Update on Acute Ischemic Stroke Treatment

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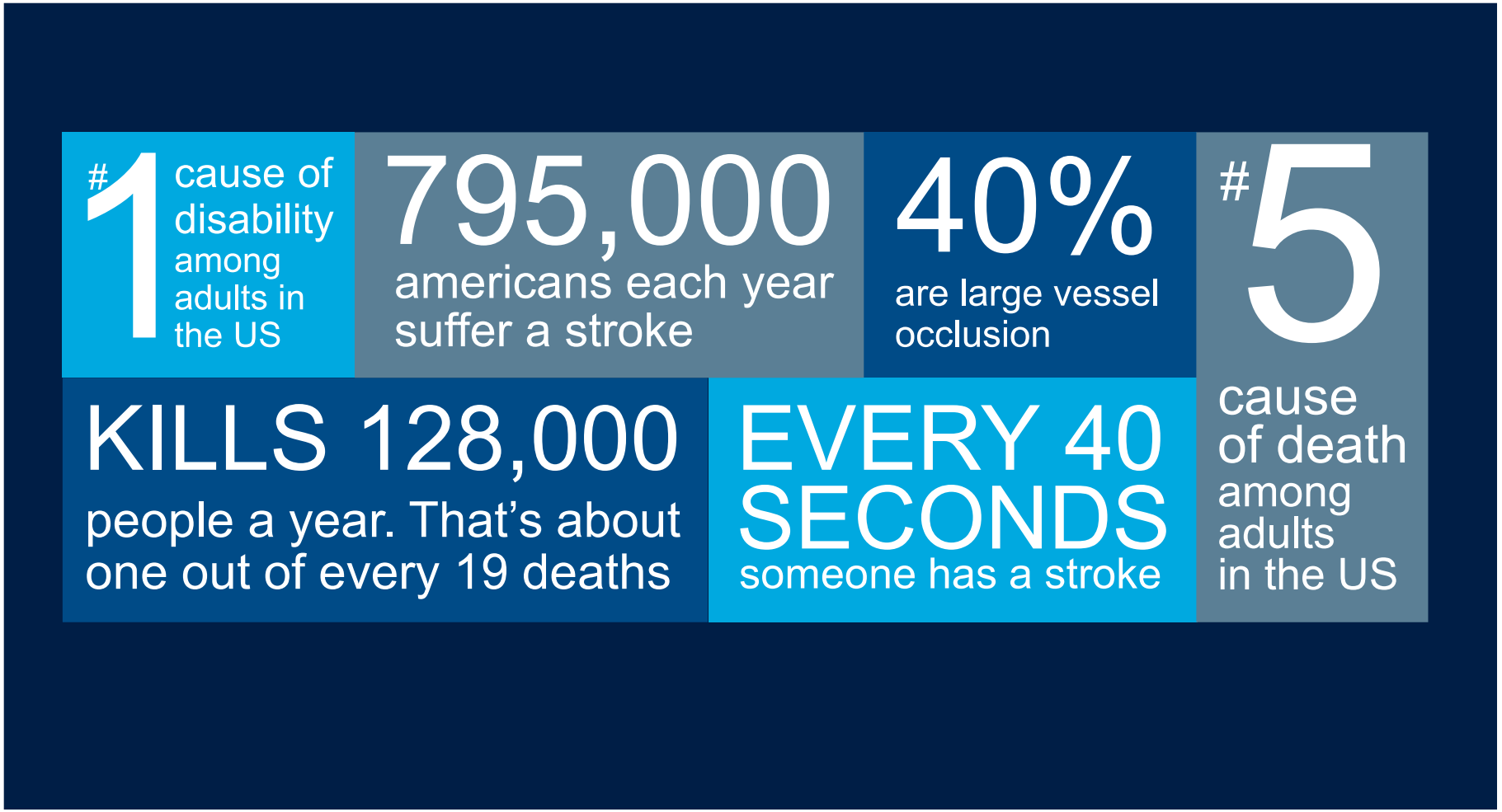
Disclosures

- None

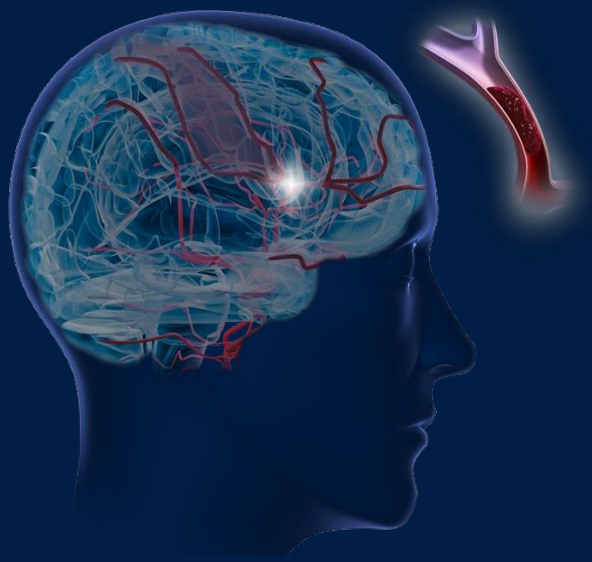
Objectives

- Review the latest developments in the endovascular treatment of stroke
- Consider the implications for practice

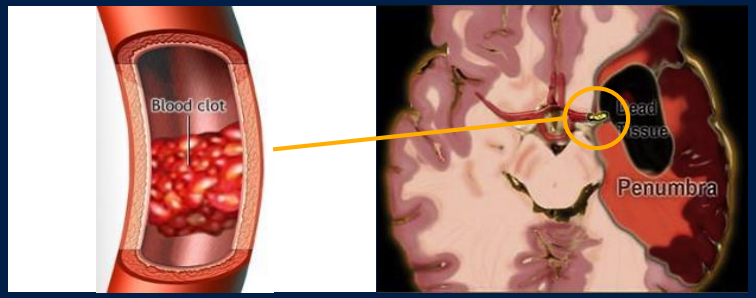

#1 cause of disability among adults in the US
795,000 americans each year suffer a stroke
40% are large vessel occlusion
#5 cause of death among adults in the US
KILLS 128,000 people a year. That's about one out of every 19 deaths
EVERY 40 SECONDS someone has a stroke

