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Stanford University Medical Center

Late Window IV thrombolysis

Gregory W Albers, MD
Professor of Neurology, Stanford University
Director, Stanford Stroke Center

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Disclosures:
iSchemaView, Genentech

Call from Stanford ER at 4:45 am

70 yo female woke-up at 4 am with L hemiplegia, last known well at 9 pm

Arrival at Stanford ER at 4:30 am and triaged directly to CT scan

Just returned from CT Stroke Protocol. Stroke Resident at bedside

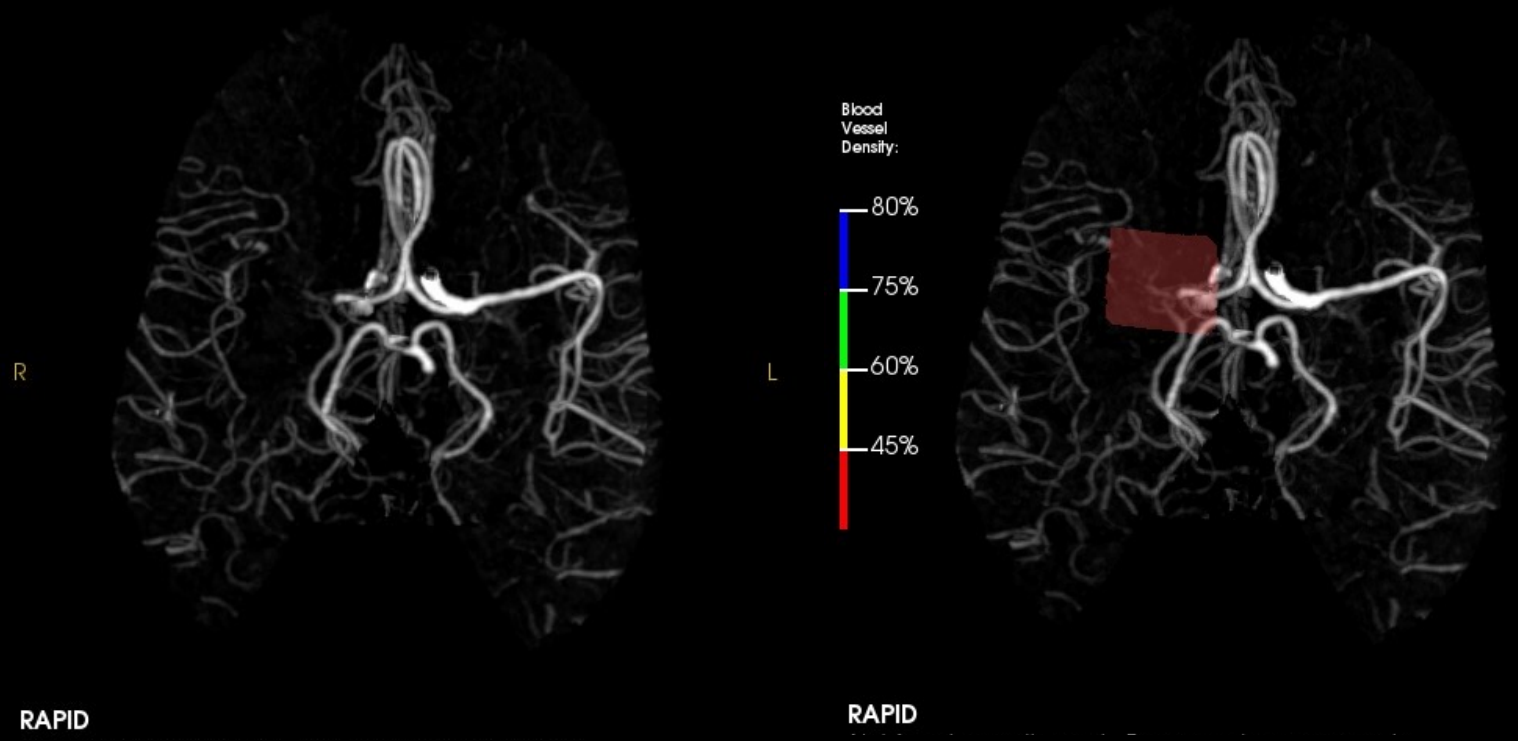
Open email or RAPID App to view images

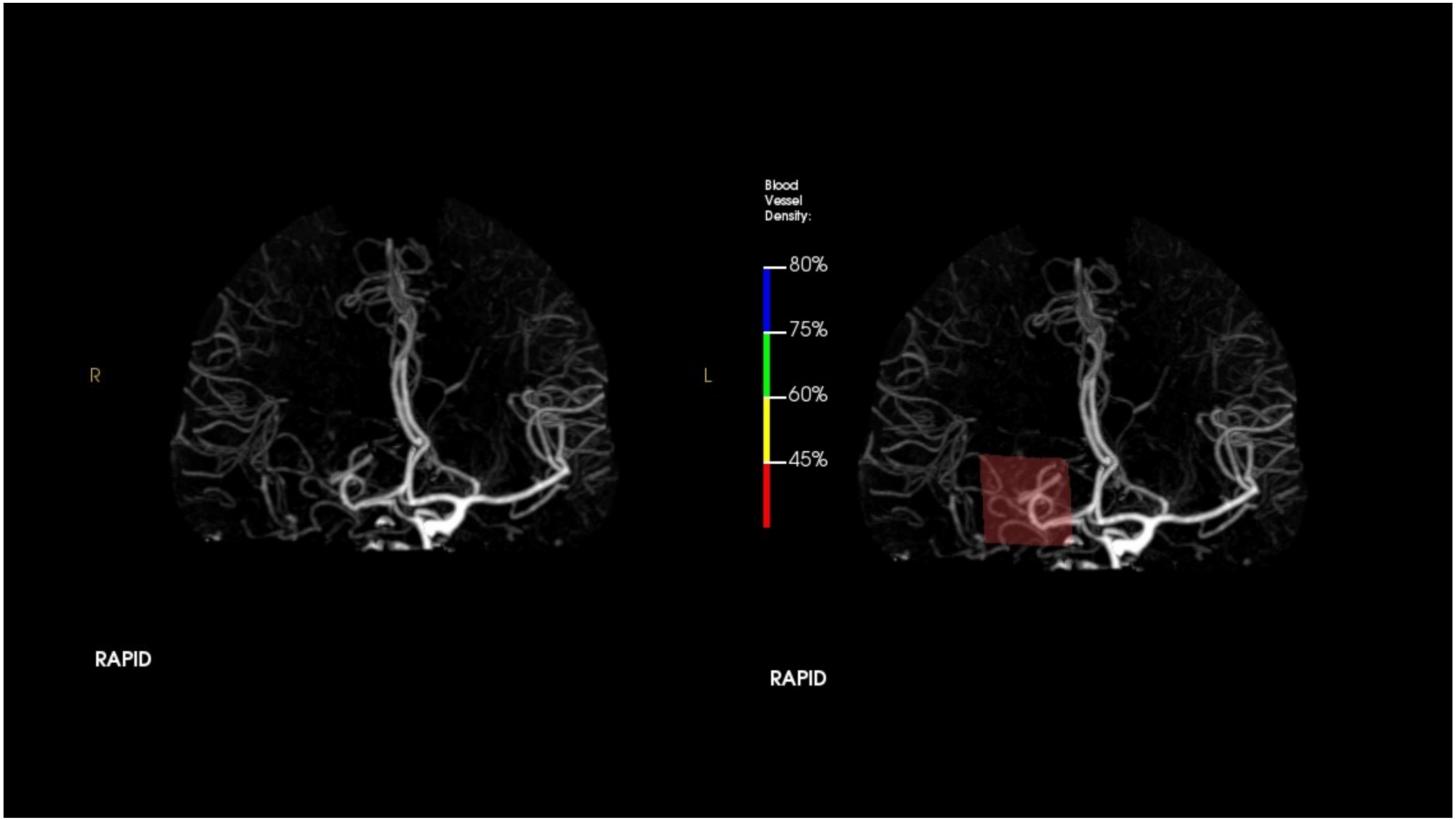
RAPID CTA processing: finished successfully

