Acute Stroke Diagnosis and management

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The High Socioeconomic Cost of Stroke

Morbidity and Mortality

- A leading cause of serious, longterm disability
- A second to only heart disease in causing death world-wide
- According to the WHO 15 million people worldwide suffer a stroke each year
- 30-day mortality is 8-12%

The High Socioeconomic Cost of Stroke

For survivors aged > 65 years:

- 50% have hemiparesis
- 30% are unable to ambulate
- 19% are aphasic
- 35% are depressed
- 26% resides in nursing home

The High Socioeconomic Cost of Stroke

- Stroke risk and mortality increase with age
- The increase in life expectancy will increase the incidence of stroke
- In the US, total direct and indirect costs are $56.8 billion annually
- The mean lifetime cost of ischemic stroke is estimated at $140,048

Stroke Impact

- The economic, social, and psychological costs of stroke are enormous.

- Many important leaders in science, medicine, and politics had their productivity end prematurely short by stroke:

  - Marcello Malpighi
  - Louis Pateur (at age 46)
  - Vladamir Lenin
  - Woodrow Wilson
  - Dwight Eisenhower
  - Richard Nixon

Ischemic Stroke

- Low blood flow to focal part of brain
- Usually caused by thromboembolism
- Acute therapy includes thrombolysis
- 2° prevention depends on source of thromboembolus
- Accounts for ~ 85% of strokes

Transient Ischemic Attack (TIA)

- Reversible focal dysfunction, usually lasts minutes
- Among TIA pts who go to ED:
  - 5% have stroke in next 2 days
  - 25% have recurrent event in next 3 months
- Stroke risk decreased with proper therapy

Five Major Stroke Syndromes for Rapid Recognition in the ED

All Occur Suddenly in Stroke Patients

- Left (dominant) cerebral hemisphere
- Right (nondominant) cerebral hemisphere
- Brainstem
- Cerebellum
- Hemorrhage

Note: The dominant cerebral hemisphere is the side that controls language function.

Left (Dominant) Cerebral Hemisphere

- Aphasia
- L gaze preference
- R visual field deficit
- R hemiparesis
- R hemisensory loss

Right (Nondominant) Cerebral Hemisphere

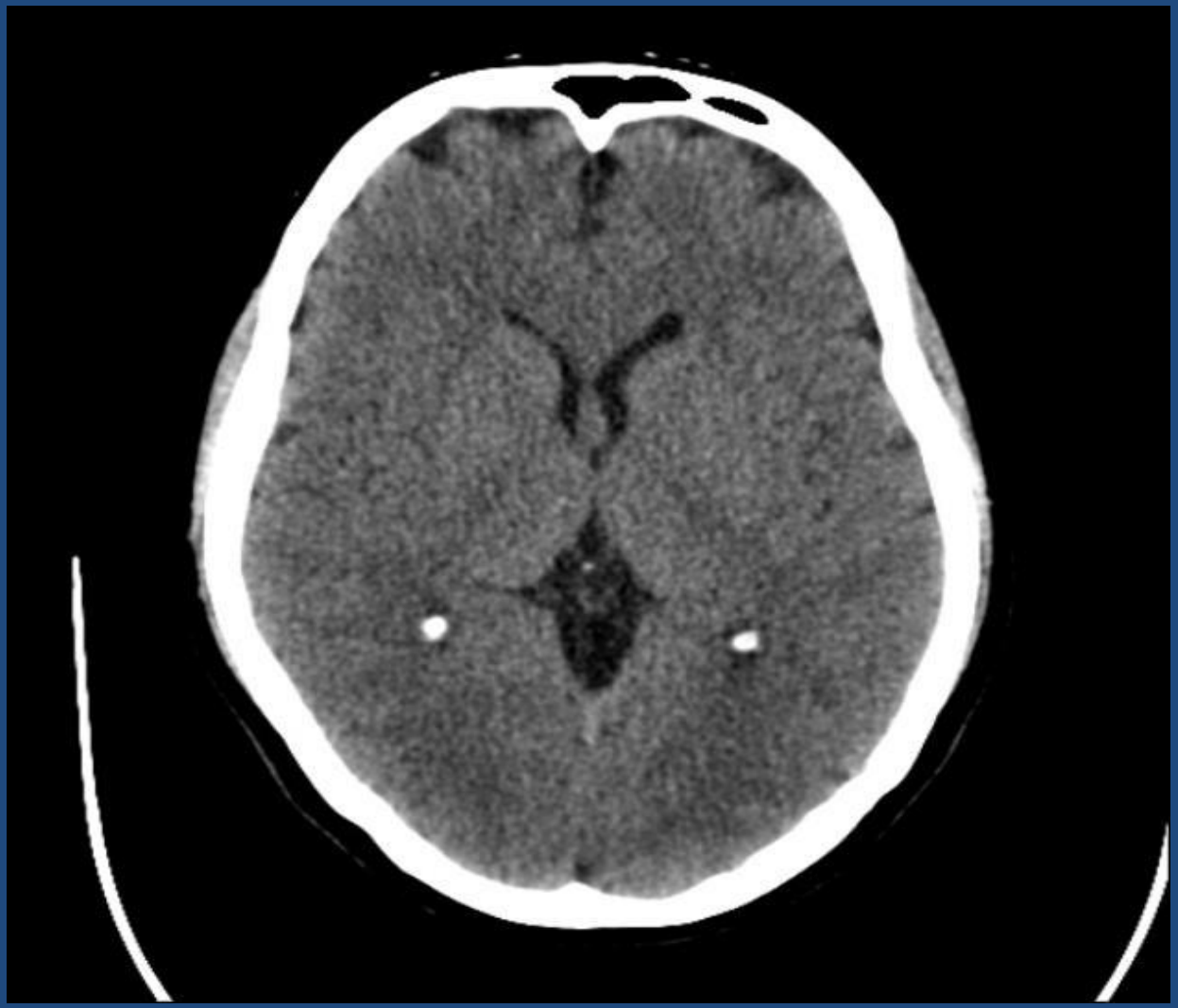
- Neglect (= L hemi-inattention)
- R gaze preference
- L visual field deficit
- L hemiparesis
- L hemisensory loss

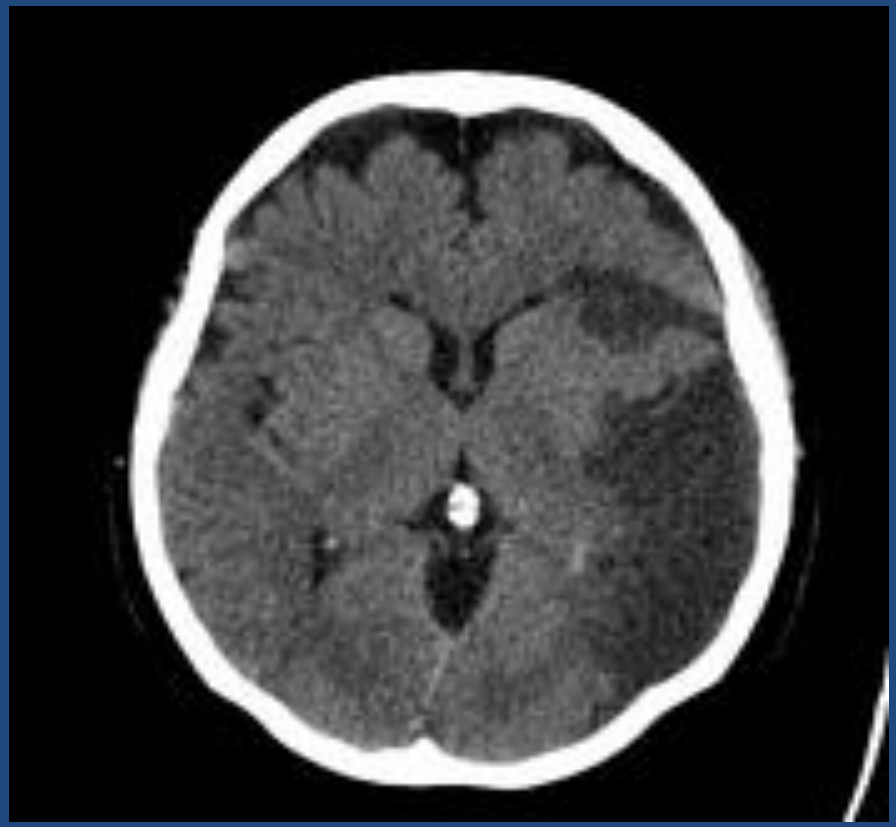
Brainstem

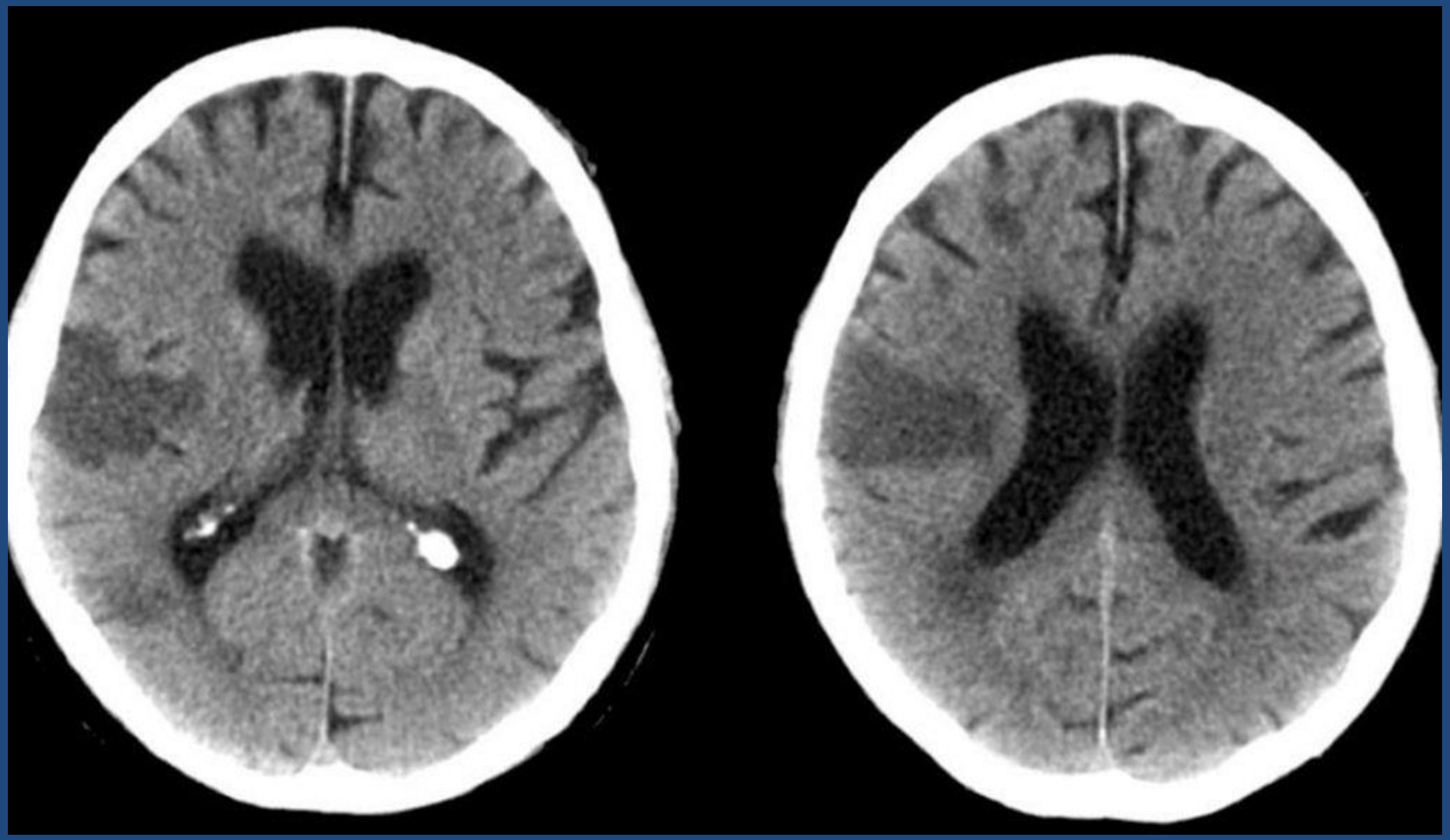
- Hemi- or quadriparesis
- Sensory loss in hemibody or all 4 limbs
- Crossed signs (face 1 side, body other side)
- Diplopia, dysconjugate gaze, gaze palsy
- Vertigo, tinnitus
- Nausea, vomiting
- Hiccups, abnormal respirations
- Decreased consciousness

