EXTEND

EXtending the time for Thrombolysis in Emergency Neurological Deficits

EXtending the time for Thombolysis in Emergency Neurological Deficits (EXTEND)

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Background

The current guideline for thrombolysis in acute ischemic stroke is **less than 4.5 hours** from stroke onset

But advanced imaging studies from our group and others suggest that the ischemic penumbra can exist up to 24 hours after onset and its salvage can lead to improved clinical outcome.*

EPITHET phase 2 trial demonstrated that perfusion imaging enabled the identification of an enriched cohort with clinically significant penumbra who might benefit from thrombolytic therapy beyond the current time window.#

Ma H et al, Int J Stroke 2015, Markus R et al Brain 2004 and Read Sj et al. Ann Neurol 2004.*
Davis SM et al. Lancet Neurology 2008.

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Hypothesis

Ischaemic stroke patients selected with significant **penumbral mismatch** at 4.5 - 9 hours post stroke onset, or following 'Wake Up Stroke', will have improved clinical outcomes when given intravenous tPA compared to placebo

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Study Design

Phase III randomised, multicentre, double-blinded, stratified, placebo controlled trial (tPA 0.9mg/kg vs placebo) with imaging selection (CTP or MR Diffusion/Perfusion)

Stratified for time of randomisation after stroke

1. 4.5 – 6 hours
2. >6 – 9 hours
3. Wake Up Stroke

Sample size = 310 patients

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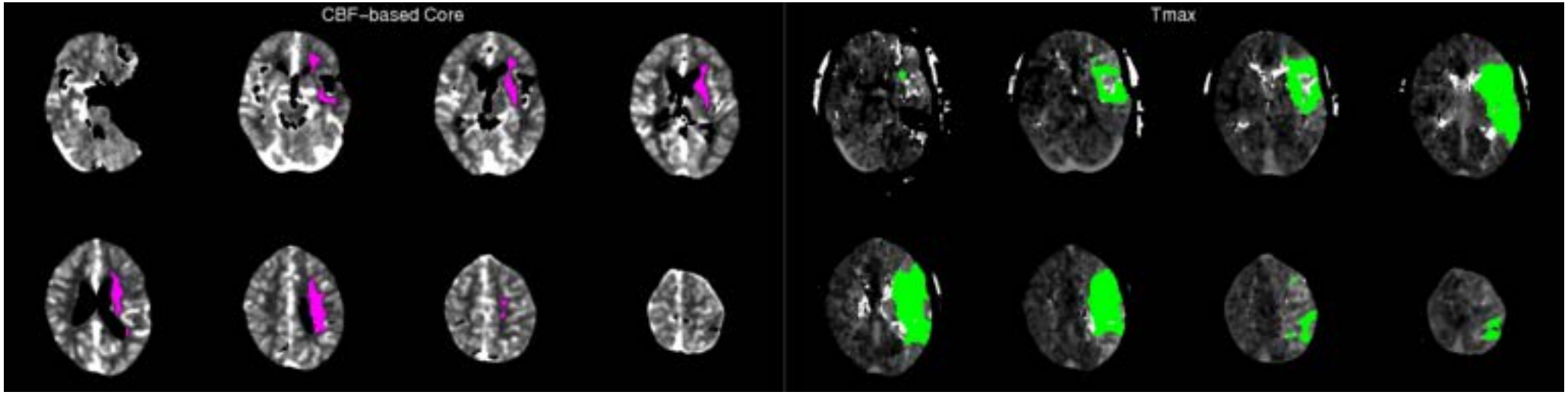
Perfusion Imaging Selection



RAPID* automated CT perfusion or MR perfusion

- **Penumbral mismatch criteria**

1. Hypoperfusion to core volume ratio	> 1.2
2. Perfusion lesion - core absolute difference	>10 ml
3. Ischaemic core lesion volume	≤70 ml

* iSchemaView

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Early Cessation of Recruitment

After the publication of the WAKE UP Study, the Steering committee sought a recommendation from the DSMB and a decision was made to cease recruitment on 6th June 2018.

In total there were **225 patients** recruited.

There were 112 patients received placebo and 113 patients received thrombolysis.