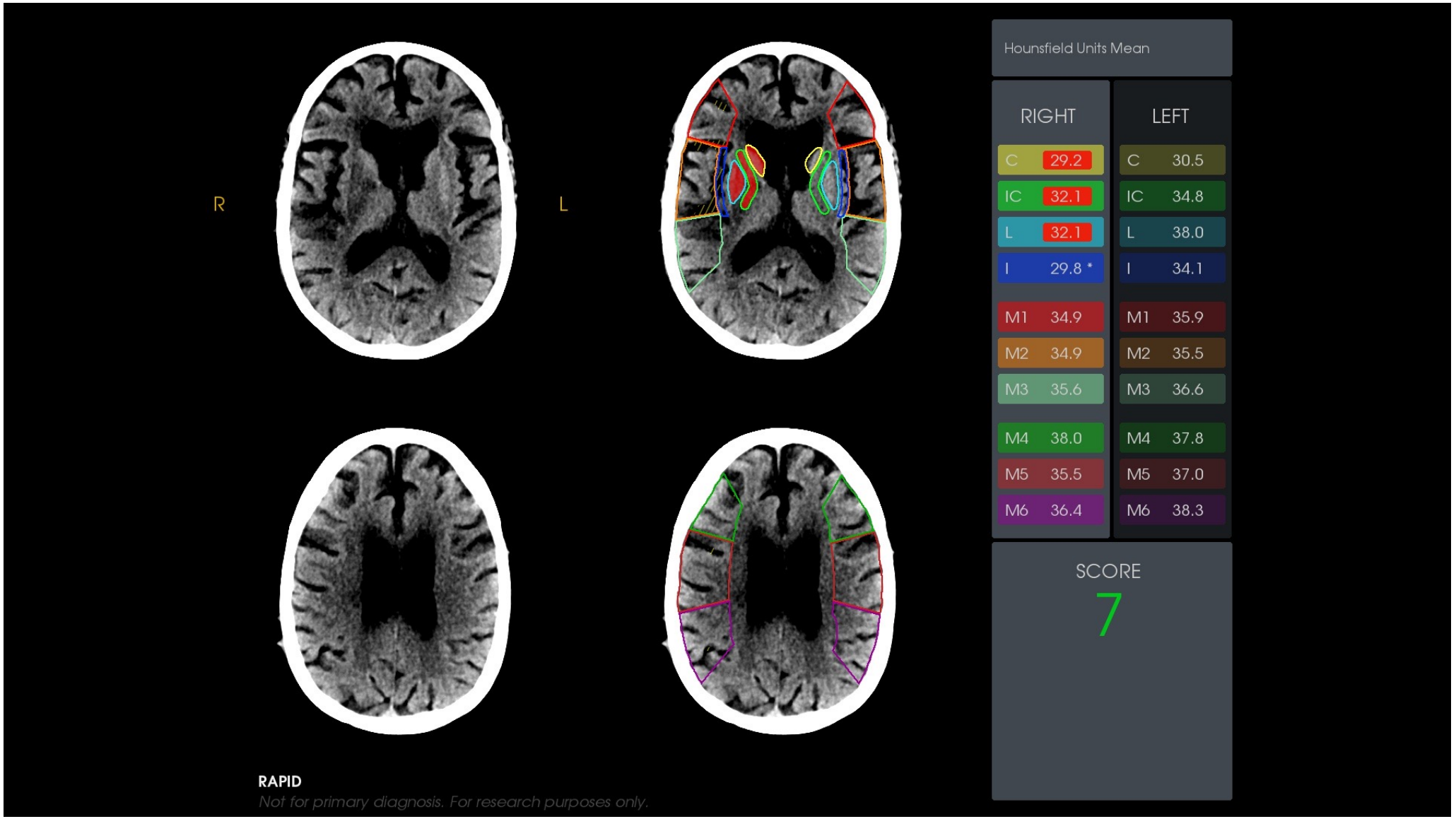
Review results on the RAPID server

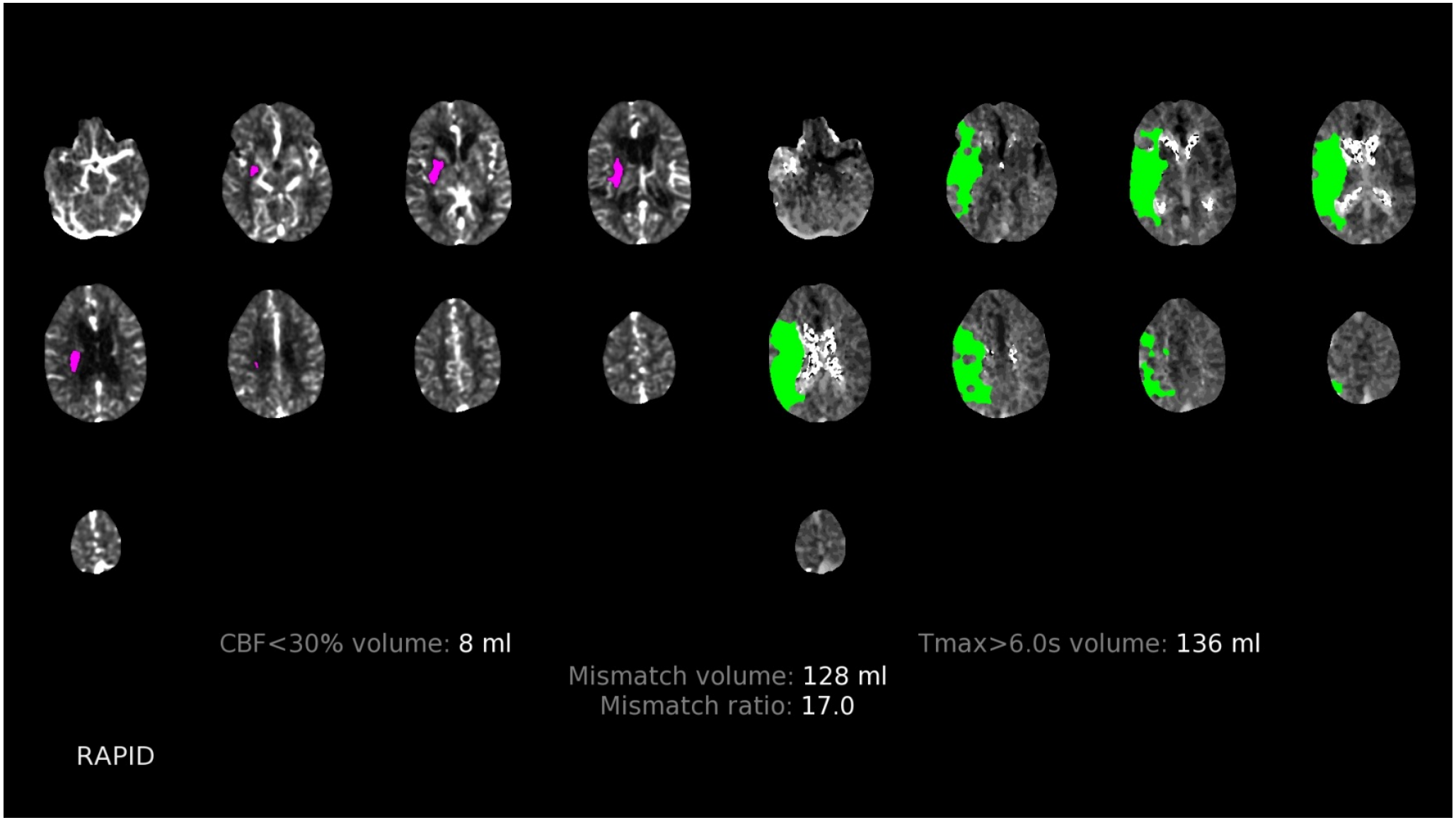
Institution:	SH300P
RAPID AnonID:	501d_10435
Patient Gender:	Female
Patient Age:	070Y
Series:	#14 Head_Neck CTA 0.75 I30f 2, 2019/09/24 04:43:56
Station:	SIEMENS, SOMATOM Definition Flash

LVO Suspected




R
L
Blood
Vessel
Density:
80%
75%
60%
45%
RAPID
RAPID


R
L
Hounsfield Units Mean
RIGHT
C 29.2
IC 32.1
L 32.1
I 29.8 *
M1 34.9
M2 34.9
M3 35.6
M4 38.0
M5 35.5
M6 36.4
LEFT
C 30.5
IC 34.8
L 38.0
I 34.1
M1 35.9
M2 35.5
M3 36.6
M4 37.8
M5 37.0
M6 38.3
SCORE
7
RAPID
Not for primary diagnosis. For research purposes only.


CBF<30% volume: 8 ml
Tmax>6.0s volume: 136 ml
Mismatch volume: 128 ml
Mismatch ratio: 17.0
RAPID

Currently 7.5 hrs since last known well

Clinical decision making:

IV tPA?
TIMELESS trial?
Endovascular therapy?
No acute intervention?

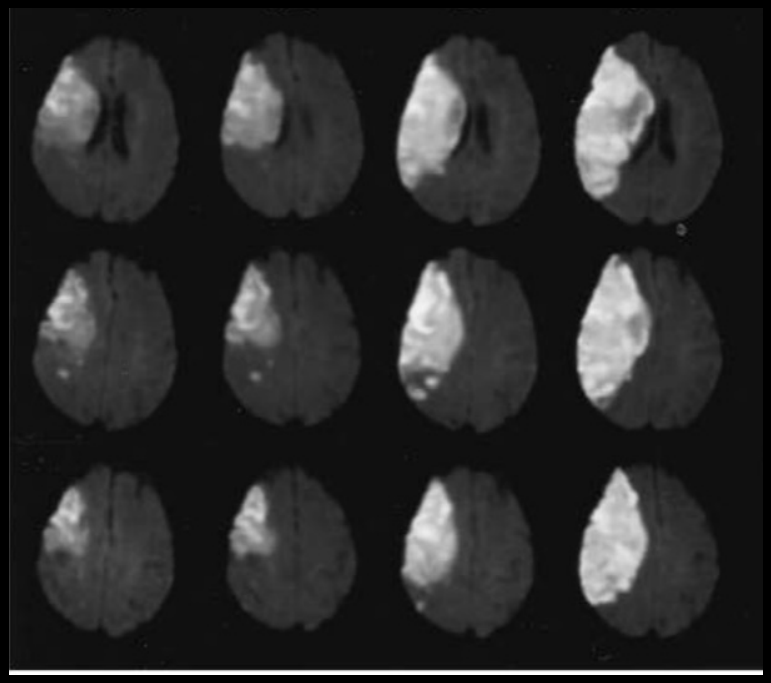
Late Window Intravenous Thrombolysis

- Stroke evolution over time
- Lessons from late-window endovascular therapy
- How long can the penumbra survive?
- Results of late window thrombolysis trials
- tPA vs TNK
- Ongoing studies

Longitudinal Magnetic Resonance Imaging Study of Perfusion and Diffusion in Stroke

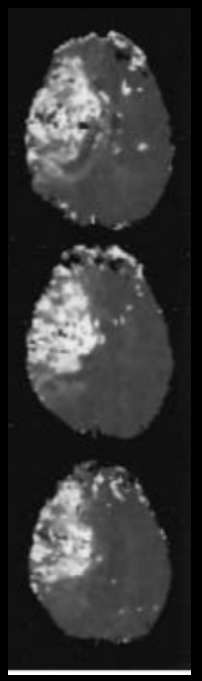
Stanford Stroke Center, Annals of Neurology, 1999