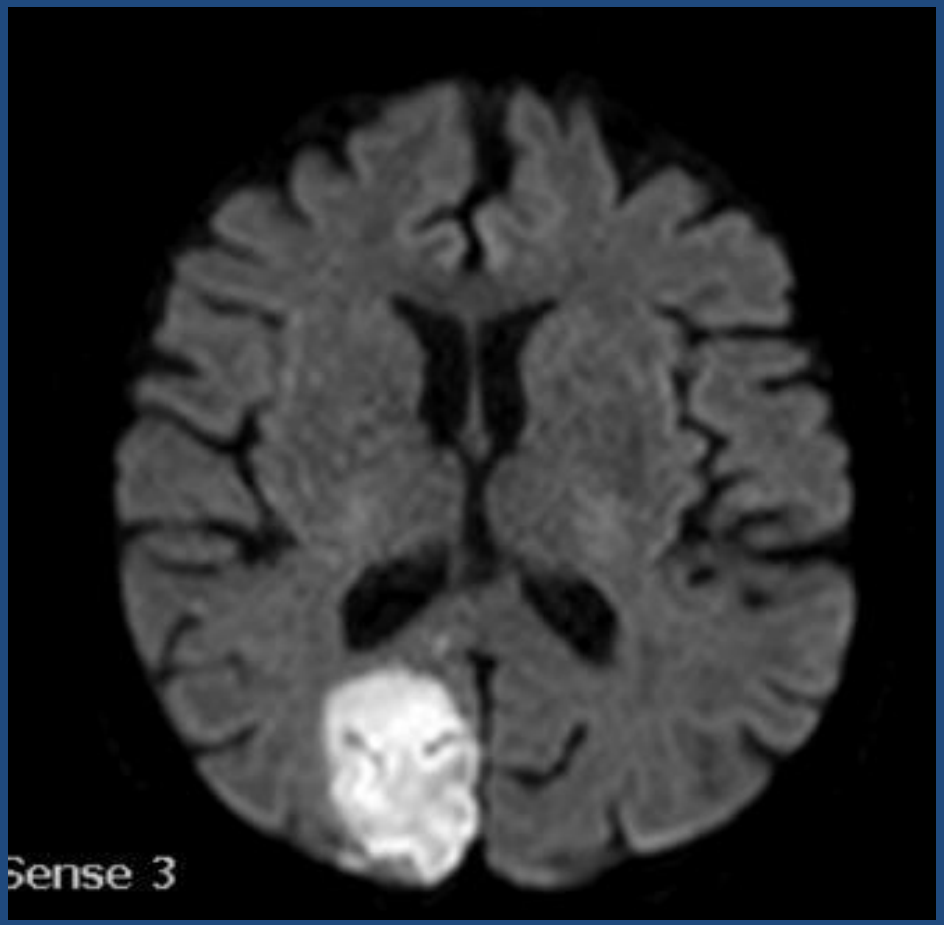
Cerebellum

- Truncal = gait ataxia
- Limb ataxia





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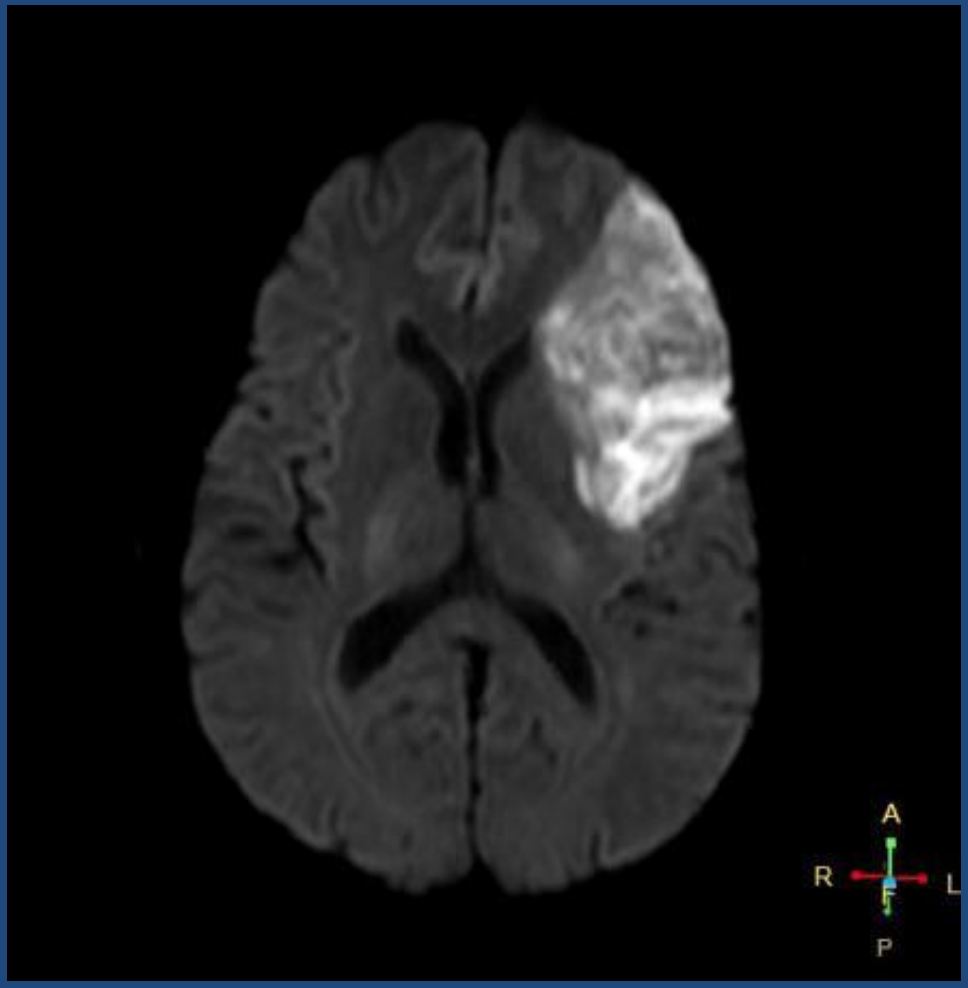
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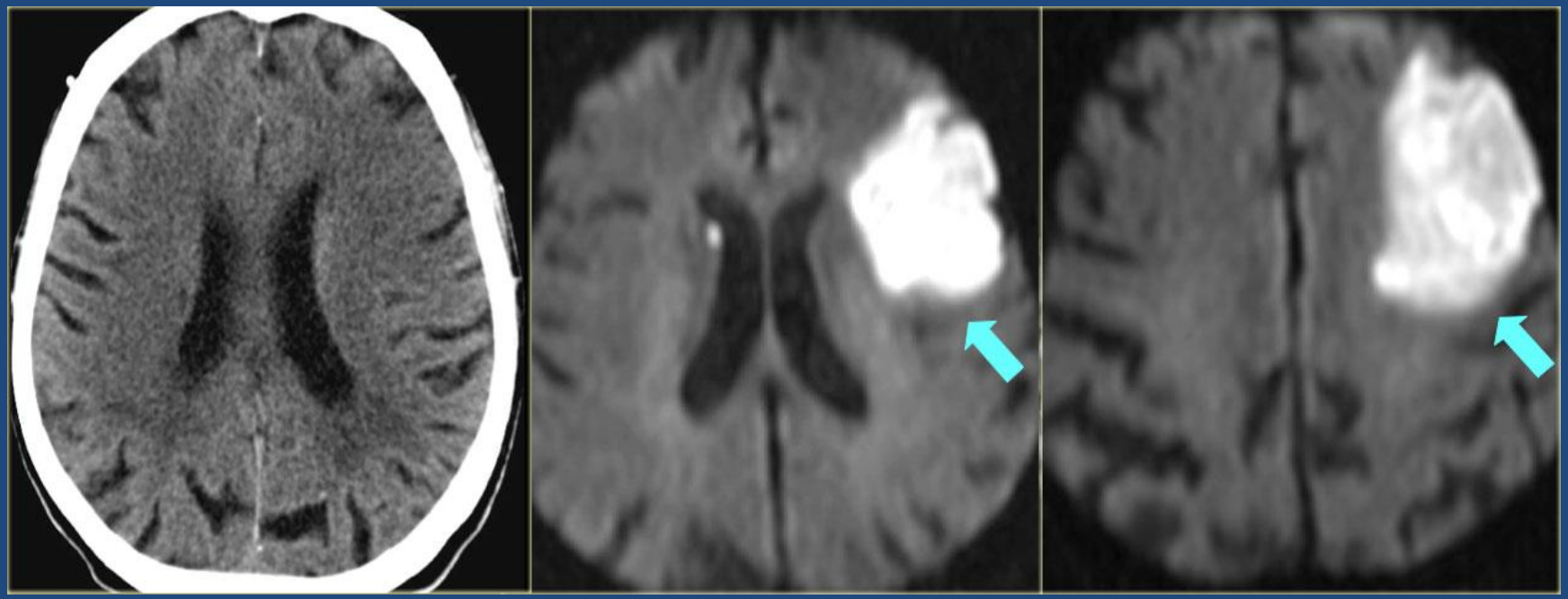
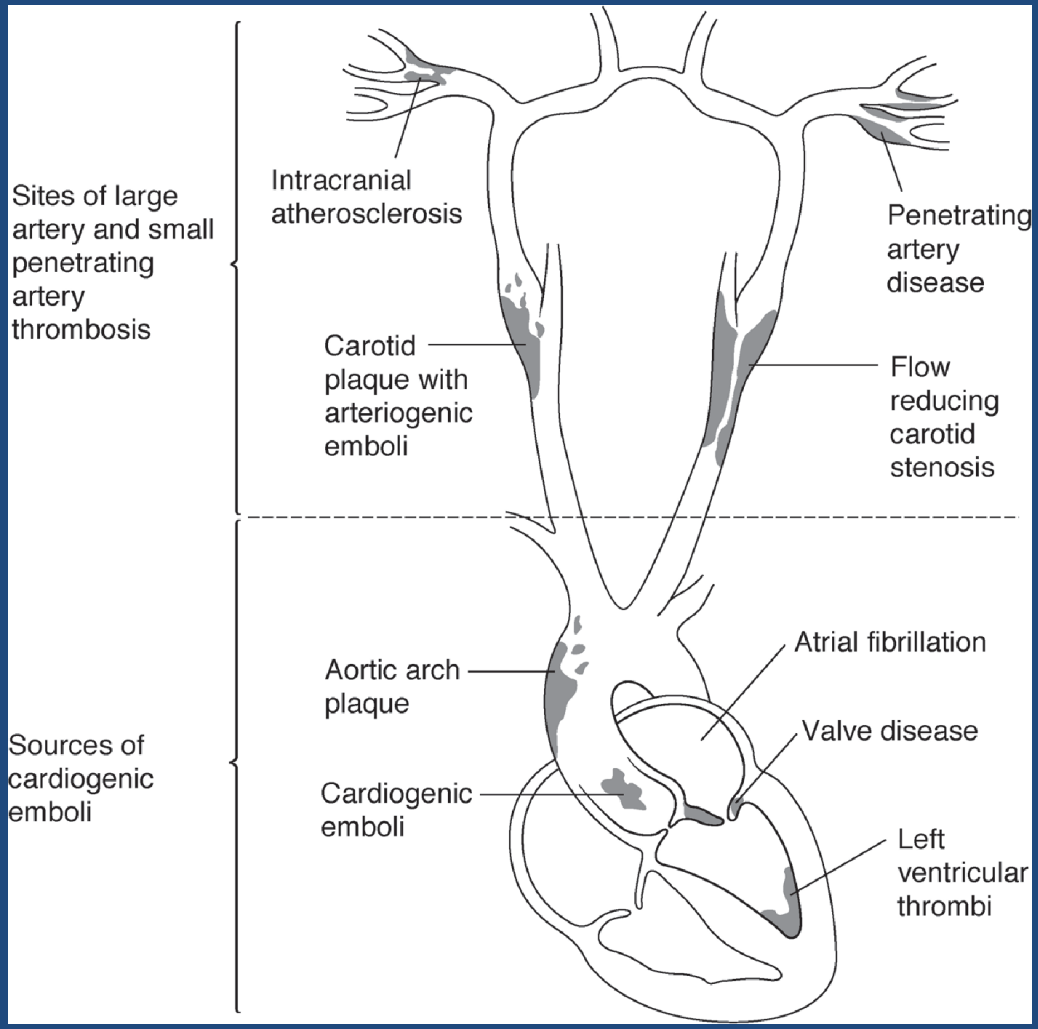


Major sites and sources of ischemic stroke



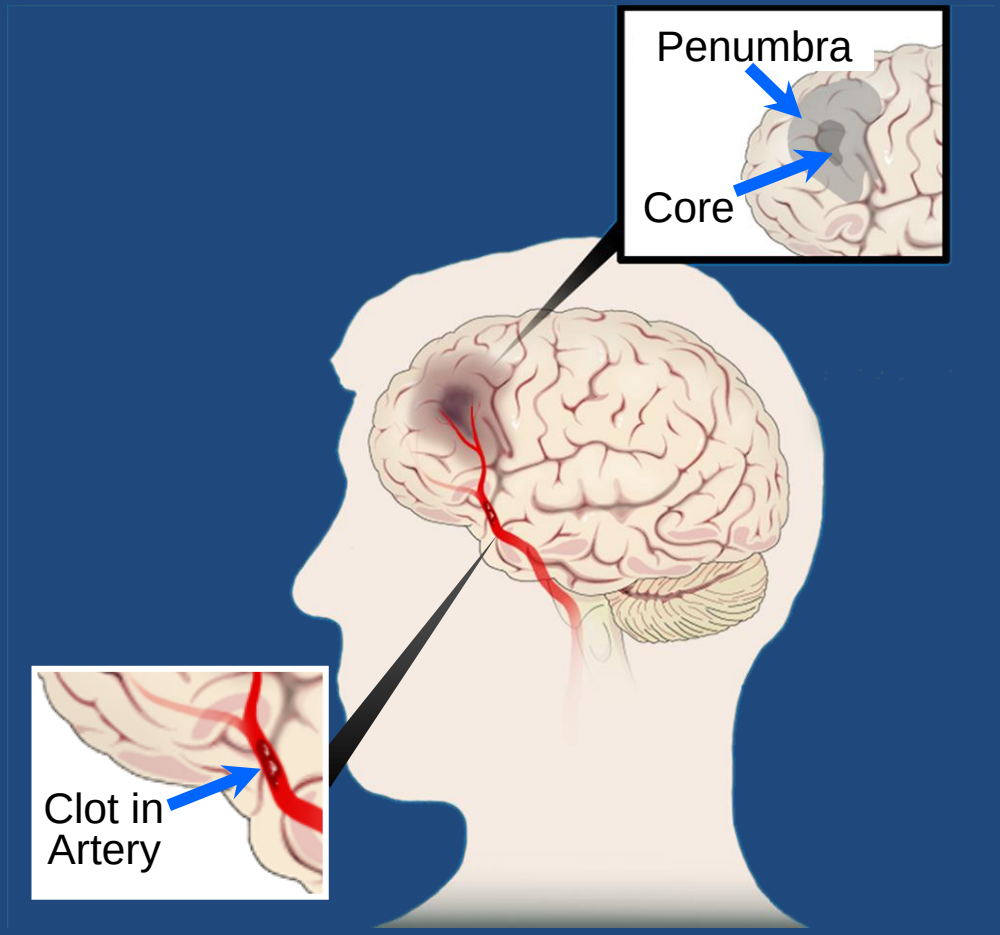
Thrombolytic Treatment of Acute Ischemic Stroke

- Prior to two decades ago, no treatment was offered for acute stroke victims because of the misconception that arterial occlusion in the brain leads to irreversible necrosis and dead tissue within minutes
- Stroke was wrongly named Cerebrovascular Accident (CVA)
- Stroke care was focused on supportive care, stroke prevention and rehabilitation

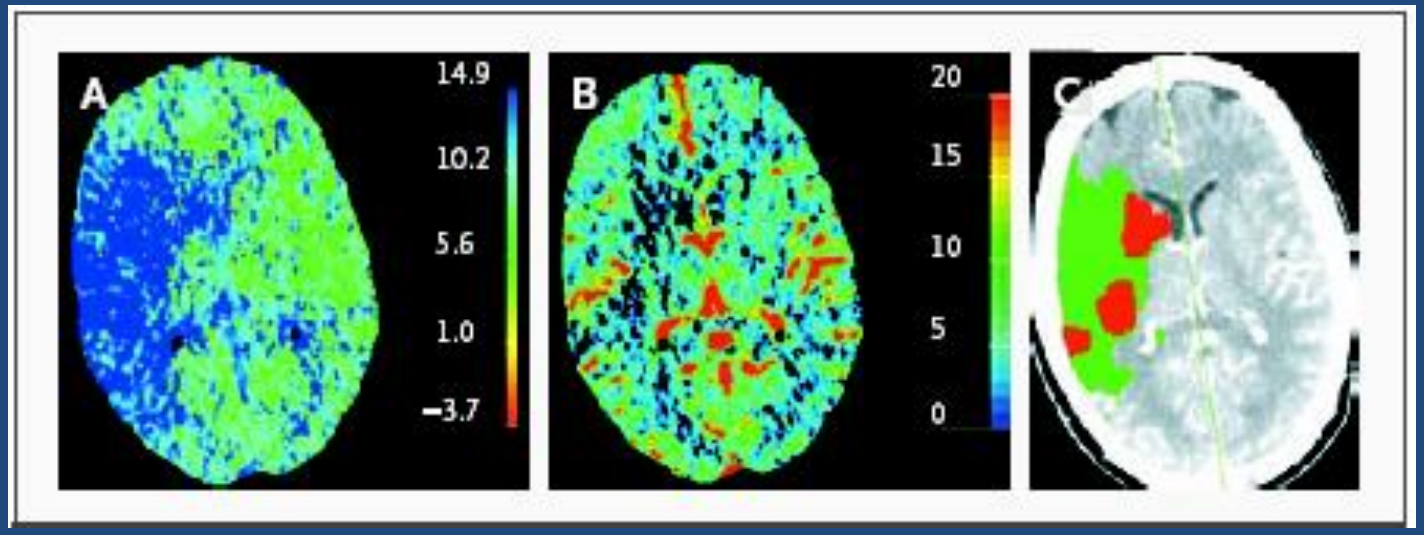
ISCHEMIC STROKE PATHOPHYSIOLOGY
The First Few Hours

