Late Window Treatment: DAWN, AURORA, and the Effect of Time

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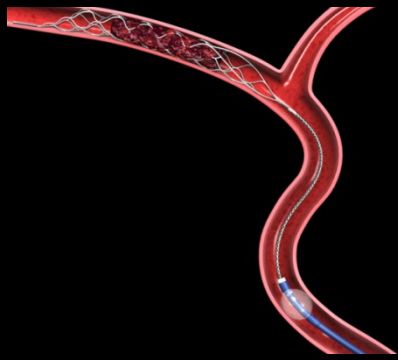

MARCUS STROKE &
NEUROSCIENCE CENTER

Grady

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Disclosures:

Stryker Neurovascular (unpaid)

- DAWN Trial PI
- Trevo Registry Steering Committee
- Trevo-2 Trial PI

Medtronic

- SWIFT and SWIFT-PRIME Trial Steering Committee (unpaid)
- STAR Trial Core Lab

Penumbra (unpaid)

- 3-D Separator Trial Executive Committee

Genentech (Modest)

Neuravi (unpaid)

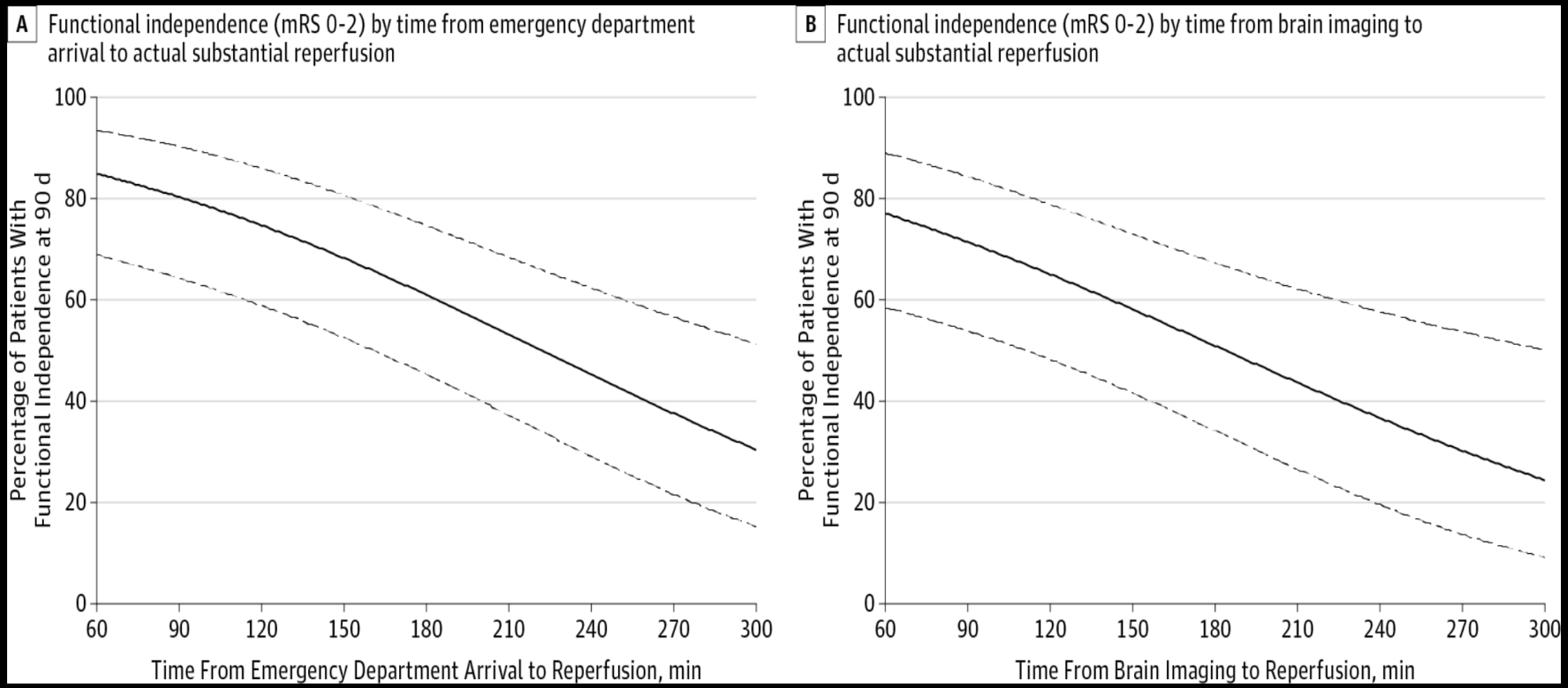
- ARISE-II Trial Steering Committee

Interventional Neurology Journal (unpaid)

- Editor-In-Chief

The Irrefutable Truth:

Time is Brain:



↑ Time to Reperfusion = ↓ Good Clinical Outcome

For every 15-min delay after ED arrival: ~4% of pts ↑ disability

Saver J et al. JAMA. 2016;316(12):1279-1288

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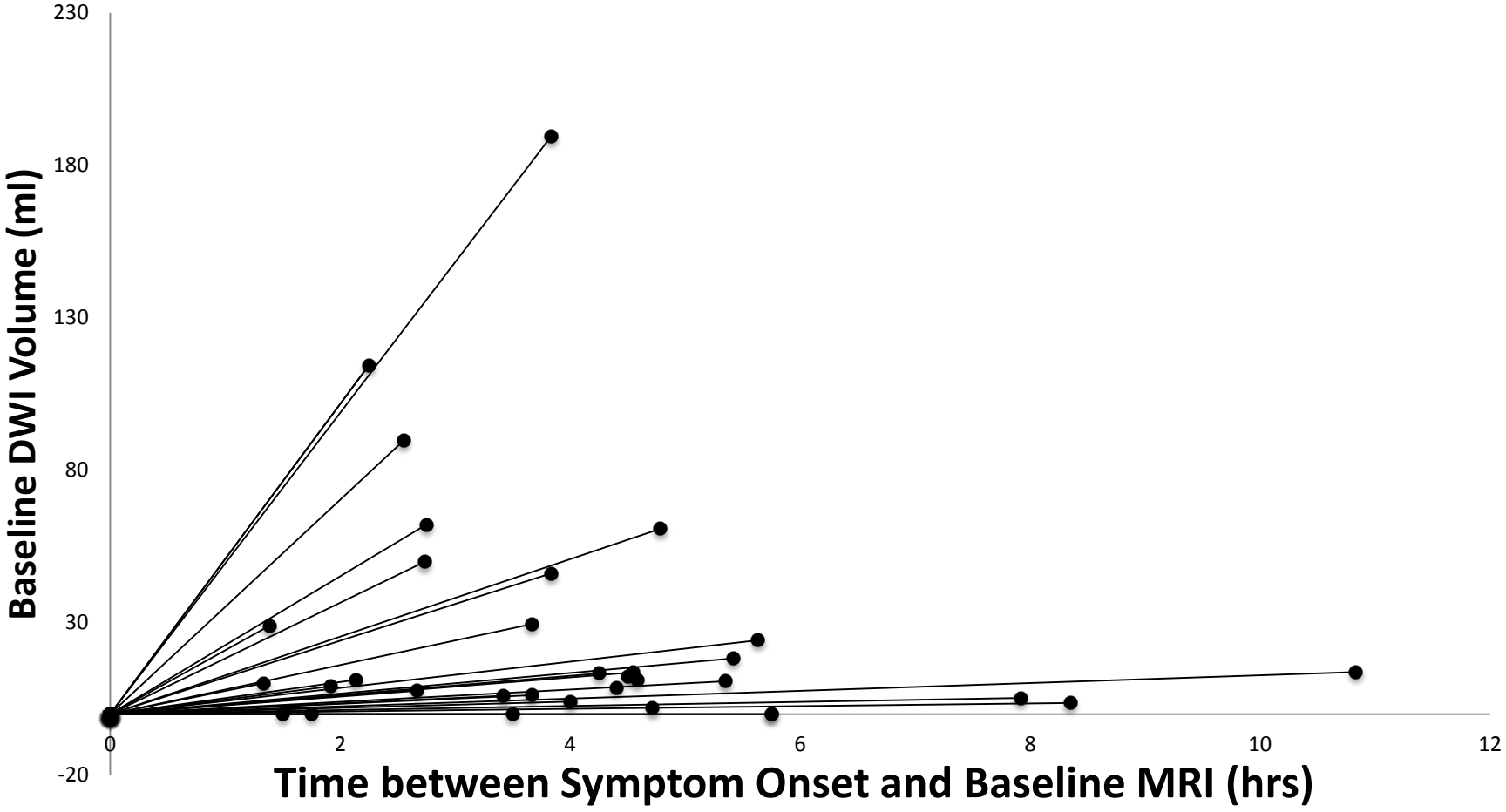
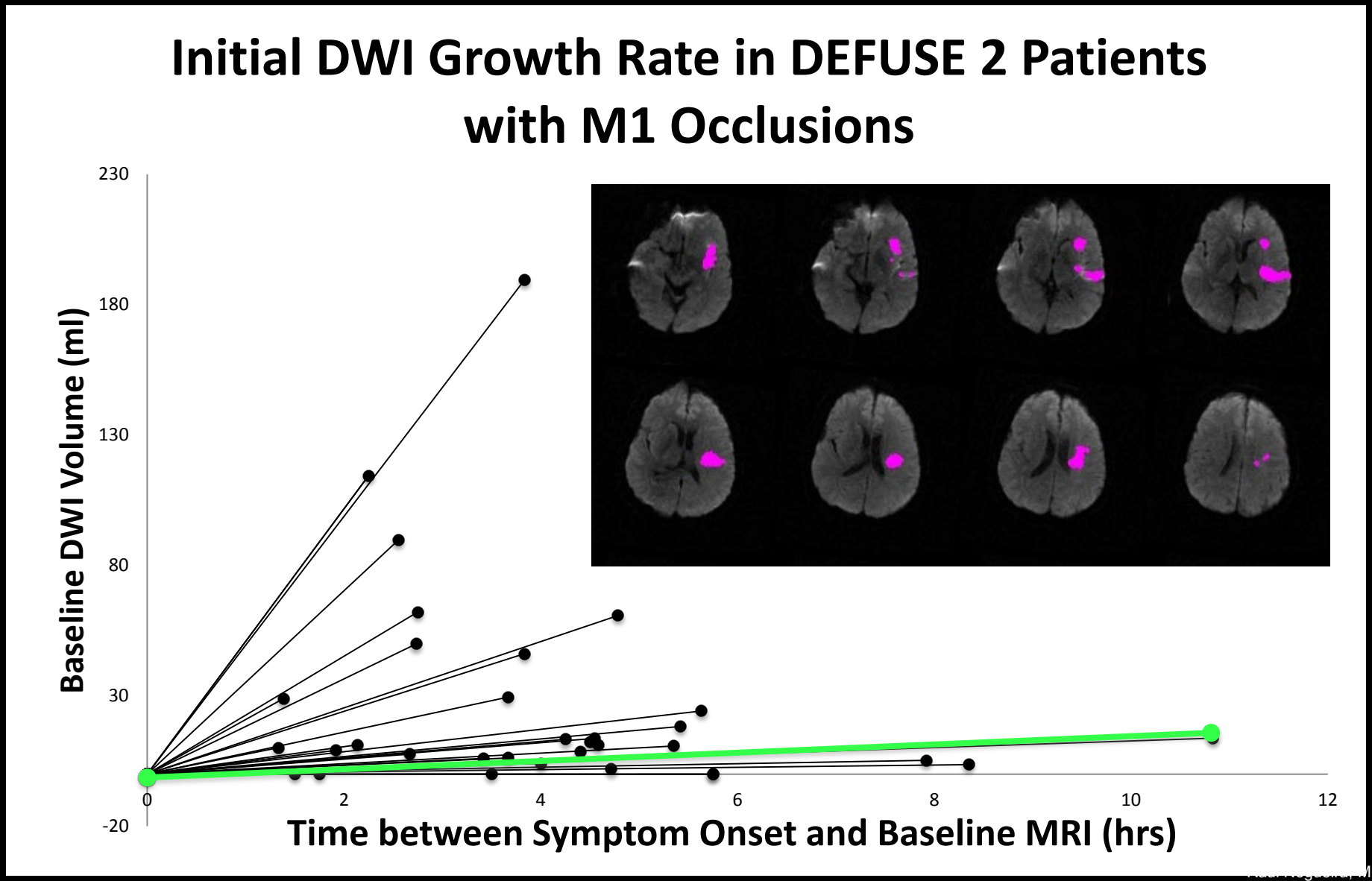
…But Is Time Everything?

Challenging Isolated Time Based Decisions

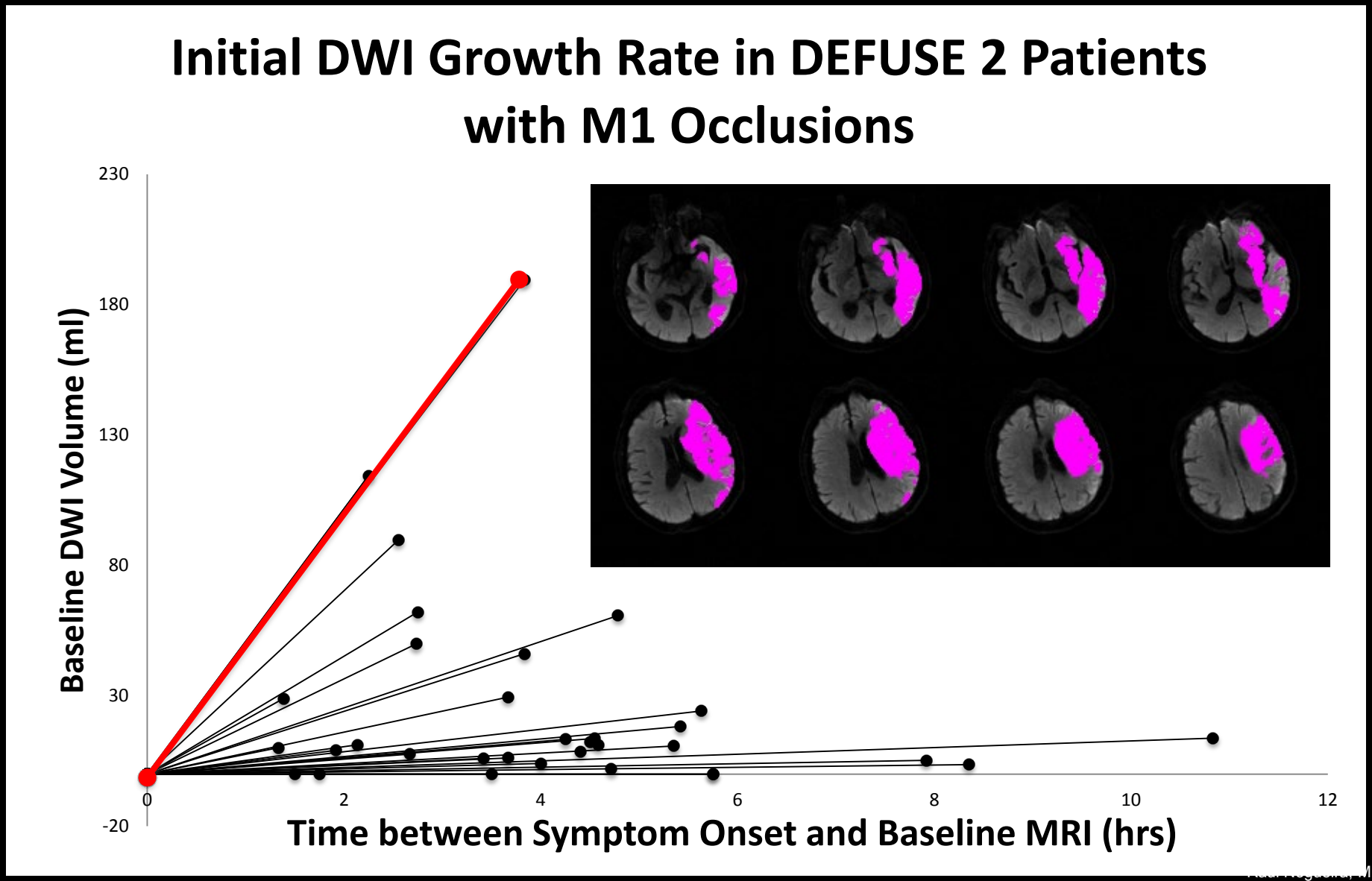
DEFUSE-2: High Variation in DWI Volumes over Time



DEFUSE-2: High Variation in DWI Volumes over Time



DEFUSE-2: High Variation in DWI Volumes over Time



Collateral Flow

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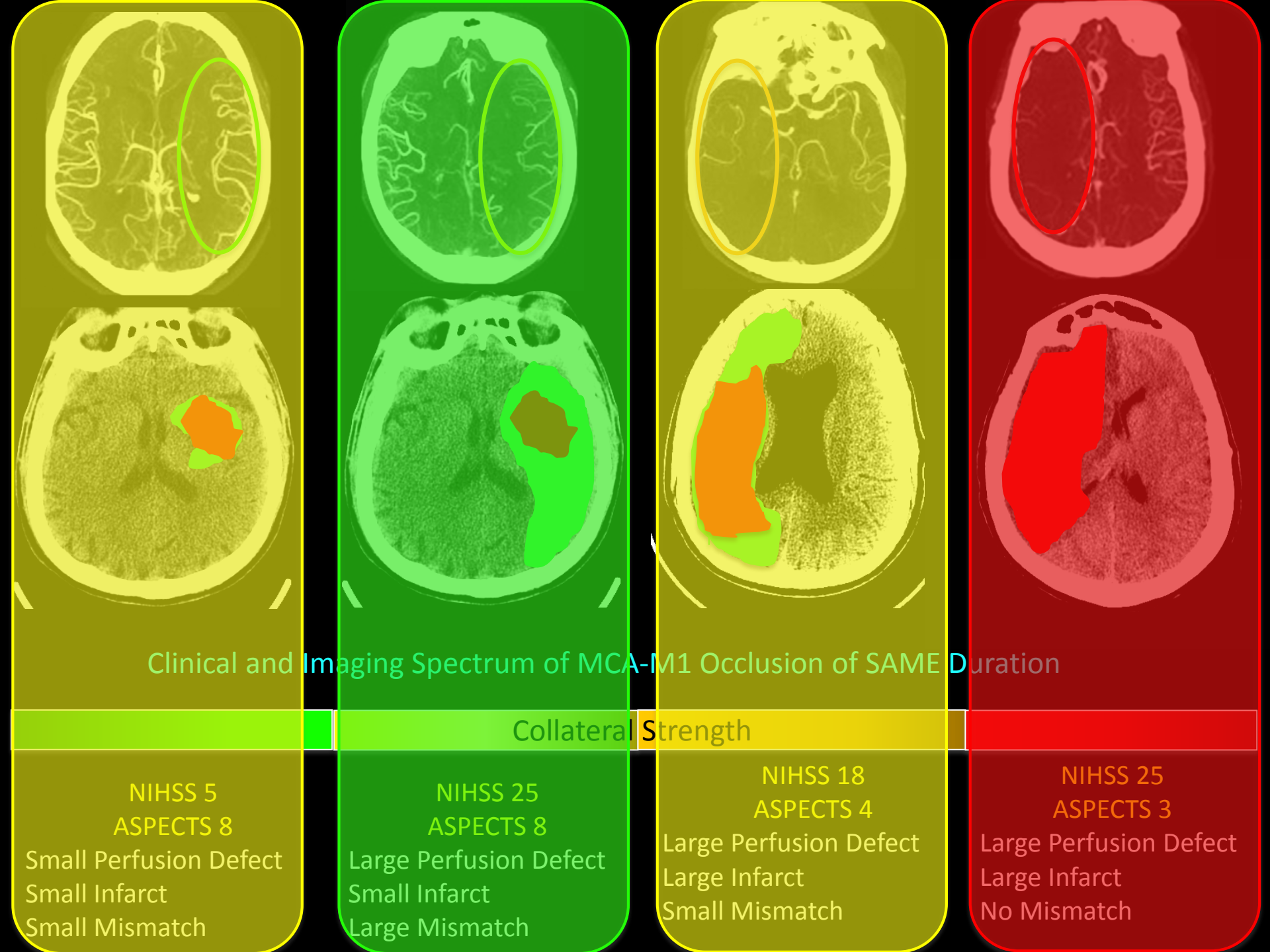
Clinical and Imaging Spectrum of MCA-M1 Occlusion of SAME Duration
Collateral Strength
NIHSS 5
ASPECTS 8
Small Perfusion Defect
Small Infarct
Small Mismatch
NIHSS 25
ASPECTS 8
Large Perfusion Defect
Small Infarct
Large Mismatch
NIHSS 18
ASPECTS 4
Large Perfusion Defect
Large Infarct
Small Mismatch
NIHSS 25
ASPECTS 3
Large Perfusion Defect
Large Infarct
No Mismatch

Refining the Therapeutic Window for Acute Reperfusion Therapy: The Time x Collateral Interaction

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Post Reperfusion Outcomes Equations:

$$\text{Outcomes} = \frac{1}{\text{Final Infarct Volume} \times \text{Regional Eloquence} \times \text{Biological Age}}$$

$$\text{Final Infarct Volume} = \frac{\text{Time of Occlusion}}{\text{Collaterals}}$$

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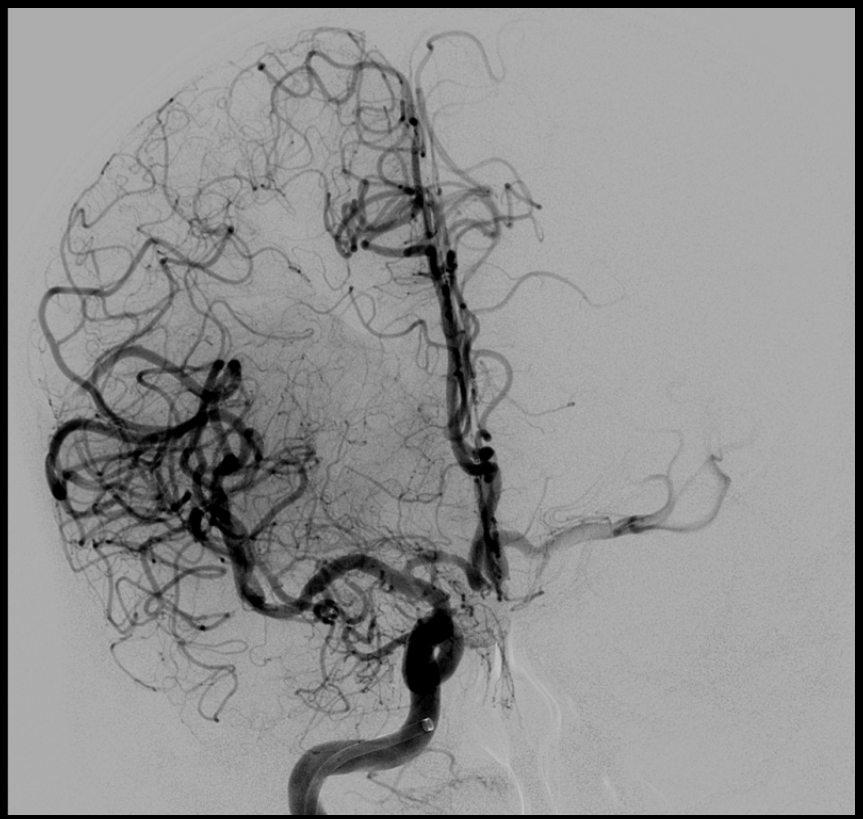
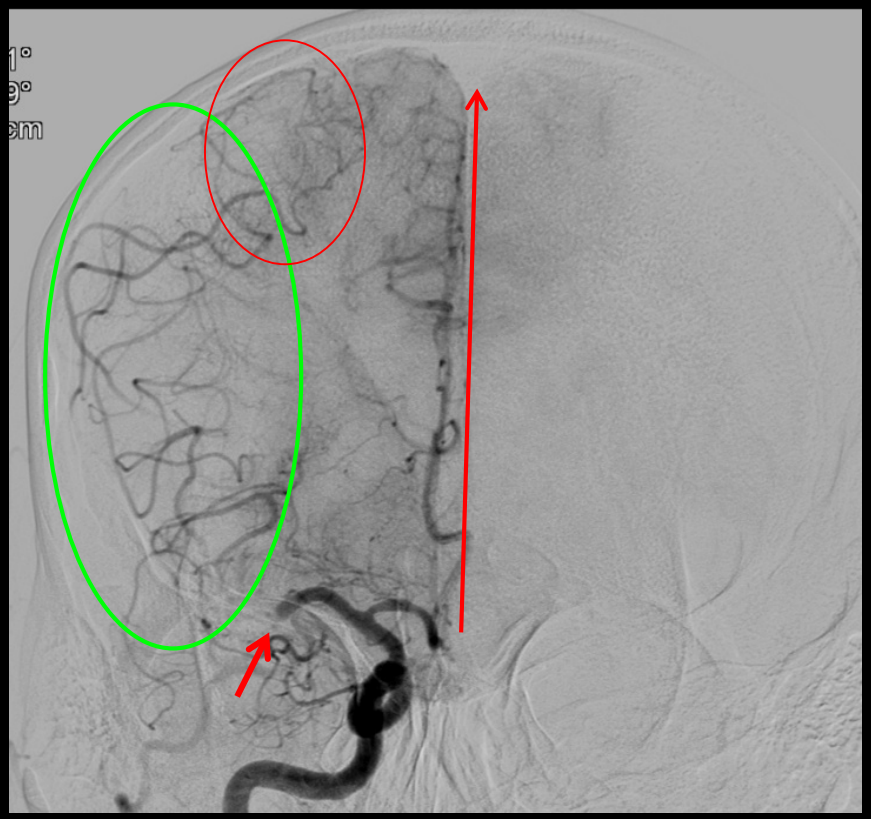
Times is Brain: an Over-Simplistic Concept!

Outcomes = 1 / FIV x Regional Eloquence x Age

Final Infarct Volume = Occlusion Time / Collaterals





Collaterals buy Time....

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Oct/31/2014: Acute Left MCA-M1 Occlusion: Age 74 NIHSS 26

Stroke Onset: 3PM - IV tPA: 4:48PM - CTP:4:53PM – No IAT (<2h onset)

Early Time
but
Poor Collaterals
=
Poor Outcome

FAST PROGRESSOR!