DWI



7 hr 13 hr 28 hr 12 days

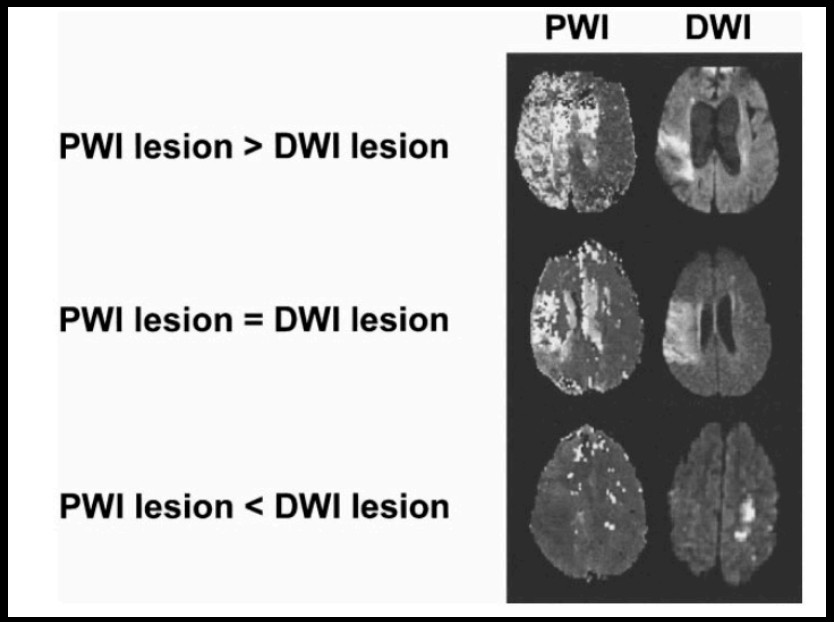
Perfusion

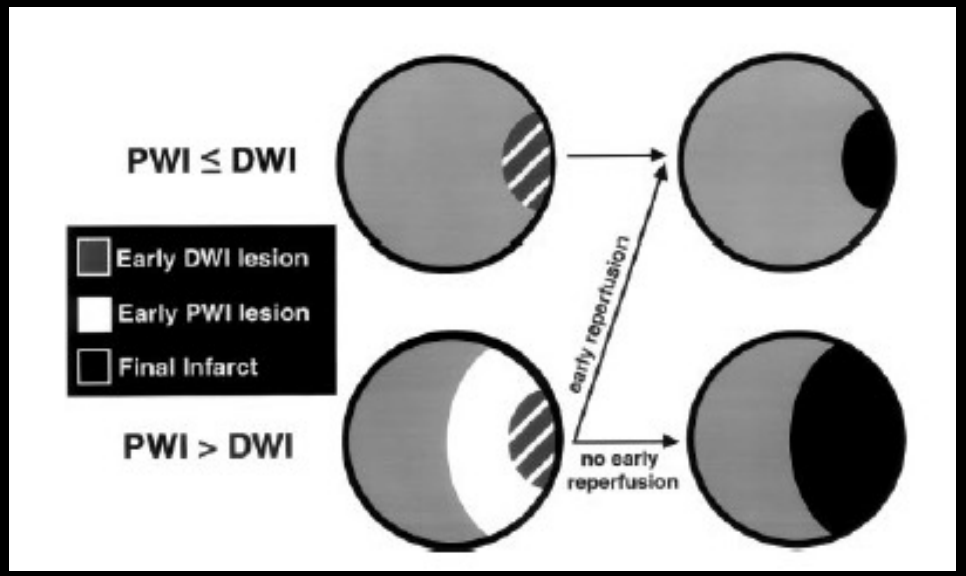


Albers, Stroke, 1999

Expanding the Window for Thrombolytic Therapy in Acute Stroke

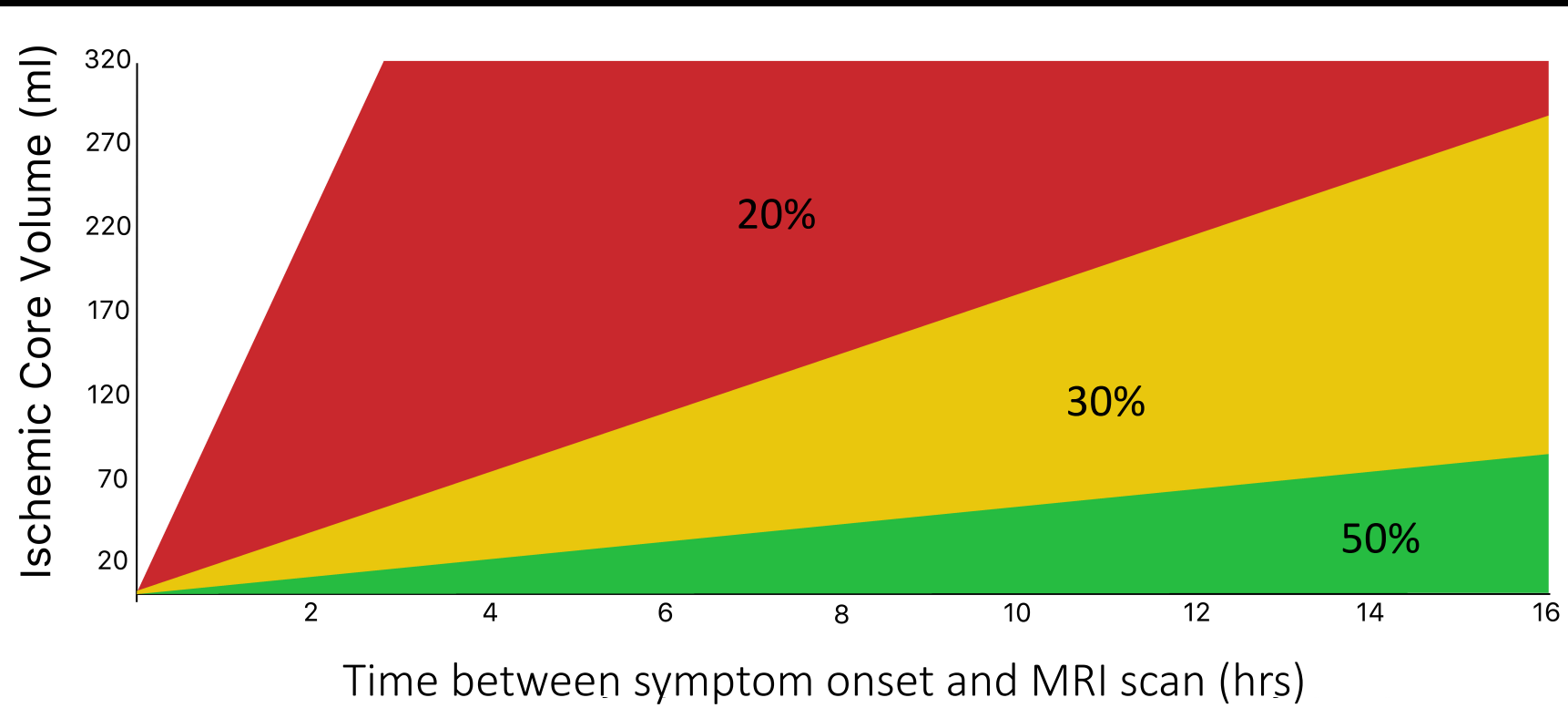
The Potential Role of Acute MRI for Patient Selection





Imaging profiles could predict tissue fate and expand the window for reperfusion

Infarct Growth Rate is Highly Variable



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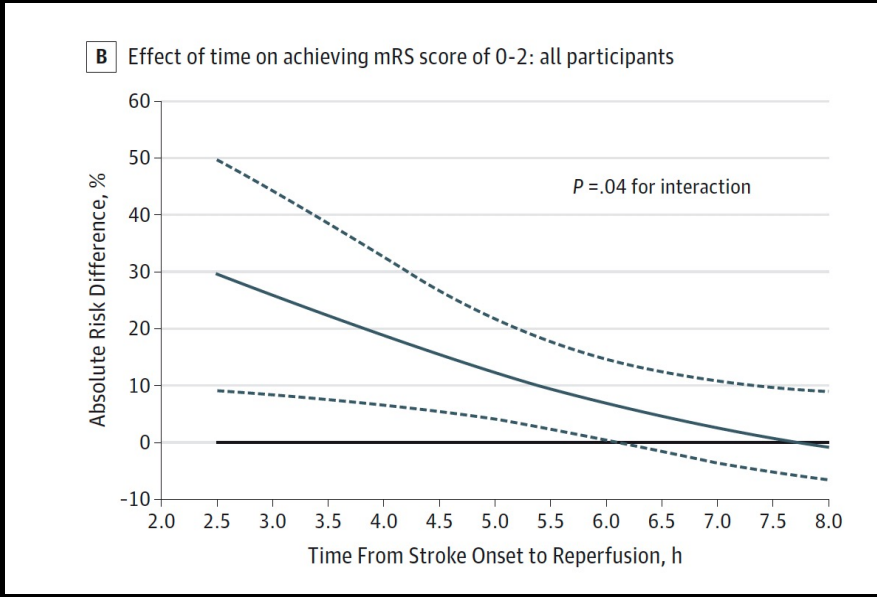
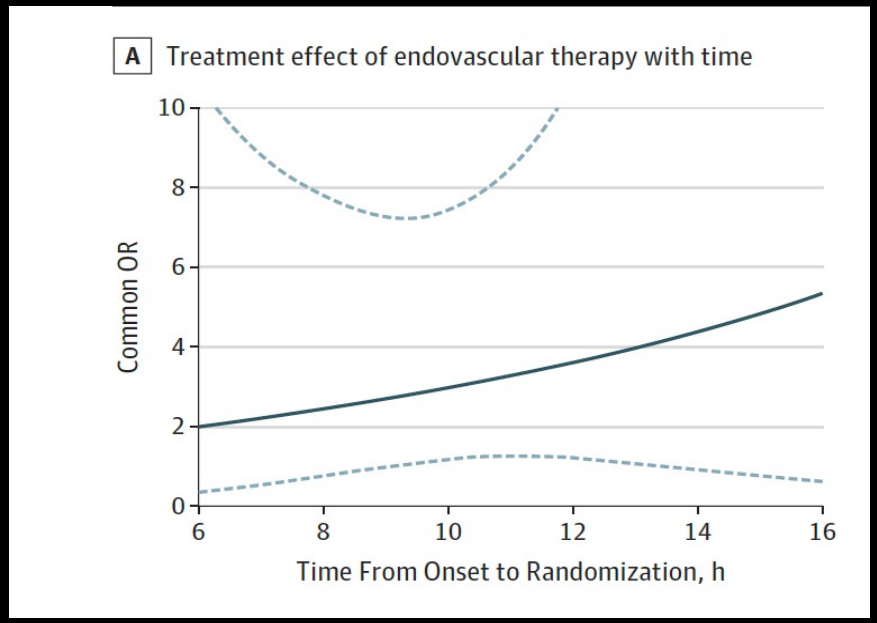
Treatment effect modification
Early vs. Late Time Window



MR CLEAN: Treatment effect modified by time

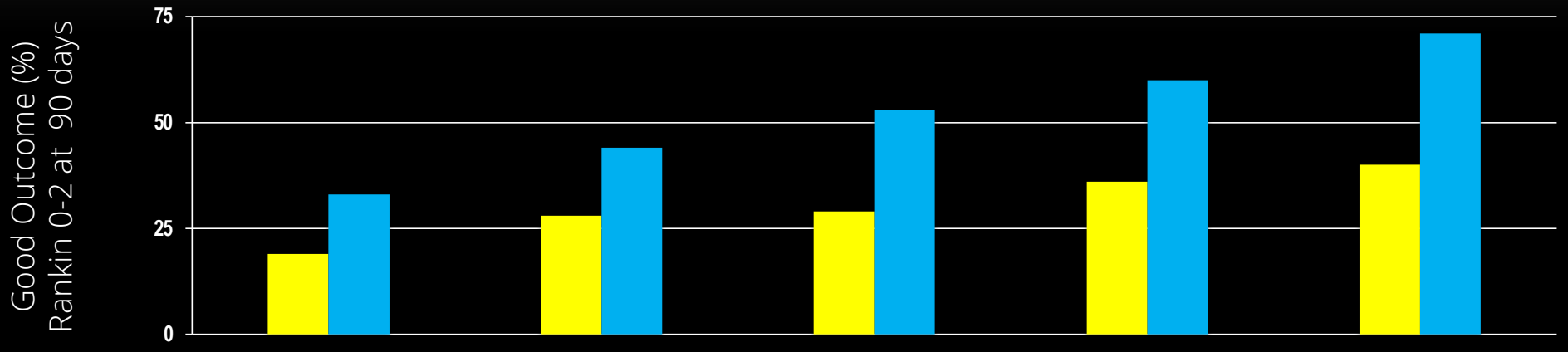
OR for treatment effect = 1.0 by 8 hours



DAWN and DEFUSE 3: Treatment effect NOT modified by time

OR for treatment effect >2 at 8 hours and longer

RANDOMIZED CLINICAL TRIALS OF ENDOVASCULAR THERAPY (NEJM 2015)



	MR CLEAN P<0.05 CT	REVASCAT P<0.05 ASPECTS	ESCAPE P<0.001 ASPECTS CTA Collaterals	SWIFT PRIME P<0.001 CTP/MRP 90%	EXTEND-IA P<0.01 CTP 100%
Endovascular	**33%**	**44%**	**53%**	**60%**	**71%**
Control	19%	28%	29%	35%	40%

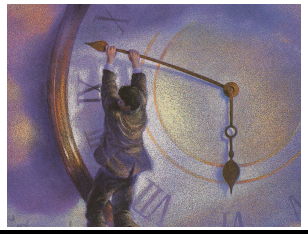
AHA Guidelines 2015

Endovascular therapy with a stent retriever is recommended
(Class 1 Level A)

