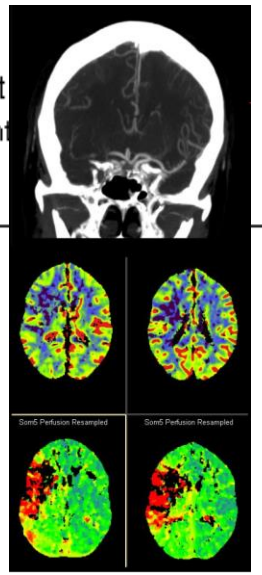
Rationale for the timing of thrombolysis

"Timing is everything" or "Everyone is different"



Barthel Index 95–100, NIHSS 0–1) at
fidence interval by stroke onset to treatment
T population (N = 2799)

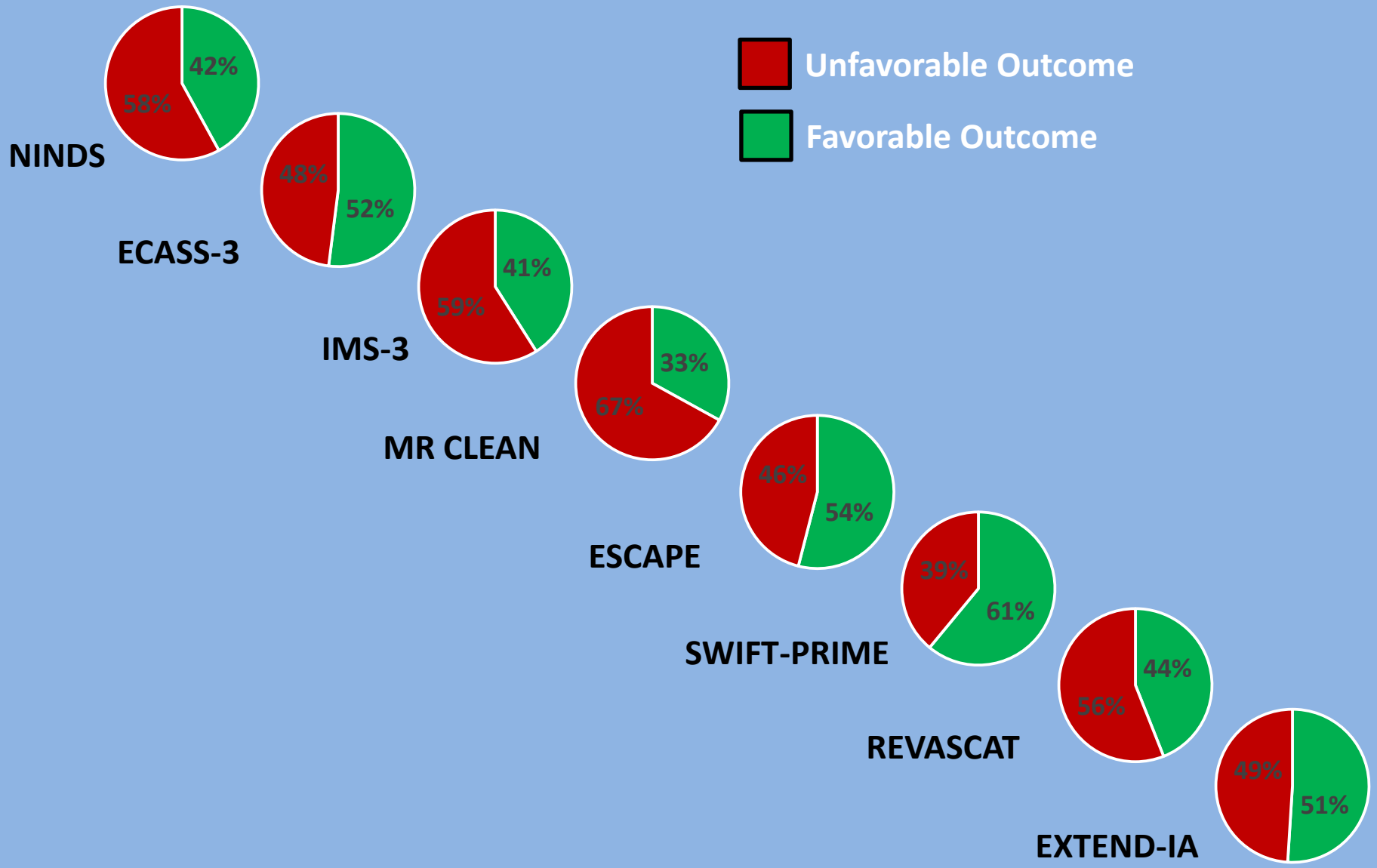
Yes, endovascular therapy is new standard of care--but

