

LERN Stroke Webinar #9

Intra-arterial tPA and Mechanical Thrombectomy

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Disclosures

- Consultant
 - Stryker
- Speaker's bureau
 - Stryker
 - Penumbra Inc.
 - Genentech Inc.

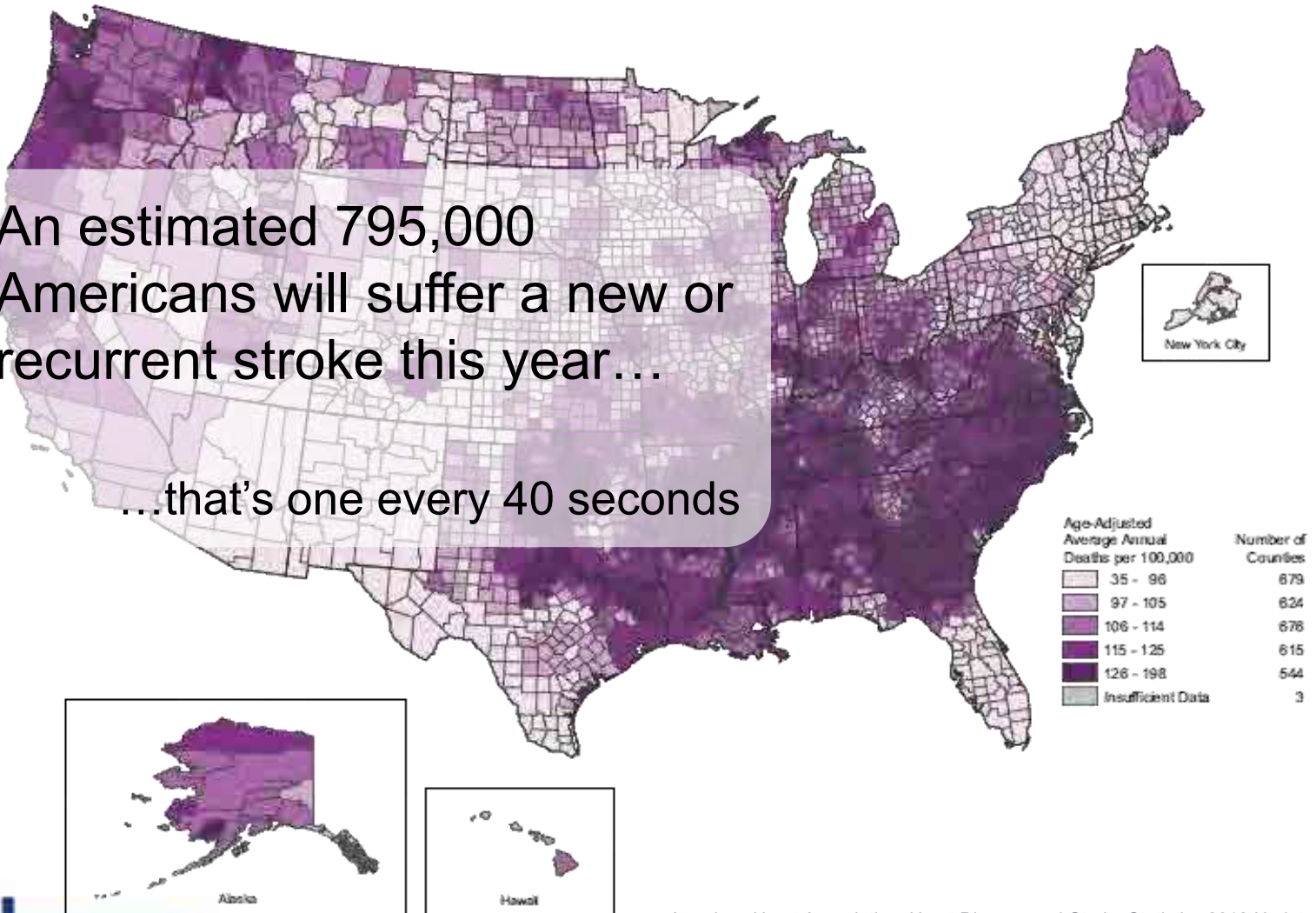
Objectives

- Review acute stroke treatment options including endovascular stroke
- Discuss data supporting endovascular treatment of stroke

Stroke

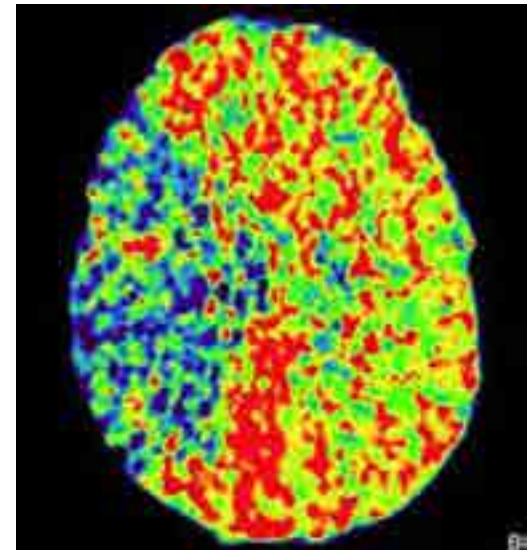
An estimated 795,000
Americans will suffer a new or
recurrent stroke this year...

...that's one every 40 seconds

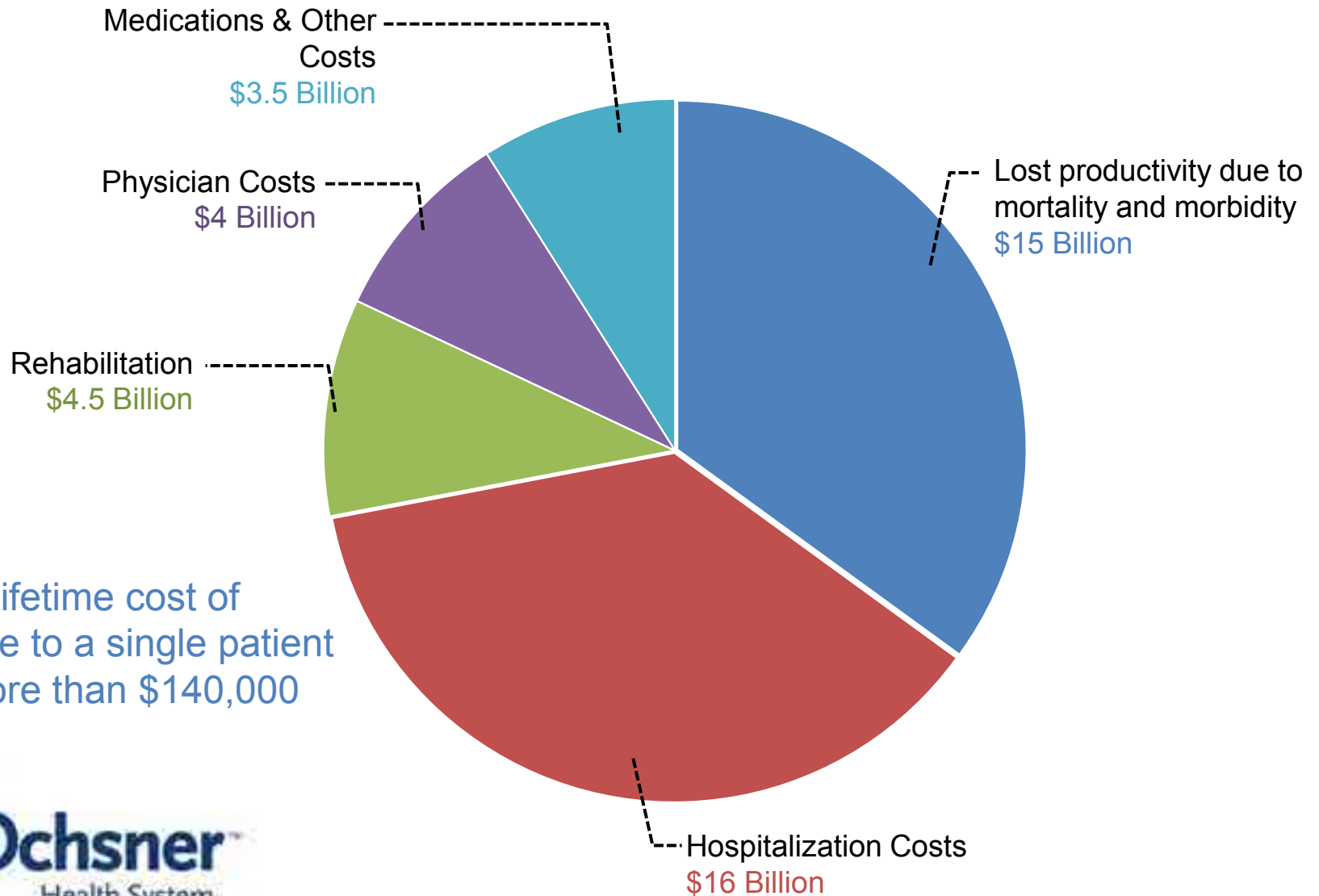


Stroke

- 4th leading cause of death in US
- *#1 cause of adult disability*
- Stroke is a growing global epidemic
 - 1 in 6 people will have a stroke
 - 15 million new strokes each year
 - 6 million deaths
 - *30 million survivors with disabilities*

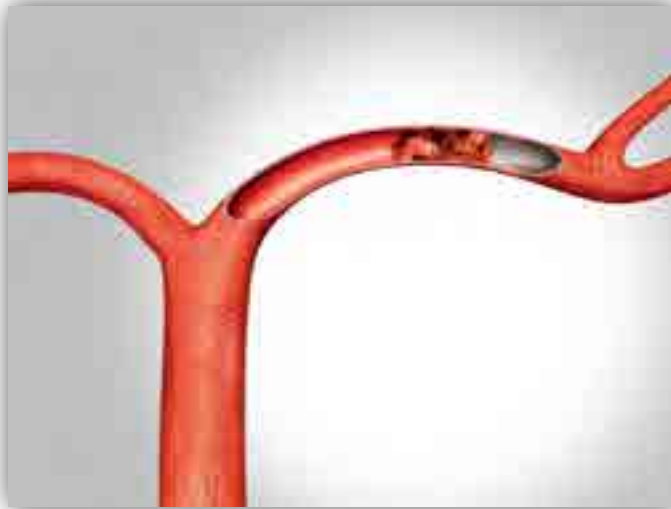


The Total Estimated Cost of Stroke is \$48 Billion



Two Types of Stroke

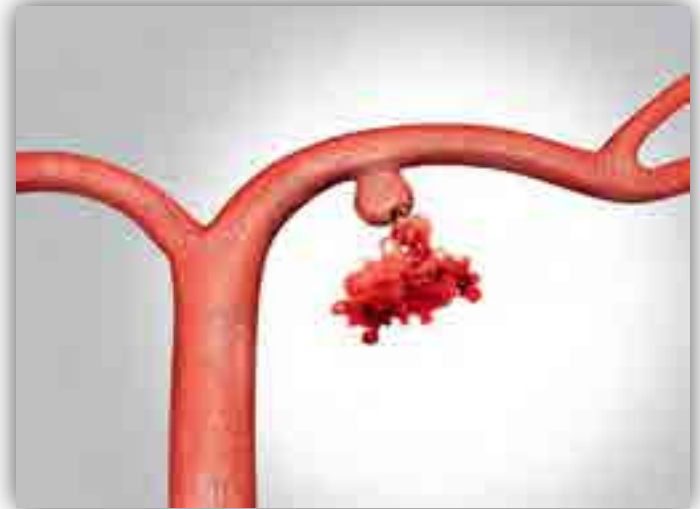
Ischemic Stroke



Ischemic = type of condition in which oxygen is deficient

Often caused by a blood clot or plaque buildup that blocks blood flow

Hemorrhagic Stroke



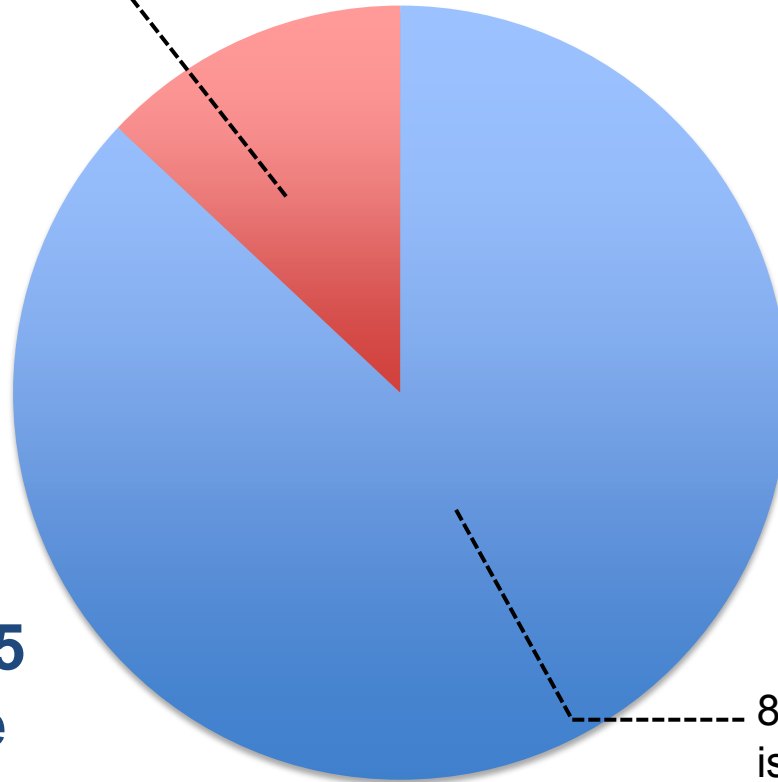
Hemorrhage = bleeding

Occurs when a blood vessel ruptures, causing blood to leak into the surrounding tissue

Two Types of Stroke

13% of strokes are hemorrhagic:

- 10% intracerebral
- 3% subarachnoid



87% of strokes are ischemic; only 1% of these patients get intervention.