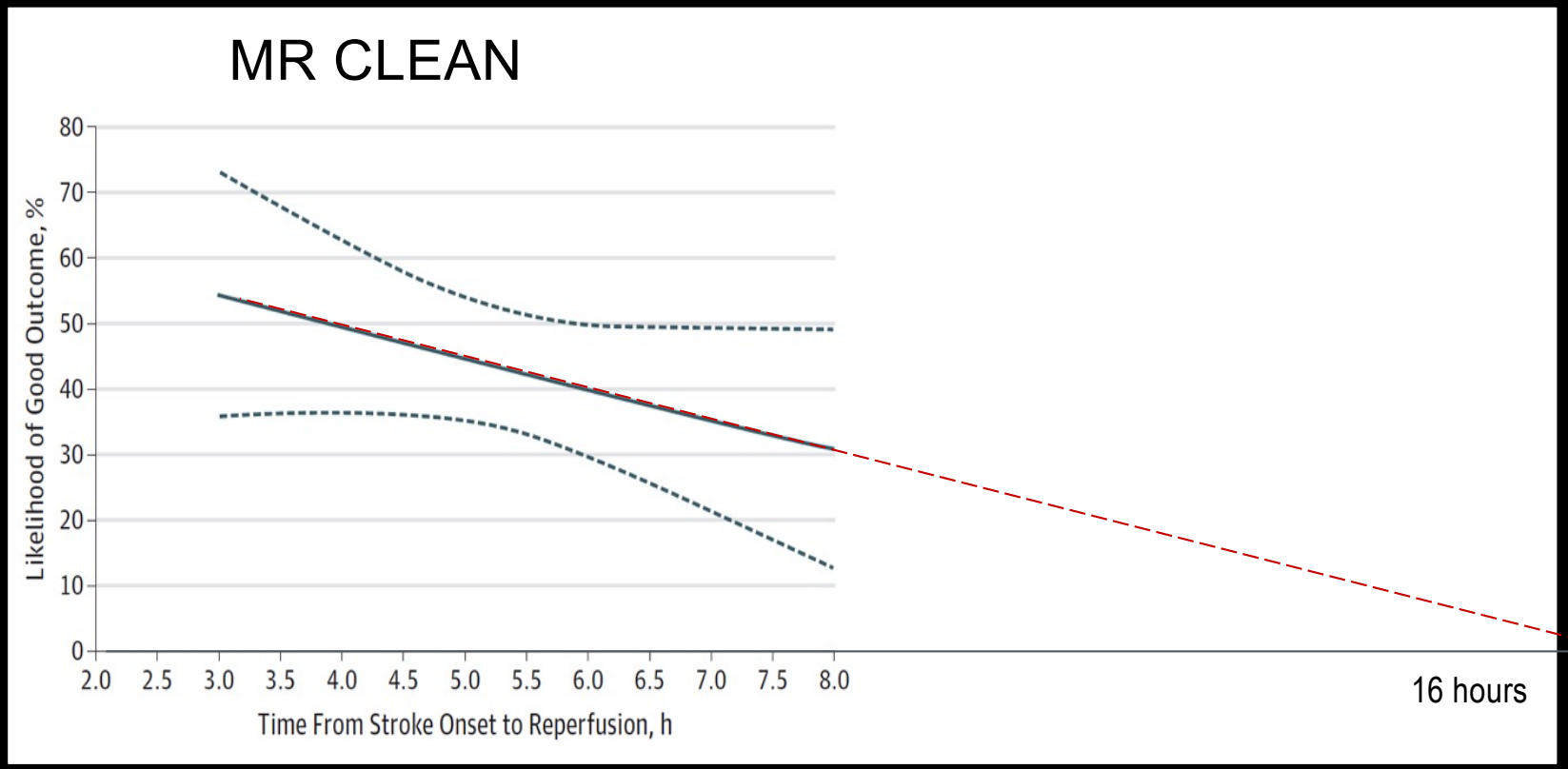
Proximal MCA or ICA occlusion
Within 6 hours of symptom onset
NIHSS Score 6 or more
Small ischemic core (ASPECTS 6-10)

A New Standard of Care for Stroke!

6 hours is not long enough…
Can we shatter the stroke stopwatch?

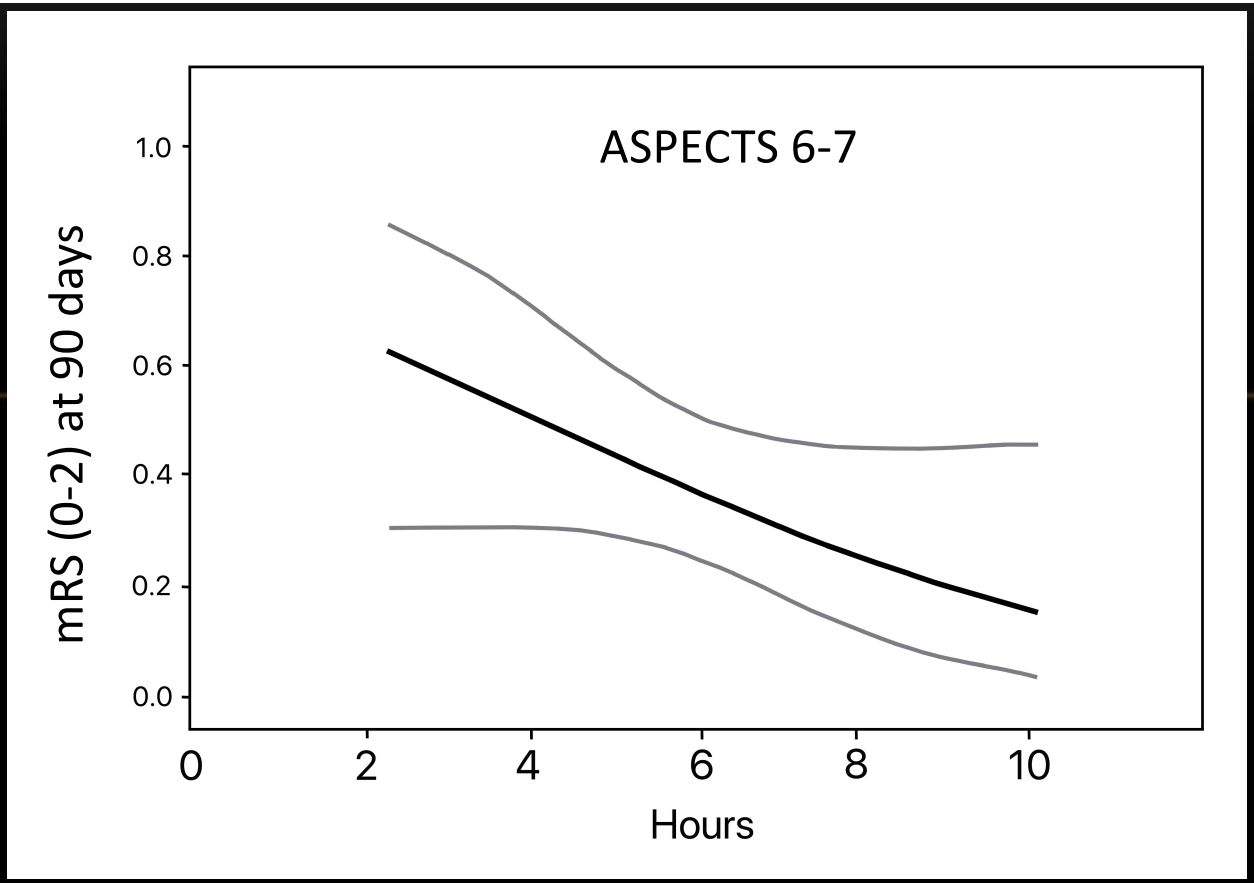


Effect of Time on Achieving Functional Outcome After Endovascular Reperfusion



Fransen P., et al. JAMA Neurol. 2015

Can We Select Late Window Patients with ASPECTS?
REVASCAT: Time from Onset to Recanalization



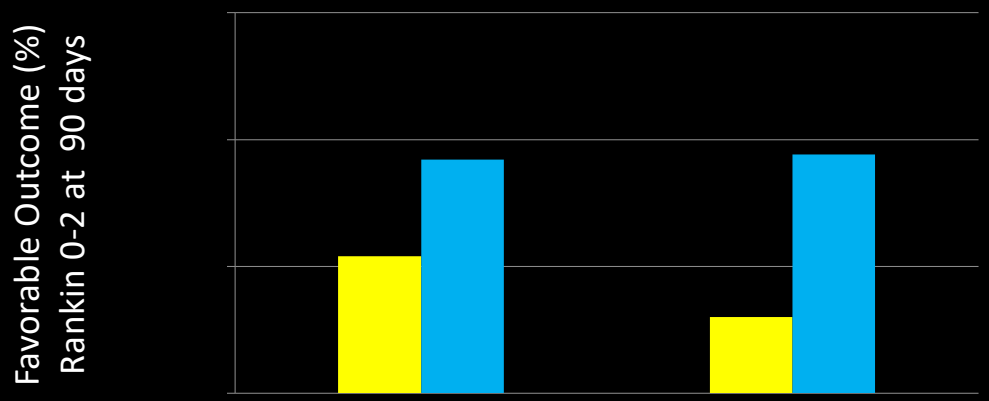
Ribo M, et al. Stroke. 2016

Randomized Trials of Late Window Therapy

- DAWN (6 - 24 hr window)
- DEFUSE 3 (6-16 hr window)

