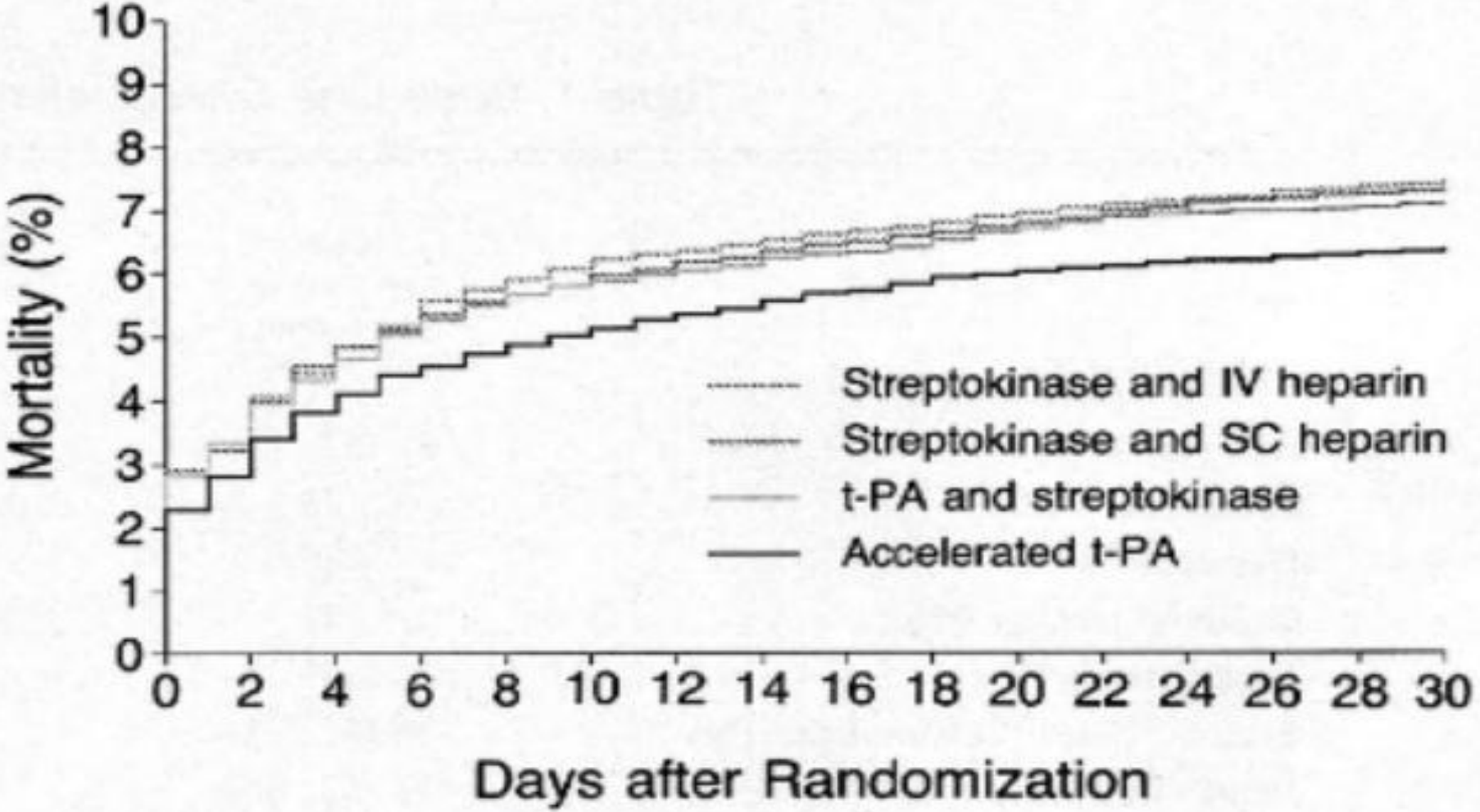
Acute Stroke Reperfusion 2025

tPA vs TNK


Mortality (%)
10
9
8
7
6
5
4
3
2
1
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Days after Randomization
Streptokinase and IV heparin
Streptokinase and SC heparin
t-PA and streptokinase
Accelerated t-PA

