KANSAS INITIATIVE FOR STROKE SURVIVAL

A PROJECT BY AND FOR KANSANS

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Extending tPA Past 4.5 Hours

"First Tuesdays" Lecture Series

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Introduction and Goal of “First Tuesdays”

- Didactic lecture series as part of the Kansas Initiative for Stroke Survival (KISS)
- Updates in Practice and FAQ’s on Acute Stroke Care
- 20 minute didactic, 10 minutes for questions/discussion

Current guidelines

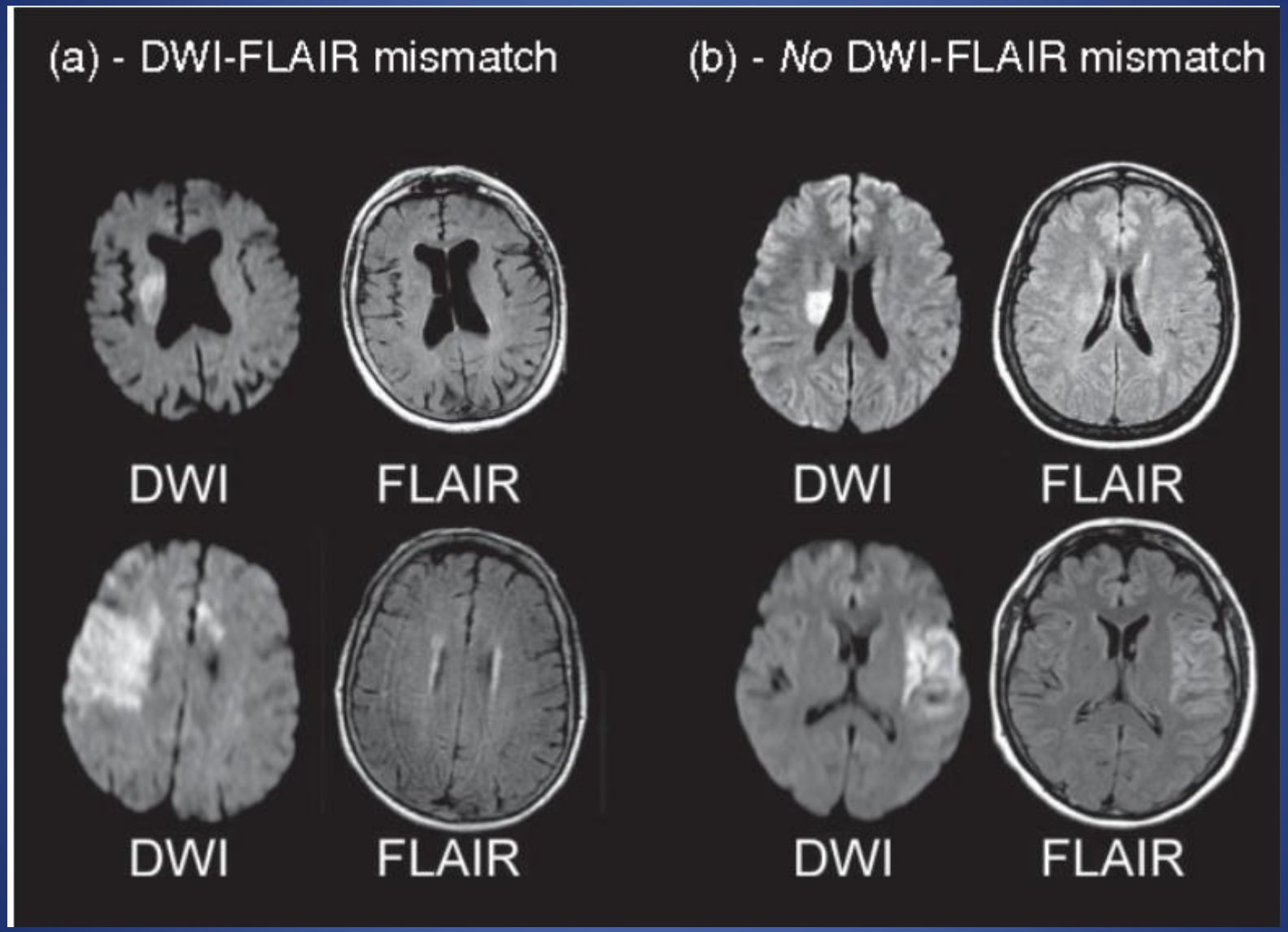
- IV alteplase (tPA) for all patients who have **disabling symptoms** of acute stroke
  - Earlier was within 3 hours of last well
  - Within 4.5 hours of last well now established in clinical practice[1]

