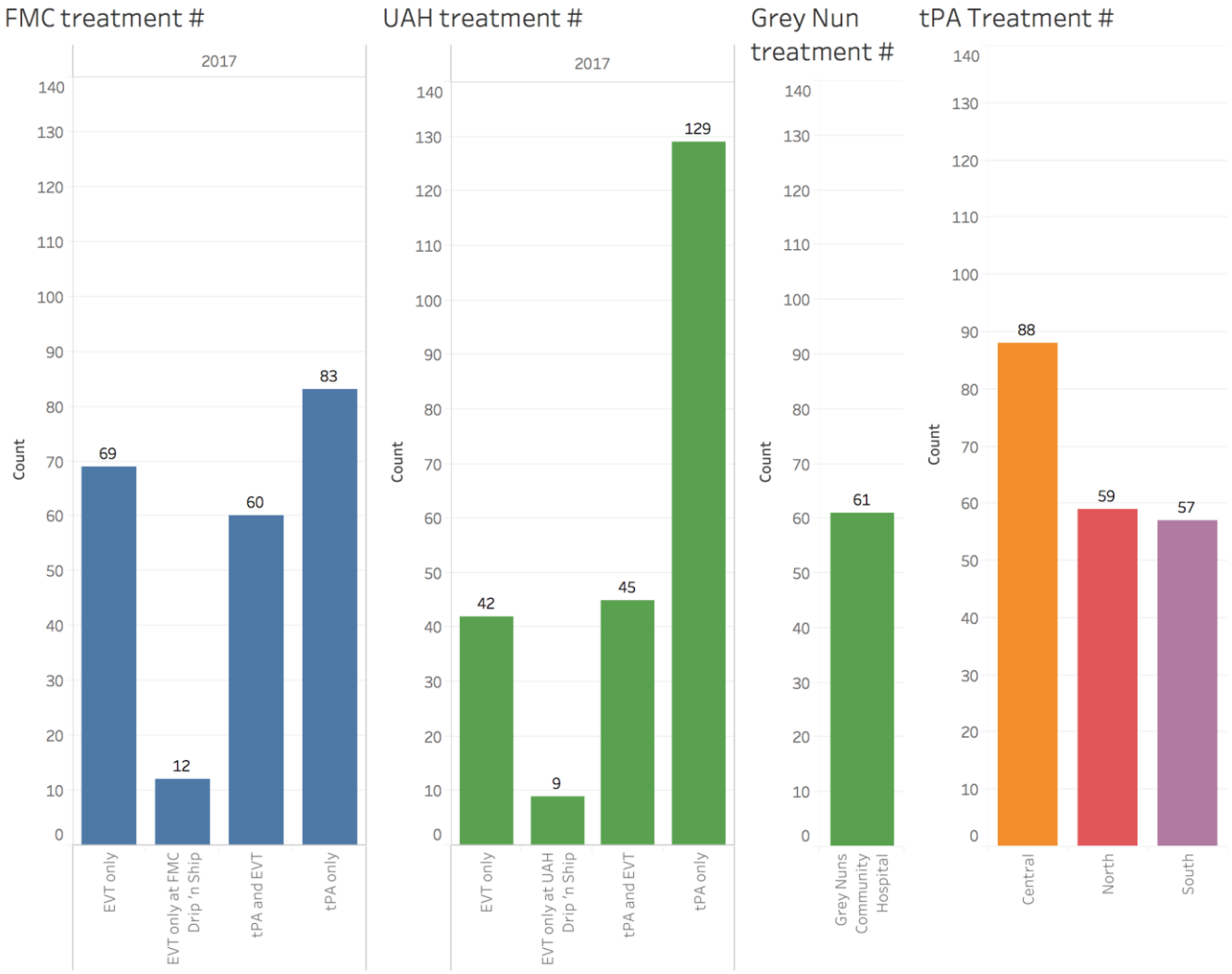
	Tenecteplase (n=549)	Alteplase (n=551)
(Continued from previous column)		
Premorbid modified Rankin Scale score		
0	435 (79%)	425 (77%)
1	62 (11%)	65 (12%)
2	25 (5%)	26 (5%)
≥3	27 (5%)	35 (6%)
NIHSS score		
Mean (SD)	5·6 (5·4)	5·8 (5·2)
Median (IQR)	4 (2–7)	4 (2–8)
Mild (0–7)	426 (78%)	401 (73%)
Moderate (8–14)	75 (14%)	98 (18%)
Severe (≥15)	48 (9%)	52 (9%)
TOAST classification*		
Large vessel disease (atherosclerosis)	92 (20%)	94 (20%)
Cardioembolism	100 (21%)	129 (27%)
Small vessel disease (lacunar infarct)	72 (15%)	60 (12%)
Other causes	23 (5%)	27 (6%)
Unknown or several causes	183 (39%)	171 (36%)
Time (min)†		
Onset to admission	79·0 (46–131)	74·5 (47–123)
Admission to thrombolysis	32·0 (22–47)	34·0 (25–50)
Onset to thrombolysis	118·0 (79–180)	111 (80–174)

