
CALGARY
STROKE PROGRAM

ESCAPE-NA1 trial

ESCAPE-NA1 Investigators

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IN PARTNERSHIP WITH

Alberta Health Services

CLINICAL NEURO SCIENCES CALGARY CANADA

HOTCHKISS BRAIN INSTITUTE

UNIVERSITY OF CALGARY

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Statement of funding and disclosures

- The trial was funded by:
  - Canadian Institutes for Health Research
  - Alberta Innovates
  - NoNO Inc.

- NoNO Inc was the regulatory sponsor for the trial, provided study drug, and monitored regulatory compliance of the study
- The trial was organized as an academic-industry collaboration and coordinated at the University of Calgary

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Background

1,026 Experimental Treatments in Acute Stroke

Victoria E. O'Collins, B.Sci,[1] Malcolm R. Macleod, MRCP, PhD,[3] Geoffrey A. Donnan, MD, FRACP,[2] Laura L. Horky, MD, PhD,[2] Bart H. van der Worp, MD, PhD,[4] and David W. Howells, PhD[1]

Ann Neurol 2006;59:467–477

- Publications of over 1000 treatments, largely neuroprotectants, have shown promise in pre-clinical models of ischemic stroke
- A smaller percentage (~10%) have been studied in human clinical trials, but no neuroprotectants have shown a clinical benefit
- Nerinetide (NA-1;Tat-NR2B9c) is a promising agent that has shown neuroprotection in cell cultures, rodents, primates and in a phase 2 study in humans undergoing endovascular repair of intracranial aneurysms*

**Hill et al., Lancet Neurol. 2012;11:942-950*

Safety and efficacy of NA-1 in patients with iatrogenic stroke after endovascular aneurysm repair (ENACT): a phase 2, randomised, double-blind, placebo-controlled trial

*Michael D Hill, Renee H Martin, David Mikulis, John H Wong, Frank L Silver, Karel G terBrugge, Geneviève Milot, Wayne M Clark, R Loch MacDonald, Michael E Kelly, Melford Boulton, Ian Fleetwood, Cameron McDougall, Thorsteinn Gunnarsson, Michael Chow, Cheemun Lum, Robert Dodd, Julien Poublanc, Timo Krings, Andrew M Demchuk, Mayank Goyal, Roberta Anderson, Julie Bishop, David Garman, and Michael Tymianski, for the ENACT trial investigators**

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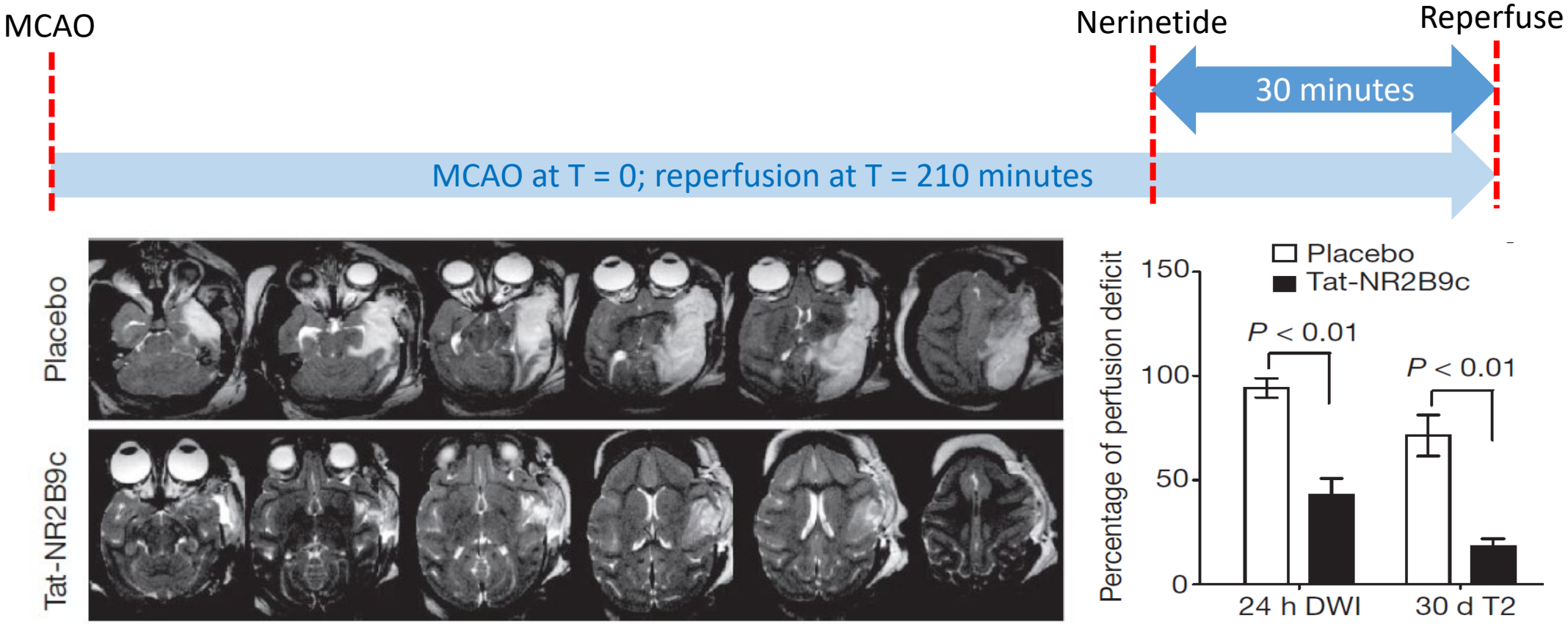
Nerinetide reduces infarct volume in Cynomolgous macaques subjected to ischemia-reperfusion*



*Cook, Teves, Tymianski. *Nature*. 2012;483:213-217

LETTER

doi:10.1038/nature10841

Treatment of stroke with a PSD-95 inhibitor in the gyrencephalic primate brain

Douglas J. Cook[1], Lucy Teves[1] & Michael Tymianski[1,2,3,4]

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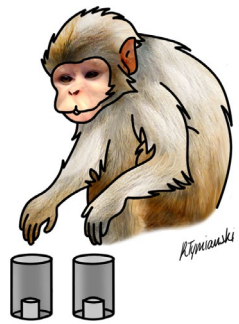
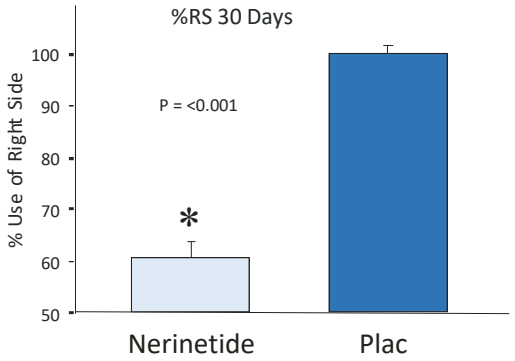
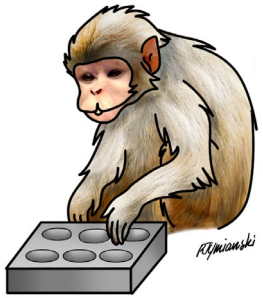
Nerinetide improves neurological function in a range of behavioral tests*