JACC Vol. 9, No. 6
June 1987:1205–13

COOPERATIVE STUDIES

A Multicenter, Randomized, Placebo-Controlled Trial of a New Form of Intravenous Recombinant Tissue-Type Plasminogen Activator (Activase) in Acute Myocardial Infarction*

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A new, predominantly single chain preparation of recombinant tissue-type plasminogen activator was evaluated to determine coronary thrombolytic efficacy in 100 patients with acute myocardial infarction. At 3.6 ± 1.2 hours (mean ± SD) from symptom onset, patients received either intravenous tissue plasminogen activator (1.25 mg/kg body weight over 3 hours) or placebo on a 3:1 randomized, double-blind basis. Coronary angiography, performed 68 ± 13 minutes after initiation of the study drug infusion, demonstrated patency of the infarct-related artery in 40 (57%) of 70 patients in the tissue plasminogen activator group compared with 3 (13%) of 23 patients in the placebo group ($p < 0.001$). Patients in the placebo group were then eligible to receive intracoronary streptokinase. At 90 minutes the patency was observed in 49 (69%) of 71 tissue plasminogen activator patients compared with 5 (24%) of 21 placebo patients ($p < 0.001$). At 120 minutes patency was observed in 59 (79%) of 75 patients of the tissue plasminogen activator group and in 10 (40%) of 25 in the intracoronary streptokinase/placebo group.

A nadir value of <100 mg/dl fibrinogen occurred in 8 (11%) of 73 patients receiving tissue plasminogen activator versus 8 (40%) of 20 patients treated with intracoronary streptokinase ($p = 0.002$). Moderate or severe bleeding episodes occurred in 39% of patients treated with tissue plasminogen activator compared with 32% of patients who received placebo/intracoronary streptokinase (p = NS). Thus, this tissue plasminogen activator preparation achieves a high rate of recanalization and, at the doses employed, exhibits increased fibrinogen sparing compared with intracoronary streptokinase.

(J Am Coll Cardiol 1987;9:1205–13)

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.)

FIBRINOLYTIC AGENTS

- ALTEPLASE (recombinant tissue-type plasminogen activator, tPA)
  - **naturally occurring enzyme** (serine protease)
  - In contrast to streptokinase, it is **fibrin-specific**
  - **fibrin-bound tPA has increased affinity for plasminogen and enhances its activation.**
  - Non-fibrin-bound tPA does not extensively activate plasminogen.
  - **Short half-life** (three to four minutes).
  - **Not associated with allergic or hypotensive effects**
  - **Intravenous heparin required** as concomitant therapy to maintain vessel patency and to prevent reocclusion

FIBRINOLYTIC AGENTS

- TNK-tPA (Tenecteplase)
  - **Genetically engineered**, multiple point mutant of recombinant tissue-type plasminogen activator (tPA)
  - Longer plasma half-life allowing for a **single intravenous bolus injection**.
  - **14 times more fibrin specific**
  - **80-fold higher resistance to inhibition** by plasminogen activator inhibitor 1 (PAI-1) than standard tPA
  - When compared to tPA
    - **Similar efficacy**
    - **Modestly less bleeding risk**
    - **Easier administration**

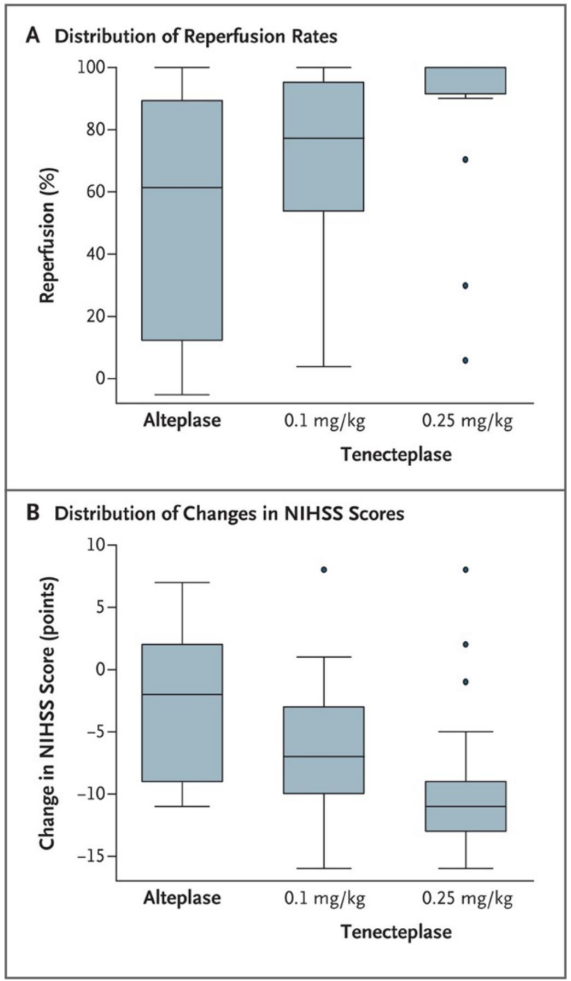
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke

Mark Parsons, M.D., Neil Spratt, M.D., Andrew Bivard, B.Sc., Bruce Campbell, M.D., et al.

March 22, 2012
N Engl J Med 2012; 366:1099-1107
DOI: 10.1056/NEJMoa1109842



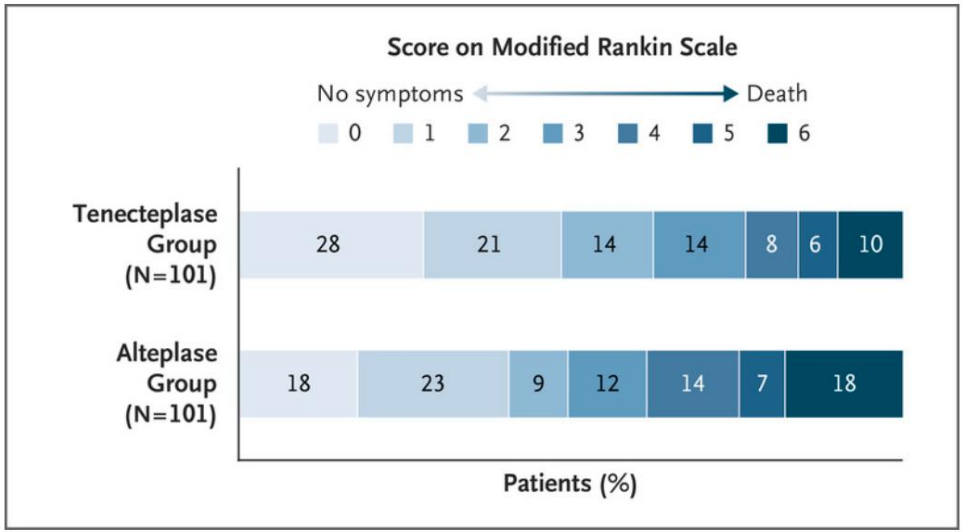
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

Bruce C.V. Campbell, Ph.D., Peter J. Mitchell, M.Med., Leonid Churilov, Ph.D., Nawaf Yassi, Ph.D., et al., for the EXTEND-IA TNK Investigators*

April 26, 2018
N Engl J Med 2018; 378:1573-1582
DOI: 10.1056/NEJMoa1716405



Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial

Bijoy K Menon, Brian H Buck, Nishita Singh, Yan Deschaintre, Mohammed A Almekhlafi, Shelagh B Coutts, Sibi Thirunavukkarasu, Houman Khosravani, Ramana Appireddy, Francois Moreau, Gord Gubitz, Aleksander Tkach, Luciana Catanese, Dar Dowlatshahi, George Medvedev, Jennifer Mandzia, Aleksandra Pikula, Jai Shankar, Heather Williams, Thalia S Field, Alejandro Manosalva, Muzaffar Siddiqui, Atif Zafar, Oje Imoukhuede, Gary Hunter, Andrew M Demchuk, Sachin Mishra, Laura C Gioia, Shirin Jalini, Caroline Cayer, Stephen Phillips, Elsadig Elamin, Ashkan Shoamanesh, Suresh Subramaniam, Mahesh Kate, Gregory Jacquin, Marie-Christine Camden, Faysal Benali, Ibrahim Alhabli, Fouzi Bala, MacKenzie Horn, Grant Stotts, Michael D Hill, David J Gladstone, Alexandre Poppe, Arshia Sehgal, Qiao Zhang, Brendan Cord Lethebe, Craig Doram, Ayoola Ademola, Michel Shamy, Carol Kenney, Tolulope T Sajobi, Richard H Swartz, for the AcT Trial Investigators