Powers et al, *Stroke* 2018; 1. Hacke et al, *NEJM* 2008

WAKE-UP Trial

- RCT of patients with unknown time of stroke onset
- Excluded patients with NIHSS>25 and patients planning to undergo EVT
- MRI criteria showing ischemia on DWI but no hyperintensity on FLAIR
- Randomized to alteplase vs placebo if mismatch on MRI

Thomalla et al, *NEJM* 2019

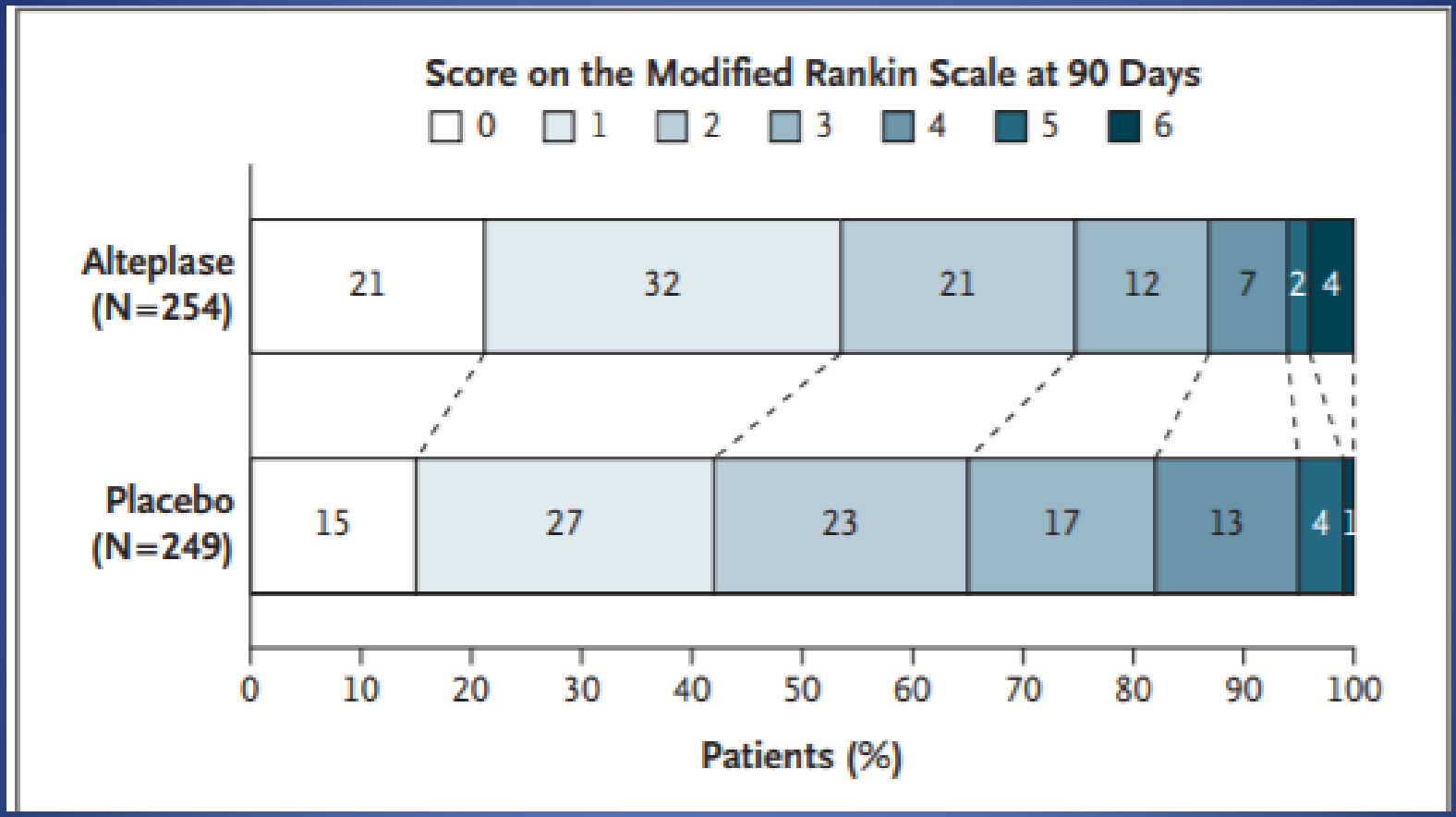


Thomalla et al, *Int J Stroke* 2014

Table 2. Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population).*

Outcome	Alteplase Group (N=254)	Placebo Group (N=249)	Effect Variable	Adjusted Value (95% CI)†	P Value
Primary efficacy end point					
Favorable outcome at 90 days — no./total no. (%)‡	131/246 (53.3)	102/244 (41.8)	Odds ratio	1.61 (1.09 to 2.36)	0.02
Secondary efficacy end points					
Median score on modified Rankin scale at 90 days (IQR)§	1 (1–3)	2 (1–3)	Common odds ratio	1.62 (1.17 to 2.23)	0.003¶
Correlation between treatment response at 90 days and deficit level at baseline — no./total no. (%)‖	72/246 (29.3)	44/244 (18.0)	Odds ratio	1.88 (1.22 to 2.89)	0.004¶
Global Outcome Score at 90 days**			Odds ratio	1.47 (1.07 to 2.04)	0.02¶
Median score on Beck Depression Inventory at 90 days (IQR)††	6.0 (2.0–11.0)	7.0 (2.0–14.0)	Mean difference ($\log_e$)	−0.04 (−0.22 to 0.15)	0.69¶
Total score on EQ-5D at 90 days‡‡	1.9±2.1	2.4±2.4	Mean difference	−0.52 (−0.88 to −0.16)	0.004¶
Score on visual analog scale on EQ-5D at 90 days§§	72.6±19.7)	64.9±23.8	Mean difference	7.64 (3.75 to 11.51)	<0.001¶