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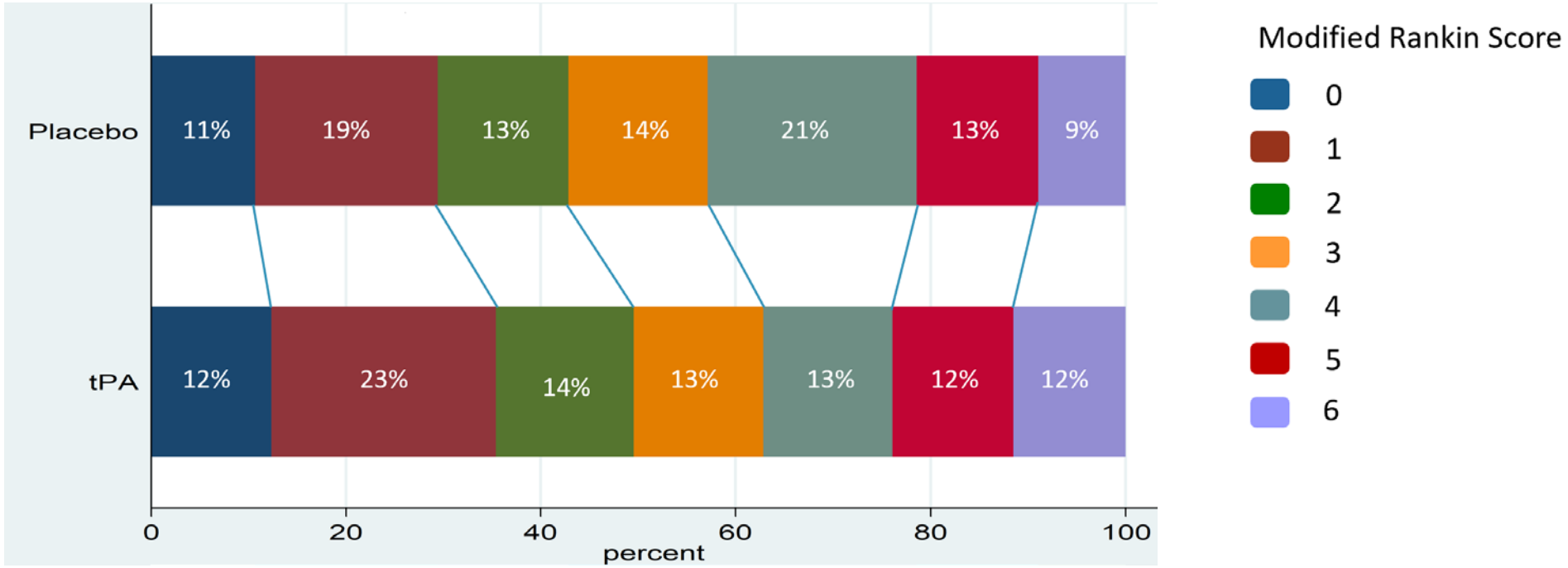
Intention to Treat: Primary End Point



mRS 0-1 at 90 days

tPA **35%** vs Placebo **29%**

Adjusted Relative Risk **1.44** (95%C.I. 1.01, 2.06) **P=0.04**

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Current aims:

- Per protocol analysis
- Secondary and other outcome events

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EXTEND: Per Protocol Analysis

	tPA	Placebo
Total Number	**99**	**105**
Imaging exclusions:		
Large core	**6**	**0**
Posterior circulation	**2**	**2**
Artefact	**2**	**5**
Small Mismatch	**2**	**0**
Excluded for Other Reasons:		
Subarachnoid Haemorrhage	**1**	**0**
Investigation product not given	**1**	**0**
Total Number Excluded	**14**	**7**

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Results: Per Protocol Analysis: Baseline Characteristics

Characteristics	Placebo	tPA
Number	105	99
Age, mean (SD)	71.5 (12.5)	74.0 (11.6)
Male (%)	59 (56%)	54 (51%)
Median NIHSS admission	11.0 (IQR 7.0, 17)	12.0 (IQR 7.0,17.0)
4.5-6 hours	10 (10%)	11 (10%)
6-9 hours	26 (25%)	26 (25%)
Wake Up Stroke	69 (65%)	69 (65%)
Median time from onset to therapy (hours)	7.5 (IQR 6.2, 8.3)	7.2 (IQR 6.2, 8.1)
Median time from last known well to therapy (hours)	8.9 (IQR 7.0, 11.5)	9.9 (IQR 6.8, 11.6)
Median Ischemic Core volume (ml)	6.33 (IQR 0, 19.48)	4.45 (IQR 0, 20.28)
Median Perfusion lesion (ml)	79.0 (IQR 50.71, 110.04)	74.24 (IQR 40.08, 126.2)
Large vessel occlusion (%)	81 (72%)	74 (70%)