582 patients received thrombolysis last year.



Data courtesy of Dr Noreen Kamal

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Alberta Stroke Program

ONGOING TRIALS

Trial	Design	Time Window	TNK/comparator Dose(s)	Sample Size	Outcomes
TASTE ACTRN 12613000243718	RCT	0-4.5 h with ischemic penumbra on CTP	0.25 mg/kg tPA 0.9 mg/kg	500 (1:1)	mRS 0-2 at days
ATTEST2 NCT02814409	RCT	0-4.5 h	0.25 mg/kg tPA 0.9 mg/kg	1 870 (1:1)	mRS 0-2 at days
TEMPO-2 NCT02398656	PROBE	0-12 h	0.25 mg/kg standard of care	900 (1:1)	mRS 0-2 at days
EXTEND IA-TNK Part 2 NCT03340493	RCT	0-4.5 h with LVO treated with EVT	0.25 mg/kg 0.4 mg/kg	188 (1:1)	Arterial pat on initial diagnostic angiogram

Our Proposed Trial

The Proposed Trial

Tenecteplase Alteplase Pragmatic

QuiCR Registry-based

Randomized Controlled Trial

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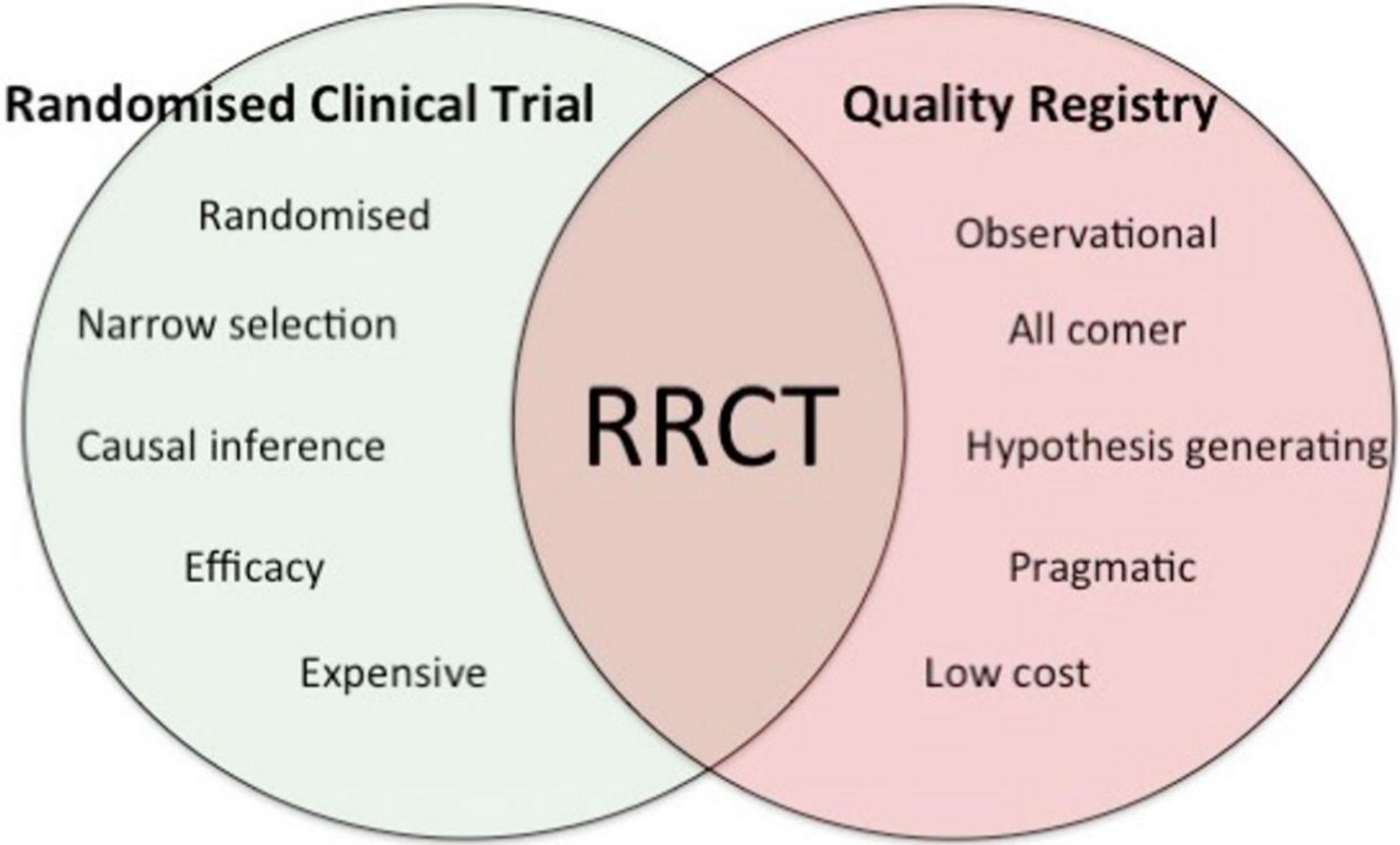
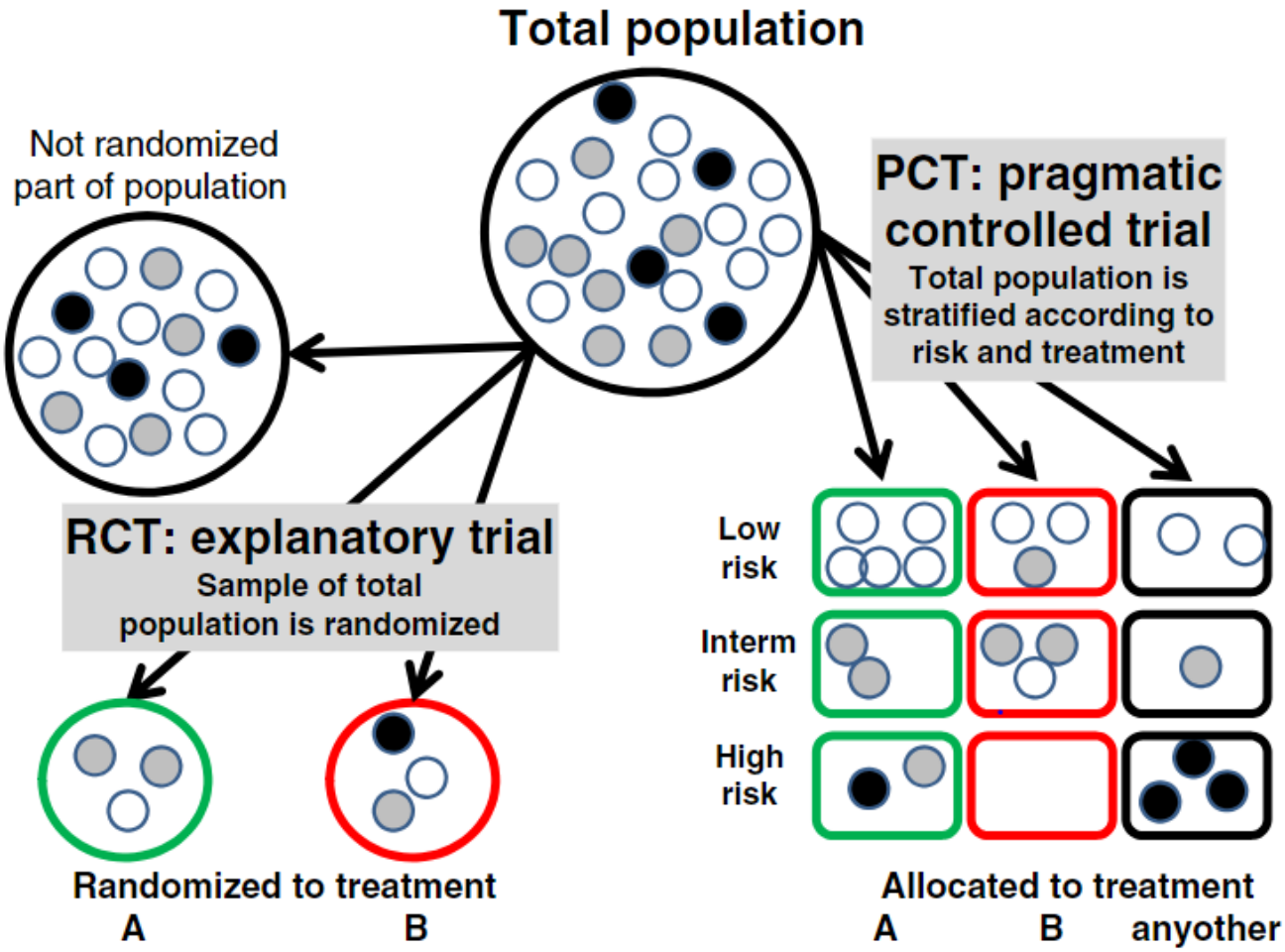