All patients selected with CT or MR perfusion, or DWI, automated processing

Endovascular therapy: Late Window Paradox

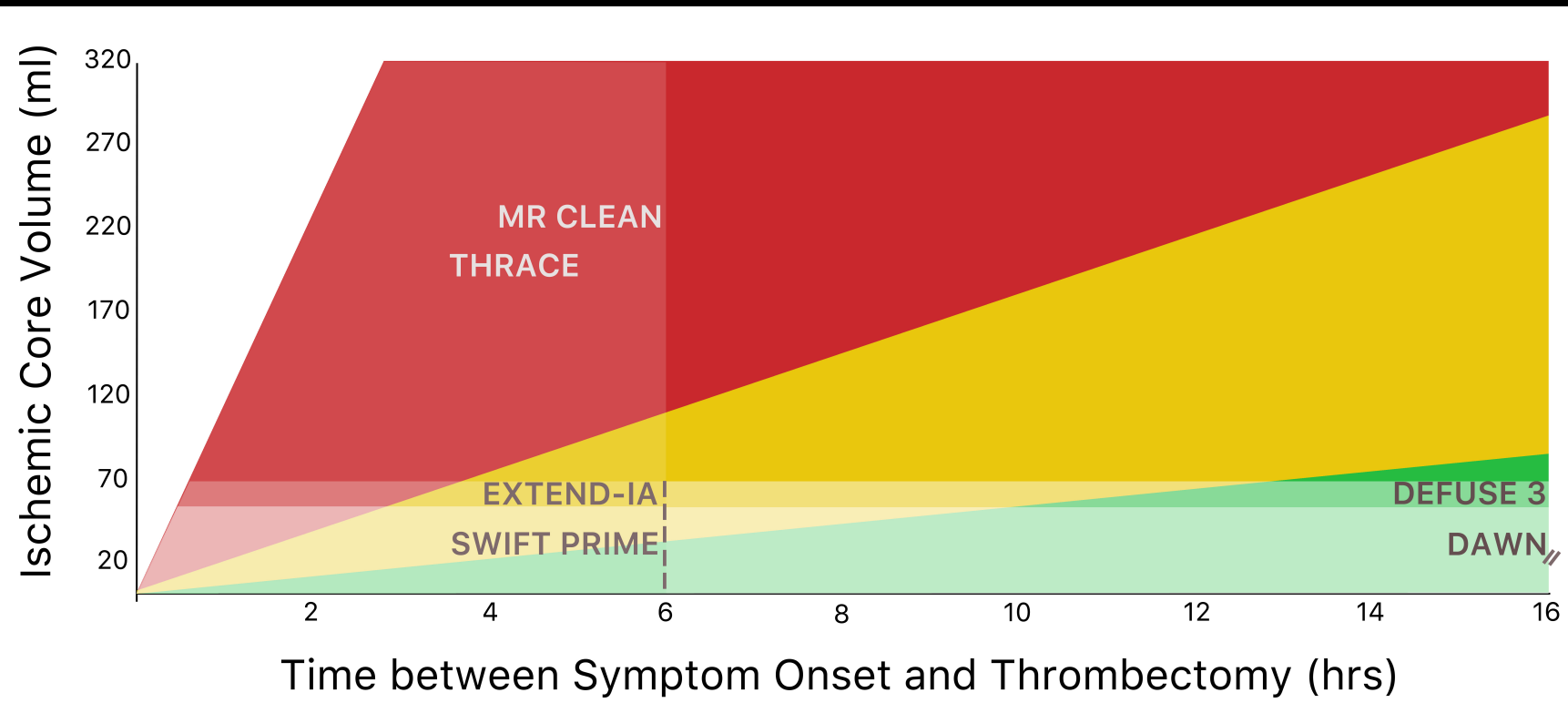


	Early Window	Late Window
Endovascular	**46%**	**47%**
Control	27%	15%

P = 0.006 for difference in treatment effect

Albers GW, Late Window Paradox, Stroke, 2018

Early and Late Window Endovascular Trials

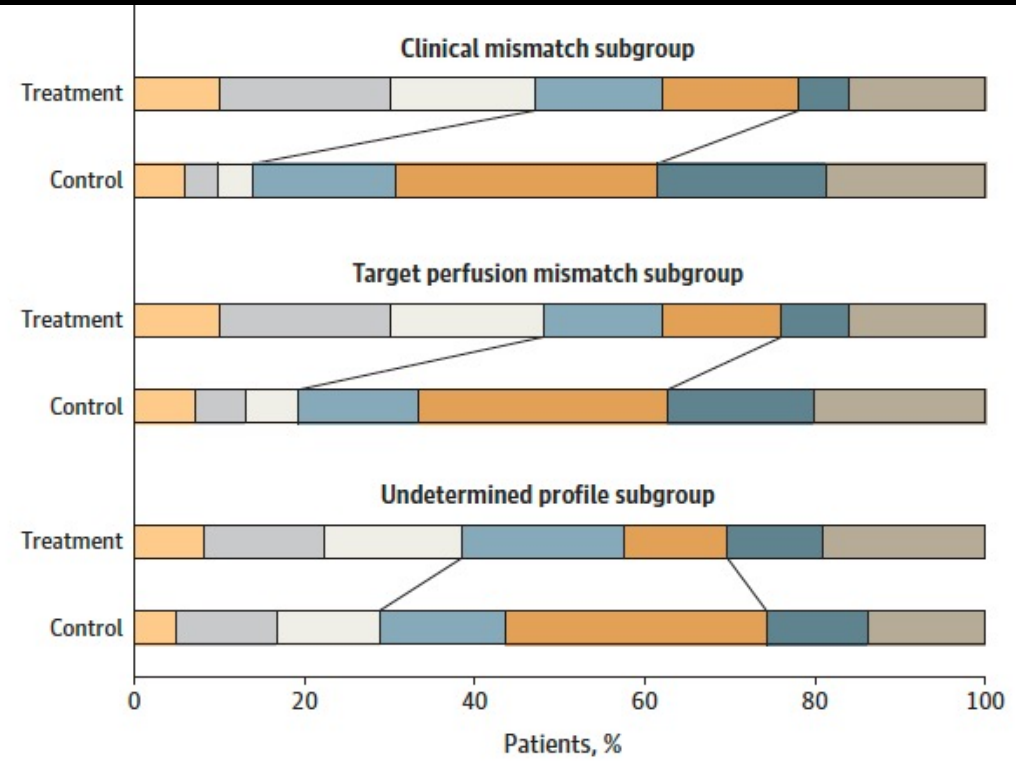


JAMA Neurology | Original Investigation

Assessment of Optimal Patient Selection for Endovascular Thrombectomy Beyond 6 Hours After Symptom Onset

A Pooled Analysis of the AURORA Database

Albers GW, et al, July, 2021



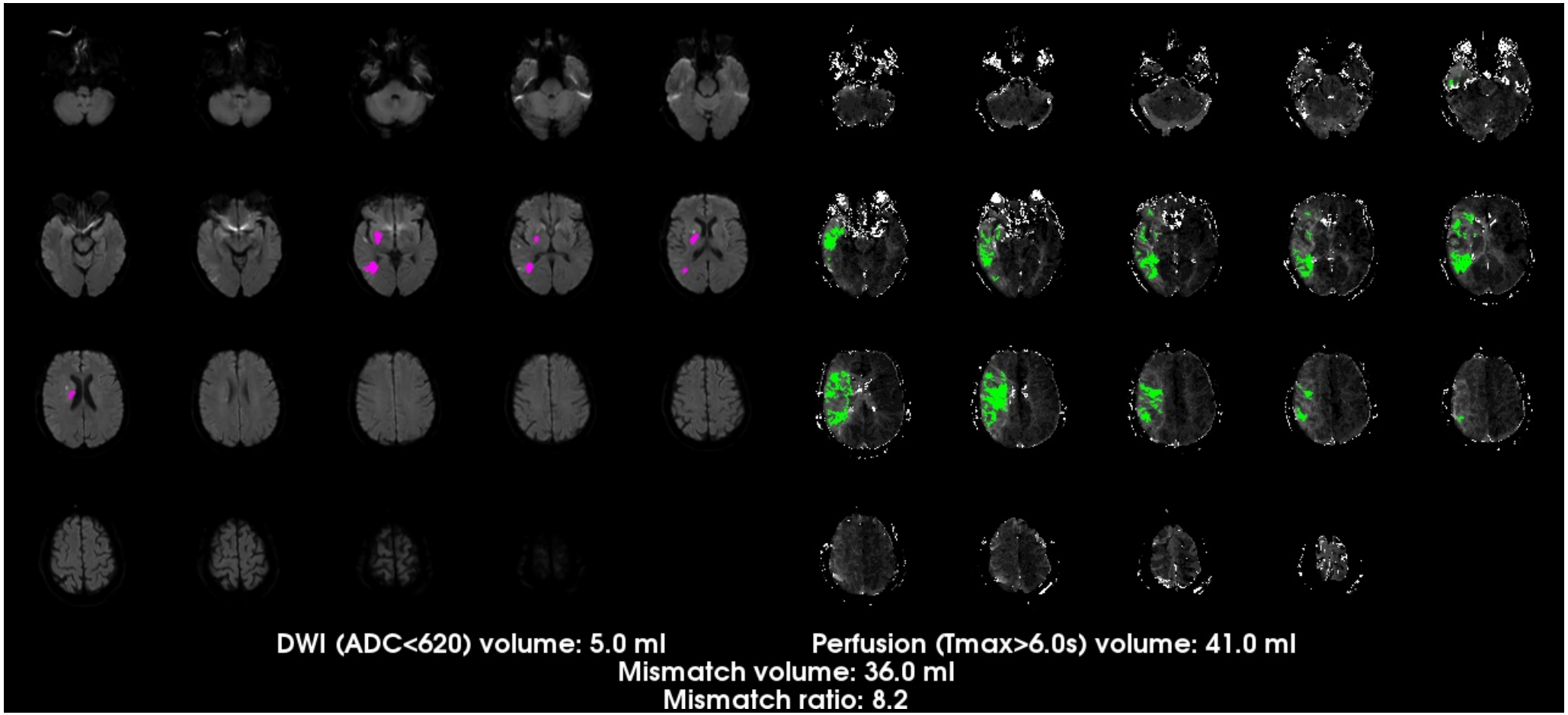
The interaction between treatment effects for the clinical and target perfusion mismatch subgroups vs the undetermined profile subgroup was significant (OR, 2.28; 95%CI, 1.11-4.70; P = .03).

Christensen S, Stroke, 2019

How long can salvageable tissue persist?

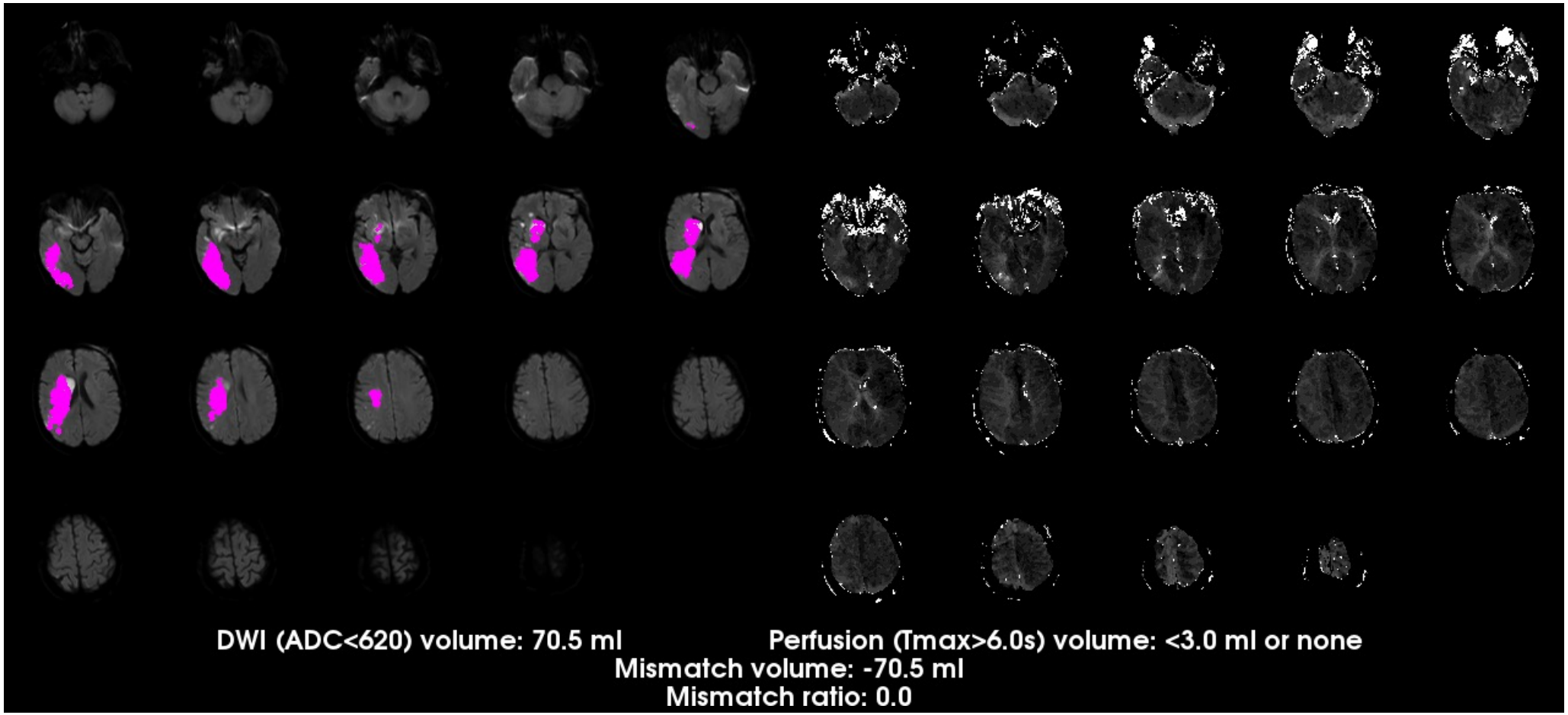
- Imaging performed 37 hrs (IQR 33-39) since last known well
- 20% continued to have the Target mismatch profile in medical arm!!
- Median mismatch volume 50 ml (IQR 35 – 83)
- Continued growth on subsequent imaging
- 88% were disabled (mRS 3 or more) at 90 days