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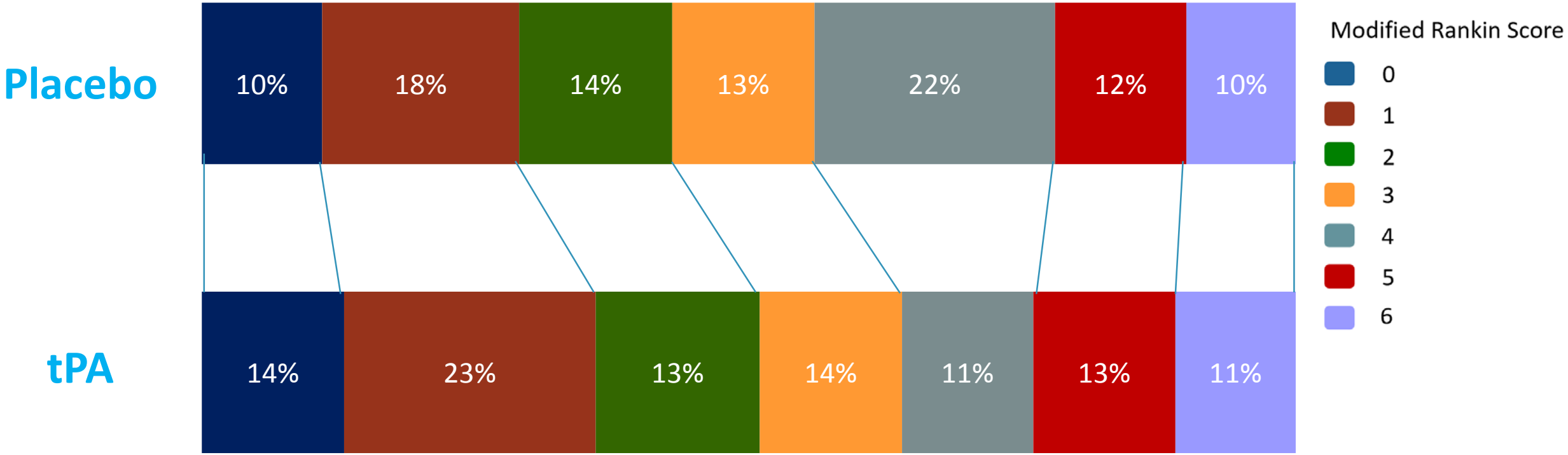
Result: Per Protocol Analysis
Primary End Point: mRS 0-1



mRs 0-1 tPA **37%** vs Placebo **29%**

Adjusted Relative Risk **1.45** (95%C.I. 1.01, 2.10) **P=0.045**

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Results – Per Protocol Analysis: Other Endpoints

Results	Placebo	tpa	Adjusted Relative Risk (CI)	P value
mRS 0-2 at 90 days	43%	51%	1.30 (1.00, 1.49)	***0.049***
mRS Shift at 90 days			Adjusted Common O.R. 1.43 (0.87, 2.34)	0.156
Early Neurological improvement NIHSS reduction =>8 points or 0-1 at 24 hours	10%	25%	2.67 (1.41, 5.04)	***0.002***
Reperfusion 90% at 24 hours	28%	51%	1.78 (1.24, 2.55)	***0.001***
Reperfusion 50% at 24 hours	53%	73%	1.33 (1.07, 1.64)	***0.009***
Recanalization at 24 hours	40%	70%	1.71 (1.31, 2.23)	***<0.001***

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Per Protocol Analysis Results: Safety

Death at 90 days

- Placebo 9.5%
- tPA 11.1%
- Adjusted Relative Risk: 1.03 (CI 0.49, 2.17) **p=0.77**

Symptomatic Intracranial Haemorrhage at 36 hours

- Placebo 1 (1%)
- tPA 6 (6%)
- Adjusted Relative Risk 6.48 (CI 0.85, 49.35) **p =0.066**

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Conclusions

tPA treated patients presenting within 9 hours or with wake up stroke selected by automated perfusion imaging achieved a **significantly higher rate of excellent functional outcome** compared to placebo.

Per Protocol Analysis showed a **similar primary outcome** as the **positive** Intention To Treat Analysis result but **under-powered** due to loss of patients.

For secondary and other outcomes in per protocol analysis: there was **superior reperfusion, recanalization and early neurological improvement** compared to placebo

There was an increase in the rate of sICH **consistent with other thrombolytic trials**, but this was not associated with increased mortality and did not negate the positive result of improved rate of excellent functional outcome.

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EXTEND is the **first** positive thrombolysis trial in an extended time window using automated penumbral imaging

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AUSTRALIA
Royal Melbourne Hospital (VIC)
Austin Hospital (VIC)
John Hunter Hospital (NSW)
Box Hill Hospital (VIC)
Royal Brisbane & Women's Hospital (QLD)
Flinders Medical Centre (SA)
Royal Adelaide Hospital (SA)
Royal Perth Hospital (WA)
Epworth Healthcare (VIC)
Monash Medical Centre (VIC)
Sir Charles Gairdner Hospital (WA)
St Vincent's Hospital (NSW)

AUSTRALIA
Western Hospital (VIC)
Lyell McEwin Hospital (SA)
Royal North Shore Hospital (NSW)
Nambour General Hospital (QLD)
Westmead Hospital (NSW)
The Queen Elizabeth Hospital (SA)
Gosford Hospital (NSW)
Geelong hospital (VIC)
Gold Coast hospital (QLD)
Fiona Stanley hospital (WA)

NEW ZEALAND
Auckland Hospital

TAIWAN
China Medical University Hospital
En Chu Kong Hospital
Shuang Ho Hospital
China Medical University Beigang Hospital
Kaohsiung Veterans General Hospital
National Cheng Kung University Hospital
Tri-Service General Hospital
National Taiwan University Hospital
Changhua Christian Hospital
Wan Fang Hospital
Shin Kong Memorial Hospital

FINLAND
Helsinki Hospital

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Neuroscience Trial Australia

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