- For about 20-25% of tPA treated patients max.
- For about 5% of all AIS patients max.

Yes, endovascular therapy works-but

- 50% of patients are still left disabled
- Majority have residual clot

Suboptimal Outcomes with Current Reperfusion Therapy



Suboptimal Outcomes with Current Reperfusion Therapy

Trial	% IA Patients with Complete Reperfusion (TICI=3)
MR CLEAN IA arm: n=233 control: n=267	**24%**
ESCAPE IA arm: n=165 control: n=150	**24.4%**
EXTEND-IA IA arm: n=35 control: n=35	**48%**
SWIFT-PRIME IA arm: n=98 control: n=97	**68.7%**
REVASCAT IA arm: n=103 control: n=103	**18.6%**

Majority of patients have residual clot

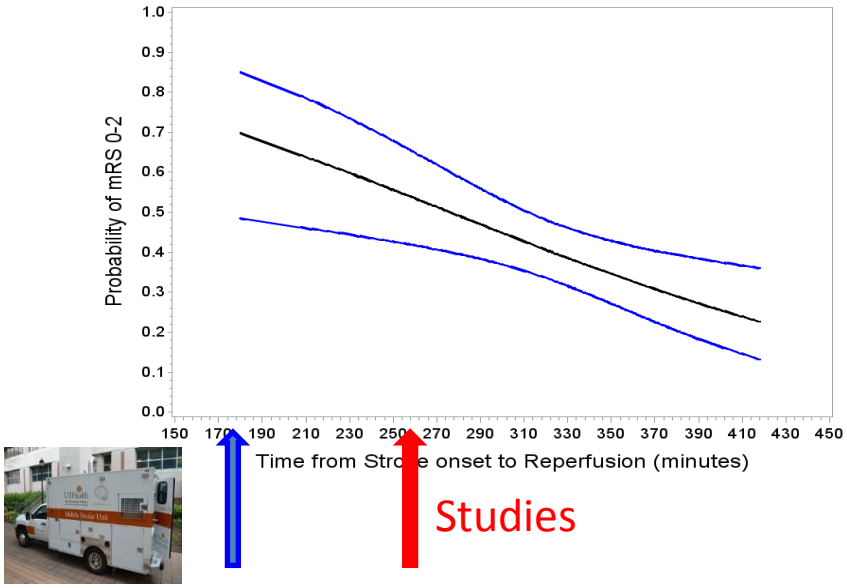
Therefore, plenty of room for more research for both for patients who do and who do not qualify for IAT

- Prehospital efforts to speed/select treatment
- Preserving the penumbra/preventing reperfusion injury
- Augmenting collateral flow/enhancing tPA