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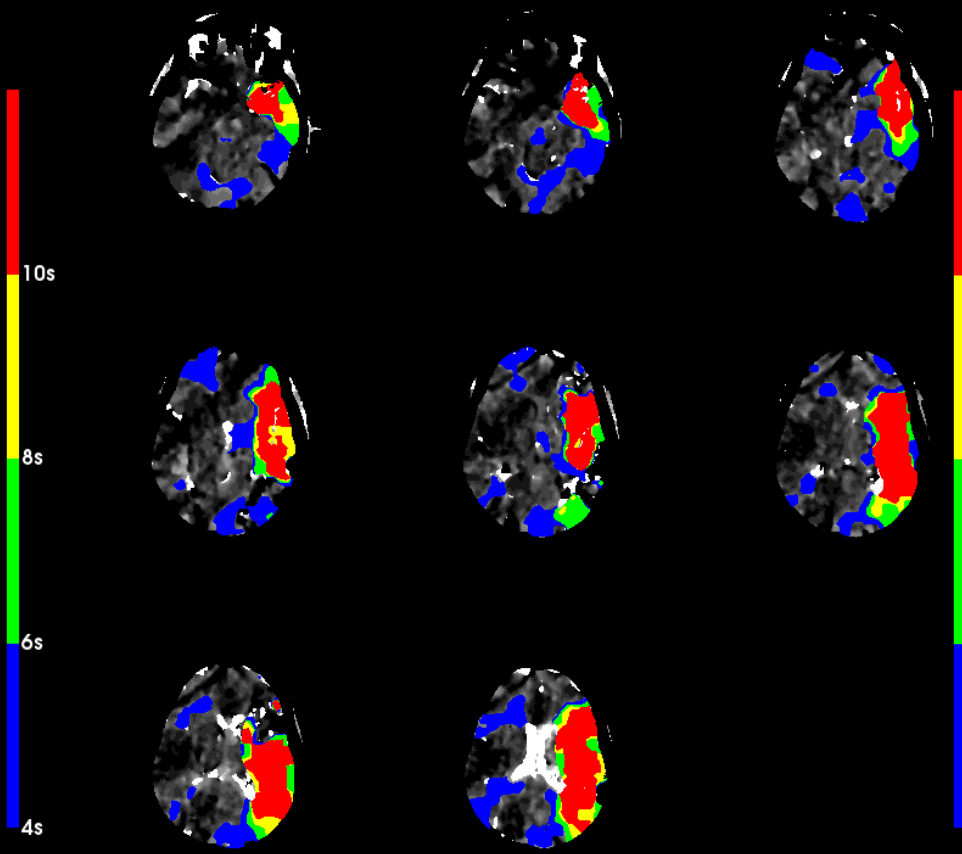
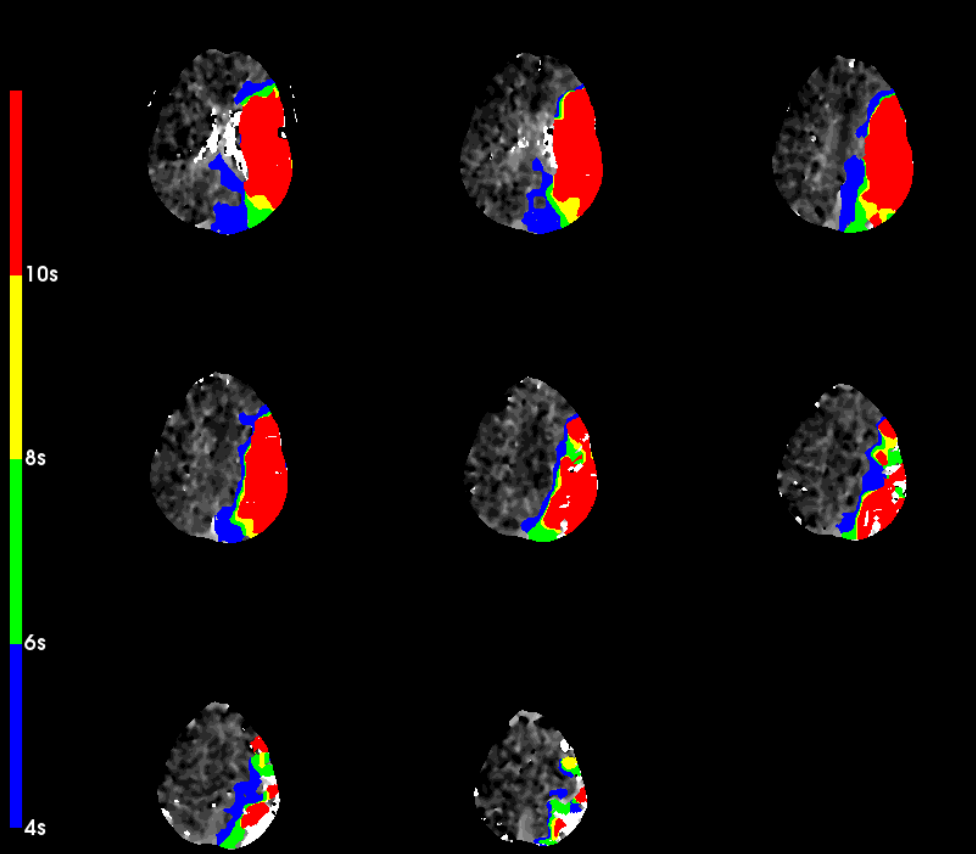
Oct/31/2014: Acute Left MCA-M1 Occlusion: Age 74 NIHSS 26

Stroke Onset: 3PM - IV tPA: 4:48PM - CTP:4:53PM – No IAT (<2h onset)

Tmax MAPS = Collateral Strength = Time to Reperfuse





Perfusion (Tmax>10.0s) volume: 72.3 ml
Perfusion (Tmax>8.0s) volume: 85.3 ml
Perfusion (Tmax>6.0s) volume: 107.9 ml
Perfusion (Tmax>4.0s) volume: 192.1 ml

Perfusion (Tmax>10.0s) volume: 91.8 ml
Perfusion (Tmax>8.0s) volume: 101.4 ml
Perfusion (Tmax>6.0s) volume: 118.6 ml
Perfusion (Tmax>4.0s) volume: 156.7

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Oct/31/2014: Acute Left ICA/M1 Occlusion: Age 75 NIHSS 24

Last Seen Well: 8PM – No IV tPA - CTP: 11:40AM – IAT: 11:55AM (~16h LSW)

Late Time

but

Good Collaterals

=

Good Outcome

SLOW PROGRESSOR!

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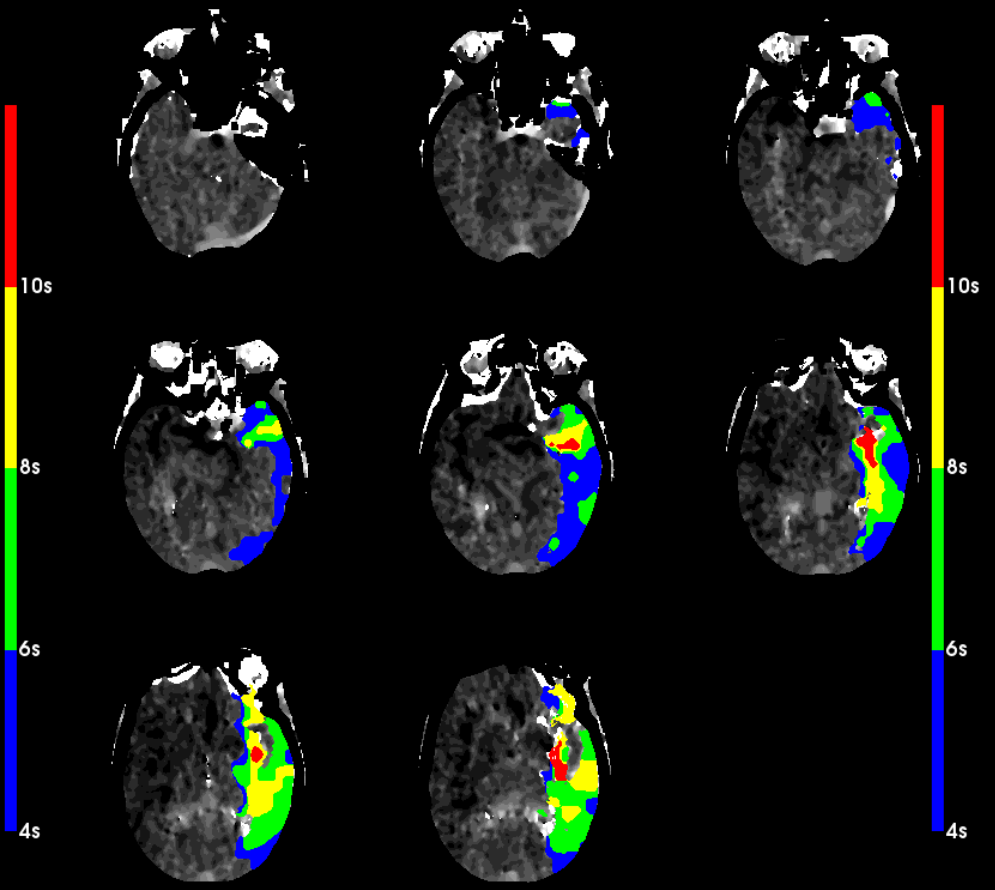
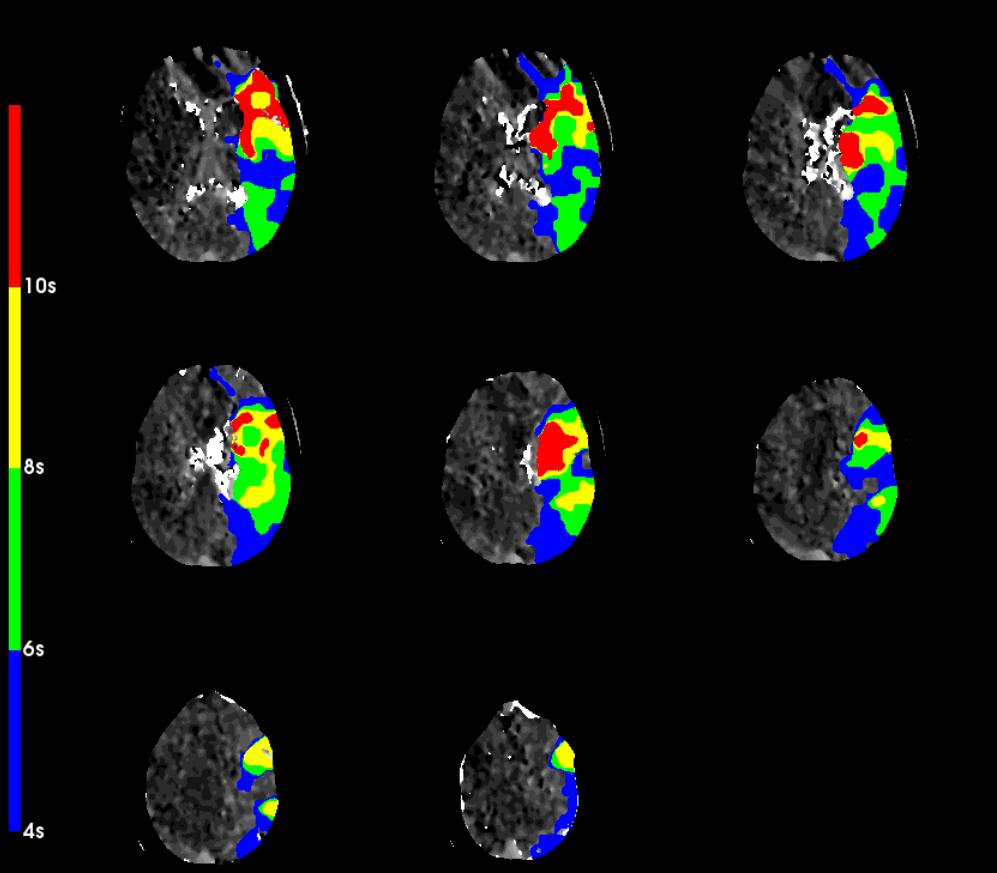
Oct/31/2014: Acute Left ICA/M1 Occlusion: Age 75 NIHSS 24

Last Seen Well: 8PM – No IV tPA - CTP: 11:40AM – IAT: 11:55AM (~16h LSW)

Tmax MAPS = Collateral Strength = Time to Reperfuse





Perfusion (Tmax>10.0s) volume: 3.0 ml
Perfusion (Tmax>8.0s) volume: 17.3 ml
Perfusion (Tmax>6.0s) volume: 43.6 ml
Perfusion (Tmax>4.0s) volume: 75.2 ml

Perfusion (Tmax>10.0s) volume: 16.8 ml
Perfusion (Tmax>8.0s) volume: 38.6 ml
Perfusion (Tmax>6.0s) volume: 78.5 ml
Perfusion (Tmax>4.0s) volume: 133.9 ml

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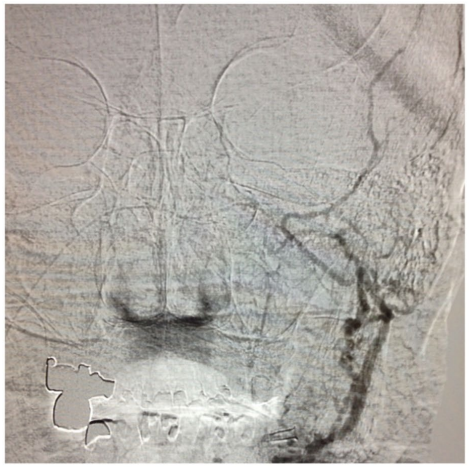
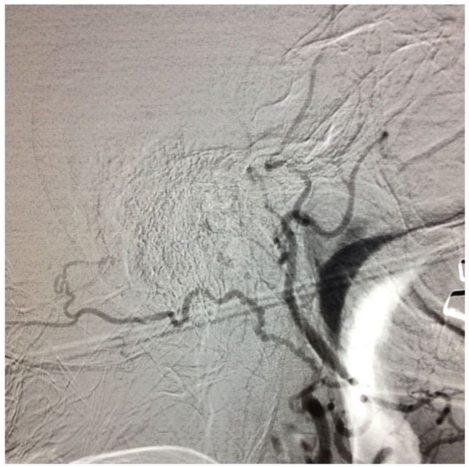
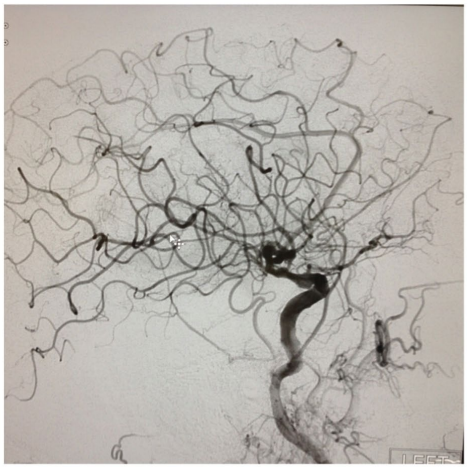
Oct/31/2014: Acute Left ICA/M1 Occlusion: Age 75 NIHSS 24

Last Seen Well: 8PM – No IV tPA - CTP: 11:40AM – IAT: 11:55AM (~16h LSW)

IAT: 9F BCG + PTAS + 1 Pass Stentriever with Navien 072



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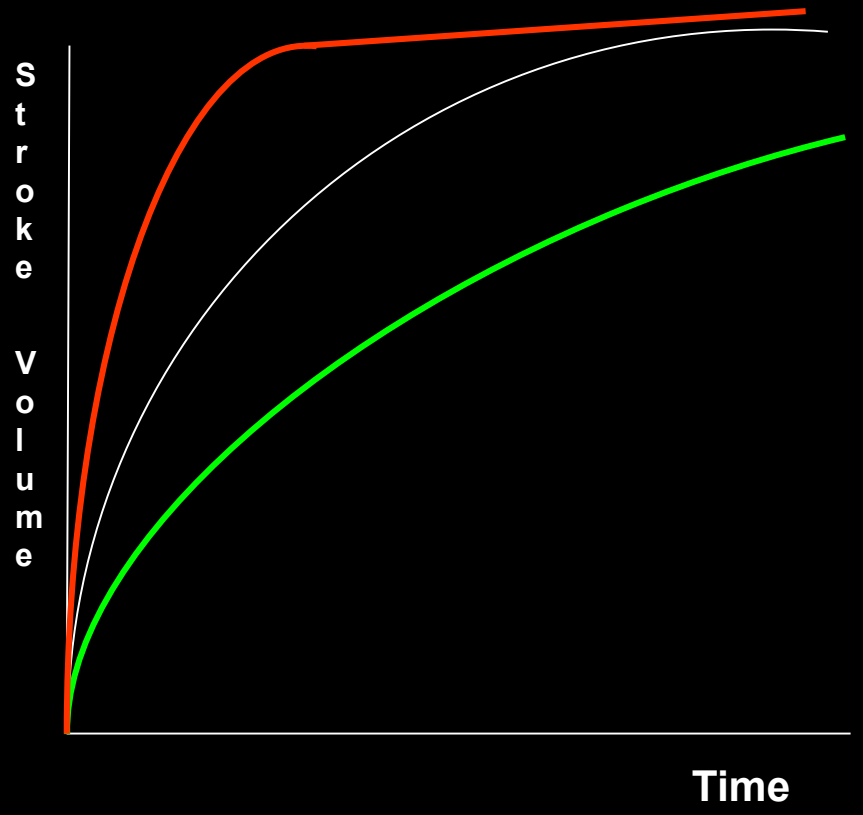
Different Brains Have Different Time Profiles!

The pace of stroke progression appears to be highly variable and is likely dependent of multiple factors other than the duration and intensity of ischemia including:

- Collateral flow (via Circle of Willis and/or leptomeningeal collaterals)
- Ischemic preconditioning
- Cerebral perfusion pressure
- Cerebral blood volume
- Serum glucose
- Body temperature
- Oxygen delivery capacity



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Time, Stroke Severity, Penunbral Tissue and Collaterals

Imaging-Based Endovascular Therapy for Acute Ischemic Stroke due to Proximal Intracranial Anterior Circulation Occlusion Treated Beyond 8 Hours From Time Last Seen Well

OUTCOMES = COLLATERALS

TIME

present beyond this timeframe. We sought to assess safety, procedural, and clinical outcomes of MRI or CT perfusion imaging-based endovascular therapy in patients with anterior circulation stroke treated beyond 8 hours from time last seen well.

Methods—We conducted a multicenter retrospective review of consecutive patients meeting the following criteria: (1) acute proximal intracranial anterior circulation occlusion; (2) endovascular treatment initiated >8 hours from time last seen well; and (3) treatment selection based on MRI or CT perfusion imaging.

Results—Two hundred thirty-seven patients were identified (mean age, 63.8±16 years; mean baseline National Institutes of Health Stroke Scale, 15±5.5; mean time last seen well to treatment, 15±11.2 hours; male gender, 46%). Successful revascularization was achieved in 175 of 237 (73.84%) patients. Parenchymal hematoma occurred in 21 of 237 (8.86%) patients. The 90-day mortality rate was 21.5% (51 of 237). The rate of good outcomes was 45% (100 of 223) in the 223 patients with available modified Rankin Scale data at 90 days or time of hospital discharge. In multivariate analyses, age (OR, 0.96; 95% CI, 0.94 to 0.98; P=0.002), admission National Institutes of Health Stroke Scale (OR, 0.93; 0.87 to 0.98; P=0.016), and successful revascularization (OR, 4.32; 1.99 to 9.39; P<0.0001) were identified as independent predictors of good outcomes.

Conclusions—Endovascular therapy can be instituted with acceptable safety beyond 8 hours from time last seen well when selection is based on advanced neuroimaging. Successful revascularization is significantly associated with higher rates of good outcomes. The benefit of this approach compared with standard medical therapy should be assessed in a prospective randomized trial. (***Stroke*. 2011;42:2206-2211.**)

The Late Window

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

R.G. Nogueira, A.P. Jadhav, D.C. Haussen, A. Bonafe, R.F. Budzik, P. Bhuva, D.R. Yavagal, M. Ribo, C. Cognard, R.A. Hanel, C.A. Sila, A.E. Hassan, M. Millan, E.I. Levy, P. Mitchell, M. Chen, J.D. English, Q.A. Shah, F.L. Silver, V.M. Pereira, B.P. Mehta, B.W. Baxter, M.G. Abraham, P. Cardona, E. Veznedaroglu, F.R. Hellinger, L. Feng, J.F. Kirmani, D.K. Lopes, B.T. Jankowitz, M.R. Frankel, V. Costalat, N.A. Vora, A.J. Yoo, A.M. Malik, A.J. Furlan, M. Rubiera, A. Aghaebrahim, J.-M. Olivot, W.G. Tekle, R. Shields, T. Graves, R.J. Lewis, W.S. Smith, D.S. Liebeskind, J.L. Saver, and T.G. Jovin, for the DAWN Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

G.W. Albers, M.P. Marks, S. Kemp, S. Christensen, J.P. Tsai, S. Ortega-Gutierrez, R.A. McTaggart, M.T. Torbey, M. Kim-Tenser, T. Leslie-Mazwi, A. Sarraj, S.E. Kasner, S.A. Ansari, S.D. Yeatts, S. Hamilton, M. Mlynash, J.J. Heit, G. Zaharchuk, S. Kim, J. Carrozzella, Y.Y. Palesch, A.M. Demchuk, R. Bammer, P.W. Lavori, J.P. Broderick, and M.G. Lansberg, for the DEFUSE 3 Investigators*

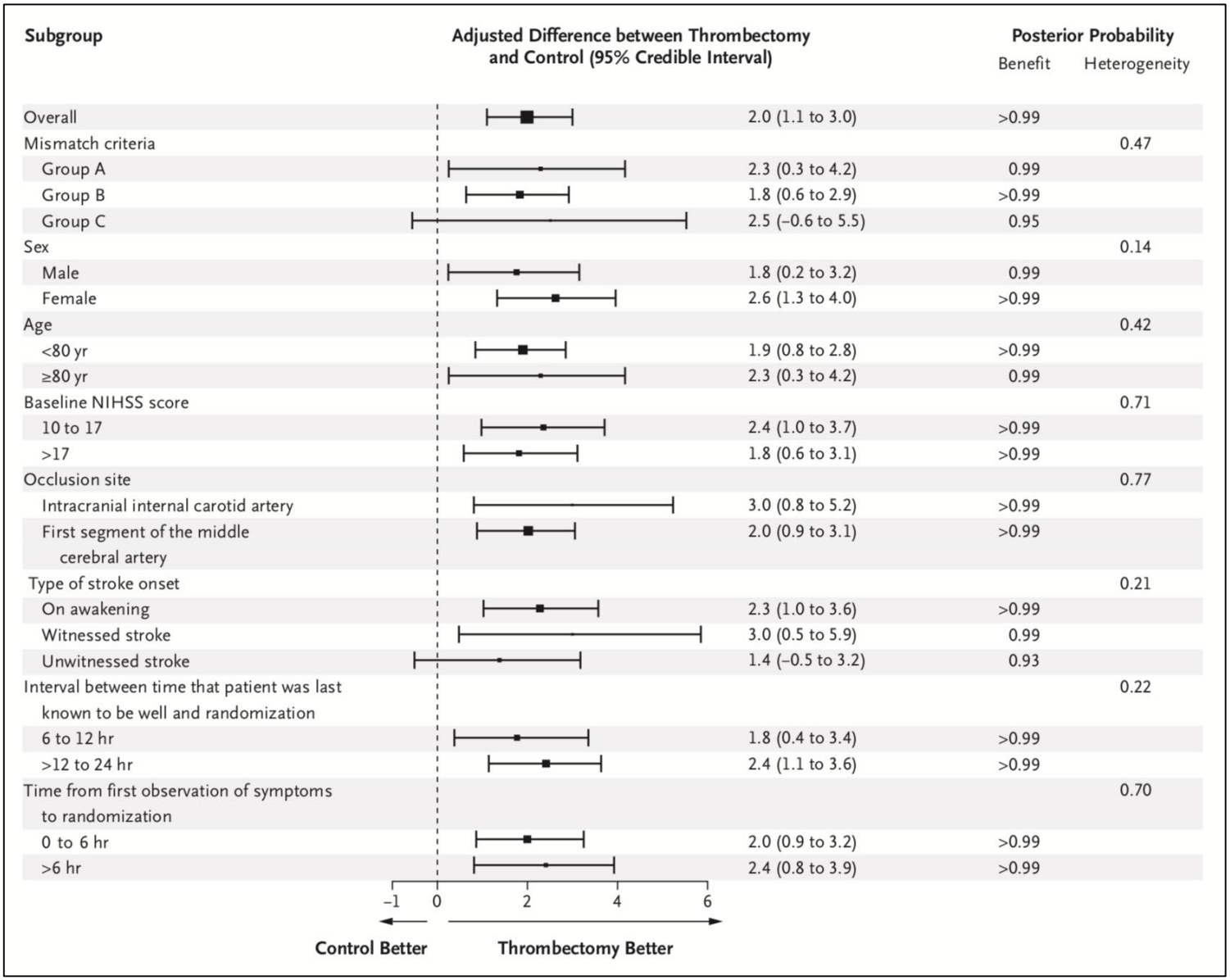
Baseline Patient Characteristics

	DAWN		DEFUSE 3	
	Treatment N=107	Control N=99	Treatment N=92	Control N=90
Baseline NIHSS	17 [13–21]	17 [14–21]	16 [10–20]	16 [12–21]
Baseline infarct volume (cc)	8.0 [2.0-18.0]	8.8 [3.0-18.1]	9.4 [2.3–25.6]	10.1 [2.1–24.3]
Occlusion ICA:MCA	21:79%	19:81%	35:65%	40:60%
Age (years)	72 [60-79]	73 [61-82]	70 [59-79]	71 [59-80]
Wake-Up Stroke	63%	47%	53%	47%
TLSW to Imaging (hours)	11.9 [9.2, 15.8]	12.8 [8.5, 15.2]	10.5 [8.2, 11.7]	9.9 [7.9, 12.3]