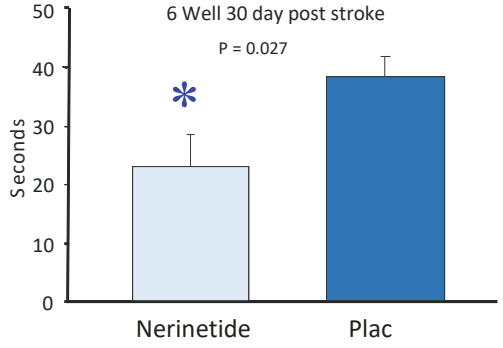
Two Tube Test



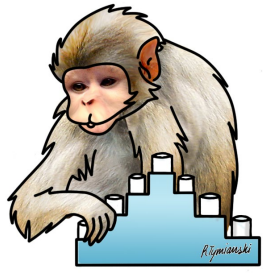


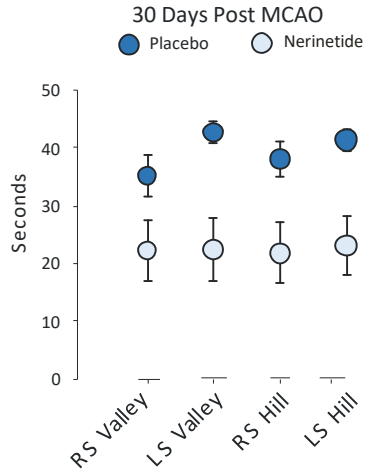
6 Well Test





Hill/Valley tests





*Cook, Teves, Tymianski. *Nature*. 2012;483:213-217

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Treatment of stroke with a PSD-95 inhibitor in the gyrencephalic primate brain

Douglas J. Cook[1], Lucy Teves[1] & Michael Tymianski[1,2,3,4]

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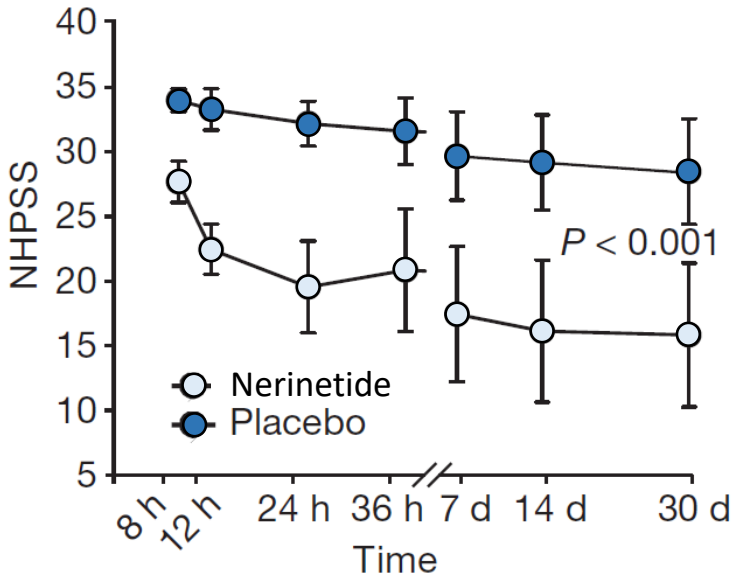
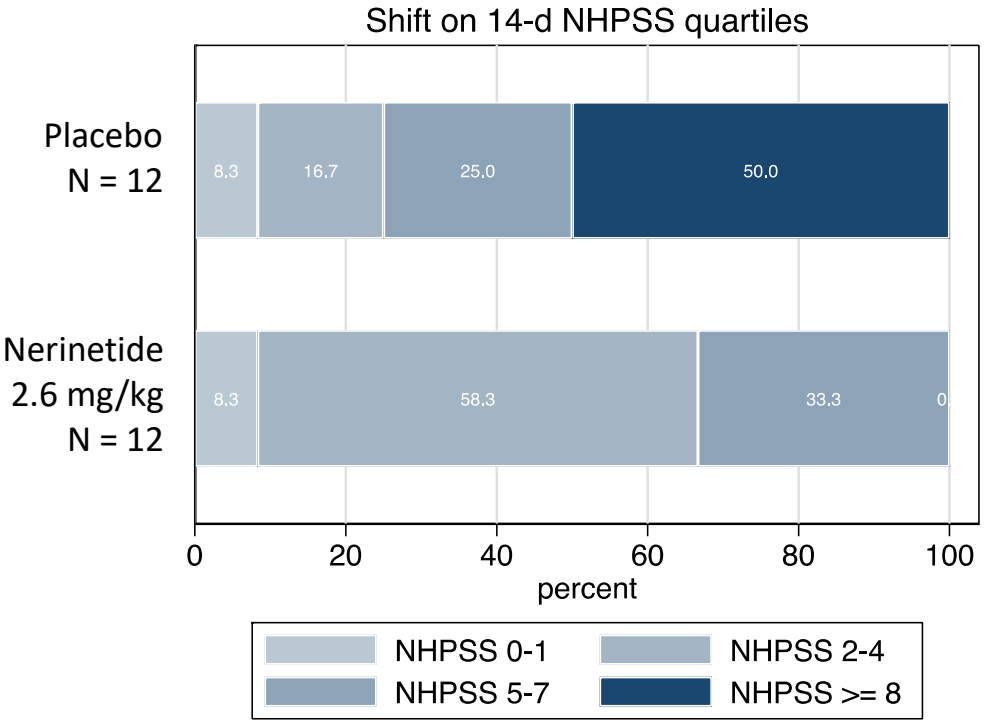
“Shift” on NIHPSS suggests that neuroprotection can improve function on top of reperfusion (cOR = 8.19)





cOR = 8.19 (1.48-45.3), p=0.016

N=24; 0 Dead

Adapted from data in:
Cook, Teves, Tymianski. Nature. 2012;483:213-217

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Study Design

ESCAPE-NA1 aimed to recapitulate the primate model in community-onset ischemic stroke, accounting for existing standards of care including alteplase

- Phase 3, multicentre, blinded, placebo-controlled, parallel group, single-dose design.
- Up to 1120 male and female subject will be enrolled
- Randomization 1:1 nerinetide to placebo, stratified by alteplase use and by declared first choice of device

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Inclusion Criteria

1. Acute ischemic stroke (AIS) for immediate endovascular treatment.
2. Age 18 or greater.
3. Onset (last-seen-well) time to randomization time within 12 hours.
4. Disabling stroke defined as a baseline NIHSS > 5 at the time of randomization.
5. Pre-stroke (24 hours prior to stroke onset) independent functional status in activities of daily living with modified Barthel Index (BI) > 90 (95 or 100). Patient must be living in their own home, apartment or seniors lodge where no nursing care is required.