STROKE DISEASE STATE
795,000 STROKES PER YEAR U.S.*

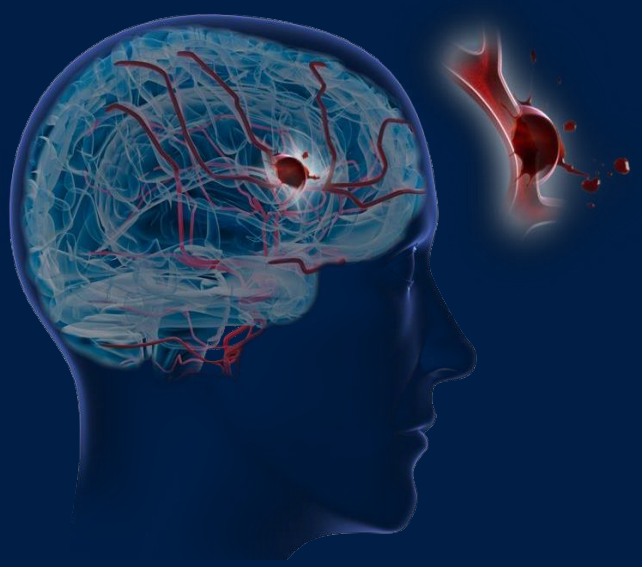
ISCHEMIC STROKE: 87%*



Acute Ischemic Stroke

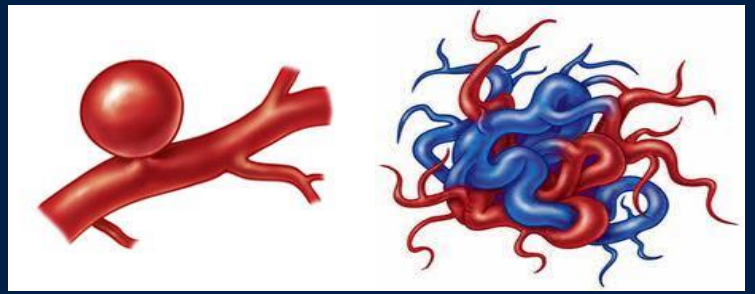


HEMORRHAGIC STROKE: 13%*



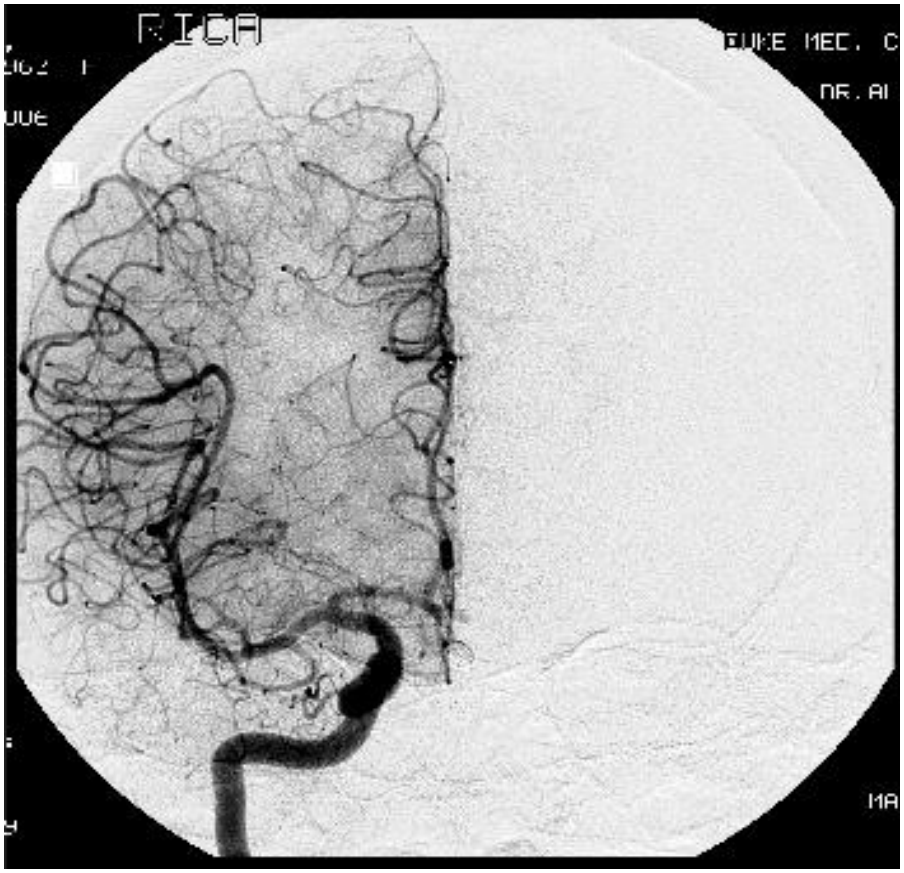
Brain Aneurysm

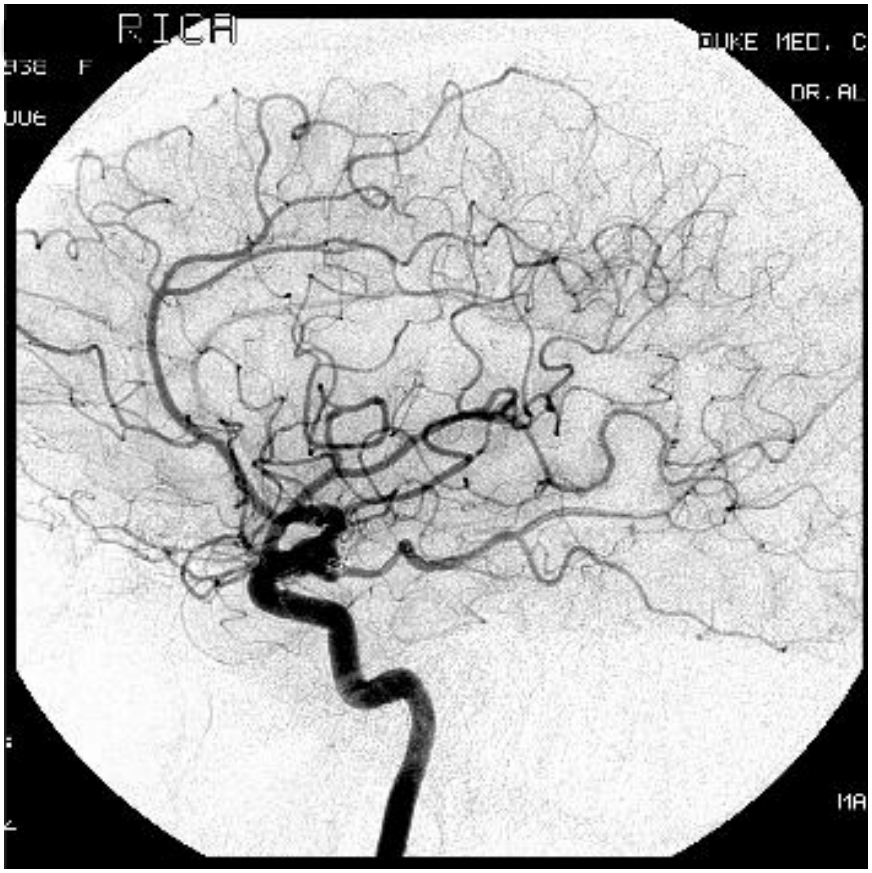
Brain AVM

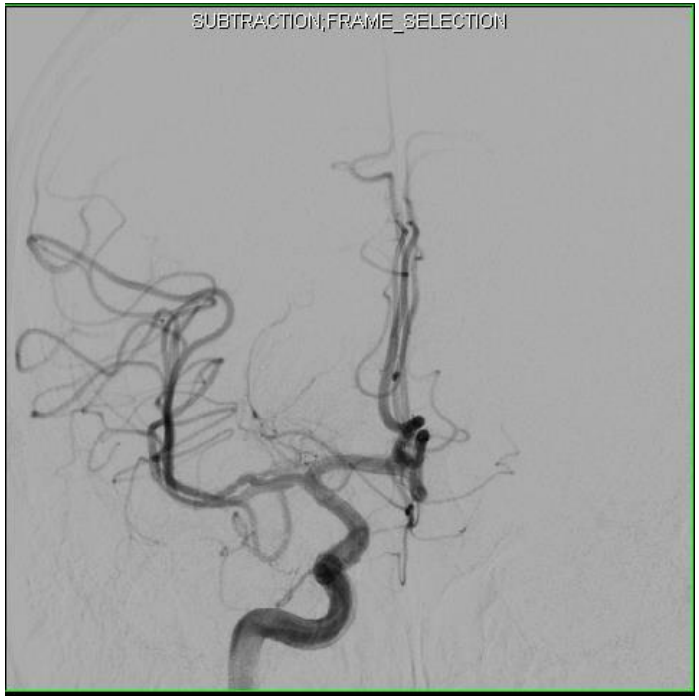


*National Stroke Association. (2012). Stroke 101 Fact Sheet. Retrieved from National Stroke Association: http://www.stroke.org/site/PageServer?pagename=factsheets

Angiographic Anatomy Review



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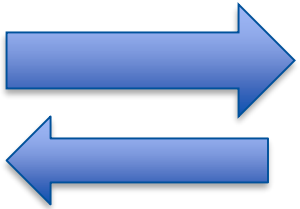

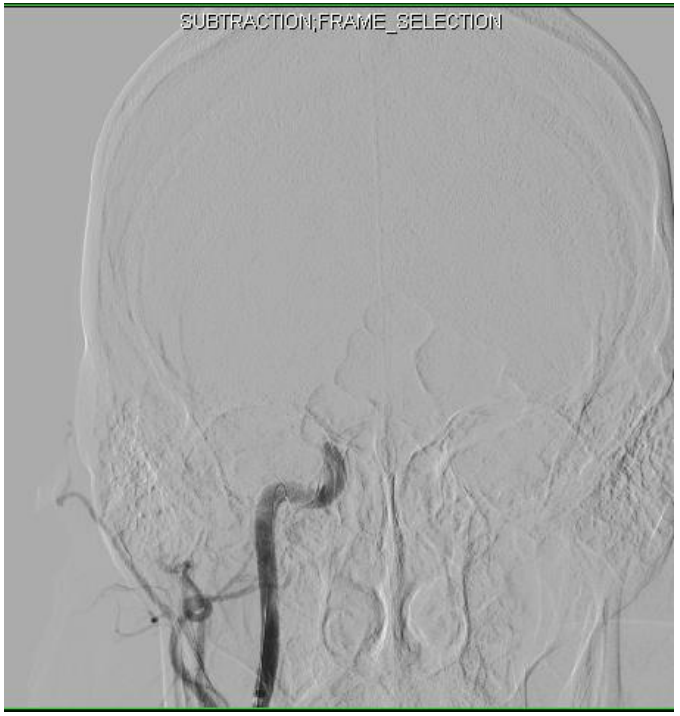
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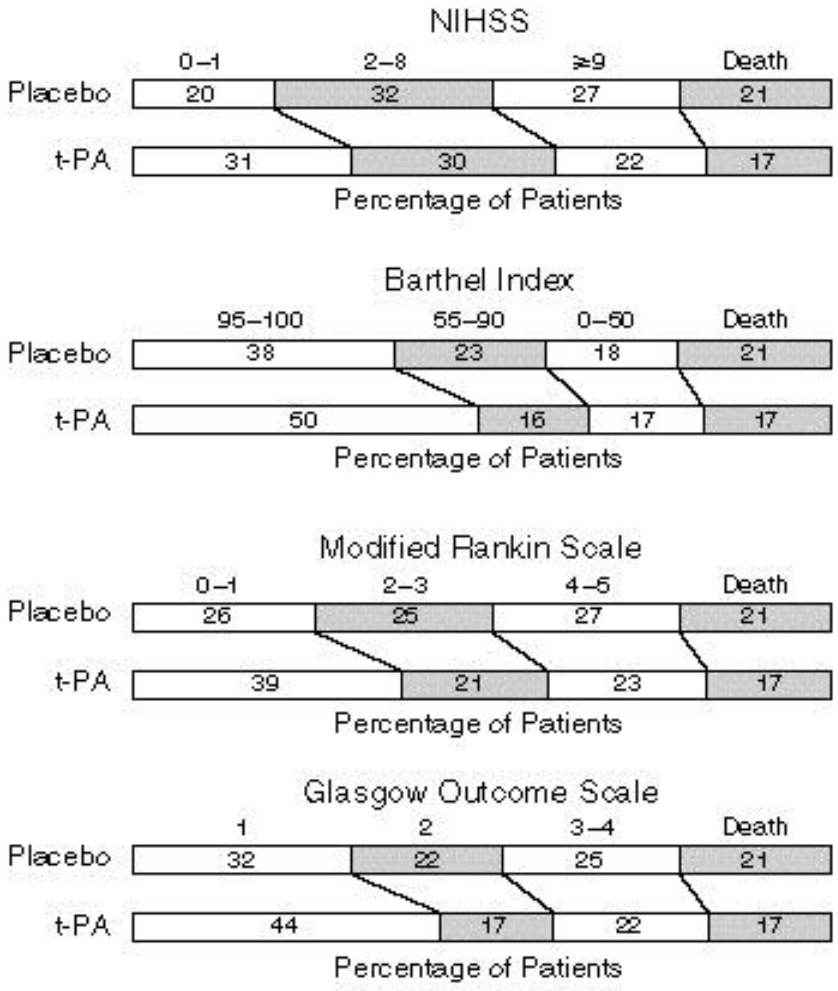
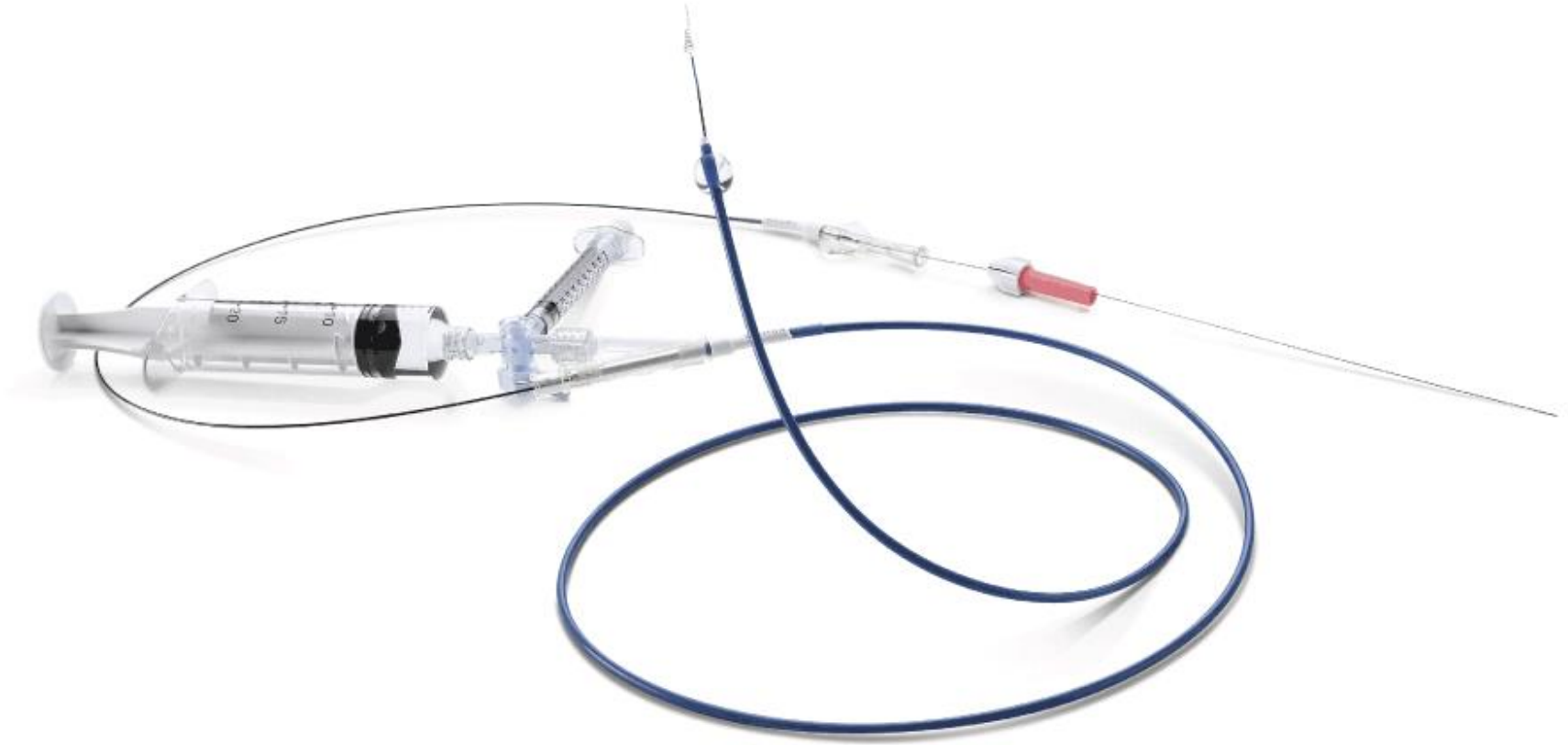
Outcome at Three Months in Part 2 of the Study, According to Treatment.