Summary

Background Intravenous thrombolysis with alteplase bolus followed by infusion is a global standard of care for patients with acute ischaemic stroke. We aimed to determine whether tenecteplase given as a single bolus might increase reperfusion compared with this standard of care.

Published Online June 29, 2022 https://doi.org/10.1016/S0140-6736(22)01054-6

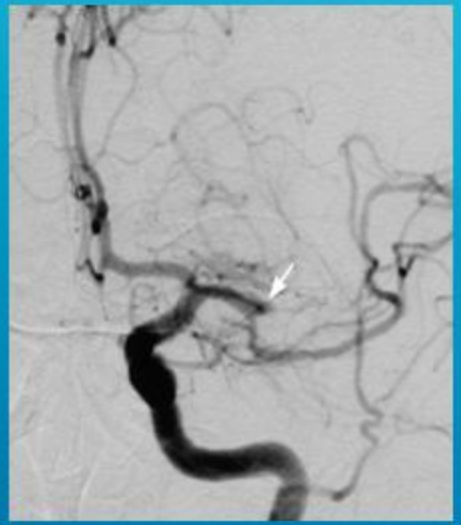
When to treat with thrombolytic?

NIHSS ≥ 4

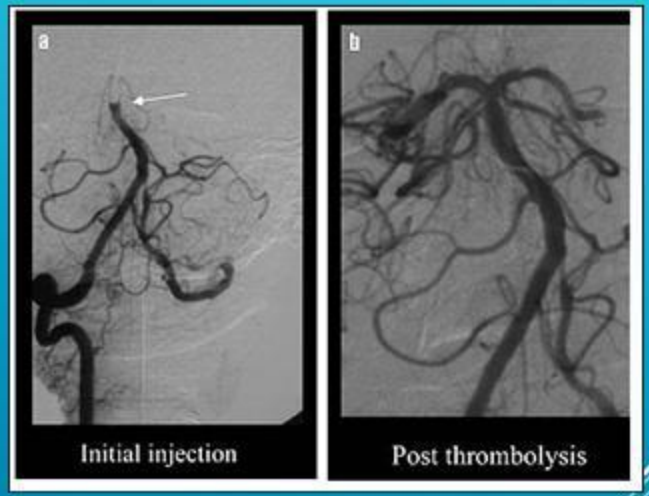
Disabling deficit even if stroke score < 4.
Examples: vision loss, speech/aphasia, gait.

Mild deficits we do not treat acutely.