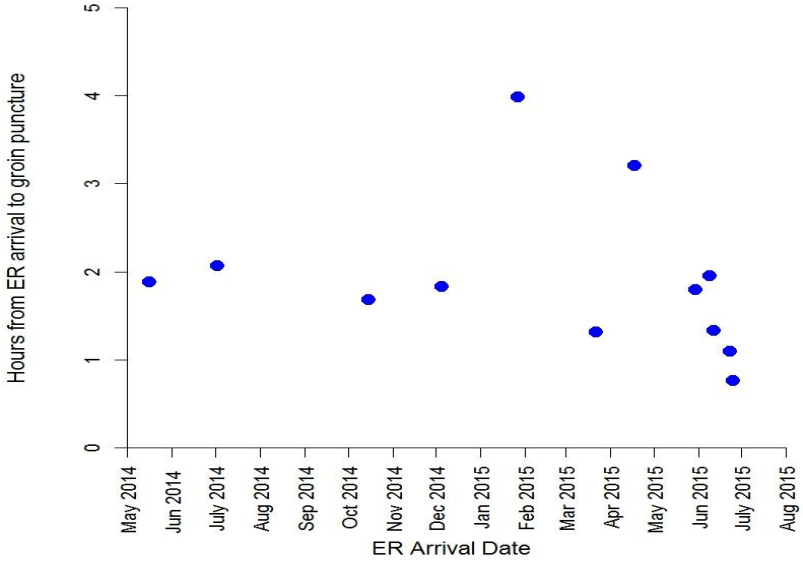
Impact of IAT on Pre-Hospital Studies

- Increase the number of patients receiving IAT?
- Speed onset- and door-to-groin time?
- What criteria should be used to select/triage patients for IAT?
- What is the role of pre-hospital CTA?

ONSET TO GROIN PUNCTURE IN MSU PATIENTS—PILOT DATA

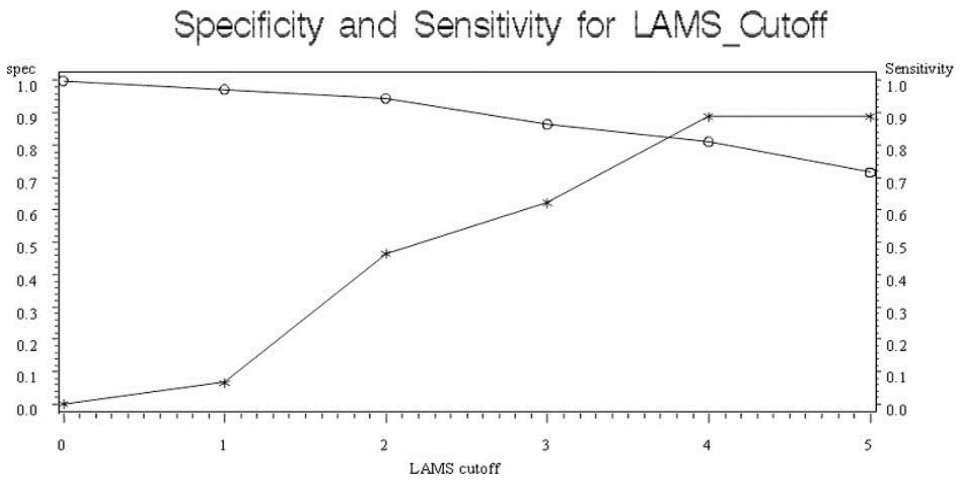


DOOR TO GROIN PUNCTURE IN MSU PATIENTS—THE NEXT HURDLE



Pre-hospital identification of patients for IAT

Lost Angeles Motor Score



Full NIHSS sensitivity and specificity from MSU

NIHSS > 4	100% sensitivity, 10% specificity
NIHSS > 9	83% sensitivity, 58% specificity
NIHSS > 16	72% sensitivity, 81% specificity

Impact on studies aimed at preserving the penumbra; preventing reperfusion injury