The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333:1581-1588.

The MERCI Device



	IMS III (Endovascular)++	IMS III (tPA)+++
N	434	222
Age	69	68
Male	50.2%	55%
Baseline NIHSS, median	17	16
% ICA occlusions	15%	Unk
% VBA occlusions	1%	unk
Successful recanalization	38% **(ICA)** 44% **(M1)** TICI >2b	unk
mRS ≤ 2 at 3 months	40.8%	38.7%
Mortality at 3 months	19.1%	21.6%
Symptomatic ICH at 24 hrs	6.2%	5.9%

*Dávalos A, Mendes Pereira V, Chapot R, et al; Retrospective Multicenter Study of Solitaire FR for Revascularization in the Treatment of Acute Ischemic Stroke. *Stroke. 2012;43:2699-2705.*

**Saver J, Jahan R, Levy E, et al; SWIFT Trialists. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet. 2012;380(9849):1241-1249.

***TREVO1 data from presentation by N. Wahlgren, International Stroke Congress 2012.

+Trevo Versus Merci Retrievers for Thrombectomy Revascularisation of Large Vessel Occlusions in Acute Ischaemic Stroke (TREVO 2): a randomised trial. Nogueira et. al., doi:10.1016/S0140-6736(12)61299-9.

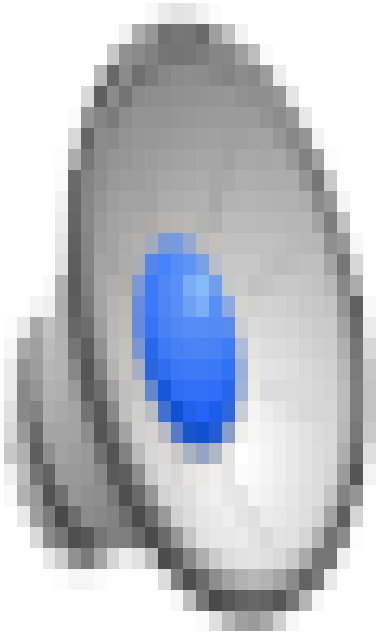
x. STAR Study: Vitor M. Pereira, et. Al. Prospective, Multicenter, Single-Arm Study of Mechanical thrombectomy Using Solitaire Flow Restoration in Acute Ischemic Stroke. Stroke. published online August 1, 2013;

++Broderick, Joeseph, et. Al. Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke. NEJM. vol. 368 no. 10

****Presented by Dr. Dippel, Erasmus University at World Stroke Congress 2014

Mechanical Thrombectomy

- Video



Study Overview
Inclusion and Exclusion Criteria

Study	MR CLEAN
Enrollment Period	December 2010 – March 2014
Study Design	Prospective, multi-center, randomized, controlled, blinded-endpoint trial
Tx Window	6 hrs
NIHSS	2 or more
Study Arm	Endovascular treatment: intra-arterial thrombolysis (urokinase or alteplase), mechanical treatment (retraction or aspiration of the thrombus with a catheter guided device, or stenting) or both
Control Arm	Medical management
Target Vessels	Distal ICA, middle (M1/M2) or anterior (A1/A2) cerebral artery
Sample Size/Sites	500 pts, 18 sites in Netherlands
Primary Endpoints	mRS at 90 days Rankin Shift
Secondary Endpoints	NIHSS at 24 hours, vessel patency at 24 hours, infarct size at day 5-7, and the occurrence of major bleeding
Follow-up	24 hrs, 5-7 days, discharge, 90 days
Key In/Exclusion Criteria	• Intracranial occlusion of the distal intracranial ICA, middle (M1/M2) or anterior (A1/A2) cerebral artery, demonstrated with CTA, MRA, DSA or transcranial Doppler/duplex (TCD).

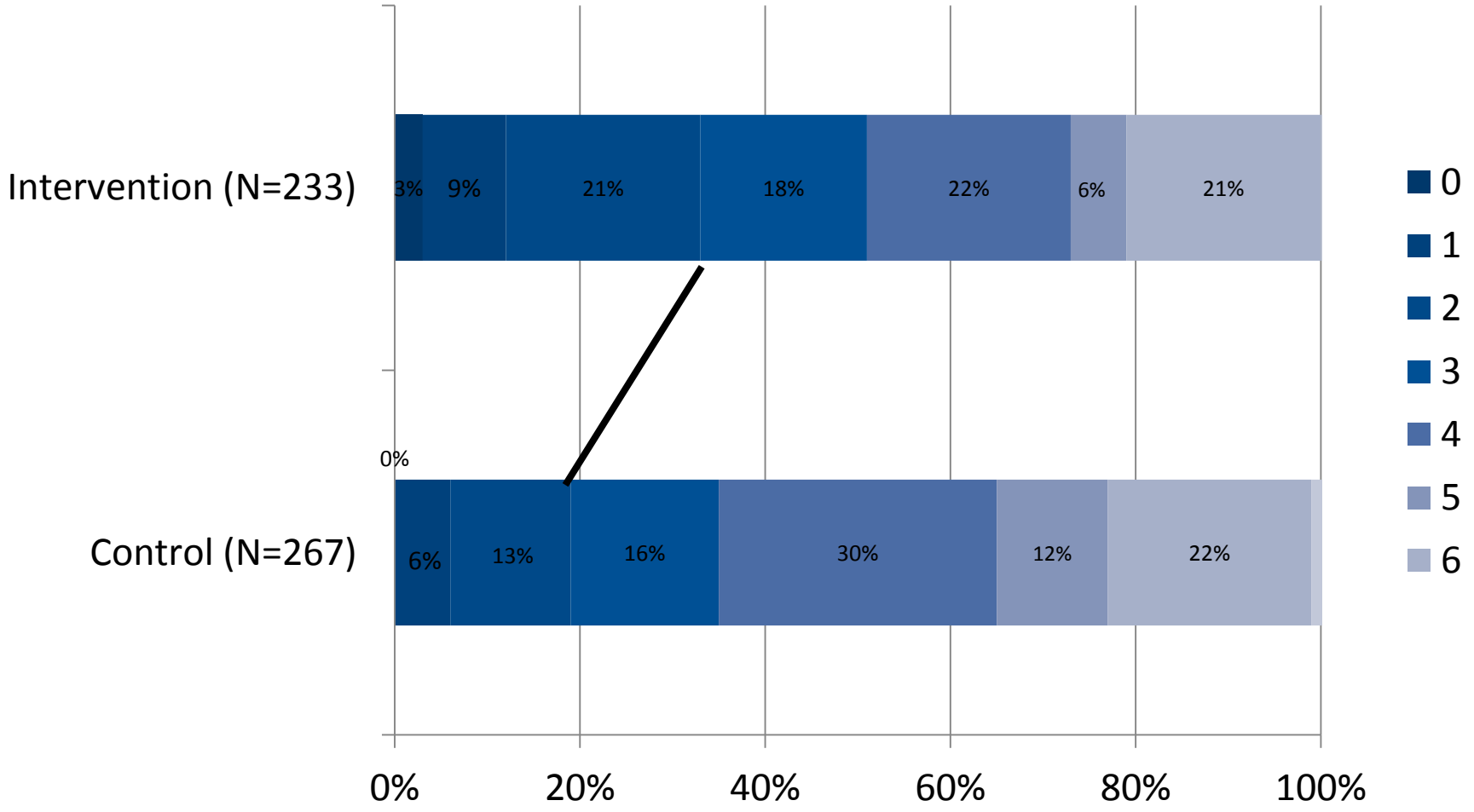
Source: http://www.mrclean-trial.org/index.html, accessed 05Jun2014

MR CLEAN Study Details**

- Overall, even in this very complex population, the study observes that the addition of stent thrombectomy for acute ischemic stroke care significantly improves good neurological outcomes with no additional safety risks.
  - MR CLEAN demonstrated a 71% improvement in good neurological outcomes for patients treated with intervention compared to medical management/TPA (32.6% (76/233) vs. 19.1% (51/267))
  - There was no safety difference in adverse events (47% vs. 42%) , ICH (7.8% vs. 6.4%) or 90 day mortality (21% vs 22%) between the two groups.
  - Lower absolute rates of 90day mRS 0-2 and higher complication rates seen in MR CLEAN vs. prior studies reflect the 'real-world' experience in the Netherlands, particularly the relatively high rate of ICA lesions vs. prior studies like IMS3 (26% vs. 15%)
- 97% of interventions employed a stent retriever device the greatest contributor to the data was the **Trevo™ Pro Retriever.** The specific breakdown of device usage is unknown.
- Further studies are needed to confirm these results outside the Netherlands and examine the effect of stent thrombectomy in global systems of care and with varying patient populations.