"TIME IS BRAIN:
SAVE THE PENUMBRA"

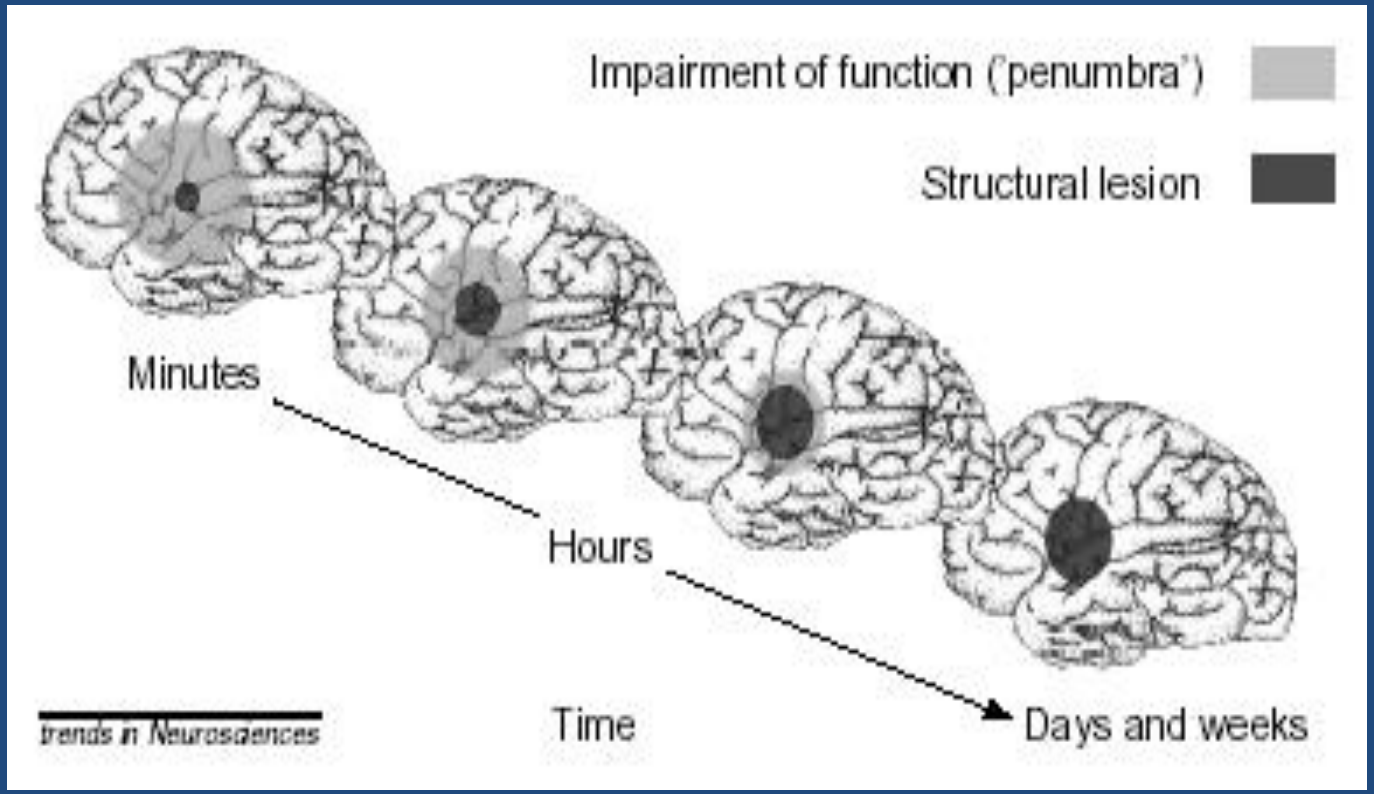
Penumbra is zone of reversible ischemia around core of irreversible infarction—salvageable in first few hours after ischemic stroke onset



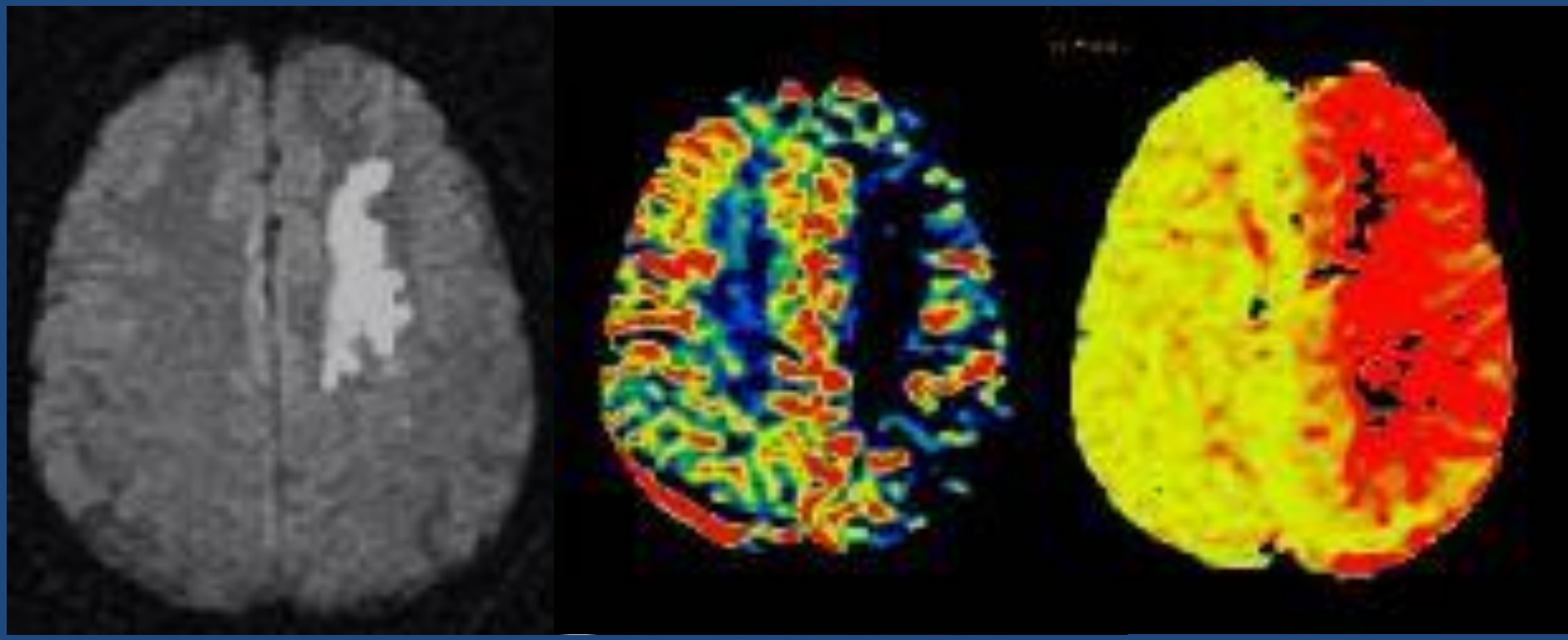
Perfusion CT Scans Obtained 1 Hour 45 Minutes after the Onset of Ischemia in the Territory of the Right Middle Cerebral Artery



A large area shows prolongation of the mean transit time (in seconds) (Panel A), and a smaller area shows a reduction in cerebral blood volume (in ml per 100 g) (Panel B). These two maps suggest a large penumbra and a small infarct core (Panel C, with the penumbra shown in green and the suggested infarct core in red).

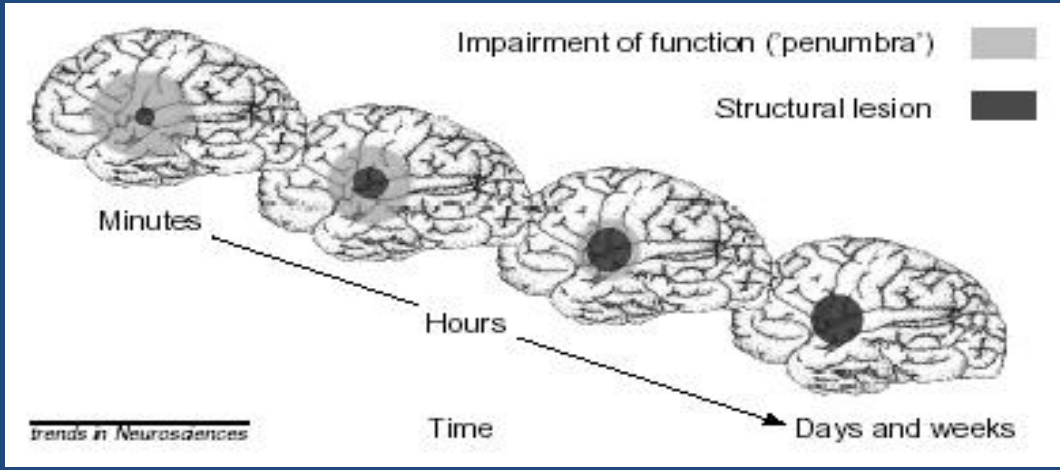

Impairment of function ('penumbra')
Structural lesion
Minutes
Hours
Time
Days and weeks
trends in Neurosciences

Perfusion/Diffusion MRI



Diffusion rCBV MTT

Penumbra



- In every ischemic stroke there is ischemic core and penumbra
- Penumbra is the region of tissue at risk of being recruited into the ischemic core
- Ischemic Penumbra presents a Window of Opportunity

National Institute of Neurological Disorders and Stroke (NINDS) Trial

- 624 acute stroke patients were randomized to either Placebo or 0.9mg/kg of IV rt-PA within 3 hours from the stroke onset.

- Primary outcome: complete or nearly complete neurological recovery at 3 months after stroke

National Institute of Neurological Disorders and Stroke (NINDS) Trial

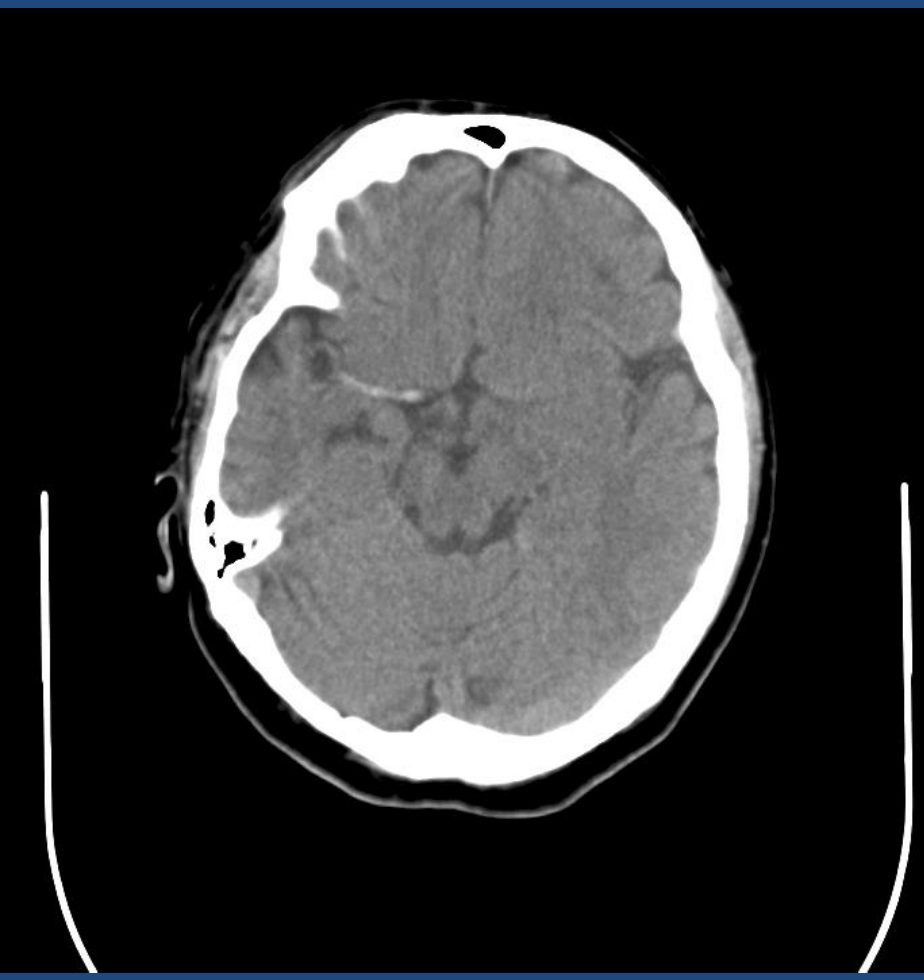
Outcome	IV t-PA	Placebo
MRS < 1	39%	26% (P=.019)
Mortality	21%	17%
ICH	6.4%	0.6%

National Institute of Neurological Disorders and Stroke (NINDS) Trial:

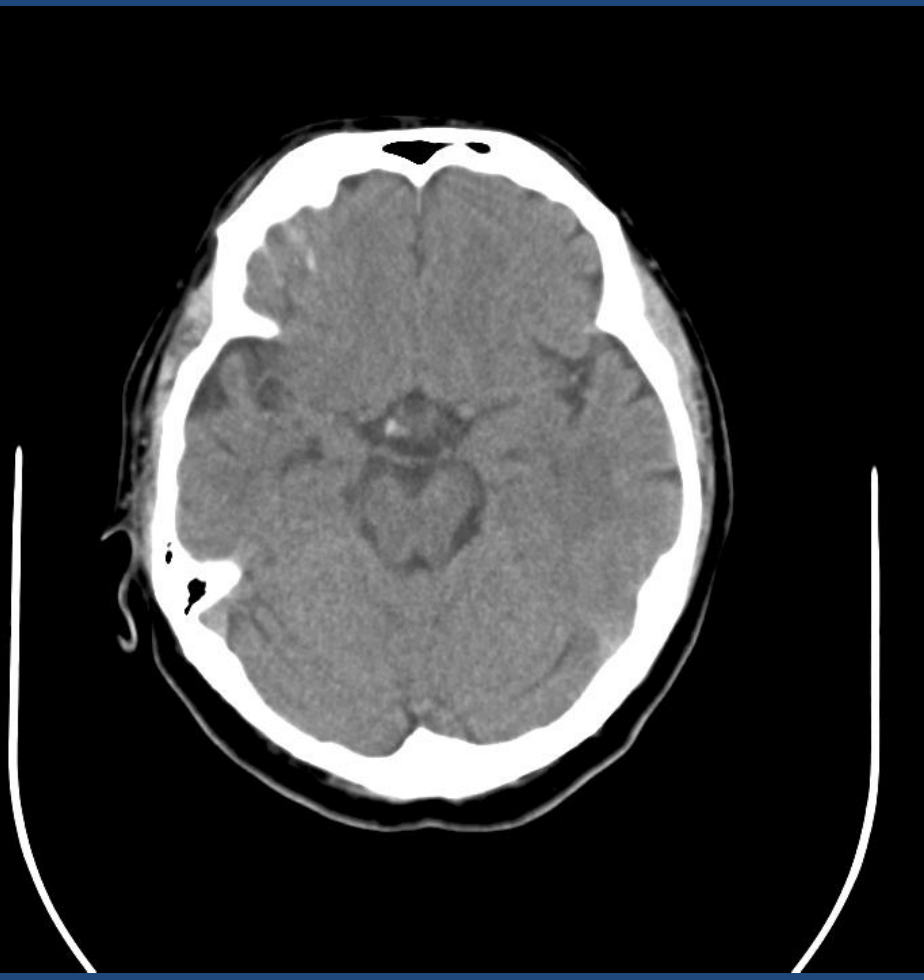
- Those treated with IV rt-PA were 30% more likely to have no or only minor disability at 3 months post stroke
- Absolute risk reduction of poor outcome in the t-PA patients is 13%
- OR for favorable outcome (MRS 0-1) in the t-PA patients 1.9
- No difference in mortality between the two groups
- 6.4% symptomatic hemorrhage in the t-PA group compared to 0.6% in the Placebo group

National Institute of Neurological Disorders and Stroke (NINDS) Trial

- Based on the NINDS trial results, the FDA in 1996 approved IV t-PA for the treatment of acute ischemic stroke within 3 hours from stroke onset.



CT Prior to IV t-PA



CT Post IV t-PA

Pharmacological re-canalization

European Cooperative Acute Stroke Study (ECASS II):

- Acute stroke patients were treated with either 0.9 mg/kg rt-PA or Placebo within 6 hours after stroke onset

- Results showed increase intracerebral hemorrhage in the t-PA group

European Cooperative Acute Stroke Study (ECASS III)

- A total of 821 acute stroke patients were treated with either 0.9 mg/kg rt-PA or Placebo within 4.5 hours of the stroke symptoms onset
- Additional exclusion criteria to the NINDS trial include age >80, oral anticoagulant, NIHSS > 25, CT showing > 1/3 MCA infarct, and history of both stroke and diabetes

European Cooperative Acute Stroke Study (ECASS III)

Outcome	t--PA	Placebo
MRS < 2	54.4%	45.2% P=0.04
Mortality	7.7%	8.4% P=0.68
Hemorrhage	2.4%	0.2% P=0.008

European Cooperative Acute Stroke Study (ECASS III)

- Absolute risk reduction of poor outcome is 7%
- A second pooled analysis including ECASS and EPITHET showed consistent results
- The AHA,ASA, and ESA endorsed the use of alteplase within 4.5 hours of the symptoms onset

Outcome with IV-t-PA:

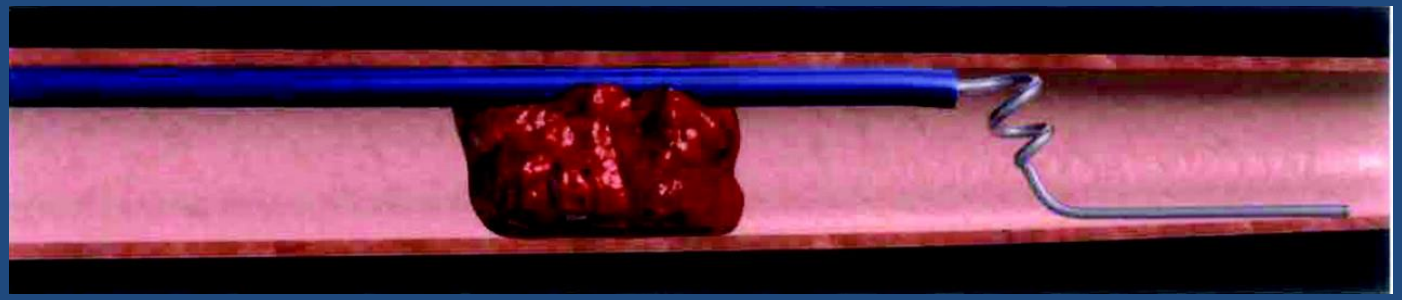
Odds Ratios for Favorable Outcome

Time	Odds Ratio	95% (CI) Interval
0-90	2.8	1.8 - 4.5
91-180	1.5	1.1 - 2.1
181-270	1.4	1.1 - 1.9
271-360	1.2	0.9 - 1.5

Tissue Plasminogen Activator (t-PA)

The introduction of t-PA 2 decades ago marked the end of one era dominated by nihilism, in which stroke was considered untreatable and the beginning of another

After the microcatheter transverses the thrombus, the first loops of the Merci Retriever are delivered distal to the occlusion site



Pierre Gobin, Y. et al. Stroke 2004;35:2848-2854

Stroke

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The Merci Retriever is pulled back at the contact of the thrombus, additional loops are delivered within the thrombus, and the Merci Retriever is torqued to ensnare the thrombus

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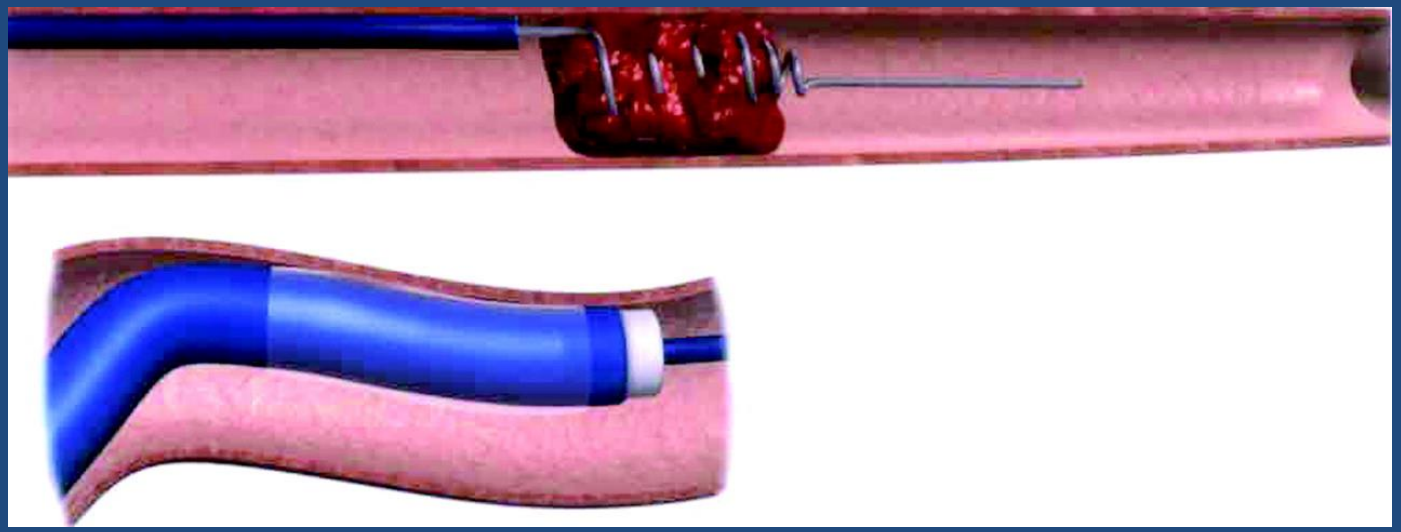
The balloon of the balloon guide catheter (BGC) (insert) is inflated to control antegrade flow, and the Merci Retriever is pulled back with the ensnared thrombus toward the tip of the BGC where it is aspirated



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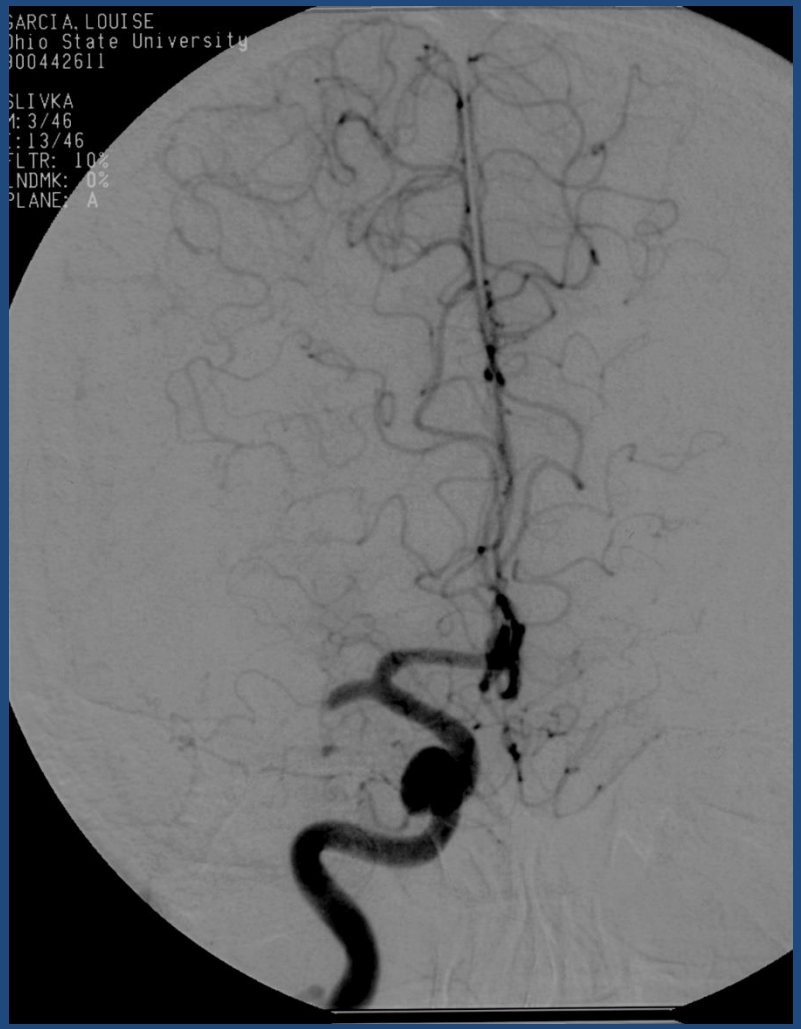
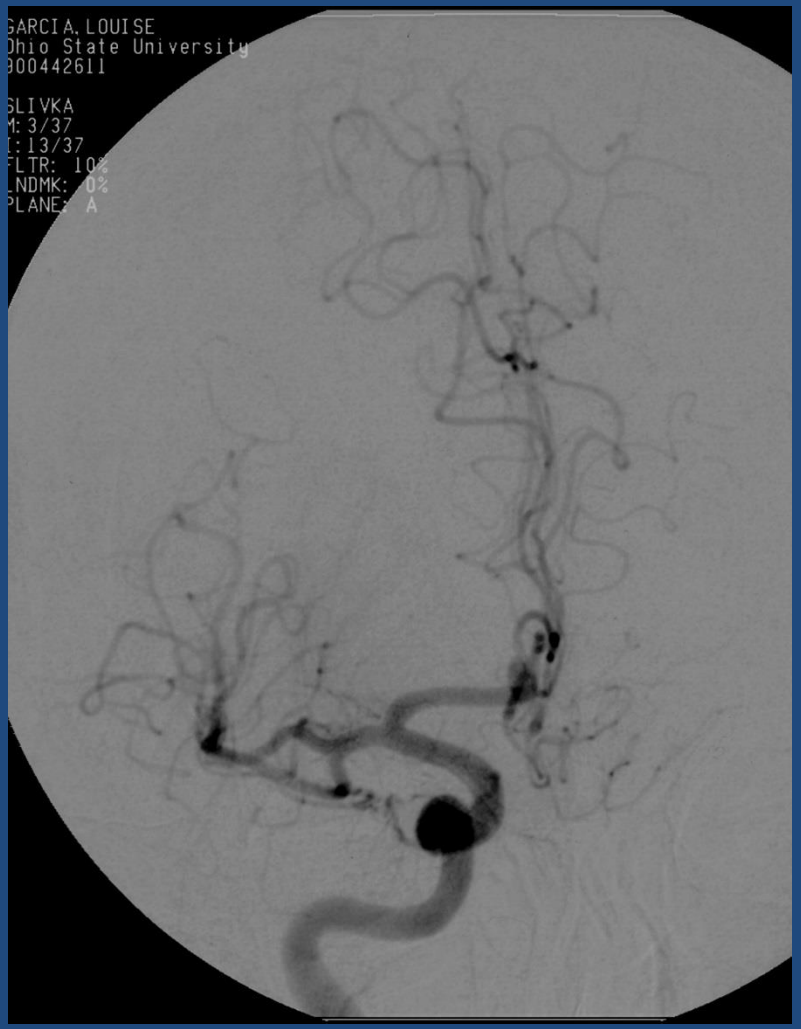
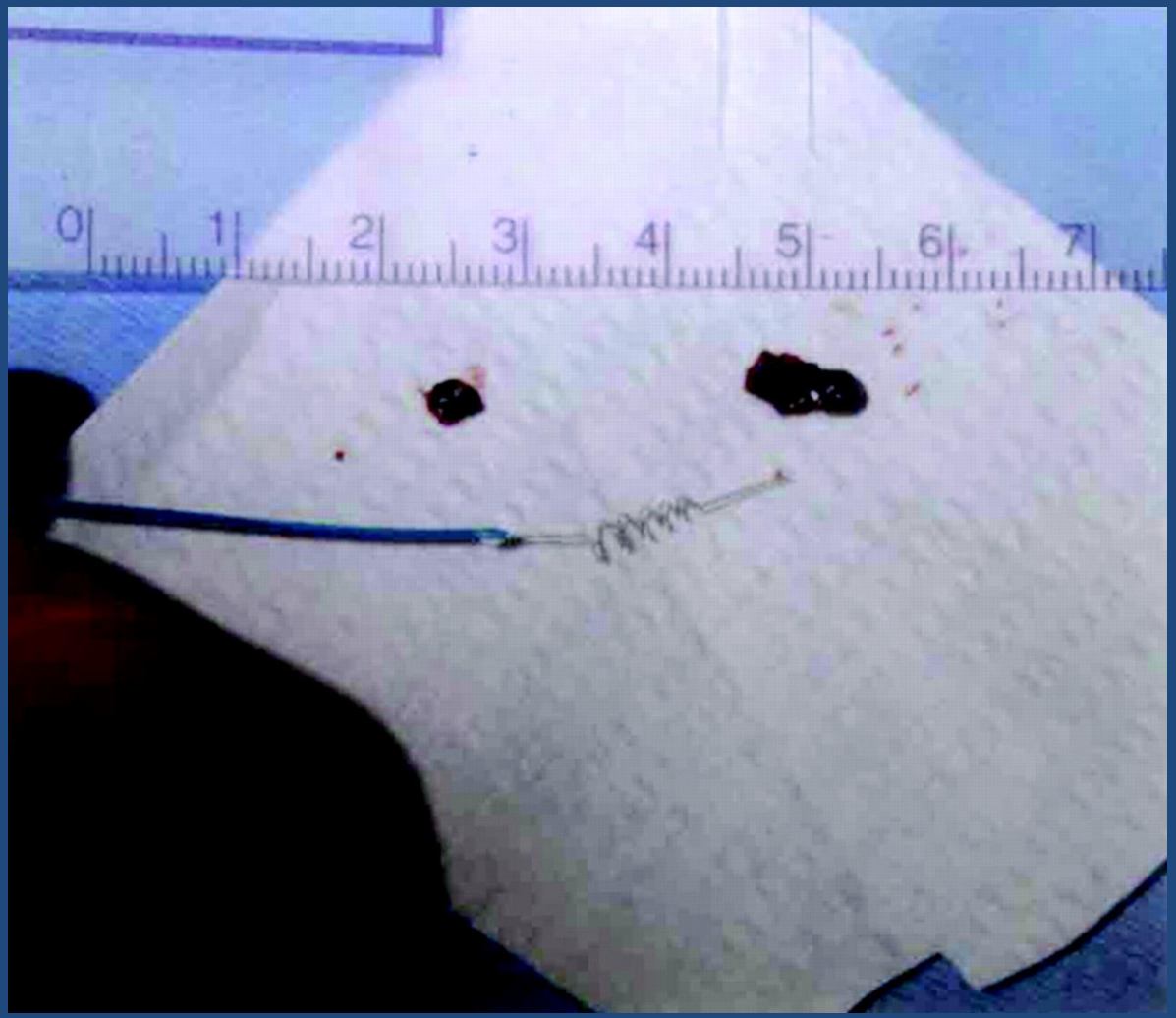
Thrombolysis