Median infarct volume at 22–36 hr (IQR) — ml ¶¶	3.0 (0.8–17.7)	3.3 (1.1–16.6)	Mean difference ($\log_e$)	−0.16 (−0.47 to 0.15)	0.32¶

Thomalla et al, *NEJM* 2019



Thomalla et al, *NEJM* 2019

Table 3. Safety Outcomes.

Outcome	Alteplase Group (N=251)	Placebo Group (N=244)	Adjusted Odds Ratio (95% CI)*	P Value
	no. (%)			
Primary†				
Death or dependency at 90 days	33 (13.5)	44 (18.3)	0.68 (0.39–1.18)	0.17
Death at 90 days	10 (4.1)	3 (1.2)	3.38 (0.92–12.52)	0.07
Secondary				
Symptomatic intracranial hemorrhage				
As defined in SITS-MOST‡	5 (2.0)	1 (0.4)	4.95 (0.57–42.87)	0.15
As defined in ECASS II§	7 (2.8)	3 (1.2)	2.40 (0.60–9.53)	0.21
As defined in ECASS III¶	6 (2.4)	1 (0.4)	6.04 (0.72–50.87)	0.10
As defined in NINDS‖	20 (8.0)	12 (4.9)	1.78 (0.84–3.71)	0.13
Parenchymal hemorrhage type 2**	10 (4.0)	1 (0.4)	10.46 (1.32–82.77)	0.03
Other††				
Space-occupying brain infarction or edema with clinical deterioration	6 (2.4)	2 (0.8)		
Recurrent ischemic stroke				
Asymptomatic‡‡	58 (23.1)	55 (22.5)		
Symptomatic	17 (6.8)	8 (3.3)		
Major extracranial bleeding	3 (1.2)	0		
Severe anaphylactic reaction	0	1 (0.4)		

Thomalla et al, *NEJM* 2019

Conclusions from WAKE-UP

- Functional outcome more favorable with alteplase than placebo based on MRI criteria
- More deaths and ICH in tPA group, but not significant
- Trial stopped early due to lack of funding and fewer patients enrolled.