4 out of every 5 families will be affected by stroke

35- 40% of Ischemic Strokes are Considered “Large Vessel”

- This subset of ischemic stroke comprises blockages in the:
 - Internal Carotid Artery (ICA)
 - Middle Cerebral Artery (MCA)
 - Vertebral / Basilar Artery
- If left untreated, patient prognosis with these types of stroke is poor

Vessel	Mortality Rate
ICA	53% ¹
MCA	27% ²
Basilar Artery	89-90% ³

Physiological Impact of Stroke

Estimated Pace of Neural Circuitry Lost in a Typical Large Vessel Acute Ischemic Stroke

Time	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
1 second	32,000	230 million	218 yards	8.7 hours
1 minute	1.9 million	14 billion	7.5 miles	3.1 weeks
1 hour	120 million	830 billion	447 miles	3.6 years
Avg. stroke	1.2 billion	8.3 trillion	4470 miles	36 years

Saver, Jeffrey, *Time is Brain – Quantified*. Stroke 2006; 37: 263-266.

Options for Patients Experiencing an Ischemic Stroke

IV tPA

Gold-standard in ischemic stroke care. Drug is designed to break apart the clot.

Bridging Therapy

Endovascular Clot Removal

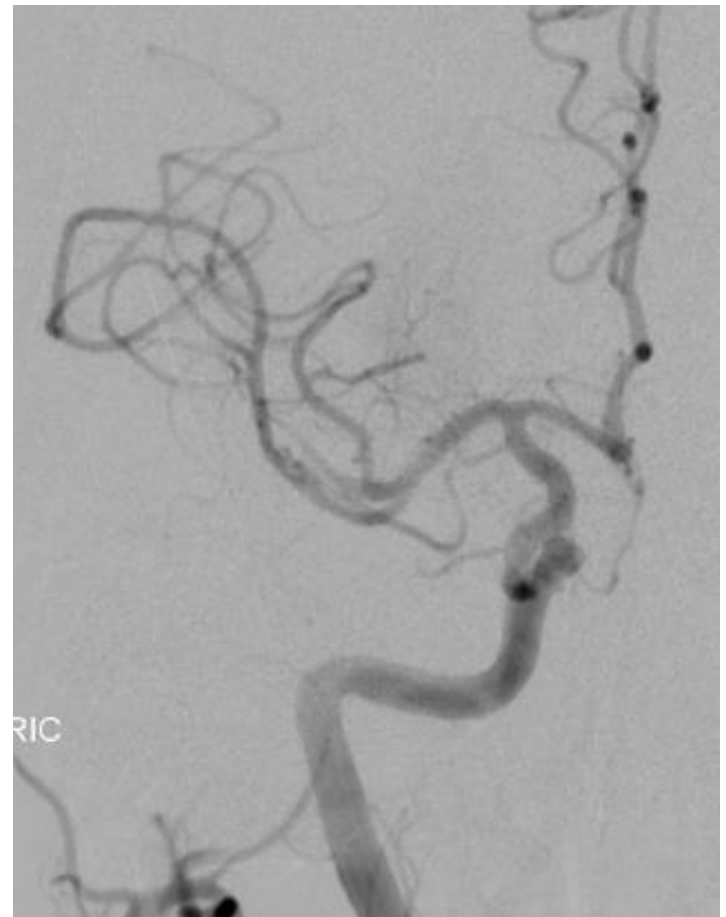
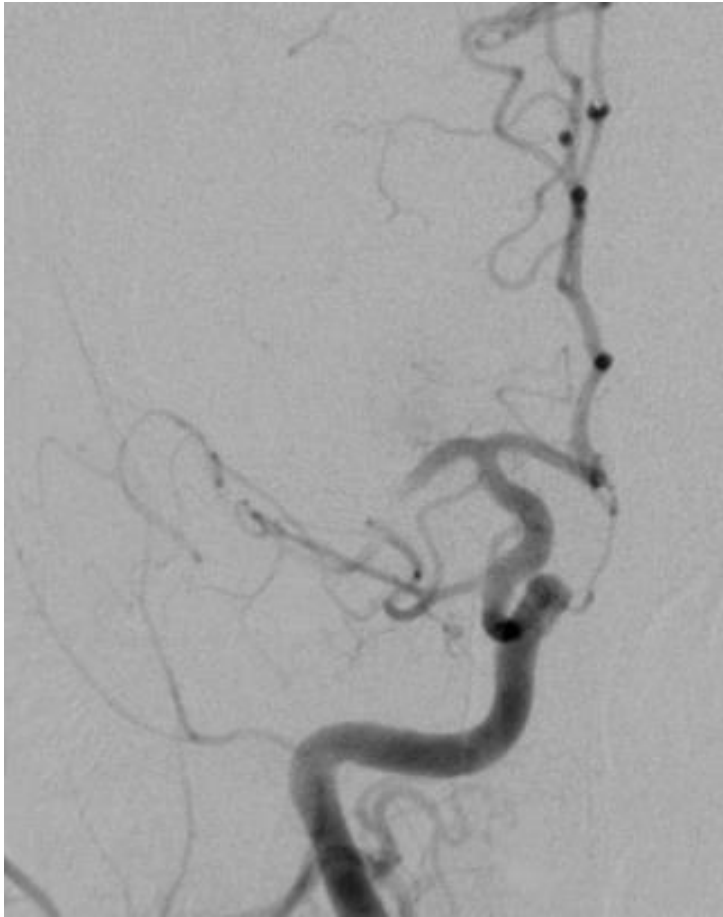
Mechanical disruption or removal of the clot using standard endovascular approaches

Medical Management

Monitor vitals and provide secondary stroke prevention.

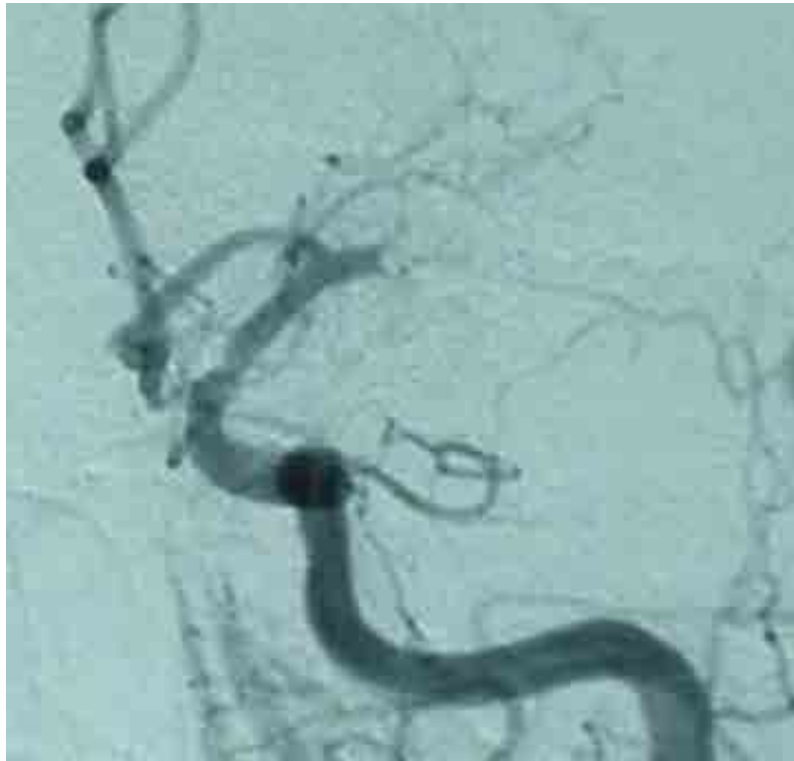


Endovascular Therapy-Idea



Endovascular Therapy-Idea

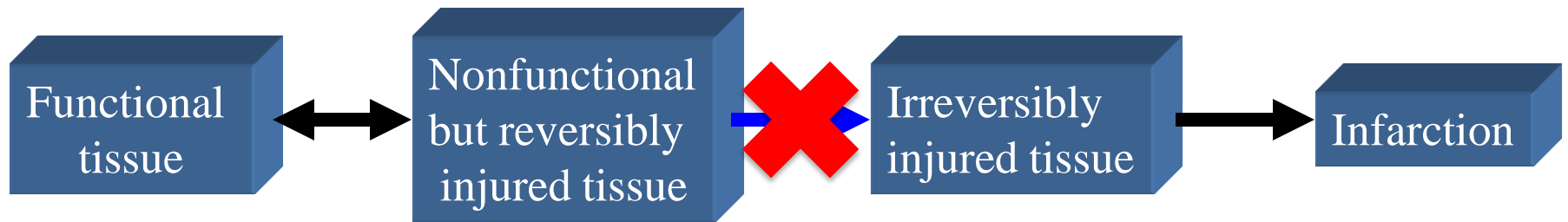
Before



After



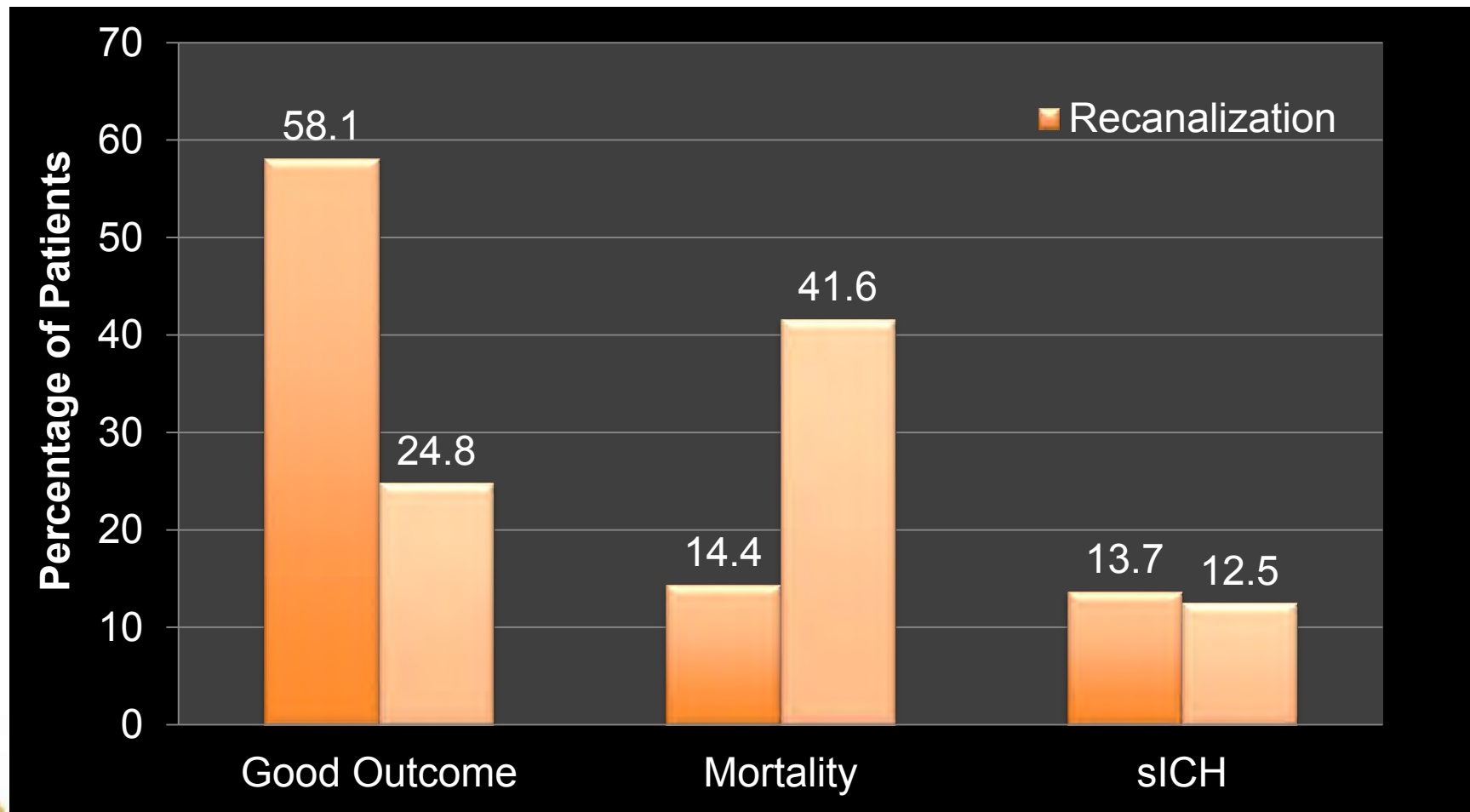
Stroke as a Process



Recanalization helps
FACT

Impact of Recanalization

Review of Published Data



IV thrombolytics is the first line of therapy

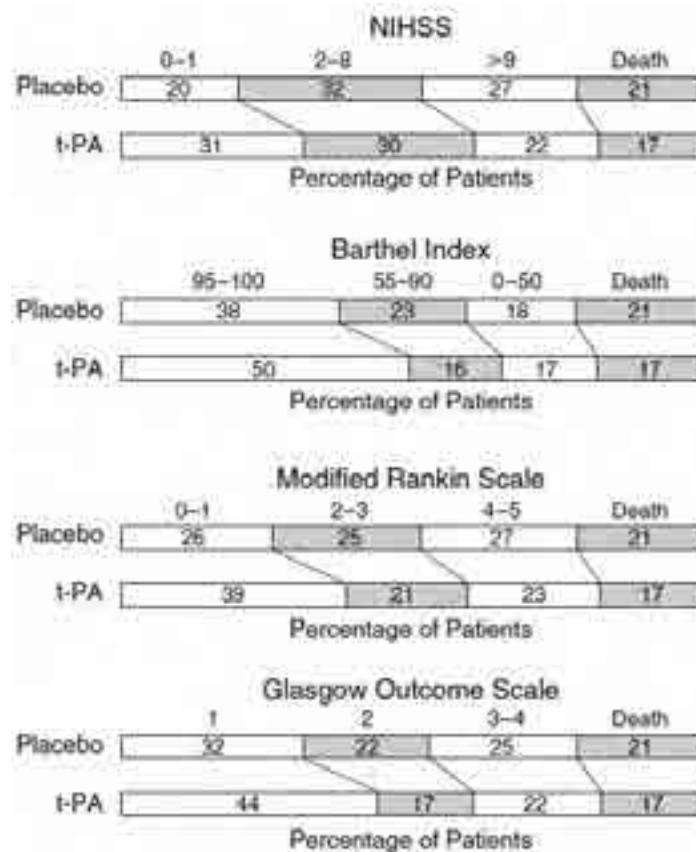
FACT

Acute Treatment

- IV t-PA (Gold Standard)
- Key Clinical Trials
 - 0 to 3 hours (1996)
 - ⦿ NINDS IV t-PA
 - 3 to 4.5 hours (2008)
 - ⦿ ECASS III