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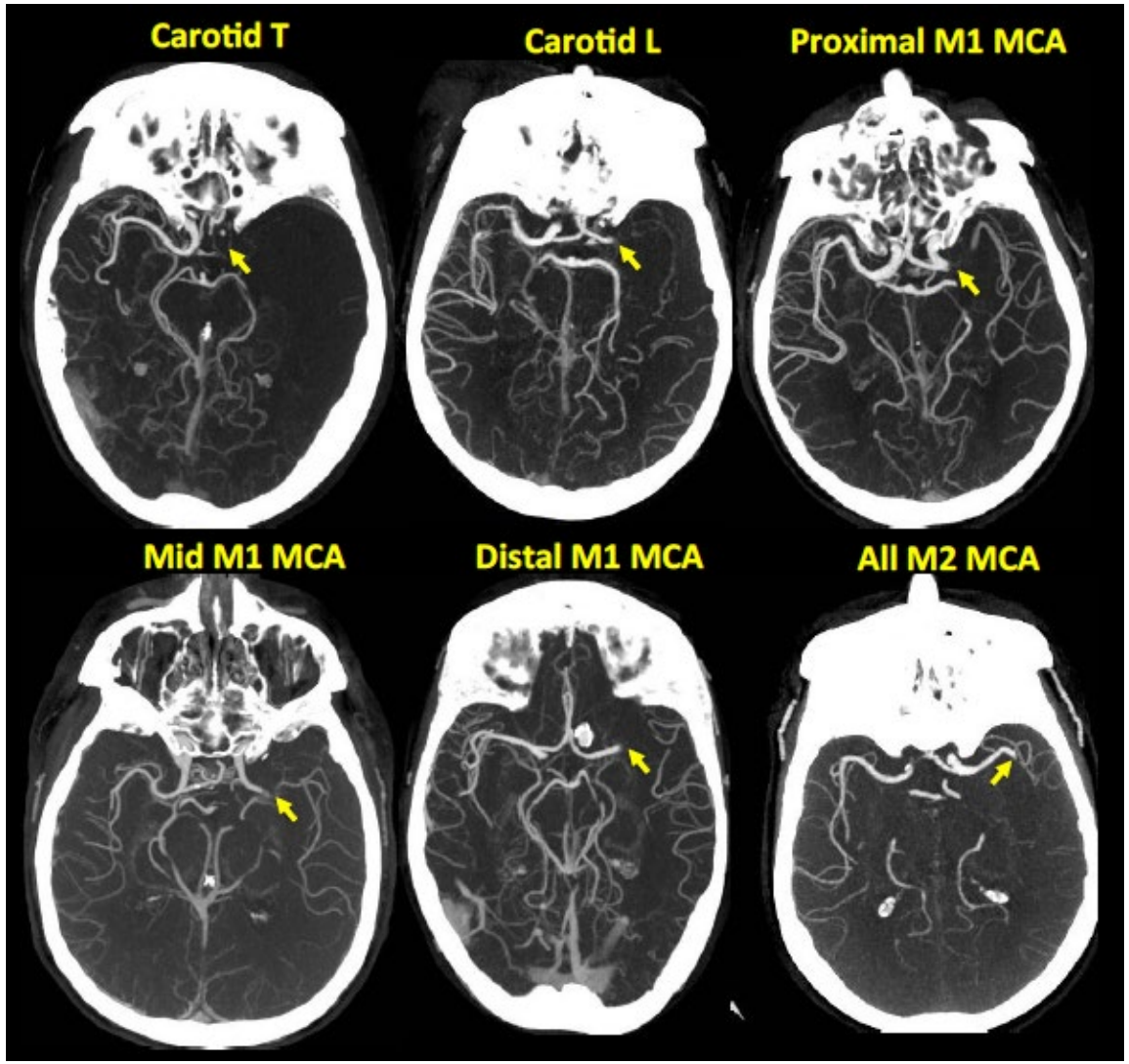
Imaging criteria

- CT head: ASPECTS >= 5 (exclude large core)
- mCTA: ICA + M1 or M1 or functional M1 (all M2s)
- mCTA: moderate to good collaterals



Radiology

Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke[1]