All values: median, [IQR]
TLSW: Time Last Seen Well

Subgroup Analysis

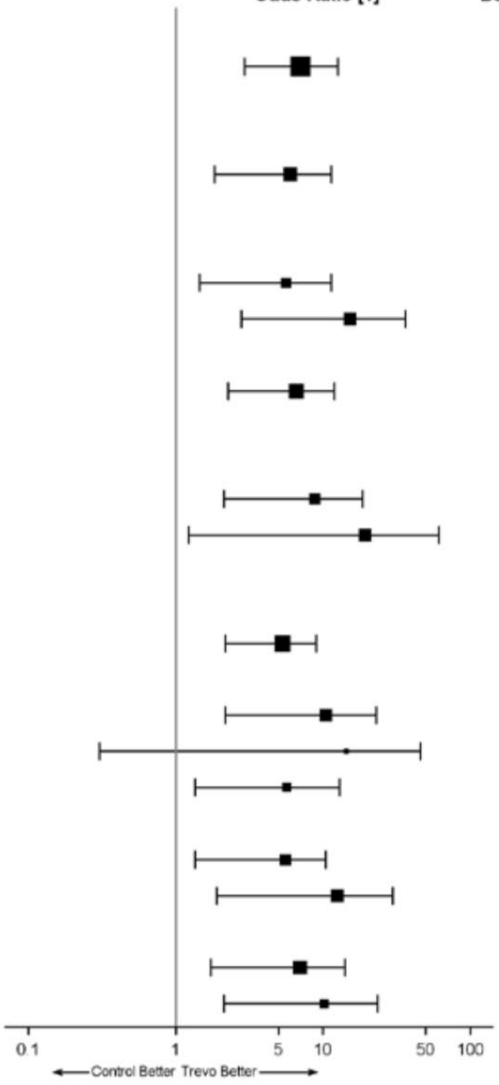
90-Day UW-mRS vs. Subgroups



Subgroup	Adjusted Difference between Thrombectomy and Control (95% Credible Interval)	Posterior Probability: Benefit	Posterior Probability: Heterogeneity
Overall	2.0 (1.1 to 3.0)	>0.99	
Mismatch criteria			0.47
Group A	2.3 (0.3 to 4.2)	0.99	
Group B	1.8 (0.6 to 2.9)	>0.99	
Group C	2.5 (−0.6 to 5.5)	0.95	
Sex			0.14
Male	1.8 (0.2 to 3.2)	0.99	
Female	2.6 (1.3 to 4.0)	>0.99	
Age			0.42
<80 yr	1.9 (0.8 to 2.8)	>0.99	
≥80 yr	2.3 (0.3 to 4.2)	0.99	
Baseline NIHSS score			0.71
10 to 17	2.4 (1.0 to 3.7)	>0.99	
>17	1.8 (0.6 to 3.1)	>0.99	
Occlusion site			0.77
Intracranial internal carotid artery	3.0 (0.8 to 5.2)	>0.99	
First segment of the middle cerebral artery	2.0 (0.9 to 3.1)	>0.99	
Type of stroke onset			0.21
On awakening	2.3 (1.0 to 3.6)	>0.99	
Witnessed stroke	3.0 (0.5 to 5.9)	0.99	
Unwitnessed stroke	1.4 (−0.5 to 3.2)	0.93	
Interval between time that patient was last known to be well and randomization			0.22
6 to 12 hr	1.8 (0.4 to 3.4)	>0.99	
>12 to 24 hr	2.4 (1.1 to 3.6)	>0.99	
Time from first observation of symptoms to randomization			0.70
0 to 6 hr	2.0 (0.9 to 3.2)	>0.99	
>6 hr	2.4 (0.8 to 3.9)	>0.99	

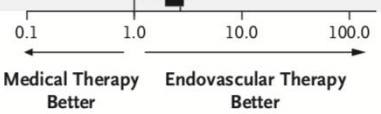
90-Day mRS 0-2 vs. Subgroups

Subgroup	Trevo Successes/N (%)	Standard Care Successes/N (%)	Core-size-adjusted OR (95% CI)	Posterior Probability of Benefit	Posterior Probability of Heterogeneity [2]
Overall	52/107 (48.6%)	13/99 (13.1%)	7.1 (2.9-12.6)	>0.99	
CIM Groups (as Randomized) [2]					NE
CIM Group A	8/25 (32.0%)	1/29 (3.5%)	NE	NE	
CIM Group B	41/73 (56.2%)	12/61 (19.7%)	6.0 (1.8-11.3)	>0.99	
CIM Group C	3/9 (33.3%)	0/9 (0.0%)	NE	NE	
Sex					0.13
Male	21/42 (50.0%)	9/51 (17.7%)	5.6 (1.5-11.3)	>0.99	
Female	31/65 (47.7%)	4/48 (8.3%)	15.2 (2.8-36.3)	>0.99	
Age [3]					NE
< 80	44/82 (53.7%)	12/70 (17.1%)	6.6 (2.3-11.9)	>0.99	
>=80	8/25 (32.0%)	1/29 (3.5%)	NE	NE	
Baseline NIHSS					0.32
10 to 17	37/52 (71.2%)	11/45 (24.4%)	8.8 (2.1-18.6)	>0.99	
>17	15/55 (27.3%)	2/54 (3.7%)	19.3 (1.2-61.4)	>0.99	
Occlusion Location (By Corelab) [4]					NE
ICA	10/22 (45.5%)	0/19 (0.0%)	NE	NE	
M1	41/83 (49.4%)	13/77 (16.9%)	5.3 (2.2-9.0)	>0.99	
Mode of Presentation					0.27
Wake-up	33/67 (49.3%)	5/47 (10.6%)	10.4 (2.2-23.1)	>0.99	
Witnessed	7/11 (63.6%)	3/14 (21.4%)	14.4 (0.3-45.6)	0.99	
Unwitnessed	12/29 (41.4%)	5/38 (13.2%)	5.7 (1.4-13.0)	>0.99	
TLSW to Randomization					0.18
6-12 Hours	27/49 (55.1%)	9/45 (20.0%)	5.6 (1.4-10.4)	>0.99	
>12-24 Hours	25/58 (43.1%)	4/54 (7.4%)	12.4 (1.9-29.7)	>0.99	
TSFO to Randomization					0.66
0-6 Hours	34/74 (46.0%)	7/54 (13.0%)	7.0 (1.7-14.1)	>0.99	
Greater than 6 Hours	18/33 (54.6%)	6/45 (13.3%)	10.1 (2.1-23.5)	>0.99	



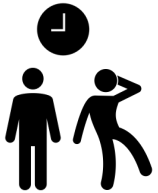
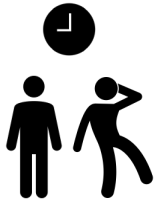
defuse·3

Subgroup	No. of Patients	Endovascular Therapy	Medical Therapy	Risk Ratio for Functional Independence at Day 90 (95% CI)	P Value for Interaction
		functional independence (%)			
Overall	182	45	17	2.67 (1.60–4.48)	
Time from stroke onset to randomization					0.21
<9 hr	50	40	28	1.43 (0.65–3.15)	
9–12 hr	72	50	17	3.00 (1.35–6.68)	
>12 hr	60	42	7	6.08 (1.64–69.93)	
Volume of ischemic core					0.47
<10.0 ml	92	42	20	2.04 (1.04–3.99)	
10.0–25.0 ml	44	55	13	4.40 (1.41–20.33)	
>25.0 ml	46	42	14	3.06 (1.01–13.53)	
Baseline NIHSS score					0.20
<13	55	69	46	1.49 (0.92–2.42)	
13–18	55	48	12	4.18 (1.36–29.67)	
>18	72	21	0	—	
Age					1.00
<70 yr	84	59	28	2.15 (1.23–3.76)	
≥70 yr	98	31	8	3.91 (1.36–15.46)	
ASPECTS					0.65
<8	57	32	7	4.66 (1.14–44.44)	
≥8	85	46	24	1.88 (0.99–3.60)	
Site of occlusion					0.69
Middle cerebral artery	113	48	21	2.33 (1.29–4.19)	
Internal carotid artery	68	38	8	4.50 (1.39–29.67)	
Baseline imaging method					0.41
CT	133	39	16	2.50 (1.32–4.75)	
MRI	49	61	19	3.17 (1.35–7.43)	
Determination of time of stroke					0.87
Time that patient was last known to be well	116	38	13	2.96 (1.38–6.36)	
Exact time of symptom onset	66	58	23	2.54 (1.29–5.01)	
Sex					0.71
Female	92	35	13	2.67 (1.15–6.21)	
Male	90	54	20	2.66 (1.41–5.04)	
Race					0.58
White	158	46	16	2.84 (1.64–4.93)	
Other or unknown	24	36	20	1.79 (0.42–11.38)	
Ethnic group					0.61
Hispanic	24	57	10	5.71 (1.11–158.73)	
Non-Hispanic	157	43	18	2.45 (1.43–4.21)	
Atrial fibrillation					0.21
Yes	62	38	4	10.71 (1.91–294.11)	
No	120	48	23	2.14 (1.26–3.64)	
Eligible for DAWN trial					0.96
Yes	112	38	13	3.00 (1.39–6.49)	
No	70	56	24	2.36 (1.20–4.63)	



Mode of Presentation

Different Presentation Times

	Likely Longer than Real Onset Time		Real Onset Time		Likely Shorter than Real Onset Time
	Time Last Seen Well		Ictus Time		Time Symptoms First Observed
Wake-Up Stroke		≠		≠	
Unwitnessed Stroke		≠		≠	
Witnessed Stroke		=		=	

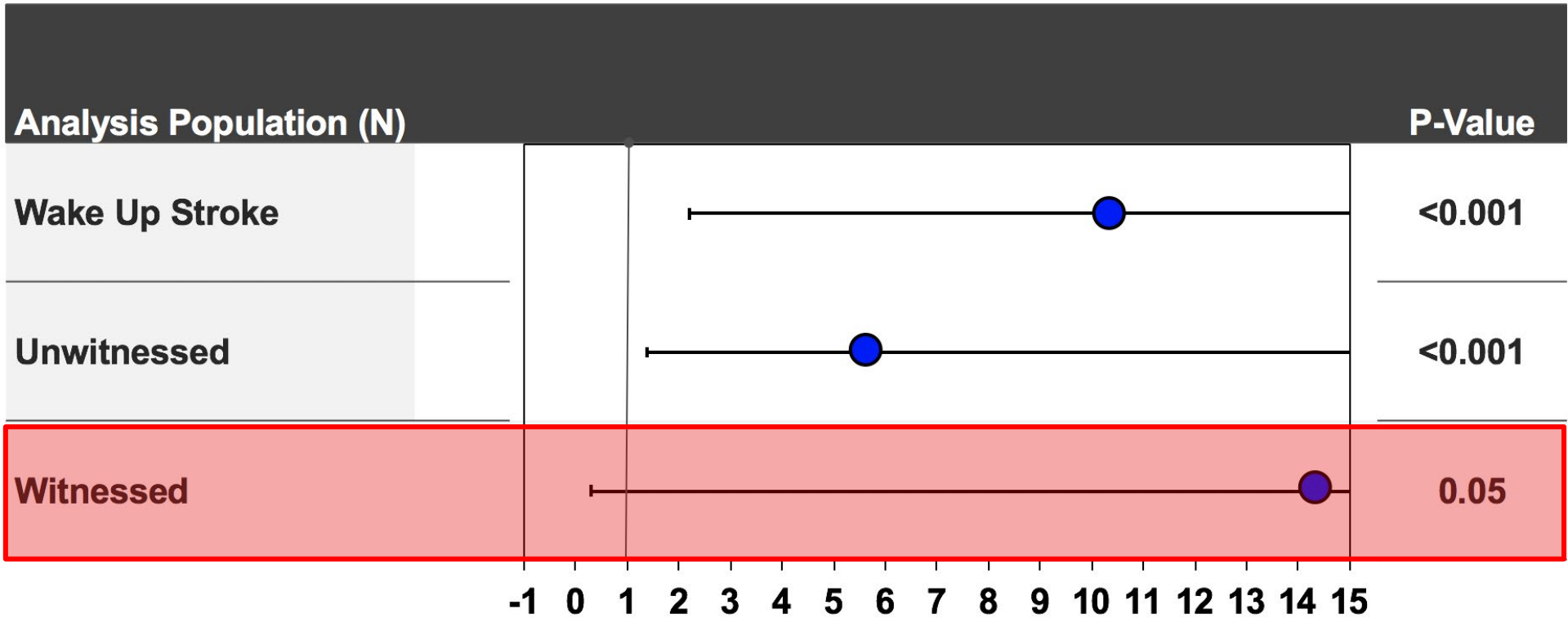
Patient Mode of Presentation

	Treatment arm N=107	Control arm N=99	P- value
Time since time last seen well to randomization (hrs)			
Mean ± SD Median (Q1, Q3) Range (min, max)	13.4 ± 4.1 12.2 (10.2, 16.0) (6.1, 23.5)	13.0 ± 4.5 13.2 (9.4, 15.8) (6.4, 23.9)	0.53
Stroke sub-population			
Wake up stroke	64.5%	47.5%	0.01
Witnessed stroke	10.3%	14.1%	0.52
Un-witnessed stroke	25.2%	38.4%	0.05

Functional Independence by Mode of Presentation

	Trevo + MM	MM	Absolute Difference (95% CI)	P-Value
Overall	48.6% (52/107)	13.1% (13/99)	35.5% (23.2, 46.2)	<0.001
Wake Up Stroke	49.3% (33/67)	10.6% (5/47)	38.6% (22.0,51.8)	<0.001
Unwitnessed	41.4%(12/29)	13.2% (5/38)	28.2% (7.0, 47.6)	0.012
Witnessed	63.6% (7/11)	21.4% (3/14)	42.2% (3.7, 67.5)	0.049

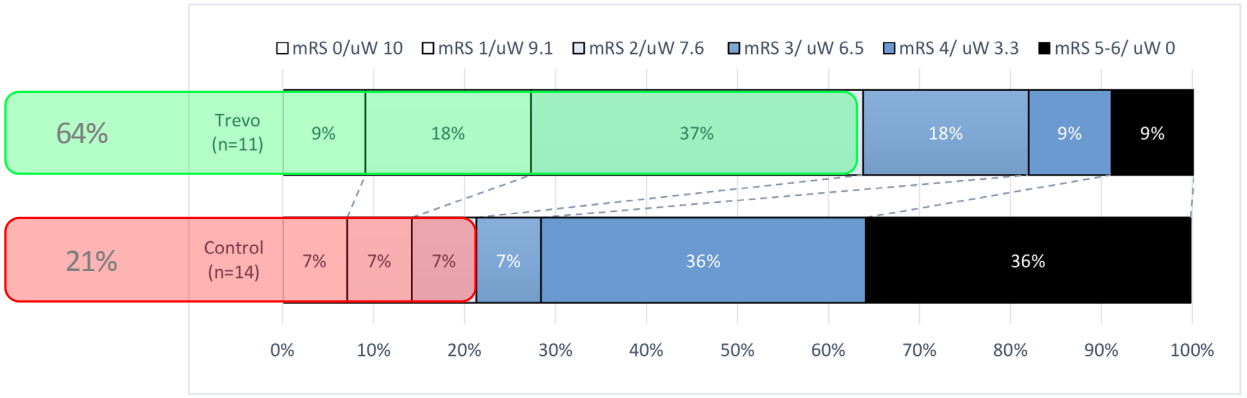
Adjusted Treatment Effect (Odds Ratios) by Modes of Presentation



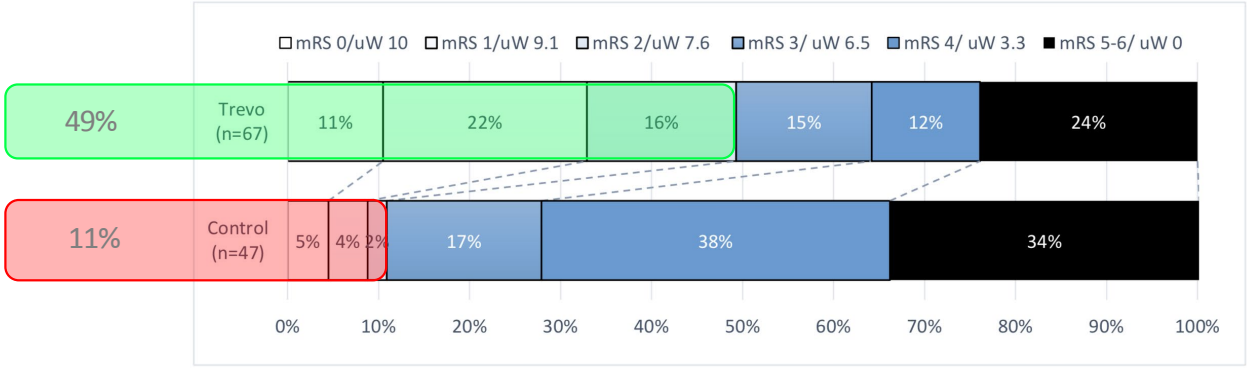
DAWN - Outcomes By Mode of Presentation

Infarct Volume = $\frac{\text{Time}}{\text{Collaterals}}$

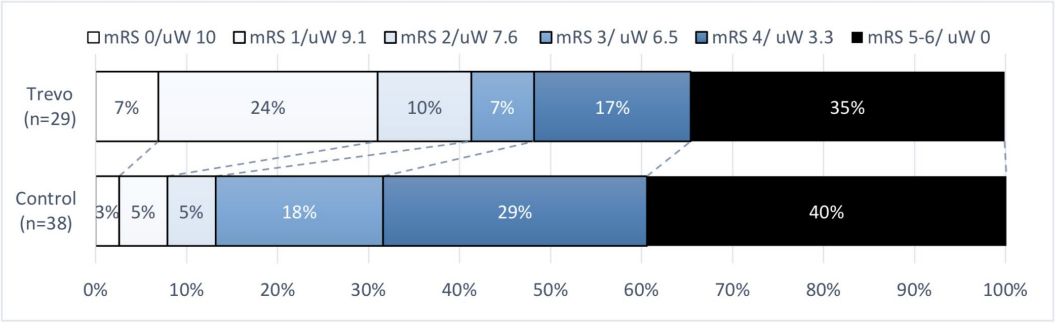
Witnessed



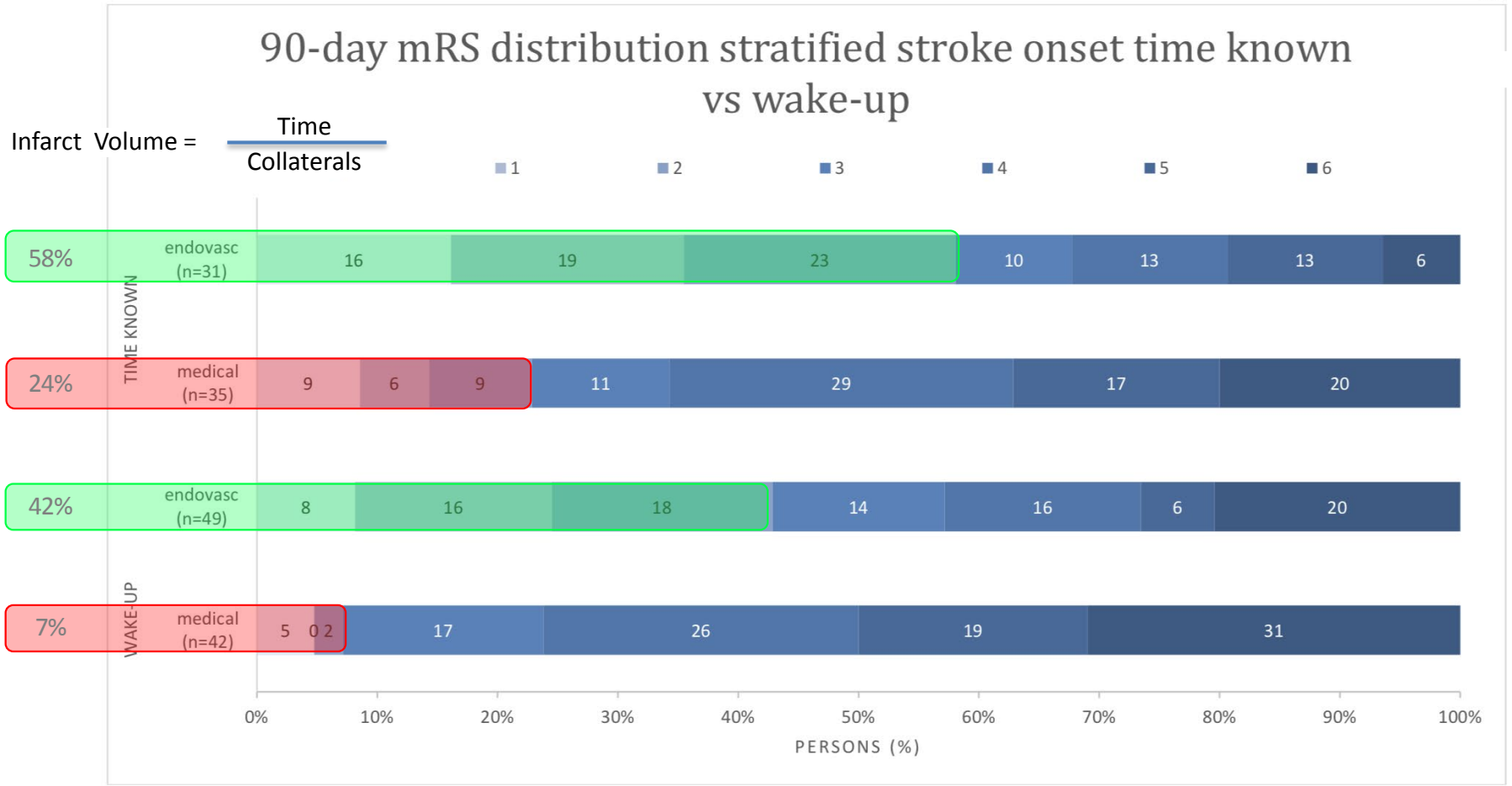
Wake up



Unwitnessed



DEFUSE 3 - Outcomes By Mode of Presentation



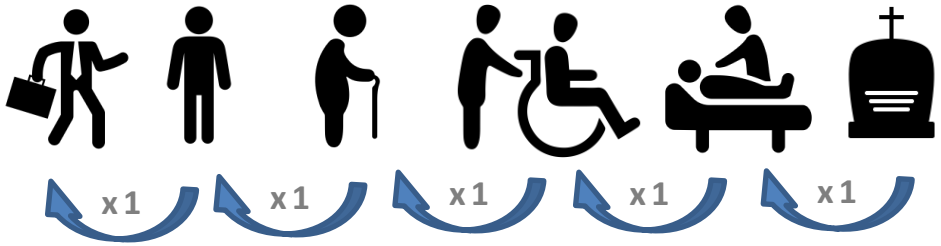
Stroke onset time known, OR= 3.41 (1.40, 8.32); Wake-up stroke, OR= 3.44 (1.60, 7.38), P value for interaction = 0.94

Effect of Time on Outcomes and Treatment Effect

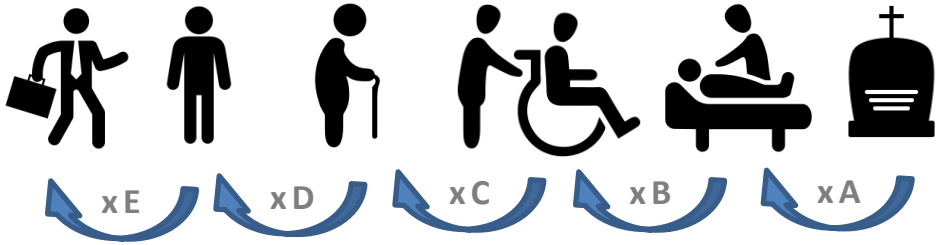
Different Outcomes Measures

Dichotomized
90-Day mRS 0-2
vs 3-6

90-Day mRS
Ordinal Shift



90-Day mRS
Utility-Weighted

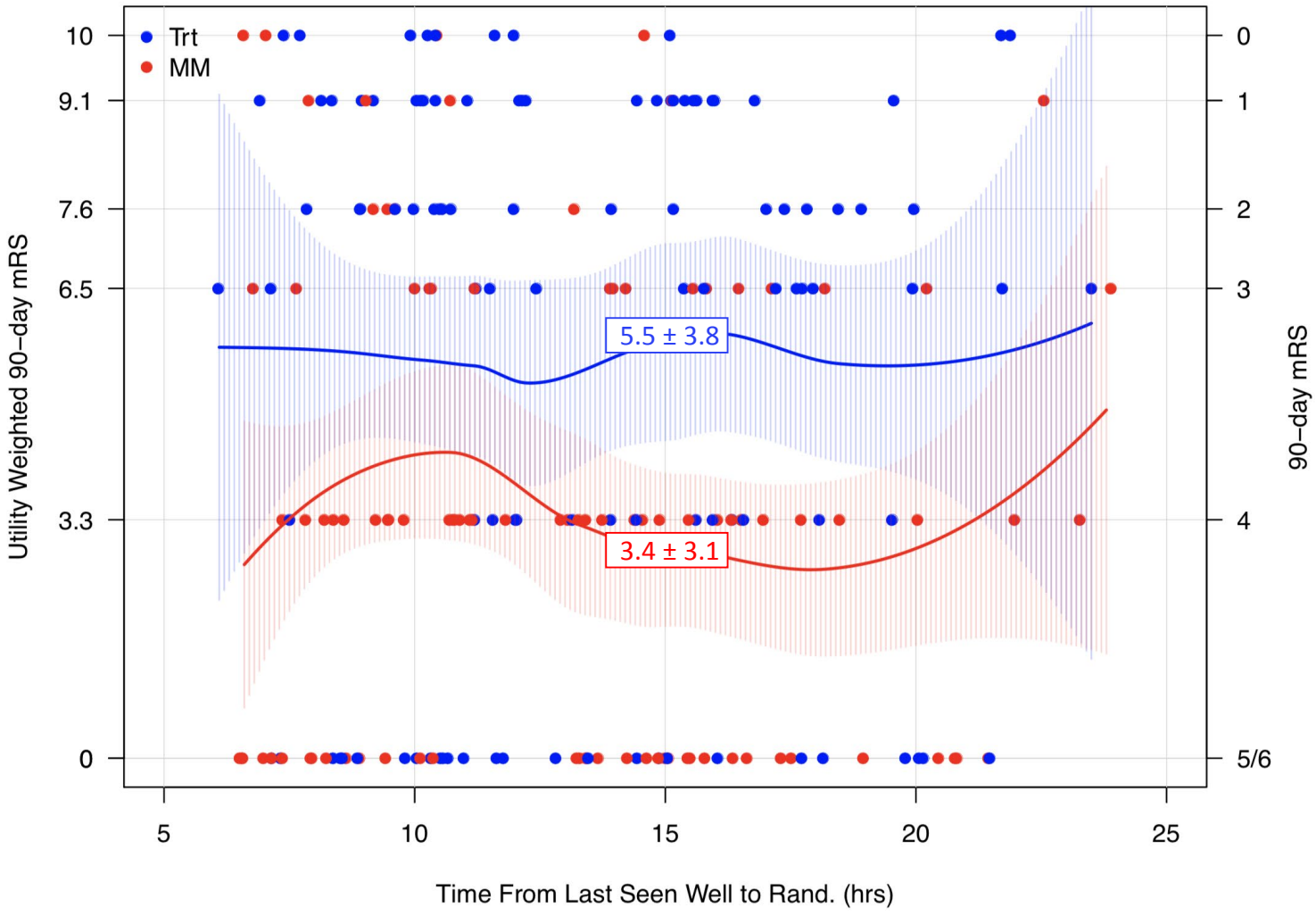


mRS	0	1	2	3	4	5	6
Weight	**10**	**9.1**	**7.6**	**6.5**	**3.3**	**0**	**0**

Time Last Seen Well

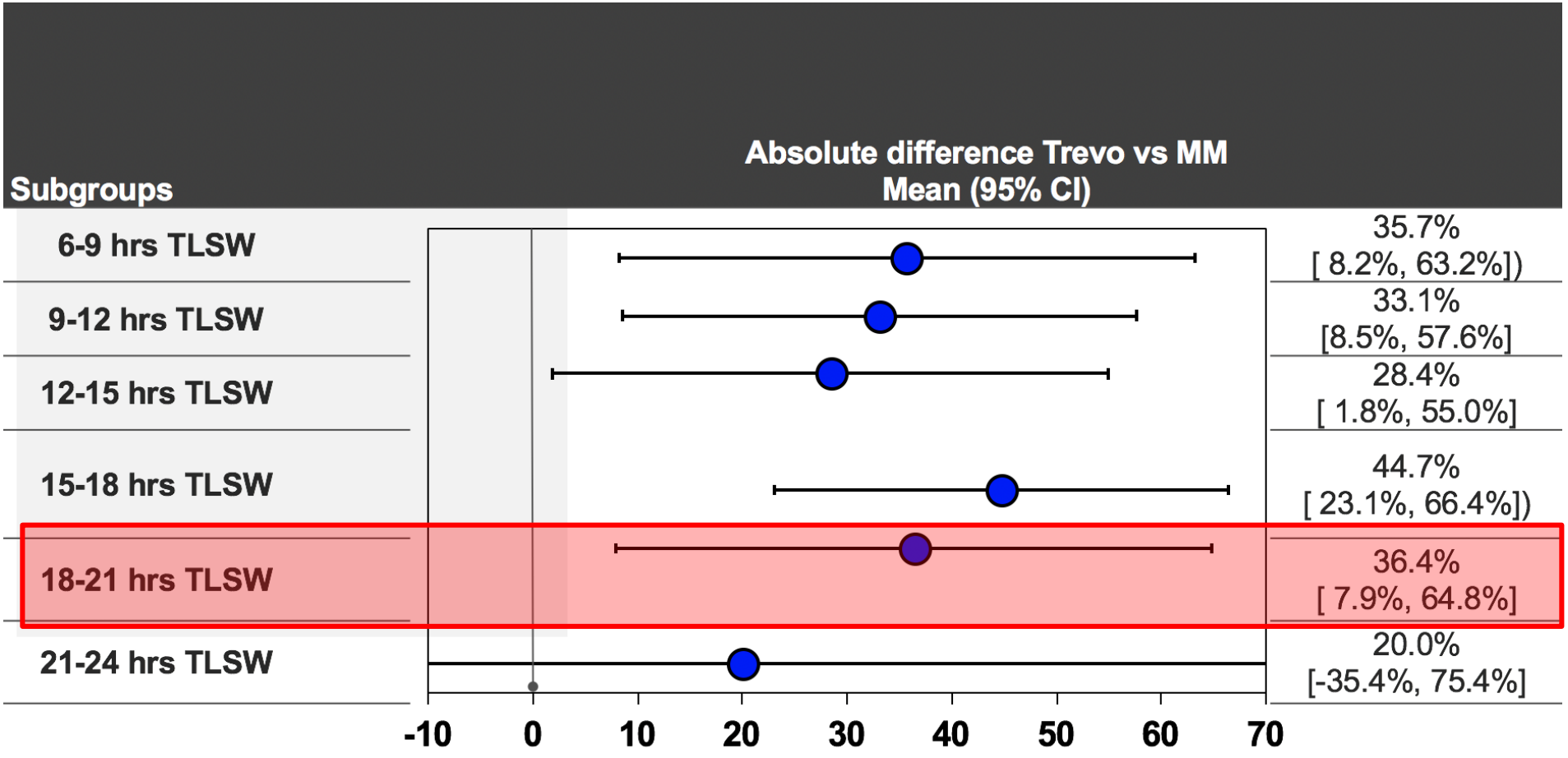
Day 90 Utility-Weighted mRS

90 Day UW-mRS vs TLSW to Randomization



Lines are moving averages for the scatter plots (UW-mRS and mRS)

Absolute Difference in Functional Independence by TLSW



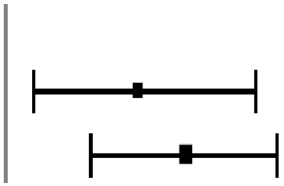
Treatment Effect remains statistically significant all the way to 21 hours!