CLINICAL OUTCOME IN PATIENTS WITH LARGE VESSEL OCCLUSION



75% dependence or death in non-treatment arm of PROACT II

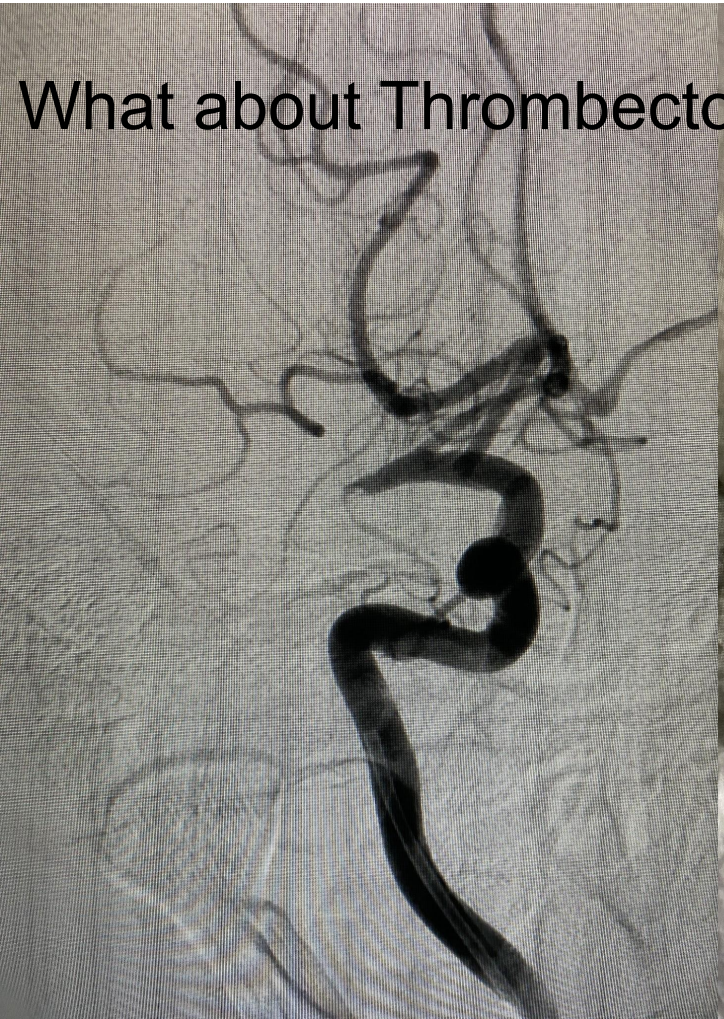


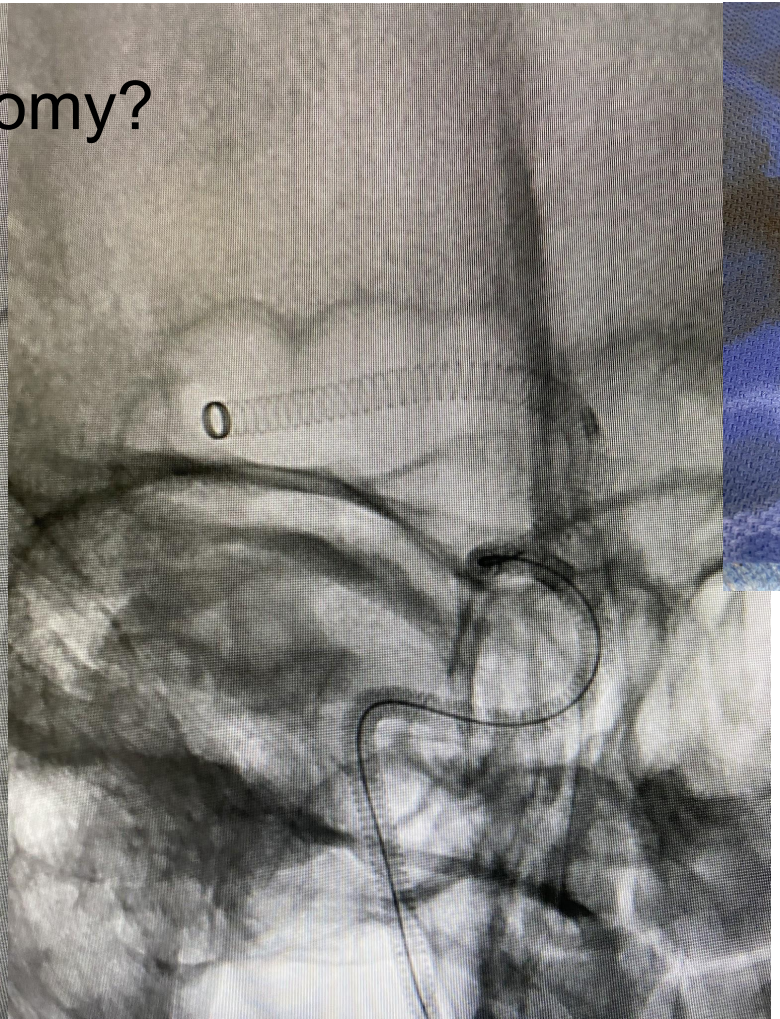
Natural history of 80-90% death and dependency.

Furlan, et al. JAMA. 1999;282:2003-2011.

Neurol Sci (2001) 22:399–402

What about Thrombectomy?