73 yo woman, R MCA syndrome, wake-up stroke



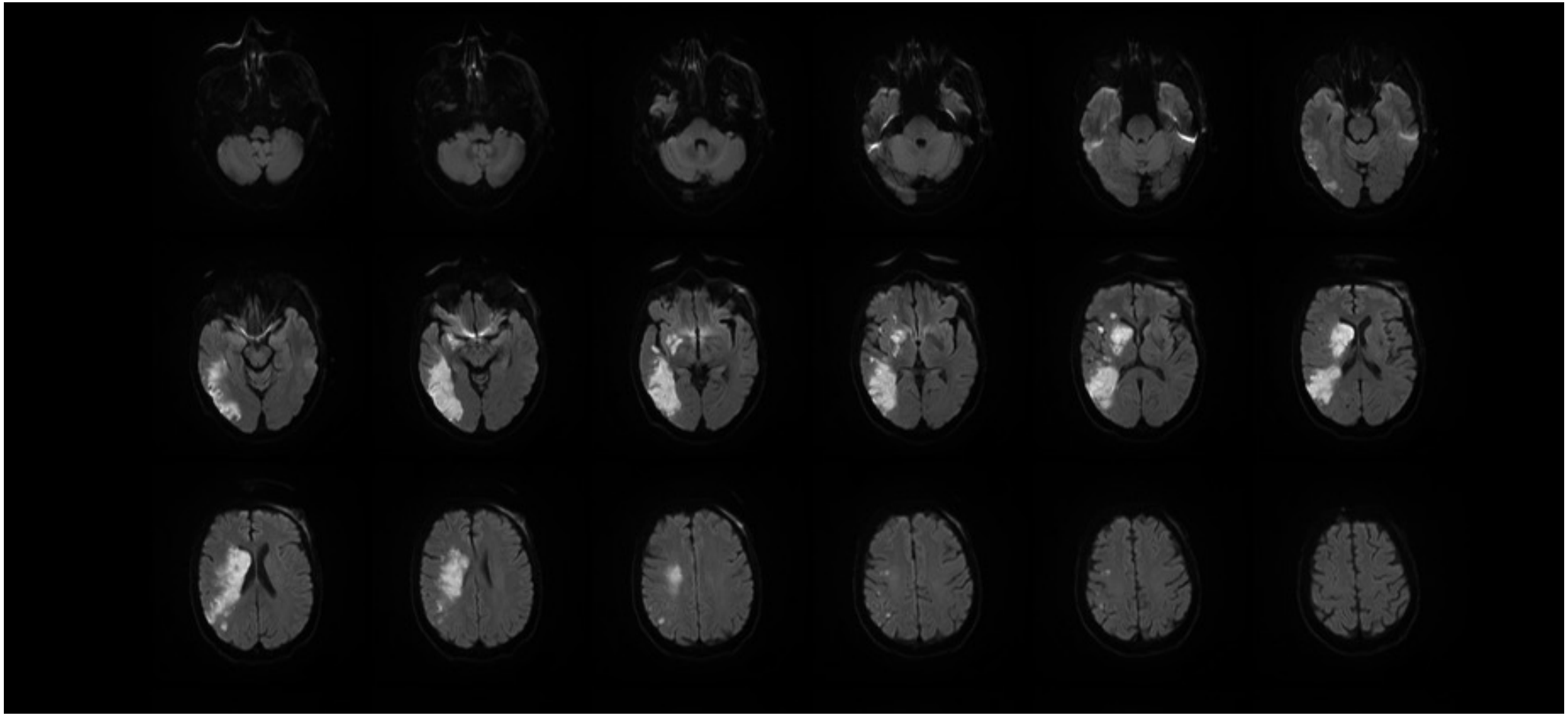
defuse·3

24 hr follow up



24 hours after randomization

3 days after randomization



Endovascular Treatment for Patients Presenting Very Late From Time Last Known Well

- Case-control study: 150 patients retrospectively identified
- ICA/MCA occlusion, NIHSS>5, arrived ≥16 hours from time last known well (median 44 hrs)
- Perfusion imaging available for 109 patients (post-processed with RAPID)
- 24 patients treated with EVT

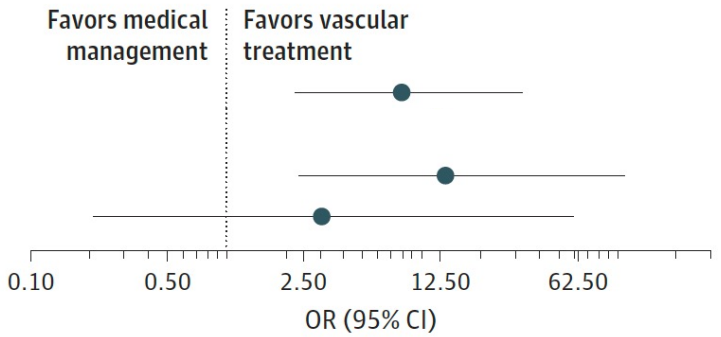
BJ Kim, et al, JAMA Neurol, 2020

Endovascular Treatment for Patients Presenting Very Late From Time Last Known Well

Figure 2. Benefit of Endovascular Recanalization According to Imaging Criteria of the Selected Endovascular Treatment (EVT) Trials

A mRS score of 0-2 at 3 mo after stroke

Trials	OR (95% CI)
Effectiveness of EVT	7.89 (2.25-32.42)[a]
DEFUSE 3,[6] 2018	
Eligible for DEFUSE 3	13.26 (2.37-108)
Ineligible for DEFUSE 3	3.05 (0.21-59.11)

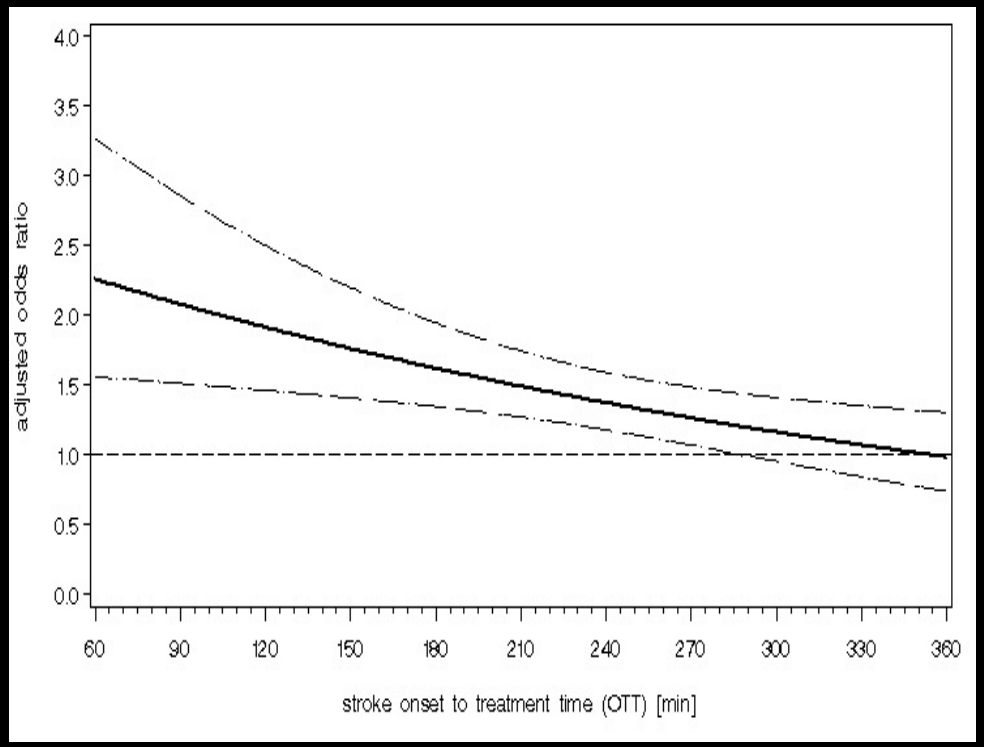


"… approximately one-third of the patients with LVO presenting 16 hours or more from the time LKW may benefit … image criteria for the DEFUSE 3 trial may have the potential to determine the treatment response…"

BJ Kim, et al, JAMA Neurol, 2020

Historical Randomized Trials of IV Thrombolysis

With patients enrolled at >4.5 hours



- MAST-E
- MAST-I
- ASK
- ATLANTIS A and B
- ECASS I, II, and IV
- DIAS 2,3 and 4

Recent Randomized Trials of Late Window IV Thrombolysis

- WAKE-UP
- EXTEND (4.5-9 hr window)

Wake-up Study

NEJM, 2018

- IV tPA vs Placebo (unknown onset, 1/3 with vessel occlusion on MRA)
- DWI / FLAIR mismatch on MRI to identify if <4.5 hrs
- Primary end point (mRS 0-1) at 3 mo: 53% tPA vs. 42% placebo adjusted OR 1.61; P = 0.02.
- Death: 4.1% tPA vs. 1.2% placebo, OR 3.38; P = 0.07
- SICH 2.0% tPA vs. 0.4% placebo, OR 4.95; P = 0.15

EXTEND Study

NEJM, 2019

- IV tPA vs Placebo 4.5-9 hrs (selected wake-ups)
- Target mismatch on RAPID CTP/MRI (core<70 ml, mismatch ratio >1.2)
- Primary end point (mRS 0-1) at 3 months
- Secondary outcomes: mRS 0-2 at 90 days, early neurological improvement reperfusion, and recanalization