**Presented by Dr. Dippel, Erasmus University at World Stroke Congress 2014

MR CLEAN Rankin Shift Analysis**



*Presented by Dr. Dippel, Erasmus University at World Stroke Congress 2014

MR CLEAN Trial Data Overview** Safety Endpoints

Outcome	Intervention (N=233)	Control (N=267)
Death Within 7 days – n (%)	27 (12%)	33 (12%)
Death Within 30 days – n (%)	44 (19%)	49 (19%)
Hemicraniectomy – n (%)	14 (6.0%)	13 (4.9%)
Patients with at least one SAE – n (%)	110 (47%)	113 (42%)
Symptomatic ICH – n (%) Any type Parenchymal hematoma type 1 (PH1)^ Parenchymal hematoma type 2 (PH2)^ Hemorrhagic infarction type 1 (HI1) Hemorrhagic infarction type 2 (HI2) Subarachnoid Hemorrhage	 18 (7.8%) 0 (0%) 14 (6.0%) 1 (0.4%) 1 (0.4%) 2 (0.9%)	 17 (6.4%) 2 (0.7%) 14 (5.2%) 0 (0%) 1 (0.4%) 0 (0%)
New ischemic stroke in different vascular territory – n (%)	13 (5.6%)	1 (0.4%)
Progressive ischemic stroke – n (%)	46 (20%)	47 (18%)
Pneumonia – n (%)	25 (11%)	41 (15%)
Other infection – n (%)	16 (6.9%)	9 (3.4 %)
Cardiac ischemia – n (%)	1 (0.4%)	4 (1.5%)
Extracranial hemorrhage – n (%)	0 (0.0%)	2 (0.7%)
Allergic reaction – n (%)	1(0.4%)	0 (0.0%)
Other complication – n (%)	22 (9.4%)	33 (12%)

**Presented by Dr. Dippel, Erasmus University at World Stroke Congress 2014

MR CLEAN (in summary)

- Groin puncture must be performed within 6 hrs of LKN
- No upward age restriction; NIHSS as low as 2
- tPA was given to 87% of patients
- CTA at 2 hrs showed MCA or ICA occlusion in 92% of patients
- Though randomization was 2 hrs after tPA, median ASPECTS score was 9

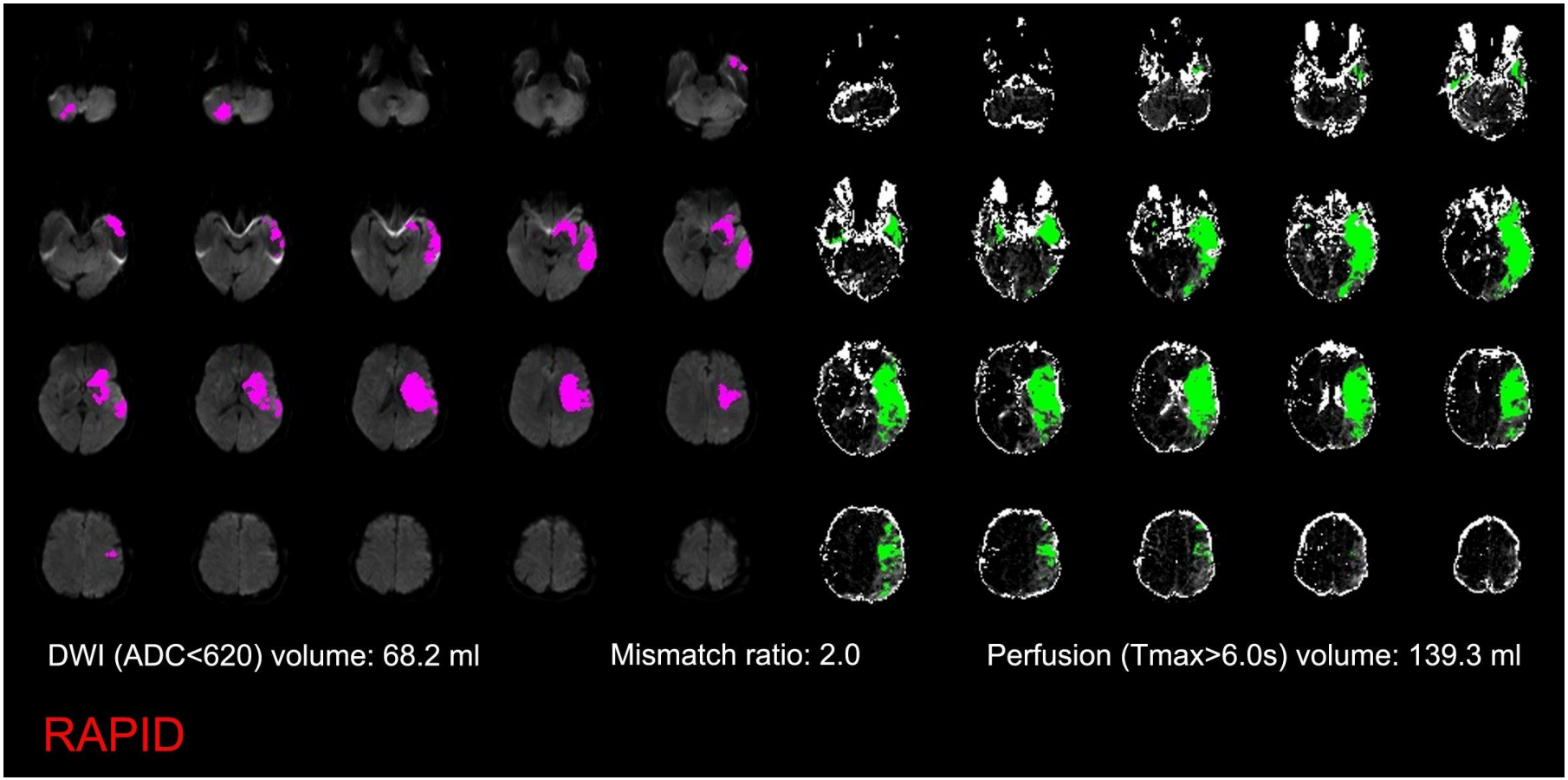
EXTEND-IA Study Overview

- Background: The EXTEND-IA trial was conducted to test the hypothesis that anterior circulation ischemic stroke patients, selected with a “dual target” of vessel occlusion and evidence of salvageable tissue on perfusion imaging within 4.5h of onset, would have improved reperfusion and early neurological improvement when treated with endovascular thrombectomy using the Solitaire™ stent thrombectomy device after intravenous (IV) alteplase, compared to alteplase alone.

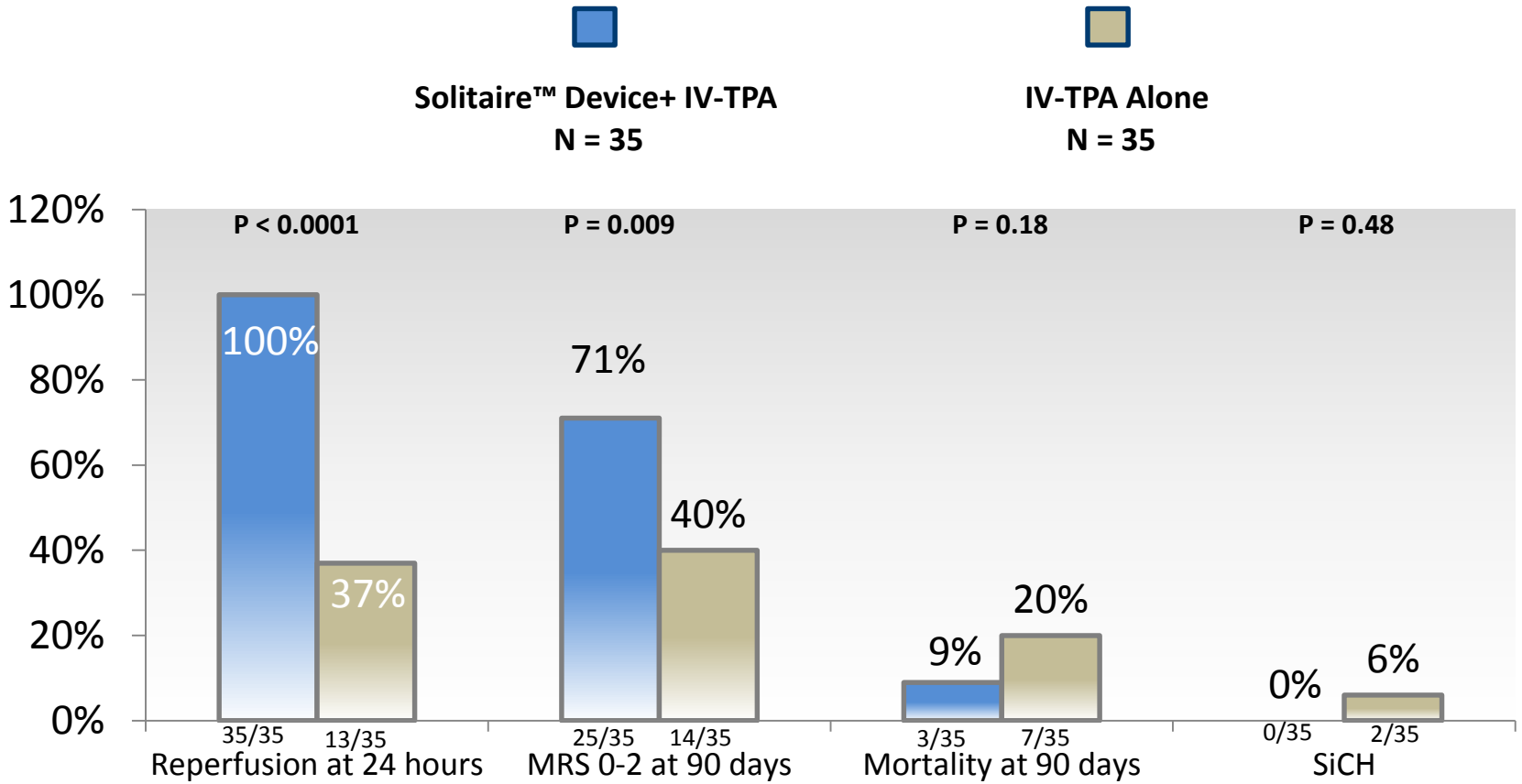
- Methods: Stroke patients receiving 0.9mg/kg alteplase <4.5h after stroke onset,with internal carotid or middle cerebral artery occlusion and CT perfusion imaging evidence of salvageable tissue and ischemic core <70ml, were randomized to either alteplase followed by endovascular thrombectomy <6h with the Solitair™ device , or alteplase alone. The co-primary outcomes were reperfusion at 24h and early neurological improvement (≥8 point reduction in National Institutes of Health Stroke Scale (NIHSS) or reaching 0-1 by day 3). The secondary outcome was modified Rankin scale (mRS) at day 90.

- The trial was stopped early because of efficacy after 70 patients had been randomized (35 patients in each group).

