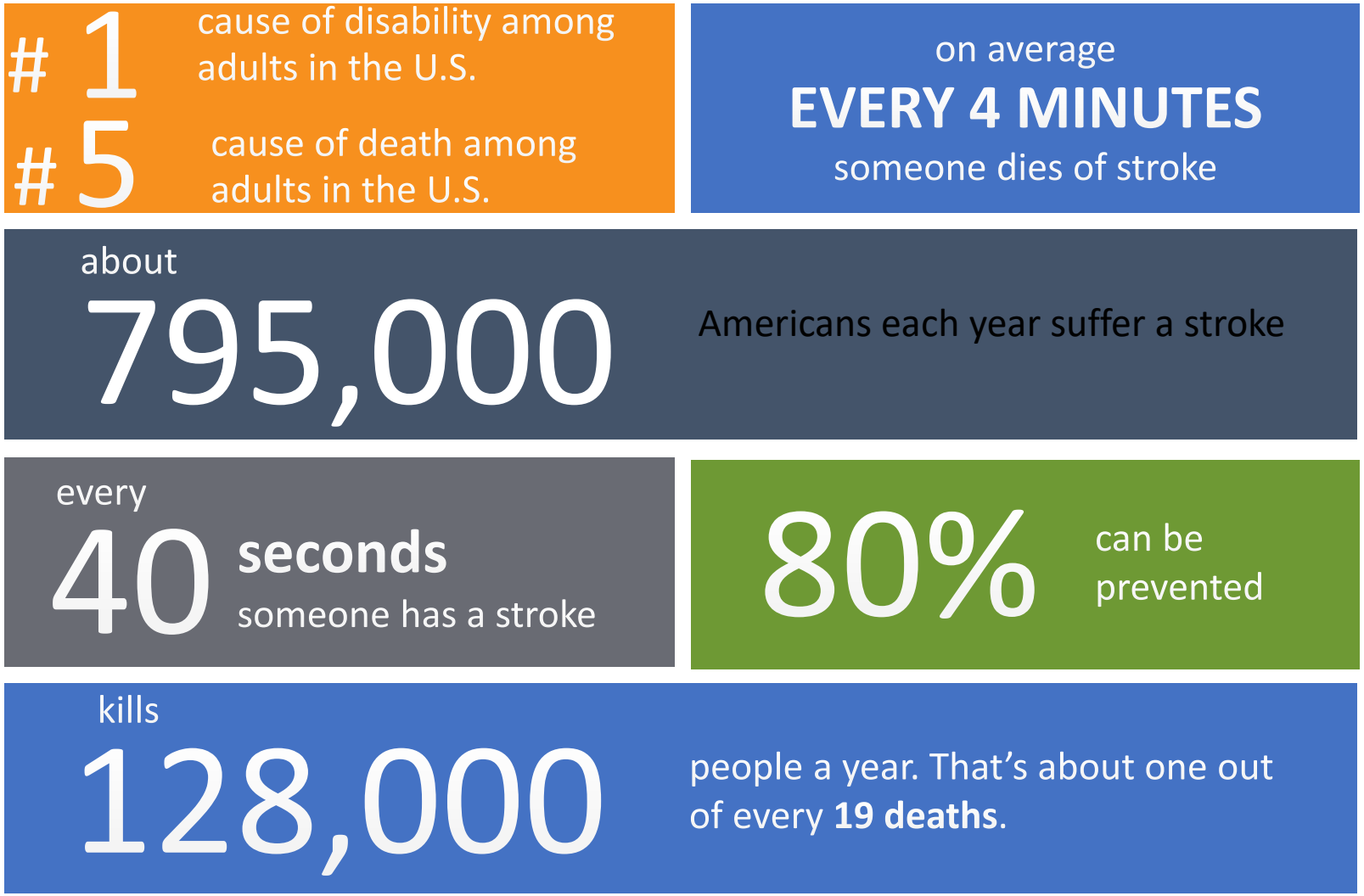
Acute Stroke Interventions

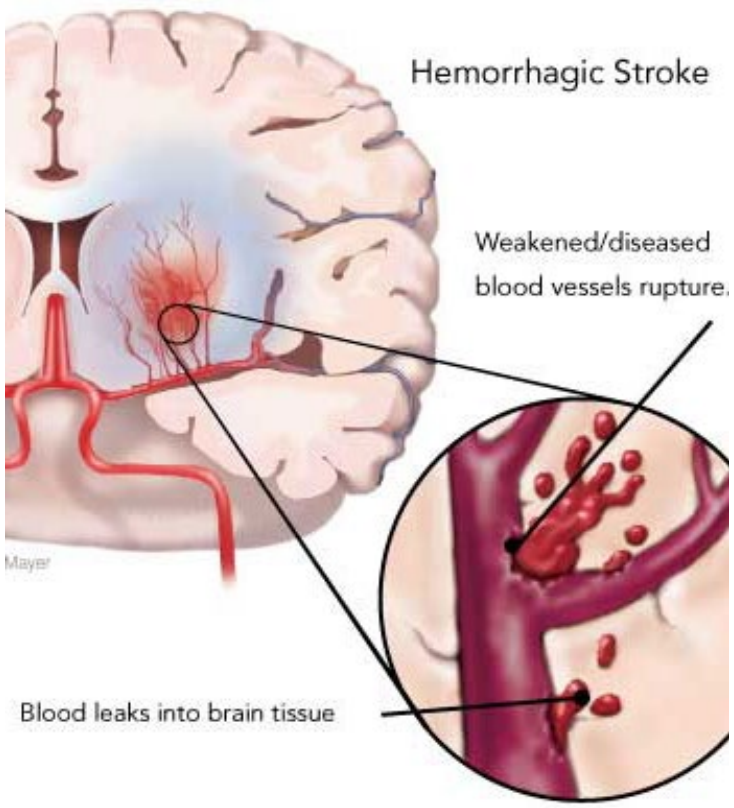
Gautam Sachdeva,MD
Vascular and Interventional Neurology,
Medical Director, Comprehensive Stroke Center, Sanford Fargo,
Chair- North Dakota Stroke Task Force

Stroke Burden is Immense

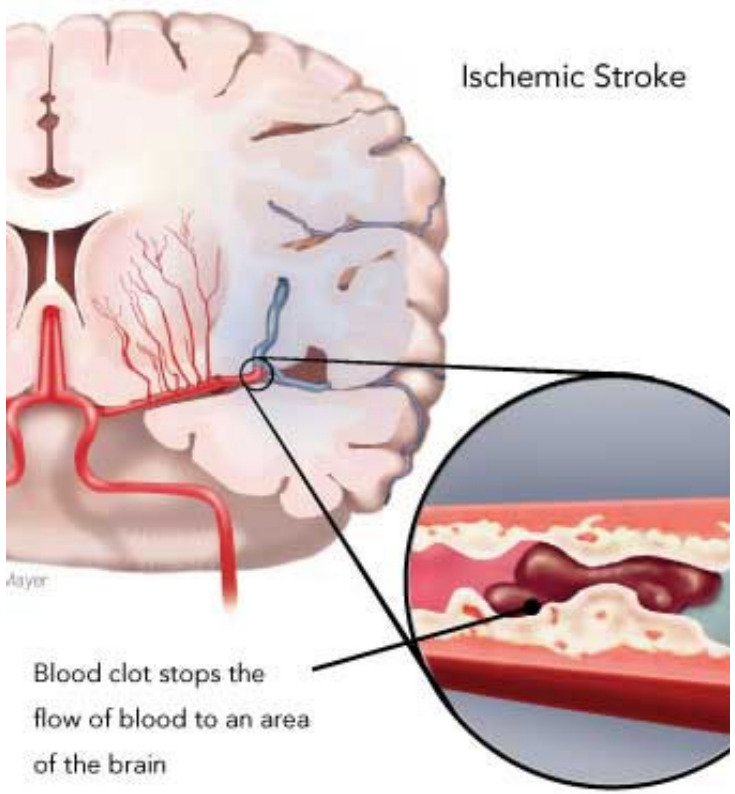


Statistics from the American Heart Association/American Stroke Association, World Health Organization and Centers for Disease Control and Prevention. 1/13DS6139

Types of strokes



Heart and Stroke Foundation of Canada



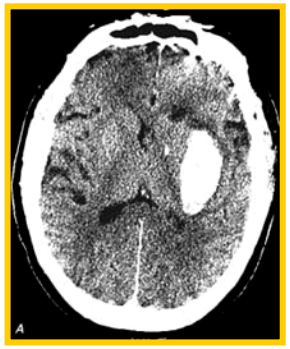
Heart and Stroke Foundation of Canada

- **Ischemic Stroke:** 87% of all strokes.
  - Blood flow blocked by blood clots or plaque in blood vessel linings
  - **Transient ischemic attack (TIA)** is a "warning stroke
  - is now defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (new definition- updated 2009 AHA)

- **Hemorrhagic Stroke:** 13 % of all strokes.
  - When a blood vessel bursts in the brain. Blood accumulates and compresses the surrounding brain tissue. two types :
    - **Intracerebral hemorrhage** when an artery in the brain bursts, flooding the surrounding tissue with blood.
    - **Subarachnoid hemorrhage** is bleeding in the area between the brain and the thin tissues that cover it. Most likely due to aneurysms

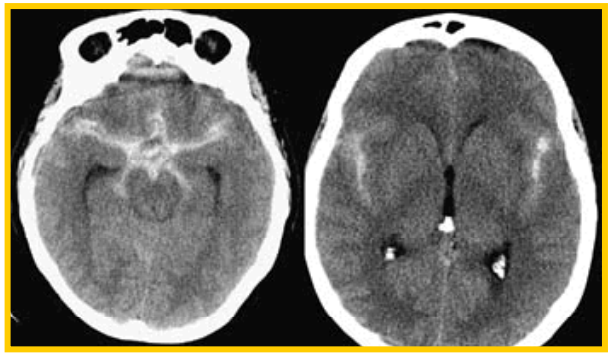
Stroke Subtypes

Hemorrhagic Stroke (17%)



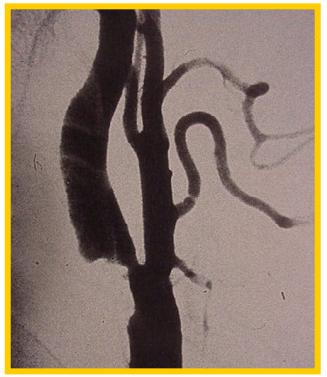
Intracerebral Hemorrhage (59%)

Subarachnoid Hemorrhage (41%)



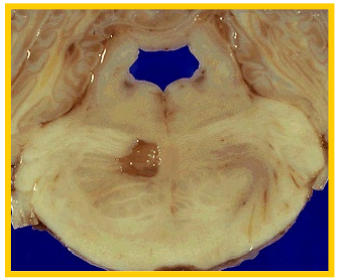
Ischemic Stroke (83%)

Atherothrombotic Cerebrovascular Disease (20%)

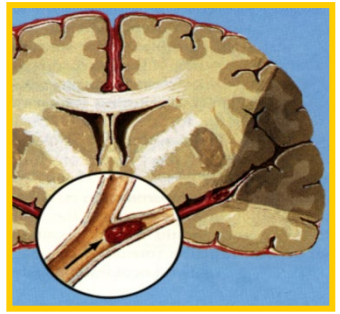


Cryptogenic and Other Known Cause (30%)

Lacunar (25%)
Small vessel disease



Embolism (20%)

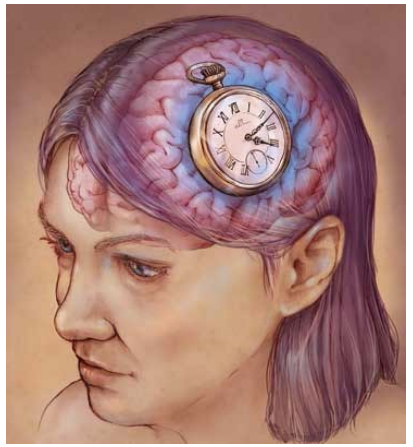


Acute Ischemic Stroke

Time is Brain

Stroke
Journal of the American Heart Association

American Heart Association | American Stroke Association



Time Is Brain—Quantified
Jeffrey L. Saver

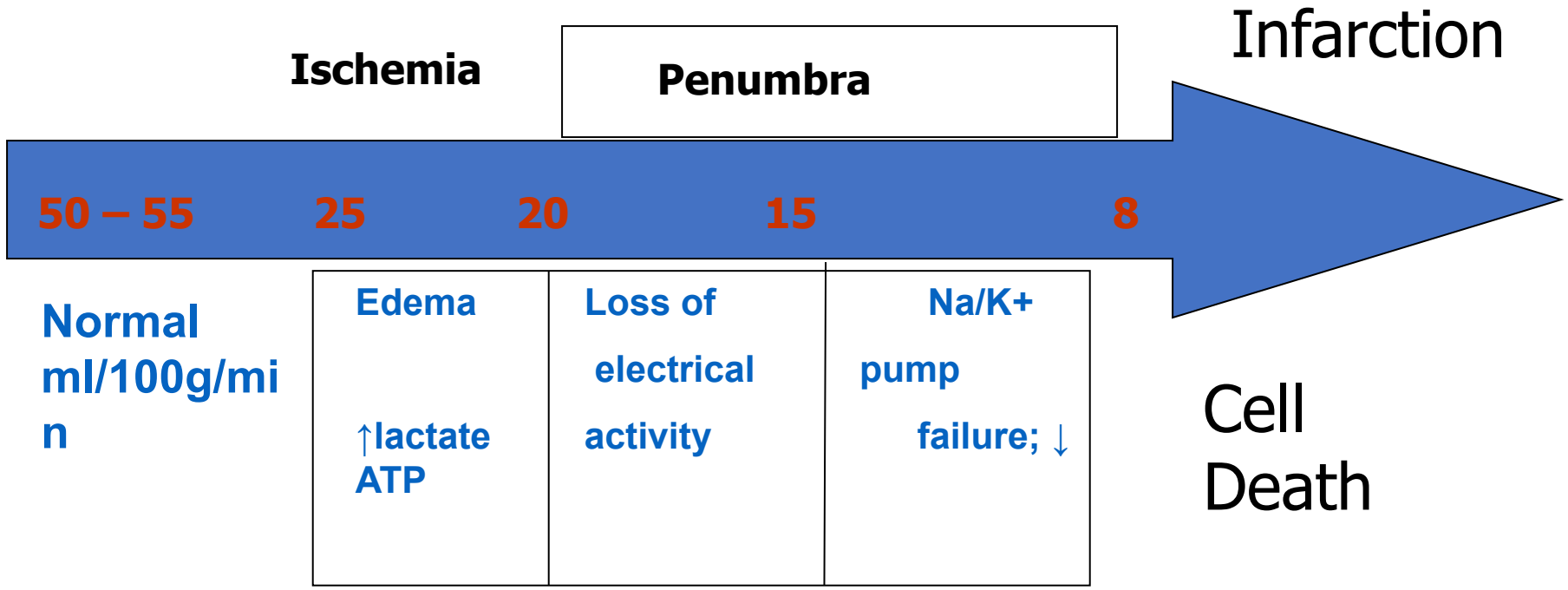
Stroke. 2006;37:263-266; originally published online December 8, 2005;
doi: 10.1161/01.STR.0000196957.55928.ab
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km/4470 miles	36 y
Per Hour	120 million	830 billion	714 km/447 miles	3.6 y
Per Minute	1.9 million	14 billion	12 km/7.5 miles	3.1 wk
Per Second	32 000	230 million	200 meters/218 yards	8.7 h

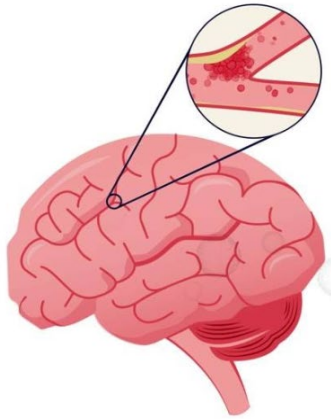
Effects of Reduced CBF



Evolution in acute stroke management

tPA

Dissolves blood clots in the brain



IV TPA

NINDS Trial 1995

The New England
Journal of Medicine

Volume 333 DECEMBER 14, 1995 Number 24

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

Abstract *Background.* Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke.