- Hypothermia
- Other Cytoprotection

Pat Lyden—RHAPSODY TRIAL
IAT Selection Guidelines in a Neuroprotectant Trial

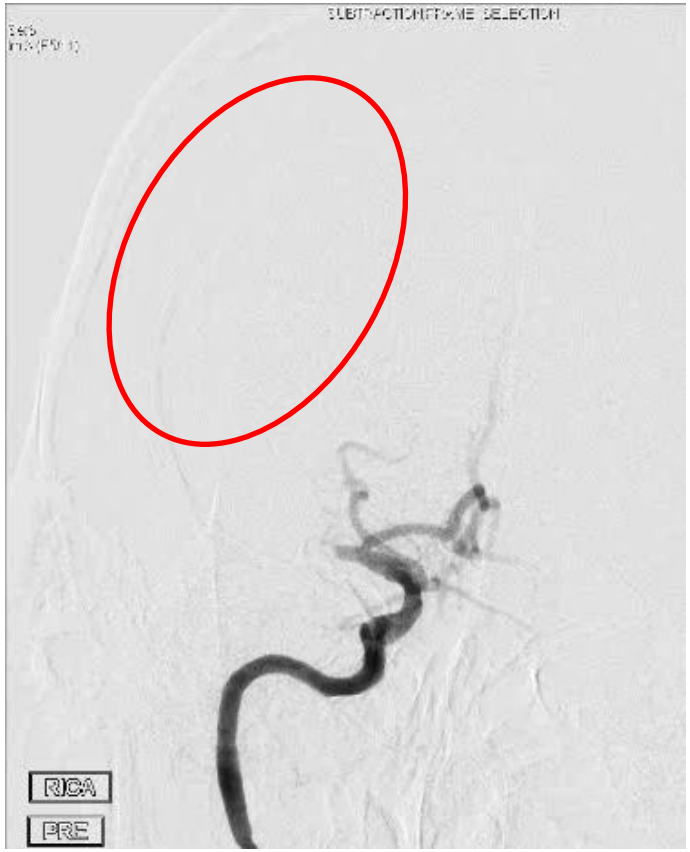
Variable	Target	Allowed Range
Age (years)	<90	< 80-90
Time: door to Puncture (min)	90	90 to 120
Time: LKNW to revascularization (hours)	6	5 to 8
Devices	Stent retrievers	Any 2nd or 3rd generation device
NIHSS	>=8	5 to 32
Imaging Modality	NCCT	CT or MRI
Vascular imaging	ELVO on CTA/MRA	ELVO on any modality
Perfusion imaging	Salvageable penumbra	Mismatch
Core size	ASPECTS > 7	ASPECTS >6, CT hypo > 1/3, DWI > 70cc

Impact on studies aiming to augment tPA and collaterals

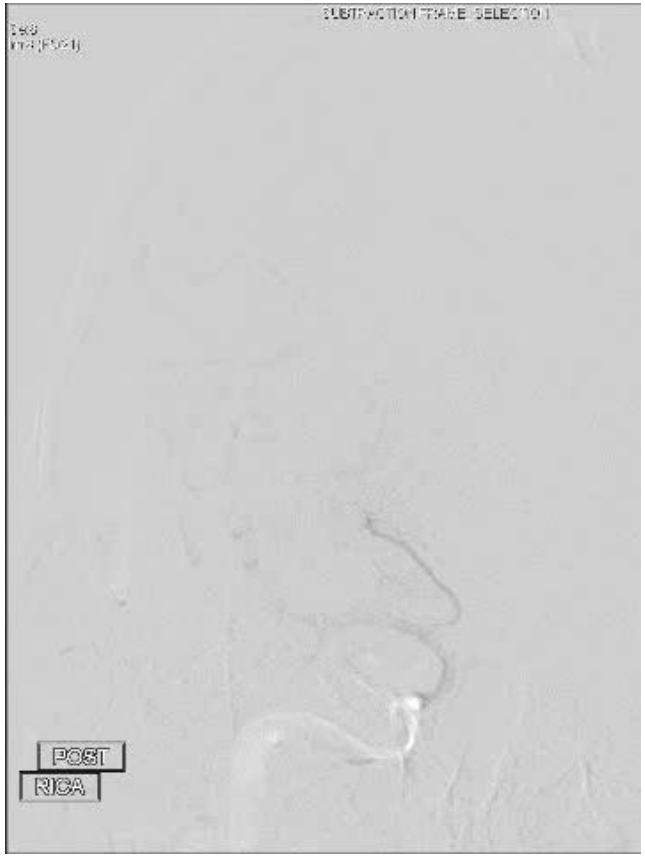
- MOST- Multi-arm Optimization of Stroke Thrombolysis Stroke Trial
  - IV-tPA + argatroban
  - IV-tPA + eptifibatide

Residual proximal & distal microcirculation thrombosis likely contribute to lack of treatment response