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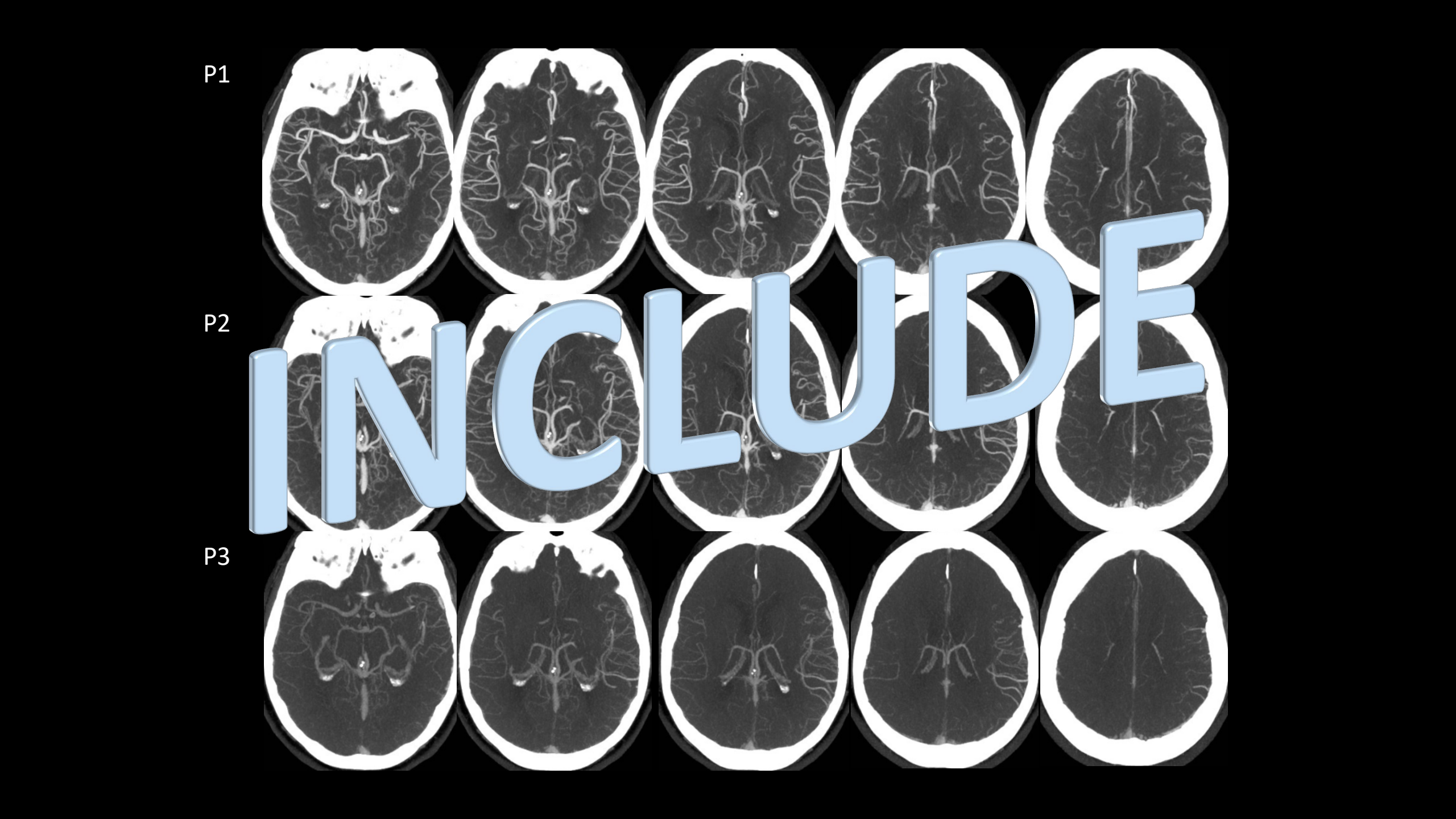
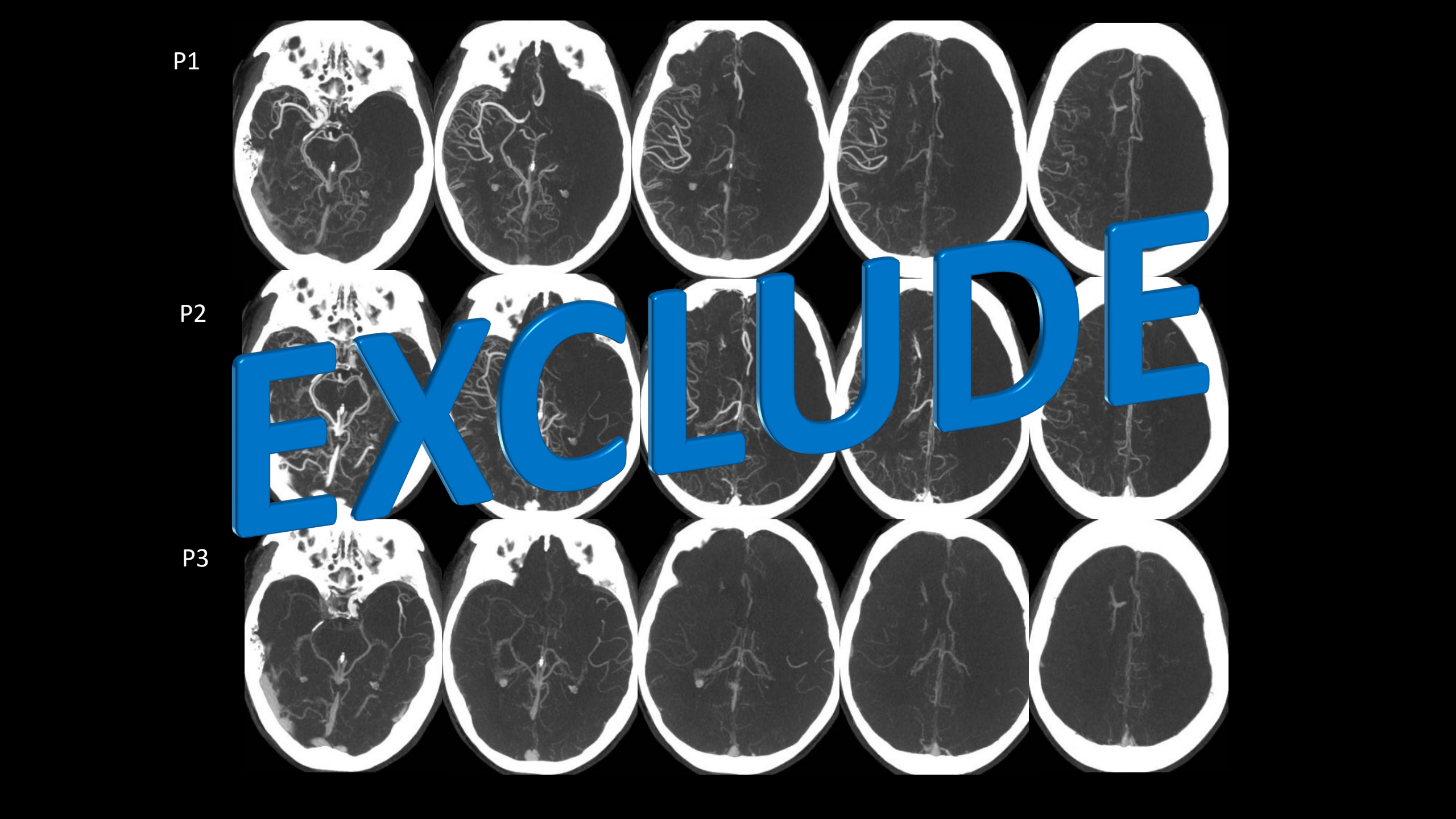

P1
P2
P3
INCLUDE


P1
P2
P3
EXCLUDE

Intervention

- Single, ten minute infusion of 2.6 mg/kg intravenous dose of nerinetide or (saline) placebo as soon as enrollment criteria met, and started within 30 minutes of randomization.