Thomalla et al, *NEJM* 2019

EXTEND trial

- Acute stroke with last well between 4.5-9 hours OR wake-up stroke symptoms if midpoint of sleep was <9 hrs
- NIHSS 4-26
- Excluded patient who were planned for EVT
- Imaging criteria was CTP or MRP with RAPID software: core volume 10-70 mL, mismatch ratio between core and penumbra >1.2
- Randomized to alteplase vs placebo

Ma et al, *NEJM* 2019

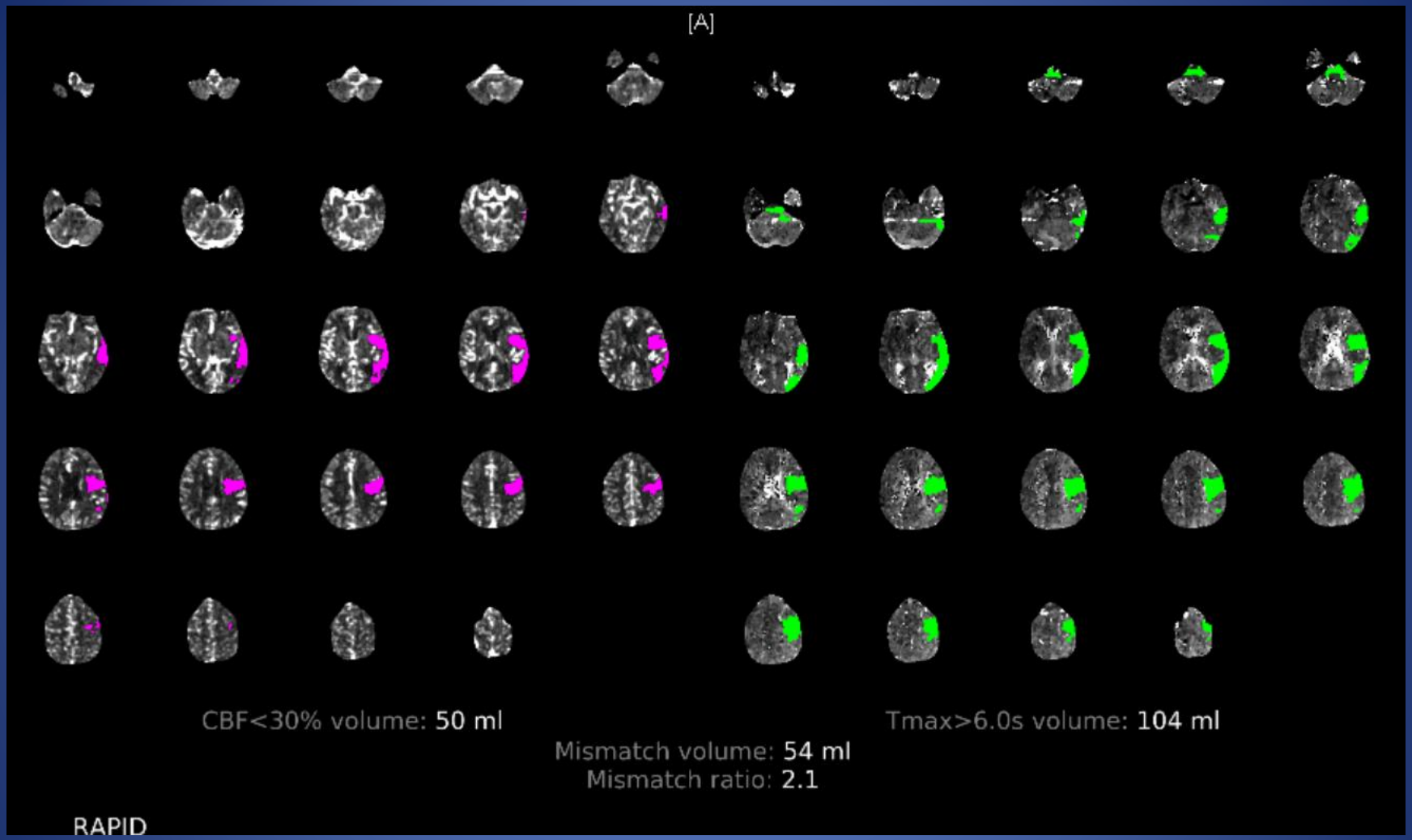

[A]
CBF<30% volume: 50 ml
Tmax>6.0s volume: 104 ml
Mismatch volume: 54 ml
Mismatch ratio: 2.1
RAPID