	SWIFT PRIME (Global)	EXTEND IA (AUS, NZ)	REVASCAT (Spain)	ESCAPE (Global)
Randomization of patients to IV TPA vs. IV TPA + Endovascular	✓	✓	✓	✓
Time Window Studied	Onset to 6 hours	Onset to 6 hours	Onset to 8 hours	Onset to 12 hours
Trial Funding Support	Funded by Medtronic	Funded by Medtronic Investigator Initiated	Funded by Medtronic Investigator Initiated	Funded by Medtronic Investigator Initiated
Number of Patients	196	70	206	316
Analysis of Primary Endpoint	Rankin Shift	Reperfusion at 24 hrs without sICH <72 hours	Rankin Shift	NIHSS 0-2 or mRS 0-2 at 90 days
Trial status	Efficacy endpoint met Trial Stopped	Efficacy endpoint met Trial Stopped	Efficacy endpoint met Trial Stopped	Efficacy endpoint met Trial Stopped
Data Status	Statistically significant benefit for stent thrombectomy with the Solitaire™ Device	Statistically significant benefit for stent thrombectomy with the Solitaire™ Device	Statistically significant benefit for stent thrombectomy with the Solitaire™ Device	Statistically significant benefit for stent thrombectomy with the Solitaire™ Device
ASPECTS	9	20 cc core infarct	7.5	9
Time to Treatment	**252 min**	**210 min**	**300 min**	**241 min**
Reperfusion Rate ≥ TICI 2b	88%	86%	65%	72%
Absolute Benfeit/NNT	**25%/4**	**31%/3**	**15%/6**	**24%/4**

**EXTEND-IA Study presented by Dr. Bruce Campbell at the International Stroke Congress 2015
*ESCAPE Study presented by Dr. Michael Hill at the International Stroke Congress 2015
*SWIFT PRIME Study presented by Dr. Jeff Saver at the International Stroke Congress 2015

True Impact of Stroke Intervention

If a particular intervention gives you a 10% benefit over another treatment, then 10 people would benefit out of 100 treated.

Number Needed to Treat=How many do you have to treat to achieve a benefit.

How many patients must go to a Level 1 Trauma Center to prevent 1 death?

How many patients must receive a PCI during a STEMI to prevent a death?

Day 90 mRS (0-2)	48.6%	13.1%	35.5% (23.9%, 47.0%)	>0.9999*

NNT for 90-day functional independence = 2.8

From 7/2013 to 4/2017, we have performed 70 interventions beyond 8 hours.