- All patients had EVT

- Patients received intravenous alteplase according to current stroke guidelines (best medical management)

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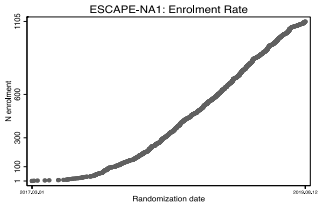
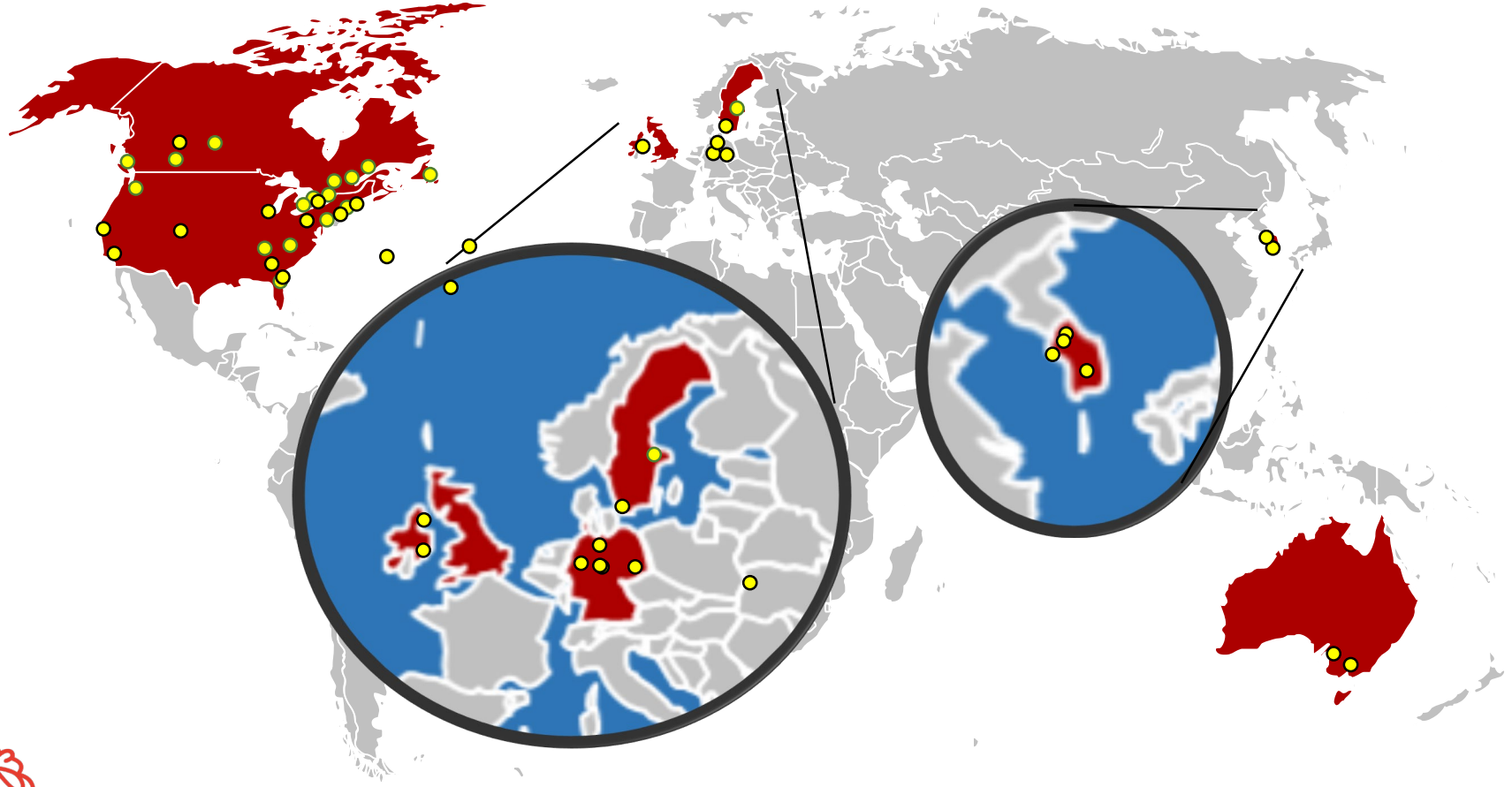
48 ESCAPE-NA1 Sites





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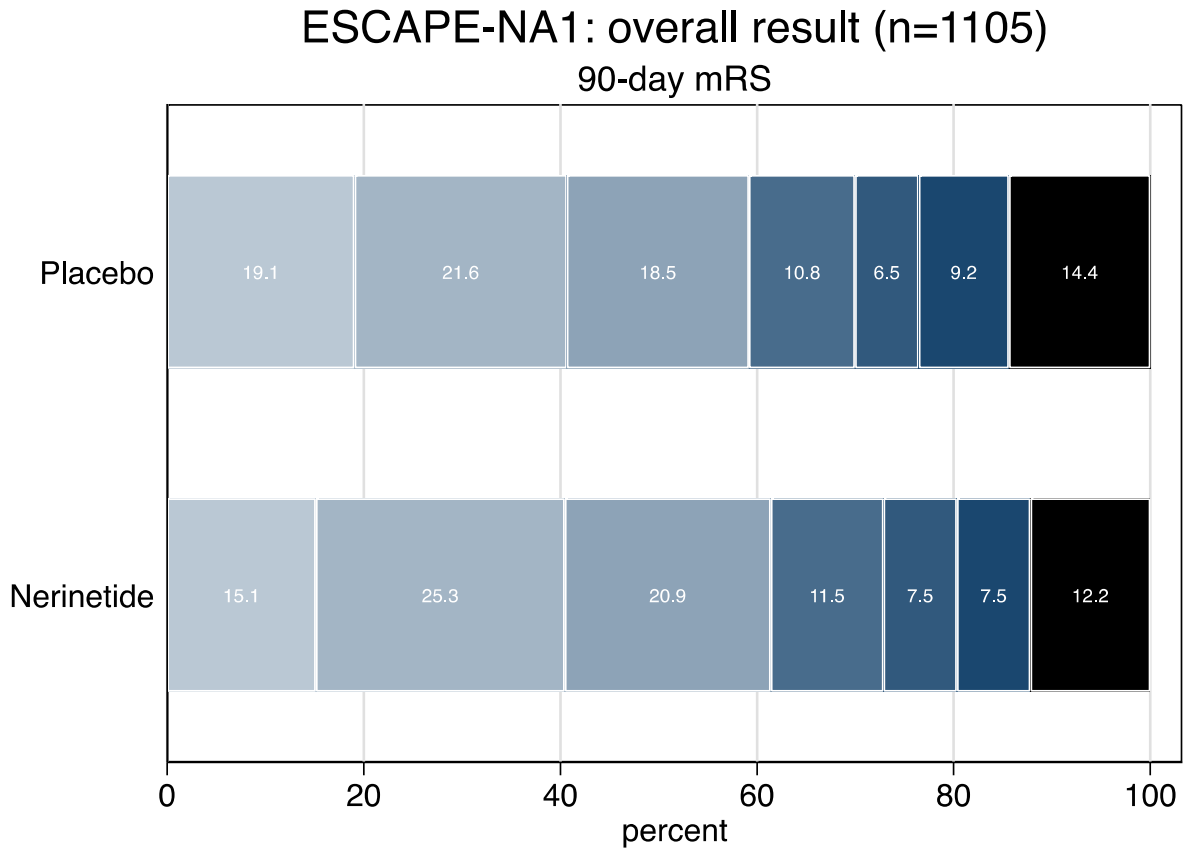
Nerinetide did not significantly improve functional independence in the entire trial population