EXTEND
EXtending the time for Thrombolysis in Emergency Neurological Deficits

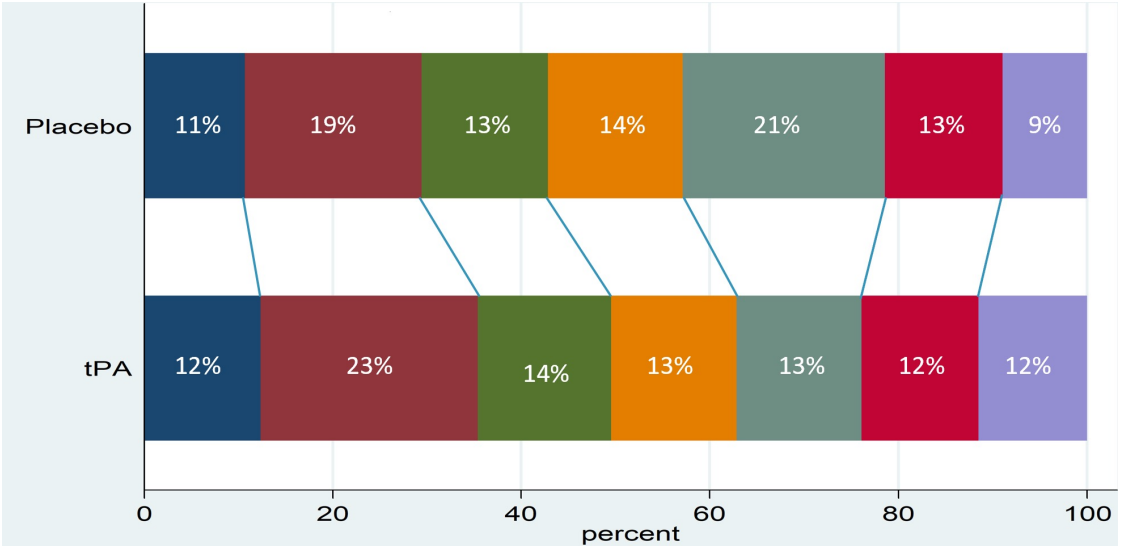
Results: Baseline Characteristics

Characteristics	Placebo	tPA
Number	112	113
Age, mean (SD)	71.0 (12.7)	73.7 (11.7)
Male (%)	66 (59%)	59 (52%)
Median NIHSS admission	10.0 (IQR 6.0, 16.5)	12.0 (IQR 8.0,17.0)
4.5-6 hours	11 (11%)	12 (11%)
6-9 hours	28 (25%)	28 (25%)
Wake Up Stroke	73 (65%)	73 (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)	2.36 (IQR 0, 19.46)	4.64 (IQR 0, 23.15)
Median Perfusion lesion (ml)	78 (IQR 47.73, 111.81)	74.45 (IQR 40.08, 134)
Large vessel occlusion (%)	81 (72%)	78 (69%)

EXTEND

EXtending the time for Thrombolysis in Emergency Neurological Deficits

Results: Primary End Point



mRS 0-1 at 90 days

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

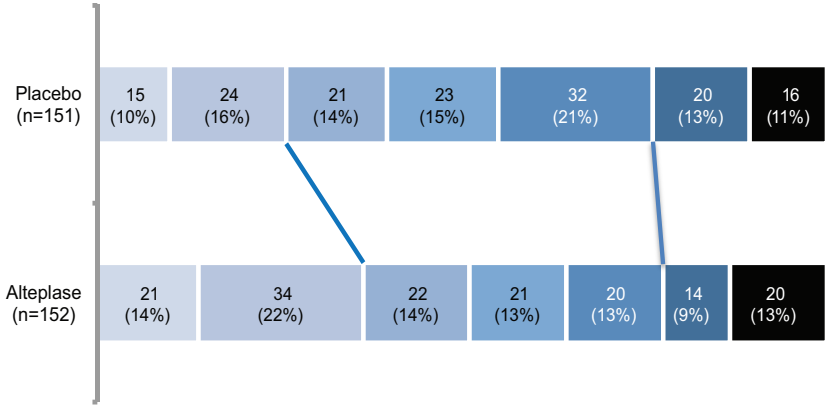
EXTEND
EXtending the time for Thrombolysis in Emergency Neurological Deficits

Results – Secondary Endpoints

Results	Placebo	tpa	Adjusted Relative Risk (CI)	P value
mRS 0-2 at 90 days	43%	50%	1.36 (1.06, 1.76)	***0.017***
mRS Shift at 90 days			Adjusted Common O.R. 1.55 (0.96, 2.49)	0.072
Early Neurological improvement NIHSS reduction =>8 points or 0-1 at 24 hours	10%	24%	2.76 (1.45, 5.26)	***0.002***
Reperfusion 90% at 24 hours	28%	50%	1.73 (1.22, 2.46)	***0.002***
Reperfusion 50% at 24 hours	52%	72%	1.35 (1.09, 1.67)	***0.005***
Recanalization at 24 hours	39%	67%	1.68 (1.29, 2.19)	***<0.001***

Lancet, 2019

Primary Outcome: Excellent Outcome mRS 0-1 at 90 Days



AUTOMATED PERFUSION MISMATCH (RAPID)

Modified Rankin scale

0 1 2 3 4 5 6

Alteplase (tPA) vs Tenecteplase (TNK) in Stroke

Potential TNK advantages:

- Higher fibrin specificity
- Bolus administration facilitates endovascular transfers
- TNK may have better recanalization rates and fewer hemorrhagic complications than tPA

Clinical Trial data highlights:

- Parsons 2012, CT perfusion selected patients, TNK safer and more efficacious than tPA
- NOR-TEST 2017, TNK (0.4 mg/kg) vs tPA similar outcomes and ICH rates in mild stroke patients (median NIHSS 4)
- EXTEND-IA-TNK 2018, (n=202) TNK (0.25 mg/kg) vs. tPA up to 4.5 hrs in EVT eligible patients. Patients who reperfused prior to EVT: 22% with TNK vs. 10% with tPA

Parsons, NEJM, 2012

TNK vs. tPA CT perfusion selection

	Tenecteplase 0.1 mg/kg N=25	Tenecteplase 0.25 mg/kg N= 25	p-value (T 0.1 vs T 0.25)	Alteplase 0.9 mg/kg N=25
sICH*, n (%)	1/25 (4%)	1/25 (4%)	>0.99	3/25 (12%)
Mean % Reperfusion at 24 h (+/-SD)	69.3±31.2	88.8±23.1	0.0166	55.4±38.7
Complete Recanalization at 24 h, n (%)	8/23 (35%)	20/25(80%)	0.002	8/22 (36%)
mRS 0-2 at 90 d, n (%)	15/25 (60%)	21/25 (84%)	0.114	11/25 (44%)
mRS 0-1 at 90 d, n (%)	9/25 (36%)	18/25 (72%)	0.011	10/25 (40%)

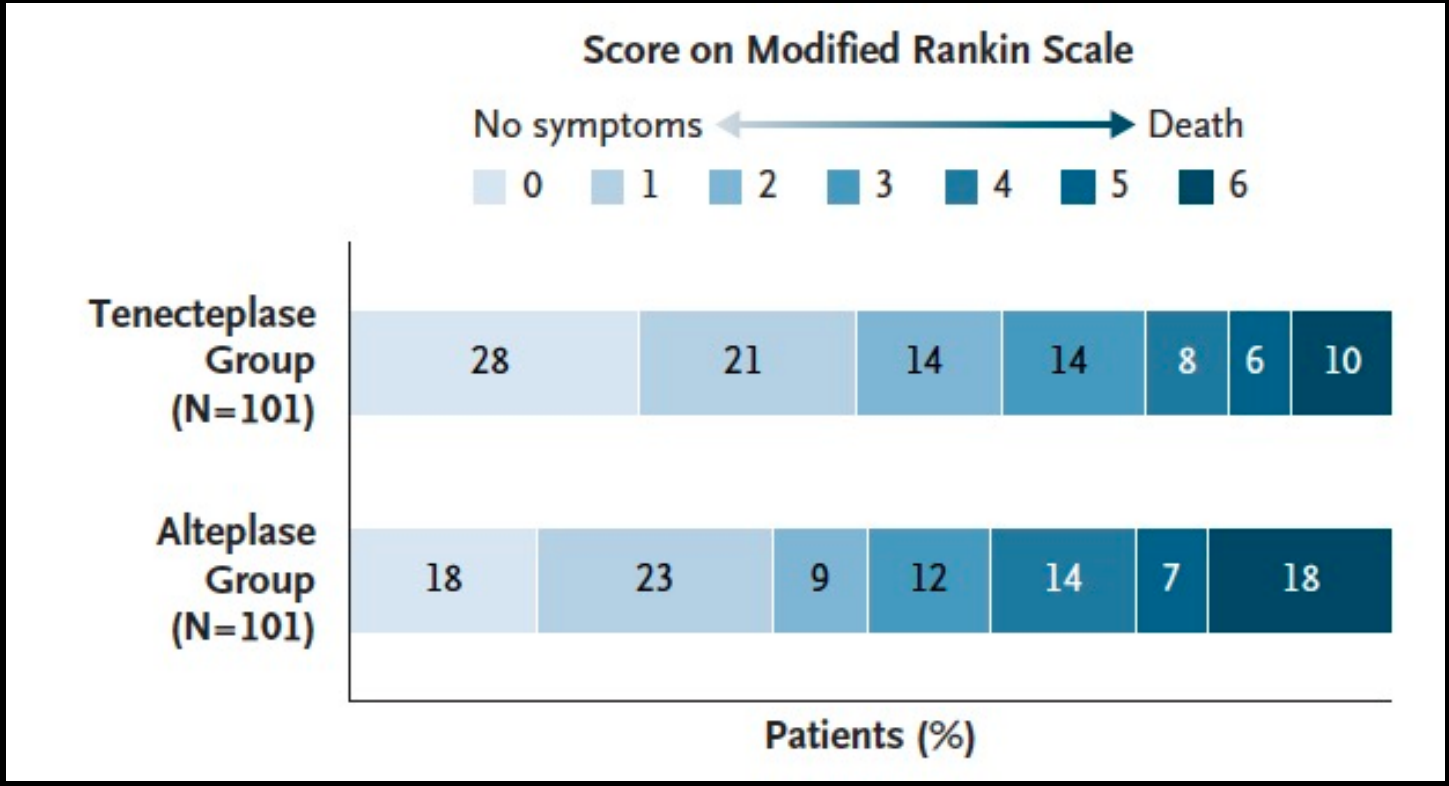
EXTEND-IA TNK

Campbell, NEJM, 2018

	Tenecteplase N=101	Alteplase N=101	Adjusted OR (95% CI)	p-value
mTICI 2b/3 or absence of retrievable thrombus at initial angiography, %	22%	10%	2.6 (1.1-5.9)	0.02
mRS 0-1 at 90 d, %	51%	43%	1.4 (0.8-2.6)	0.23
Median mRS score (IQR) on ordinal analysis‡ at 90 d	2 (0–3)	3 (1–4)	1.7 (1.0–2.8)	0.04
sICH‖ within 36 h after treatment, %	1%	1%	1 (0.1-16.2)	0.99
Mortality within 3 mo, %	10%	18%	0.4 (0.2-1.1)	0.08