NINDS IV t-PA (3 months): 0 to 3 hours



Treatment window

- Treatment within the first 3 hours only
 - IV t-PA
- Treatment within the first 4.5 hours
 - IV t-PA

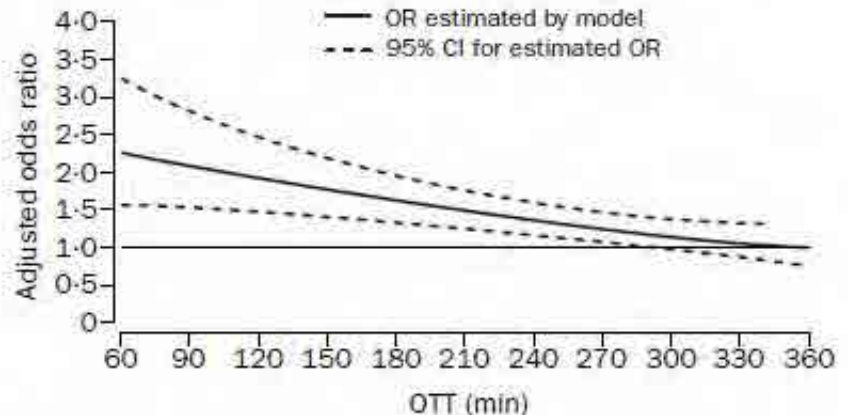
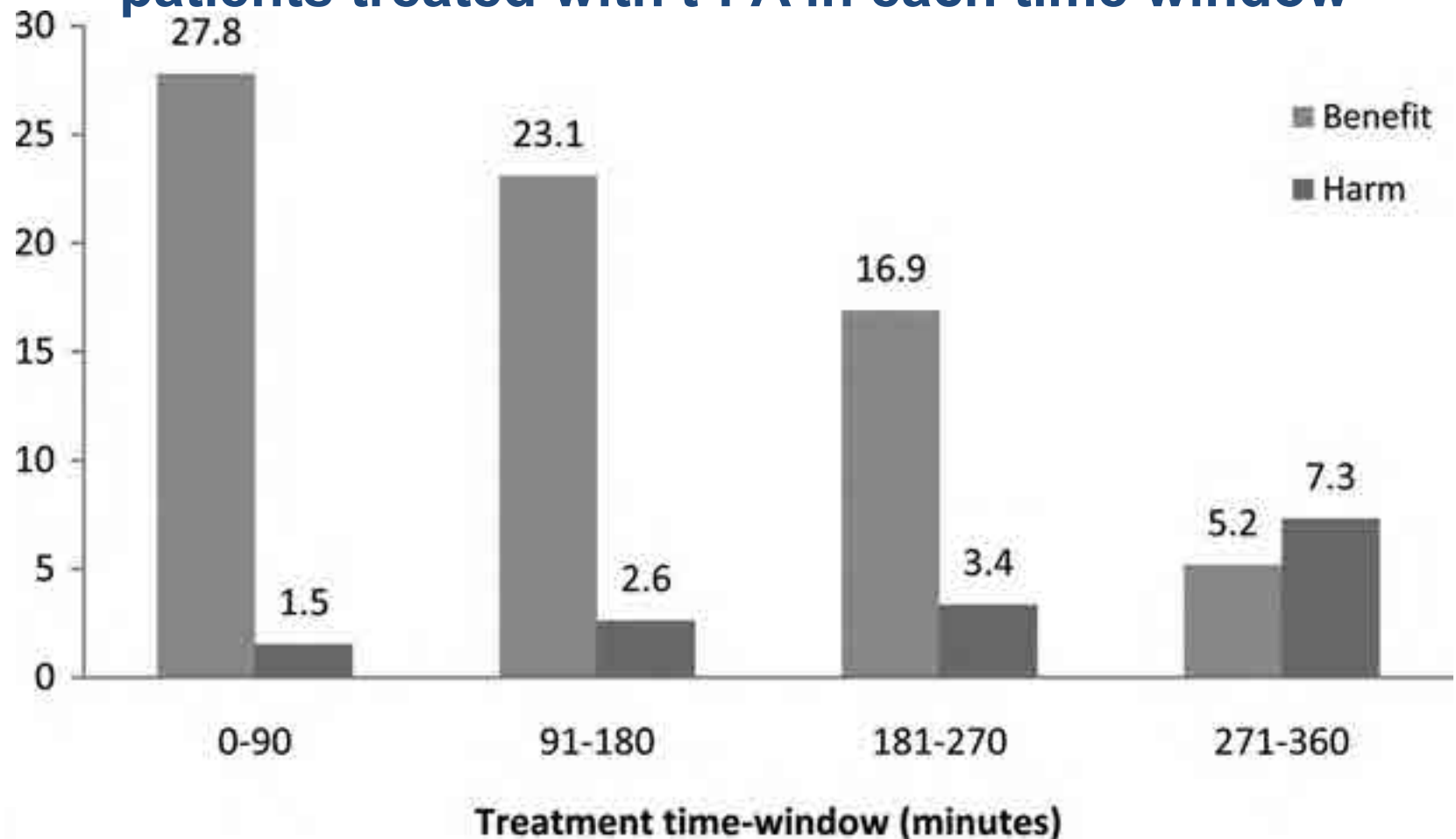


Figure 3: Model estimating odds ratio for favourable outcome at 3 months in rt-PA-treated patients compared with controls by OTT

Adjusted for age, baseline glucose concentration, baseline NIHSS measurement, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIHSS measurement.

Number of patients who benefit and are harmed per 100 patients treated with t-PA in each time window



Limitations of t-PA

- Time dependent
 - Reduced benefit with increased time
- Not effective for large thrombus
- Risk for systemic hemorrhage

**Proximal vessel occlusions do not
respond well to IV lytics**

FACTS

Proximal Vessel Occlusion

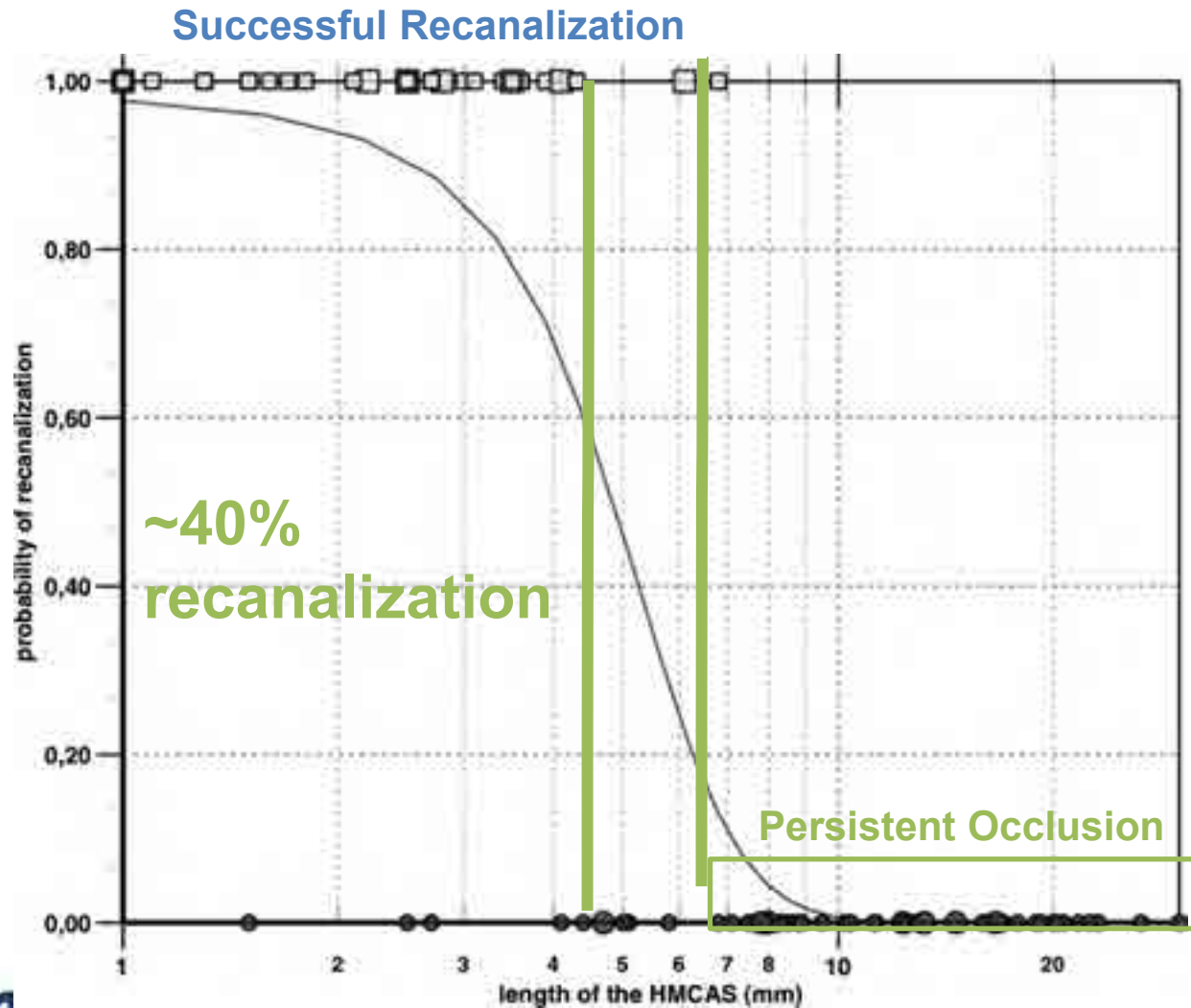
Table 2. Baseline Occlusions and Proportional Recanalization

Occlusion Location	Recanalization (All)	Recanalization After IV rt-PA	Recanalization After Endovascular Treatment	No Recanalization
M1-MCA	75.4% (49)	32.3% (21)	43.1% (28)	24.6% (16)
ICA terminus (T, L) occlusion	43.5% (10)	4.4% (1)	39.1% (9)	56.5% (13)
M2-MCA	92.3% (12)	30.8% (4)	61.5% (8)	7.7% (1)
BA	56.0% (14)	4.0% (1)	52.0% (13)	44.0% (11)
All	67.7% (86)	21.3% (27)	46.5% (59)	32.3% (41)

BA indicates basilar artery; ICA, internal carotid artery; IV, intravenous; MCA, middle cerebral artery; rt-PA, recombinant tissue plasminogen activator.

127 patients evaluated w IV tPA

Impact of Clot Burden on Success Rate of IV tPA



What is TICI Score?

0: No perfusion

1: Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion

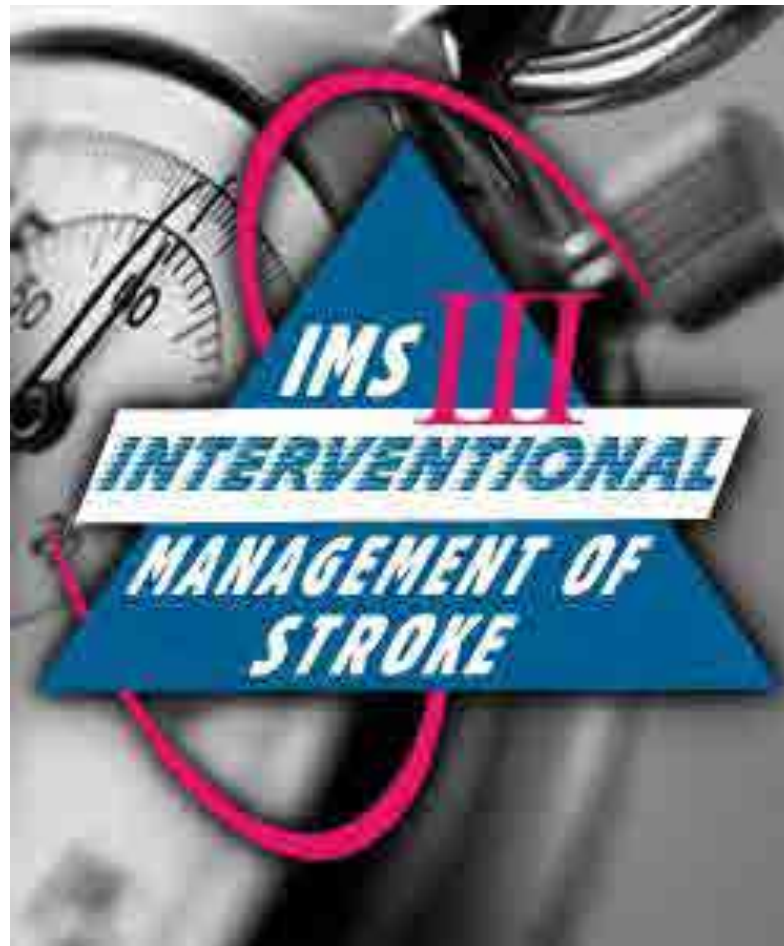
2a: Perfusion of less than half of the vascular distribution of the occluded artery

2b: Perfusion of half or greater of the vascular distribution of the occluded artery

3: Full perfusion with filling of all distal branches

- Successful recanalization is considered by most to be TICI 2b or TICI 3

CLINICAL TRIALS



IMS III Trial Design

- Patients must have moderate to severe neurologic deficits
 - NIHSS ≥ 10
- Patients who received IV tPA within 3 hours of symptoms onset were randomized 2:1
 - IV tPA alone
 - IV tPA plus IA therapy
- Primary outcome: mRS ≤ 2 @ 90 days