Methods. The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical activity, as indicated by an improvement of 4 points over base-line values in the score of the National Institutes of Health stroke scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS.

Results. In part 1, there was no significant difference between the group given t-PA and that given placebo in the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only 0.6 percent of patients given placebo ($P<0.001$). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group ($P=0.30$).

Conclusions. Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7.)

tPA

1995- NINDS 1 and 2 trials

Part 1: 291 patients with onset within 3 hours, randomized to rt-PA (0.9 mg/kg max of 90 mg, 10% dose bolus over 1 minutes, remaining 90% over next 59 minutes)

-No significant difference in % of patients clinically improved (ΔNIHSS 4 or more/resolution) at 24 hours

Part 2: 333 patients, same protocol, assessed at 90 days for functional outcome by mRS/Barthel Index/NIHSS

-12% absolute increase (NNT = 8) in tPA-treated patients with minimal or no disability at 90 days

-36-hour 6.4% SICH rate versus 0.6 placebo

ECASS 3Trial - 2008

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2008 VOL. 359 NO. 13

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, M.D., Markku Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D., Donata Guidetti, M.D., Vincent Larrue, M.D., Kennedy R. Lees, M.D., Zakaria Medeghri, M.D., Thomas Machnig, M.D., Dietmar Schneider, M.D., Rüdiger von Kummer, M.D., Nils Wahlgren, M.D., and Danilo Toni, M.D., for the ECASS Investigators*

ABSTRACT

BACKGROUND

Intravenous thrombolysis with alteplase is the only approved treatment for acute ischemic stroke, but its efficacy and safety when administered more than 3 hours after the onset of symptoms have not been established. We tested the efficacy and safety of alteplase administered between 3 and 4.5 hours after the onset of a stroke.

METHODS

After exclusion of patients with a brain hemorrhage or major infarction, as detected on a computed tomographic scan, we randomly assigned patients with acute ischemic stroke in a 1:1 double-blind fashion to receive treatment with intravenous alteplase (0.9 mg per kilogram of body weight) or placebo. The primary end point was disability at 90 days, dichotomized as a favorable outcome (a score of 0 or 1 on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms at all and 6 indicating death) or an unfavorable outcome (a score of 2 to 6 on the modified Rankin scale). The secondary end point was a global outcome analysis of four neurologic and disability scores combined. Safety end points included death, symptomatic intracranial hemorrhage, and other serious adverse events.

RESULTS

We enrolled a total of 821 patients in the study and randomly assigned 418 to the alteplase group and 403 to the placebo group. The median time for the administration of alteplase was 3 hours 59 minutes. More patients had a favorable outcome with alteplase than with placebo (52.4% vs. 45.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; P=0.04). In the global analysis, the outcome was also improved with alteplase as compared with placebo (odds ratio, 1.28; 95% CI, 1.00 to 1.65; P<0.05). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0% vs. 17.6%; P=0.001; for symptomatic intracranial hemorrhage, 2.4% vs. 0.2%; P=0.008). Mortality did not differ significantly between the alteplase and placebo groups (7.7% and 8.4%, respectively; P=0.68). There was no significant difference in the rate of other serious adverse events.

CONCLUSIONS

As compared with placebo, intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; alteplase was more frequently associated with symptomatic intracranial hemorrhage. (ClinicalTrials.gov number, NCT00153036.)

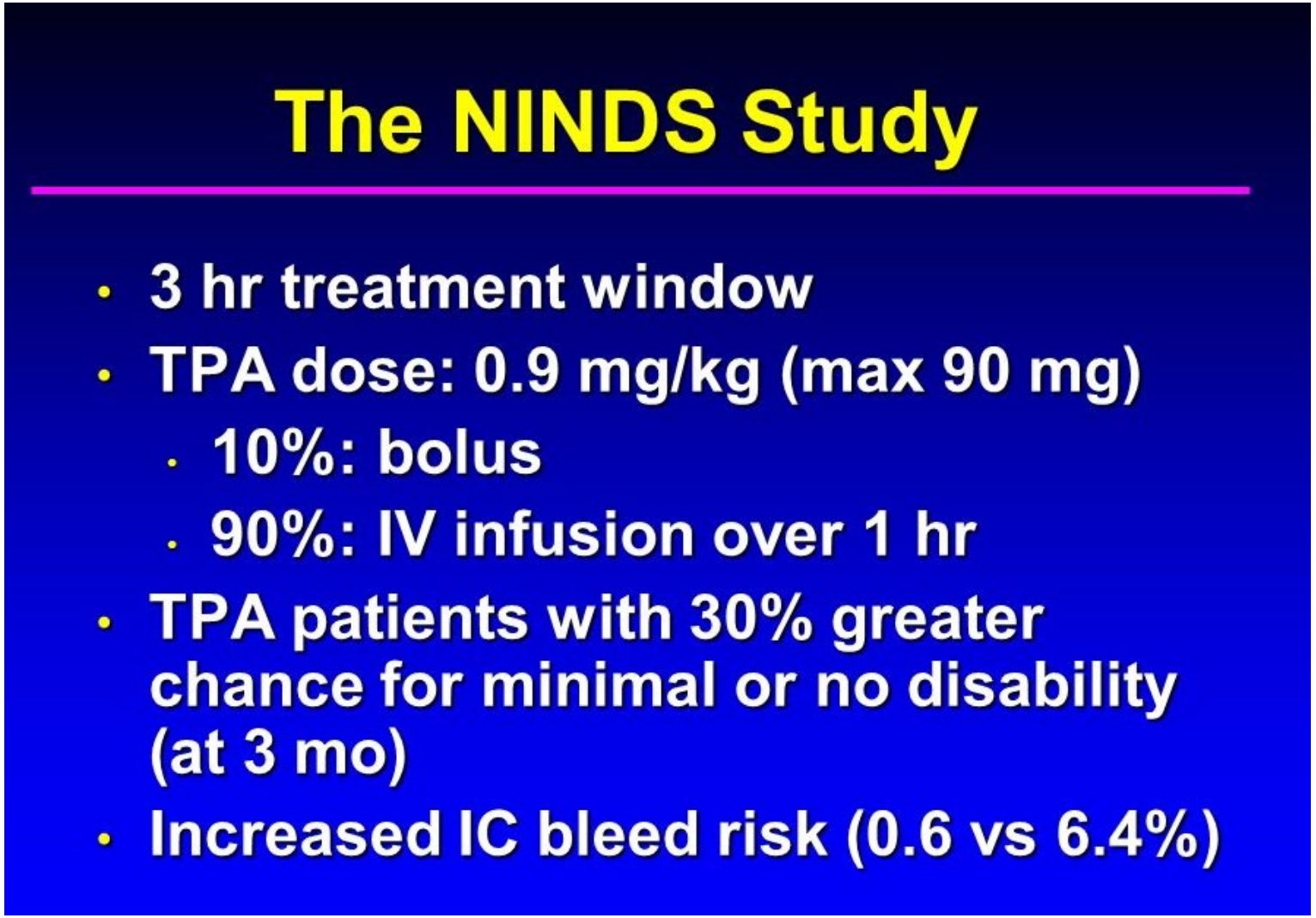
From the Department of Neurology, Universität Heidelberg, Heidelberg, Germany (W.H.); the Department of Neurology, Helsinki University Central Hospital, Helsinki (M.K.); the Department of Statistics, Boehringer Ingelheim, Biberach, Germany (E.B.); the Neurology Clinic, University Hospital Nitra, Nitra, Slovakia (M.B.); the Department of Neurosciences, Hospital Universitari Germans Trias i Pujol, Barcelona (A.D.); the Department of Neurology, Hospital of Piacenza, Piacenza, Italy (D.G.); the Department of Neurology, University of Toulouse, Toulouse, France (V.L.); the Faculty of Medicine, University of Glasgow, Glasgow, United Kingdom (K.R.L.); Boehringer Ingelheim, Reims, France (Z.M.); Boehringer Ingelheim, Ingelheim, Germany (T.M.); the Department of Neurology, Universität Leipzig, Leipzig, Germany (D.S.); the Department of Neuroradiology, Technische Universität Dresden, Dresden, Germany (R.K.); the Department of Neurology, Karolinska Institutet, Stockholm (N.W.); and the Department of Neurological Sciences, University La Sapienza, Rome (D.T.). Address reprint requests to Dr. Hacke at the Department of Neurology, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany, or at werner.hacke@med.uni-heidelberg.de.

*The European Cooperative Acute Stroke Study (ECASS) investigators are listed in the Appendix.

This article (10.1056/NEJMoa0804656) was updated on February 24, 2011, at NEJM.org.

N Engl J Med 2008;359:1317-29.

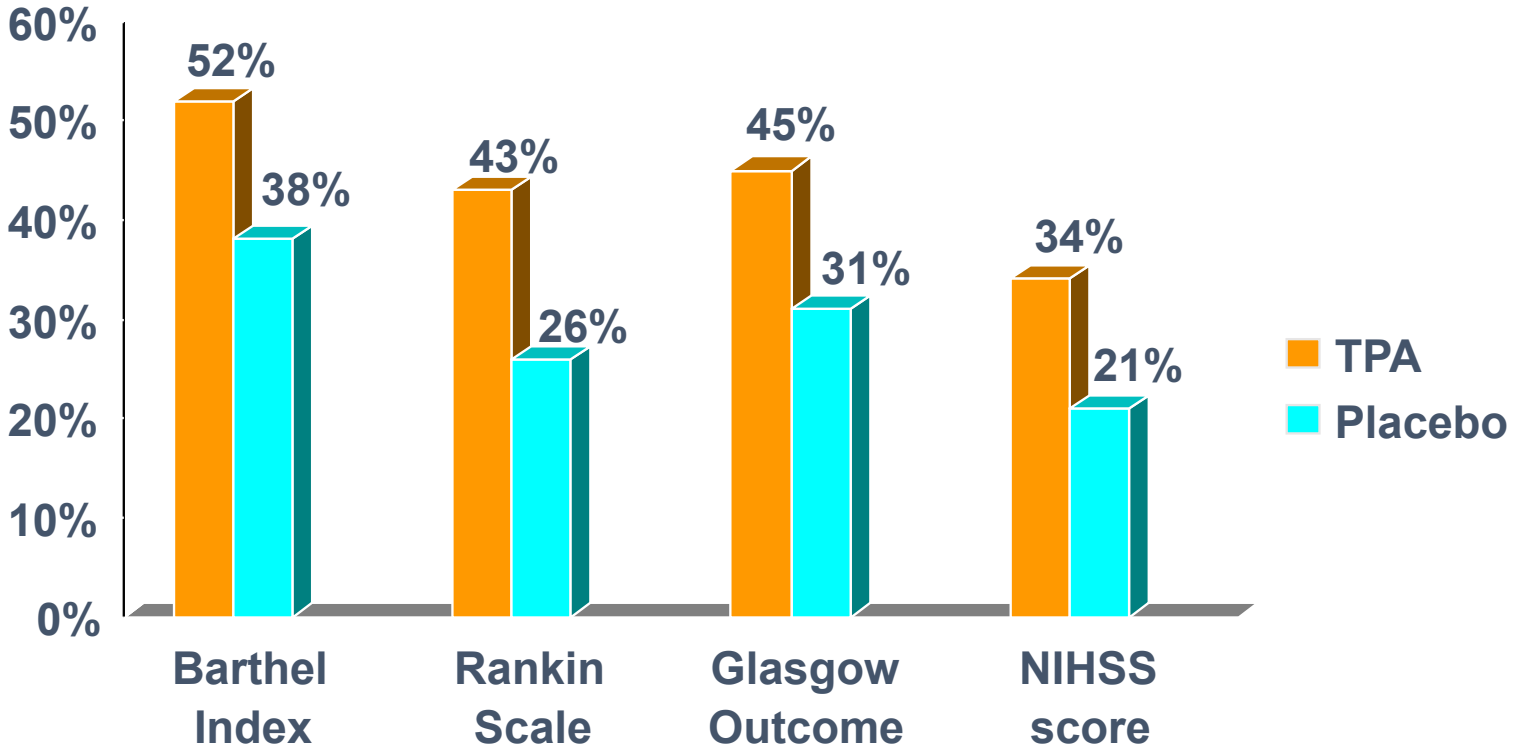
Dosage per NINDS



Systemic IV rtPA Therapy Evidence:

NINDs up to 3 hours and ECAS III up to 4.5 hours from ischemic stroke symptoms

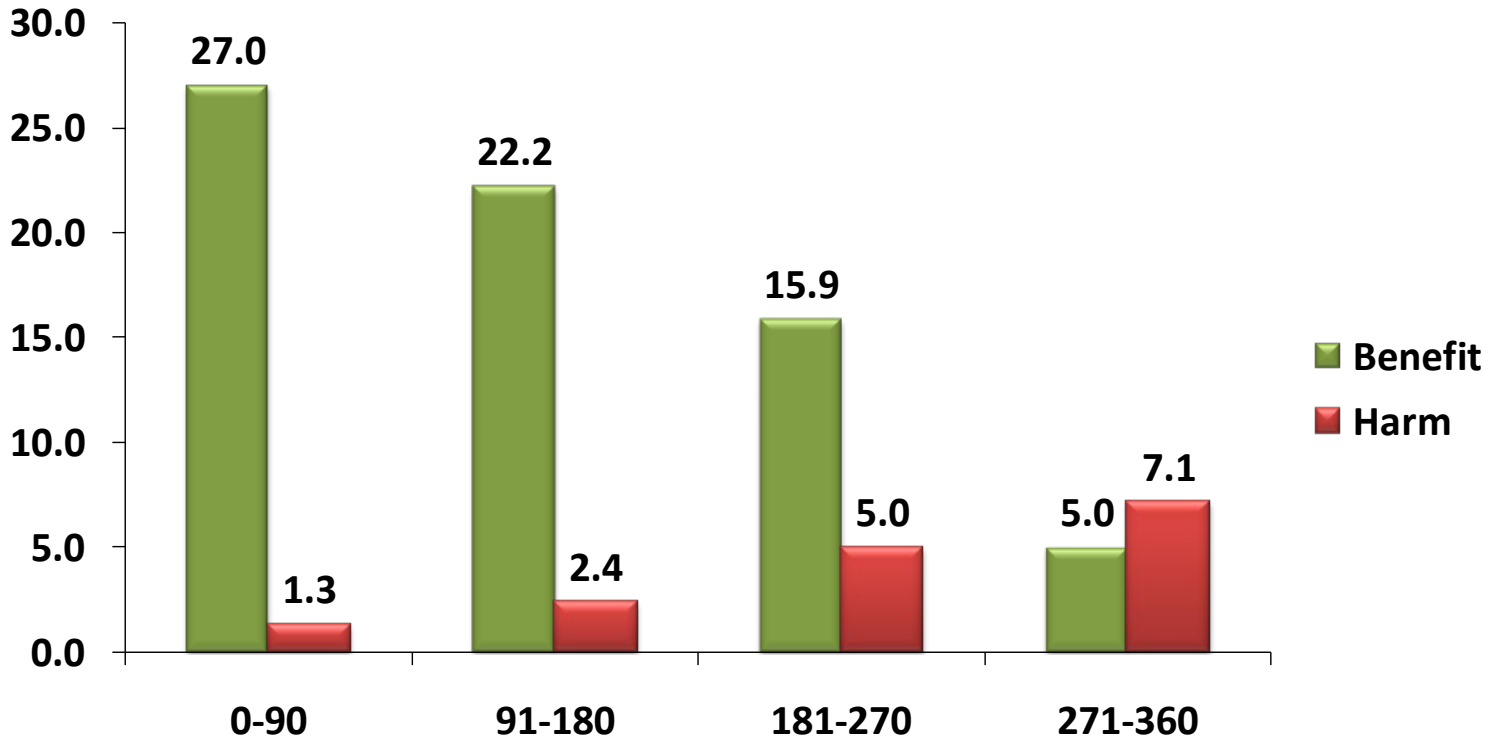
Excellent outcome at 3 months on all scales



Global outcome statistic: OR=1.7, 50% v. 38%= 12% benefit

N Engl J Med 1995;333:1581-7

Number of Patients Who Benefit and Are Harmed per 100 Patients tPA Treated in Each Time Window



--Lansberg et al, Stroke 2009

Number Needed to Treat to Benefit from IV TPA Across Full Range of Functional Outcomes

Outcome	NNT
Normal/Near Normal	8.3
Improved	3.1

For every 100 patients treated with tPA,
32 benefit, 3 harmed

Saver JL et al Stroke 2007; 38:2279-2283

better outcome by 1 or more grades on the mRS

Time to Treatment in Ischemic Stroke

Pooled data from 6 randomized placebo-controlled trials of IV rt-PA. Treatment was started within 360 min of onset of stroke in 2775 patients randomly allocated to rt-PA or placebo

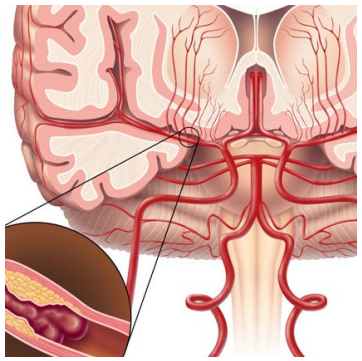
Odds of a favorable 3-month outcome increased as onset to treatment decreased (p=0.005). Odds were 2.8 (95% CI 1.8-4.5) for 0-90 min, 1.6 (1.1-2.2) for 91-180 min, 1.4 (1.1-1.9) for 181-270 min, and 1.2 (0.9-1.5) for 271-360 min in favor of the rt-PA group.

The sooner that rt-PA is given to stroke patients, the greater the benefit, especially if started within 90 minutes of symptom onset

Hacke, W., G. Donnan, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363:768-74.

Limitations of IV Thrombolytics

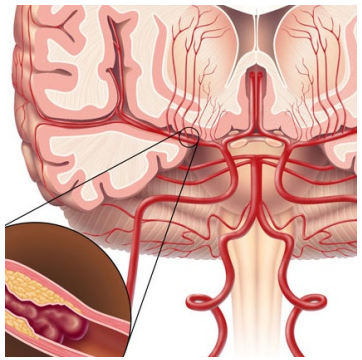
- Time window = 3 hours or 4.5 hours
- Many contraindications
- < 10% of all stroke patients receive IV t-Pa



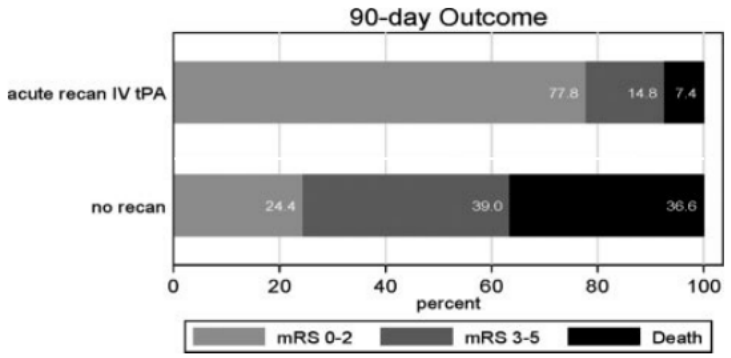
Limitations of IV Thrombolytics

A good outcome from IV thrombolysis is **more common** in stroke due to **small vessel disease** than other subtypes[1] (957 patients treated with IV tPA)

Stroke Subtype	n	Excellent outcome, mRS 0-1
Large artery atherosclerosis	217 (23%)	OR 0.69 [CI 0.5 – 0.96]
Cardioembolic	389 (41%)	OR 0.80 [CI 0.61 – 1.06]
Small vessel disease	101 (11%)	OR 2.48 [CI 1.63 – 3.79]
Other	27 (2.8%)	OR 0.32 [CI 0.11 – 0.94]
Undetermined	130 (14%)	OR 1.85 [CI 1.27 – 2.70]



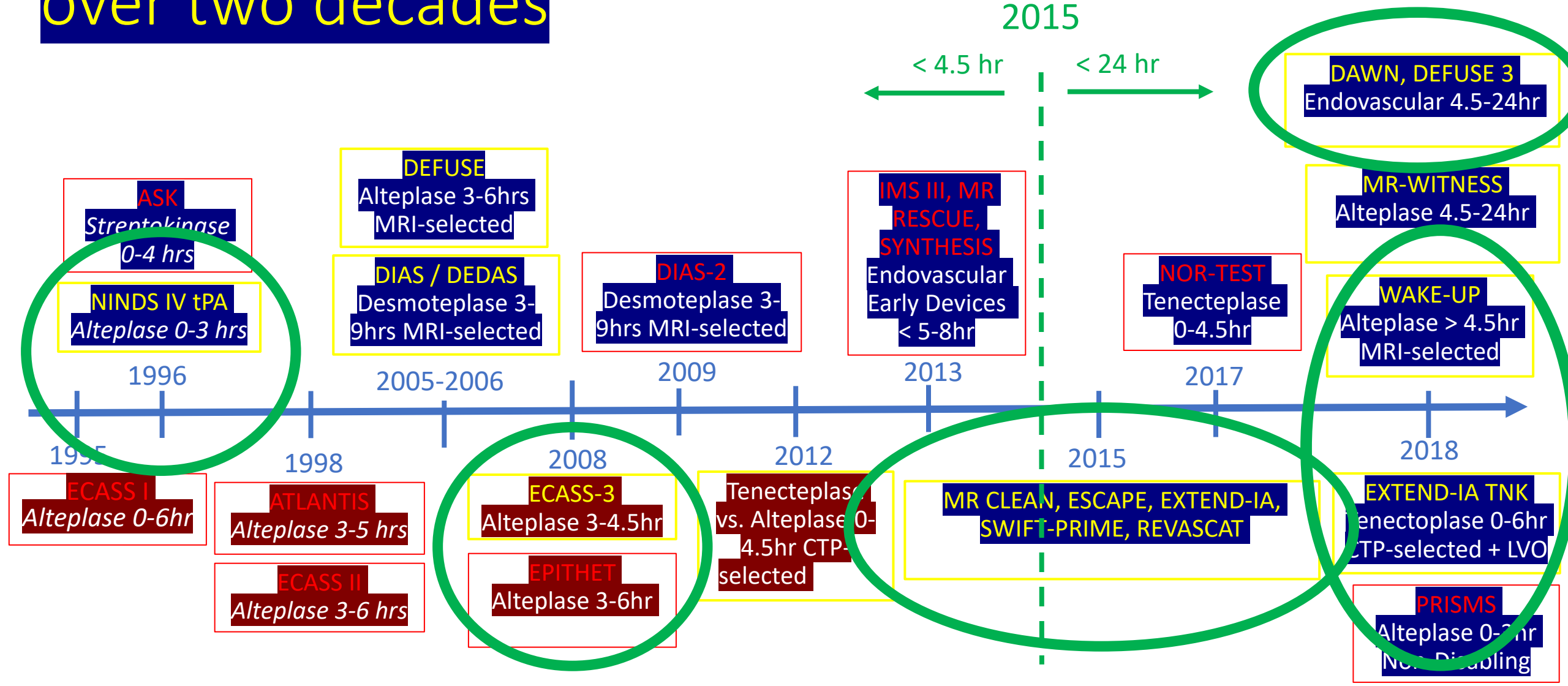
Low Rates of Acute Recanalization With IV TPA for **proximal occlusions** (127 patients treated with IV TPA) [2]



Occlusion location	Recanalization after IV TPA
M1-MCA	32.3% (21)
ICA terminus	4.4 (1)
M2-MCA	30.8% (4)
BA	4.0% (1)
ALL	21.3% (27)

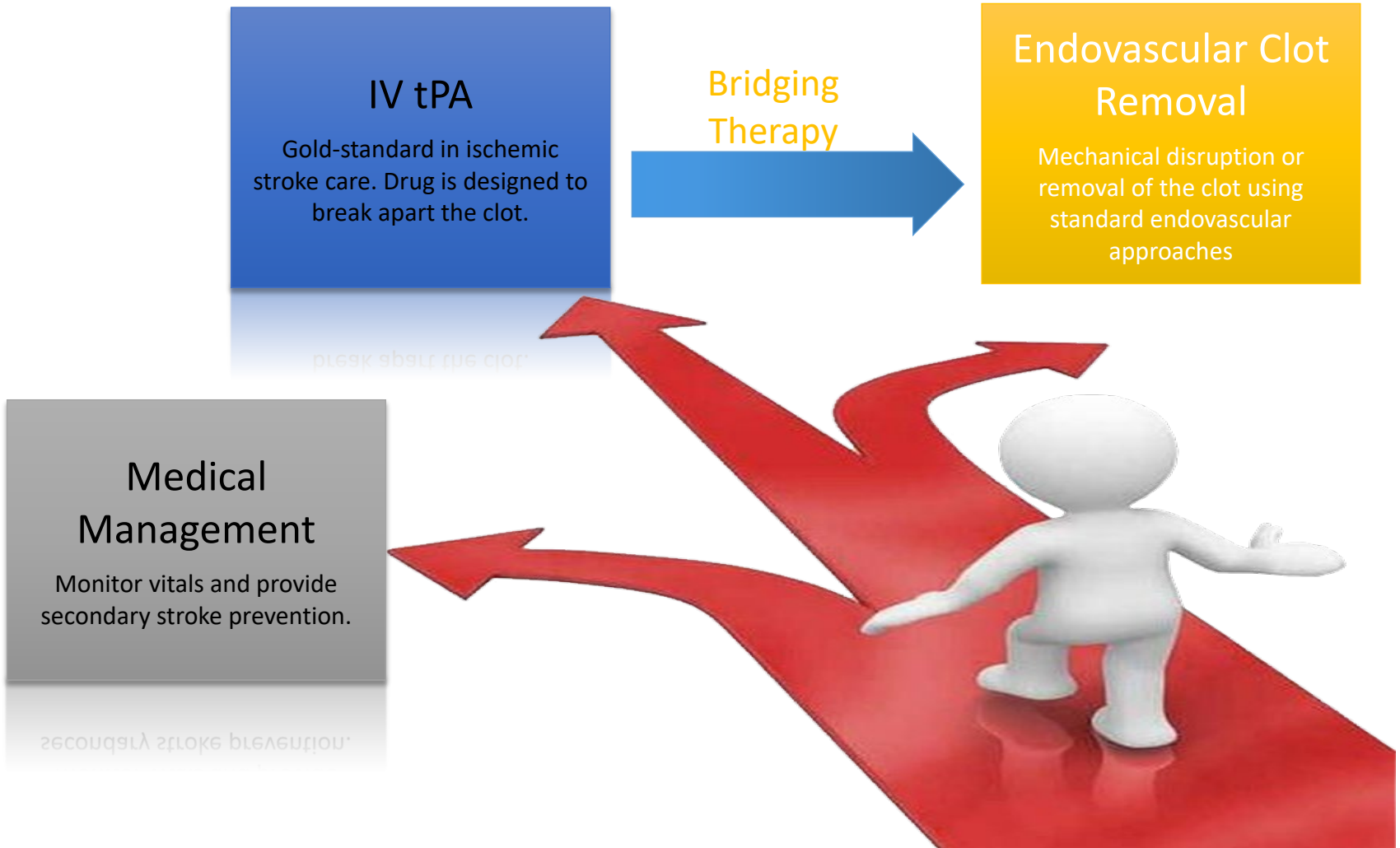
1. Mustanoja, Stroke, 2011
2. Bhatia, Stroke, 2010