No evidence that the treatment effect is different in the last vs first time slot.

Good Outcomes by "Time Last Normal to Randomization"

90-Day UW-mRS vs. TLSW

Time Last Seen Well to Randomization					
6-12 Hours	5.6± 4.1 (49)	3.8± 3.3 (45)	1.8 (0.4-3.4)		>0.99
>12-24 Hours	5.5± 3.5 (58)	3.0± 3.0 (54)	2.4 (1.1-3.6)		>0.99



0.22

90-Day mRS 0-2 vs. TLSW

TLSW to Randomization					
6-12 Hours	27/49 (55.1%)	9/45 (20.0%)	5.6 (1.4-10.4)		>0.99
>12-24 Hours	25/58 (43.1%)	4/54 (7.4%)	12.4 (1.9-29.7)		>0.99

0.18

Benefit in both subgroups and no interaction between time epochs and treatment benefit

Time Symptoms First Observed

Good Outcomes by "Time Found to Randomization"

Time Symptoms Found	Found < 6h	Found >=6h	38%
Trevo	74 (69.2%)	33* (30.8%)	
MM	54 (54.6%)	45** (45.5%)	

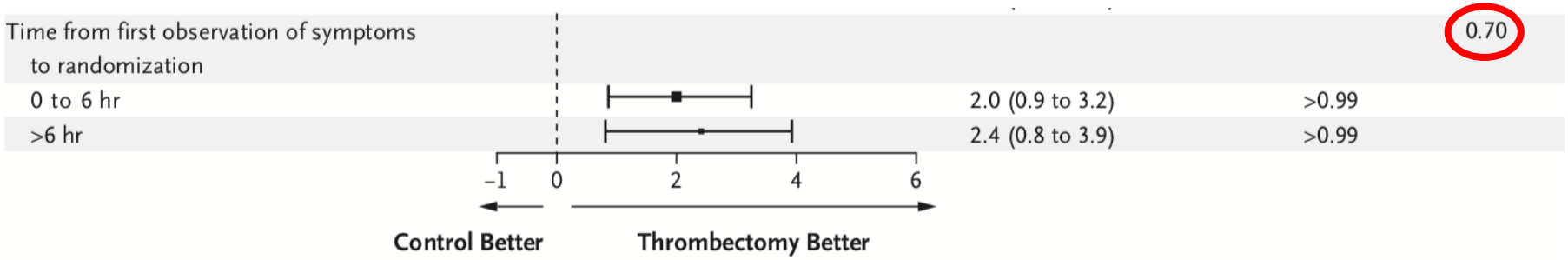
*11/33 Witnessed
**14/45 Witnessed

90-day mRS 0-2	Found < 6h	Found >=6h
Trevo	46.0%	54.6%
MM	13.0%	13.3%
Absolute benefit	33.0%	41.3%

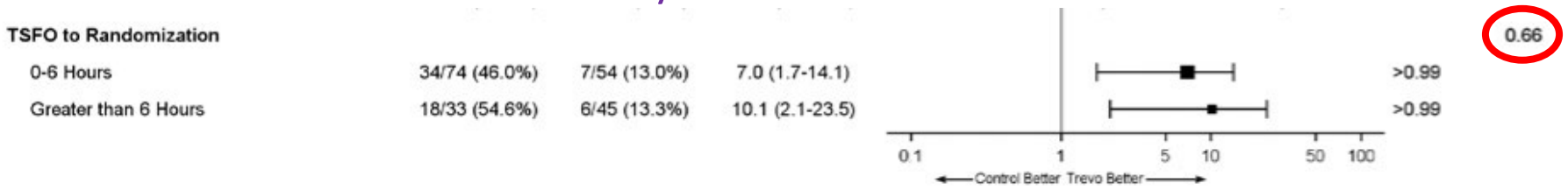
Time found to randomization rather than TLSW draws similar conclusion on treatment effect

Good Outcomes by "Time Found to Randomization"

90-Day UW-mRS vs. TSFO



90-Day mRS 0-2 vs. TSFO



Benefit in both subgroups and no interaction between time epochs and treatment benefit

Uni- and Multivariate Analyses

Multivariate Analysis Predictors of Good Outcome

Variable	Coefficient	Standard Error	Odds Ratio [95% CI]	p-value
Age (Yrs)	-0.0487	0.0143	0.95 (0.93-0.98)	0.0007
Previous Diabetes Mellitus No vs Yes	1.0152	0.4526	2.76 (1.14-6.70)	0.0249
Trevo vs MM	2.2315	0.4217	9.31 (4.08-21.3)	< 0.0001
Baseline NIHSS < 20 vs NIHSS >= 20	1.4161	0.4595	4.12 (1.67-10.1)	0.0021

Multivariate Analysis: Times and Functional Outcomes

Outcome Measure	Time Last Seen Well (TLSW)		Time Symptoms First Observed (TSFO)	
	OR [95% CI]	p-value	OR [95% CI]	p-value
90-day mRS 0-2	0.999 [0.998 -1.000]	0.129	0.992 [0.904 - 1.088]	0.860
90-day mRS shift	1.000 [0.999 - 1.001]	0.578	1.024 [0.950 - 1.104]	0.530
Average 90-day UW-mRS	Coefficient [95% CI]	p-value	Coefficient [95% CI]	p-value
	-0.018 [-0.135, 0.099]	0.767	0.046 [-0.109, 0.201]	0.560

Neither TLSW to Randomization nor TSFO to Randomization significantly affect treatment outcomes across all subtypes of functional outcomes!

AURORA

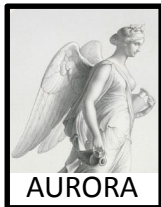
Analysis of Pooled Data from Randomized St**U**dies of Th**RO**mbectomy Mo**R**e than 6 hours **A**fter Last Known Well

Outcomes in Patients Undergoing Thrombectomy at the Extended Time Window in AURORA: a Pooled Analysis of the DAWN, DEFUSE-3, POSITIVE, ESCAPE and REVASCAT trials

Key Characteristics Across Participating Trials

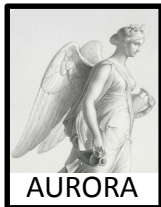
Trial	N **	Sponsor	Age	Target Vessels	NIHSS	Time Window	Treatment modality	Primary endpoint analysis
DAWN	206	Stryker	≥18	ICA, M1	≥10	6-24h	Trevo only	Utility weighted mRS & Dichotomized mRS 0-2
DEFUSE 3	182	NIH	≥18-90	ICA, M1	≥6	6-16h	All FDA cleared devices (stentriever, aspiration)	Ordinal mRS (shift)
ESCAPE	49	Consortium Academia/ Industry	≥18	ICA, M1	≥6	6-12h	All cleared devices by local regulatory agency (stentriever, aspiration)	Ordinal mRS (shift)
POSITIVE ***	33	Consortium Industry	≥18	ICA, M1	≥8	6-12h	All FDA cleared devices (stetriever, aspiration)	Ordinal mRS (shift)
REVASCAT	21	Unrestricted grant Medtronic	18-85	ICA, M1	≥6	6-8h	Solitaire only	Ordinal mRS (shift)

- Refers to patients included in AURORA only ** Number of patients contributed to AURORA
- *** not included in current analysis



Baseline Characteristics

Variable	Thrombectomy Mean ± SD (N) [Median] (IQR) or % (n/N)	Control Mean ± SD (N) [Median] (IQR) or % (n/N)	p-value
Age (years)	68.3 ± 13.8 (242) [70.0] (59.0,78.8)	69.2 ± 13.8 (216) [71.0] (60.0,80.0)	0.505
Female	56.2% (136/242)	48.1% (104/216)	0.085
NIHSS at baseline	16.3 ± 5.4 (241) [16.0] (12.0,20.0)	17.4 ± 5.9 (216) [17.0] (13.0,21.3)	0.0501
Systolic blood pressure (mmHg)	145.6 ± 23.0 (92)	145.5 ± 19.5 (90)	0.970
Hypertension	74.2% (178/240)	76.9% (166/216)	0.516
Hyperlipidemia	53.6% (127/237)	47.9% (102/213)	0.257
ASPECTS at baseline	7.8 ± 1.3 (221) [8.0] (7.0,9.0)	7.5 ± 1.5 (189) [8.0] (7.0,9.0)	0.083
Occlusion location			0.591
ICA	25.2% (61/242)	28.7% (62/216)	
M1	73.1% (177/242)	69.0% (149/216)	
M2	1.7% (4/242)	2.3% (5/216)	
Onset to randomization	684.5 ± 228.4 (242) [650.5] (511.3,820.3)	686.6 ± 232.9 (216) [642.8] (494.0,844.0)	0.923
Onset to puncture	[678.0] (532.0,842.0)		
Onset to reperfusion	[719.0] (572.0,911.0)		
mTICI 2b/3	80%(192/240)		



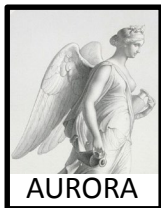
AURORA (6-24h + Mismatch) Safety

OUTCOME	EVT	Control	Unadjusted OR (LCL, UCL)	p-value	Adjusted OR (LCL, UCL)	p-value
Symptomatic Intracranial Hemorrhage (Individual Trial Definitions)	5.0% (12/242)	3.2% (7/216)	1.56 (0.60,4.04)	0.361	1.75 (0.66,4.65)	0.261
90-Day Mortality (All Causes)	16.1% (39/242)	20.5% (44/215)	0.75 (0.46,1.20)	0.23	0.93 (0.55,1.59)	0.789

HERMES (0-6 h) Safety

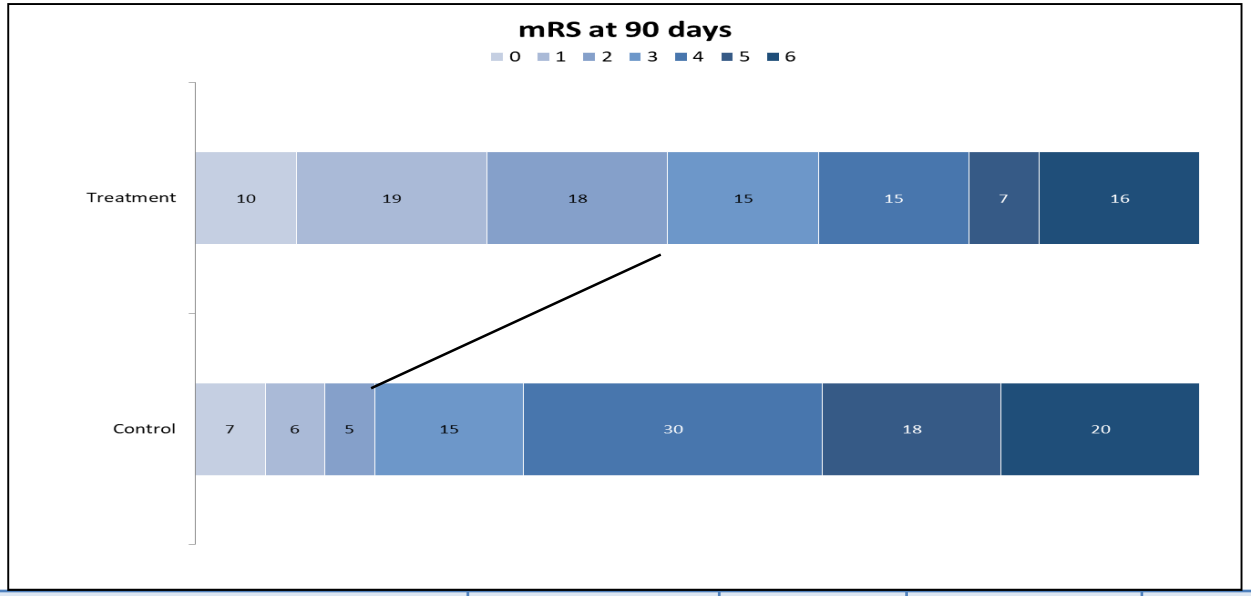
	Intervention population	Control population	Risk difference (%)	Rate ratio (95% CI)	Odds ratio (95% CI)	Adjusted rate ratio (95% CI)	Adjusted odds ratio (95% CI)
Symptomatic intracranial haemorrhage	4·4% (28/634)	4·3% (28/653)	0·1	1·06 (0·63–1·80); p=0·82	1·07 (0·62–1·83); p=0·81	1·07 (0·62–1·80); p=0·81	1·07 (0·62–1·84); p=0·81
Mortality	15·3% (97/633)	18·9% (122/646)	−3·6	0·82 (0·63–1·07); p=0·15	0·77 (0·54–1·10); p=0·16	0·82 (0·62–1·08); p=0·15	0·73 (0·47–1·13); p=0·16

[1] Goyal et al., The Lancet, 2016



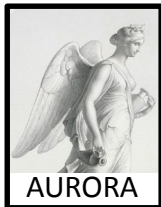
AURORA Primary Endpoint

Heterogeneity of Treatment Effect Across Sites: P-Value = 0.40



NNT = 2.5

OUTCOME AURORA	Unadjusted OR (LCL, UCL)	p-value	Adjusted OR (LCL, UCL)	p-value
MRS AT 90 DAYS	2.81 (2.00,3.95)	<0.001	2.77 (1.95,3.94)	<0.001
OUTCOME HERMES				
MRS AT 90 DAYS	2.26 (1.67, 3.06)	<0.0001	2.49 (1.76,3.53)	<0.001

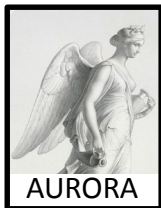


AURORA Secondary Endpoints

OUTCOME	EVT	Control	Unadjusted OR (LCL, UCL)	p-value	Adjusted OR (LCL, UCL)	p-value
MRS 0-1 AT 90 DAYS	28.9% (70/242)	12.1% (26/215)	2.96 (1.80,4.86)	<0.001	2.57 (1.18,5.60)	0.018
MRS 0-2 AT 90 DAYS	46.7% (113/242)	16.7% (36/215)	4.36 (2.81,6.76)	<0.001	4.65 (2.02,10.72)	<0.001
NIHSS SCORE 0-2 AT 24H	16.7% (40/239)	4.7% (10/213)	4.08 (1.98,8.40)	<0.001	4.61 (2.06,10.35)	<0.001
EARLY NEUROLOGICAL RECOVERY AT 24H	41.4% (99/239)	22.7% (29/213)	4.53 (2.82,7.27)	<0.001	5.07 (3.07,8.36)	<0.001

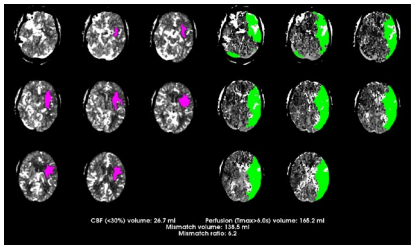
NNT = 3.3

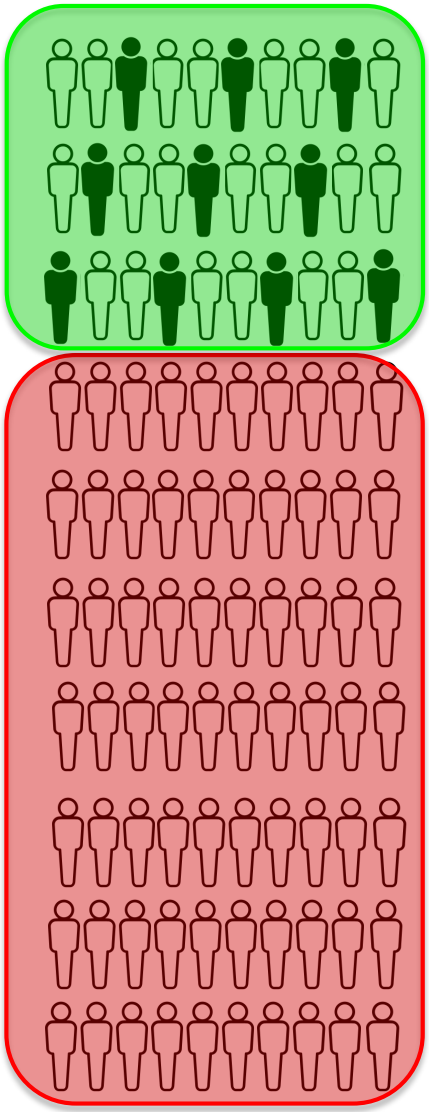
OUTCOME	EVT	Control	Adjusted Difference (LCL, UCL)	p-value
UW-MRS (MEAN)	5.5 +/- 3.6	3.5 +/- 3.4	1.8 (1.2, 2.3)	<0.001



Over-Selection

CT PERFUSION

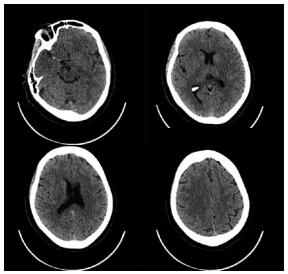


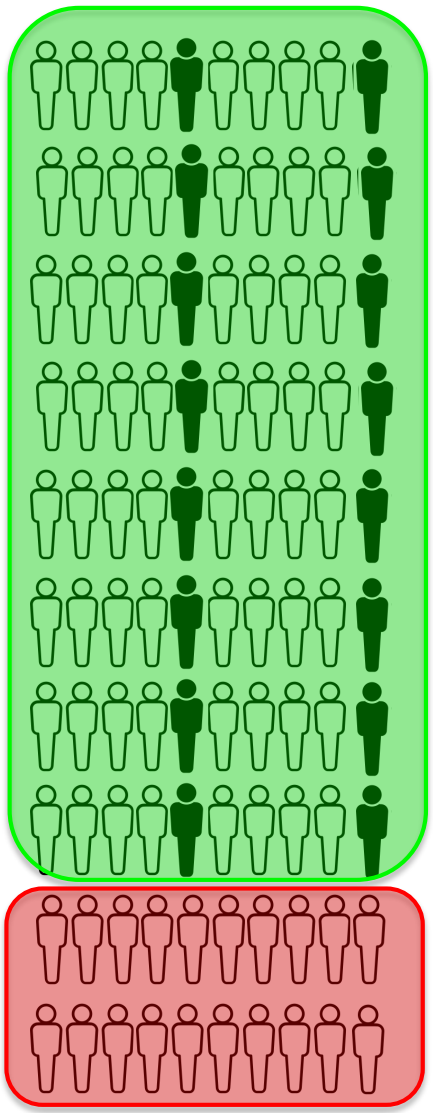


Treated Patients:
NNT = 3
90-Day mRS 0-2: 70%

Benefit in the Overall Population:
10:100 pts

NON-CONTRAST CT

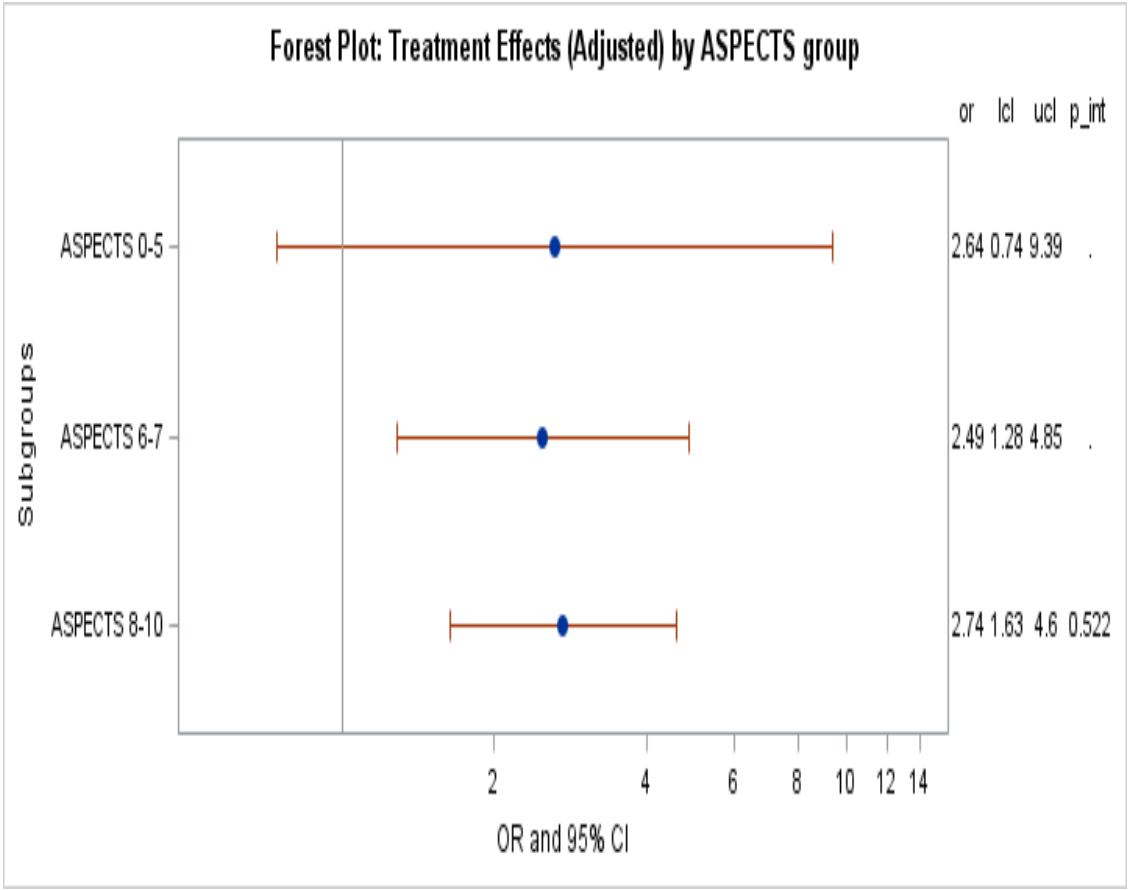




Treated Patients:
NNT = 5
90-Day mRS 0-2: 35%

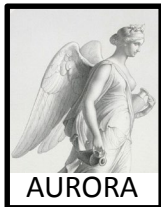
Benefit in the Overall Population:
16:100 pts

Treatment Effect by ASPECTS: 8-10, 6-8, 0-5

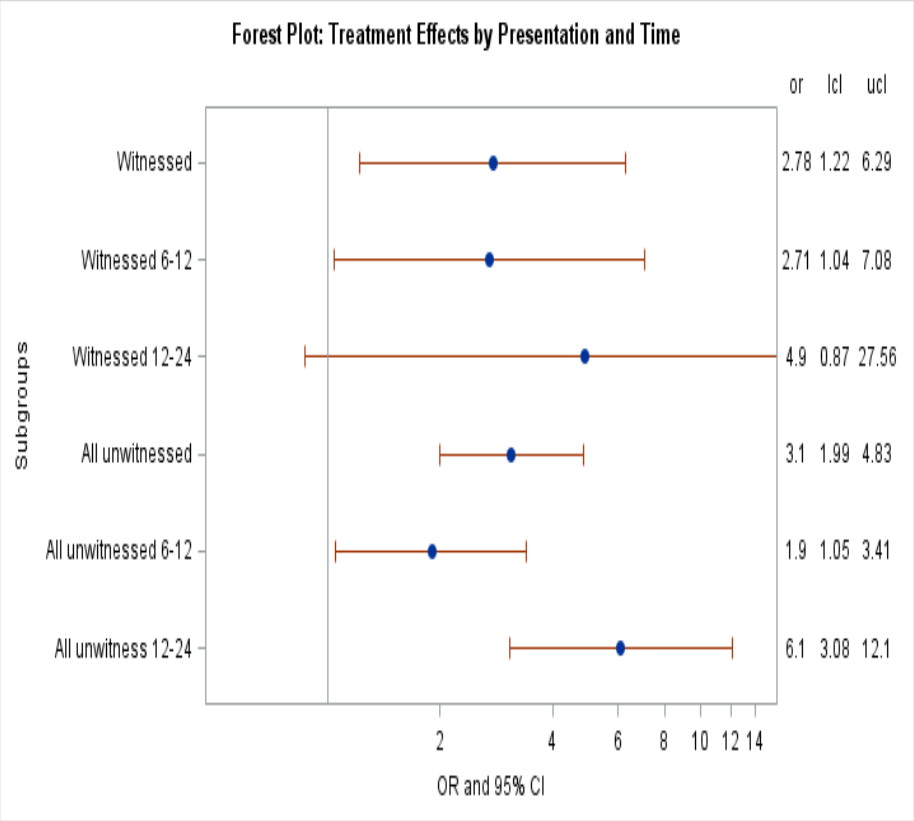


90-Day mRS 0-2

Subgroup	EVT	Control
ASPECTS 0-5	25.0% (4/16)	14.3% (3/21)
ASPECTS 6-7	37.9% (25/66)	10.1% (7/69)
ASPECTS 8-10	51.1% (71/139)	21.4% (21/98)