Published in the New England Journal of Medicine. **DOI: 10.1056/NEJMoa1414792**


DWI (ADC<620) volume: 68.2 ml
Mismatch ratio: 2.0
Perfusion (Tmax>6.0s) volume: 139.3 ml
RAPID

EXTEND-IA Study Summary



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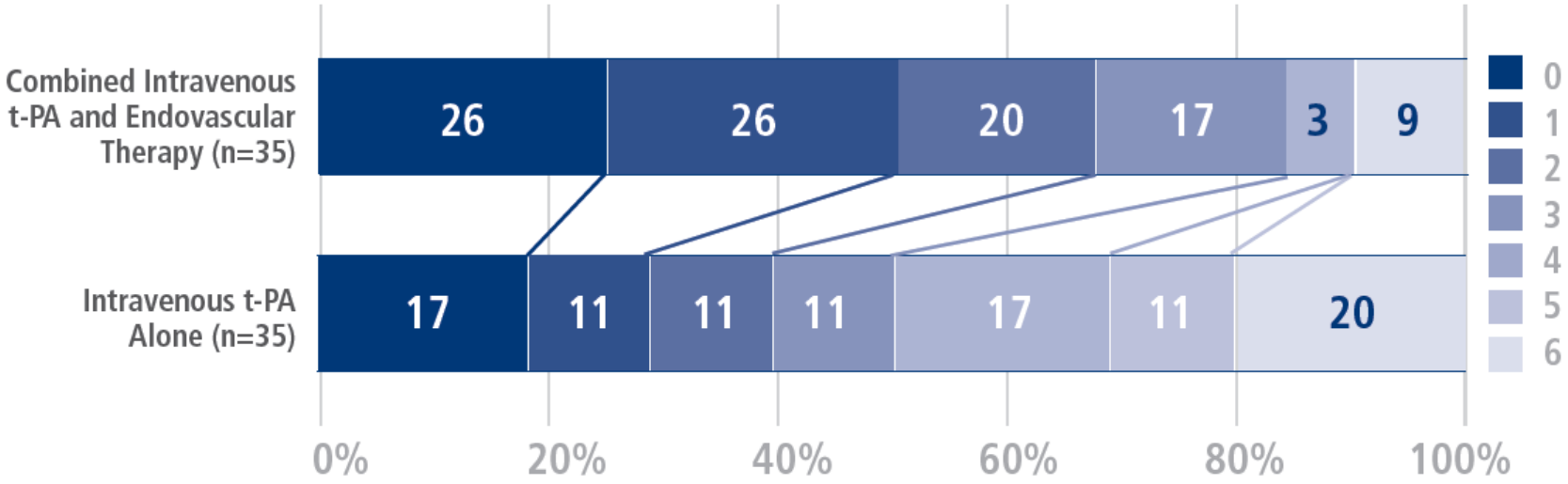
Statistically significant improvement in rate of good outcomes at 90 days with intervention using the Solitaire™ device as primary treatment.



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SWIFT PRIME Study Overview

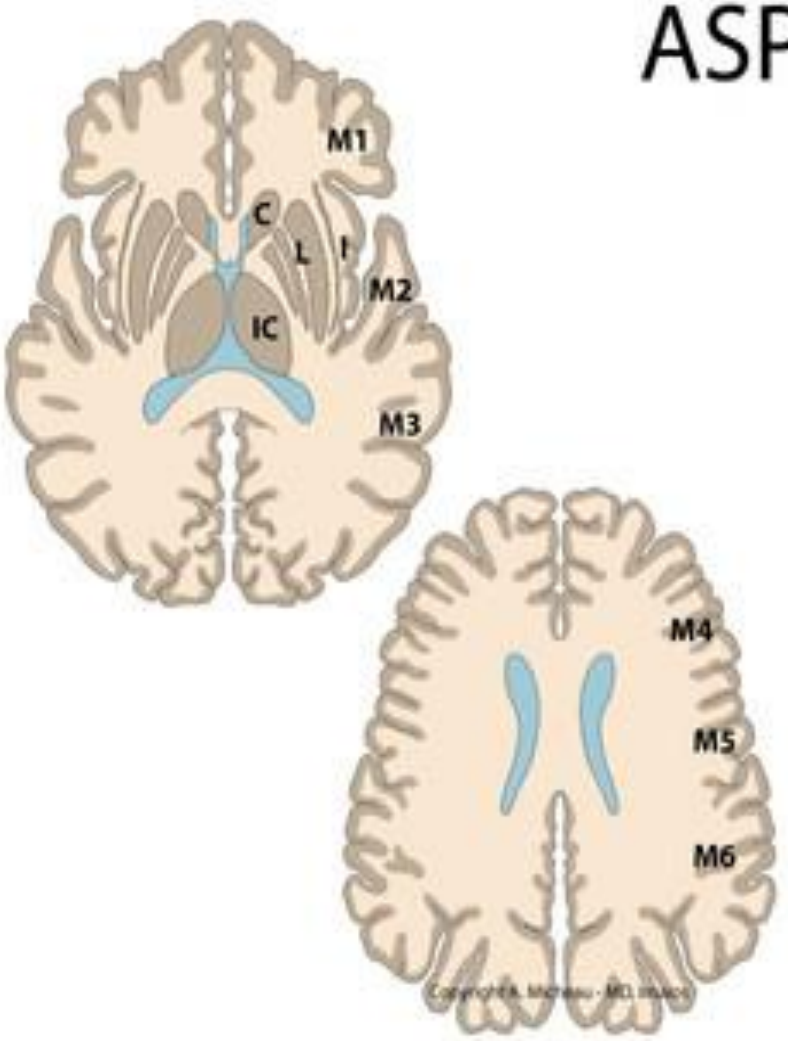
- Background: Among patients with acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, less than 40% regain functional independence when treated with intravenous tissue plasminogen activator (t-PA) alone. Thrombectomy with the use of a stent retriever, in addition to intravenous t-PA, increases reperfusion rates and may improve long-term functional outcome.

- Methods: We randomly assigned eligible patients with stroke who were receiving or had received intravenous t-PA to continue with t-PA alone (control group) or to undergo endovascular thrombectomy with the use of a stent retriever within 6 hours after symptom onset (intervention group). Patients had confirmed occlusions in the proximal anterior intracranial circulation and an absence of large ischemic-core lesions. The primary outcome was the severity of global disability at 90 days, as assessed by means of the modified Rankin Scale (with scores ranging from 0 [no symptoms] to 6 [death]).

- The trial was stopped early because of efficacy after 98 patients had been randomized (196 patients in each group).

*Solitaire™ with the Intention for thrombectomy as primary endovascular treatment for acute ischenmic stroke (SWIFT PRIME) trial. Saver JL, et al. New England Journal of Medicine In Press

ASPECTS Score

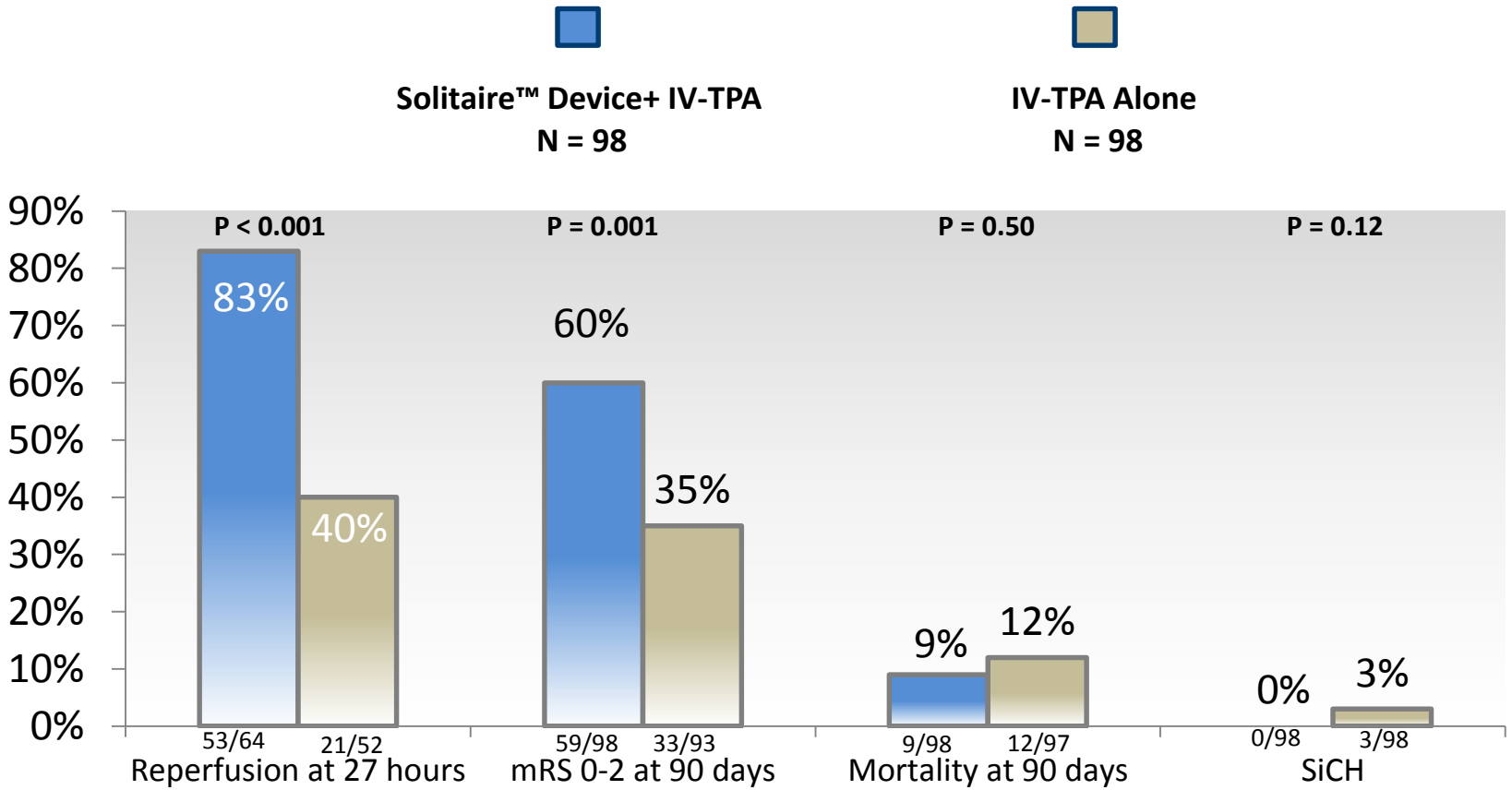


- ☐ C- Caudate
- ☐ I- Insular ribbon
- ☐ IC- Internal Capsule
- ☐ L- Lentiform nucleus
- ☐ M1- Anterior MCA cortex
- ☐ M2- MCA cortex lateral to the insular ribbon
- ☐ M3- Posterior MCA cortex
- ☐ M4- Anterior MCA superior territory
- ☐ M5- Lateral MCA superior territory
- ☐ M6- Posterior MCA superior territory