Randomised Clinical Trial
Randomised
Narrow selection
Causal inference
Efficacy
Expensive
RRCT
Quality Registry
Observational
All comer
Hypothesis generating
Pragmatic
Low cost

Pragmatic vs Explanatory Trials



Porzsolt et al. Journal of Public Health 21(3):307-313

Inclusion / Exclusions Criteria

Is this stroke patient eligible for tPA in my practice?

Inclusion / Exclusions Criteria

Is this stroke patient eligible for tPA in my practice?

YES

Inclusion / Exclusions Criteria

Is this stroke patient eligible for tPA in my practice?

YES

Randomize

Inclusion / Exclusions Criteria

Is this stroke patient eligible for tPA in my practice?

NO

Exclude

Inclusion / Exclusions Criteria

Is this stroke patient eligible for tPA in my practice?

YES

NO

Randomize

Exclude

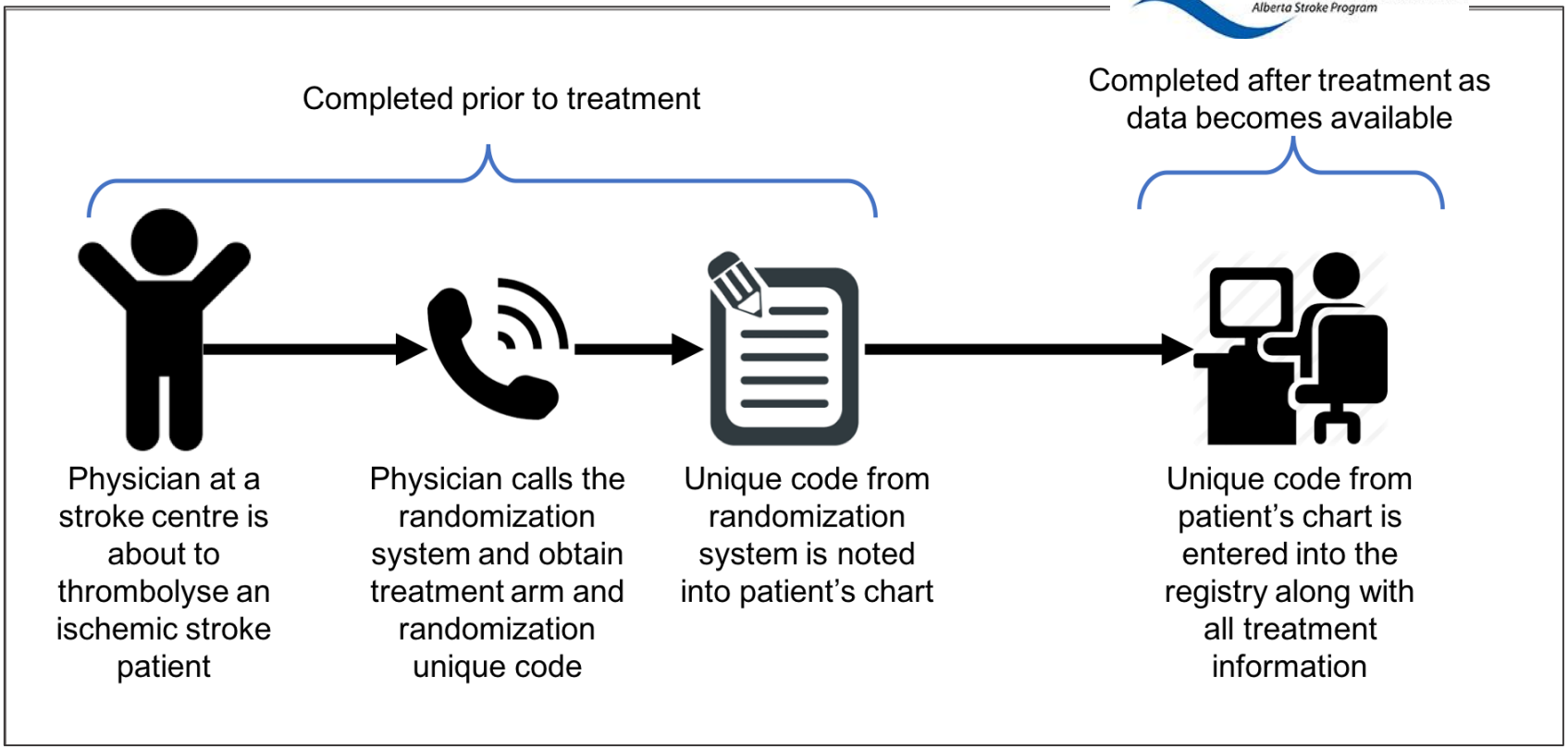
Note-worthy Points

- Advanced imaging (CTA/ CTP)
  - NOT A PREREQUISITE
- Underlying occlusion
  - NOT A PREREQUISITE
- Anterior AND posterior circulation
- Patient is EVT eligible
  - YOU CAN STILL RANDOMIZE

Mention-worthy
Exclusions Criteria

- Stroke patients beyond 4.5 hours from onset (LSW)
- Minor stroke (that you would NOT usually thrombolyse)
- Resolving stroke symptoms (that you would NOT usually thrombolyse)

Randomization & Flow



Planned Trial Interventions

Intravenous tenecteplase **at a dose of 0.25 mg/kg**

Vs.