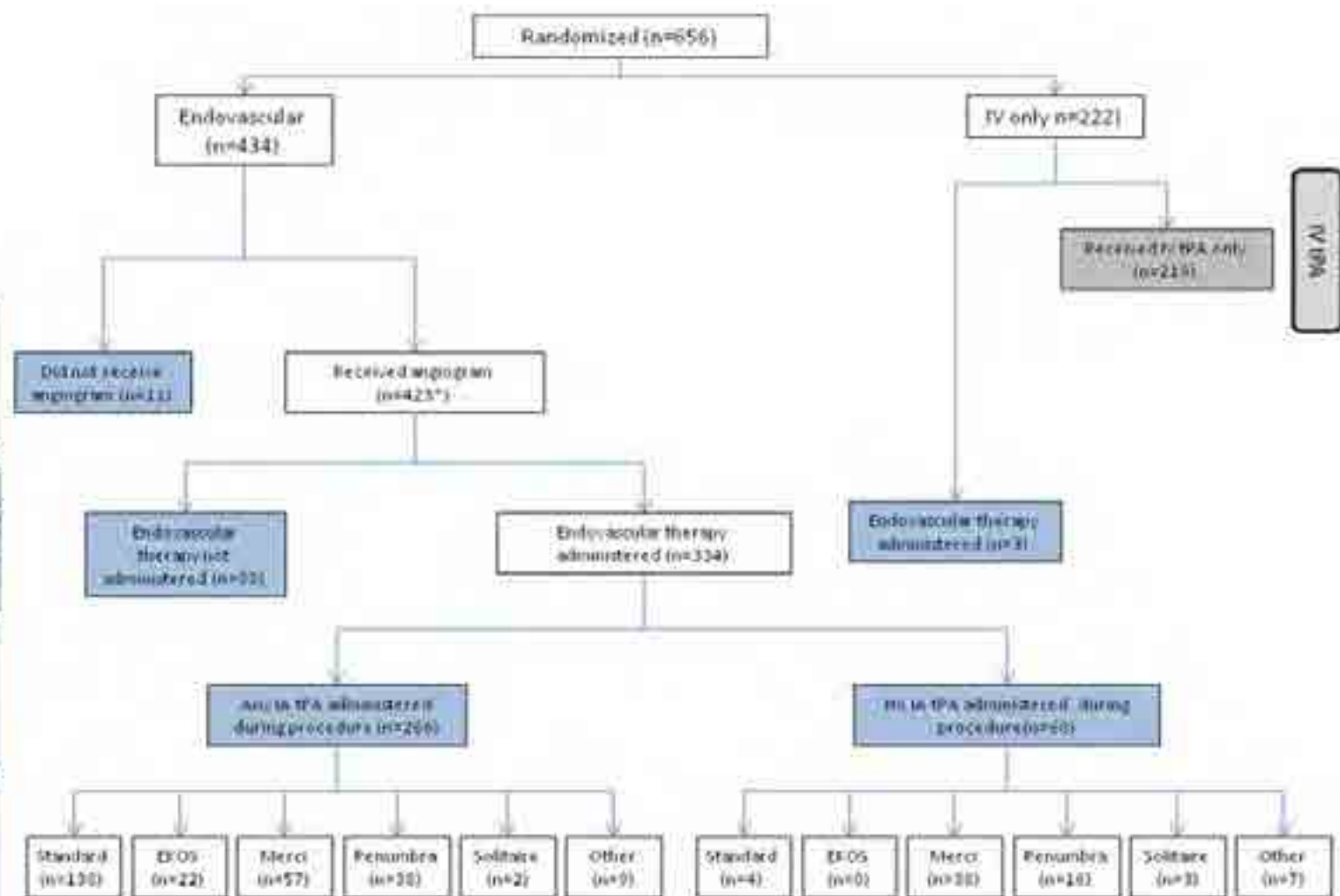
IMS III: Primary Outcome

- mRS ≤ 2
 - 40.8 % with endovascular therapy
 - 38.7 % with IV tPA alone
 - ⊙ 95% CI: -6.1% to +9.1%

IMS III: Conclusions

- No significant difference in functional independence with endovascular therapy after intravenous t-PA, as compared with intravenous t-PA alone
- No difference in safety

IMS III: Patient Tracking



IMS III: Patient Tracking

- 434 randomized to IA/IV
 - 11 did not get an angiogram
 - 89 did not get endovascular therapy
- 23.0% of patients in “IA arm” did not get ANY IA therapy

IMS III: EVT Rates

- 49% of patients in EVT arm (164/334) were treated with IA tPA +/- ECHOS catheter
 - Not current standard
- 28% of patients (95/334) were treated with MERCI
 - Not current standard
- 77% of patients were treated with obsolete tools!!!!

Need for Quality Revascularization



Revascularization Predicts Good Outcome For ICA, M1 Occlusion

	TICI=0	TICI=1	TICI=2a	TICI=2b	TICI=3	
	n= 32	n= 16	n= 67	n= 80	n= 5	
% 90 Day mRS 0-2	3.1%	12.5%	19.4%	46.3%	80%	
	6.3%		35.5%			p < .0001
	13.9%			48.2%		p < .0001

Need for Speed – TIME MATTERS

Final Multivariable Model

Risk Ratios

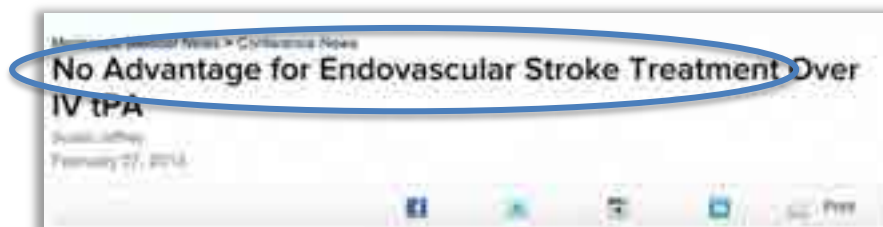
	Risk Ratio	95% CI	p-value
Time to Reperfusion (every 30 minutes)	0.90	0.82-0.99	0.02

Every 30 minute delay in reperfusion is associated with a 10% relative reduction in probability of good clinical outcome (mRS 0-2).

IMS III: Conclusions

- Basic CT alone is insufficient for selection of patients for IA therapy in most cases
- Interventional techniques yielding a low rate of TICI 2b and 3 flow do not improve outcomes in patients w stroke
 - IA tPA alone
 - MERCI
- Recanalization helps
- Time is brain

News Cycle 2/2013



Need for Quality Revascularization



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Recent Stroke Trials

- MR CLEAN
- ESCAPE
- EXTEND-IA
- SWIFT PRIME



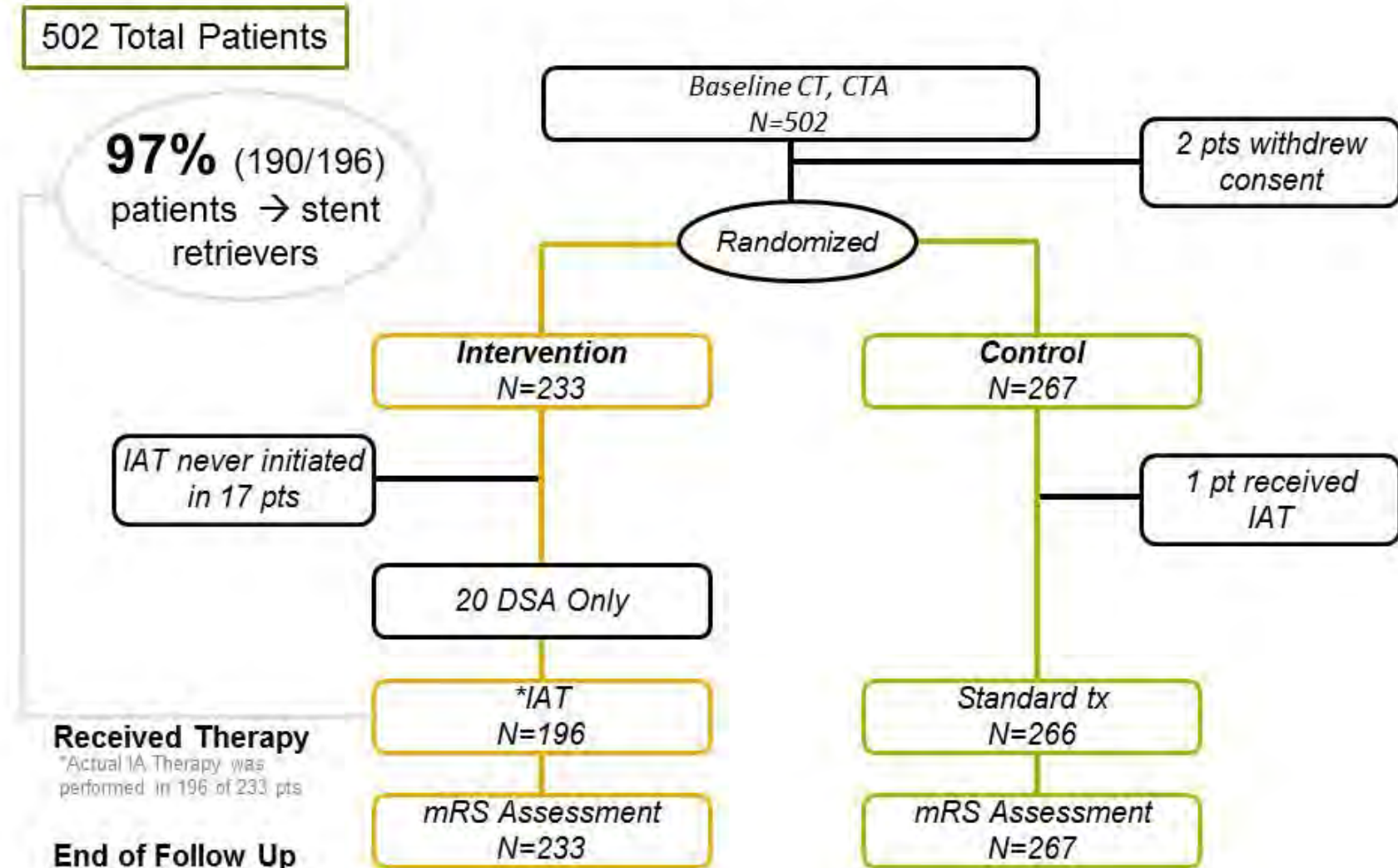
MR CLEAN

Results of the Multicenter
Randomized Clinical trial of
Endovascular Treatment of Acute
Ischemic Stroke in the Netherlands

Design

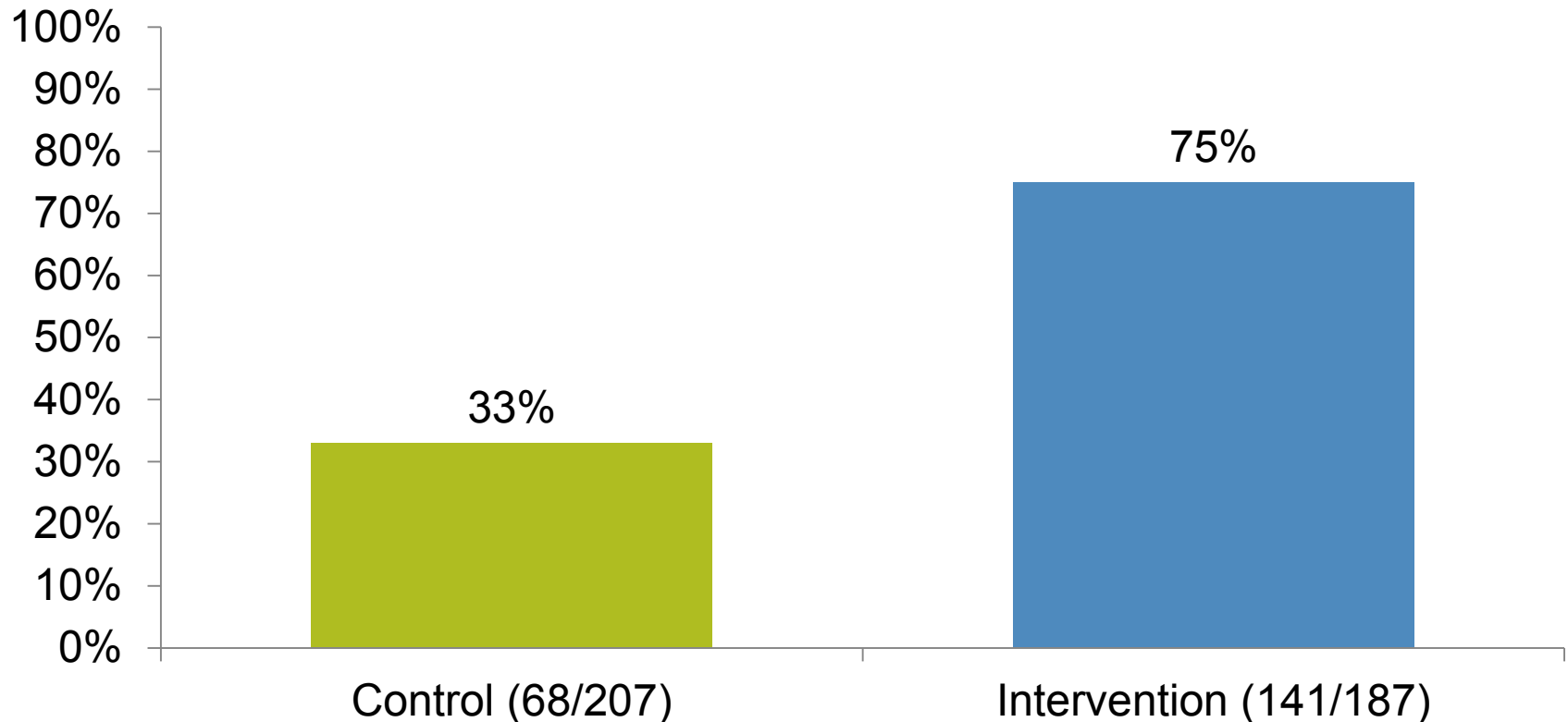
- **502 patient**, multicenter (16 Centers in Netherlands), prospective, **randomized trial**, open label treatment and:
 - Blinded assessment of functional outcome at 90 days
 - Blinded assessment of neuro-imaging at baseline and follow-up
- Masked, web-based, 1:1 random treatment allocation
 - Endovascular vs medical management
- Inclusion Criteria
 - Acute ischemic stroke, Age ≥ 18 , NIHSS ≥ 2
 - **Intracranial anterior circulation occlusion (confirmed by CTA)**
 - Initiation of IA treatment within 6 hours from onset