Evolution of Acute Ischemic Stroke (AIS) Care over two decades

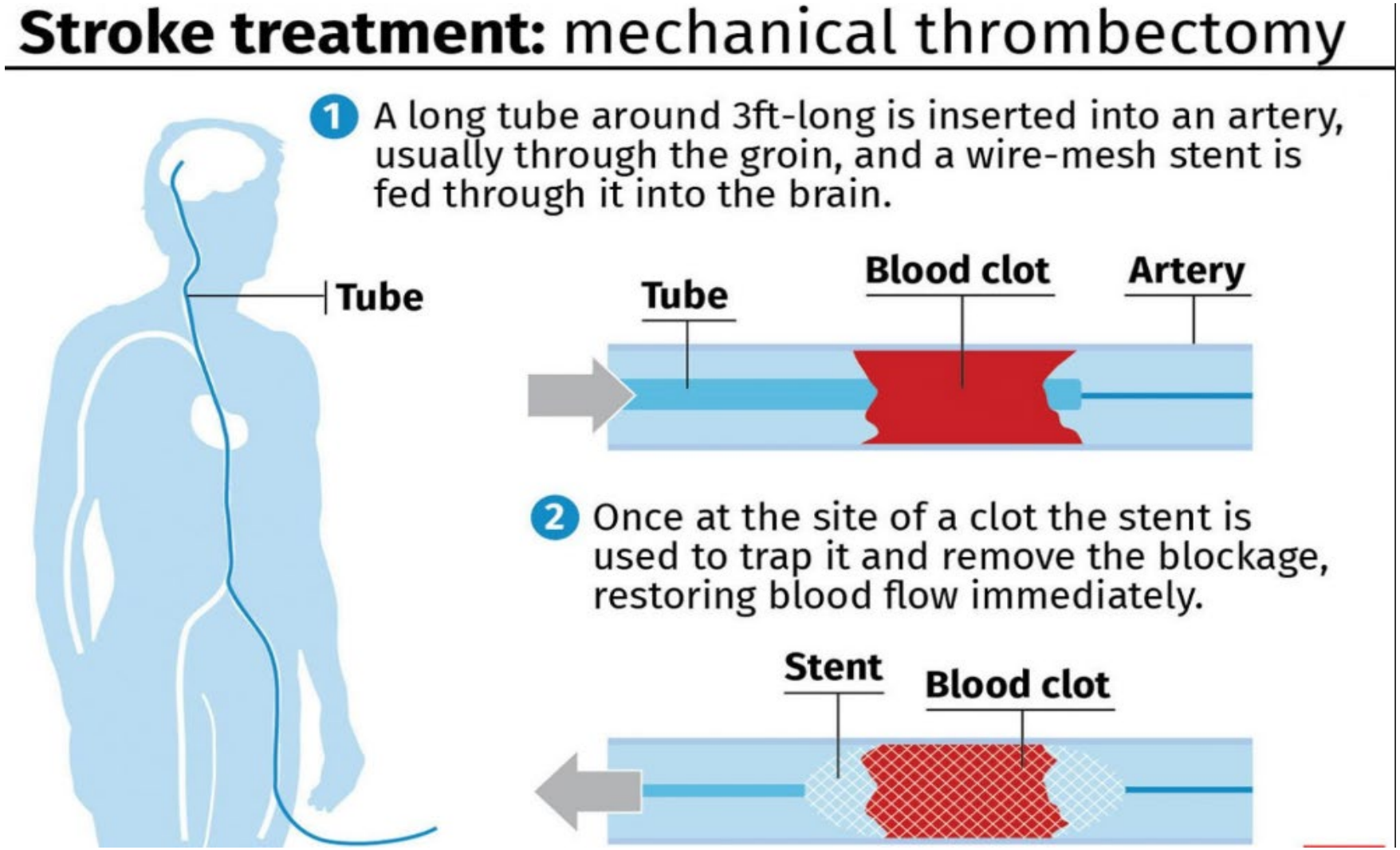


What else can we offer .?

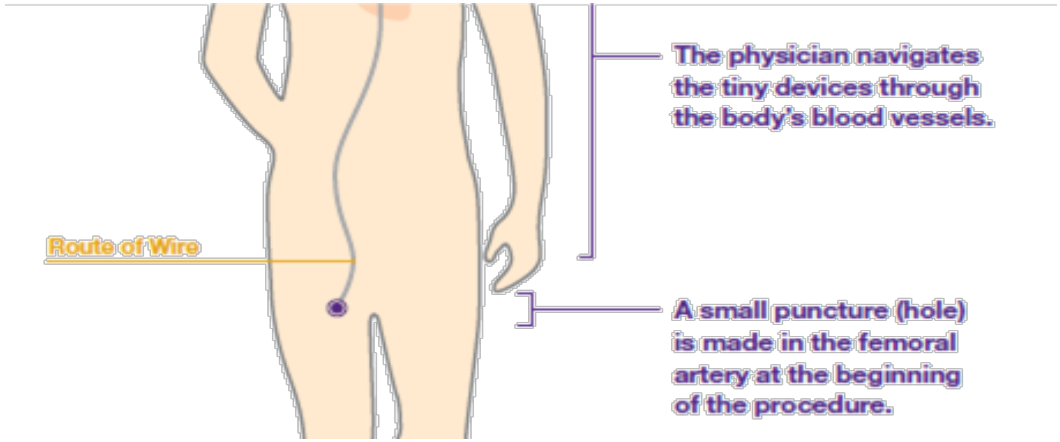
Treatment Options for Patients Experiencing an Acute Ischemic Stroke

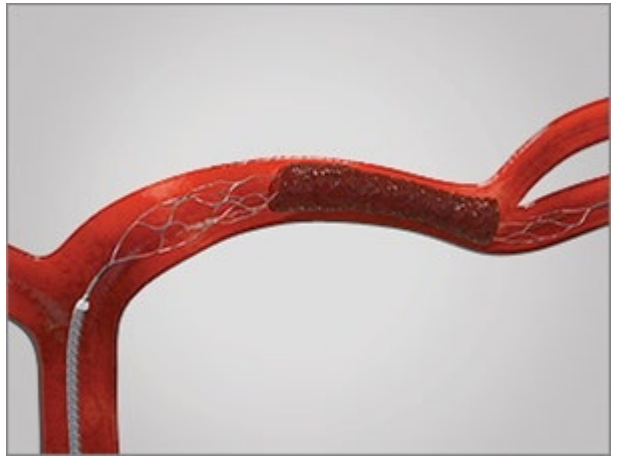


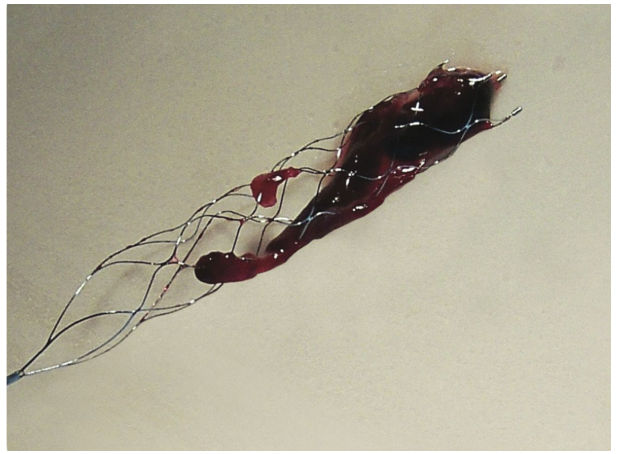
Mechanical Thrombectomy



Endovascular Clot Removal





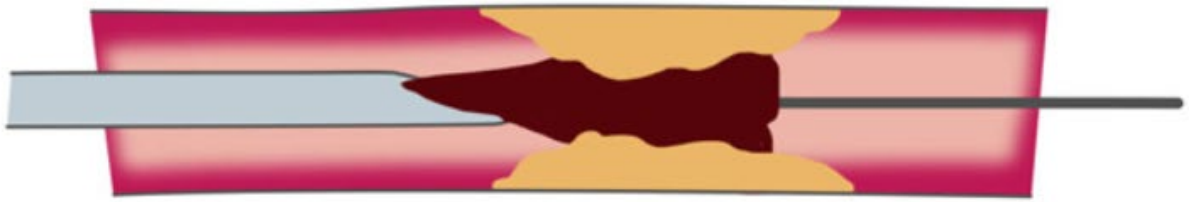


Endovascular clot removal is a type of minimally invasive surgery that allows the physician to access various parts of the body, including the brain, through the body's major blood vessels.

Thrombectomy

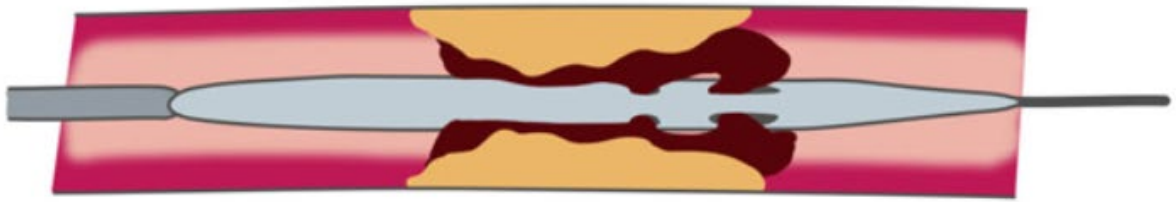
Thrombectomy

Catheter aspiration thrombectomy



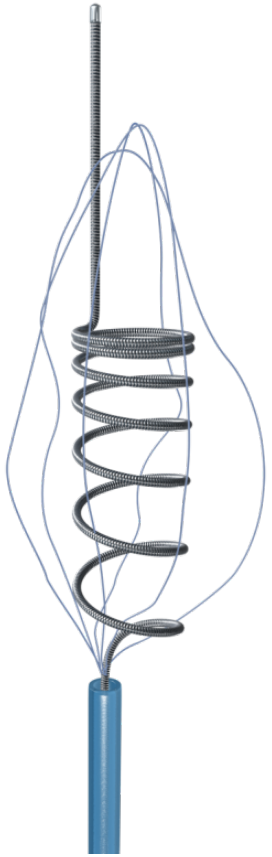
Blood clot is removed using suction

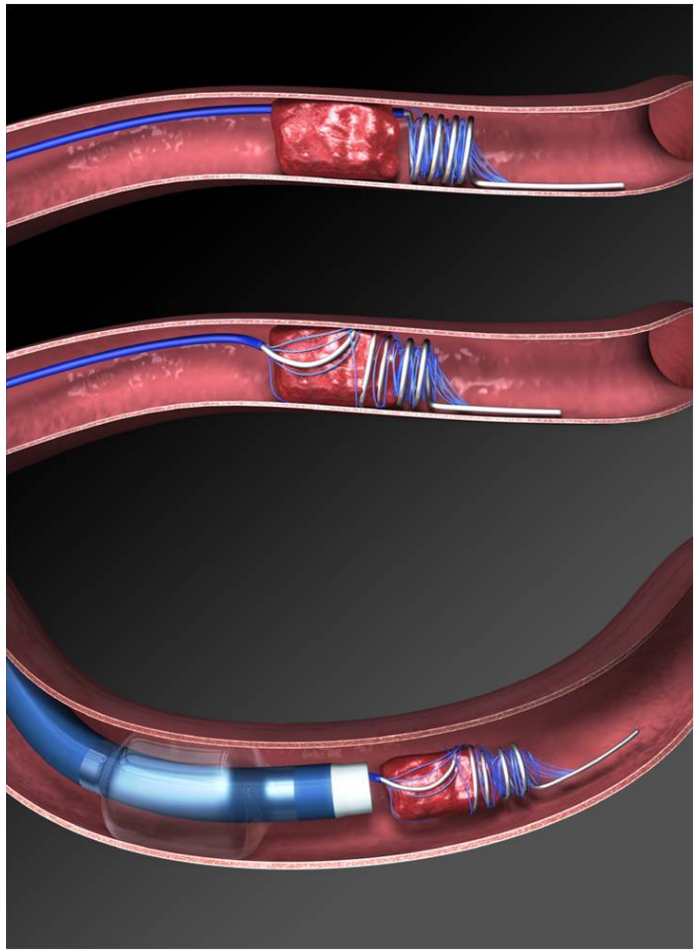
Mechanical thrombectomy



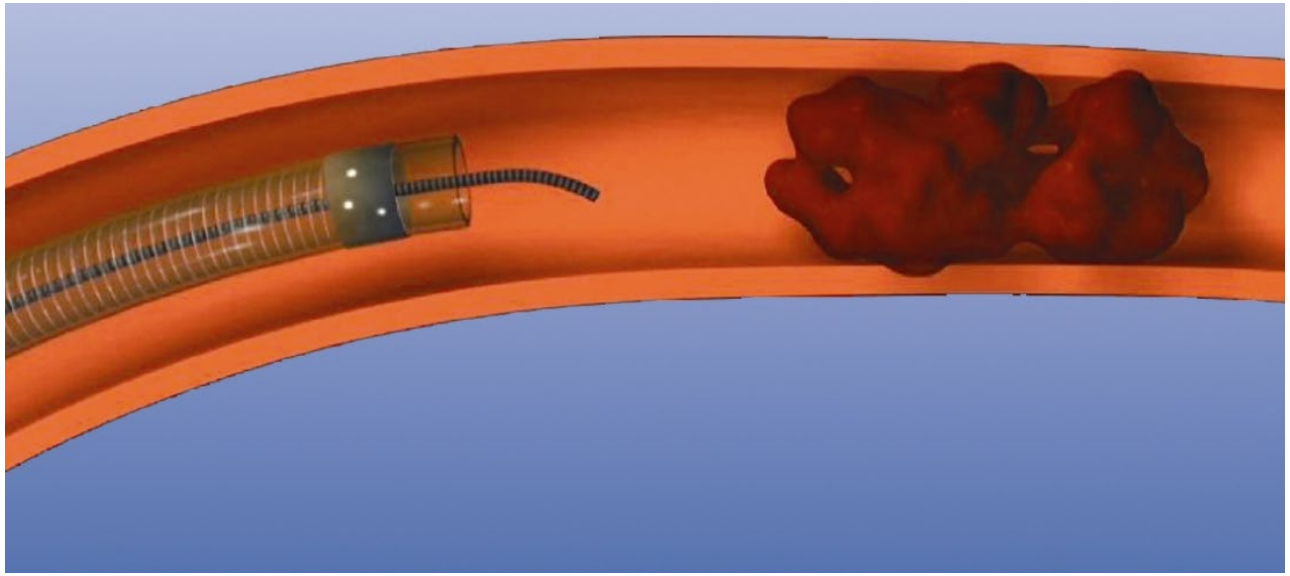
Blood clot is broken up into small pieces and removed