Photograph showing the Merci Retriever and the 2 thrombi, which were retrieved in case 9



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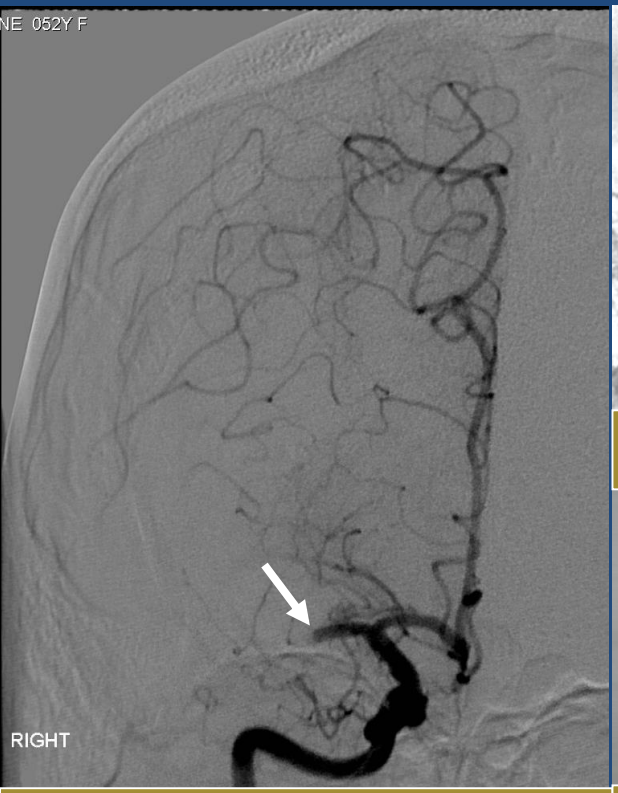
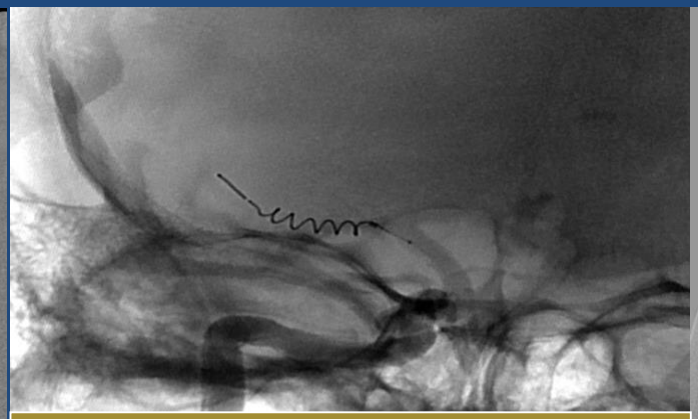
MERCI retriever

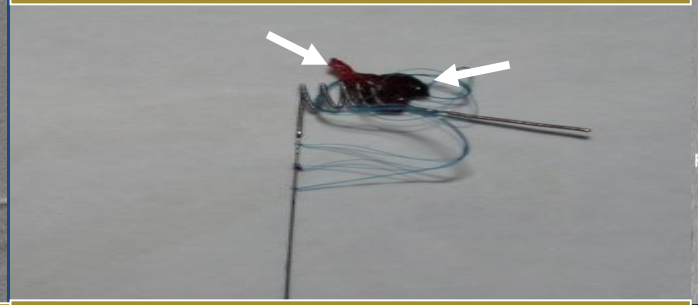
Embolectomy performed using a MERCI retriever device can also result in successful recanalization. The patient presented here had significant clinical improvement following MERCI assisted embolectomy.



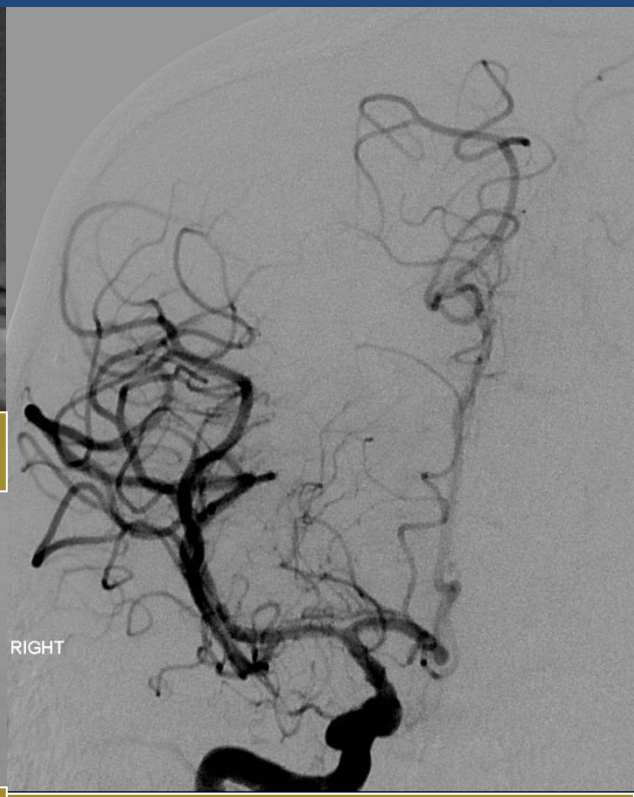
LICA angiogram showing MCA occlusion (arrow)



MERCI retriever in MCA



Tip of MERCI device with removed thrombus (arrows)



Complete recanalization

Acute Stroke Treatment: Mechanical Thrombolysis

Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Trial:

- Recanalization: 48% (19% PROACT control)
- Complications: 7% (emboli, dissection, SAH)
- Good outcome: 28% (46% recanalized, 10% occluded)
- Mortality: 43% (32 recanalized, 54% occluded)
- Symptomatic hemorrhage occurred in 5%.

Mechanical Recanalization

Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Trial:

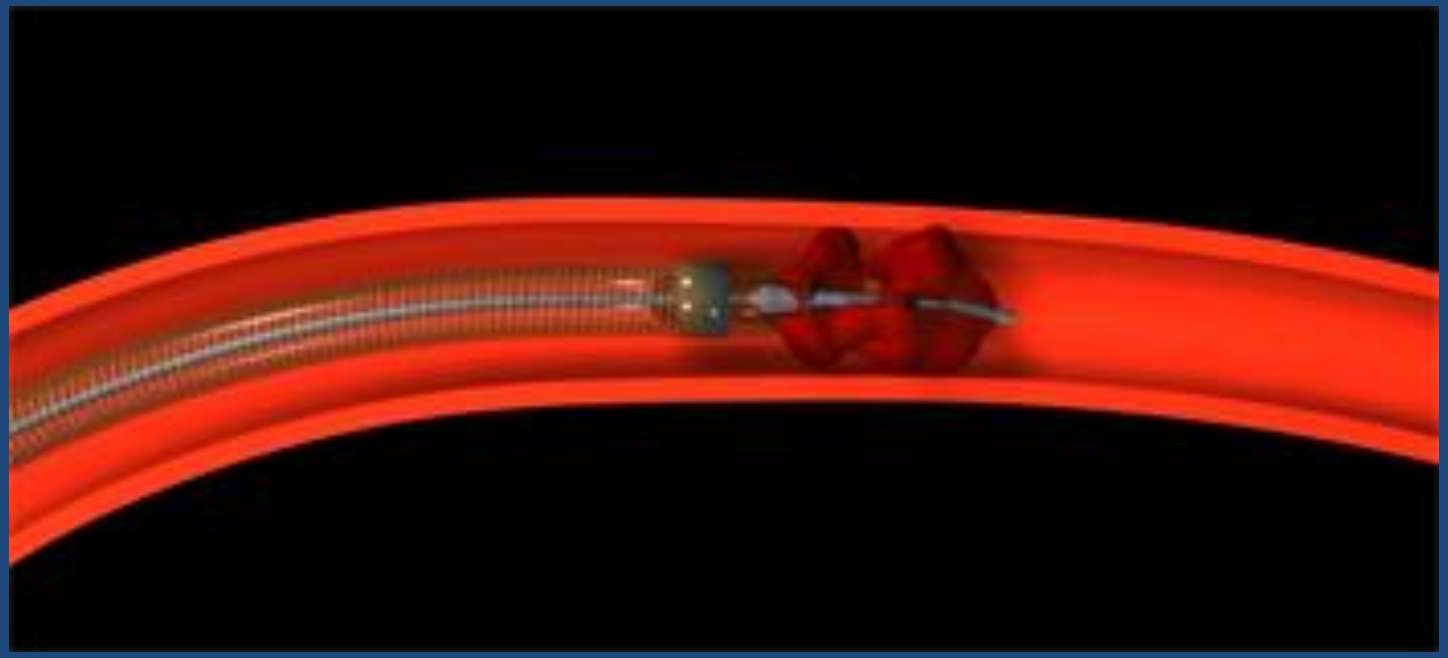
- Based on the MERCI trial results, the FDA in 2005 approved the MERCI retriever for removing clot within 8 hours of stroke symptoms.

Penumbra

Penumbra microcatheters, shown here with separator wires, are available in sizes ranging from 2.3 French to 4 French. This device uses aspiration assisted by a separator wire to suction out thrombus.

ADVANTAGES
- Can be used in some patients with contraindications to thrombolysis
- 8-hour window
- Initial data indicates higher revascularizton rates relative to other methods.
- Preliminary data shows better outcome at 90 days relative to other devices show

DISADVANTAGES
- Vessel tortuosity precludes use
- Distal vessels not reachable
- Operator experience
- Higher rate of symptomatic intra-cerebral hemorrhage



Penumbra

Penumbra

Trial Design

- Prospective, single arm, multi-center
- Enrolled 125 patients at 24 international centers
- Patients in the trial presented within 8 hours from symptoms onset, had an NIHSS >8 and had complete occlusion of a large intracranial vessel

Penumbra

Recanal	Hemorr	≥4 NIHSS Imp	MRS<2	Mortal
81.6%	11.2%	57.8%	25%	26%

Endovascular Thrombolysis vs IV t-PA

Randomized Phase 3 trial:

- IMS III
- Synthesis Expansion
- MR Rescue

Endovascular Thrombolysis vs IV t-PA

IMS III

- A randomized study to assess the efficacy and safety of IV t-PA combined with mechanical thrombolysis compared with IV t-PA alone, in acute stroke patients presenting within 3 hours of the symptoms onset

- The primary outcome was a MRS of <2 (indicating functional independence) at 90 days

Endovascular Thrombolysis vs IV t-PA

IMS III

Outcome	IV t-PA	IV t-PA/MT
MRS <2	38.7%	40.8%
Mortality	21.6%	19.1% P=0.52
sICH	5.9%	6.2% P=0.83

Endovascular Thrombolysis vs IV t-PA

Synthesis Expansion

- 362 patients with acute ischemic stroke within 4.5 hours of symptoms onset, were randomized to endovascular therapy (IA t-PA, mechanical disruption or retrieval or a combination of these approaches) or IV t-PA

- Primary outcome is MRS < 0-1 (indicating survival free of disability)

Endovascular Thrombolysis vs IV t-PA

Synthesis Expansion

Outcome	IV t-PA	ET
MRS 0-1	34.8%	30.4% (OR 0.71; 95% CI 0.44-1.41)
Mortality	Same	
sICH	6%	6%

Endovascular Thrombolysis vs IV t-PA

MR Rescue

- A randomized, controlled, open label blinded outcome, multicenter trial in North America.
- Patients presenting with 8 hours of symptoms onset and received t-PA for LVO were randomized to mechanical thrombolysis (MERCI or Penumbra) vs. Placebo
- Primary outcome MRS <2