Patients were Randomized 1:1



7x Higher Odds of Recanalizing with Intra-Arterial Treatment*

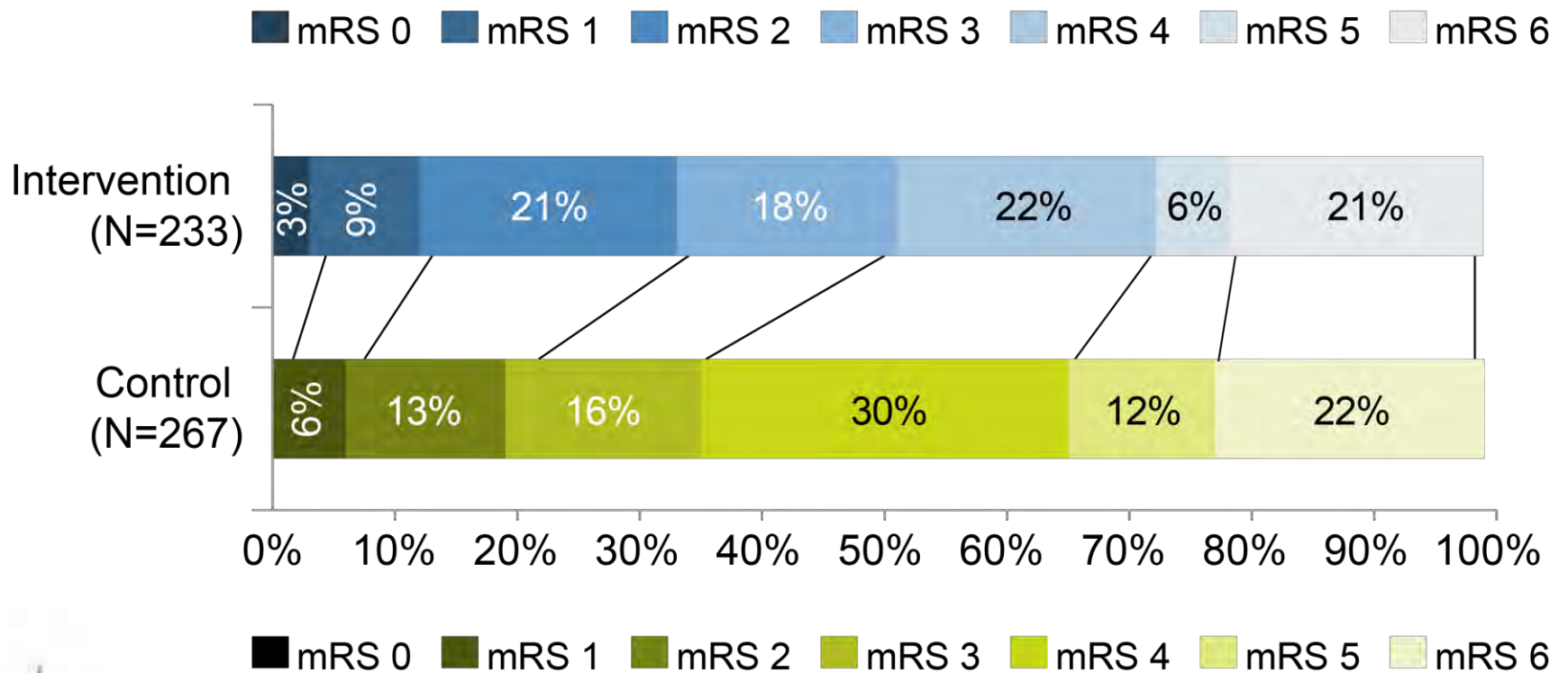
Recanalization on CTA after 24 Hours



*Adjusted value odds ratio (95% CI) for "no intracranial occlusion on follow up CT angiography" in the intervention group versus the control group was 6.88 (4.34 to 10.94). Values were adjusted for age, NIHSS at baseline, time from onset to randomization, status with respect to previous stroke, atrial fibrillation, diabetes mellitus and occlusion of the ICAT. Data for follow up CT angiography were not available for 106 patients.

Effect of Intervention on Primary Outcome

Common adjusted odds ratio: 1.67 (95% CI: 1.21 to 2.30)



No Significant Between-Group Difference in the Occurrence of Serious Adverse Events at 90 days (P=0.31)

Serious Adverse Events	Intervention (N=233)	Control (N=267)
Any serious adverse event	110 (47.2%)	113 (42.3%)
Parenchymal hematoma type 2	14 (6.0%)	14 (5.2%)
New ischemic stroke in different vascular territory*	13 (5.6%)	1 (0.4%)
Pneumonia	25 (10.7%)	41 (15.4%)
Hemicraniectomy	14 (6.0%)	13 (4.9%)
Death		
Within 7 days	27 (11.6%)	33 (12.4%)
Within 30 days	44 (18.9%)	49 (18.4%)

MR CLEAN Study Conclusions

- In patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation, **intra-arterial treatment** administered within 6 hours after stroke onset **was effective and safe**
- This **treatment leads to** a clinically significant increase in the **functional independence** in daily life by 3 months, without an increase in mortality

ESCAPE

Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times

M Goyal et. al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. *NEJM* published on February 11, 2015

Purpose and Methods

Purpose: To answer the question “Do I take this patient for endovascular thrombectomy?”

Methods:

- 316 patients
- 22 centers in Canada, US, Korea, UK and Ireland
- Randomized, open-label with blinded outcome evaluation, parallel group trial
 - *Intervention*: Endovascular mechanical thrombolysis with an approved approach/device (use of retrievable stents and balloon guide catheters recommended)
 - *Control*: Guideline-based standard of care (IV tPA if <4.5 hrs / stroke unit care)
- Enter consecutive ESCAPE-eligible patients – no “cherry-picking”
- 25 cases sequentially per site
- Choose “small core / proximal occlusion / good collaterals” patients
- Be fast, efficient and safe

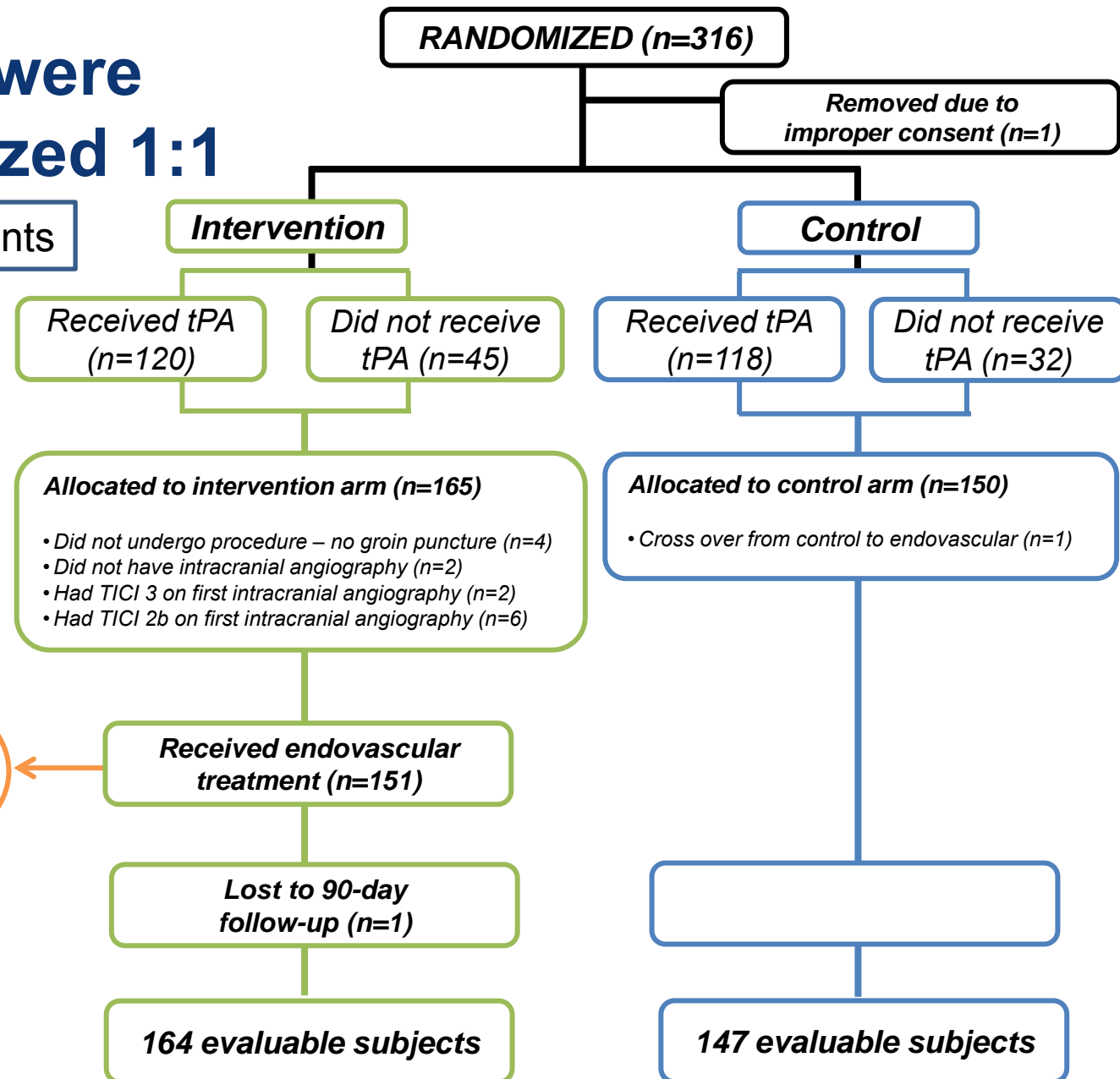
Inclusion Criteria

- Acute ischemic stroke
- Age ≥ 18 years
- **Last-seen-well time to randomization < 12 hours**
- **ASPECTS > 5**
- Baseline NIHSS > 5 at time of randomization
- Good functional status: pre-stroke modified Barthel Index ≥ 95 , not living in a nursing home; fully independent
- Confirmed symptomatic intracranial occlusion based on CTA in anterior anatomy (Carotid T/L, M1, 2 or more M2's not including the anterior temporal artery)
- Moderate to good collaterals on CTA
- Endovascular treatment can be initiated within 60 minutes of baseline NCCT with target CT to first recanalization of 90 minutes