- MERCI Device
- Aproved in 2004

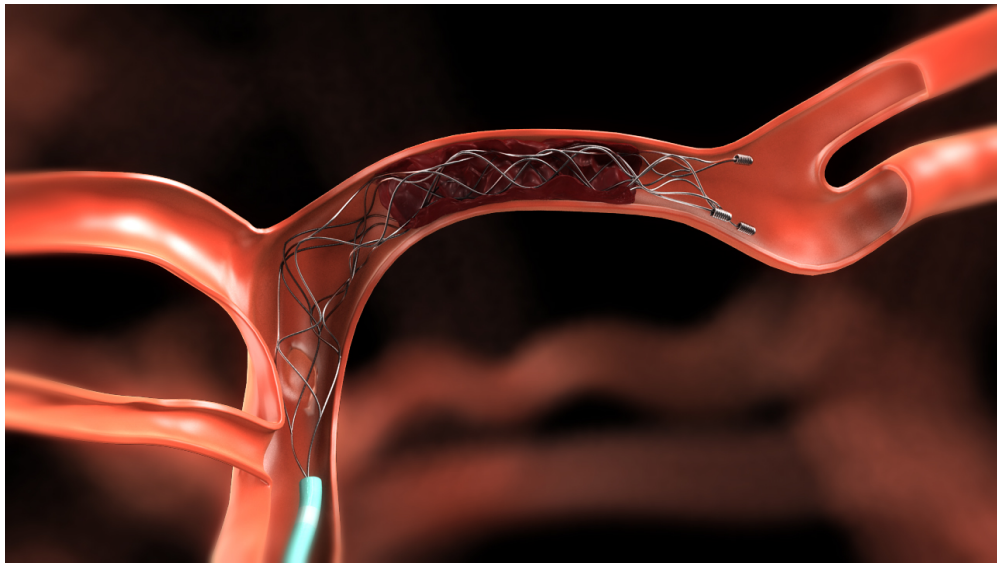


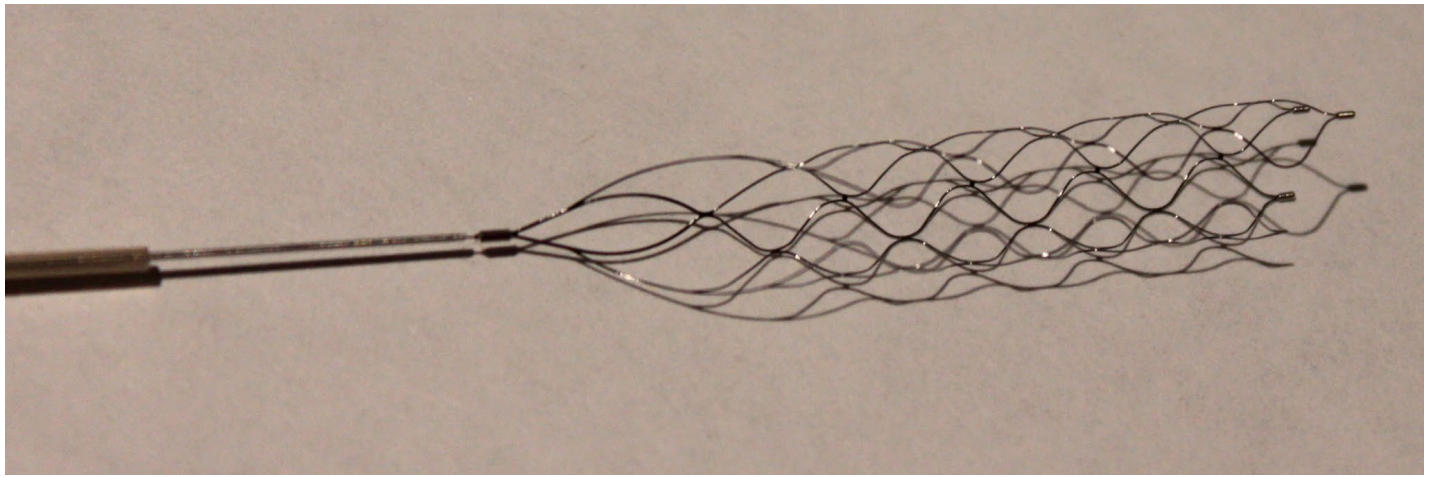


- Penumbra aspiration system
- Approved - 2008



- Solitaire FR
- Approved 2012





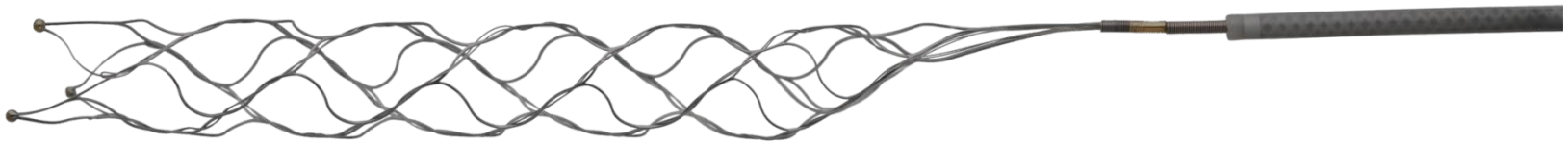
Turning Point

The Era of Stent-Retrievers

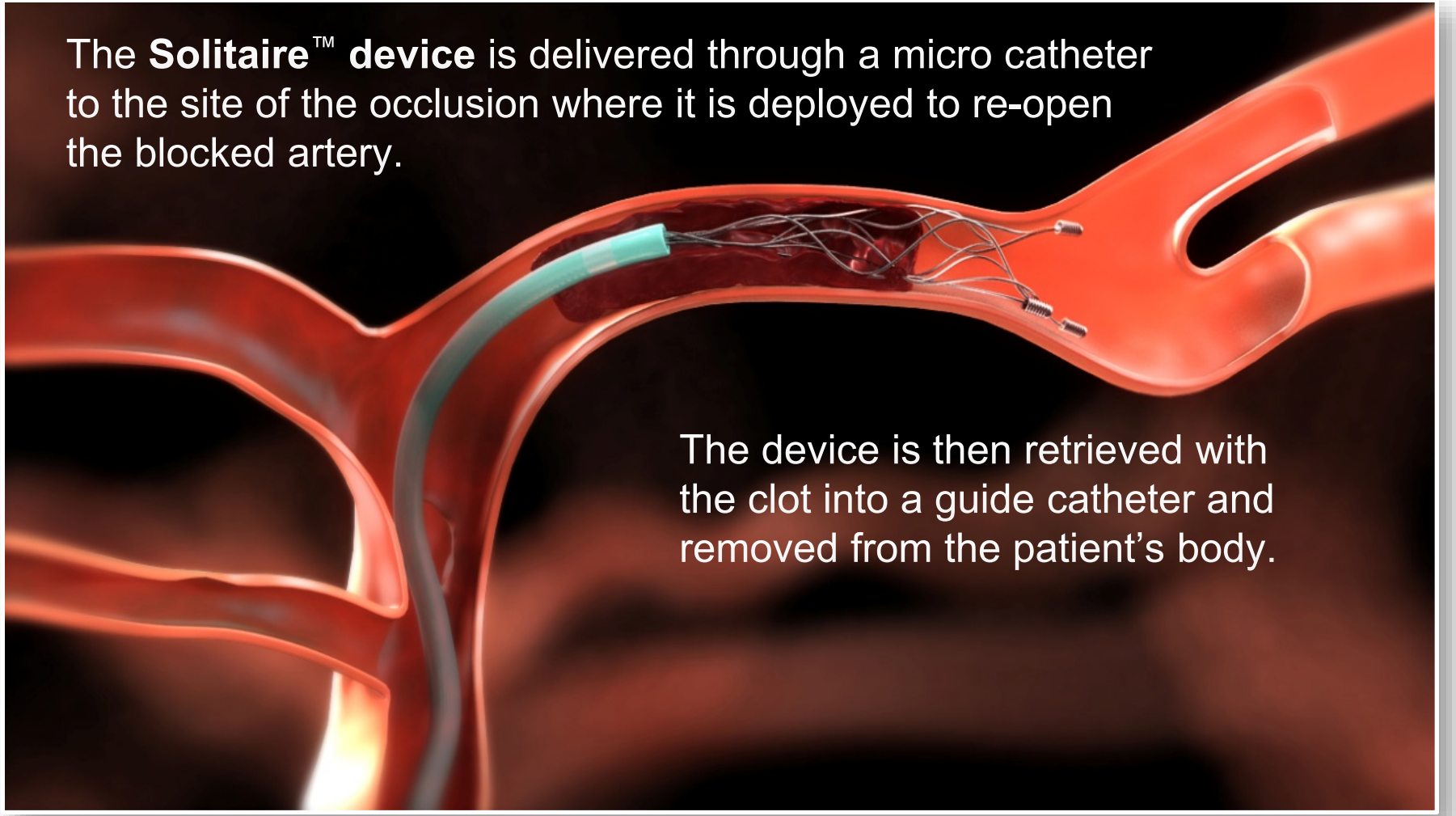
Technological advances

- Stent-retriever technology for safe, reliable performance

- Significant improvement in revascularization and patient outcomes vs older technology, proven in randomized clinical trials*

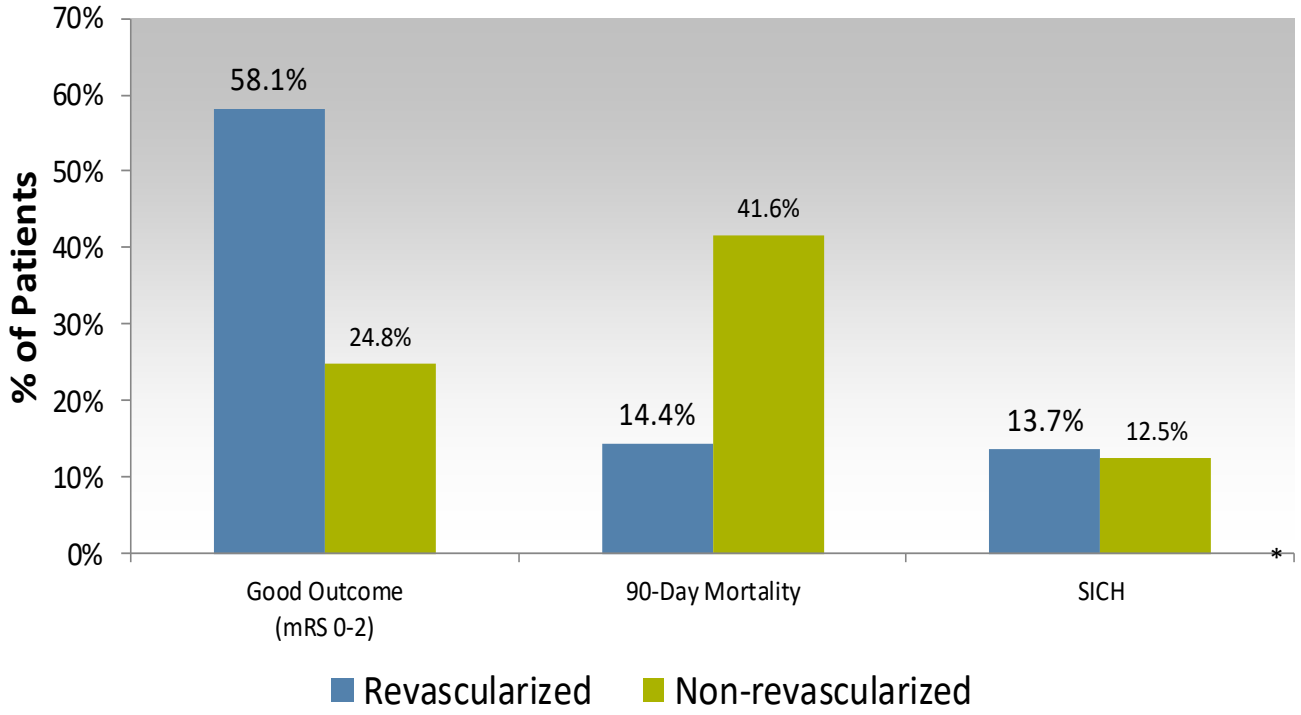


Breakthrough Stroke Treatment



Minimizing stroke damage

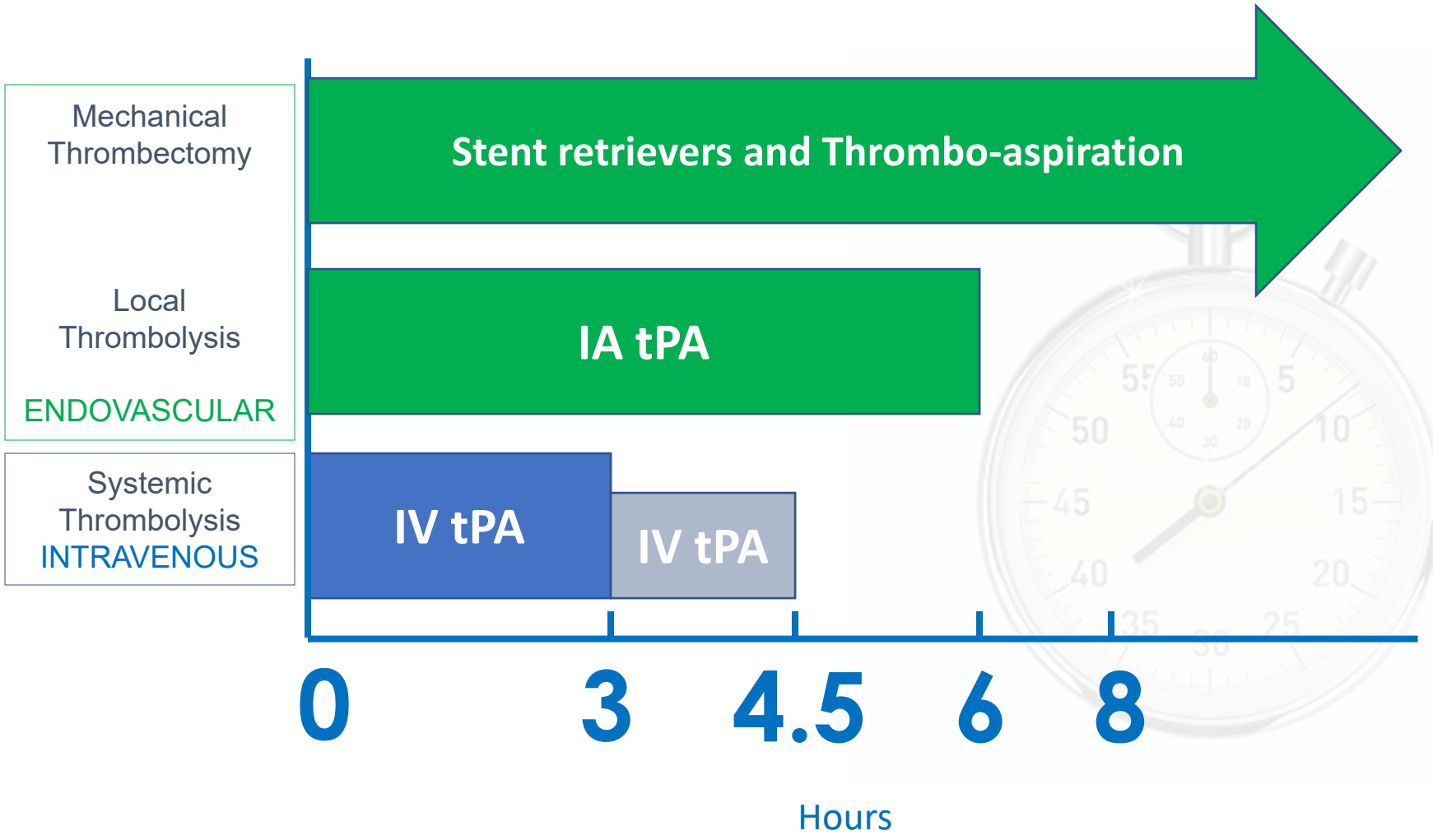
Meta-analysis Shows a Strong Correlation Between Revascularization and Good Patient Outcomes



*Differences in sICH were not statistically significant between the revascularized and non-revascularized groups

Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke. 2007 Mar;38(3):967-73.