Endovascular Thrombolysis vs IV t-PA

MR RESCUE

Outcome	IV t-PA	t-PA/MT
Mean MRS	3.9	3.9 P=0.99
Mortality	Same	NS
sICH	Same	NS

Endovascular Thrombolysis vs IV t-PA

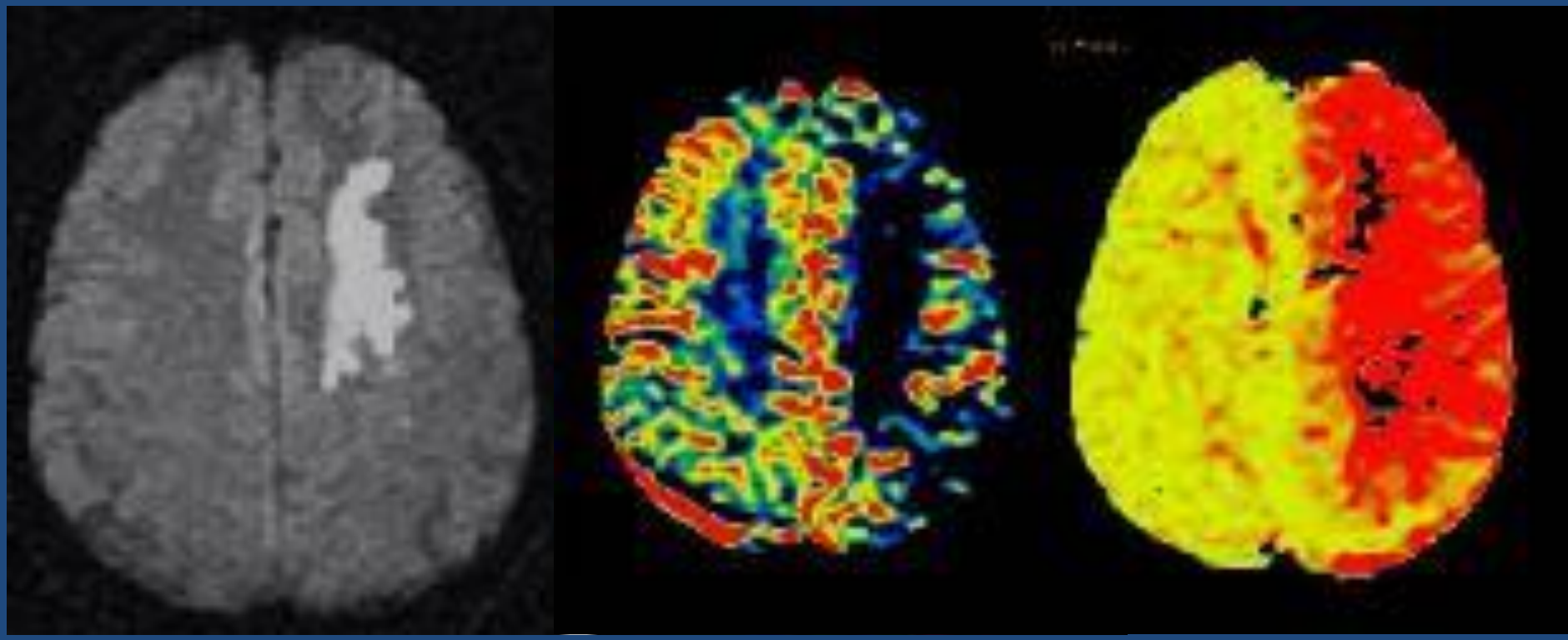
Despite a sound pathophysiologic rationale and promising results from non-randomized studies, treatment of patients with endovascular therapy has not been proven to be superior in improving outcome compared to IV t-PA

Endovascular Thrombolysis

Stent-retriver technology (2nd generation devices for mechanical thrombolysis):

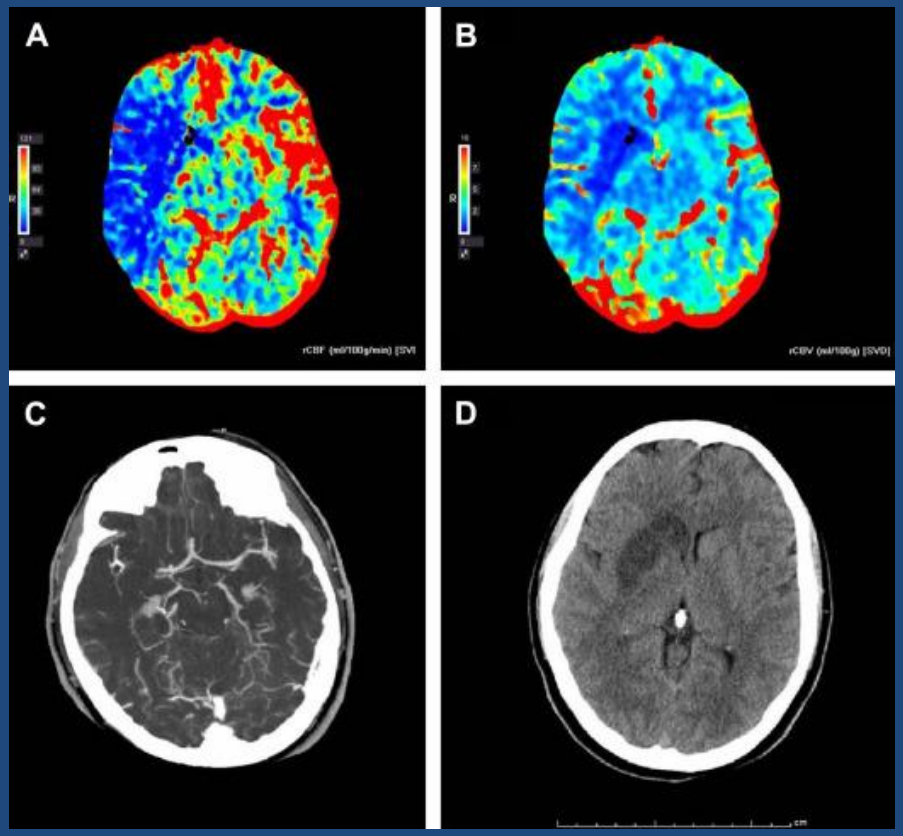
- Solitaire Device
- Trevo Stent-retrieveer

Perfusion/Diffusion MRI

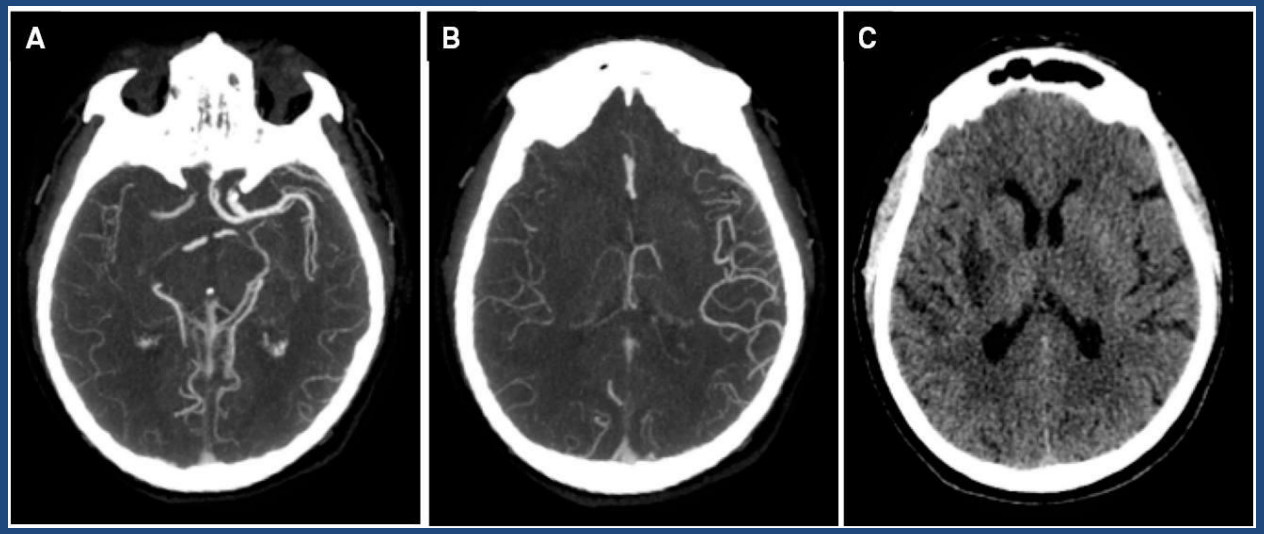


Diffusion rCBV MTT

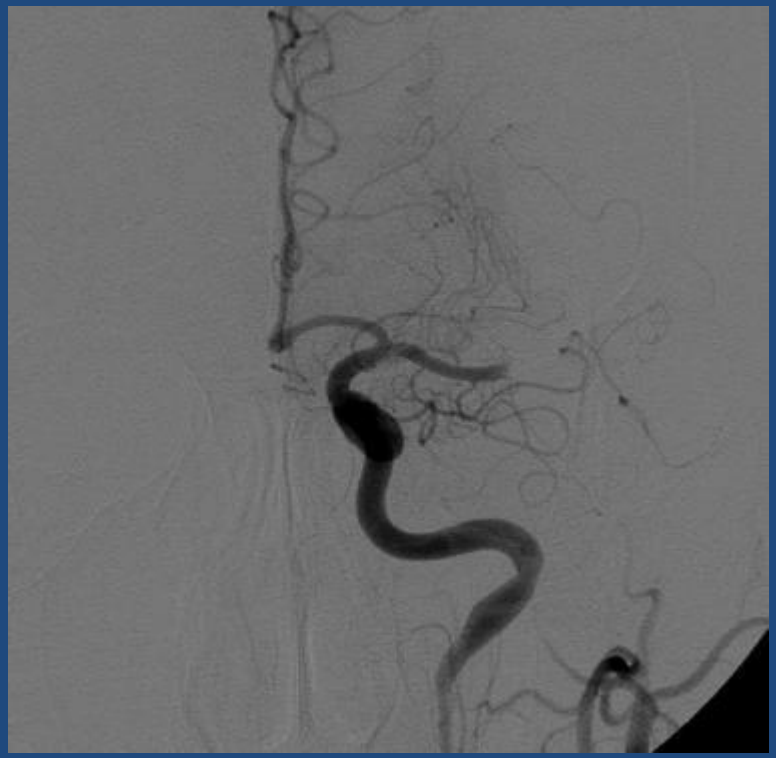
CT perfusion imaging of acute left MCA infarct. Example of radiological findings in a patient with a right hemisphere stroke who underwent successful recanalization: baseline perfusion CT: (*A*) CBF, (*B*) CBV. (*C*) CTA shows right MCA occlusion; (*D*) 24-hour NCCT. The mismatch between the area of reduced CBV and the area of reduced CBF represents the penumbral zone. The infarct at 24 hours correlates with the area of reduced CBV.