EXTEND-IA TNK

Campbell, NEJM, 2018



TIMELESS Study Design
Marriage of DEFUSE 3 and EXTEND IA TNK

- **Design:** Phase 3, prospective, double-blind, randomized, placebo controlled trial; Superiority study comparing TNKase to placebo
- **Study Size:** 464 patients
- Time window 4.5-24 hours
- **Study Drug:** tenecteplase 0.25 mg/kg
- **Primary Endpoint:** 90 day functional outcome (mRS shift analysis)
- **Sites:** 90 Sites (45 hubs, 45 spokes) (90 US / Canadian Sites)

TIMELESS Inclusion/Exclusion Criteria

Key inclusion criteria	Key exclusion criteria
• ≥18 years, functionally independent at baseline (mRS 0–2) • Signs and symptoms consistent with acute anterior circulation ischemic stroke • Onset = last known to be at their neurologic baseline (wake-up strokes are eligible if they meet time limits) • Baseline NIHSS ≥5 that remains ≥5 immediately prior to randomization • **Neuroimaging:** ICA or M1, M2 occlusion (carotid occlusions can be cervical or intracranial, with or without tandem MCA lesions) by MRA or CTA **AND** target mismatch profile on CT perfusion or MRI (if ischemic core volume <70 mL, mismatch ratio is >1.8 and mismatch volume is >15 mL)	• Severe, uncontrolled hypertension (systolic BP >180 mmHg or diastolic BP >110 mmHg) • Unable to undergo either MRI or CT • Significant mass effect with midline shift • Acute symptomatic arterial occlusions in more than one vascular territory

TIMELESS imaging criteria

Target mismatch (data obtained from RAPID maps MRI or CTP)

Ischemic core <70 ml

Mismatch volume ≥ 15 ml

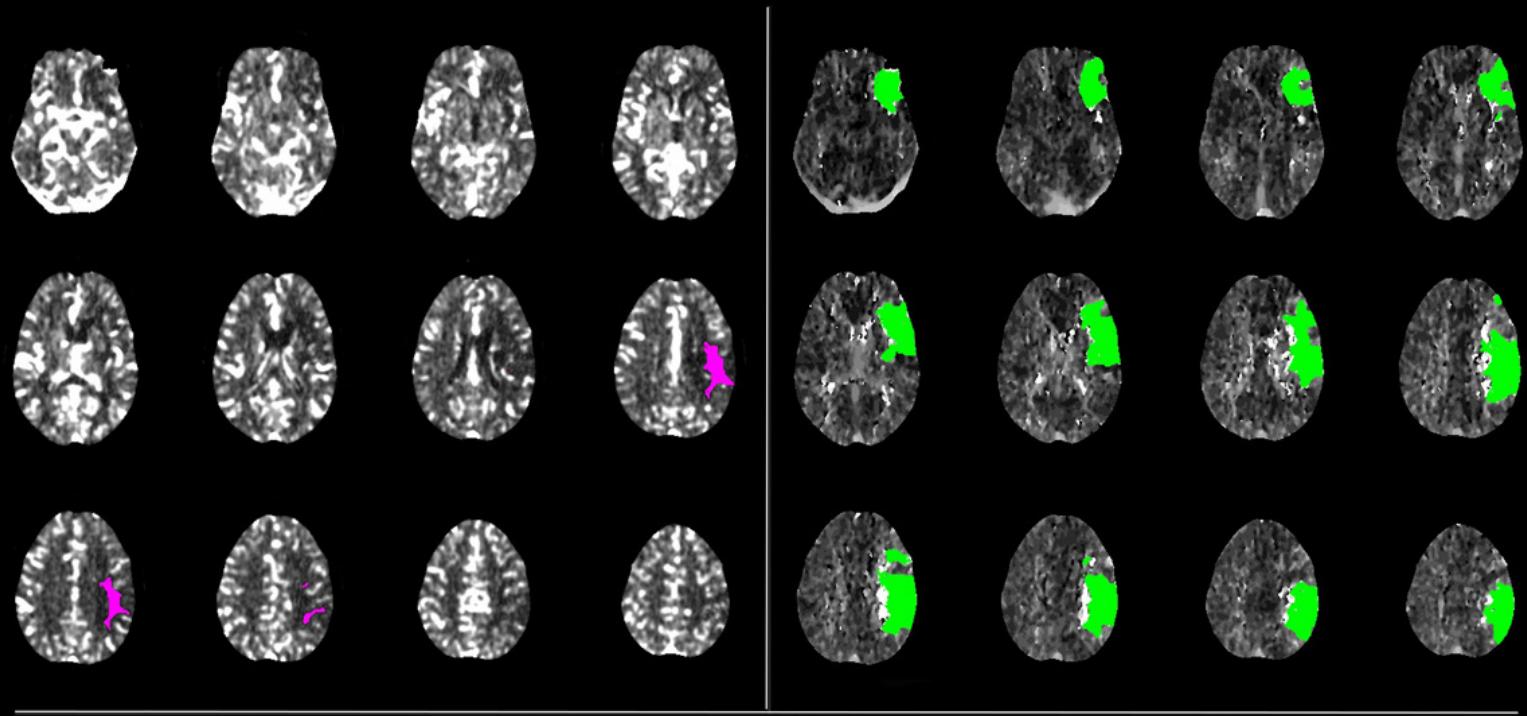
Mismatch ratio ≥ 1.8

Vessel occlusion (data obtained from MRA or CTA)

Occlusion of ICA (cervical or intracranial) and/or MCA – M1 or M2

TIMELESS eligible patient

Mismatch map: directly compare volumes of ischemic core and hypoperfusion

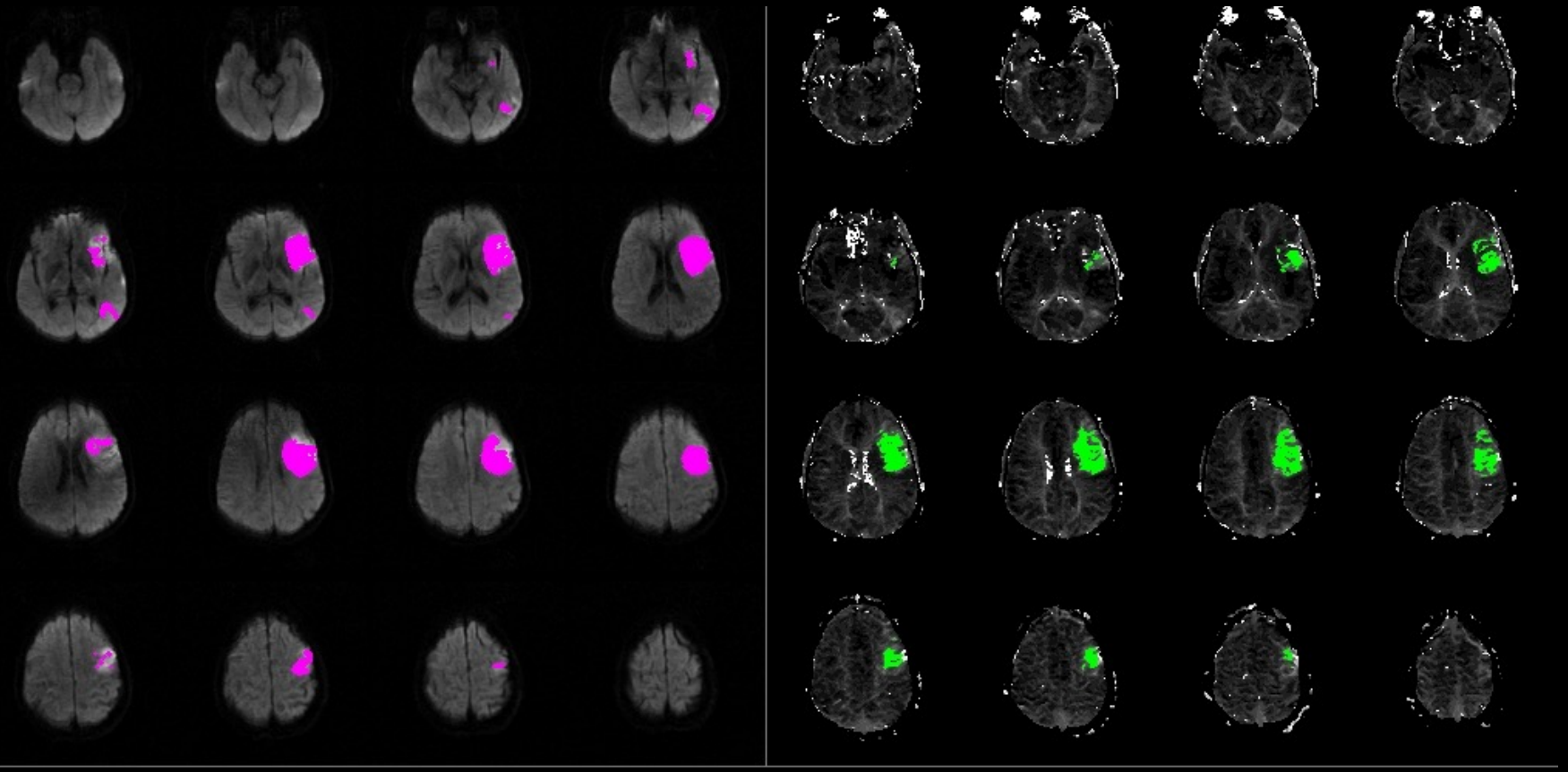


CBF (0.3 threshold) 6 ml

Hypoperfusion (Tmax>6s) 82 ml

Mismatch Volume: 76 ml
Mismatch Ratio: 14

TIMELESS ineligible patient



DWI (ADC < 620) volume: 48 ml

Perfusion (Tmax>6s) volume: 31 ml

Mismatch ratio: 0.6 Mismatch volume: -17 ml

Current status of late window IV thrombolysis

- Guidelines in evolution (only single positive studies available):

  DWI/FLAIR for wake-up

  EXTEND criteria for 4.5-9 hours + selected wake-up

- Awaiting results of ongoing studies:
  - TIMELESS
  - TEMPO-2, Canada: (TIA) or minor stroke <12 hours TNK (0.25 mg/kg) vs antiplatelet therapy. CTA/MRA occlusion and delayed washout on multiphase CTA or focal perfusion abnormality
  - Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST) Norway: TNK vs standard medical therapy. Exclusion: infarct in >1/3 of the middle cerebral artery territory on plain CT or CT perfusion

Ongoing tenecteplase trials
0–4.5 hours, lytic eligible (ATTEST2, AcT)
0–4.5 hours, wake-up stroke (TWIST)
0–4.5 hours, imaging selected (TASTE)
0–4.5 hours, tenecteplase 0.4 mg/kg vs alteplase 0.9 mg/kg (NORTEST2)
4.5–12 hours, imaging selected, non-LVO (RESILIENT-EXTEND IV)
4.5–24 hours, imaging selected (TIMELESS)
4.5–24 hours, imaging selected (ETERNAL LVO)