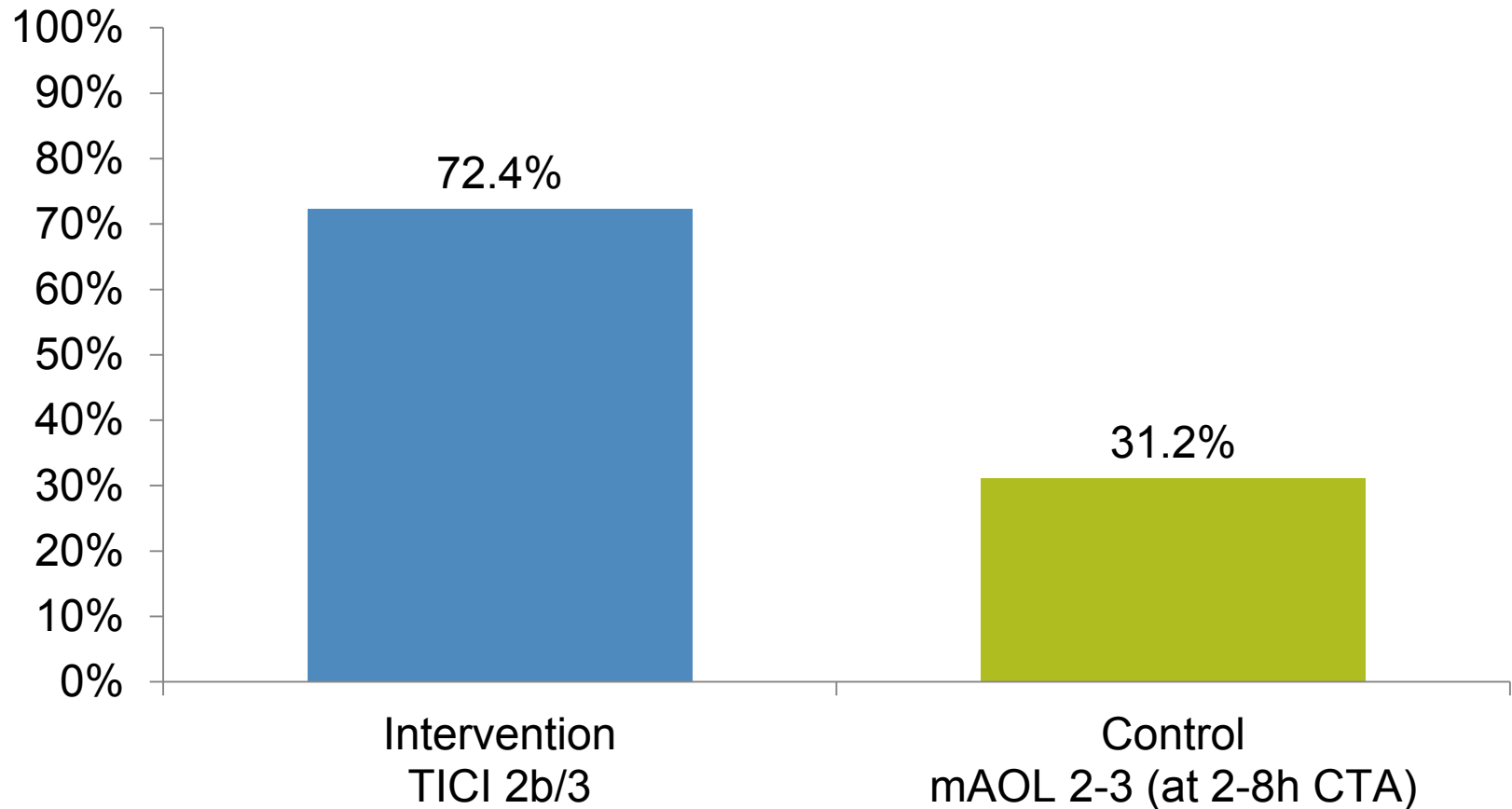
Patients were Randomized 1:1

316 Total Patients

86% (130/151) →
stent retrievers

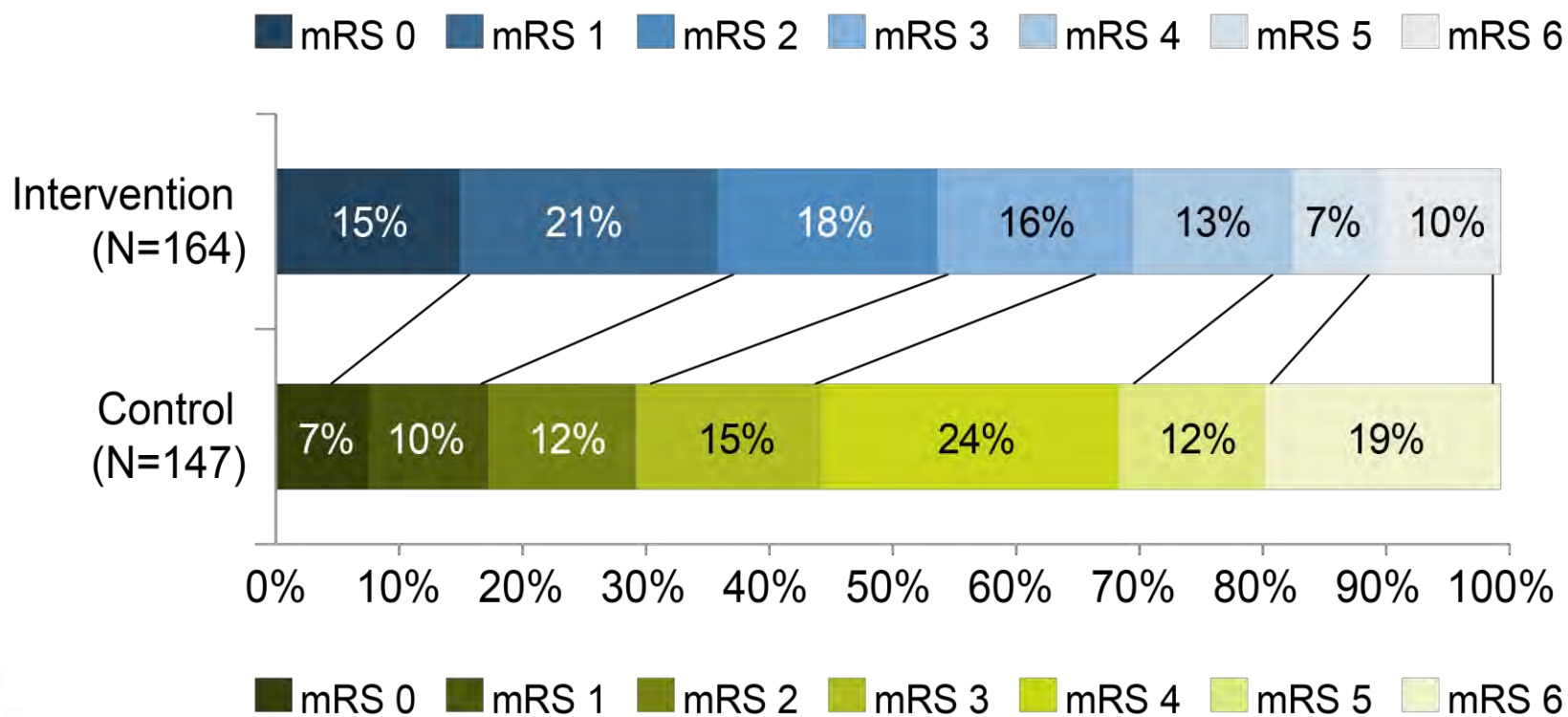


Revascularization



90-day mRS

Common adjusted odds ratio: 3.1 (95% CI: 2.0 to 4.7)



Safety Endpoints/Mortality

Serious Adverse Events	Intervention (N=165)	Control (N=150)	Adjusted RR (CI 95%)
Death	10.4%	19.0%	0.5 (0.3 to 0.8)
Large MCA / malignant MCA stroke	4.8%	10.7%	0.3 (0.1 to 0.7)
sICH (clinically determined at site)	3.6%	2.7%	1.2 (0.3 to 4.6)
Access site hematoma	1.8%	0%	
MCA perforation	0.6%	0%	

Conclusions

- Endovascular thrombectomy is a safe, highly effective procedure that saves lives and dramatically reduces disability WHEN:
 - Patients are carefully selected by imaging to identify proximal occlusions and exclude large core and exclude patients with absent collaterals
 - Treatment is extremely fast with target first slice
 - ⊙ Imaging to groin puncture <60 minutes
 - ⊙ Imaging to reperfusion <90 minutes
 - Safe effective technology (retrievable stents) is used

SWIFT PRIME

Solitaire FR with the intention for Thrombectomy as
PRIMary Endovascular treatment for acute ischemic
stroke

Results of the SWIFT PRIME Trial were presented by Dr. Jeffrey Saver and Dr. Michael D. Hill at the International Stroke Conference in Nashville, TN on Wednesday, February 11, 2015.



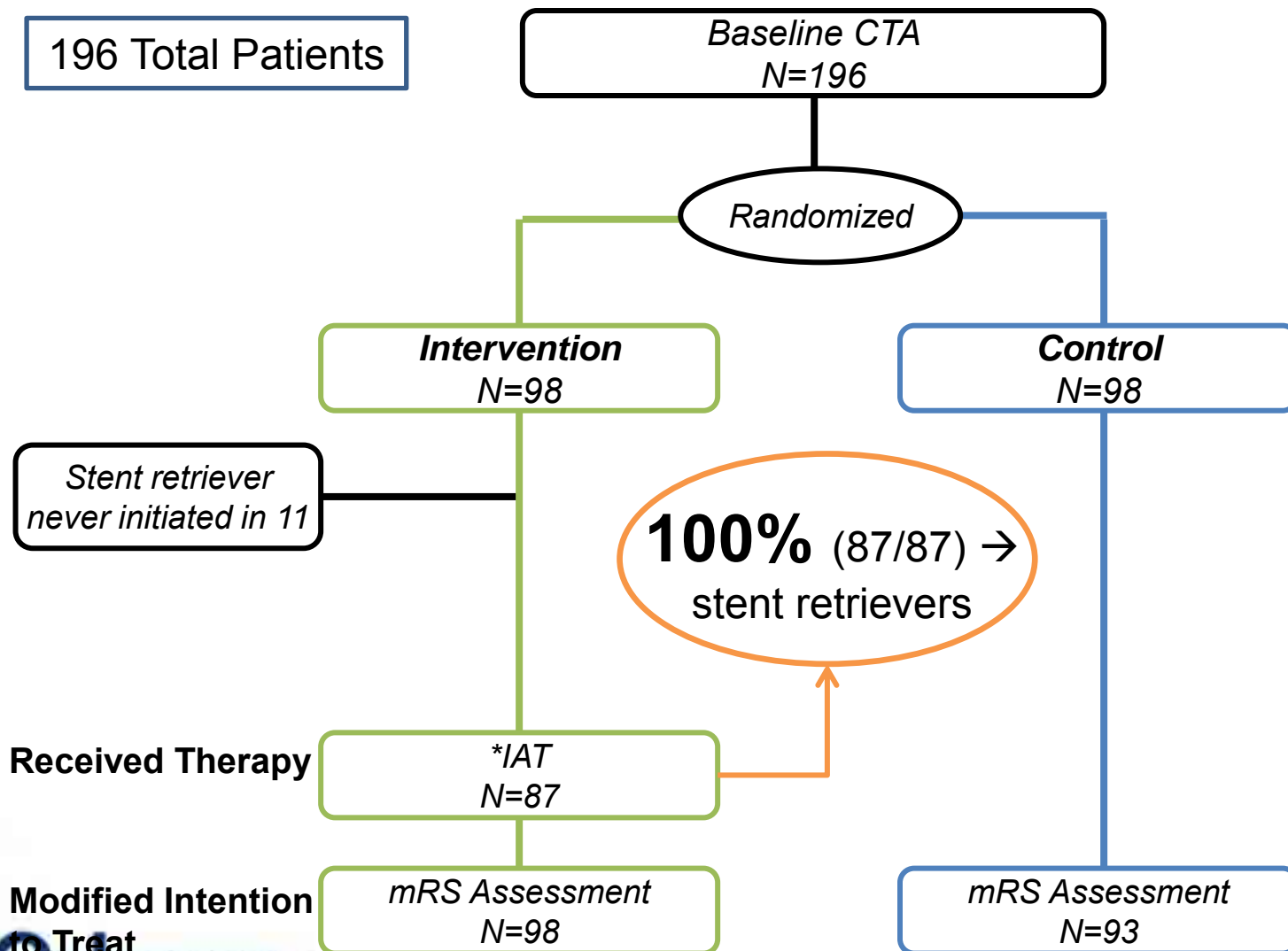
Purpose and Methods

- Purpose:
 - To determine if patients experiencing an Acute Ischemic Stroke due to large vessel occlusion, treated with combined IV tPA and Solitaire FR within 6 hours of symptom onset have less stroke-related disability than those patients treated with IV tPA alone.
- Methods:
 - Randomized, open-label with blinded outcome evaluation, parallel group trial
 - ⊙ *Intervention:* IV tPA with Solitaire FR Device
 - ⊙ *Control:* IV tPA alone
 - 39 enrolling sites in the USA and Europe
 - 196 patients

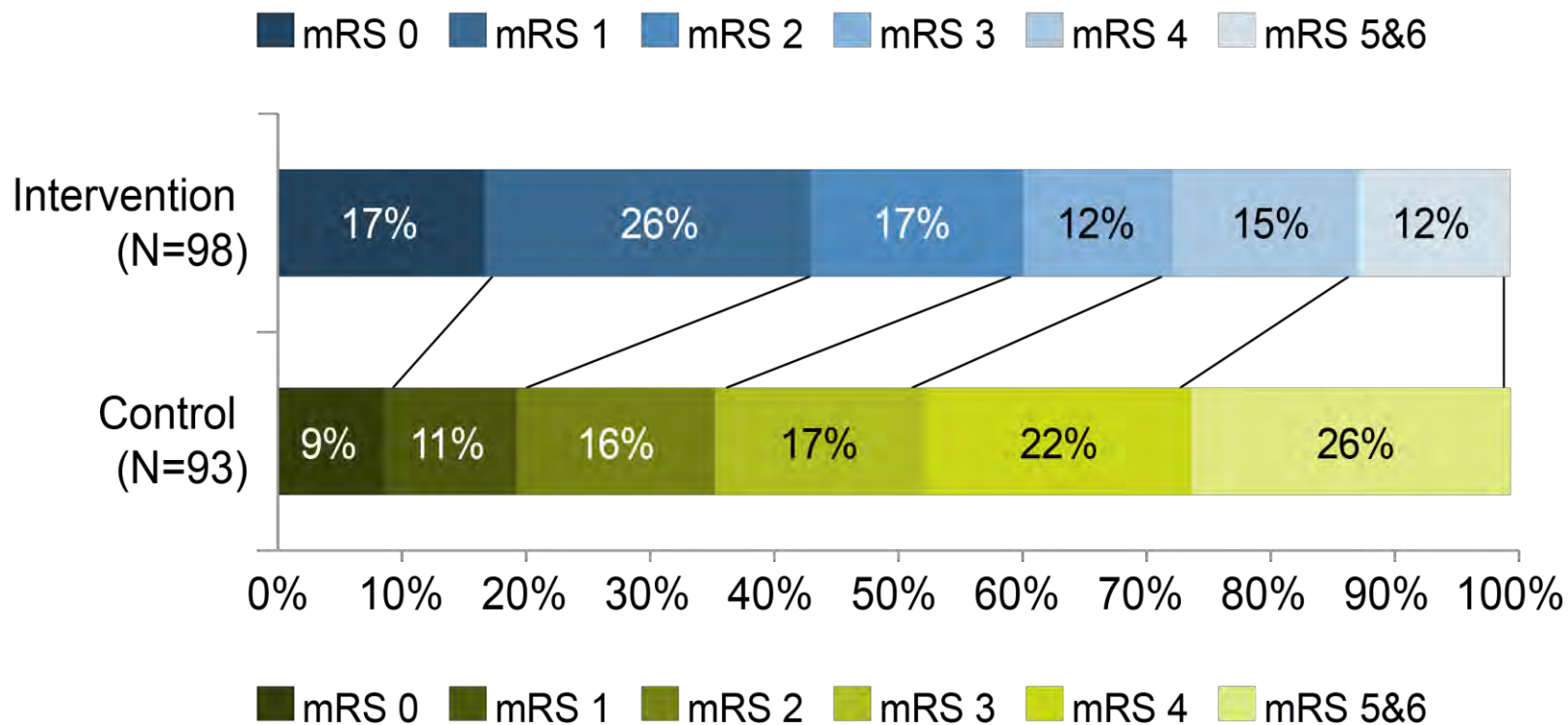
Inclusion Criteria

- Acute ischemic stroke
- Age 18-80
- Pre-stroke mRS \leq 1
- **ASPECTS \geq 6**
- Baseline NIHSS 8-29 at time of randomization
- CTA or MRA confirmation of large vessel occlusion in ICA, M1 segment of MCA or carotid terminus
- **Initiation of IV tPA within 4.5 hours of onset of stroke**
- Endovascular treatment can be initiated within 6 hours of onset of stroke symptoms and within 90 minutes from CTA/MRA to groin puncture

Patients/Randomization



90-day mRS



Safety Endpoints/Mortality

Serious Adverse Events	Intervention (N=98)	Control (N=97)	OR (CI 95%)
Death (p=0.50)	9.2	12.4	0.72 (0.29 to 1.79)
Any serious adverse events	35.7%	30.9%	1.24 (0.68 to 2.25)
sICH at 27 hours	1%	3.1%	0.32 (0.03 to 3.16)

Conclusions

- In AIS patients with confirmed large vessel anterior circulation occlusions treated with IV tPA, rapid treatment with the Solitaire stent retriever lessens post-stroke disability over the entire outcome range and increases the proportion of patients who are alive and independent 3 months after stroke
- **For every two and a half patients treated, one more patient has a better disability outcome**
- **For every four patients treated, one more patient is independent at long term follow up**

EXTEND-IA

A randomized controlled trial of endovascular thrombectomy after standard dose intravenous tPA within 4.5 hours of stroke onset utilizing dual target imaging selection