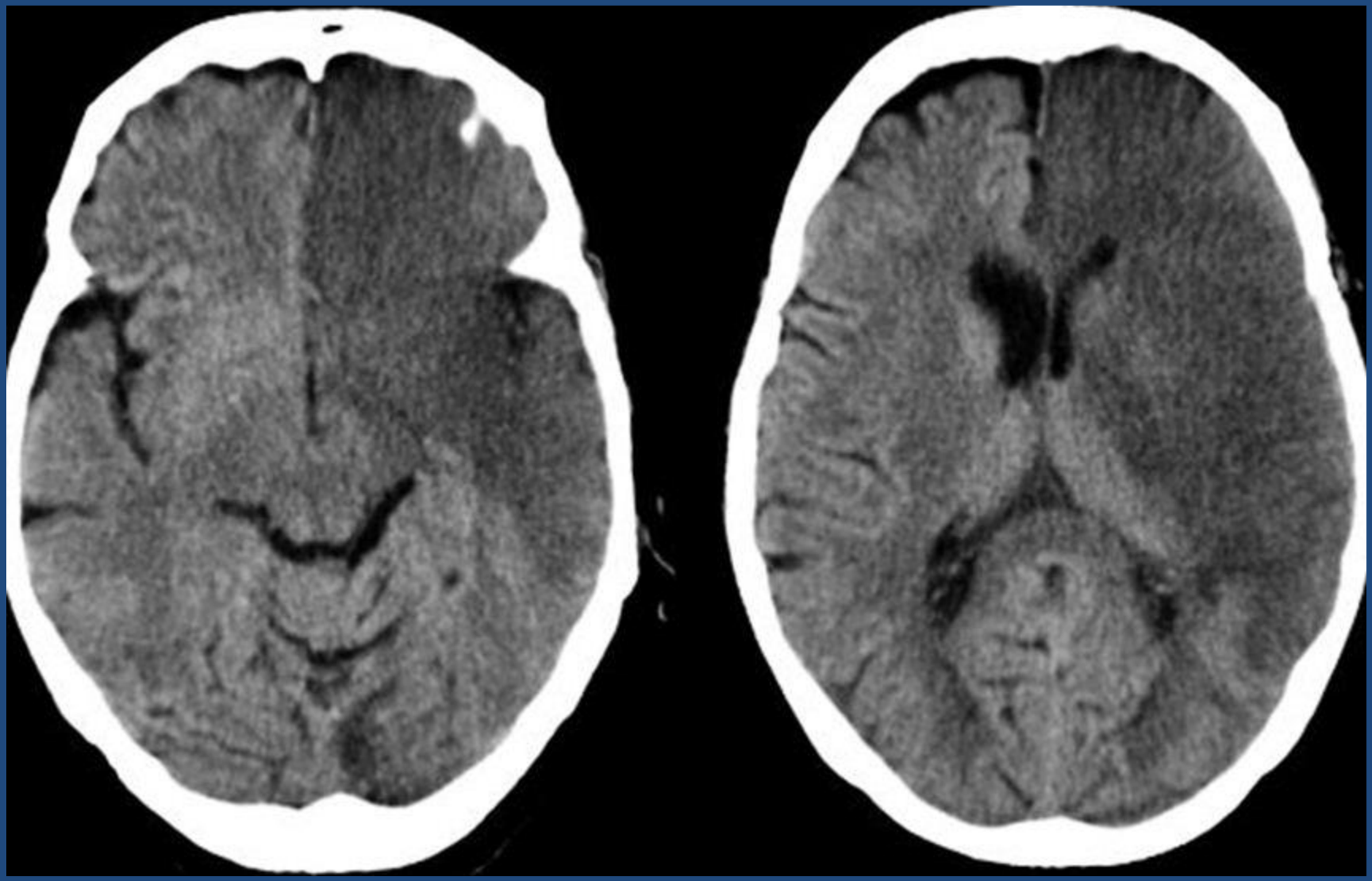


Abundant collaterals

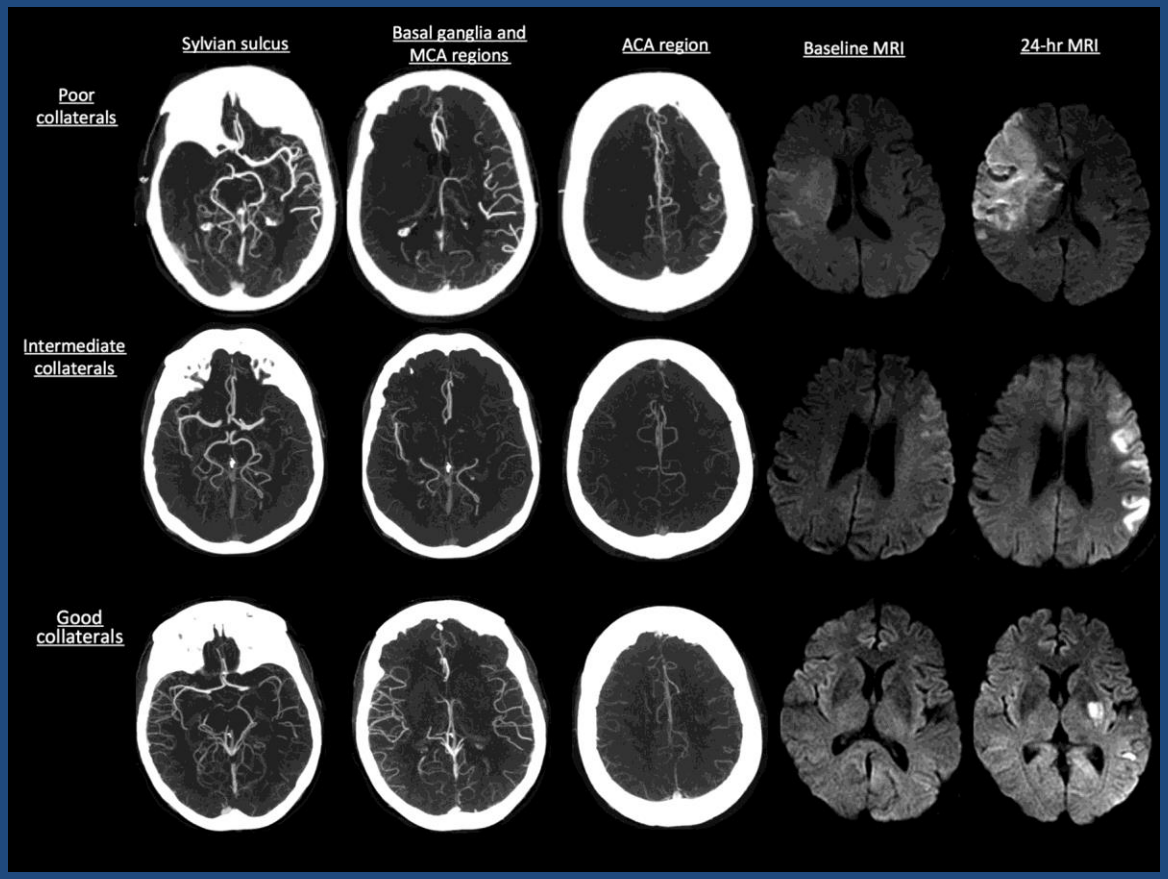


Poor collaterals





Extent of collaterals



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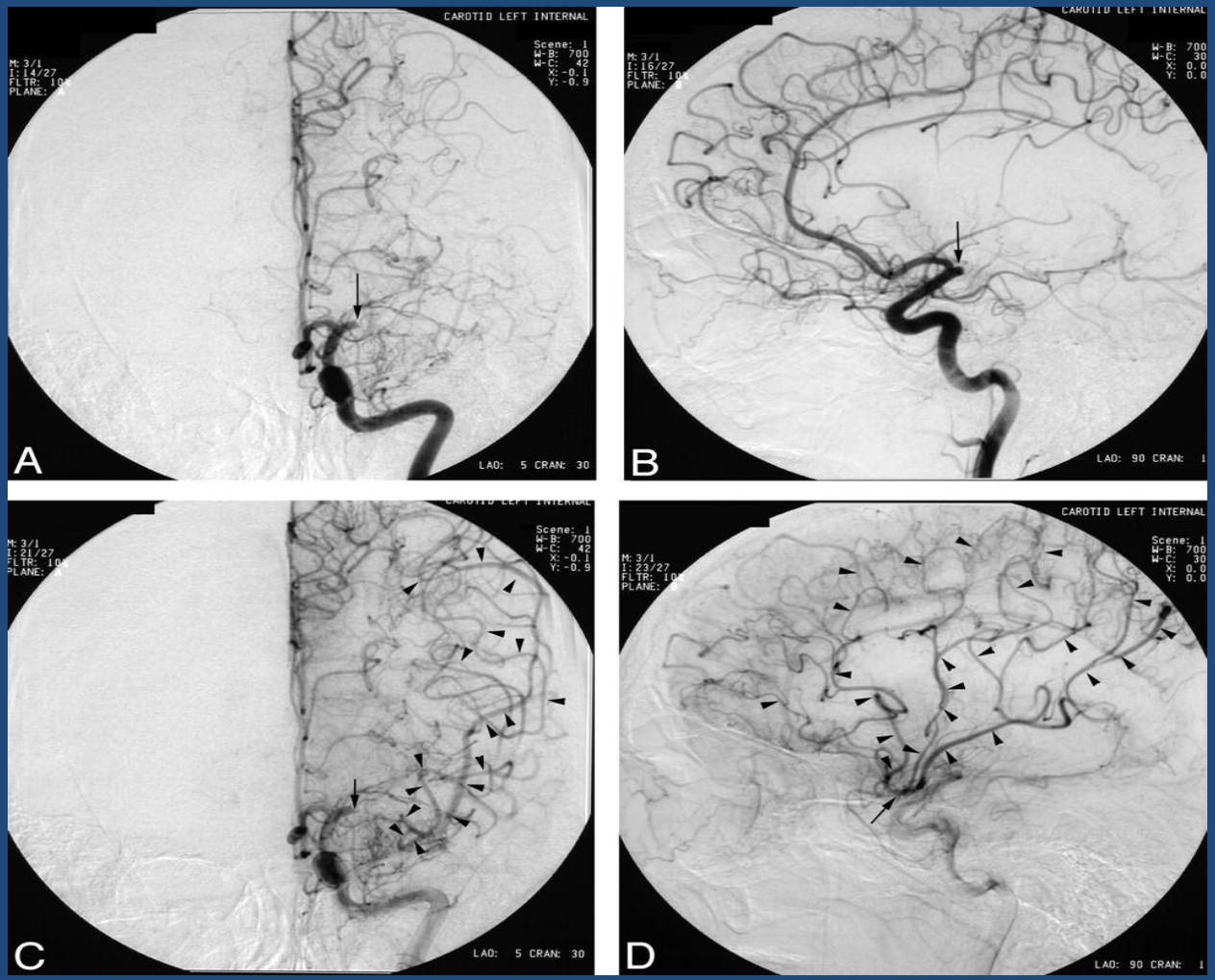
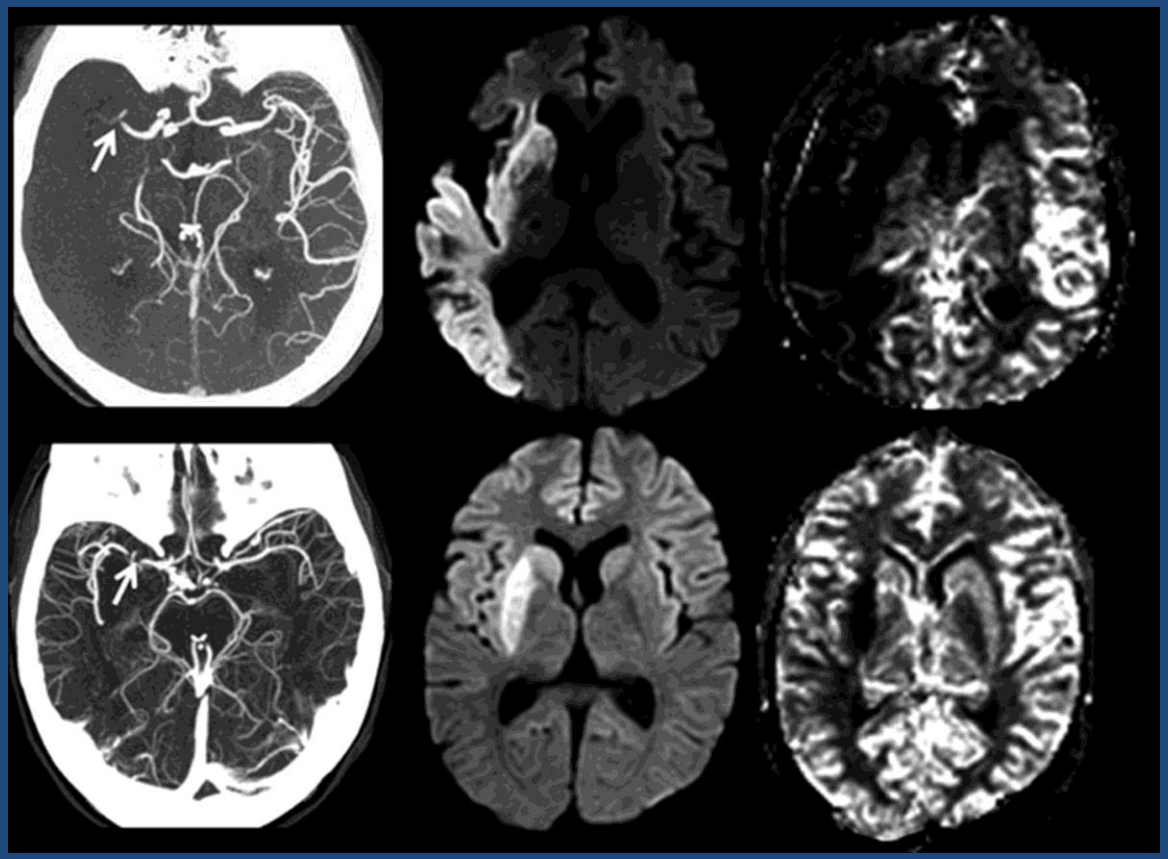


Extent of collaterals



Advance neuro-imaging techniques for acute stroke

- Advances in neuroimaging aid in the diagnosis and the treatment decisions in AIS.

- In acute stroke patients, Diffusion/perfusion sequence and CTA/CTP head and neck should be performed to assess for LVO and eligibility for endovascular therapy.

Novel Endovascular devices

Recently a much more effective and efficient endovascular devices has been introduced

Endovascular Thrombolysis

Stent-retriver technology (2nd generation devices for mechanical thrombolysis):

- Solitaire Device
- Trevo Stent-retrieveer

Stent-retriever

- They work by temporally deploying a stent that captures the thrombus and at the same time instantly restores blood flow to the affected brain territory by displacing the clot peripherally against the artery wall

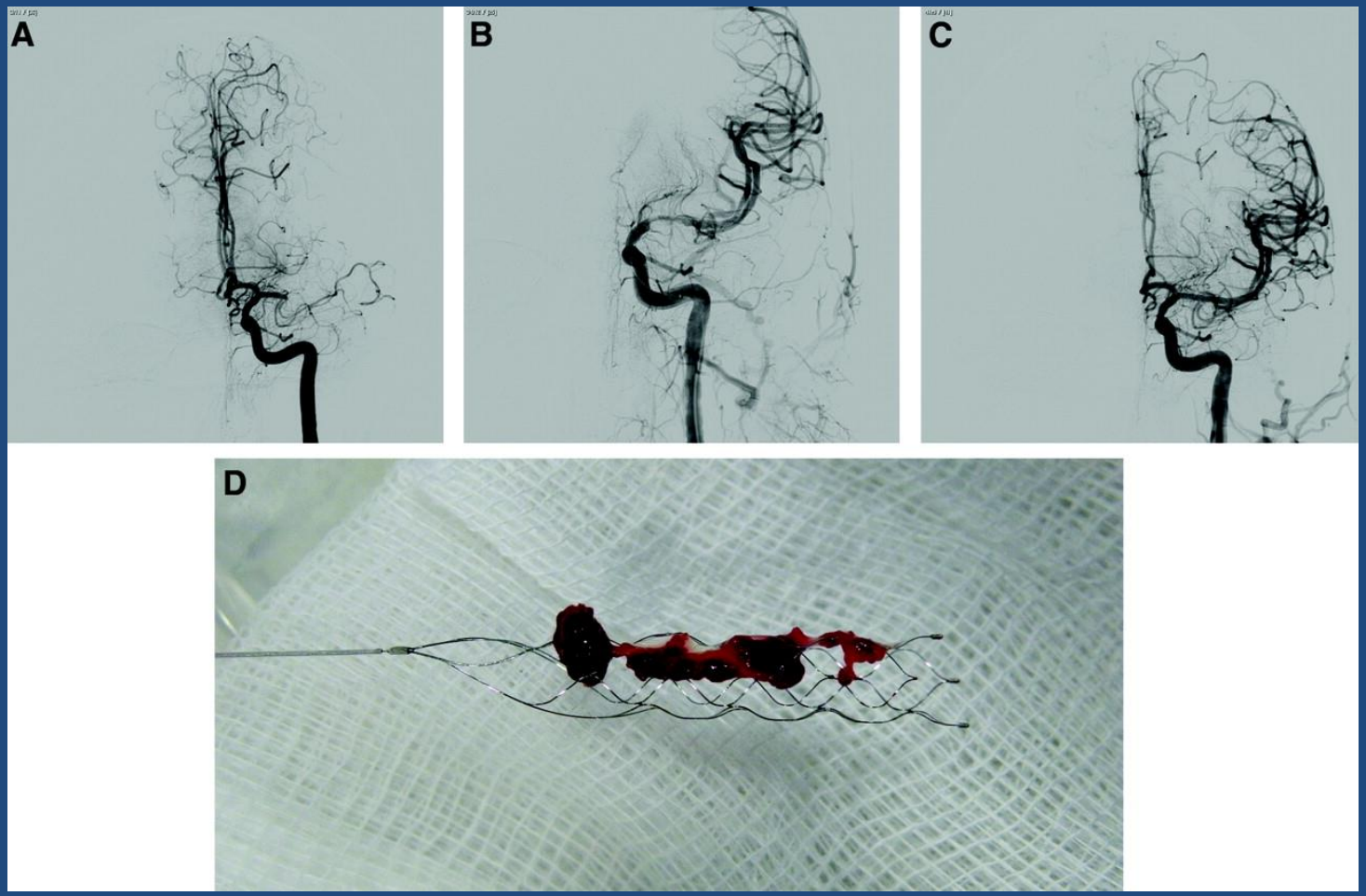
- And theoretically, such flow restoration can enhance the efficacy of systemic thrombolytic drugs if already in the circulation.