Pre-Intervention:
Right M1 MCA occlusion

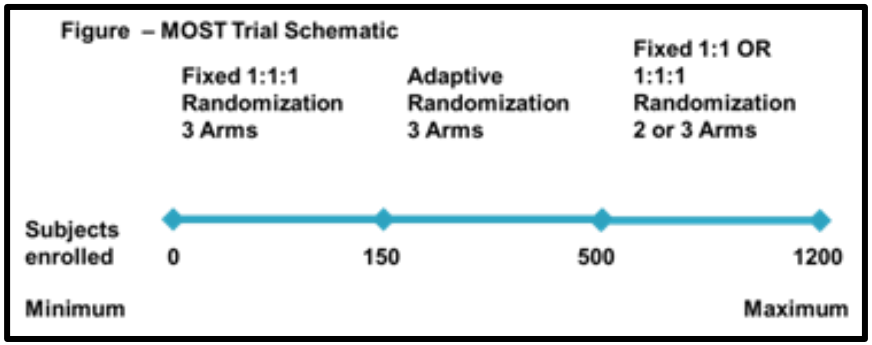


Post-Intervention:
Recanalization, but not complete *reperfusion*




Next Steps: MOST Trial


- **Multi-arm Optimization of Stroke Thrombolysis Stroke Trial**
  - ❑ U01 NIH submission; Review Nov. 12, 2015
  - ❑ <u>Features</u>
    1) **Response Adaptive Randomization of 3-arms**
       - tPA-alone, tPA+Arg, tPA+Epti
       - Bayesian predictive probabilities with ability to drop non-performing arm
    2) **Patient-Centered Primary Outcome**
       - Utility weighted mRS
       - Central video assessment of mRS
    3) **Open Label for rapid therapy overlap**
    4) **Endovascular Therapy allowed**
    5) **Interim analyses for Futility and Early Efficacy**
    6) **Minimum n=500 with maximum n=1200**
       - 83% power for 1 arm
       - 88% power if both treatments are effective



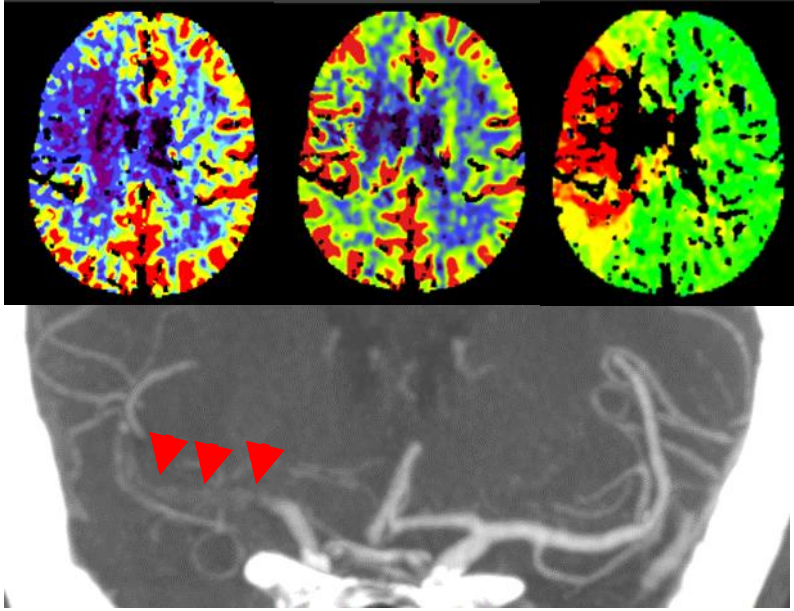
Endovascular Therapy (ET) in MOST

- **5 completed phase 2 trials** (3 randomized)
  - Safety and favorable efficacy trends with Arg and Epti added to tPA.
  - But ET not allowed
- **Patient Selection**
  - ET according to guidelines (6-hrs; ASPECTS ≥6; CTA-proven proximal LVO) but…
    - M2, A1, P1 and vertebro-basilar allowed
- **Bias Reduction**
  - Randomize into MOST after CTA & prior to groin puncture
  - Capture "Planned ET" Y/N at randomization
    - Once ET decision is made, must proceed unless major neurological deterioration or resolution of symptoms
- **ET Considerations in MOST**
  - Avoidance: GA, additional IA lytics / anti-thrombotics, emergent stenting
  - Continue Arg (12-hrs) or Epti (2-hrs) during & after IAT
    - TICI 3 - over-estimated locally & low frequency in recent IA trials
  - Heparin: No IV during ET; Avoid large IA infusions.
  - ACT & aPTT at end of procedure
  - Delayed sheath removal in Arg/Epti arms