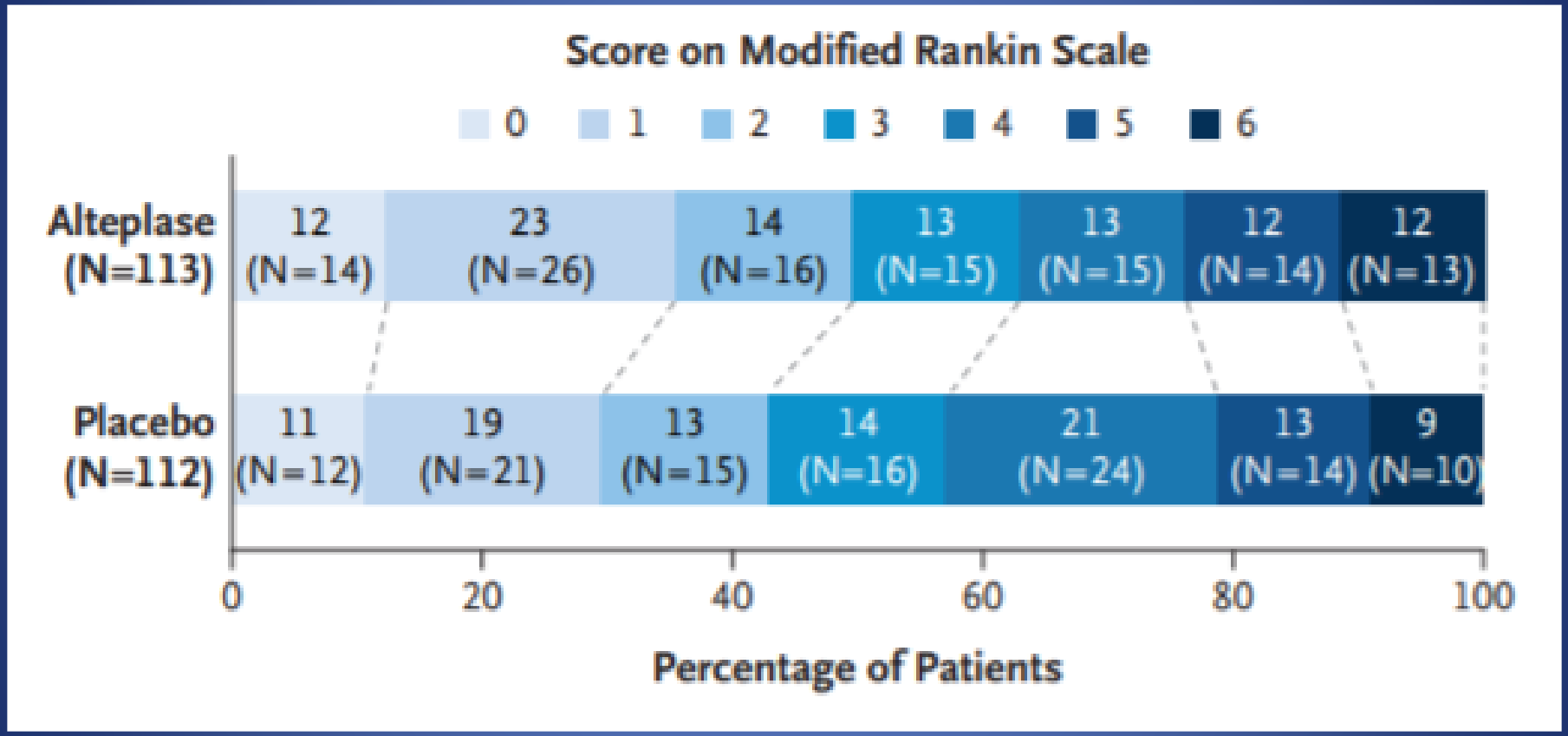
Table 2. Efficacy and Safety Outcomes.*

Outcome	Alteplase (N=113)	Placebo (N=112)	Adjusted Effect Size (95% CI)†	P Value	Unadjusted Effect Size (95% CI)†	P Value
	no./total no. (%)					
Primary outcome						
Score of 0 to 1 on the modified Rankin scale at 90 days‡	40/113 (35.4)	33/112 (29.5)	1.44 (1.01–2.06)	0.04	1.2 (0.82–1.76)	0.35
Secondary outcomes						
Score on the modified Rankin scale at 90 days						
0	14/113 (12.4)	12/112 (10.7)				
1	26/113 (23.0)	21/112 (18.8)				
2	16/113 (14.2)	15/112 (13.4)				
3	15/113 (13.3)	16/112 (14.3)				
4	15/113 (13.3)	24/112 (21.4)				
5	14/113 (12.4)	14/112 (12.5)				
6	13/113 (11.5)	10/112 (8.9)				
Functional improvement§			1.55 (0.96–2.49)		1.18 (0.74–1.87)	
Functional independence¶	56/113 (49.6)	48/112 (42.9)	1.36 (1.06–1.76)		1.16 (0.87–1.54)	
Percentage of reperfusion at 24 hr						
≥90%	53/106 (50.0)	31/109 (28.4)	1.73 (1.22–2.46)		1.76 (1.23–2.51)	
≥50%	76/106 (71.7)	57/109 (52.3)	1.35 (1.09–1.67)		1.37 (1.10–1.70)	

Ma et al, *NEJM* 2019

Tertiary outcomes						
Recanalization at 24 hr	72/107 (67.3)	43/109 (39.4%)	1.68 (1.29–2.19)		1.71 (1.30–2.23)	
Major neurologic improvement						
At 24 hr	27/113 (23.9)	11/112 (9.8)	2.76 (1.45–5.26)		2.43 (1.27–4.67)	
At 72 hr	32/112 (28.6)	22/112 (19.6)	1.56 (0.97–2.52)		1.45 (0.90–2.34)	