ASPECTS Score = /10

Alberta Stroke Program Early CT Score

SWIFT PRIME Study Summary



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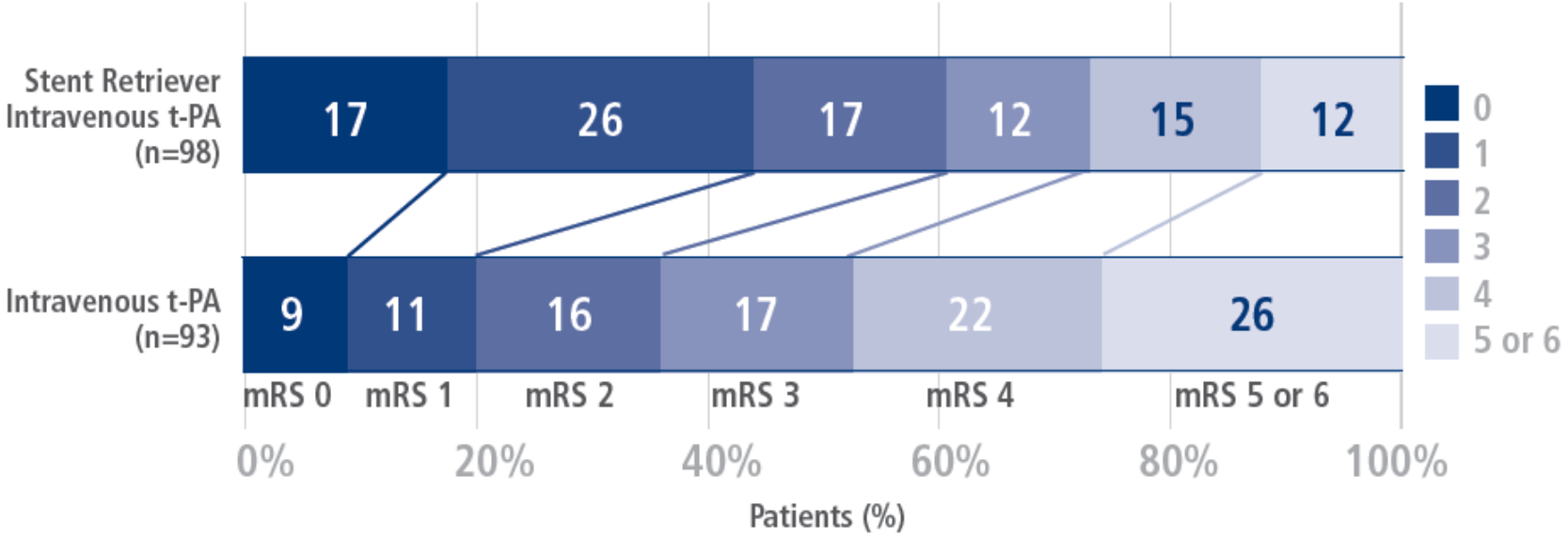


*Solitaire™ with the Intention for thrombectomy as primary endovascular treatment for acute ischenmic stroke (SWIFT PRIME) trial. Saver JL, et al. New England Journal of Medicine In Press

REVASCAT Study Overview

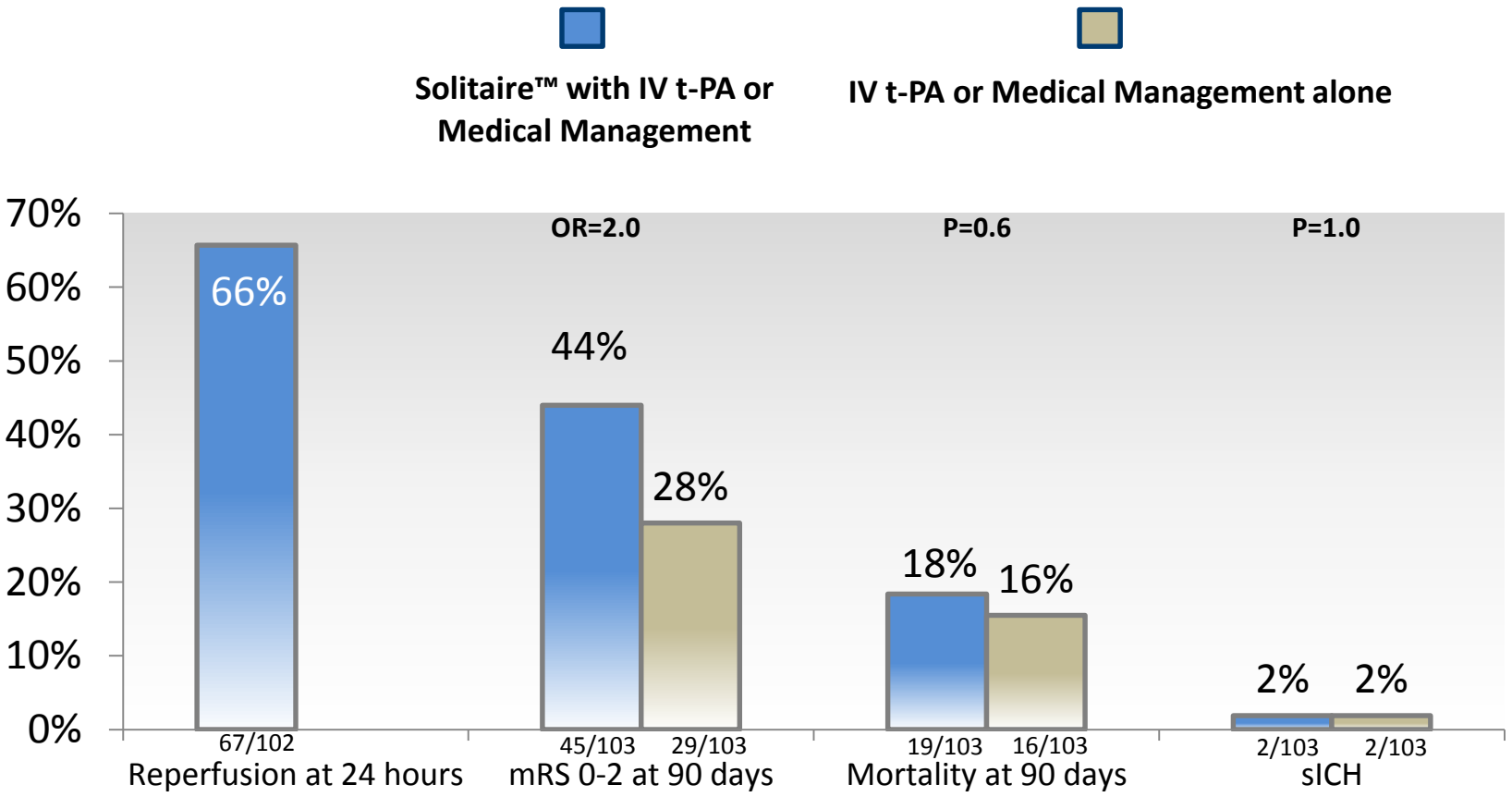
- Background: The REVASCAT study was aimed to assess safety and efficacy of thrombectomy for stroke in a trial embedded within a population based stroke reperfusion registry.

- Methods: Patients with acute ischemic stroke treatable within 8 hours of symptom onset with confirmed proximal anterior circulation occlusion and absence of large infarct on neuroimaging, were randomized to medical therapy (including iv t-PA when eligible) and endovascular treatment with Solitaire stent retriever versus medical therapy alone. Primary outcome measure was global disability at 90 days expressed as modified Rankin Scale (mRS, range 0 to 6, 0 indicates no symptoms, 5 severe disability, 6 death). Although maximum sample size was 690, enrolment was halted early following recommendation of the Data Safety Monitoring Board (DSMB) due to loss of equipoise given positive results from other trials

- The trial was stopped early because of efficacy after 206 patients had been randomized (103 patients in each group).

*Endovascular thrombectomy within 8 hours of symptom onset in ischemic stroke. Jovin TG, et al. New England Journal of Medicine. In Press