Recanalization Strategies



Previous Stroke Trials Failed to Show Benefit in Endovascular

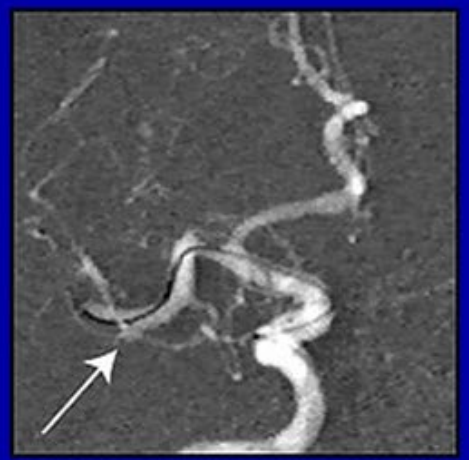
- Past trials of endovascular stroke treatment failed to show benefit in the intervention arm
  - IMS 3, MR RESCUE, SYNTHESIS-Expansion

- Key learnings to improve IA Stroke trial results:
  - Imaging to confirm large vessel occlusion
  - Imaging to exclude patients with a large infarct core
  - Improve time to treatment
  - Use newest devices to improve recanalization rates

Positive Endovascular Stroke Trials

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

Stroke Therapy Timeline



MR CLEAN
SWIFT PRIME
EXTEND IA
ESCAPE
REVASCAT
THERAPY

IV tPA

PROACT II
IA tPA

Angioplasty
Stenting

MERCI

Penumbra
Bridging IV/IA
IV tPA (4.5h)

Solitaire
Trevo
ACE

Level I
Evidence

Generation 1

Generation 2

Generation 3

1995

2000

2005

2010

2015

FDA Approved - Yellow

Off-label - Red

Evolution of IA Therapy Trials over time

Positive Trials

Negative Trials

PROACT II
1999

MELT
2007

IMS III
2013

MR Rescue
2013

Synthesis
2013

MR Clean
2014

ESCAPE
2015

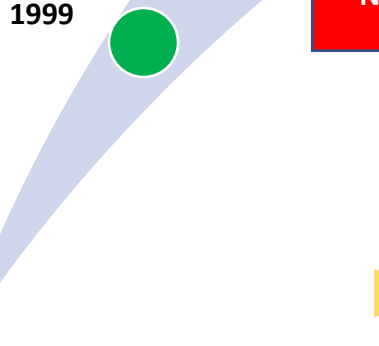
EXTEND IA
2015

SWIFT PRIME
2015

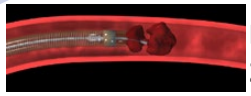
REVASCAT
2015

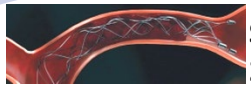
THERAPY
2015

Recanalization rate over time


Micro-catheter
1990s


MERCI
2004


Penumbra
2008


Stent-retriever
2012

More Positive Trials with newer devices and technology over time .Positive Trials: Circles at the upper border, Negative Trials: Circle at the lower border. Results Pending: Circle in the middle.

HERMES

2016 meta-analysis of ischaemic stroke trials performed 2010 to 2015:

1. MR CLEAN
2. ESCAPE
3. REVASCAT
4. SWIFT PRIME
5. EXTEND IA

Ischaemic stroke of proximal arterial circulation on CTA or MRA

Symptom onset <6hours

Use of second generation neurothrombectomy devices + standard care (Intervention) vs standard care (control).

Modified Rankin Score assessment at 90 days.

Results:

1287 participants. Median age 68. Equal gender.

Site of occlusion - internal carotid 21%, M1 69% and M2 8%.

Symptom onset to reperfusion - median 285 min (210 - 362min)

Conclusions:

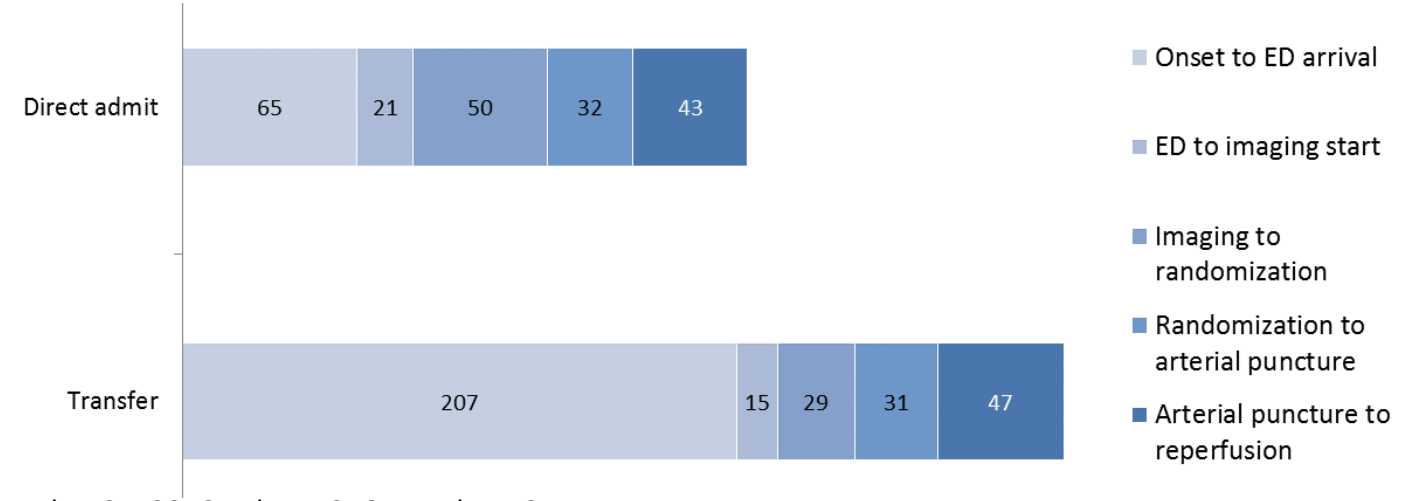
Significantly reduced disability at 90 days compared with control.

Number needed to treat to reduce disability of at least 1 point - 2.6

Mortality at 90 days and risk of IC bleed did not differ between populations.

HERMES: Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke:
A Meta-analysis

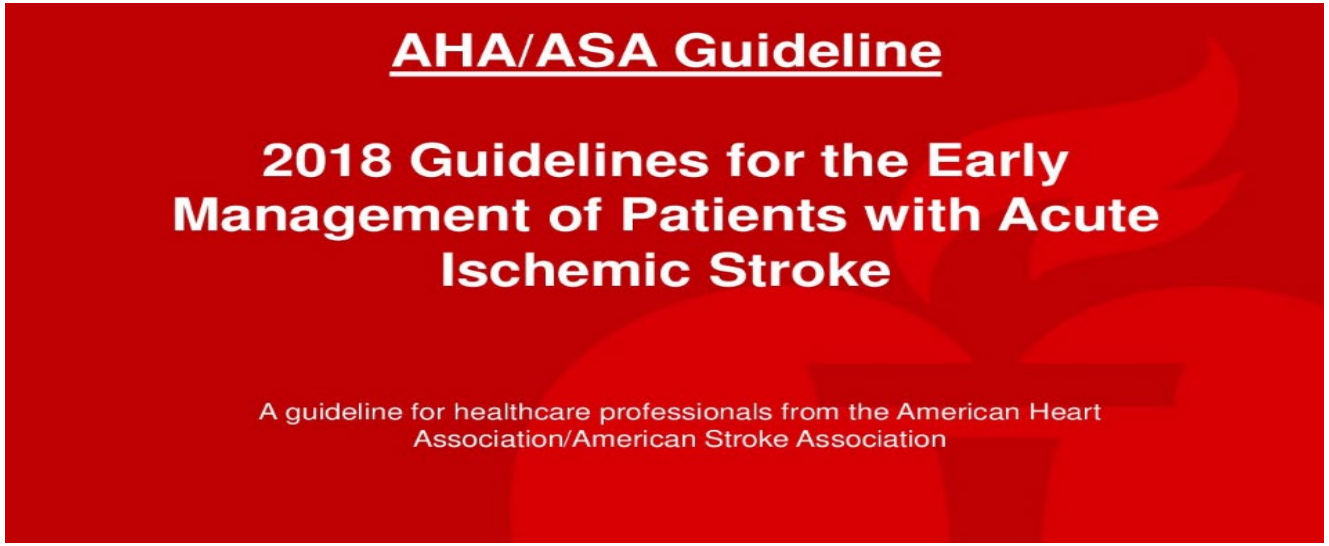
- 1287 patients : 634 patients in the interventional arm vs 653 in the control arm
- A time to treatment analysis
- Benefit of endovascular treatment retained significance through 7hrs and18 minutes
- Rates of functional independence after thrombectomy were 64% with reperfusion at 3 hours vs 46% with reperfusion at 8 hours.
- **Every 9-minute delay** in onset–to– endovascular reperfusion, **1%** of treated patients had a worse disability outcome (higher score by 1 or more levels on the mRS).
- **Every 4-minute delay** in door-to-reperfusion, **1%** of treated patients had a worse disability outcome
- Direct vs transfer patient's workflow times:



JAMA September 27, 2016 Volume 316, Number 12

2018-2019 Acute Stroke Guidelines

Who should we treat ?



defuse·3

DAWN™ TRIAL

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
7. In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.	I	A	New recommendation.
8. In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.	IIa	B-R	New recommendation.

DEFUSE3

Multicenter, randomised and blinded outcome assessment trial. NEJM - Jan 2018.

Endovascular therapy plus medical therapy v medical therapy alone.

Patient eligibility:

1. Previously well with onset of symptoms 6-16 hours to reperfusion

1. CTA or MRA with:
    a. Infarct volume <70ml
    b. Ratio of ischaemic tissue to infarct volume 1.8
    c. Potential reversible ischaemia of 15ml>
    d. Occlusion of proximal MCA or intracranial carotid

Results:

182 patients. Median age 70. Gender equal.

Site of occlusion: internal carotid (35%) and MCA (65%).

Symptom onset to reperfusion - Median 12.05hrs (9.14-14.06hrs).

Conclusions:

Favourable shift in function outcomes on the modified Rankin Scale at 90 days with reduced mortality (14% v 26%).

No significant increase in serious adverse events.

defuse·3

Conclusions

- DEFUSE 3 extends late window therapy to larger population
- Substantial clinical benefit across the disability spectrum
- Two positive trials justify a new standard of care
- Substantial impact on stroke imaging, triage and treatment
- New perspective on “time is brain”

DEFUSE 3 Investigators, NEJM, Jan 24, 2018

DAWN

Multicenter, randomised and blinded outcome assessment trial. Trial ceased early. NEJM - Jan 2018.

Endovascular therapy plus medical therapy v medical therapy alone in patients with mismatch between deficit and infarct.

Patient eligibility:

1. Previously well with onset of symptoms 6-24 hours to reperfusion

1. Mismatch between the severity of the clinical deficit and infarct volume (NIHSS score v infarct volume).

1. CTA or MRA with an occlusion of proximal MCA or intracranial carotid

Results:

206 patients. Median age 70. Gender equal.

Site of occlusion: internal carotid and MCA .

NIHSS score - median 17. Median infarct volume 7.6ml.

Symptom onset to reperfusion – 6-12hrs (55%) 12-24hrs (43%)

Conclusions:

Favourable shift in function outcomes on the modified Rankin Scale at 90 days with significant reduction in severe disability and death (25% v 42%).

No significant increase in serious adverse events.

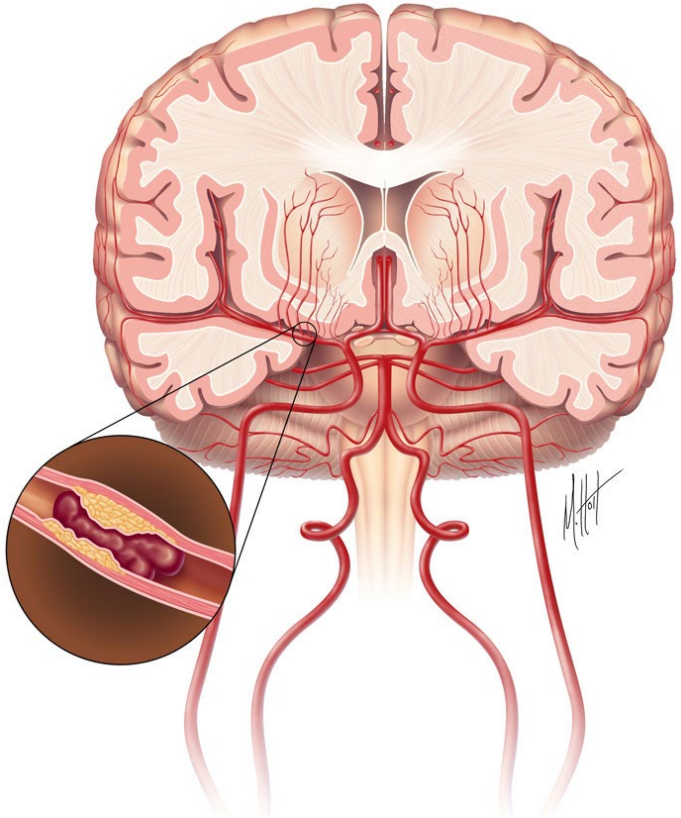
Number needed to treat to achieve an additional 1 functional point on modified Rankin score - 2.8.

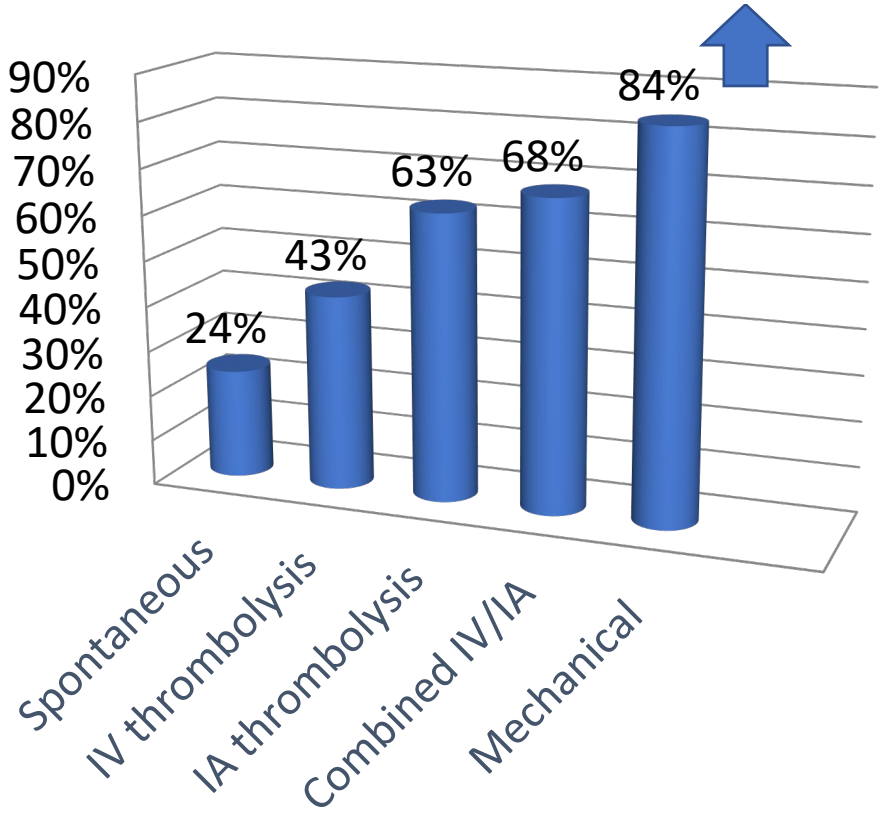
Limitations:

Patient enrolments were restricted to those with small or medium volume infarcts.