DAWN in Full Daylight

DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo

Tudor G. Jovin MD & Raul G. Nogueira MD
on behalf of the DAWN investigators

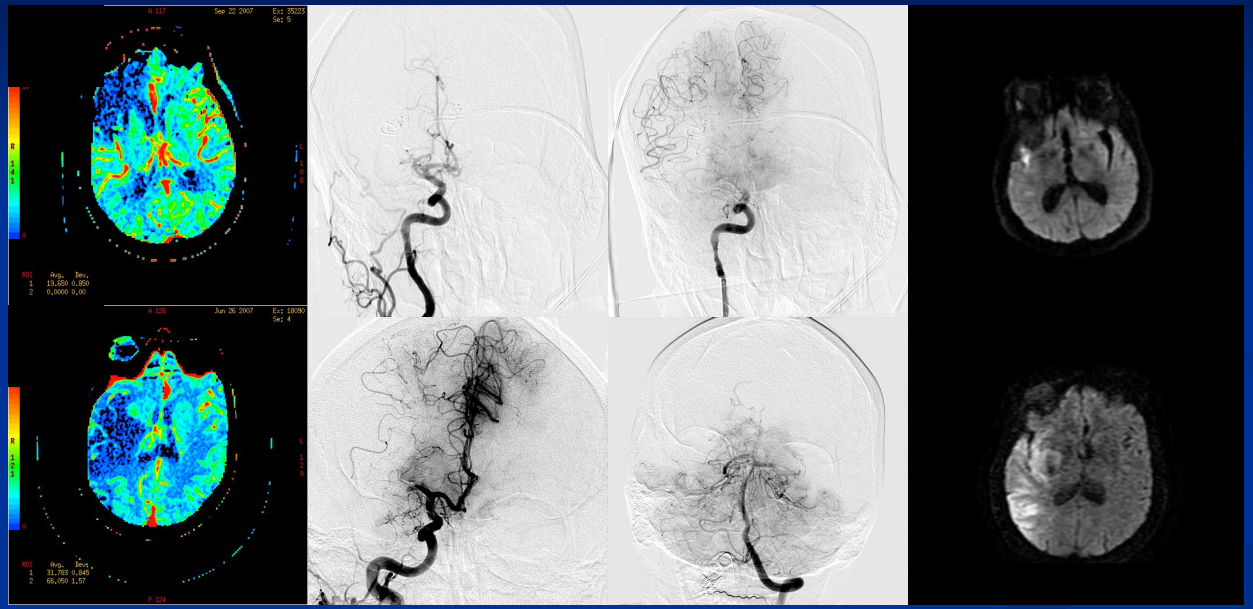
Indications for thrombectomy

Any large vessel symptomatic occlusion in the ICA, MCA, VA, Basilar artery

There is no time limit!!! Imaging will tell us whether a stroke is too far gone.

Better outcomes if we treat early and the most severe deficits. Jury is still out on mild deficits but 50% of mild deficit, LVO patients deteriorate.

2 Things about every stroke patient.



We have to stop thinking in terms of time. Every large vessel stroke patient may have the collaterals to sustain brain tissue and give them a chance at recovery if they can be re-refused.

Time is Brain

1.9 millions neurons/minute lost with ischemia.

In LVO, this can be as high as 27 million neurons/minute.

A 1 minute delay results in a loss of 5 days of independence.

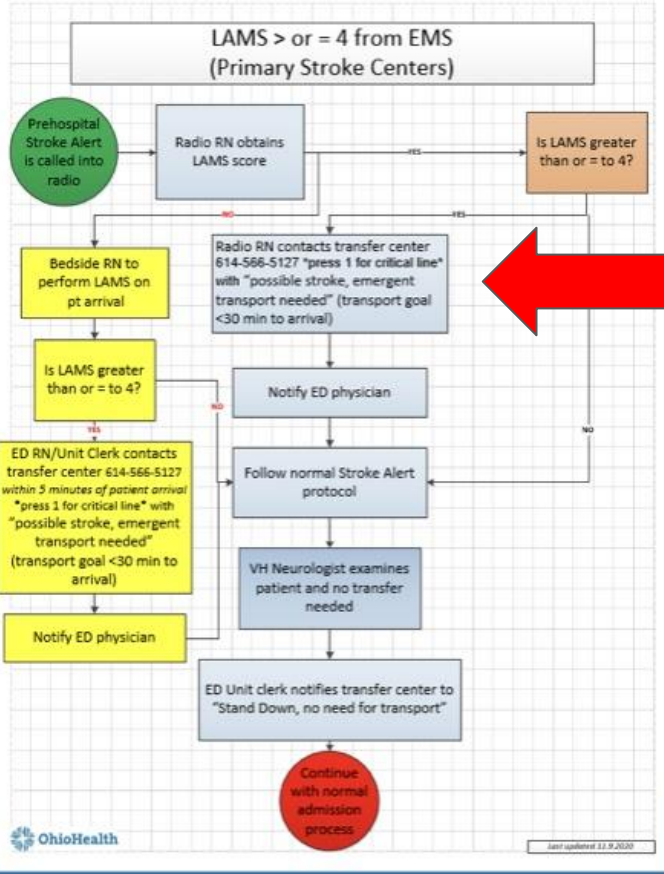
Stroke. 2006;37:263-266.
Stroke. 2019;50:34-37.
Neurology. 2017;88:2123-2127.