Overall Results: 1105 (Alteplase and No-Alteplase combined)



NA-1: 61.3%, Placebo: 59. 2%, Absolute Risk Difference: 2.1%;
adj RR = 1.04 (0.96 to 1.14); p=0.350

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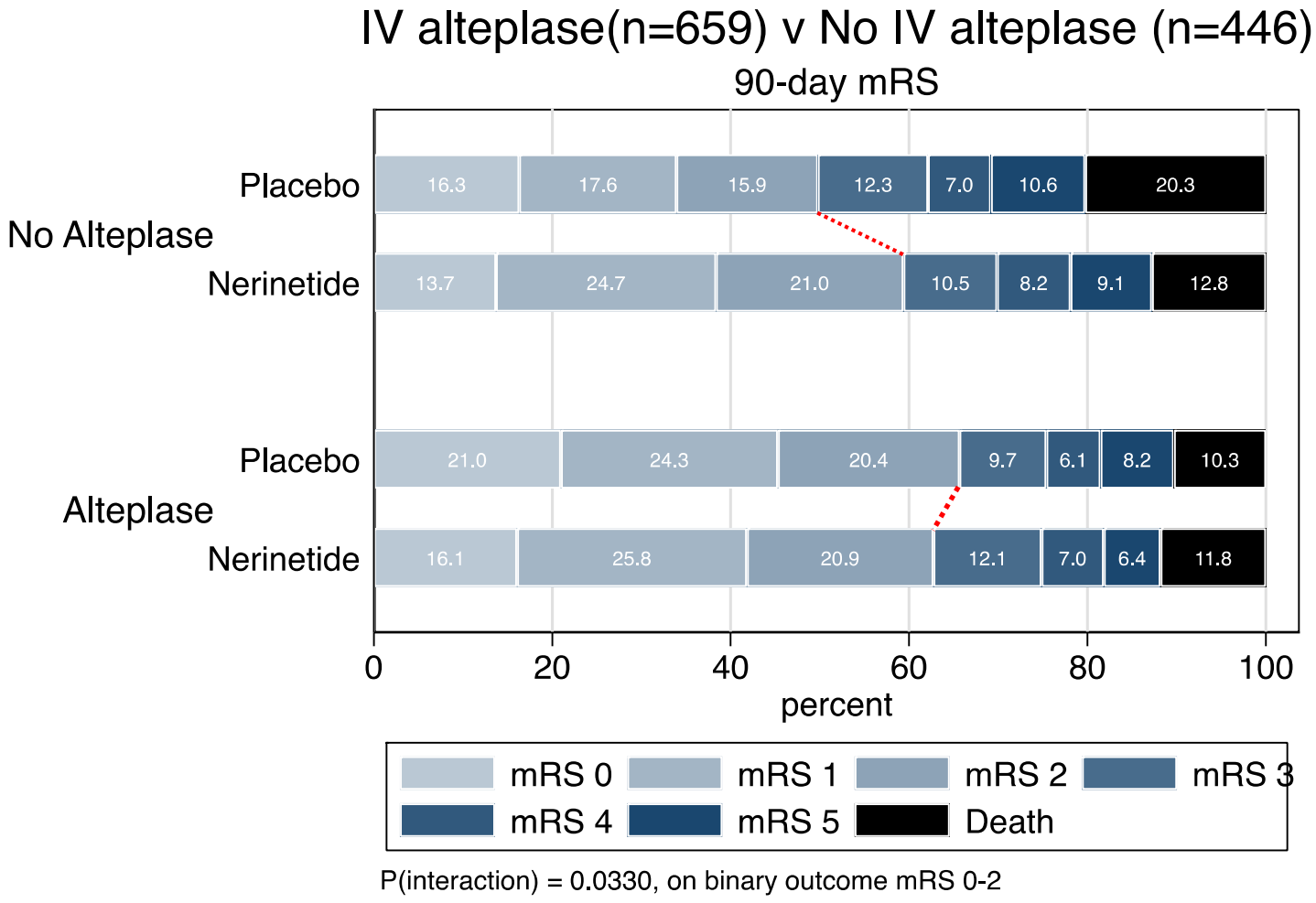
Effect modification (interaction) by alteplase treatment



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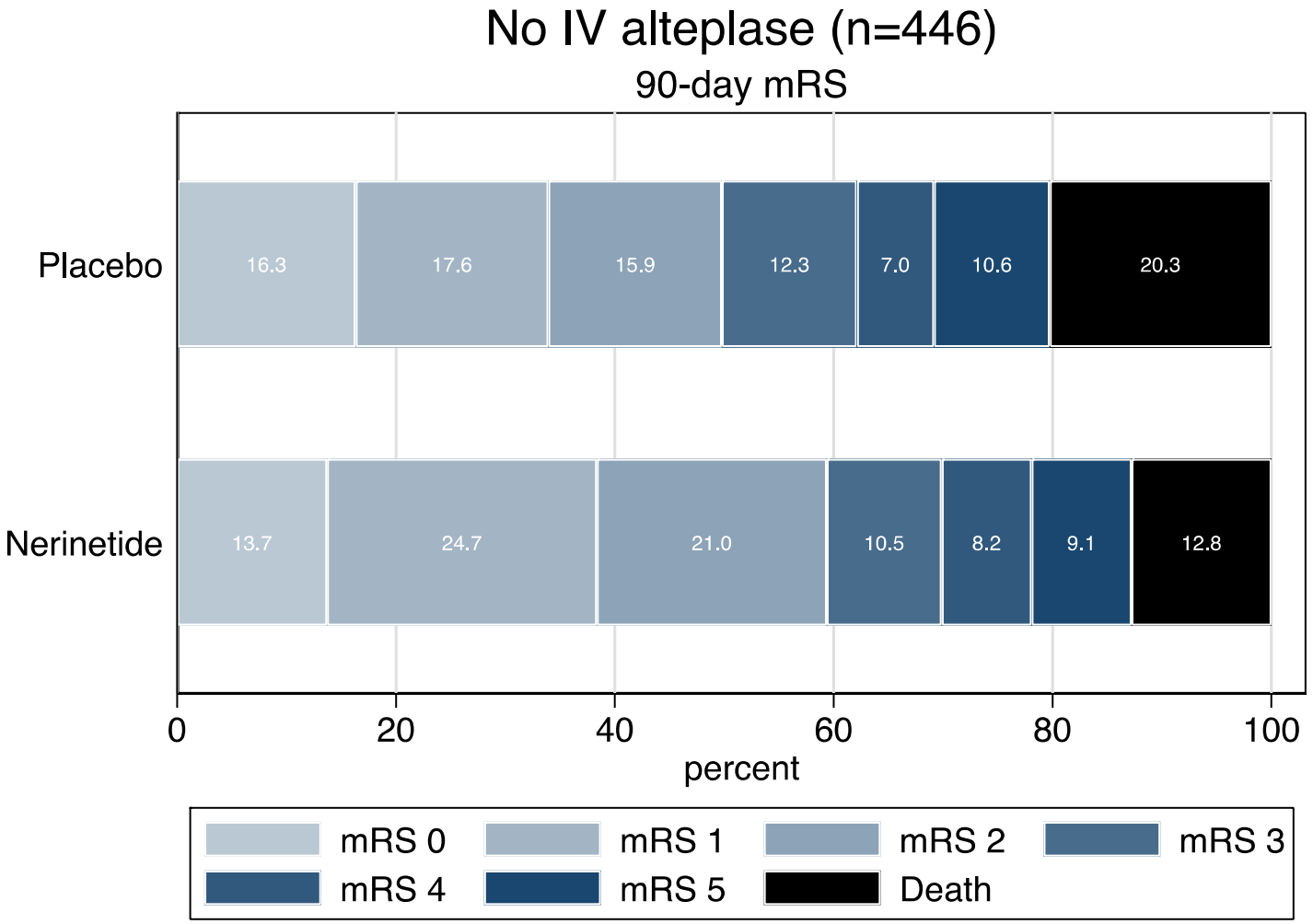
No Alteplase stratum