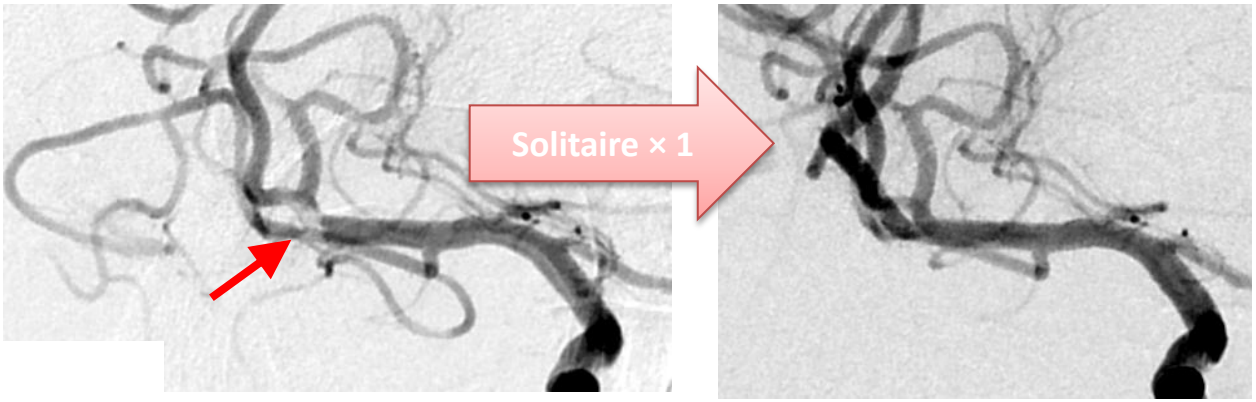
ARTSS-IA NCT02448069

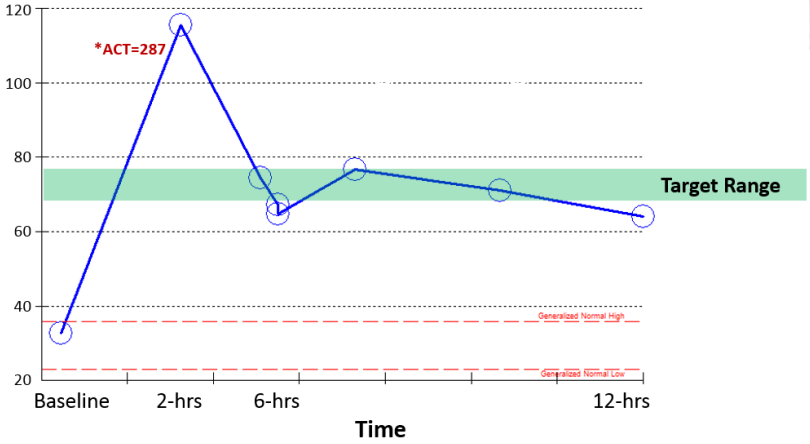
- Right MCA syndrome
- NIHSS=12
- ASPECTS=10

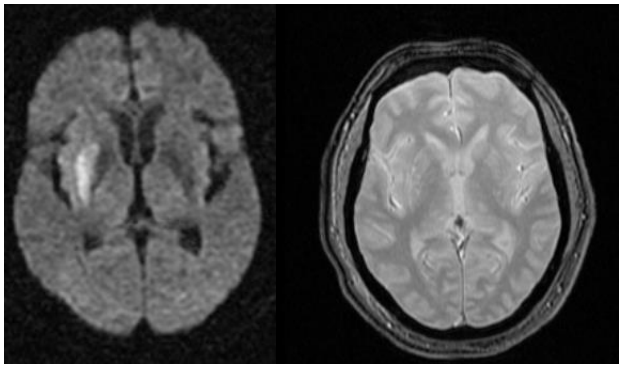
- tPA at 1.5 hours from onset
- Argatroban started → 12 hours total
- Endovascular recanalization 2.6 hours from onset



Clot length reduced 80%
20mm → 5mm







Discharged home at 48 hrs with NIHSS=1