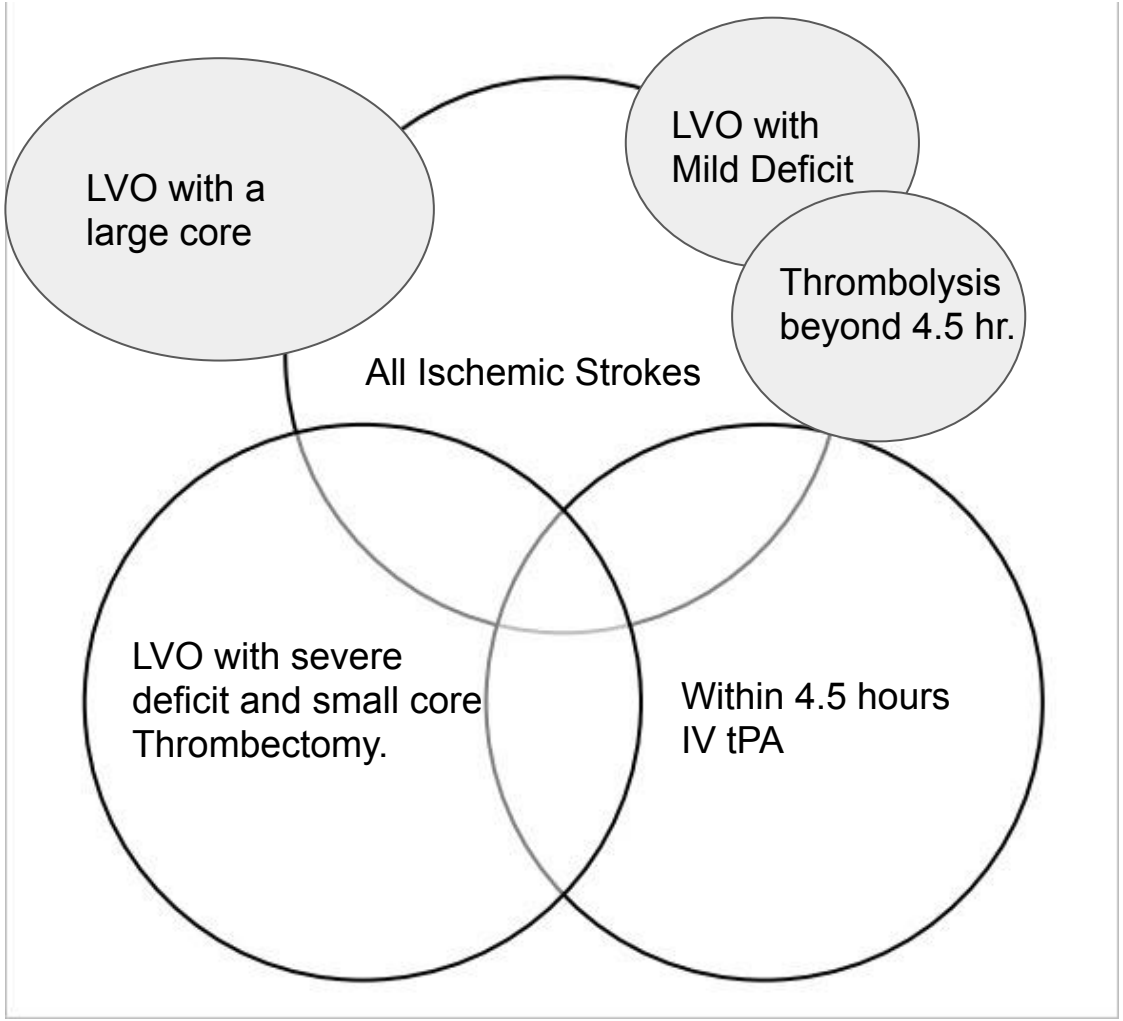
Los Angeles Motor Scale (LAMS)

Score ≥ 4
Sensitivity 81%
Specificity 89%

Facial Droop	
Absent	**0**
Present	**1**
Arm Drift	
Absent	**0**
Drifts Down	**1**
Falls Rapidly	**2**
Grip Strength	
Normal	**0**
Weak	**1**
No Grip	**2**
Total	**/5**

Annual review of LAMS protocol:




LVO with a
large core
LVO with
Mild Deficit
Thrombolysis
beyond 4.5 hr.
All Ischemic Strokes
LVO with severe
deficit and small core
Thrombectomy.
Within 4.5 hours
IV tPA

Summary

Expecting the stroke evaluation and treatment at your facility is one of the greatest impacts on a patient outcome you can have.

The pre-hospital stroke alert with a severity score is impactful communication.

Partnering with your community hospital can expedite care that patients need.