Effect size on mRS 0-2:

- 9.5% absolute risk difference
- Adj RR = 1.18 (1.01 to 1.38)

Mortality reduction:

- 7.5% absolute risk difference

Infarct volume reduction

- 39.2 vs. 26.7 ml (median)

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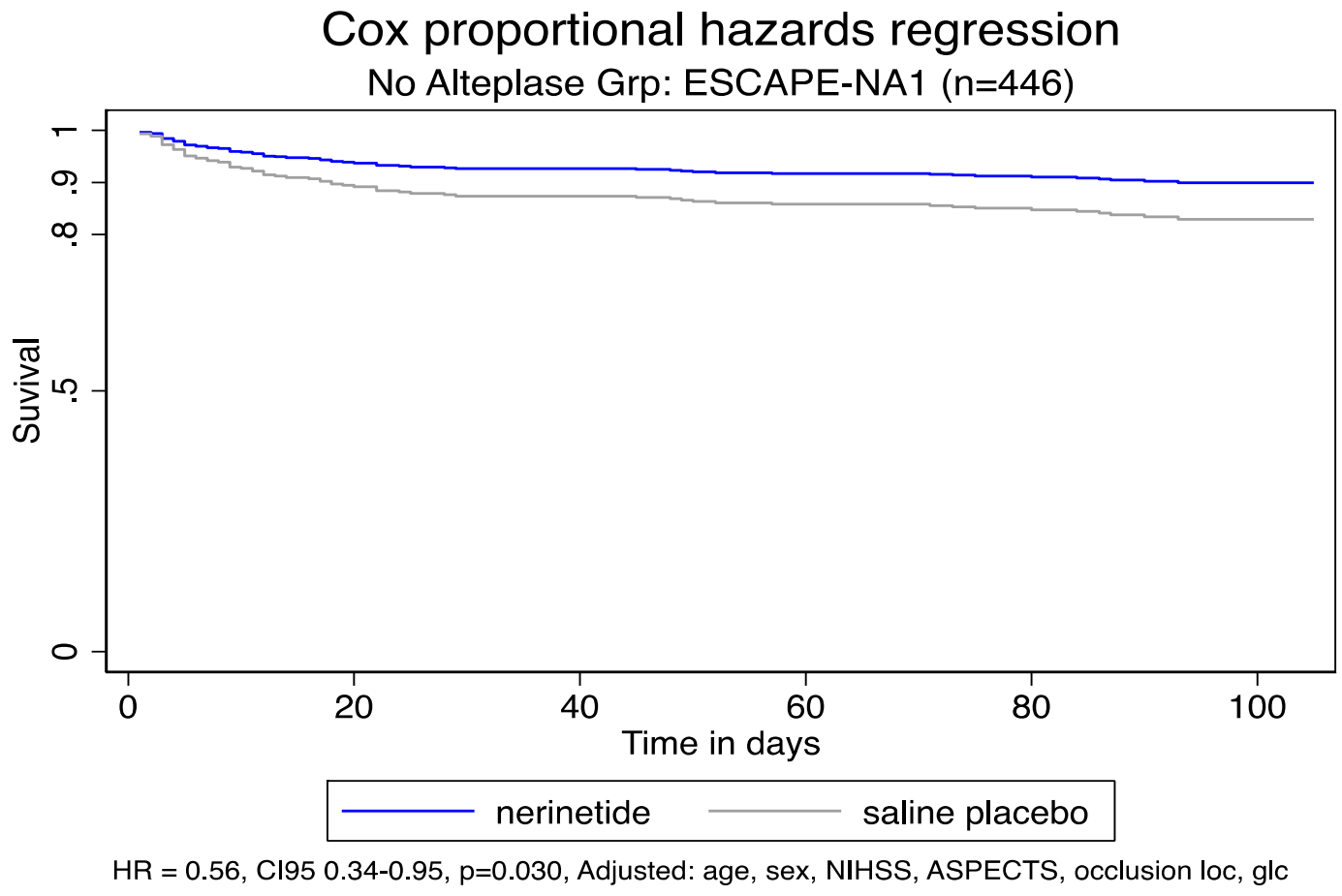
Mortality Benefit in the no-alteplase stratum



Mortality reduction:

- 7.5% absolute risk difference
- Adj HR = 0.56 (0.34-0.95)