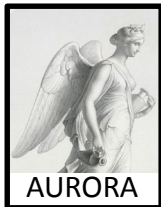


Treatment Effect by Witnessed vs Non-Witnessed Time to Randomization

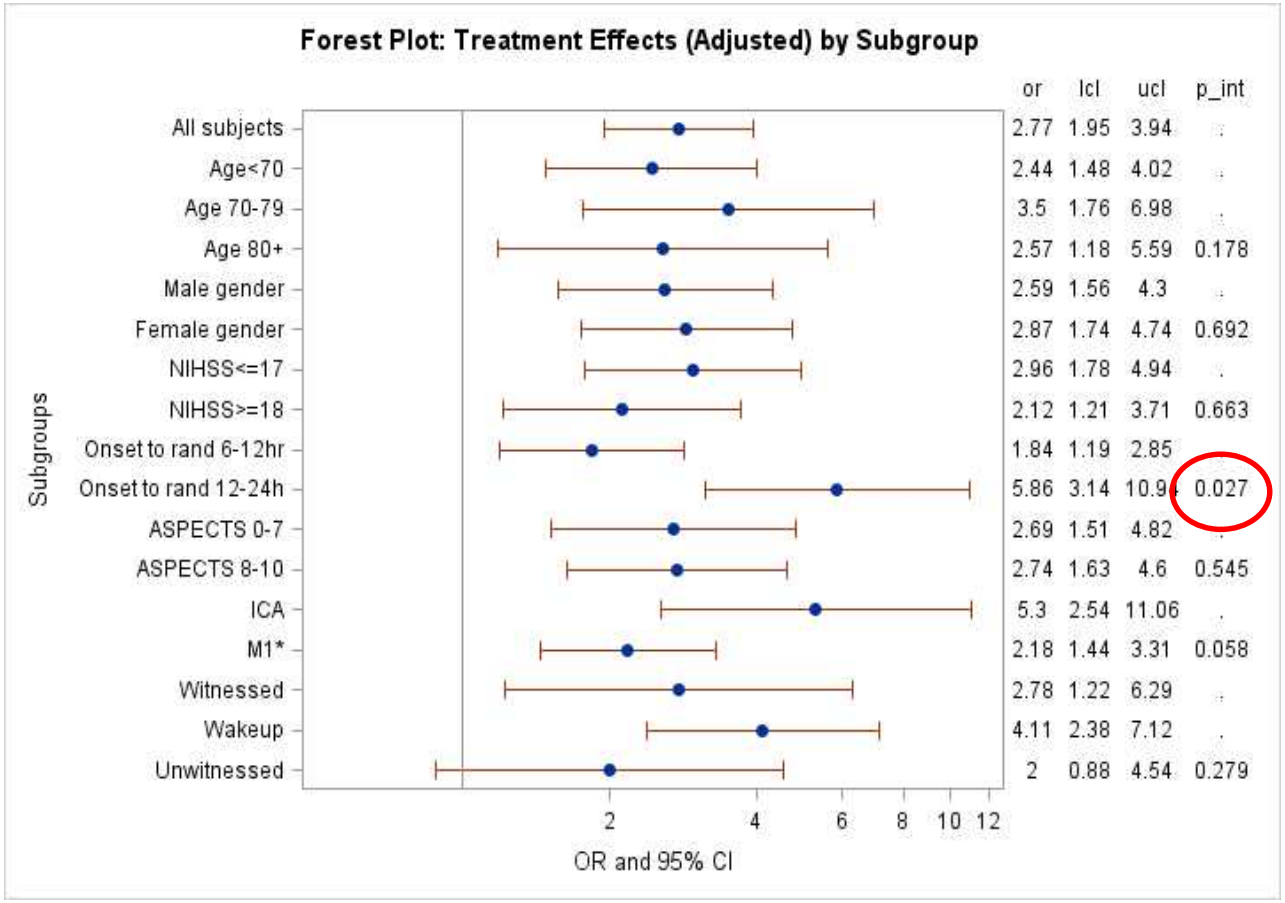


90-Day mRS 0-2

Subgroup	EVT	Control
Witnessed	59.5% (25/42)	22.4% (11/49)
Witnessed 6-12hr	64.5% (20/31)	27.8% (10/36)
Witnessed 12-24hr	45.5% (5/11)	7.7% (1/13)
Unwitnessed	43.3% (68/157)	12.1% (17/140)
Unwitnessed 6-12hr	44.3% (35/79)	17.1% (12/70)
Unwitnessed 12-24hr	42.3% (33/78)	7.1% (5/70)



Subgroup Analysis Adjusted by Baseline NIHSS, Sex, Occlusion Site, and Age



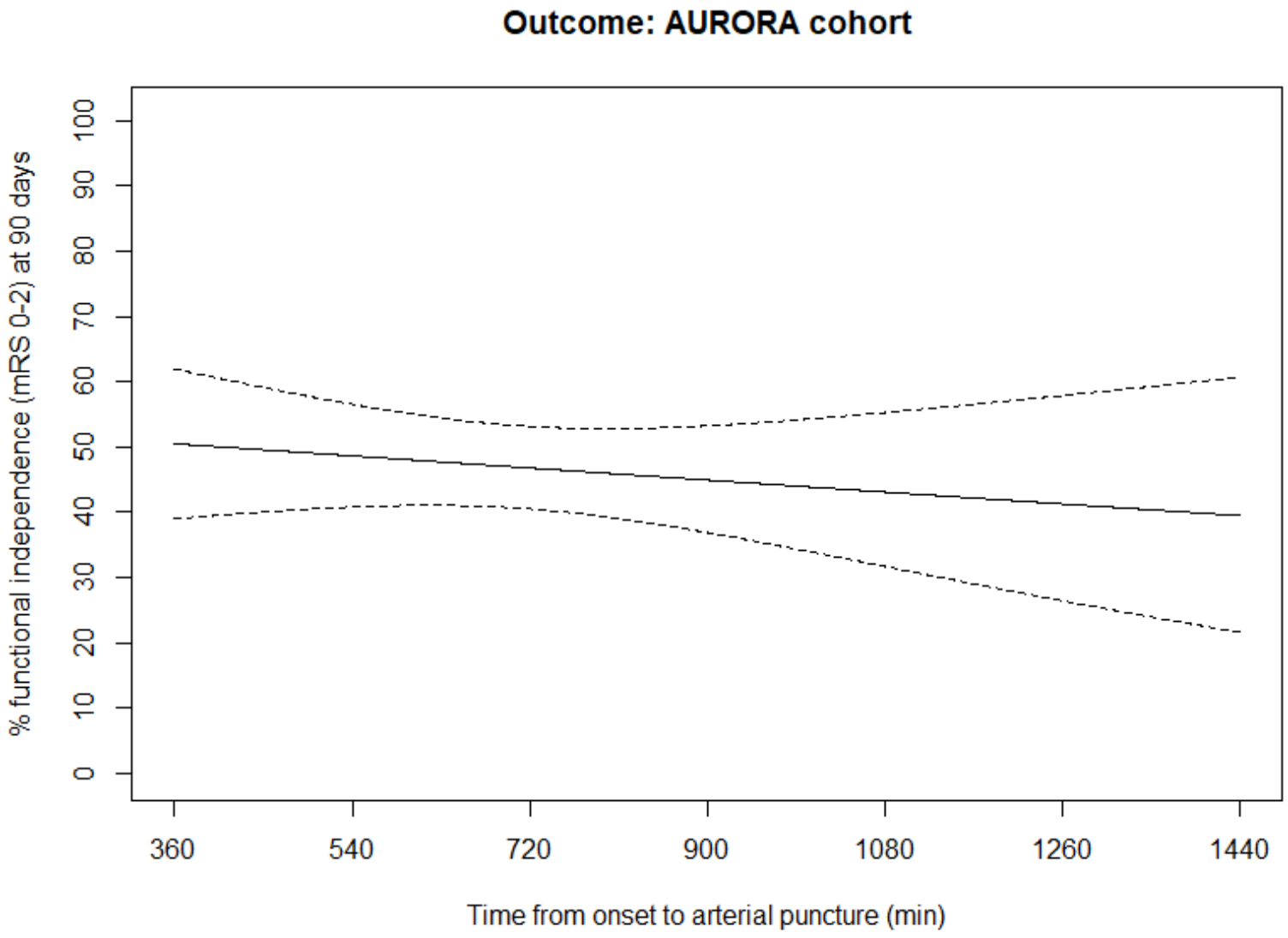
AURORA

Relationships Between Time and Outcomes in AURORA

AURORA

Analysis of Pooled Data from Randomized St**U**dies of Th**RO**mbectomy Mo**R**e than 6 hours **A**fter Last Known Well

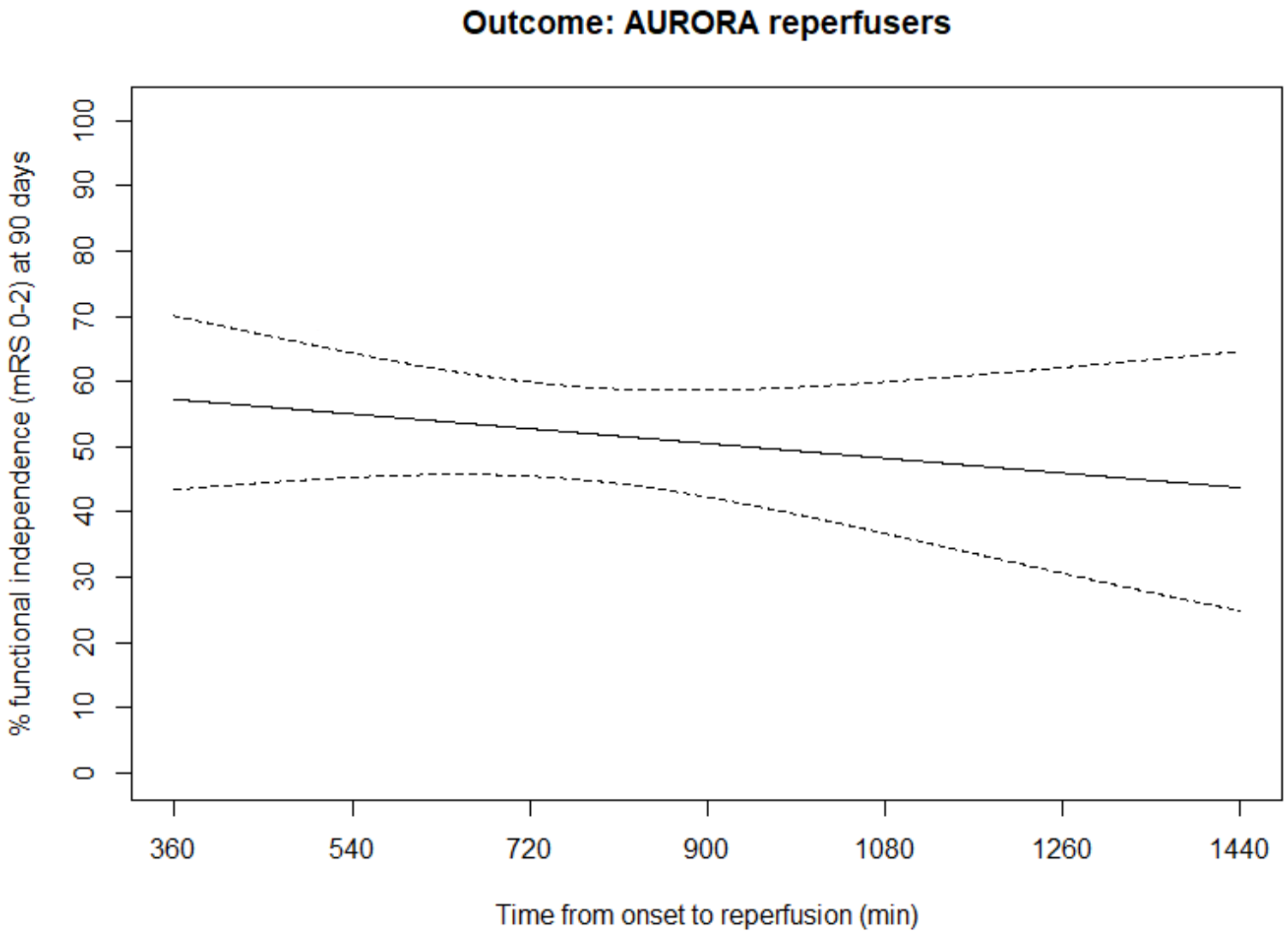
90-Day Good Outcome vs Onset to Arterial Puncture: All MT Subjects



OR per 60 min:
0.98 [0.91, 1.04]
P=0.469

AURORA

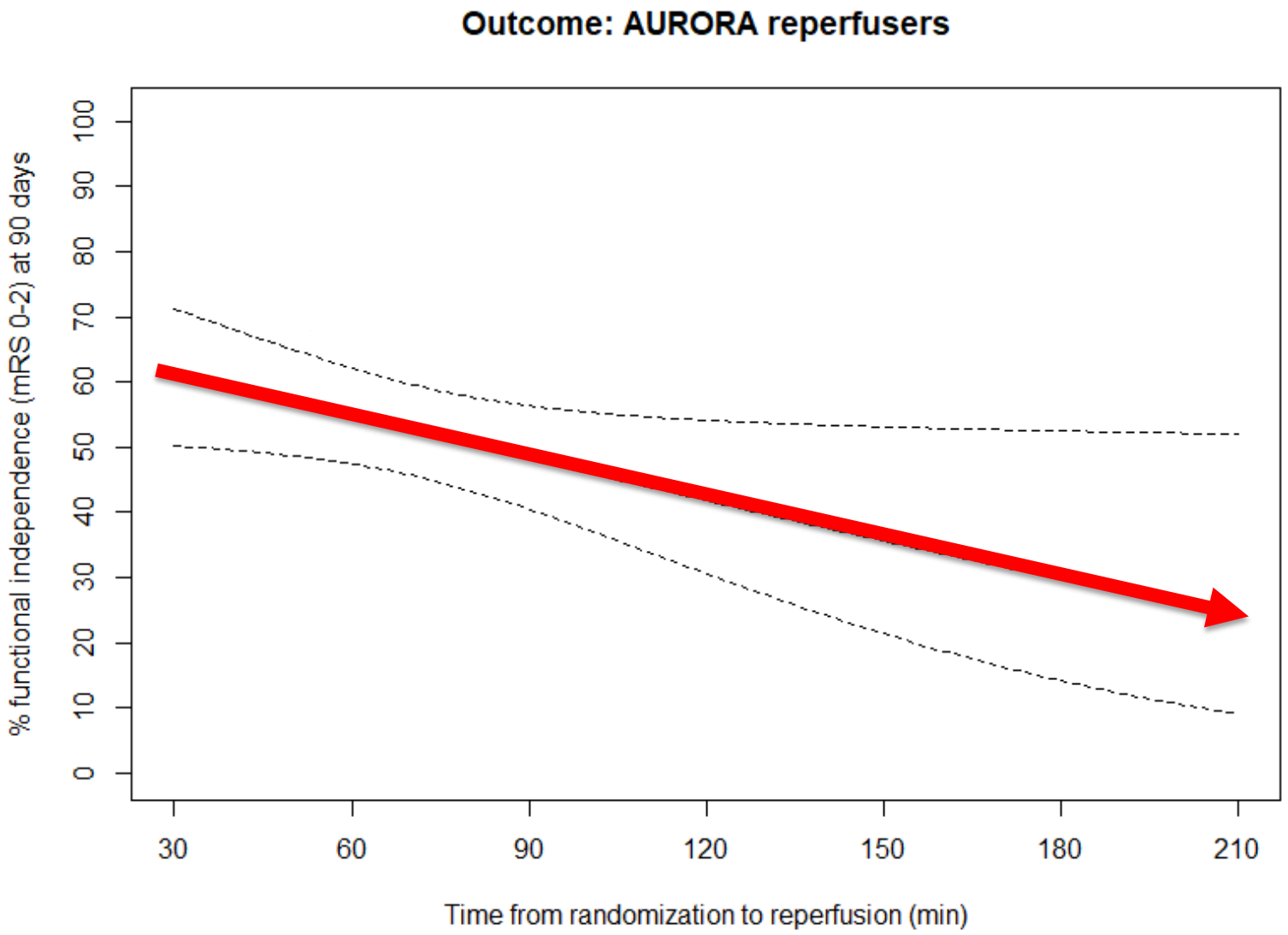
90-Day Good Outcome vs Onset to Reperfusion: MT Reperfusers Only



OR per 60 min:
0.97 [0.90, 1.04]
P=0.403

AURORA

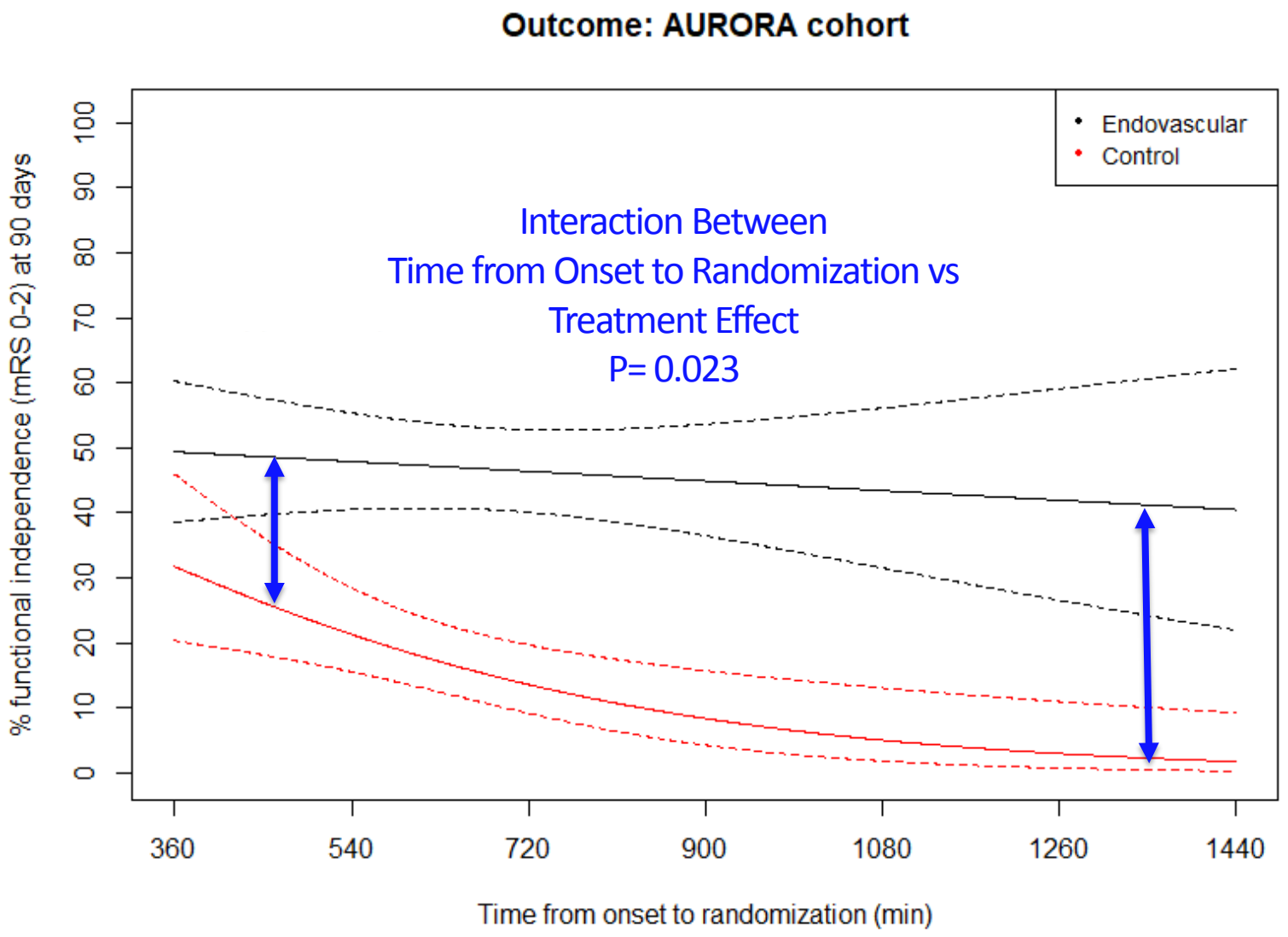
90-Day Good Outcome vs Randomization to Reperfusion: MT Reperfusers Only