At 90 days	59/101 (58.4)	49/99 (49.5)	1.17 (0.91–1.52)		1.18 (0.91–1.53)	
Safety outcomes						
Death within 90 days after intervention	13/113 (11.5)	10/112 (8.9)	1.17 (0.57–2.40)	0.67	1.29 (0.59–2.82)	0.53
Symptomatic intracranial hemorrhage within 36 hr after intervention	7/113 (6.2)	1/112 (0.9)	7.22 (0.97–53.54)	0.053	6.94 (0.86–55.73)	0.07

Ma et al, *NEJM* 2019



Ma et al, *NEJM* 2019

Conclusions from EXTEND

- Trend toward better outcome with alteplase than placebo based on CTP/MRP criteria, but only statistically significant in adjusted analysis with odds ratio of 1.44 (1.01-2.06)
- Trend towards higher ICH with tPA but no increase in mortality
- Terminated early due to publication of WAKE-UP trial

Ma et al, *NEJM* 2019

Conclusions from trials

- Recent studies (DAWN/DEFUSE-3) shows that EVT based on imaging criteria up to 24 hours from last well has much better odds of improving function.
- May be a potential area of intervention in patients who are NOT eligible for EVT (no LVO).
- WAKE UP has better evidence than EXTEND, showing that treating with tPA may be better if unknown time of onset vs known onset >4.5 hrs.
- Will need to have at your center: stat MRI capabilities to select patients

Questions?

- Call for help anytime!
- http://www.kissnetwork.us/
- email at sslavin2@kumc.edu