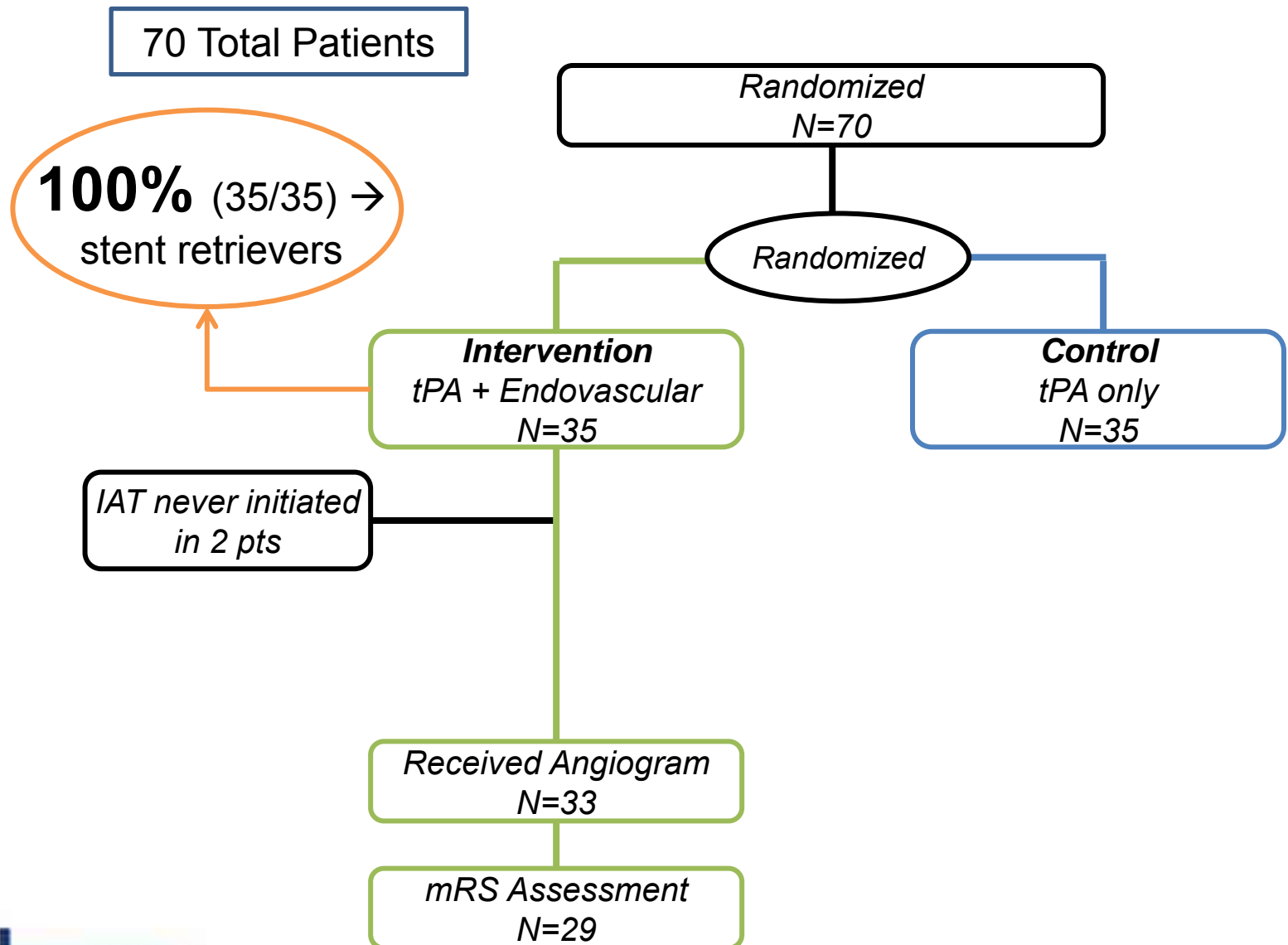
Rationale and Methods

- **Purpose:** To select patients with the best chance of benefit from reperfusion (“Dual Target”)
 - ⊙ Proven major vessel occlusion **AND**
 - ⊙ Salvageable tissue with ischemic core <70mL (CT perfusion)
 - Treat as fast as possible (no waiting to assess IV tPA “failure”)
- **Methods:**
 - Randomized, open-label with blinded endpoint (PROBE) design
 - ⊙ *Intervention:* endovascular treatment + IV tPA
 - ⊙ *Control:* IV tPA
 - 70 patients

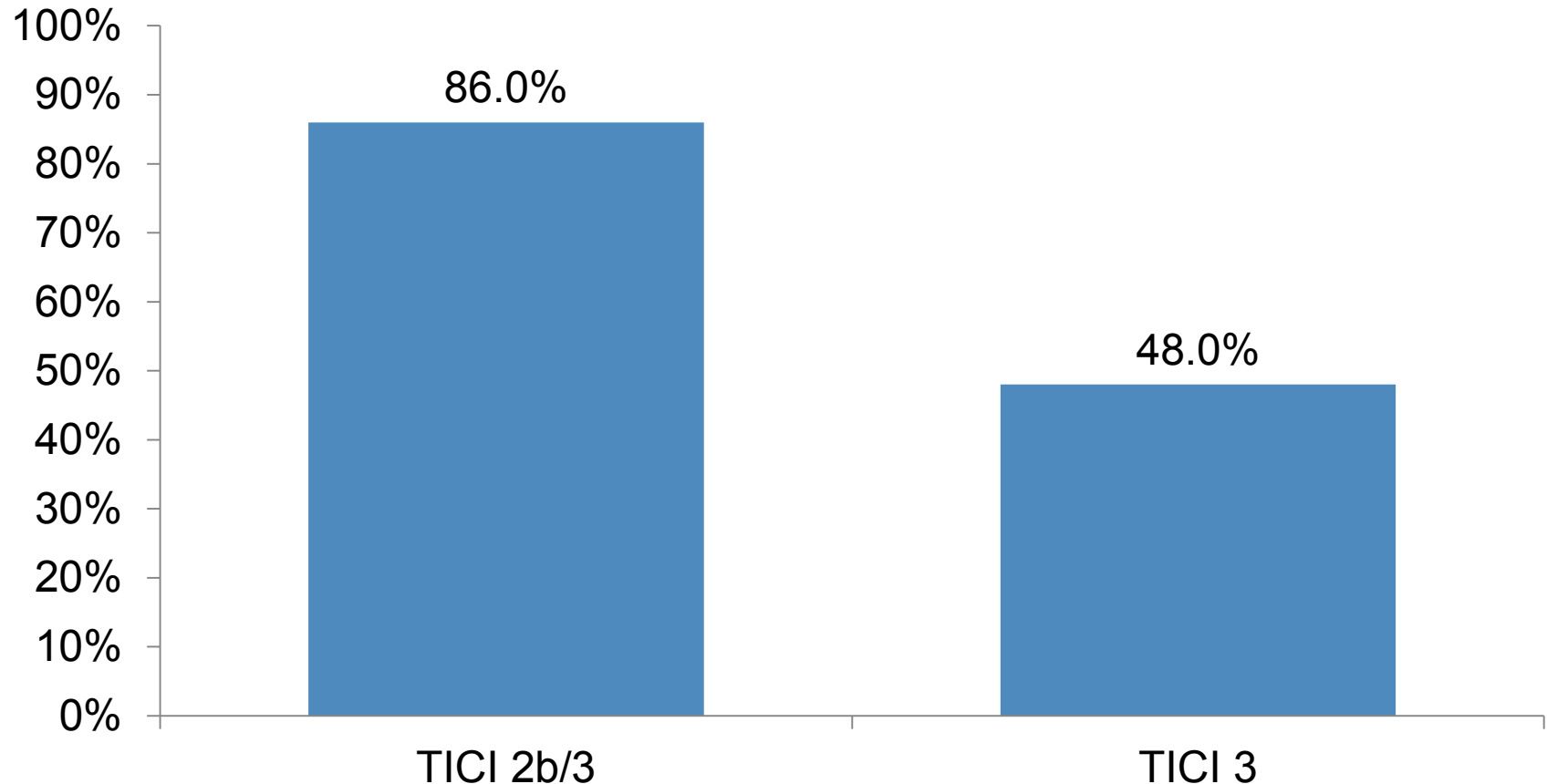
Inclusion Criteria

- Acute ischemic stroke
- Age ≥ 18 years
- Pre-stroke mRS 0-1
- Intra-arterial clot retrieval treatment can commence (groin puncture) within 6 hours of stroke onset.
- **Imaging inclusion criteria. Dual target:**
 - CTA reveals large artery occlusion in anterior anatomy (ICA, M1 or M2) **AND**
 - Mismatch - Using CT or MRI with a Tmax >6 second delay perfusion volume and either CT-rCBF or DWI infarct core volume

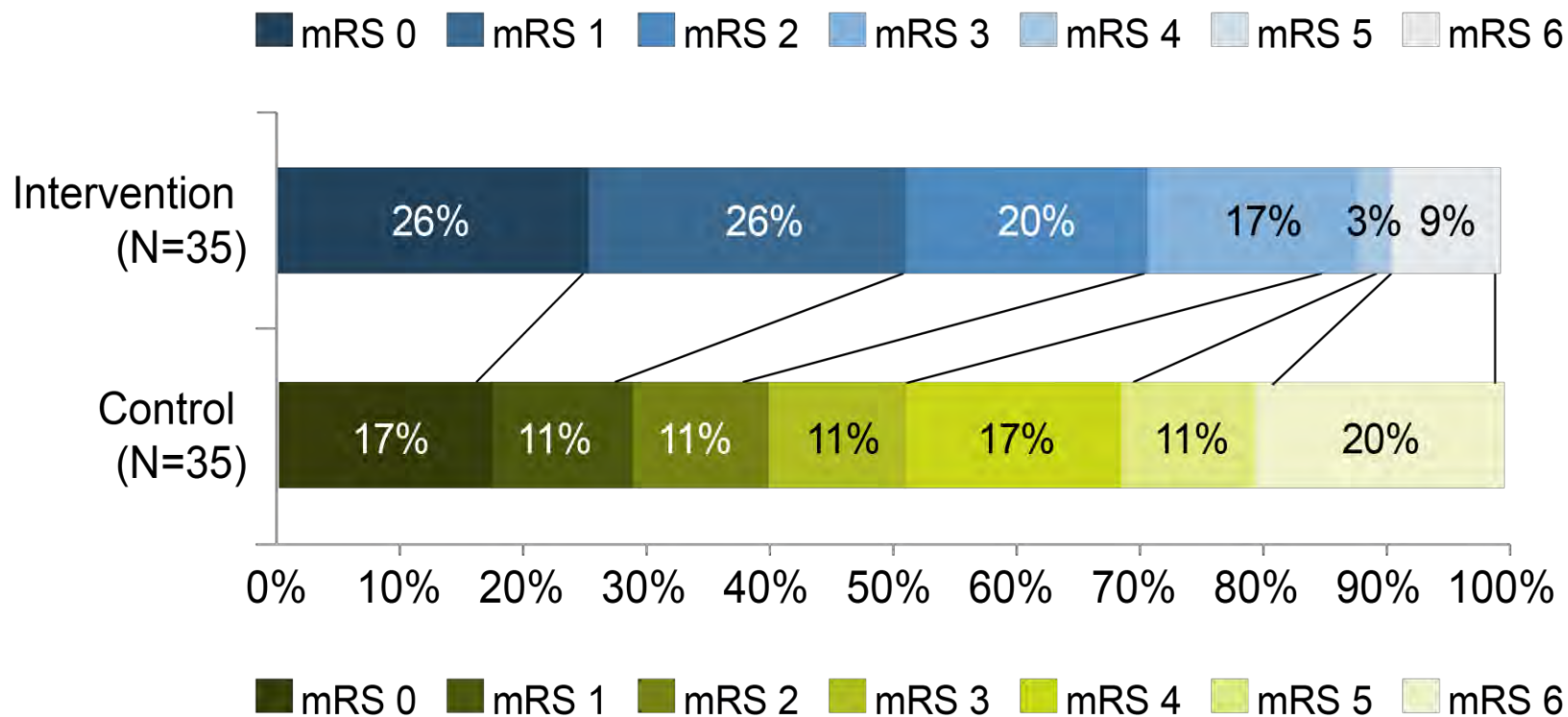
Patients/Randomization



Revascularization in the IV tPA + Endovascular Arm (N=29)



90-day mRS



Safety Endpoints/Mortality

Serious Adverse Events	IV tPA Only (N=35)	IV tPA + Endovascular (N=35)	P Value
Death	20%	9%	0.18
sICH (SITS MOST)	6%	0%	0.49
PH	9%	11%	0.99
Wire Perforation		2.9%	
Emboli		5.7%	

Endovascular Therapy-A New Era?

Medscape Medical News > Neurology

Endovascular Stroke Therapy Proven at Last: MR CLEAN Published

Sue Hughes

December 17, 2014

HEALTH

The New York Times

For First Time, Treatment Helps Patients With Worst Kind of Stroke, Study Says

By GINA KOLATA DEC. 17, 2014

Since then, two other trials evaluating endovascular interventions — ESCAPE (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke) and EXTEND IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial) — have been stopped after early interim analyses showed benefit in the intervention group.

Affirmation-ISC 2/2015

MEETING COVERAGE JAN. 2015

MEDPAGE TODAY

Triple Win for Clot Retriever Devices in Acute Stroke

— ESCAPE, EXTEND-IA, and PRIME SWIFT trials all showed benefit over thrombolysis alone.

PHARMA & HEALTHCARE 2/11/2015 @ 4:07PM 3,154 views

Clot Extractors Shown Beneficial In Stroke Patients

Forbes

+ Comment Now + Follow Comments

BUSINESS

Star-Telegram

f t g+ c

Brain stents show big promise for certain stroke patients

BY MARILYNN MARCHIONE - AP CHIEF MEDICAL WRITER

02/11/2015 12:58 PM | Updated: 02/12/2015 10:31 AM

LVO-Time is Brain

STUDY	Time to IVt-PA	Time to Groin	Time to Recan	TICI 2b-3	MRS 0-2 IA	MRS 0-2 Medical
IMS_III	121-122 min	208 min	N/A	40%	40.8%	38.7%
MR CLEAN	85-87 min	260 min	N/A	58.7%	32.6%	19.1%
ESCAPE (1)	110-125 min	185 min	241 min	72.4%	53%	29.3%
EXTEND IA (2)	127-145 min	210 min	248 min	86%	71%	40%
SWIFT PR. (3)	167.5 min	184 min	213 min	88%	60.2%	35.5%

Endovascular Therapy-A New Era?