OR per 60 min:
0.59 [0.36, 0.98]
P=0.042

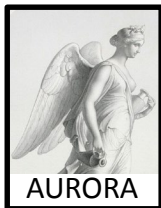
AURORA

90-Day Good Outcome vs Onset to Randomization: All Subjects

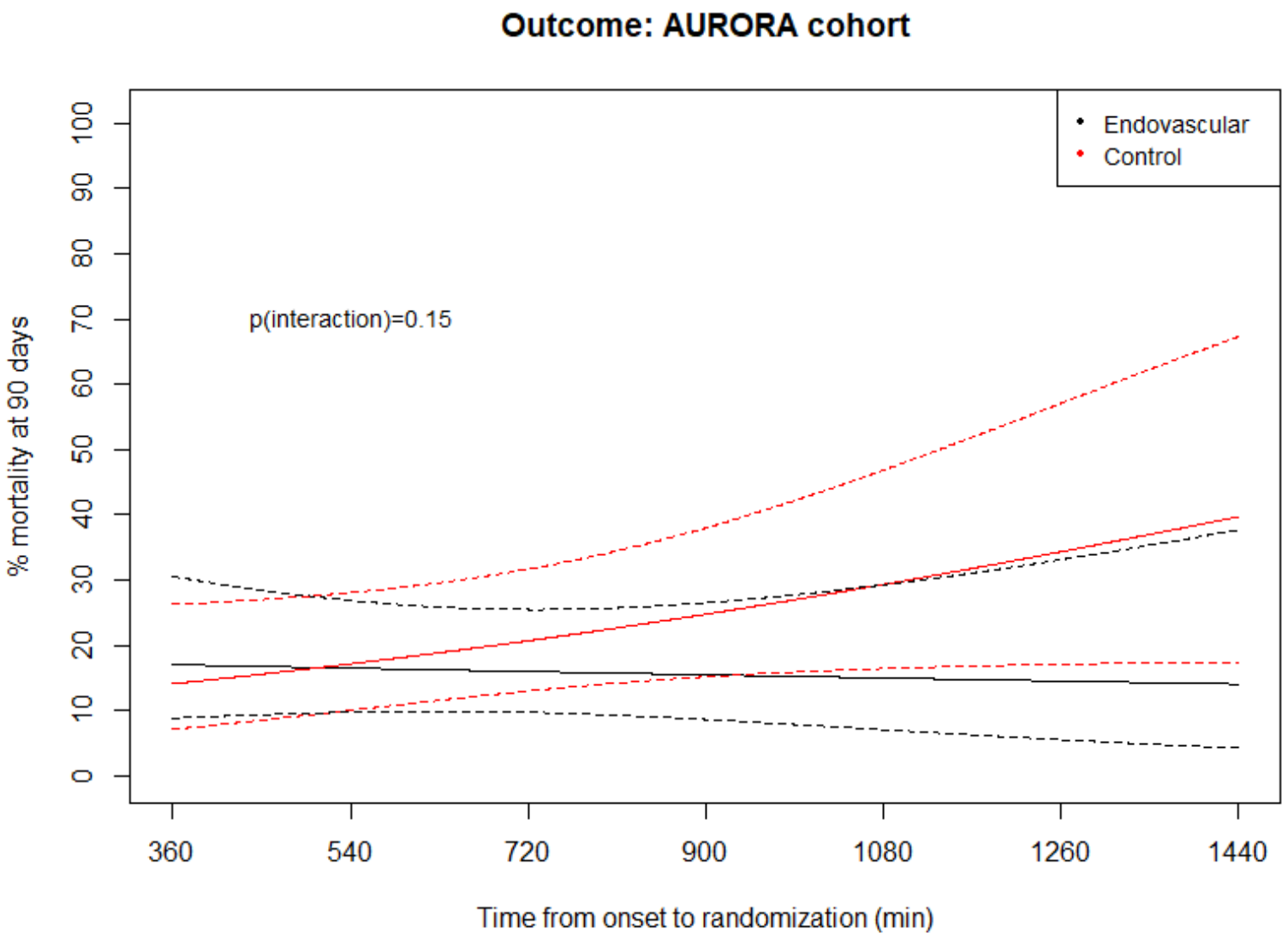


OR per 60 min:
0.98 [0.92, 1.05]
P=0.558

OR per 60 min:
0.83 [0.74, 0.94]
P=0.004

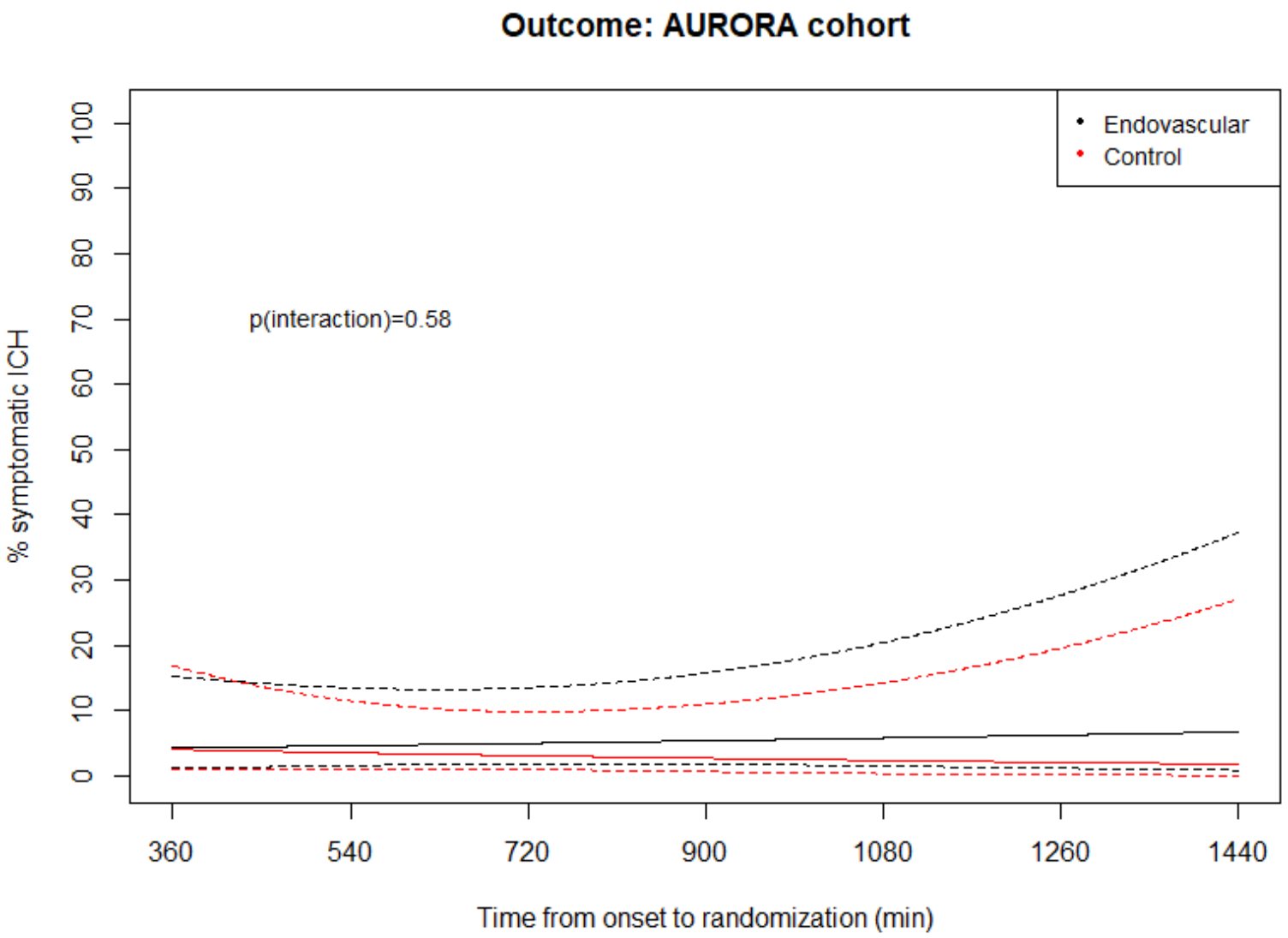


90-Day Mortality vs Onset to Randomization: All Subjects



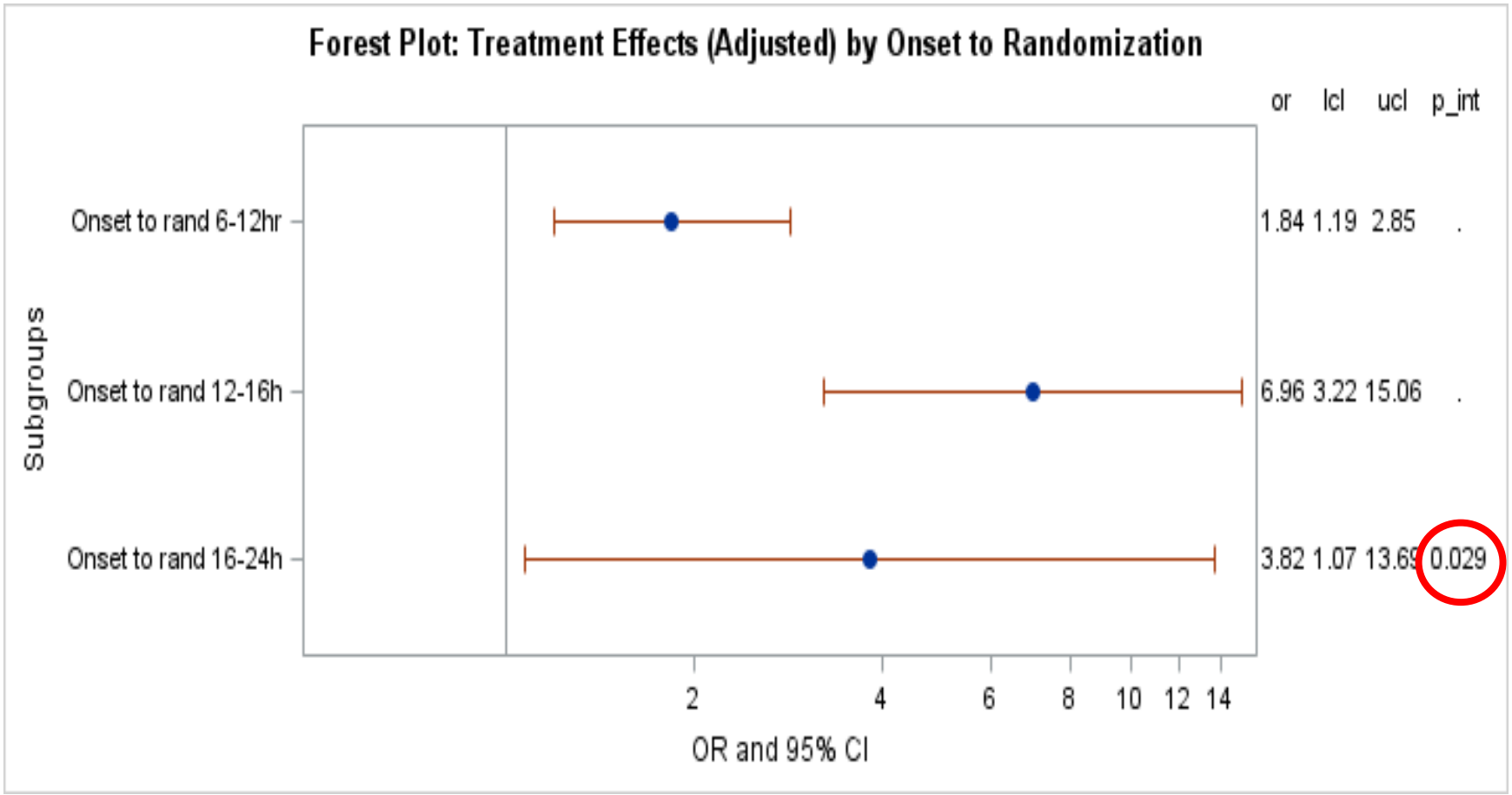
AURORA

SICH vs Onset to Randomization: All Subjects



AURORA

Treatment Effect by Time from Onset to Randomization: 6-12, 12-16 and 16-24 Hours



AURORA

Potential Conclusion:

The Presence of Clinical-Core Mismatch Resets the Time to Reperfusion Clock…

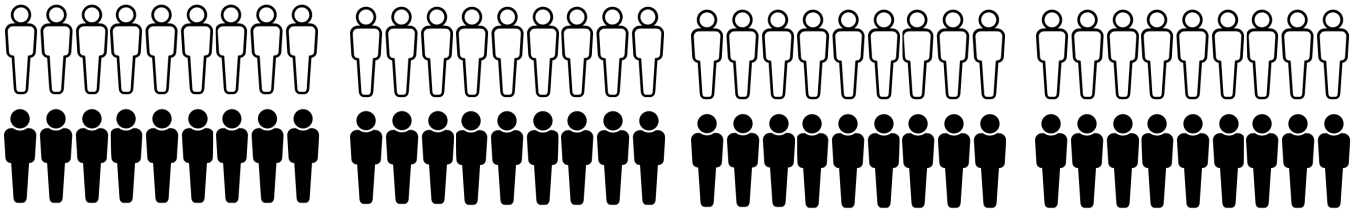
But

The chances of having a Clinical-Core Mismatch drops of time….

Therefore,

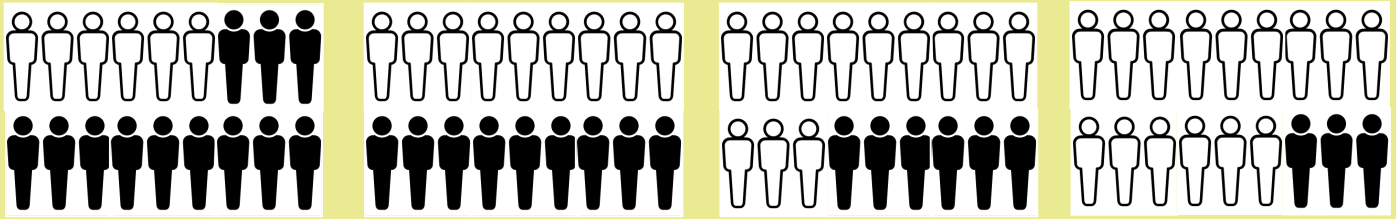
Time is still Brain!

What is the treatment benefit in patients with clinical-core mismatch over time?



0-6 hours | 6-12 hours | 12-18 hours | 18-24 hours

What is the proportion of patients with a clinical-core mismatch over time?



0-6 hours | **6-12 hours** | **12-18 hours** | **18-24 hours**

How Generalizable is the Late Treatment Data?

Real-World Applicability of Endovascular Therapy in ICA and/or MCA-M1 Occlusions Treated in the 6-24-hour Window:

Subgroup Analysis of the Prospective Registry

Raul G Nogueira, David Liebeskind, Ron Budzik, Rishi Gupta, Antonin Krajina, Joey English, Ameer Malek, Amrou Sarraj, Ana Paula Narata, Muhammad Taqi, Timothy Miller, Thomas Grobelny, Blaise Baxter, Bruno Mario Bartolini, Laurent Estrade, Tudor Jovin, Erol Veznedaroglu

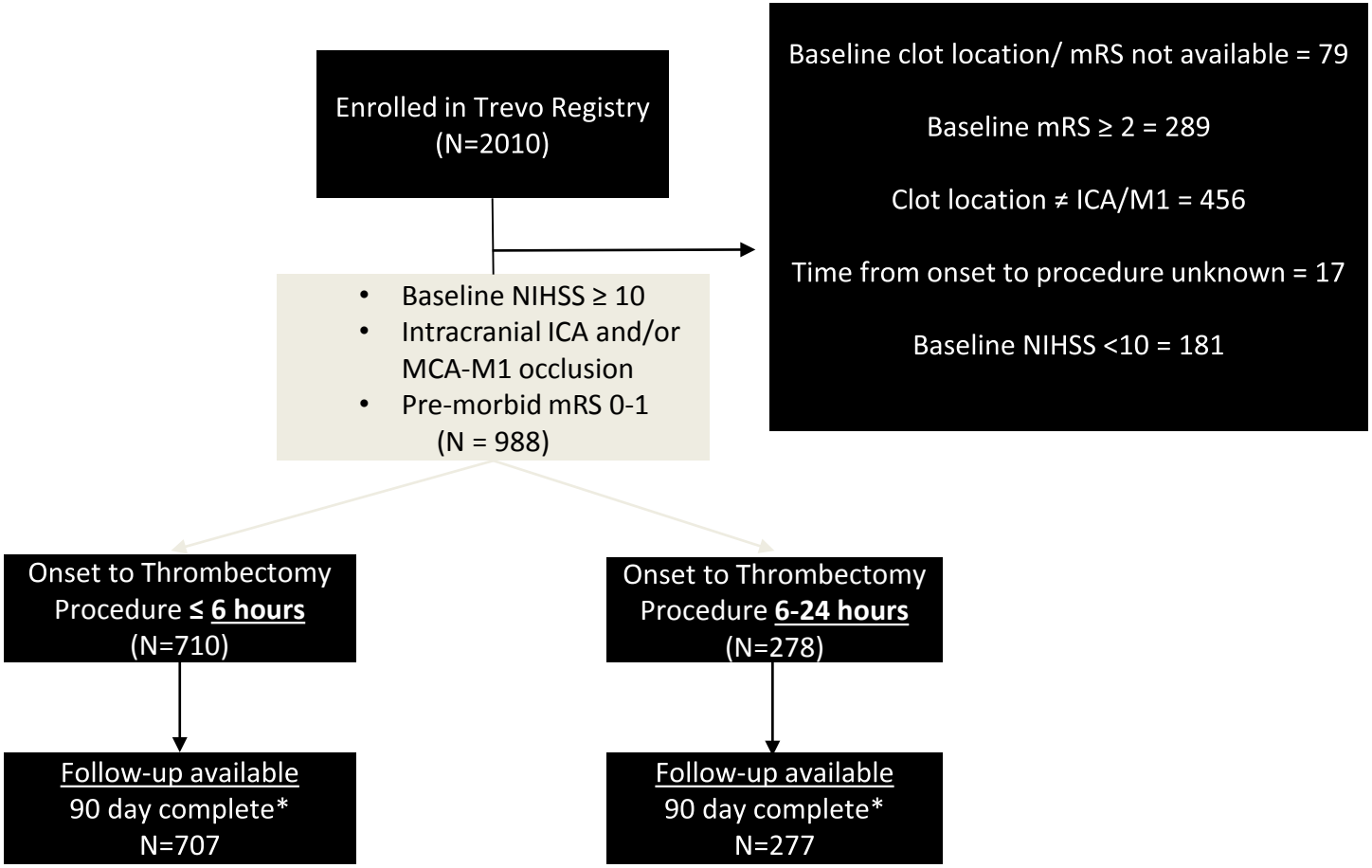
On behalf of the Trevo Retriever Registry Investigators

stryker Neurovascular

eful innovation in mind.

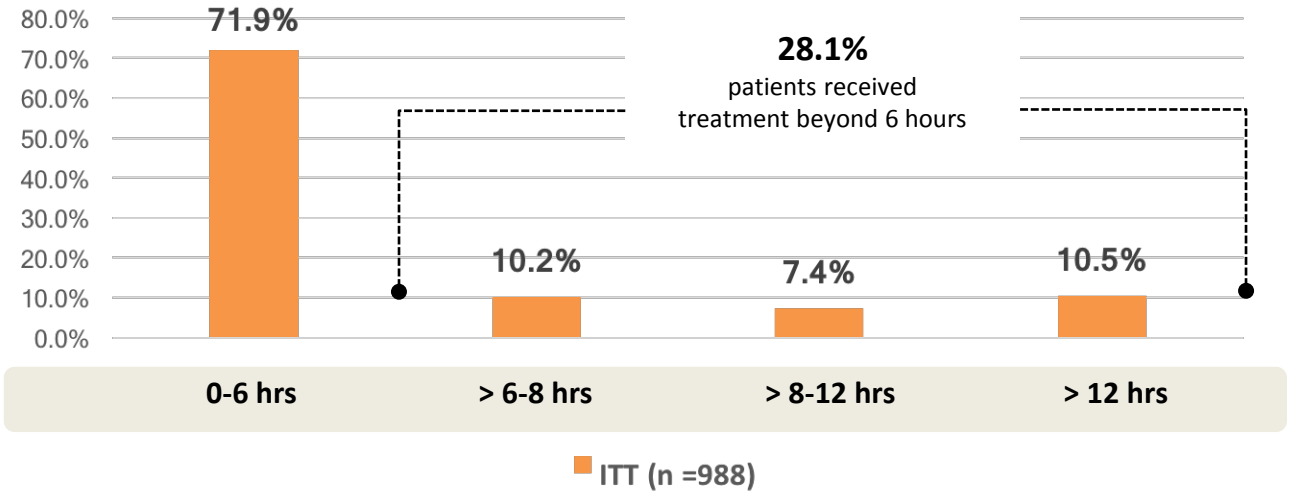
Trevo® Retriever Registry

Analysis Selection Criteria



Time Last Known Well to Groin Puncture

Time Metrics



Baseline Characteristics

	≤ 6 Hours from TLSW N=710	6-24 Hours TLSW N=278	P-Value
Age (mean ± SD)	68.0 ± 14.3	66.2 ± 14.0	0.08
% Female	50.8%	47.8%	0.44
Baseline NIHSS Median (IQR)	17.0(14.0-21.0)	17.0 (14.0-20.0)	0.82
% IV tPA	71.8%	25.3%	<0.001
ASPECTS	8 (7-9)	8(6-8)	0.1
Occlusion Location			0.006
ICA	22.7%	31.6%	--
M1	77.3%	68.4%	--
History of Extracranial Carotid Disease	5.1%	9.2%	0.03
Imaging Usage			1.00
CTP	70.2%	70.3%	--
MRI/MRA	12.1%	10.4%	--
CTP and MRI/MRA	1.1%	4.8%	--
Non-contrast CT Only	16.6%	14.5%	--

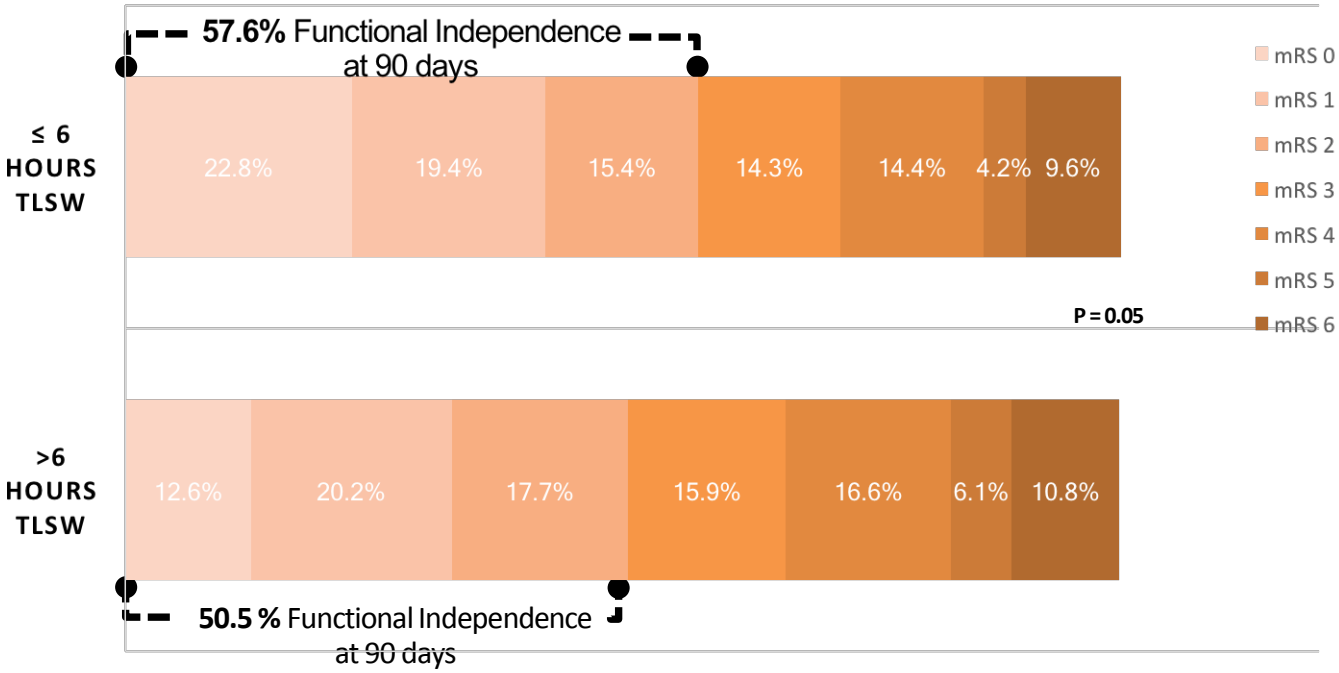
Safety First

Safety Endpoints*

	≤ 6 Hours TLSW, N=710	6-24 Hours TLSW, N=278	P-Value
sICH (ECASS III - within 48 hours)	1.7%	0.7%	0.37
Neurologic Deterioration (within 48 hours)	3.5%	4.0%	0.71
Mortality Rate (within 48 hours)	0.7%	0.4%	1.00
Device or Procedure-related Serious Adverse Events (SAEs)	2.5%	2.2%	0.82

* Safety endpoints are not CEC or core lab adjudicated

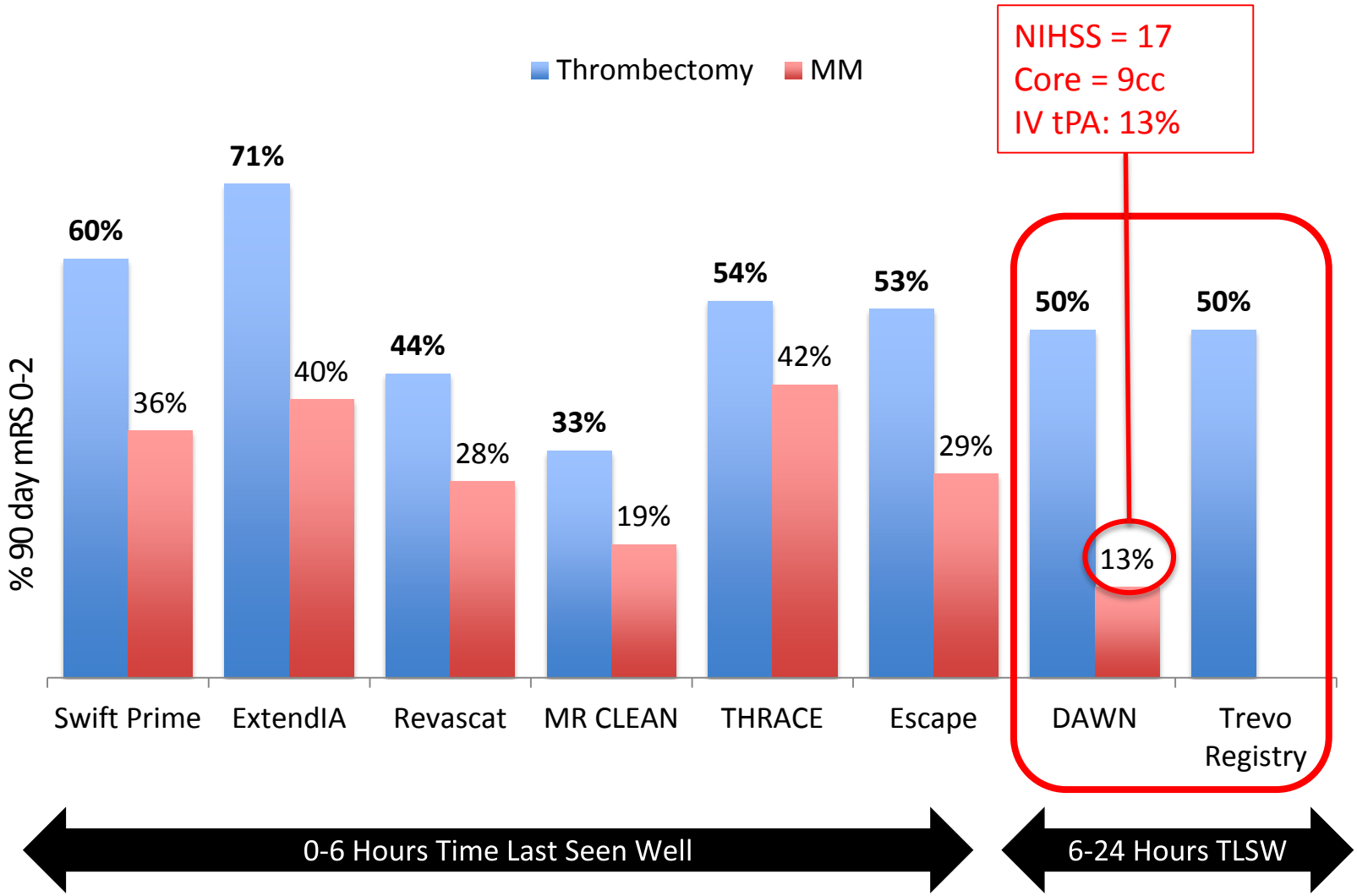
mRS Distribution



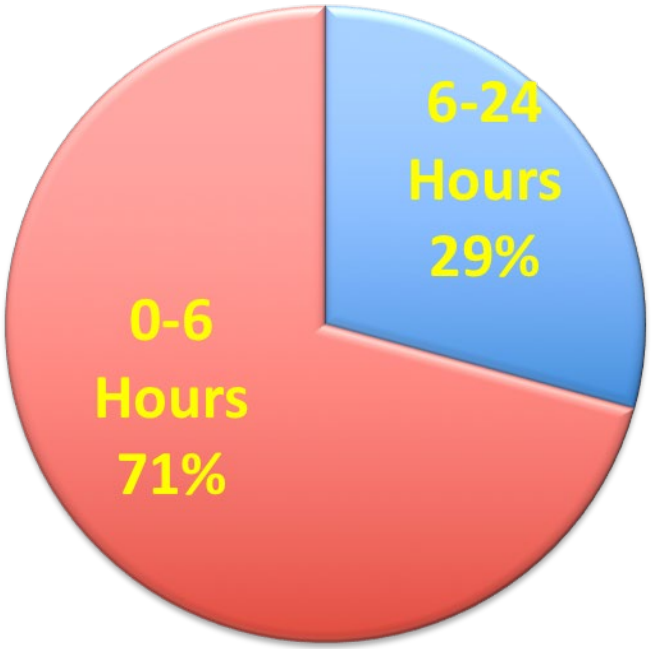
Phase III = Scientific Proof Phase IV = Generalizability

Study Type	Early Window Phase III	Early Window Phase IV	Late Window Phase III	Late Window Phase IV
Study Name	SWIFT Prime RCT (n=98)	Trevo Registry 0-6h (n=710)	DAWN RCT Trevo Arm (n=107)	Trevo Registry 6-24h (n=278)
Age	65.0±12.5	68.0±14.3	69.4±14.1	66.2±14.0
NIHSS, Baseline	17 [13-20]	17 [14-21]	17 [13-21]	17 [14-20]
ICA/M1	18%/67%	22.7%/77.3%	20.6%/73.8%	31.6%/68.4%
SICH	0%	1.7%	4.8%	0.7%
90 day mRS0-2	60 %	57.6%	48.6%	50.5%
90-day Mortality	9%	9.6%	18%	10.8%

Clinical Evidence Diaspora



Estimated Increase in EVT Eligibility in GCNK



Courtesy of Pooja Khatri, ISC 2018

~40% increase in EVT

Could be higher in denser traffic or rural regions

Extending IV Thrombolysis

Raul Nogueira, MD
EMORY UNIVERSITY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, B. Cheripelli, T.-H. Cho, F. Fazekas, J. Fiehler, I. Ford, I. Galinovic, S. Gellissen, A. Golsari, J. Gregori, M. Günther, J. Guibernau, K.G. Häusler, M. Hennerici, A. Kemmling, J. Marstrand, B. Modrau, L. Neeb, N. Perez de la Ossa, J. Puig, P. Ringleb, P. Roy, E. Scheel, W. Schonewille, J. Serena, S. Sunaert, K. Villringer, A. Wouters, V. Thijs, M. Ebinger, M. Endres, J.B. Fiebach, R. Lemmens, K.W. Muir, N. Nighoghossian, S. Pedraza, and C. Gerloff, for the WAKE-UP Investigators*

Variable	Alteplase Group (N=254)	Placebo Group (N=249)
Median lesion volume on diffusion-weighted imaging (IQR) — ml	2.0 (0.8–7.9)	2.5 (0.7–8.8)
Median NIHSS score (IQR)†	6 (4–9)	6 (4–9)
Interval between last time that the patient was last known to be well and treatment initiation (IQR) — hr	10.3 (8.1–12.0)	10.4 (8.1–12.1)
Vessel occlusion on time-of-flight MRA — no./total no. (%)		
Any	84/249 (33.7)	84/246 (34.1)
Intracranial internal carotid artery	24/249 (9.6)	11/246 (4.5)
Middle cerebral artery main stem	35/249 (14.1)	37/246 (15.0)
Middle cerebral artery branch	32/249 (12.9)	36/246 (14.6)
Other‡	12/249 (4.8)	12/246 (4.9)