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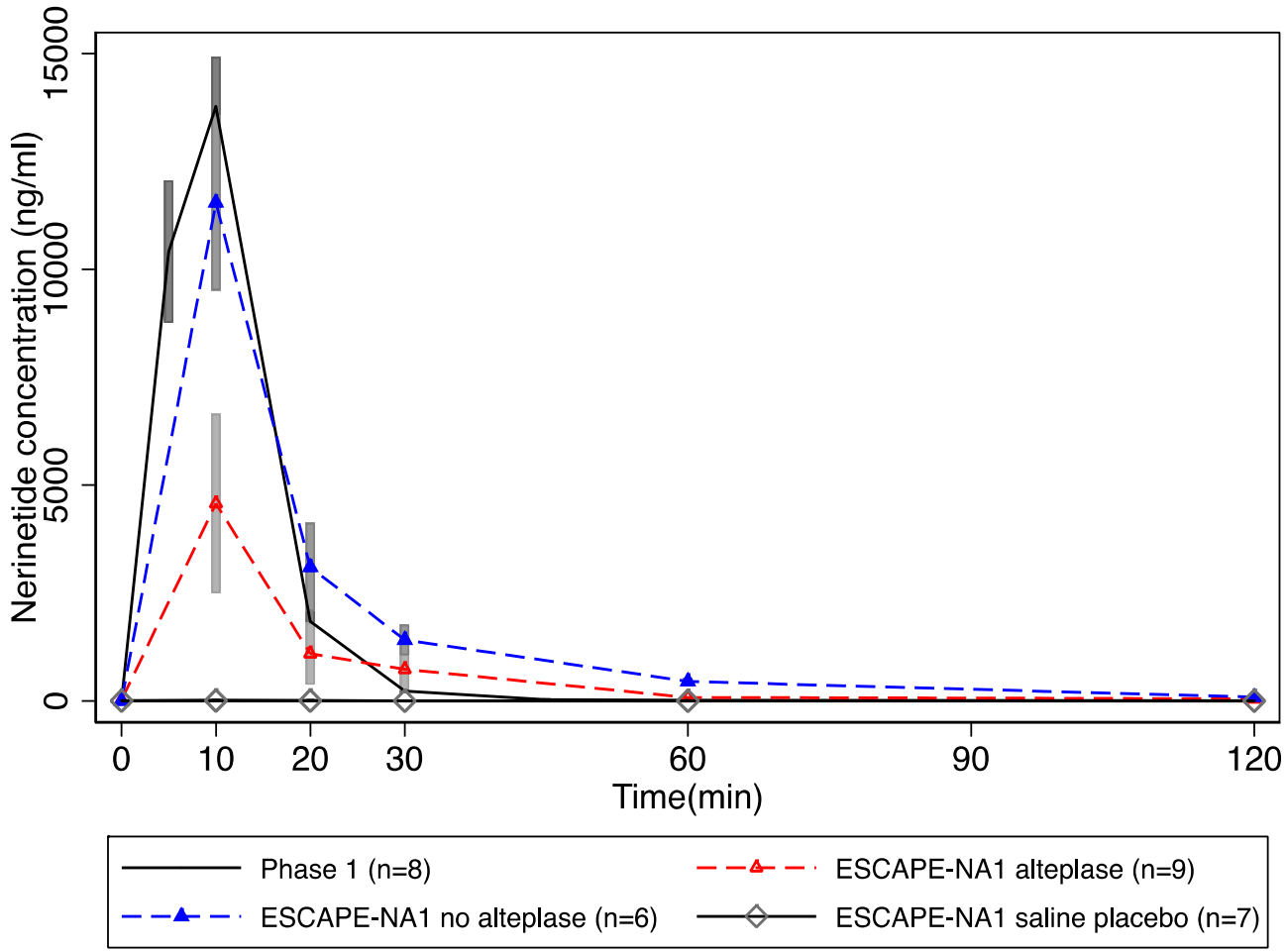
Large reduction in nerinetide levels (red line) in the alteplase group



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Safety events were similar in both groups

	Placebo (n=554)	Nerinetide (n=547)	RR* (95% CI)
Any serious adverse event	198 (35.7%)	181 (33.1%)	0.92 (0.79-1.09)
Stroke-in-evolution (progression)	43 (7.8%)	36 (6.6%)	0.85 (0.55-1.30)
Ischaemic stroke (new onset/recurrent)	20 (3.6%)	18 (3.3%)	0.91 (0.49-1.70)
Symptomatic ICH	24 (4.3%)	19 (3.5%)	0.80 (0.44-1.45)
Pneumonia	17 (3.1%)	25 (4.6%)	1.49 (0.81-2.73)
Congestive cardiac failure	4 (0.7%)	9 (1.6%)	2.28 (0.71-7.36)
Hypotension**	1 (0.2%)	7 (1.3%)	7.09 (0.88-57.4)
Urinary tract infection	7 (1.3%)	8 (1.5%)	1.15 (0.42-3.17)
Deep vein thrombosis/ pulmonary embolism	8 (1.4%)	3 (0.5%)	0.38 (0.1-1.42)
Angioedema	1 (0.2%)	1 (0.2%)	1.01 (0.06-16.1)
Hives/Urticaria/Pruritis	0	0	---

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Summary

- Including all patients, nerinetide was not superior to placebo (2.1% effect size)
- However, effect modification by alteplase was present
- In the no alteplase stratum,
  - 9.5% absolute effect size in the nerinetide group [adjRR 1.18 (1.01-1.38)]
  - 12.5 cc reduction in median infarct volume
  - 7.5% absolute mortality benefit [adjHR 0.56 (0.34-0.95)]
  - PK data show a large reduction in measureable nerinetide in the alteplase group
- **Neuroprotection in humans is possible**. This will be explored in further studies of nerinetide

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Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): a multicentre, double-blind, randomised controlled trial

Michael D Hill, Mayank Goyal, Bijoy K Menon, Raul G Nogueira, Ryan A McTaggart, Andrew M Demchuk, Alexandre Y Poppe, Brian H Buck, Thalia S Field, Dar Dowlatshahi , Brian A van Adel, Richard H Swartz, Ruchir A Shah, Eric Sauvageau, Charlotte Zerna, Johanna M Ospel, Manish Joshi, Mohammed A Almekhlafi, Karla J Ryckborst, Mark W Lowerison, Kathy Heard, David Garman , Diogo Haussen, Shawna M Cutting, Shelagh B Coutts, Daniel Roy, Jeremy L Rempel, Axel CR Rohr, Daniela Iancu, Demetrios J Sahlas, Amy Y X Yu, Thomas G Devlin, Ricardo A Hanel, Volker Puetz, Frank L Silver, Bruce C V Campbell, René Chapot, Jeanne Teitelbaum, Jennifer L Mandzia, Timothy J Kleinig, David Turkel-Parrella, Donald Heck, Michael E Kelly, Aditya Bharatha, Oh Young Bang, Ashutosh Jadhav, Rishi Gupta, Donald F Frei, Jason W Tarpley, Cameron G McDougall, Staffan Holmin, Joung-Ho Rha, Ajit S Puri, Marie-Christine Camden, Götz Thomalla, Hana Choe, Stephen J Phillips, Joseph L Schindler, John Thornton, Simon Nagel, Ji Hoe Heo, Sung-Il Sohn, Marios-Nikos Psychogios, Ronald F Budzik, Sidney Starkman, Coleman O Martin, Paul A Burns, Seán Murphy, George A Lopez, Joey English, Michael Tymianski, on behalf of the ESCAPE-NA1 Investigators

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