Standard dose intravenous alteplase (0.9 mg/kg body weight, 10% bolus and 90% infusion over 60 minutes).

Outcomes

Primary Outcome:

- **modified Rankin Scale 0-1 at 90 days**

Secondary Outcomes

- Discharge destination (home, early supported discharge, rehabilitation facility, long term care, death)
- Ambulatory status at discharge
- Home time
- Actual 90-day mRS score
- Door to needle time
- Door-in-door-out (DIDO) times at the Primary Stroke Centre
- Recanalization status at first angiographic acquisition in patients taken to the angio-suite for the purpose of administering EVT
- Proportion of patients administered EVT

Safety Outcomes

- Death
- Symptomatic ICH defined as per NINDS trials criteria as any haemorrhage post treatment associated temporally with neurological worsening

Sample Size

- A total of 1076 subjects (~ 400 recruits annually)
- 1:1 ratio
- Assuming a 90-days primary outcome is 40% and 35%, respectively.

Sites

- QuiCR registry sites:
  - 15 Primary Stroke Centers
  - 2 Comprehensive Stroke Centers
- The trial will likely recruit more centers as the registry expands into other provinces and health systems.

Potential Advantages of TNK

- Better recanalization
  - ? Fewer EVT cases
  - ? Better outcomes of distal occlusions
- Safety
- Workflow benefit
  - DTN shorter: triage, image, bolus, transfer

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Thanks