Improving stroke outcome

- Revascularize **Faster + Better**





Endovascular therapy:

DOUBLES the rate of good neurological outcomes (71% vs. 40%)

Reduces the rate of mortality by HALF (9% vs. 20%) compared to standard of care treatment alone.

THINK ABOUT IT

In order to have one additional stroke patient be independent at 90 days

Primary PCI vs. Thrombolysis for STEMI: Prevention of MI/Stroke/Death

Future effort

Penumbral Imaging – Identifying salvageable tissue

“Wake up” strokes and unknown time of onset

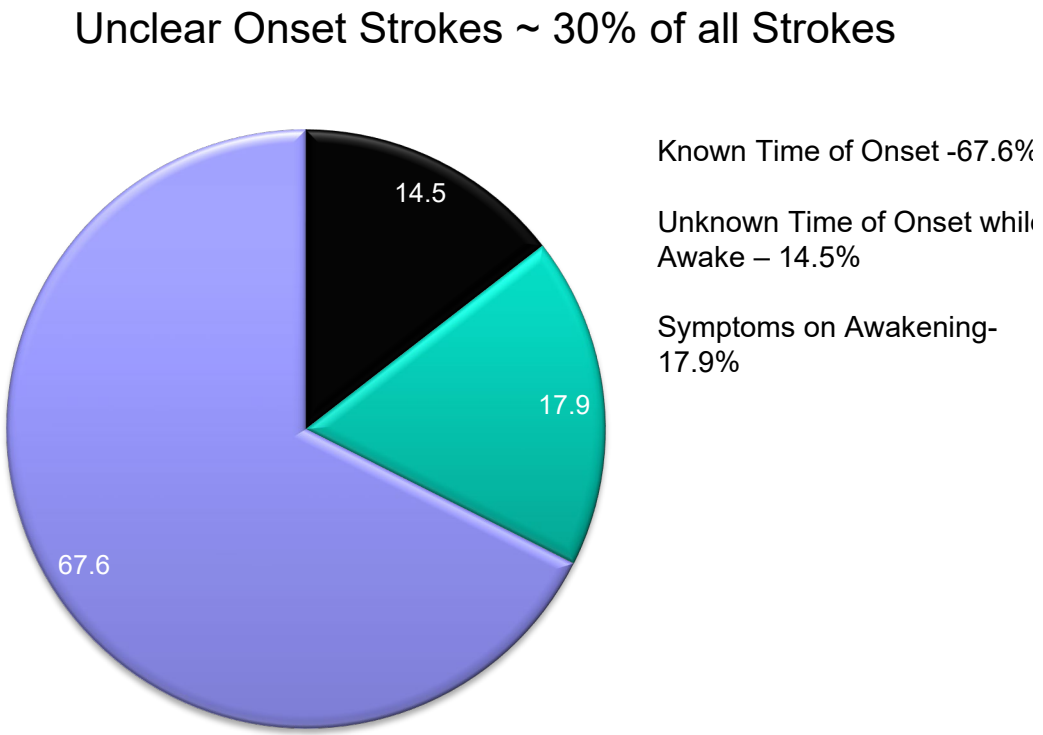
- DAWN, DEFUSE 3

Improving systems of care

- On field identification of ELVO (RACE, LAMS, VAN)
- Faster routing/transfer to CSC
- Faster door to groin times

Expanding the Therapeutic Window for Acute Ischemic Stroke: *Wake-up or Unwitnessed Stroke Onset*

- ~10% of stroke patients arrive within 4.5 hours of symptom onset and can be treated with IV tPA
- Up to 1/3 of stroke patients wake-up with stroke symptoms or have unwitnessed onset
- Historically, they are disqualified from acute treatments



J Stroke Cerebrovasc. Dis. 2011

WAKE UP TRIAL 2018

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 16, 2018 VOL. 379 NO. 7

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*

ABSTRACT

BACKGROUND

Under current guidelines, intravenous thrombolysis is used to treat acute stroke only if it can be ascertained that the time since the onset of symptoms was less than 4.5 hours. We sought to determine whether patients with stroke with an unknown time of onset and features suggesting recent cerebral infarction on magnetic resonance imaging (MRI) would benefit from thrombolysis with the use of intravenous alteplase.

METHODS

In a multicenter trial, we randomly assigned patients who had an unknown time of onset of stroke to receive either intravenous alteplase or placebo. All the patients had an ischemic lesion that was visible on MRI diffusion-weighted imaging but no parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR), which indicated that the stroke had occurred approximately within the previous 4.5 hours. We excluded patients for whom thrombectomy was planned. The primary end point was favorable outcome, as defined by a score of 0 or 1 on the modified Rankin scale of neurologic disability (which ranges from 0 [no symptoms] to 6 [death]) at 90 days. A secondary outcome was the likelihood that alteplase would lead to lower ordinal scores on the modified Rankin scale than would placebo (shift analysis).

RESULTS

The trial was stopped early owing to cessation of funding after the enrollment of 503 of an anticipated 800 patients. Of these patients, 254 were randomly assigned to receive alteplase and 249 to receive placebo. A favorable outcome at 90 days was reported in 131 of 246 patients (53.3%) in the alteplase group and in 102 of 244 patients (41.8%) in the placebo group (adjusted odds ratio, 1.61; 95% confidence interval [CI], 1.09 to 2.36; P=0.02). The median score on the modified Rankin scale at 90 days was 1 in the alteplase group and 2 in the placebo group (adjusted common odds ratio, 1.62; 95% CI, 1.17 to 2.23; P=0.003). There were 10 deaths (4.1%) in the alteplase group and 3 (1.2%) in the placebo group (odds ratio, 3.38; 95% CI, 0.92 to 12.52; P=0.07). The rate of symptomatic intracranial hemorrhage was 2.0% in the alteplase group and 0.4% in the placebo group (odds ratio, 4.95; 95% CI, 0.57 to 42.87; P=0.15).

CONCLUSIONS

In patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hemorrhages than placebo at 90 days. (Funded by the European Union Seventh Framework Program; WAKE-UP ClinicalTrials.gov number, NCT01525290; and EudraCT number, 2011-005906-32.)

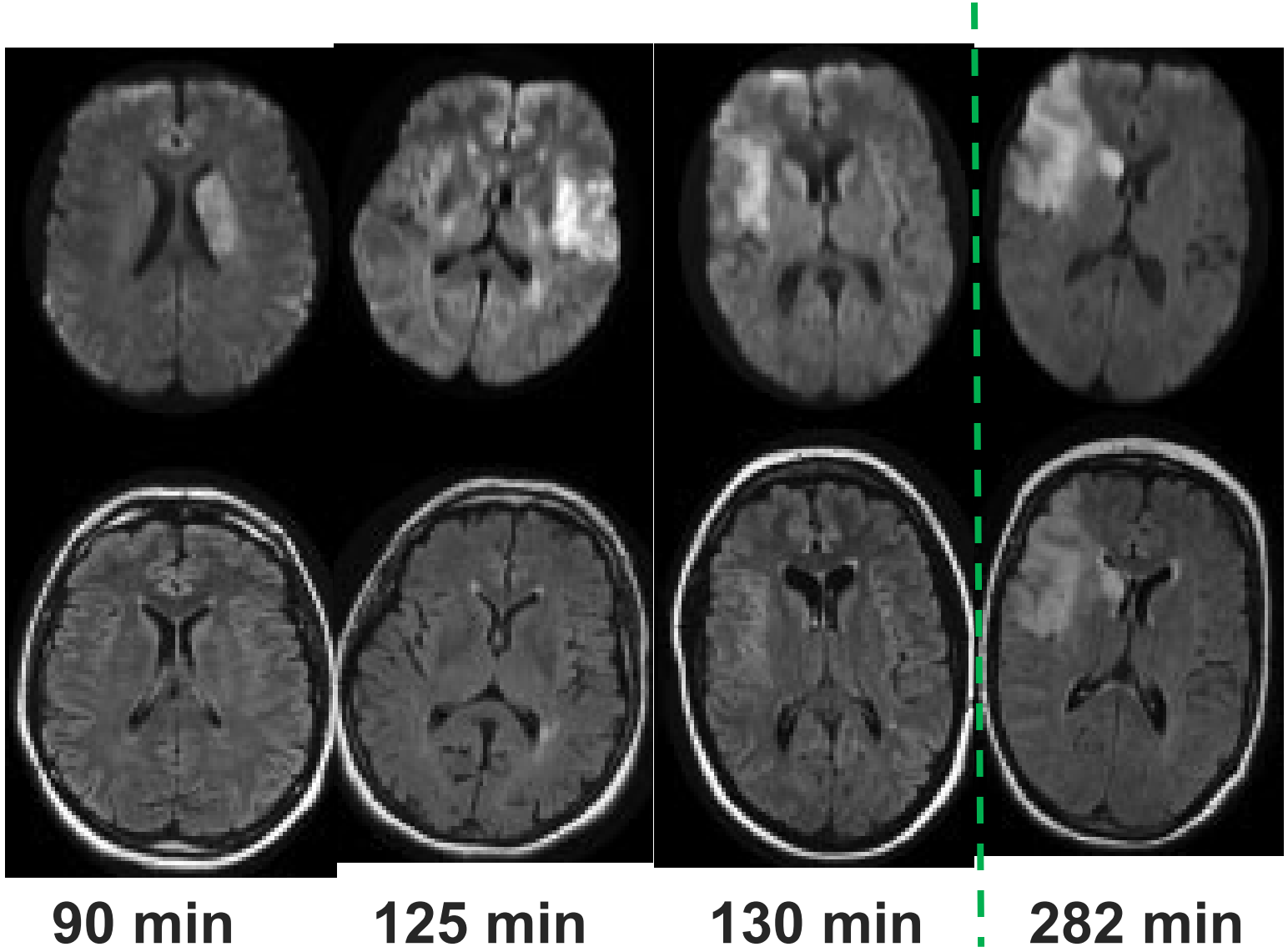
The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Thomalla at Klinik und Poliklinik für Neurologie, Universitätsklinikum Hamburg–Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany, or at thomalla@uke.de; or to Dr. Gerloff at gerloff@uke.de.

*A complete list of investigators in the WAKE-UP trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 16, 2018, at NEJM.org.

N Engl J Med 2018;379:611-22.
DOI: 10.1056/NEJMoa1804355

DWI (positive) FLAIR (negative) mismatch may identify Strokes < 4.5 hours old



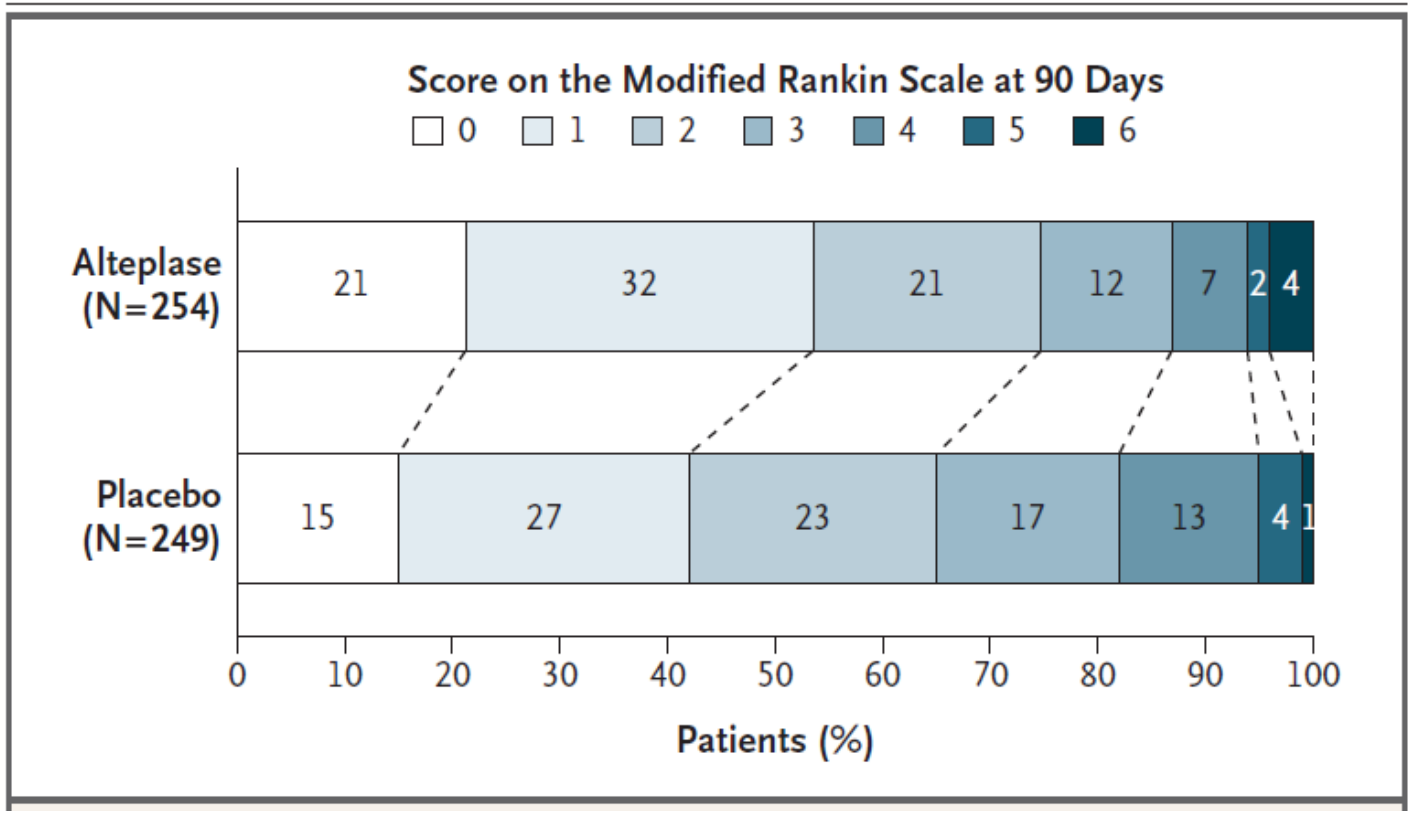
Thomalla et al. Ann Neurol. 2009

WAKE-UP Stroke Trial

- Acute stroke with “last known normal” time > 4.5 hrs (no upper time limit)
- Met standard eligibility criteria for the use of alteplase
- Had DWI-FLAIR mismatch (abnormal signal on DWI and no marked signal change on FLAIR in the region of the acute stroke).
- Excluded:
  - Large strokes > 1/3 of MCA or NIHSS > 25
  - Planned thrombectomy
- The primary endpoint was favorable outcome, defined as mRS = 0-1 at 90 days
- Randomized to Alteplase vs. Placebo within 4.5 hrs of awakening or “symptom discovery”

Thomalla et al. NEJM 2018.