Medscape Medical News > Neurology

Endovascular Stroke Therapy Proven at Last: MR CLEAN Published

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December 17, 2014

HEALTH

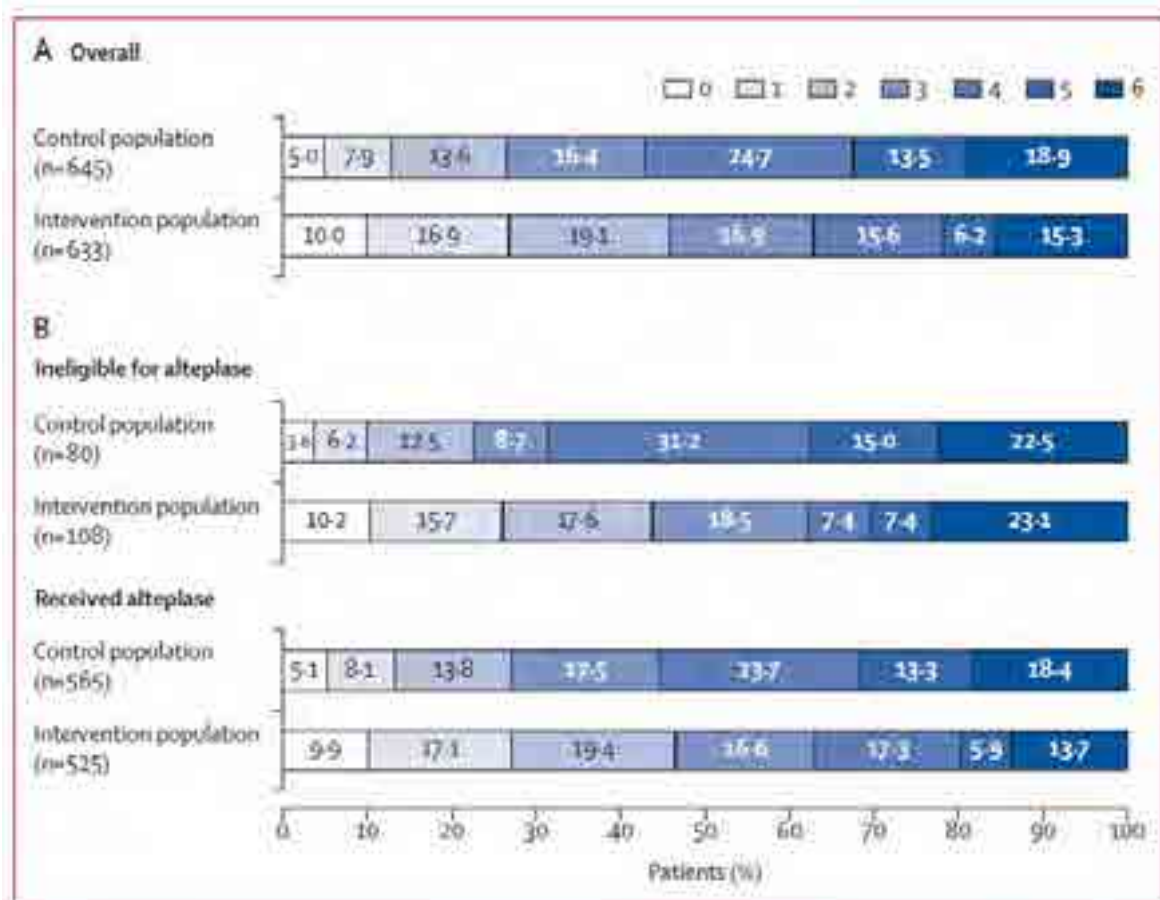
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HERMES data



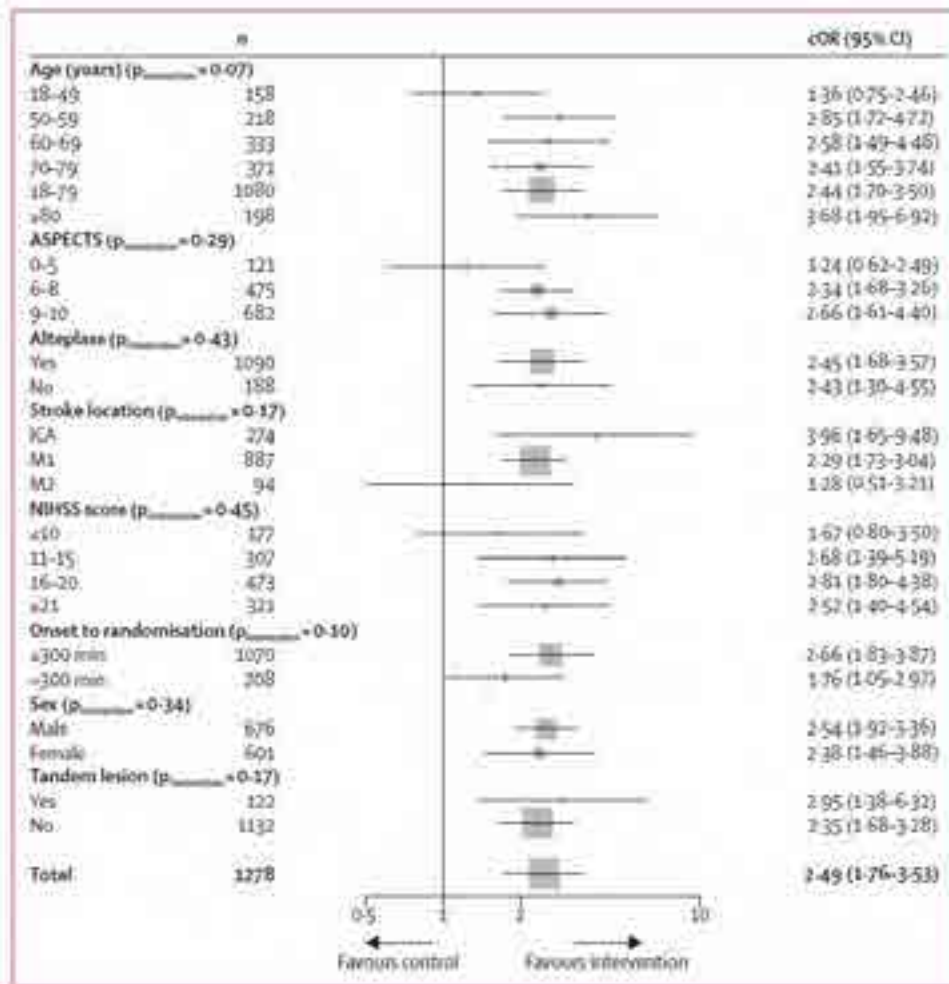
HERMES data

	Intervention population	Control population	Risk difference (%)	Rate ratio (95% CI)	Odds ratio (95% CI)	Adjusted rate ratio (95% CI)	Adjusted odds ratio (95% CI)
mRS score reduction (shift analysis; primary outcome)*					2.26* (1.67-3.06); p<0.0001		2.49* (1.76-3.53); p<0.0001
mRS score 0-1 at 90 days	26.9% (170/633)	12.9% (83/645)	14.0	2.00 (1.54-2.60); p<0.0001	2.49 (1.84-3.35); p<0.0001	2.06 (1.59-2.69); p<0.0001	2.72 (1.99-3.71); p<0.0001
mRS score 0-2 at 90 days	46.0% (291/633)	26.5% (171/645)	19.5	1.7 (1.41-2.05); p<0.0001	2.35 (1.85-2.98); p<0.0001	1.73 (1.43-2.09); p<0.0001	2.71 (2.07-3.55); p<0.0001
NIHSS score 0-2 at 24 h	21.0% (129/615)	8.3% (52/630)	12.7	2.47 (1.79-3.41); p<0.0001	2.91 (2.06-4.12); p<0.0001	2.66 (1.92-3.67); p<0.0001	3.77 (2.49-5.71); p<0.0001
Early neurological recovery at 24 h	50.2% (309/616)	21.2% (134/633)	29.0	2.34 (1.91-2.87); p<0.0001	4.04 (2.75-5.93); p<0.0001	2.34 (1.91-2.87); p<0.0001	4.36 (3.03-6.27); p<0.0001

Data show the proportion of patients with outcome (n/N), unless otherwise stated. NIHSS=National Institutes of Health Stroke Scale. mRS=modified Rankin Scale. * Common odds ratio indicating the odds of improvement of 1 point on the mRS.

Table 2: Efficacy outcomes from the pooled data

HERMES data

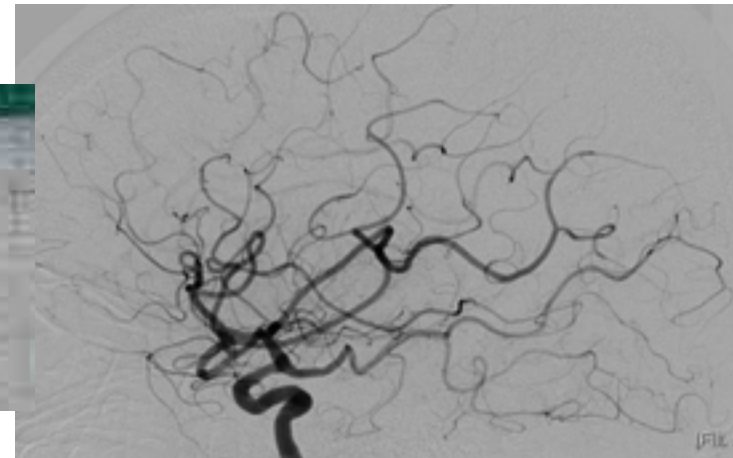
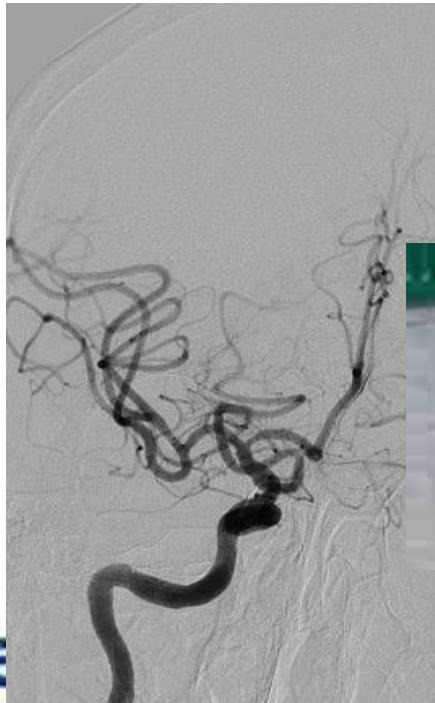
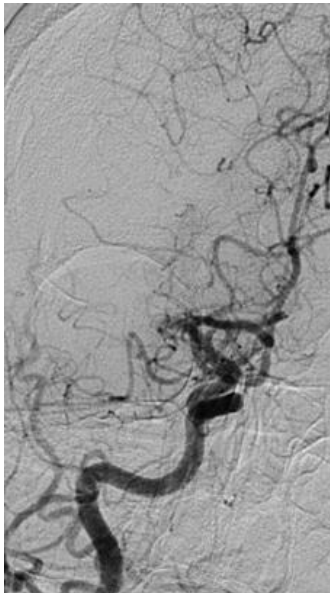
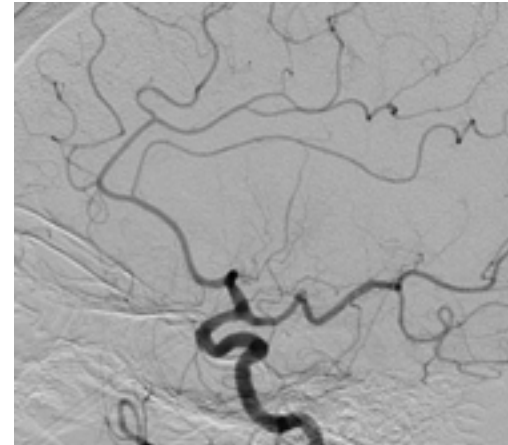


Conclusion and future of therapy

- Conclusion
 - Endovascular therapy for large vessel occlusion stroke is effective
 - Serves as an alternative to IV tPA
 - ⊙ Outside of time window
 - ⊙ Failure of therapy
- Future
 - Extending the time window
 - ⊙ Patient selection based on collaterals/tissue survival
 - ⊙ Neuroprotective agents

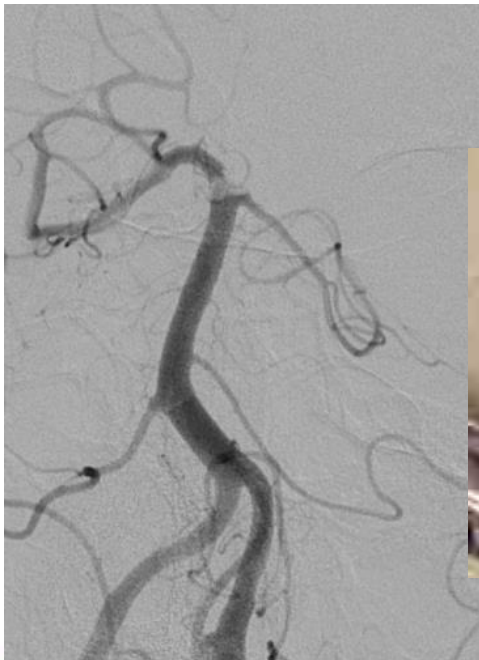
Example Case 1

- 60 yo female
- Presentation NIHSS = 18
- Puncture ~ 5 hours from LKN
- TICI 3 in 31 minutes
- Discharge NIHSS = 0 → home



Example Case 2

- 74 yo male
- Presentation NIHSS = 22
- Puncture ~ 15 hours from LKN
- TICI 3 in 20 minutes
- Discharge NIHSS = 2 → rehab



Example Case 3 – Multiple passes

- 42 yo male
- Presentation NIHSS = 19
- Puncture ~ 10 hours from LKN
- TICI 3 in 29 minutes
- Discharge NIHSS = 0 → home