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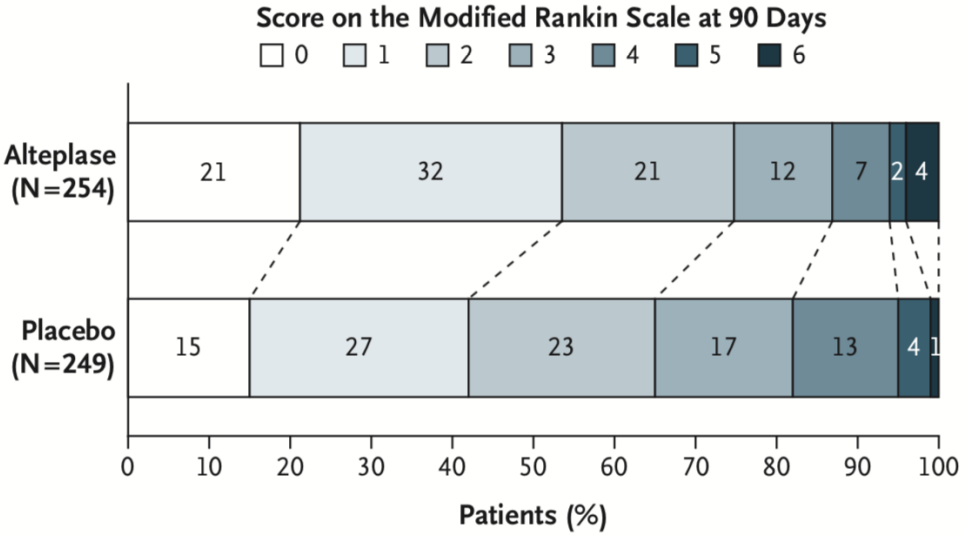


90-day mRS 0-1:
53.3 vs 41.8%
Adjusted OR: 1.61; 95% CI [1.09 to 2.36]
P=0.02

Ordinal Shift:
Adjusted cOR: 1.62; 95% CI [1.17 - 2.23];
P=0.003

- Trend towards higher mortality (4.1 vs 1.2%; adjusted OR, 3.38; 95% CI [0.92-12.52]; P = 0.07)
- Higher rate of PH2 (4.0 vs 0.4%; adjusted OR, 10.46; 95% CI [1.32-82.77]; P=0.03)
- No difference in Infarct Volume at 22-36 hours (3 vs 3.3 ml; P=0.32)
- No clear benefit for NIHSS>10 (n=109; 90-day mRS 0-1: 13.5 vs 12.3%)

Intravenous Thrombolysis in Unwitnessed Stroke Onset: MR WITNESS Trial Results

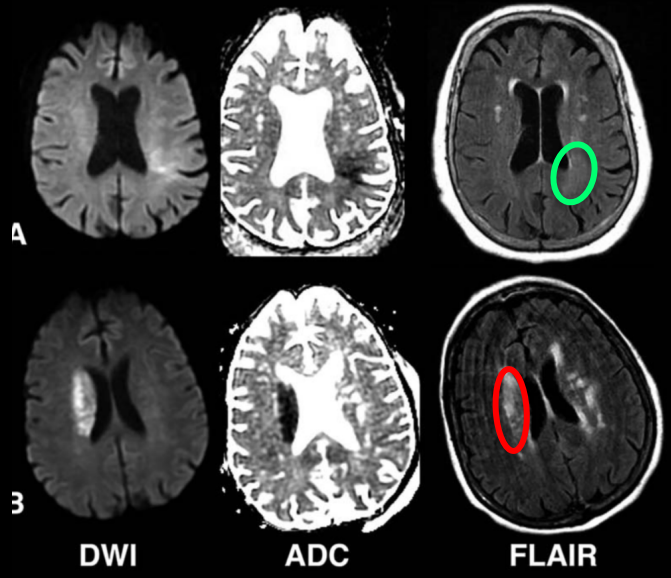
Lee H. Schwamm, MD,[1*] Ona Wu, PhD,[2*] Shlee S. Song, MD,[3] Lawrence L. Latour, PhD,[4] Andria L. Ford, MD,[5] Amie W. Hsia, MD,[4,6] Alona Muzikansky, MA,[7] Rebecca A. Betensky, PhD,[7,8] Albert J. Yoo, MD,[9,10] Michael H. Lev, MD,[10] Gregoire Boulouis, MD,[1,11] Arne Lauer, MD,[1] Pedro Cougo, MD,[1] William A. Copen, MD,[10] Gordon J. Harris, PhD,[10] and Steven Warach, MD, PhD ,[12] on behalf of the MR WITNESS Investigators

- N=80
- Quantitative FLAIR-DWI Mismatch
- Time 4.5 h
- bNIHSS: 7 (4–13.5)
- 90-day mRS 0-1: 39%
- SICH: 1.3%

Prospective, Open-Label Safety Study of Intravenous Recombinant Tissue Plasminogen Activator in Wake-Up Stroke

Andrew D. Barreto, MD, MS,[1] Christopher V. Fanale, MD,[2] Andrei V. Alexandrov, MD,[3] Kevin C. Gaffney, MD,[4] Farhaan S. Vahidy, PhD,[1] Claude B. Nguyen, MD,[5] Amrou Sarraj, MD,[1] Mohammad Rahbar, PhD,[6] James C. Grotta, MD,[7] and Sean I. Savitz, MD,[1] for the Wake-Up Stroke Investigators

- N=40
- NCCT <1/3 MCA but mean/median ASPECTS: 9/10
- Time 3 h
- bNIHSS: 6.5 (4–10.5)
- 90-day mRS 0-1: 52.6%
- SICH: 0%



- IVT and ET trials do not compete but rather complement each other:
  - Low NIHSS/Non-LVO = IVT
  - High NIHSS/LVO = ET
- FLAIR-DWI Mismatch is a biomarker for Time not Viable Tissue/ Penumbra
- Early Time = Higher Likelihood of Penumbra (but not necessarily existence)
- ?Trials of FLAIR-DWI Mismatch vs “Tiny Infarcts” with Clinical-Core Mismatch

Current Needs and Future Directions

Raul Nogueira, MD
EMORY UNIVERSITY

Do I Absolutely Need CTP or MRI to Treat Patients in the Late Window?

NCCT is Like Wine – It Ages Better…

EARLY NCCT SCANS HARD TO INTERPRET

Table 1 Interobserver reliability of ASPECTS scoring on NCCT and CTASI in different time categories from stroke onset

	NCCT		CTASI	
Time	Intraclass correlation	95% CI (lower, upper)	Intraclass correlation	95% CI (lower, upper)
0–90	0·48*	0·28–0·71	0·96*	0·93–0·98
91–180	0·80	0·66–0·90	0·94	0·89–0·97
181–360	0·81	0·69–0·91	0·87	0·78–0·94
>360	0·89	0·81–0·95	0·89	0·80–0·95
Overall	0·78	0·69–0·84	0·93	0·90–0·95

*Comparison of the intraclass correlation at 0–90 mins vs. 90 mins or greater, $P = 0{\cdot}0001$ for NCCT and $P = 0{\cdot}178$ for CTASI.
ASPECTS, Alberta Stroke Program Early CT Score; NCCT, noncontrast computed tomography; CTASI, CT angiography source image; CI, confidence interval.

Table 1 Interobserver reliability of ASPECTS scoring on NCCT and CTASI in different time categories from stroke onset

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ASPECTS, Alberta Stroke Program Early CT Score; NCCT, noncontrast computed tomography; CTASI, CT angiography source image; CI, confidence interval.

***Stroke*. 2009;40:2743-2748**

Trevo Registry: TLSW 6 - 24, ICA/M1/M2, bmRS 0-2

	NCCT (N=62)	CTP or MRI (N=367)	P-value
Age	64.5±16.2	66.8±13.9	0.253
Female	45.2%	52.6%	0.279
bNIHSS	14.7±6.7	15.1±6.5	0.654
Occlusion Site			
ICA	27.4%	24%	0.671
M1	58.1%	57.2%	
M2	14.5%	18.8%	
bASPECTS	7.5±1.7	7.4±1.7	0.138
TLSW to Puncture (hr)	10.2±4.1	10.9±4.3	0.129
IV tPA	29%	24%	0.400
Conscious sedation	45.2%	50.1%	0.600
mTICI 2b-3	95.2%	93.7%	0.663
90-day mRS 0 - 2	59.7%	55.1%	0.499
SICH	1.6%	1.4%	0.877
90-day Mortality	11.3%	11.5%	

Selection Paradigms for Large Vessel Occlusion Acute Ischemic Stroke Endovascular Therapy

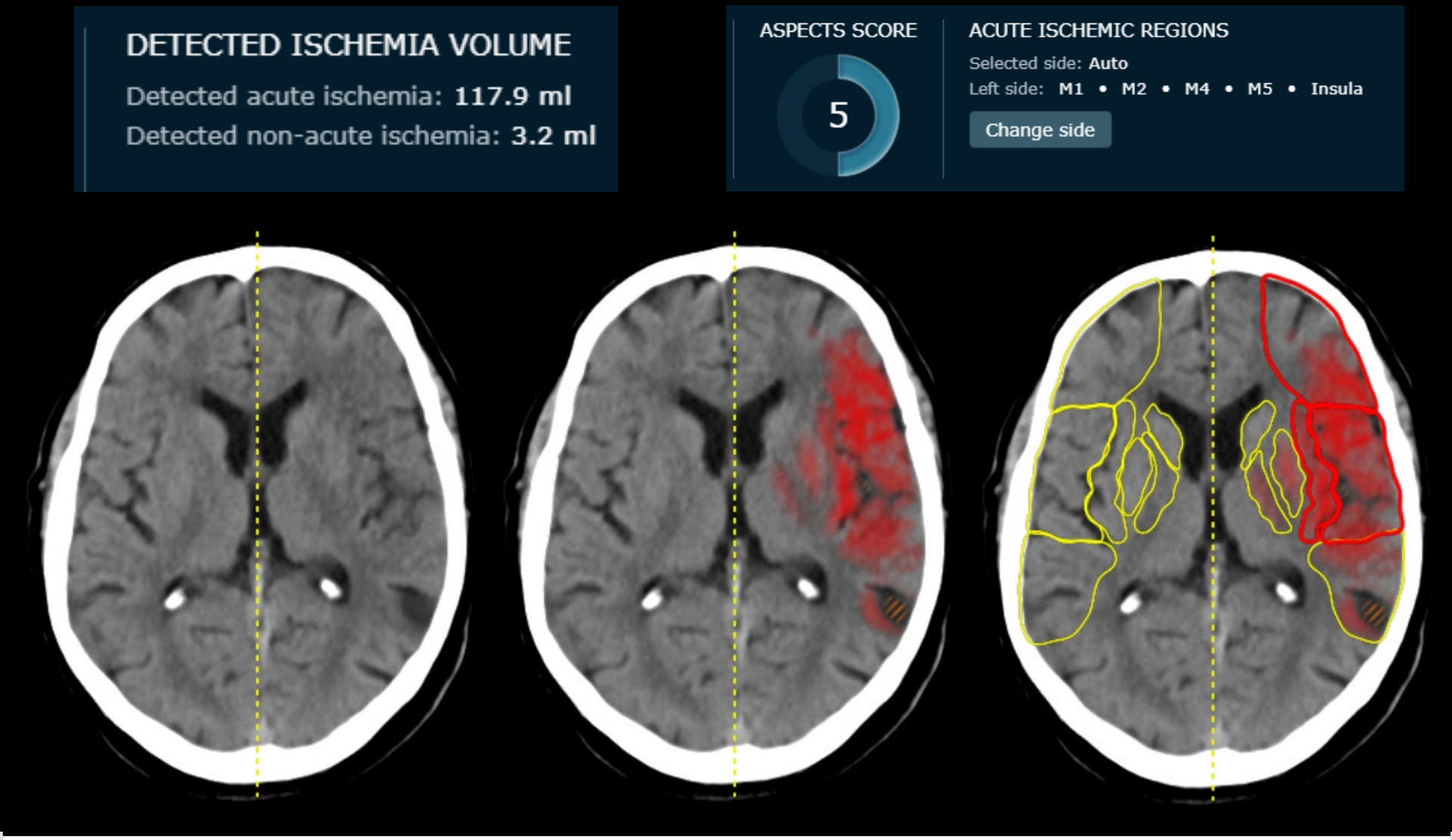
Mehdi Bouslama Meredith T. Bowen Diogo C. Haussen Seena Dehkharghani
Jonathan A. Grossberg Leticia C. Rebello Srikant Rangaraju
Michael R Frankel Raul G. Nogueira

Departments of Neurology, Radiology and Neurosurgery Grady Memorial Hospital and Emory University School of Medicine, Atlanta, GA, USA

Conclusions: For patients with NIHSS ≥10, PIM appears to disqualify more patients without improving outcomes. CCM may improve selection, combining a high inclusion rate with optimal outcome discrimination across (+) and (–) patients. Future studies are warranted.

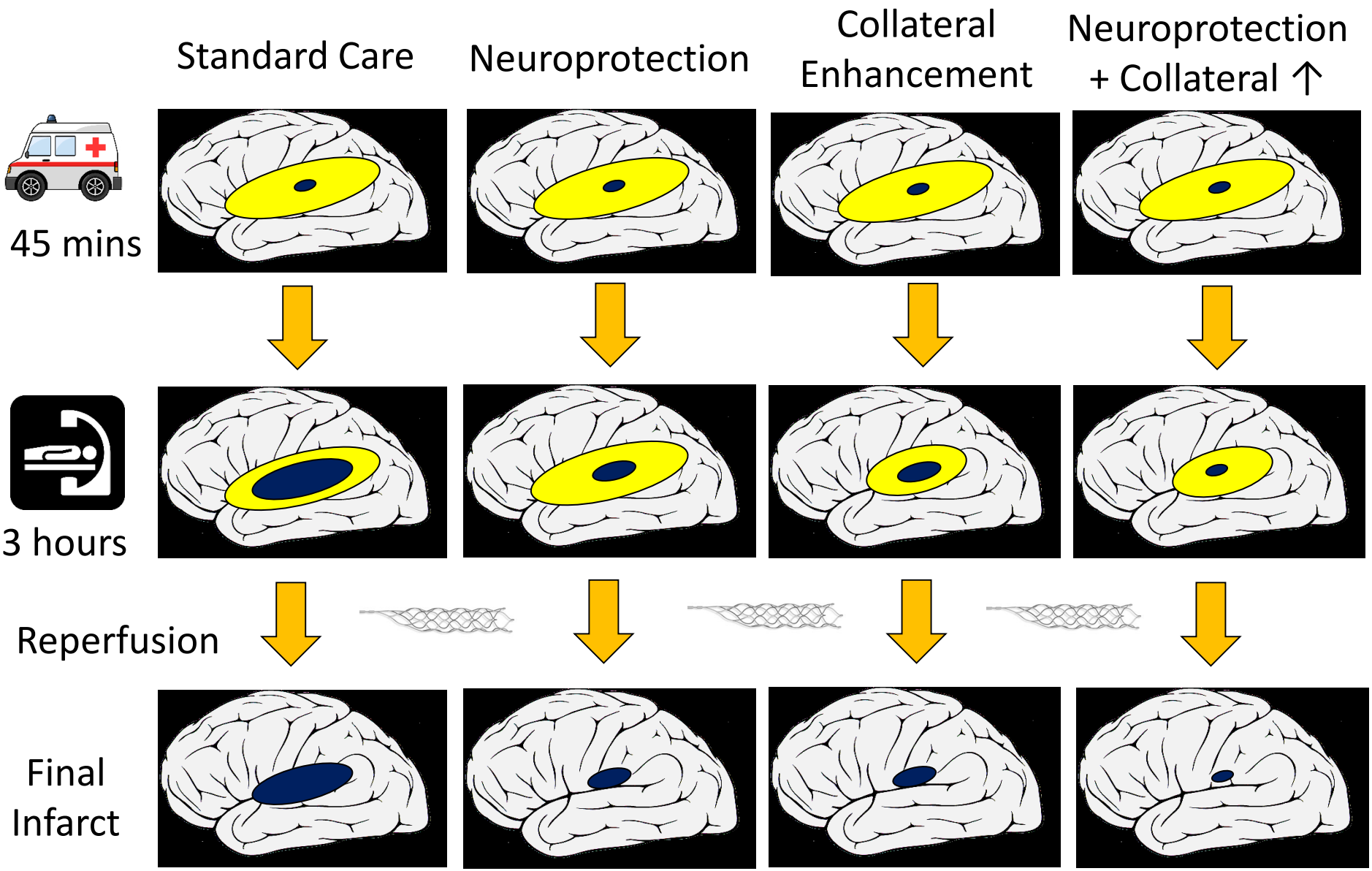
Cerebrovasc Dis 2017;44:277–284

AI for Non-Contrast CT Acute Ischemic Volume



Olea medical

Brainomix

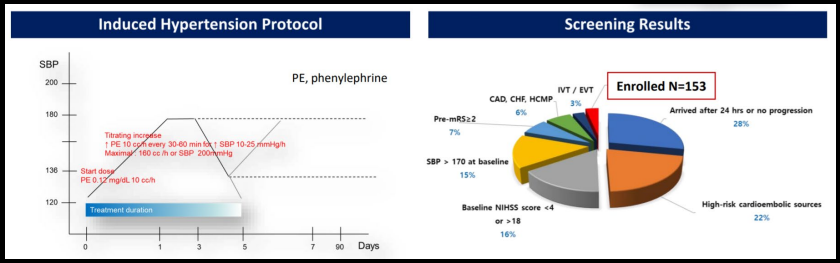


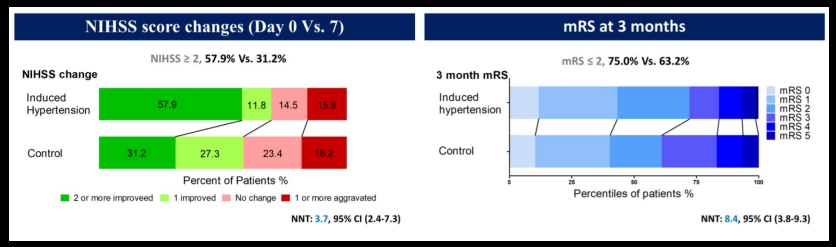
Courtesy of Jeff Saver

Collateral Enhancement Strategies

Induced HTN

SETIN Trial (n = 153)

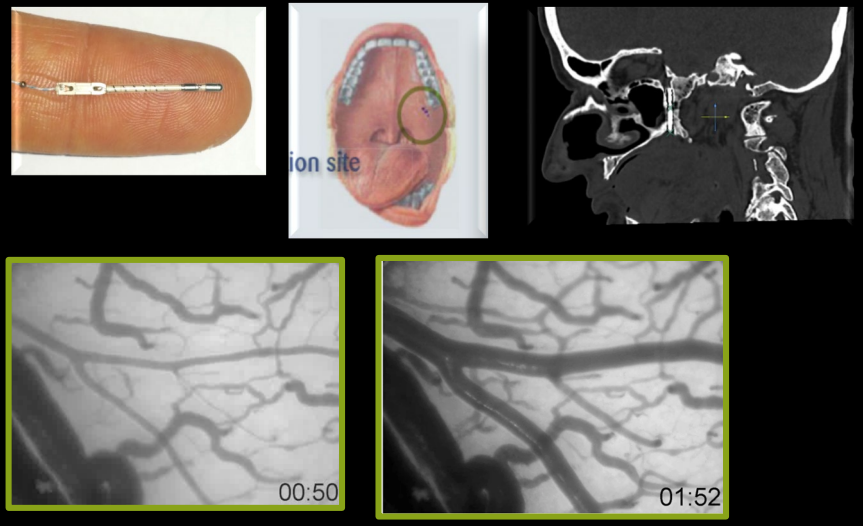




--SETIN Investigators, ESOC 2018

SPG Stimulation

ImpACT 24B Trial (n = 1000)



--Forthcoming from ImpACT 24B Investigators, WSC Oct 2018

Courtesy of Jeff Saver

ESCAPE-NA1 Clinical Trial Study Newsletter

Issue 5, September 2018

Many thanks for your continued work and dedication to the ESCAPE-NA1! As of 5th September 2018, 501 subjects have been randomized across all sites open for enrollment. This officially makes ESCAPE-NA1 the **largest** thrombectomy trial! Thank you all for your contributions!

There are now 45 sites across 8 countries open and actively enrolling. During the summer, we recruited 48 subjects per month. With the activation of more sites, we hope to increase recruitment to 60+ subjects per month moving forward. Thanks for your excellent support to date, keep up the great work!

LEADER-BOARD

Top Enrollers	# Enrolled (Jun-Aug 2018)
Lillian Uroz (Saskatoon)	7
Meagan Schultz (Atlanta)	6
Yun Jeong Lim (Seoul–SMC)	5
Loretta Jean Webb (Chattanooga)	5
Anitha Jambula (Calgary)	4
Geni Maclean (Vancouver)	4
Kim Gray (Chattanooga)	4
Marlene Lapierre (Montreal—CHUM)	4
Shannon Doppelheuer (Atlanta)	4

Top Sites	Enrolled in 2018
Atlanta	40
Rhode Island	35
Calgary	29
Montreal—CHUM	29
Hamilton	14
Melbourne	14
Toronto—SHSC	13

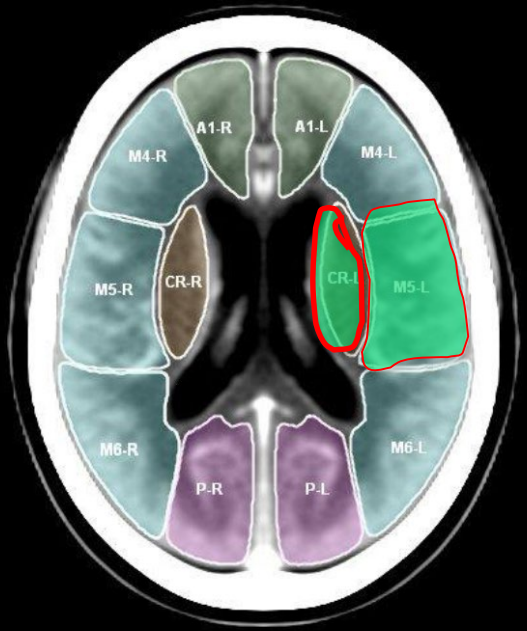
Since the last newsletter, congratulations to the following teams who have enrolled of their first (of many) subjects: Dresden, Hamburg, Gottingen, Torrance, Seoul—YUSH, Incheon, Torrance, Marietta and San Francisco!

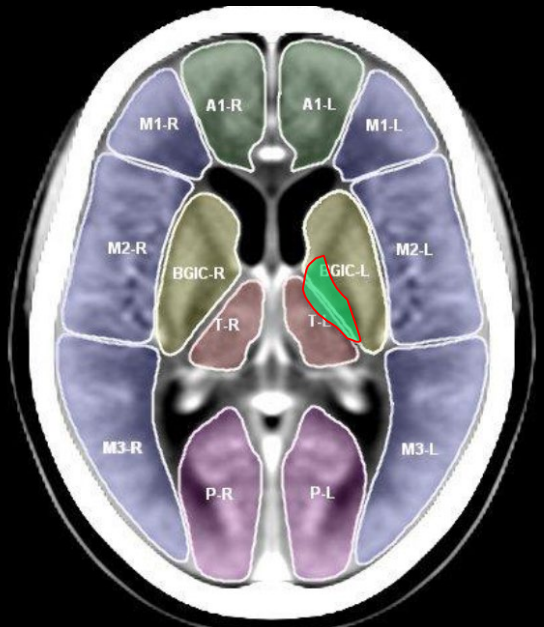
Stroke Neurology: the Real Clinical-Core Mismatch Machine….

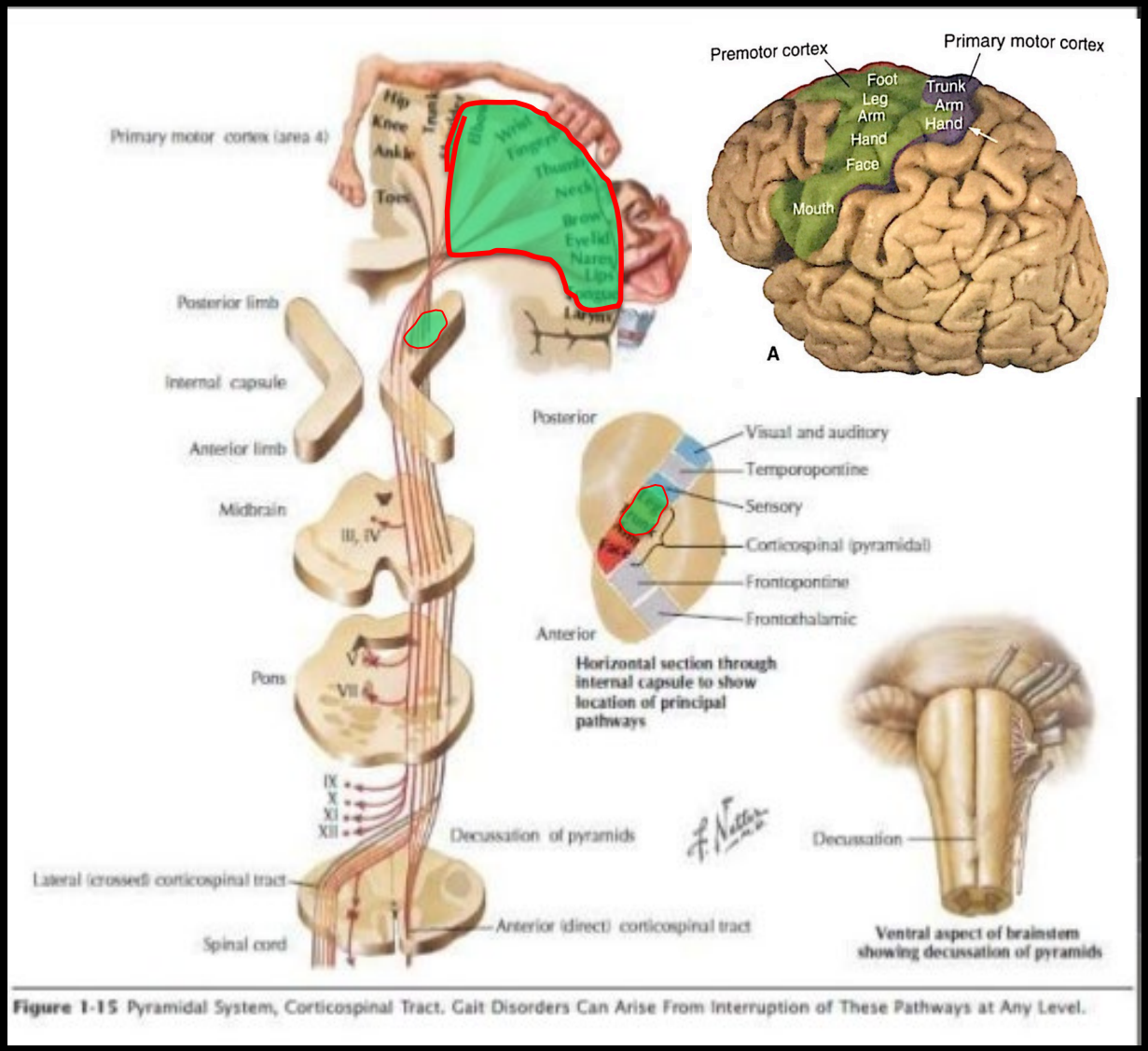
The FAST-ED Mismatch!