REVASCAT Study Summary



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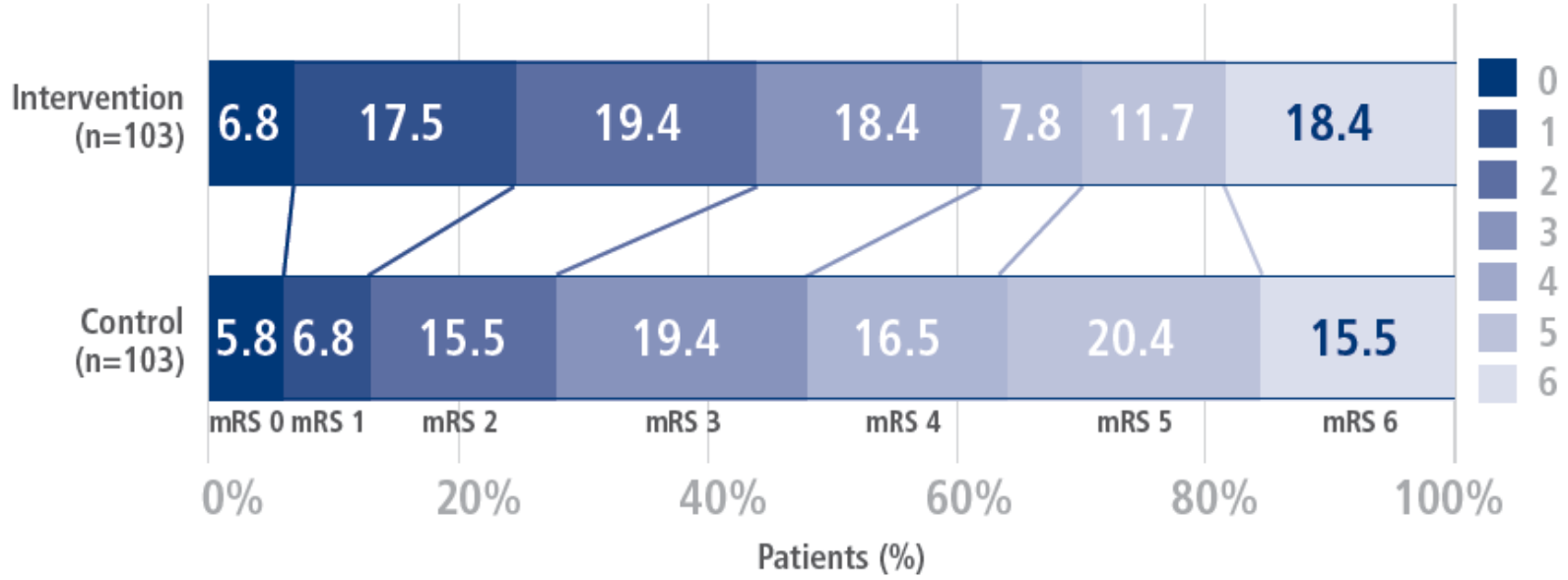
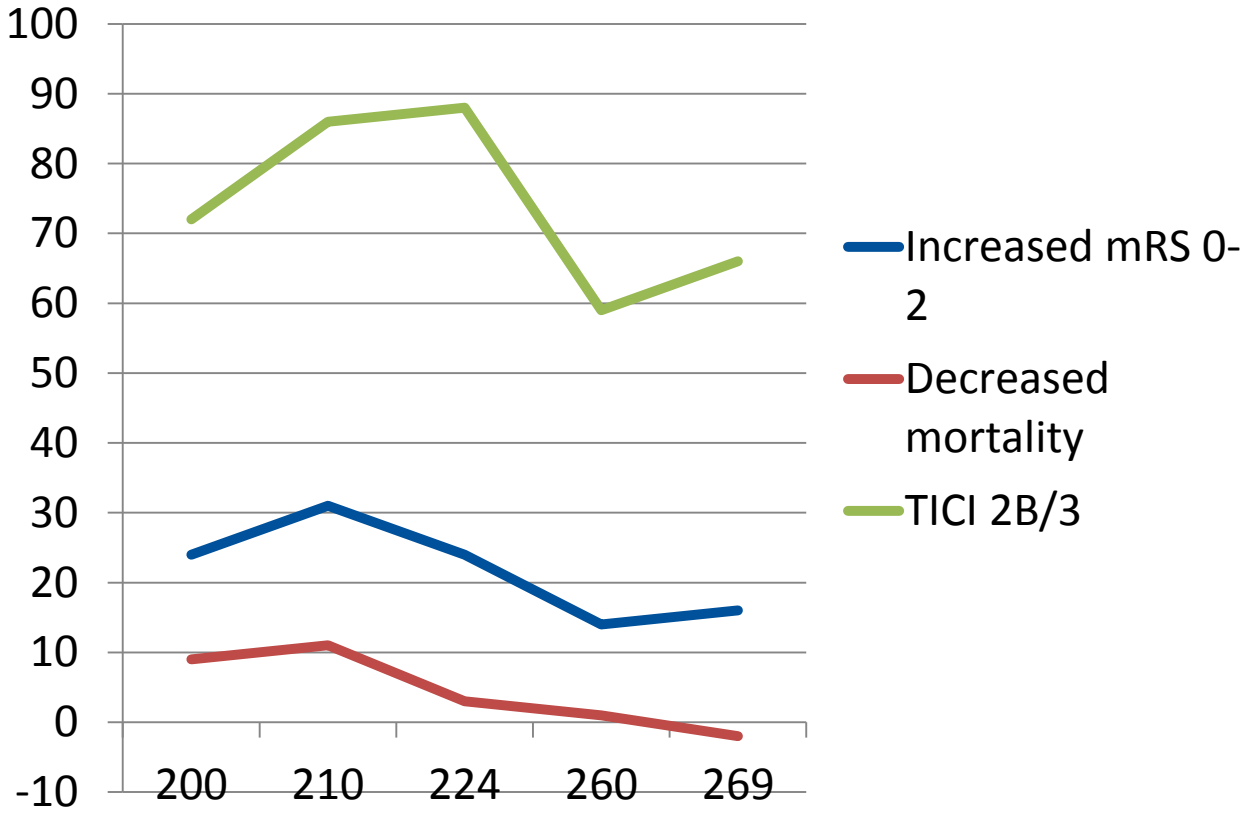


*Endovascular thrombectomy within 8 hours of symptom onset in ischemic stroke. Jovin TG, et al. New England Journal of Medicine. In Press

Summary of Trials

- Thrombectomy is very effective in the treatment of patients with stroke from ICA or MCA occlusion.
  - Relatively normal CT scans, recanalization within 6 hrs
- IV t-PA should not be with held if the patient meets criteria*
- Favorable results from thrombectomy at experienced endovascular centers with multidisciplinary teams
- Faster revascularization gives better results

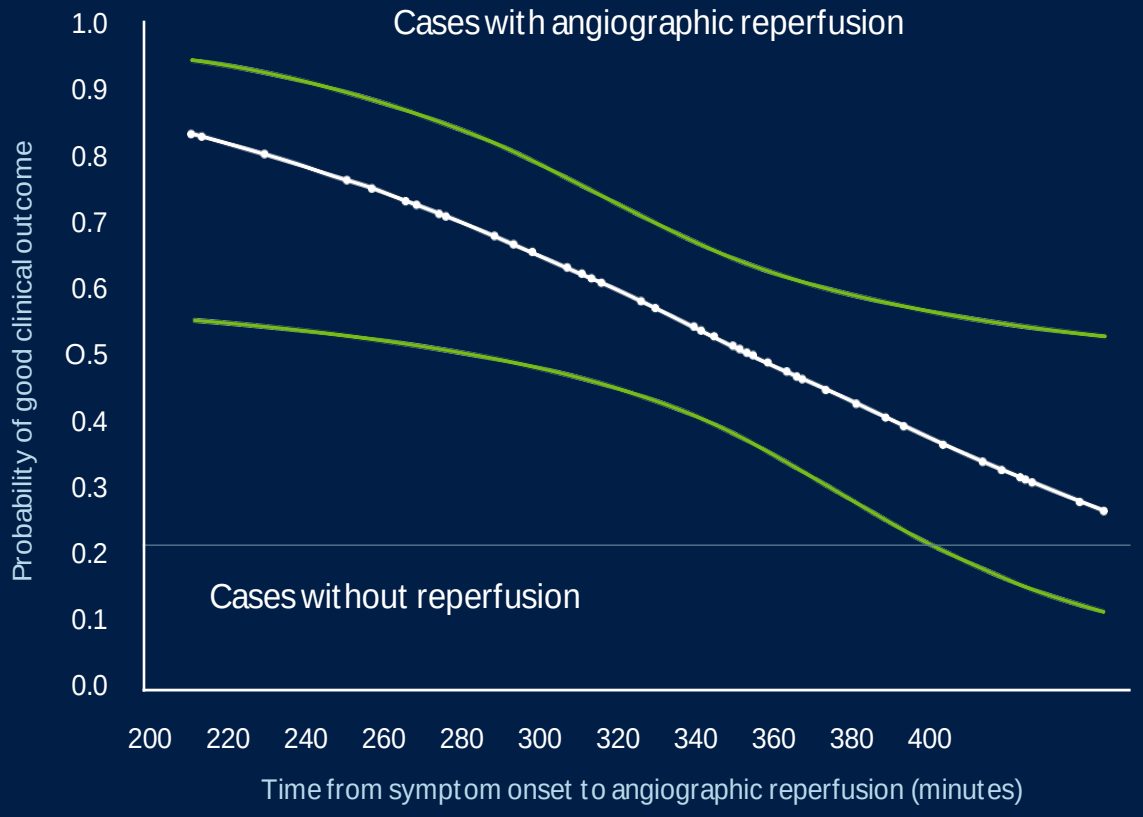
Summary of Trials

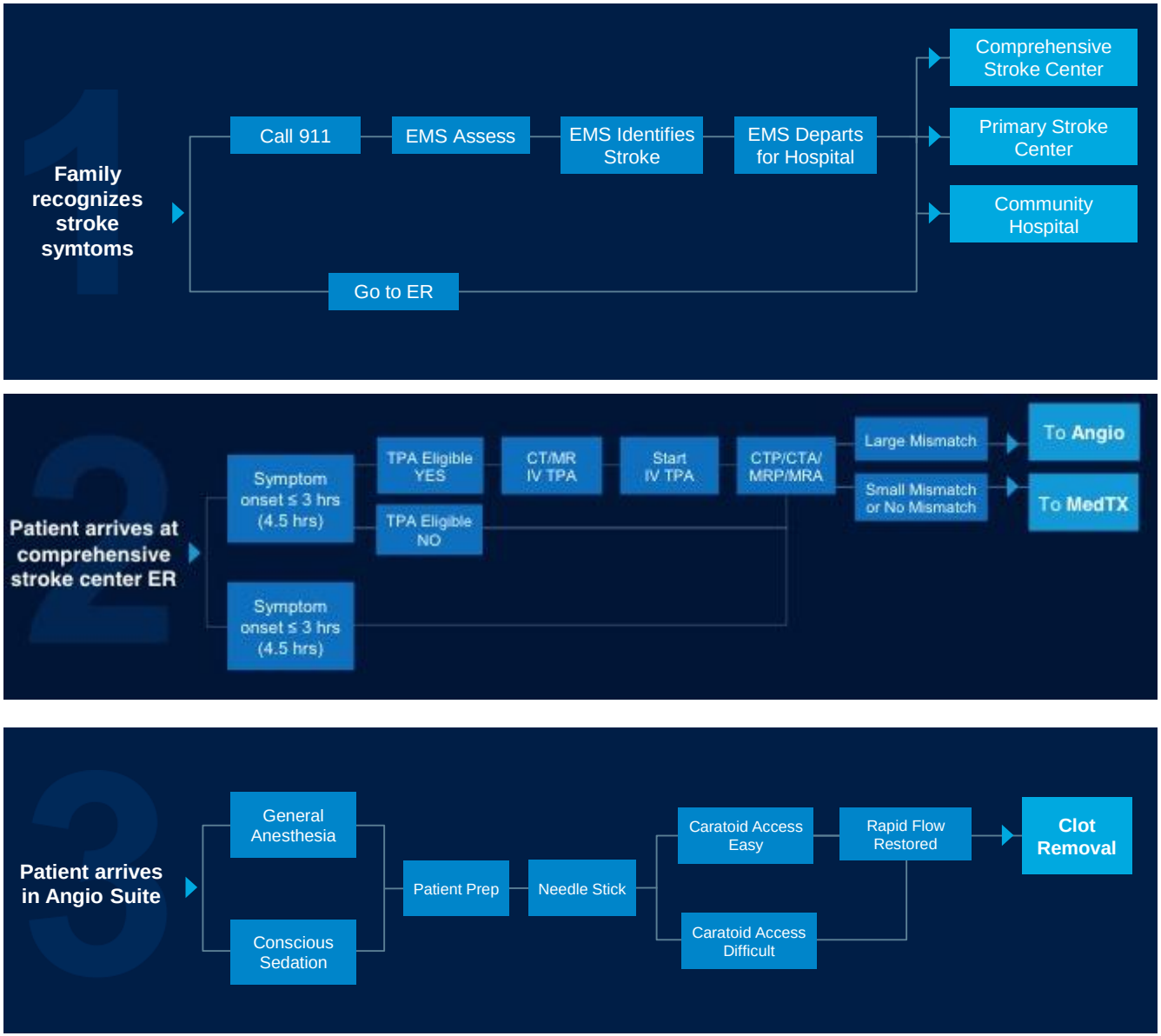


Neuronal Death

The typical LVO patient loses **2 million** neurons/min in the territory at risk

Probability of good clinical outcome over time to technically successful angiographic reperfusion