WAKE-UP Stroke Trial



Primary Outcome

Alteplase: 53.3% mRS 0-1

Placebo: 41.8% mRS 0-1

P=0.02

NNT = 8

Shift in distribution of mRS scores of 90 day functional disability

P = 0.003

Thomalla et al. NEJM

2019 AHA Acute Stroke Guidelines

3. In patients with AIS who awake with stroke symptoms or have unclear time of onset > 4.5 hours from last known well or at baseline state, MRI to identify diffusion-positive FLAIR-negative lesions can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition.	**IIa**	**B-R**	New recommendation.
The WAKE-UP trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) randomized 503 patients with AIS who awoke with stroke or had unclear time of onset >4.5 hours from last known well and could be treated with IV alteplase within 4.5 hours of stroke symptom recognition. Eligibility required MRI mismatch between abnormal signal on DW-MRI and no visible signal change on FLAIR. DW-MRI lesions larger than one-third of the territory of the middle cerebral artery (MCA), NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. The trial was terminated early for lack of funding before the designated 800 patients were randomized. Ninety-four percent were wake-up strokes. Median NIHSS score was 6. Median time from last known well was slightly over 10 hours. At baseline, one-third of the patients had vessel occlusion on time-of-flight MRA, and three-quarters of the FLAIR lesions were <9 mL. The end point of an mRS score of 0 to 1 at 90 days was achieved in 53.3% of the IV alteplase group and in 41.8% of the placebo group (P=0.02).[88]			See Table XIX in online Data Supplement 1

EXTEND-IA TNK Trial

- Campbell et al. NEJM 2018.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 26, 2018 VOL. 378 NO. 17

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

B.C.V. Campbell, P.J. Mitchell, L. Churilov, N. Yassi, T.J. Kleinig, R.J. Dowling, B. Yan, S.J. Bush, H.M. Dewey, V. Thijs, R. Scroop, M. Simpson, M. Brooks, H. Asadi, T.Y. Wu, D.G. Shah, T. Wijeratne, T. Ang, F. Miteff, C.R. Levi, E. Rodrigues, H. Zhao, P. Salvaris, C. Garcia-Esperon, P. Bailey, H. Rice, L. de Villiers, H. Brown, K. Redmond, D. Leggett, J.N. Fink, W. Collecutt, A.A. Wong, C. Muller, A. Coulthard, K. Mitchell, J. Clouston, K. Mahady, D. Field, H. Ma, T.G. Phan, W. Chong, R.V. Chandra, L.-A. Slater, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Steinfort, C.F. Bladin, G. Sharma, P.M. Desmond, M.W. Parsons, G.A. Donnan, and S.M. Davis, for the EXTEND-IA TNK Investigators*

EXTEND-IA TNK Trial Rationale

Both alteplase and tenecteplase are fibrinolytics

Tenecteplase (TNK) is a genetically modified form of alteplase with increased fibrin specificity and increased resistance to plasminogen activator inhibitor (PAI-1) thereby leading to a longer half-life.

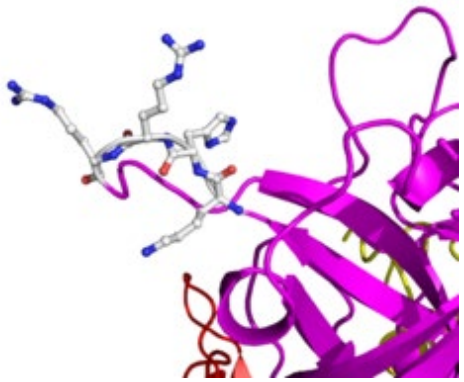
TNK is given as a single bolus rather than a one hour infusion.

~$3000 cheaper than alteplase, both made by Genentech

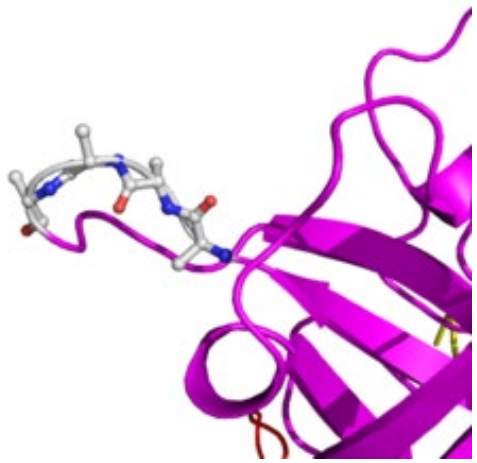
An agent with enhanced fibrinolytic activity, to reduce the need for thrombectomy, would be ideal.

TNK has replaced alteplase as standard fibrinolytic agent for acute myocardial infarction.

alteplase



tenecteplase

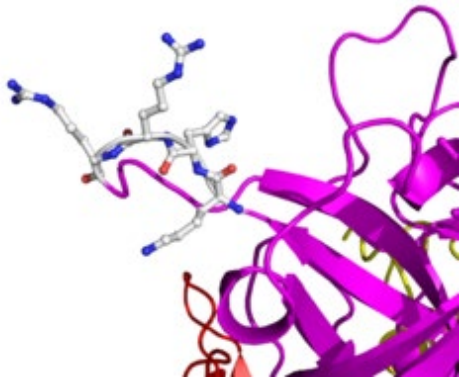


Campbell et al. NEJM 2018.

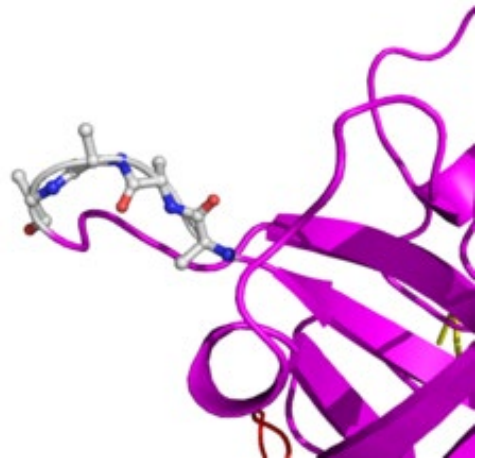
EXTEND-IA TNK Methods

Hypothesis:	Inclusion criteria:	Randomized TNK 0.25 mg/kg or alteplase 0.9 mg/kg	Primary outcome: Initial angiogram modified TICI reperfusion score
• Tenecteplase is non-inferior to alteplase in achieving reperfusion at initial angiogram in patients planning to undergo endovascular therapy • Superiority testing if non-inferiority was met	• Eligible for thrombolytics <4.5 hours • Patients with LVO (ICA, M1, M2, or basilar artery) and could undergo thrombectomy in < 6 hours		

alteplase

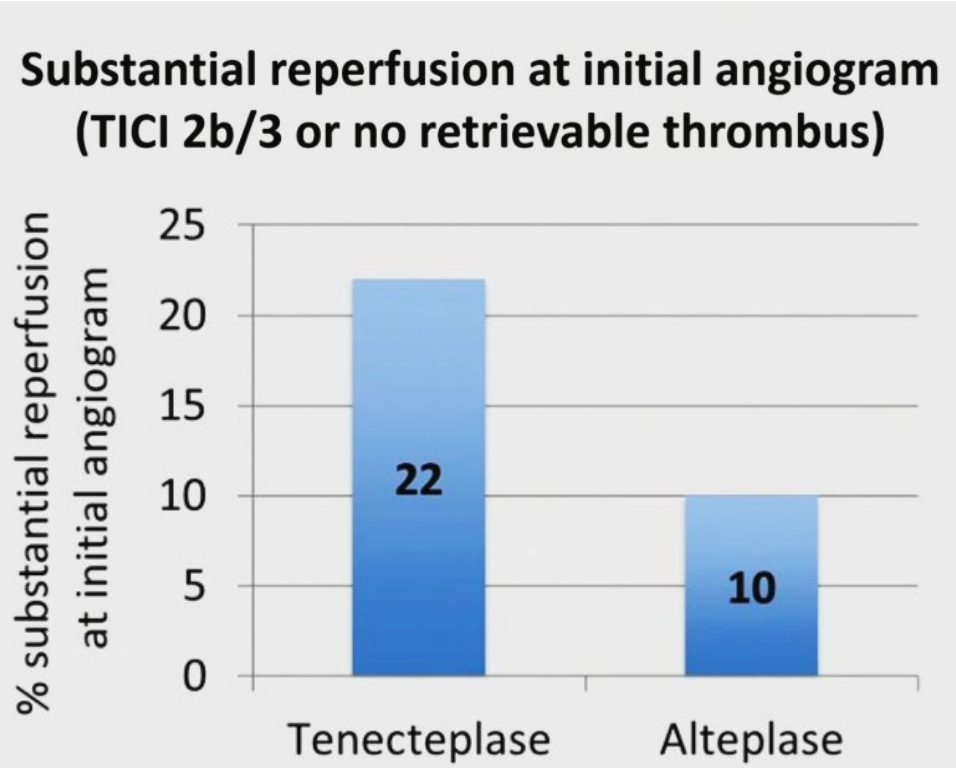


tenecteplase



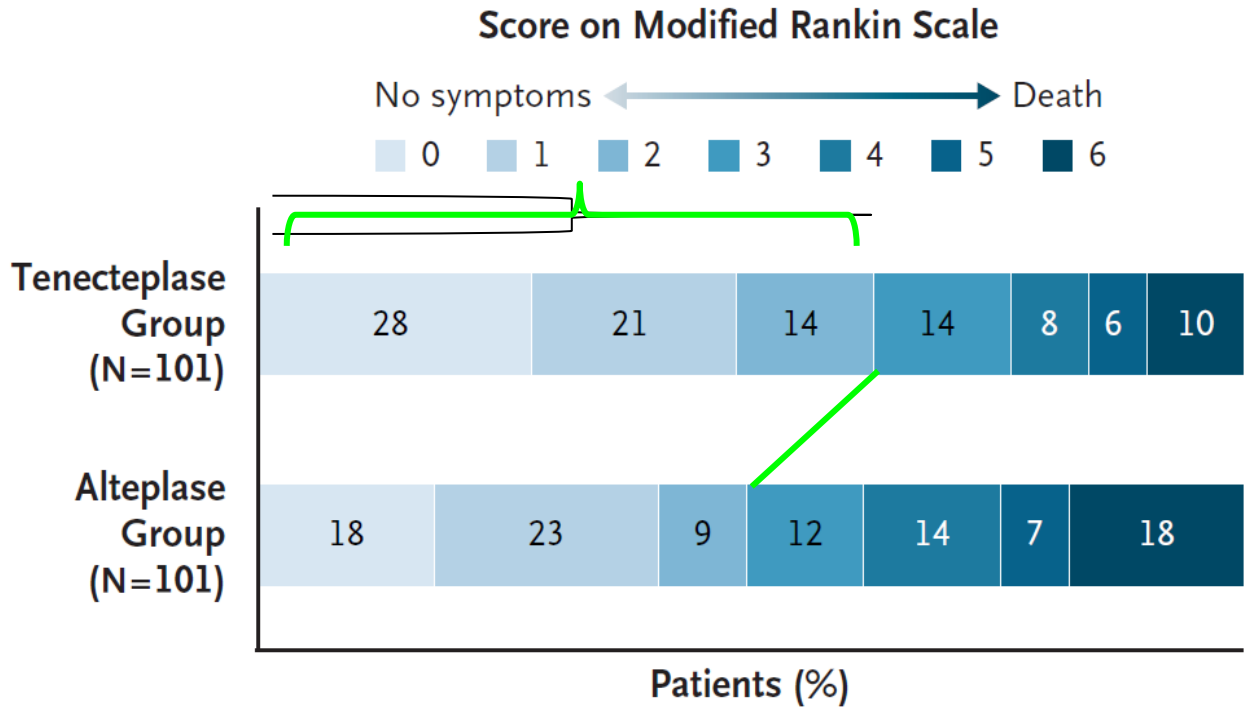
EXTEND-IA TNK Results

Primary Endpoint



P = 0.002 Non-Inferiority
P = 0.02 Superiority

Secondary Endpoint



P = 0.04

EXTEND-IA TNK Conclusions

- Superior reperfusion at initial angiogram
  - NNT 9 to avoid thrombectomy altogether
- Faster infusion / Less expensive
- *However,* giving TNK instead of alteplase to only thrombectomy candidates affects alteplase delivery to non-thrombectomy candidates as CTA must be performed prior to giving the thrombolytic to decide who will go on to thrombectomy and benefit from TNK
  - Current best application may be for OSH transferring patients in for thrombectomy
- Two trials (TASTE and ATTEST-2) are enrolling patients for comparison of tenecteplase vs. alteplase in non-thrombectomy patients

- Campbell et al. NEJM 2018.

2019 AHA Guidelines

3.6. Other IV Fibrinolytics and Sonothrombolysis	COR	LOE	New, Revised, or Unchanged
1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.	**IIb**	**B-R**	New recommendation.
IV tenecteplase (0.25 mg/kg bolus, maximum 25 mg) was compared with IV alteplase (usual dose of 0.9 mg/kg over 60 minutes, maximum 90 mg) in the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke).[178] This multicenter trial randomized 202 patients without previous severe disability and with documented occlusion of the internal carotid artery, proximal MCA (M1 or M2 segments), or basilar arteries presenting within 4.5 hours of symptom onset to receive 1 of these 2 fibrinolytic agents. Primary end point was reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The trial was designed to test for noninferiority and, if noninferiority proven, for superiority. Secondary outcomes included the mRS score at 90 days. Median NIHSS score was 17. The primary end point was achieved by 22% of patients treated with tenecteplase versus 10% of those treated with alteplase (*P*=0.002 for noninferiority and 0.03 for superiority). In an analysis of secondary end points, tenecteplase resulted in better functional outcomes at 90 days on the basis of the ordinal shift analysis of the mRS score (common OR [cOR], 1.7 [95% CI, 1.0–2.8]; *P*=0.04) but less robustly for the proportion who achieved an mRS score of 0 to 1 (*P*=0.23) or 0 to 2 (*P*=0.06). sICH rates were 1% in both groups.			See Table XLIII in online Data Supplement 1.
2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	**IIb**	**B-R**	New recommendation.
IV tenecteplase has been compared with IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase.[179–182] In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion.[182] Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.			See Table XLIII in online Data Supplement 1.

AHA/JOINT COMISSION STANDARDS

- American Heart Association and The Joint Commission have helped push evidence to the forefront of practice
- Setting up requirements for various levels of treating centers to meet current evidence-based standards to become certified
  - *Acute Stroke Ready Hospital (ASRH)*
  - *Primary Stroke Center (PSC)*
  - *Thrombectomy-Capable Stroke Center (TSC)*
  - *Comprehensive Stroke Center (CSC)*
- Defined by acute stroke team availability, 24/7 imaging, thrombectomy capability, neurosurgical consultation

Thank You