Raul Nogueira, MD
EMORY UNIVERSITY

Hemiplegia on Exam + Motor System Preservation on Imaging = Penumbra







Ciszek B et al.Stroke bricks — spatial brain regions to assess ischemic stroke localization. Folia Morphol (Warsz). 2017 Mar 29

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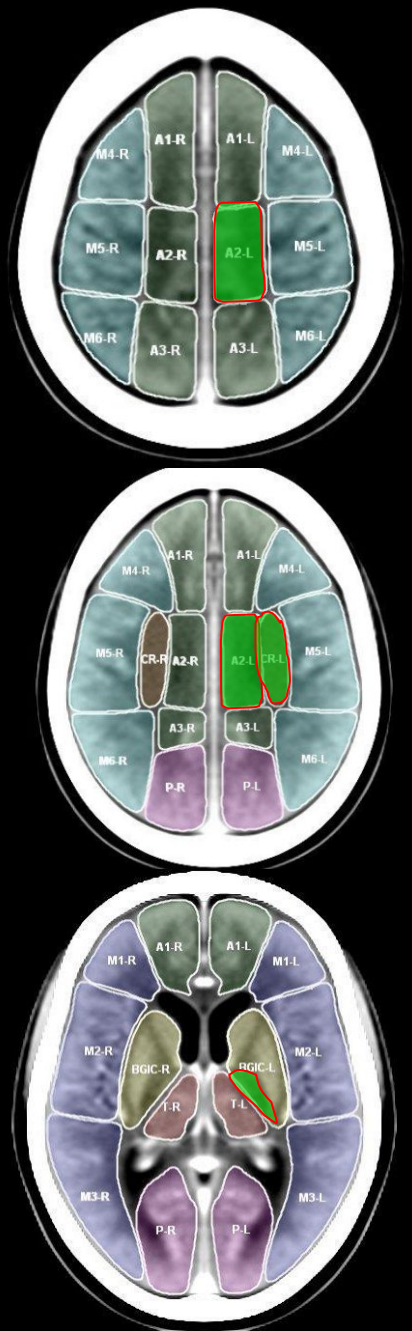
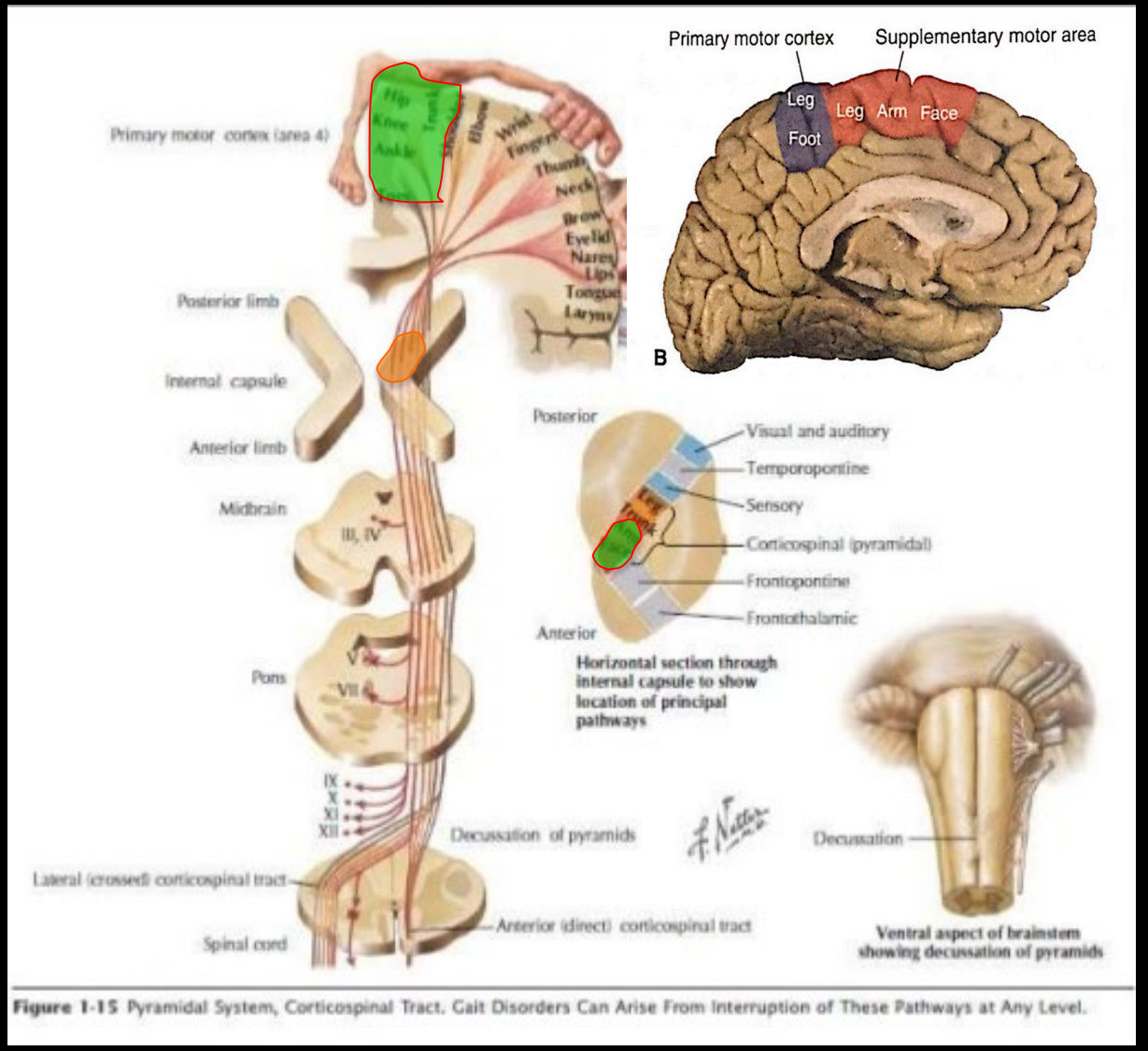




Ciszek B et al. Folia Morphol (Warsz). 2017 Mar 29

Aphasia on Exam + Language System Preservation on Imaging = Penumbra

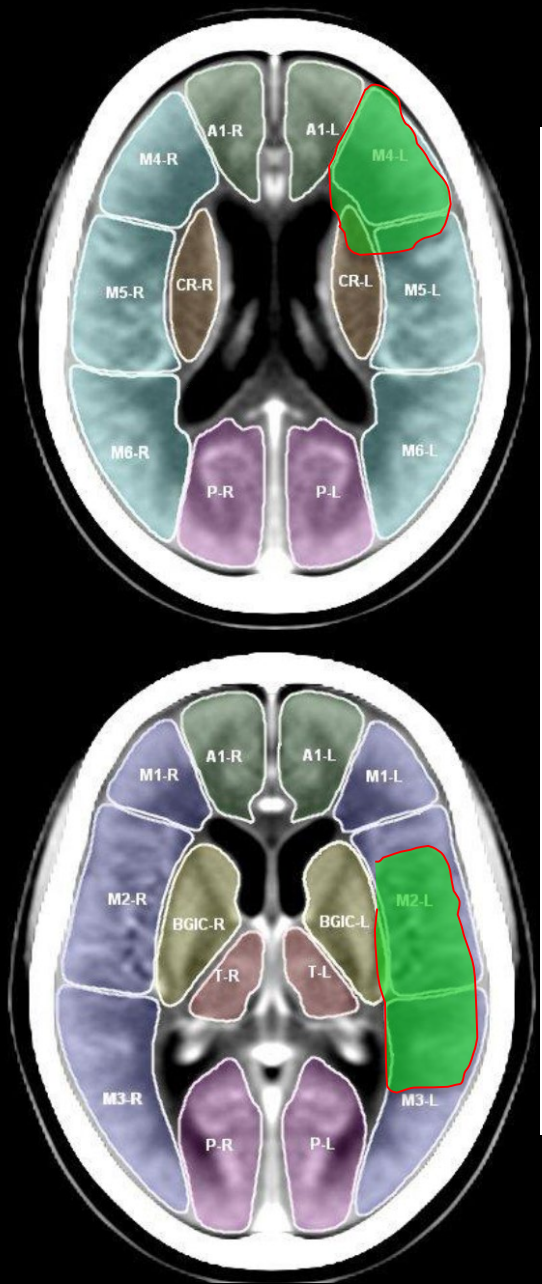
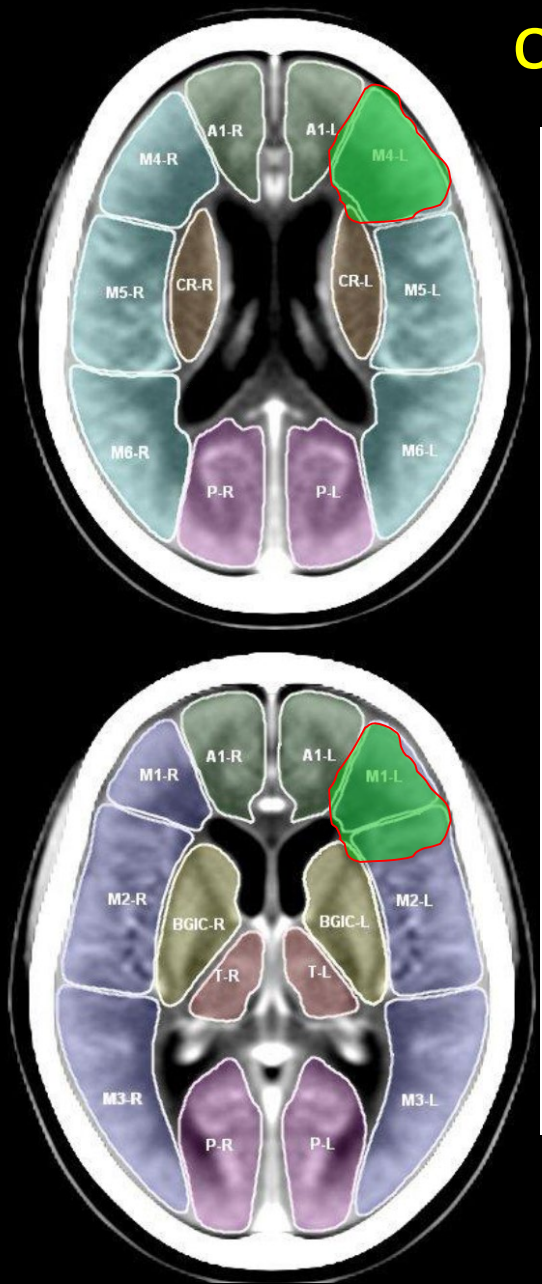


Table 1. Common neurological symptoms and corresponding *Stroke Bricks* segments.

Symptom	Regions	Symptom	Regions
gaze palsy or total gaze paresis	M1 M4	**homonymous hemianopsia**	P M2 M3
expressive (motor) aphasia	M1 M4	**upper limb paresis**	M5 CR BGIC
hemineglect	A3 M6	**lower limb paresis**	A2 CR BGIC
sensory aphasia	M3 M6	**upper limb sensory loss**	M5 CR BGIC T
disorientation	A1 M1 M4	**lower limb sensory loss**	A2 CR BGIC T
central facial nerve palsy	M5 CR BGIC	**face hemisensory loss**	M5 CR T
central hypoglossal nerve palsy	M5 CR BGIC	**dysarthria**	A1 M1 M4 BGIC

Ciszek B et al.Stroke bricks — spatial brain regions to assess ischemic stroke localization. Folia Morphol (Warsz). 2017 Mar 29

Gaze Deviation on Exam + Gaze System Preservation on Imaging = Penumbra



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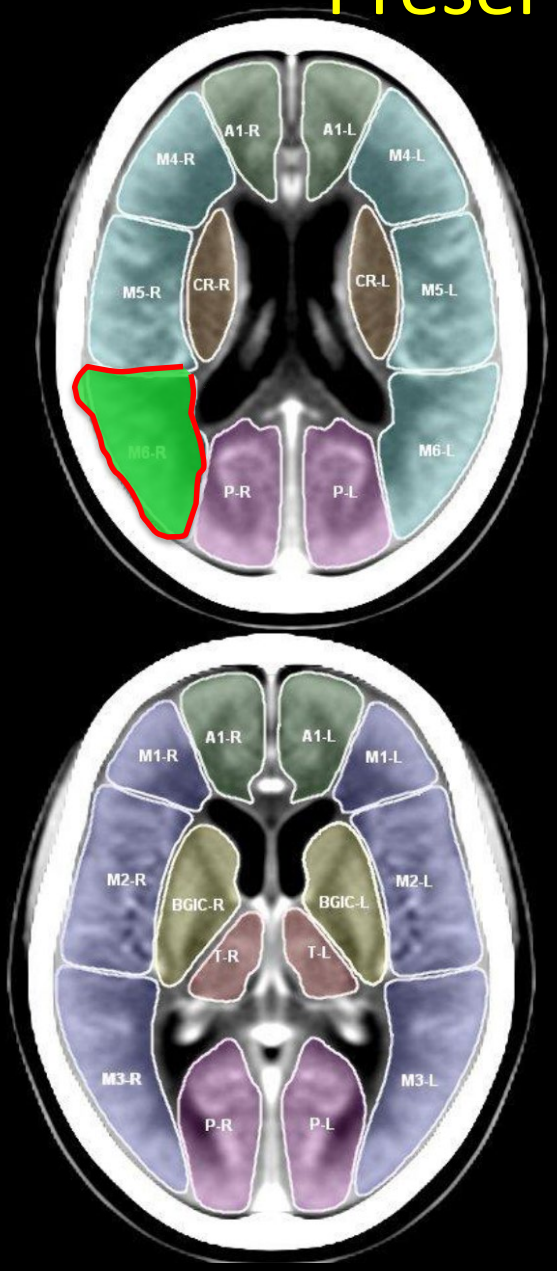
central facial nerve palsy	M5 CR BGIC	**face hemisensory loss**	M5 CR T
central hypoglossal nerve palsy	M5 CR BGIC	**dysarthria**	A1 M1 M4 BGIC

Ciszek B et al.Stroke bricks — spatial brain regions to assess ischemic stroke localization. Folia Morphol (Warsz). 2017 Mar 29

Denial (Neglect) on Exam + Spatial Attention System Preservation on Imaging = Penumbra



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The Art and Science of Medicine: Merging Data, Physiology, and Clinical Judgment

Raul Nogueira, MD
EMORY UNIVERSITY

We Must Individualize Patient Care!

$$\text{Outcomes} = \frac{1}{\text{Final Infarct Volume} \times \text{Regional Eloquence} \times \text{Biological Age}}$$

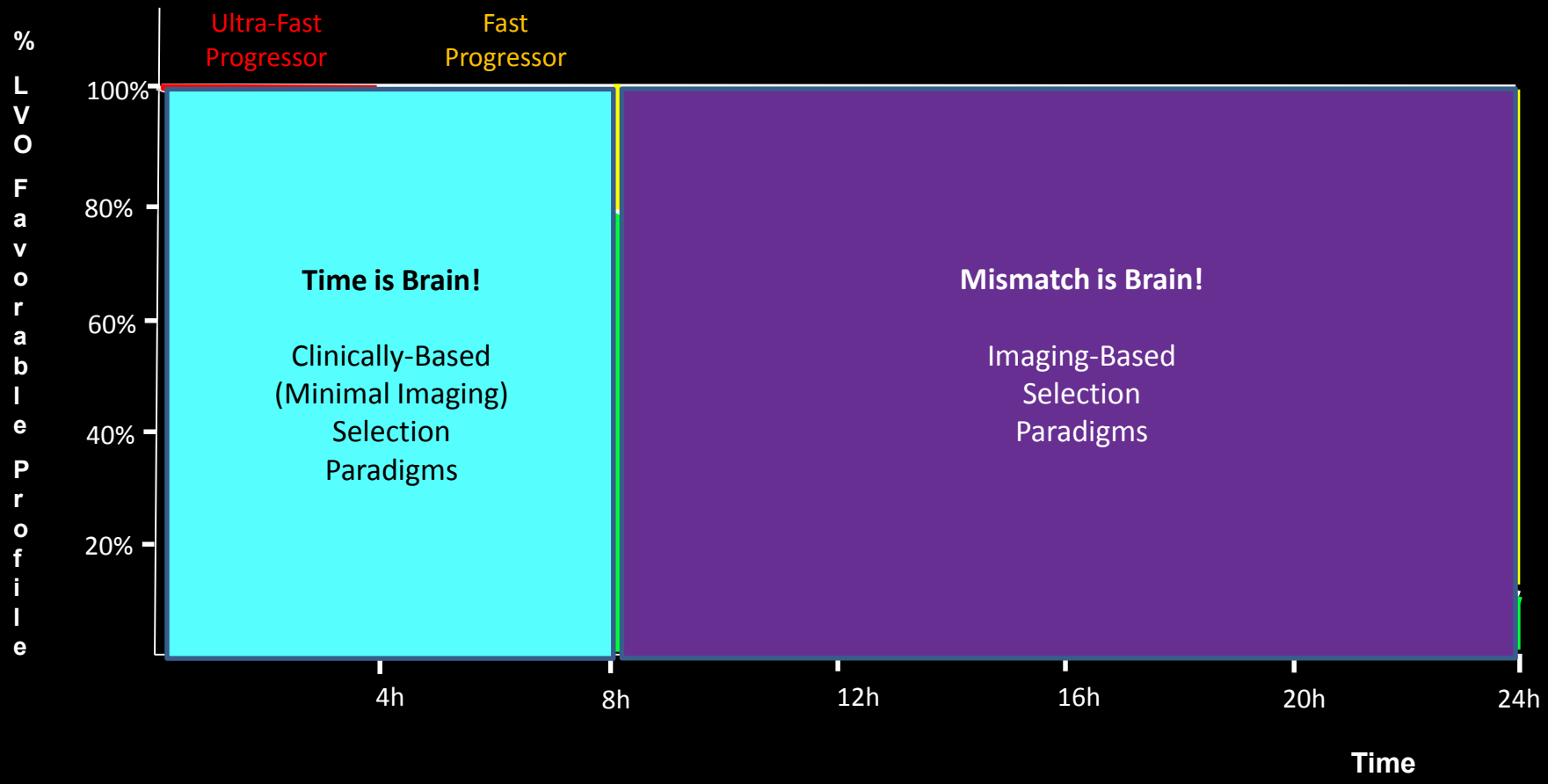
$$\text{Final Infarct Volume} = \frac{\text{Occlusion Time}}{\text{Collaterals}}$$

Raul Nogueira, MD
EMORY UNIVERSITY

Patient Selection Should be Time Dependent!

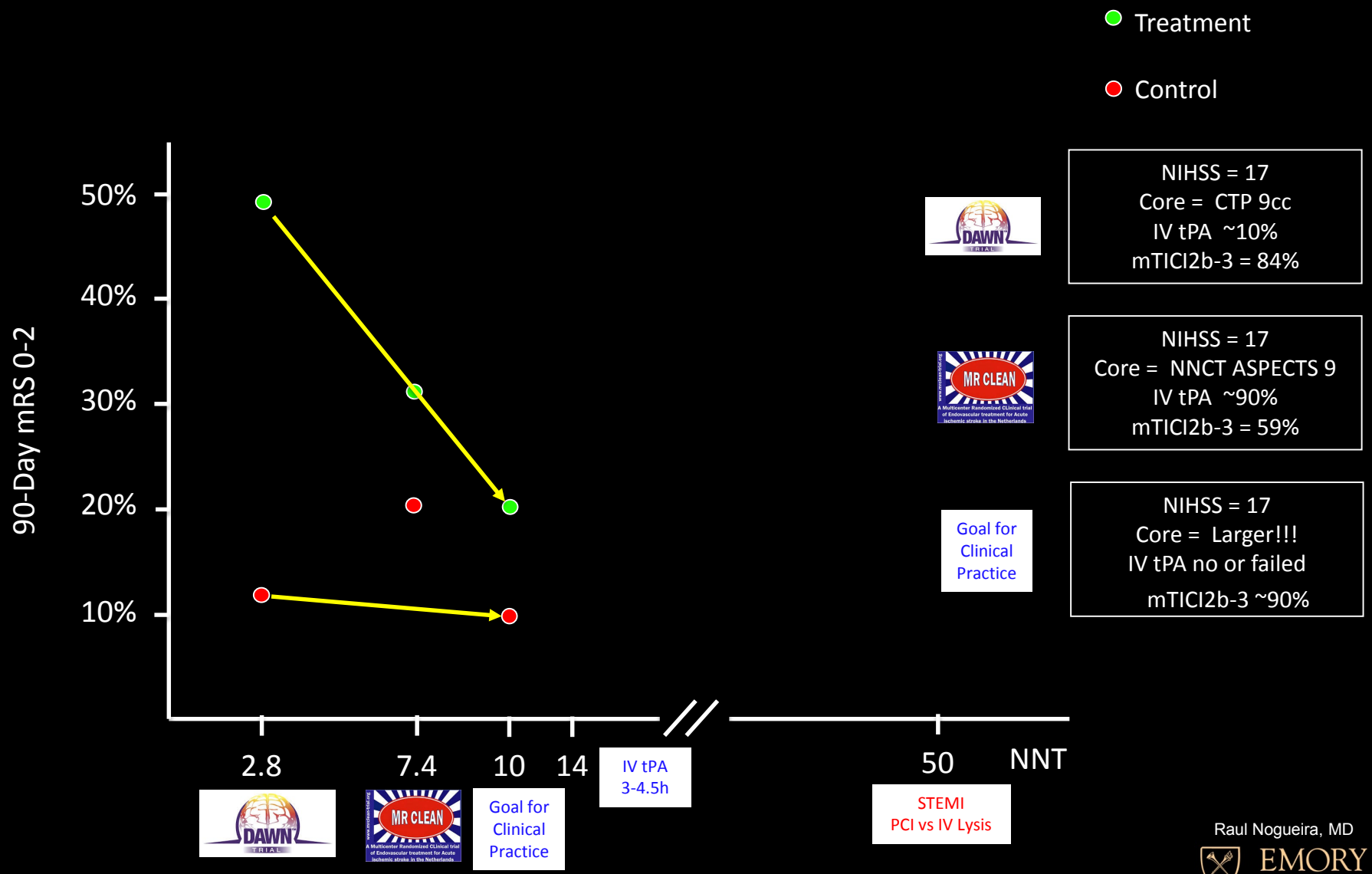
0-6 hours vs. 6-24 hours

Patient Selection Should Be Time Dependent!



Raul Nogueira, MD
EMORY UNIVERSITY

A Call for Action: (1) We Must Stop Over-Selection! (2) Don't Ever Give Up on a Severe Stroke!



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EMORY UNIVERSITY

Conclusions: Late Window (>6 Hours):

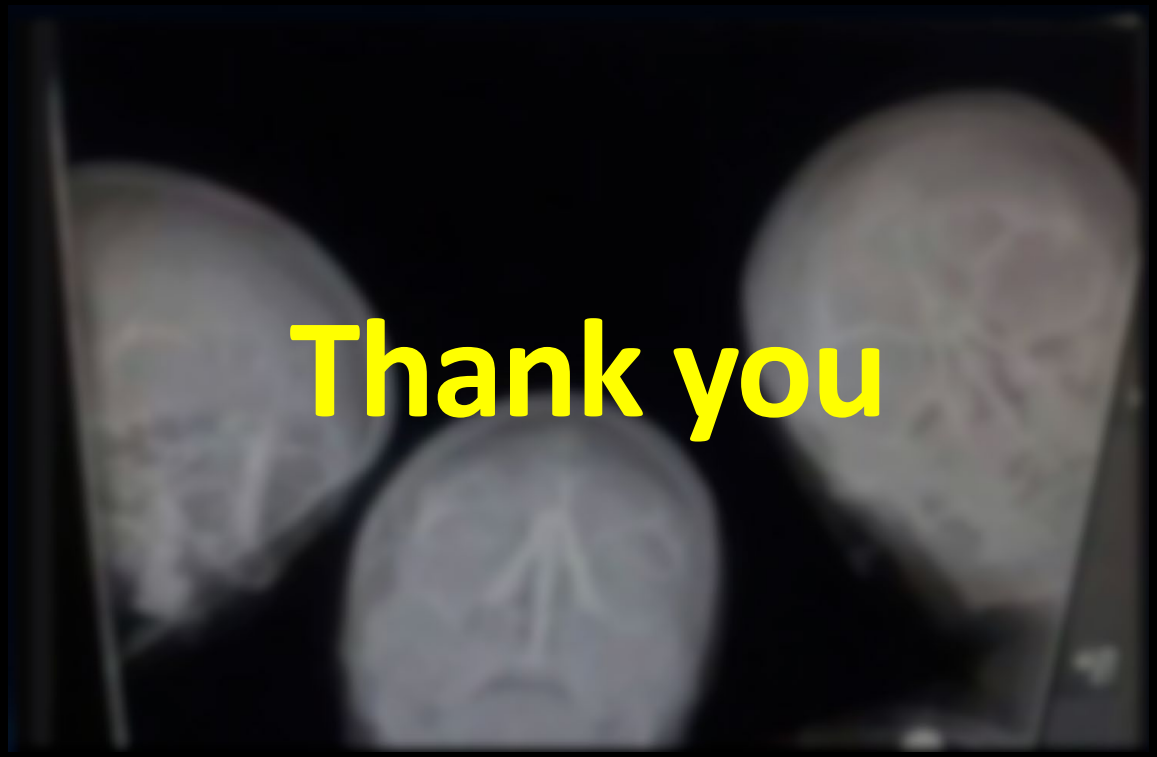
- In mismatch patients (CIM or PIM), endovascular treatment initiated >6 hours from TLSW is a highly effective therapy and no less effective than treatment 0-6 hours
- Safety profile no different than 0-6 hours
- Effectiveness is maintained across all subgroups including those defined by time, age, mode of presentation and ASPECTS scores
- A stronger treatment effect is seen in patients treated in the 12-24 hour window vs. 6-12 hour window (Late Window Paradox)
- Patients with witnessed onset of symptoms at 6-24 hours derive comparable benefit to “wake up stroke” and unwitnessed mode of presentation

DAWN has risen!

Thank you

to patients, families and all investigative sites

$$\text{Outcomes} = \frac{\text{Collaterals}}{\text{Time}}$$

When stroke interventionists take a selfie…

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