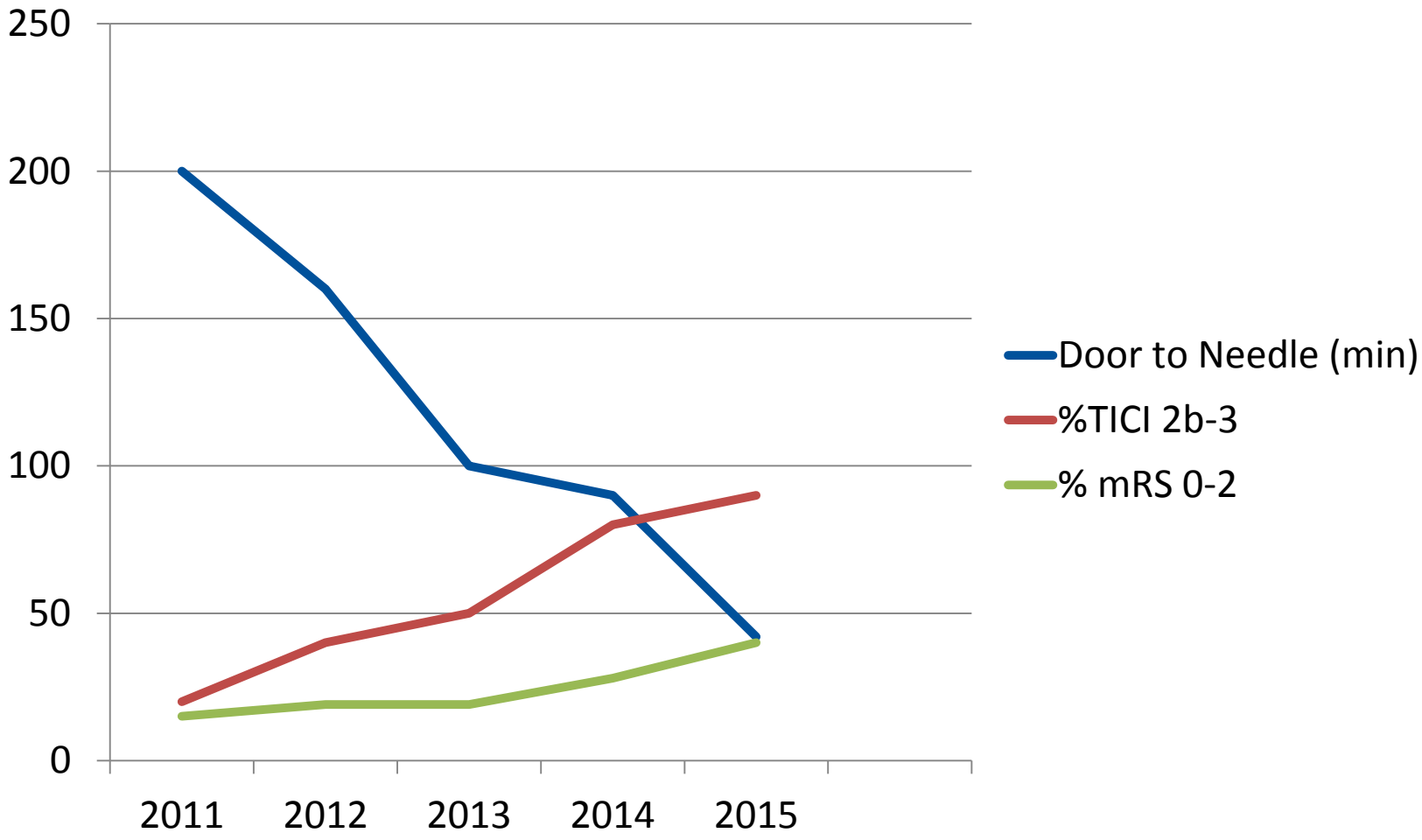



1
Family recognizes stroke symtoms
Call 911
EMS Assess
EMS Identifies Stroke
EMS Departs for Hospital
Comprehensive Stroke Center
Primary Stroke Center
Community Hospital
Go to ER
2
Patient arrives at comprehensive stroke center ER
Symptom onset ≤ 3 hrs (4.5 hrs)
TPA Eligible YES
CT/MR IV TPA
Start IV TPA
CTP/CTA/ MRP/MRA
Large Mismatch
To Angio
Small Mismatch or No Mismatch
To MedTX
TPA Eligible NO
Symptom onset ≤ 3 hrs (4.5 hrs)
3
Patient arrives in Angio Suite
General Anesthesia
Conscious Sedation
Patient Prep
Needle Stick
Caratoid Access Easy
Caratoid Access Difficult
Rapid Flow Restored
Clot Removal

Steps to Improving Door to Needle Time

- EMS Pre-Notification:
- Stroke Tools
- Rapid Triage Protocol
- Single Call Activation System
- Transfer Directly to CT Scanner
- Rapid Acquisition and Interpretation of Imaging
- Rapid Laboratory Testing
- Mix tPA ahead of time
- Rapid Administration of tPA
- Team Based Approach
- Prompt Data Feedback

Results at DRAH



Additional Issues: Imaging

- Do we need the CTA to show LVO?
- NIHSS >12 was used in MR CLEAN.
- Reasonable to not obtain CTA in patient with NIHSS >12, especially at spoke hospital where intervention will be > 1 hr away
- Are there tools to predict who may have an LVO

Additional Issues: Patients Excluded

- Wake up strokes and patients who were not t-PA candidates were not included.
- There may be a role for physiological imaging to drive patient selection

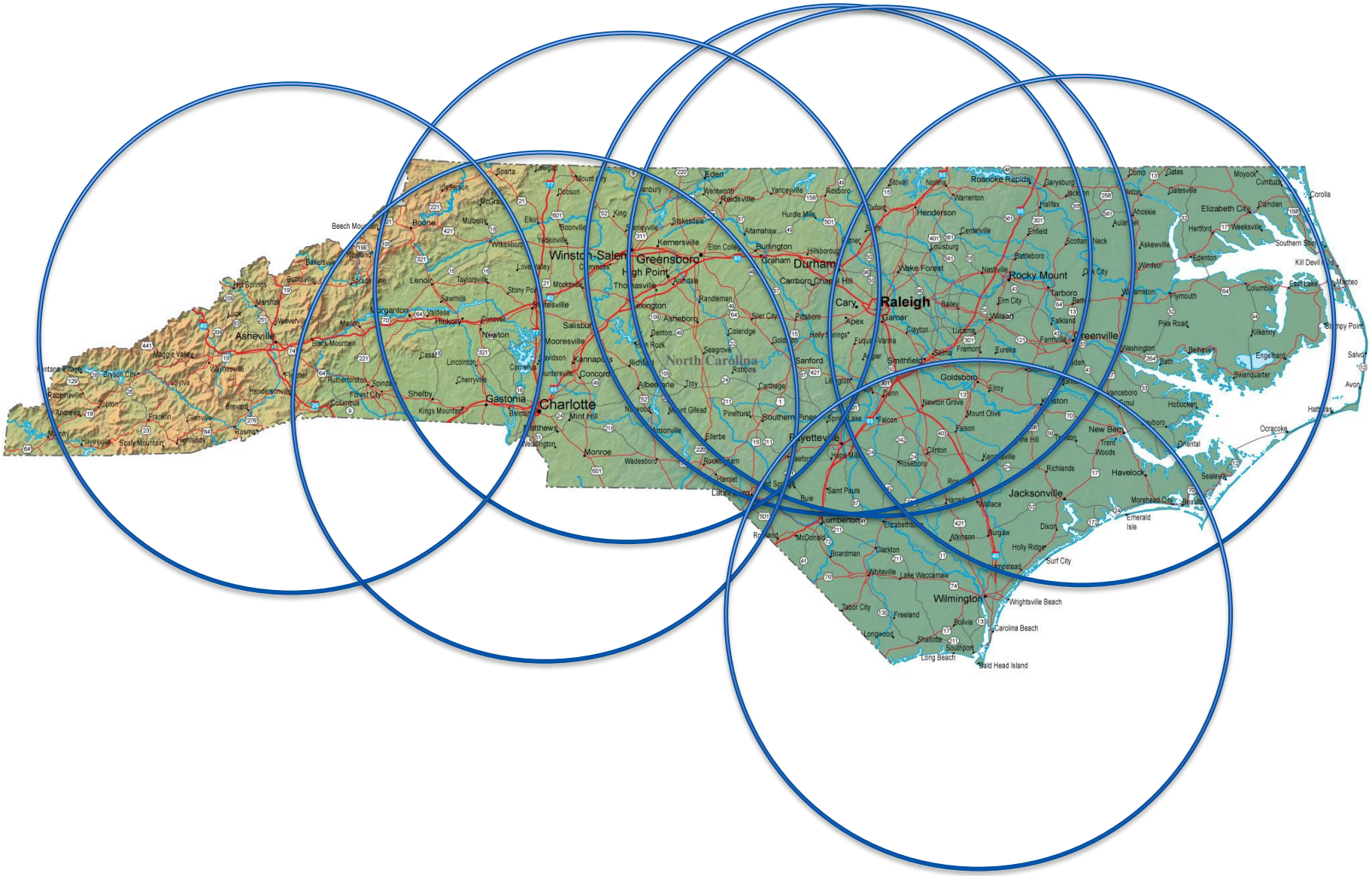
Who Does Not Benefit?

- Patients outside of the 6 hour time window
- Patients with large infarct on initial CT
- Patients with mild symptoms (NIHSS<2)
- Patients with distal occlusion (M2..)
- Patients not treated with stent retrievers (THERAPY)

Numbers Needed to Treat

- Only about 5-10% of all ischemic strokes will be candidates for thrombectomy.
- Excellent outcomes achieved in the 5 studies were in high volume referral centers with carefully selected interventionists, and carefully selected patients.
- In MR CLEAN there was 1 center per million population.

- Of 370,351 AIS primary diagnosis discharges,14,926 (4%) received IV t-PA and 1889 (0.5%) had endovascular therapy
- By ground, 81% had access to IV-capable hospitals within 60 minutes and 56% had access to endovascular-capable hospitals
- By air, 97% had access to IV-capable hospitals within 60 minutes and 85% had access to endovascular hospitals
- More than half of the US population has geographic access to hospitals that actually deliver acute stroke care but treatment rates remain low


Asheville
Charlotte
Gastonia
Winston-Salem
Greensboro
High Point
Durham
Raleigh
Cary
Rocky Mount
Greenville
Fayetteville
Jacksonville
Wilmington
North Carolina

There is more to do

- 29% to 67% of patients had a poor outcome despite this treatment

Questions??