Stent retriever

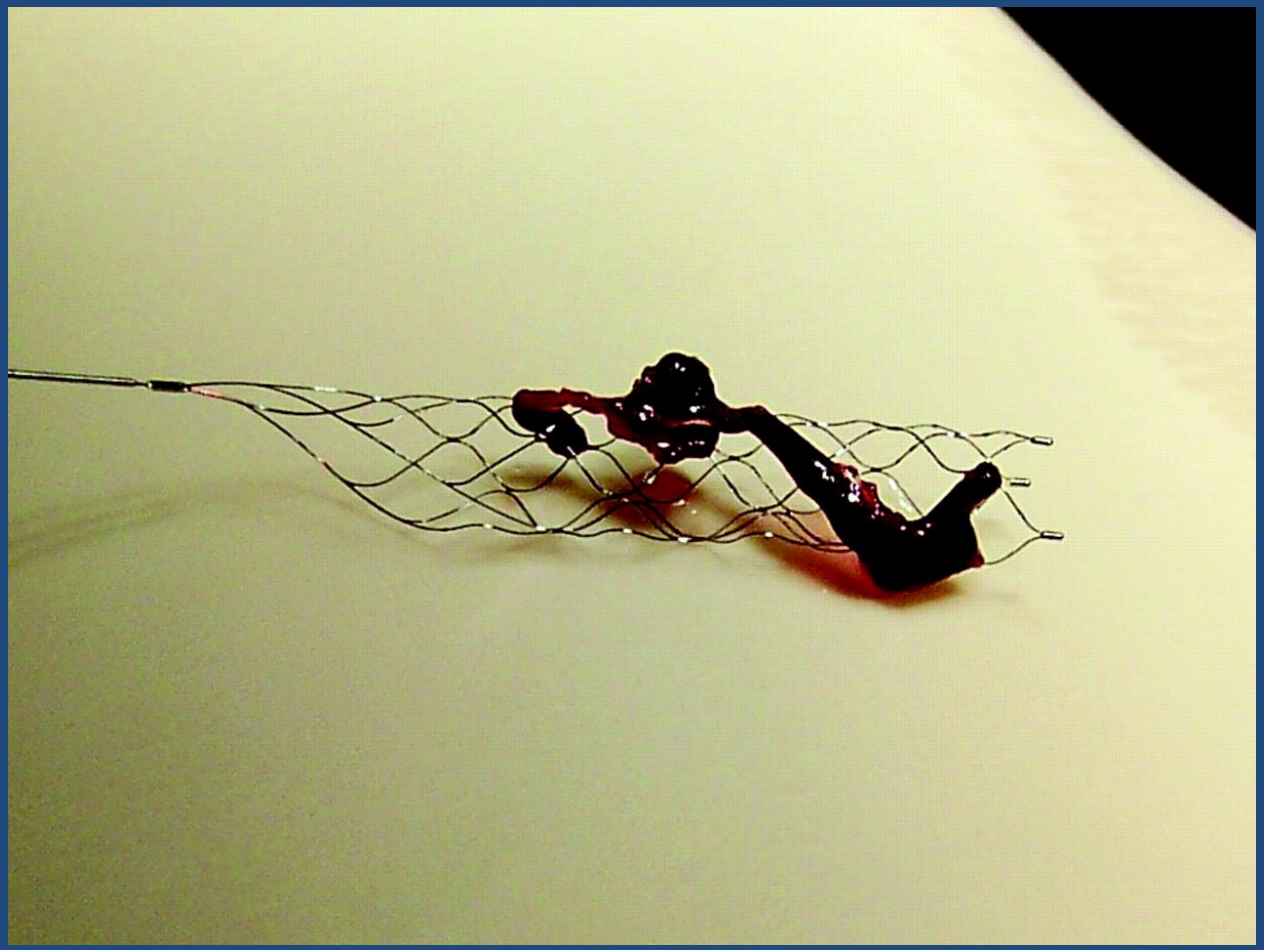
- After a period of up to 10 minutes, usually 3 to 5 minutes depending of the location and clot-size, the stent can be retrieved by pulling back the deployed stent into the guide catheter under proximal aspiration through the guide catheter.

- The addition of a proximal balloon guide catheter (BGC) can aid aspiration and help thrombus retrieval when the stent retriever is being dragged back into the guide catheter

Solitaire Device

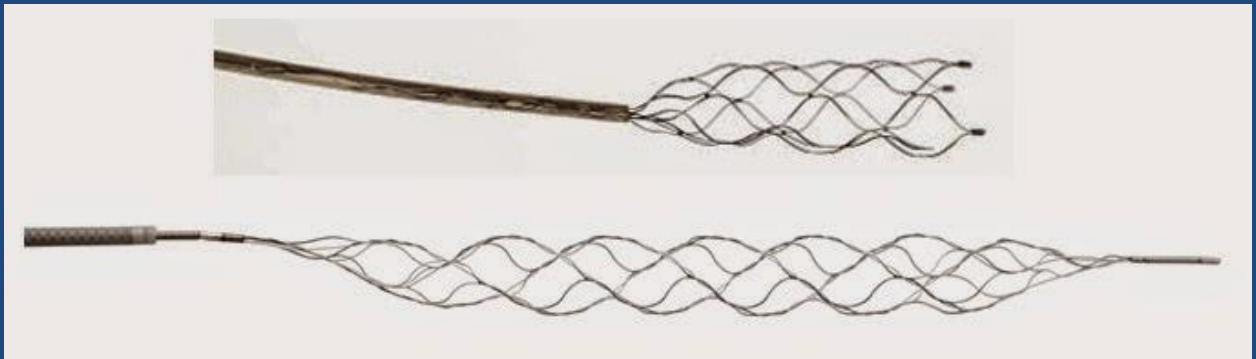


Stent retriever



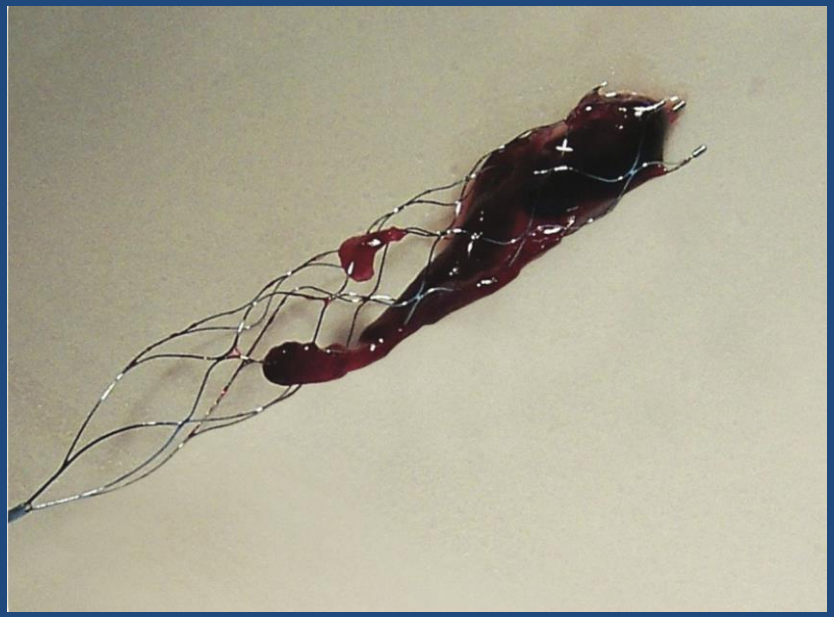
Trevo Stent-retiever

Stent retrievers or Stentrievers are self-expandable stent for thrombectomy that are deployed past the occlusion site with the use of



Trevo Stent-retiever

Stent retriever



Stent-retriever

- A review of prospective trials related to mechanical thrombolysis since 1999 showed a significant improvement in recanalization over the last 2 decades

- Stent-retrievers achieved successful recanalization in around 85% compared 50% in the first generation devices

Outcome with IV-t-PA:

Odds Ratios for Favorable Outcome

Time	Odds Ratio	95% (CI) Interval
0-90	2.8	1.8 - 4.5
91-180	1.5	1.1 - 2.1
181-270	1.4	1.1 - 1.9
271-360	1.2	0.9 - 1.5

Mechanical Thrombolysis

- Acute strokes with diffusion/perfusion match on presentation to the ED, lacks salvagable brain tissue and hence would not respond to mechanical thrombolysis

- Acute strokes with poor collaterals on CT angiogram lacks salvagable brain tissue and hence would not respond to mechanical thrombolysis

New neuro-imaging techniques and endovascular devices

- The advanced neuro-imaging techniques reliably identify the extent of salvagable ischemic brain tissues

- The novel endovascular devices (stent retriever) achieve a fast and more effective recanalization

Acute Stroke Treatment

5 recent randomized clinical trials assessing the efficacy and safety of stent retriever in acute ischemic stroke:

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

Mechanical Thrombolysis in AIS

- The 5 trials demonstrated endovascular (EV) therapy promoted recanalization with significant improvement in modified Rankin scores (mRS) with no increase in sICH or mortality

- The number needed to treat for endovascular thrombectomy to reduce disability at least one level of mRS is 2.6

Mechanical Thrombolysis in AIS

- ASA recommends that patients should be transported rapidly to primary or comprehensive stroke centers (Class I; Level A evidence), and regional systems of stroke care should be developed to provide access to centers capable of performing endovascular stroke treatment (Class I; Level A evidence)

Mechanical Thrombolysis in AIS

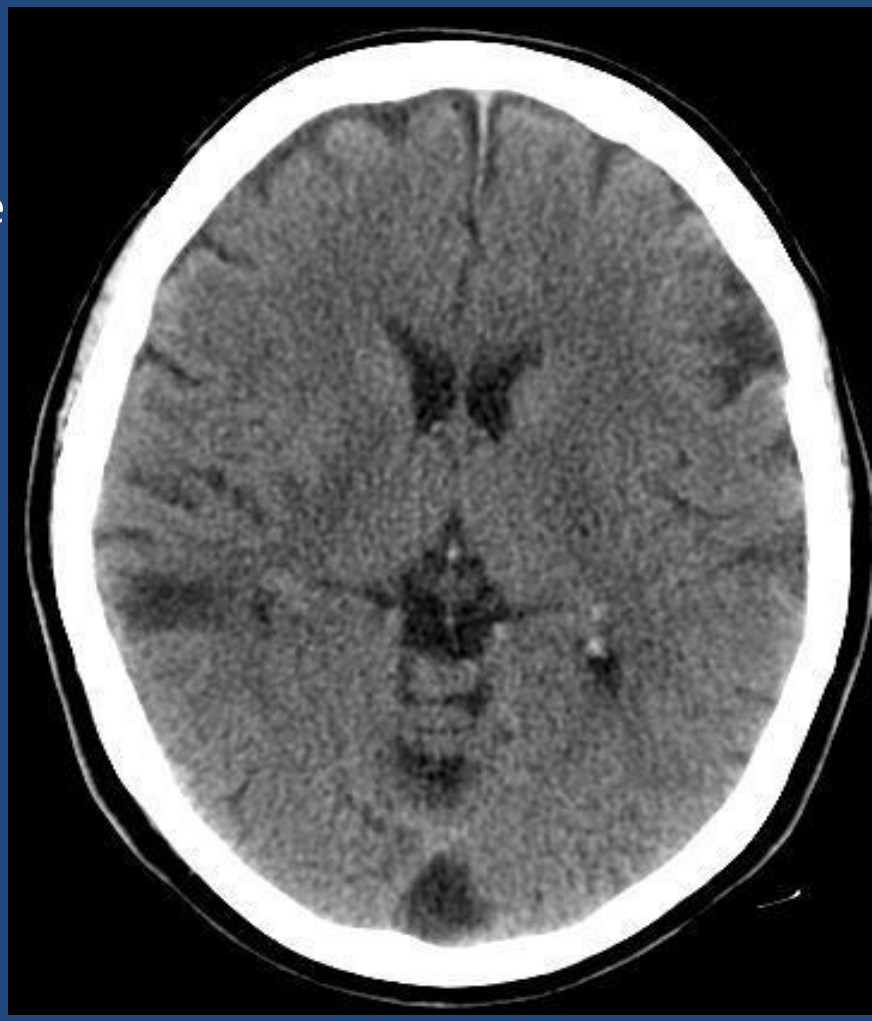
- Mechanical thrombectomy is a landmark change in stroke management, and guidelines should recommend mechanical thrombectomy as a level 1 evidence-based treatment worldwide. In terms of technical aspects of mechanical thrombectomy, stent retrievers (Solitaire FR or Trevo device) as the primary method

clinical deficit/infarct volume Mismatch

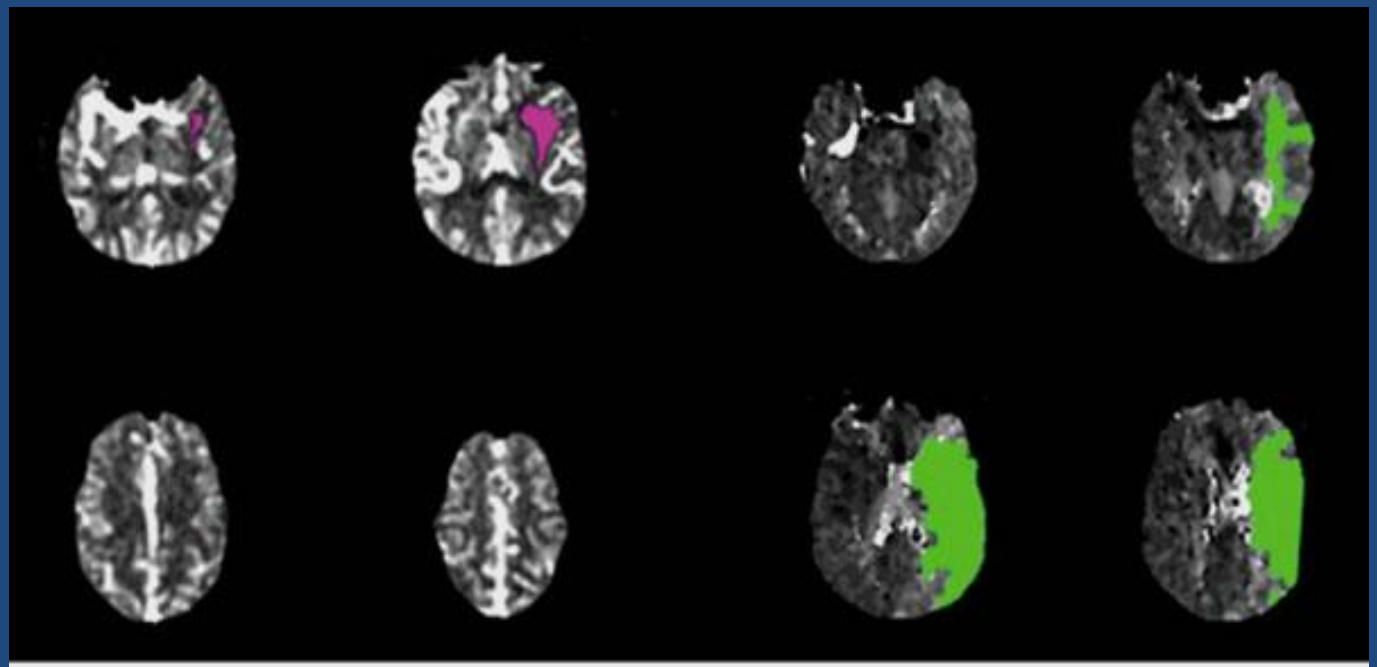
- A 61 year old male Presenting with left arm and leg paralysis, dysarthria, right gaze deviation and left Visual Field defect. He was Last seen normal 14 hours from the time of CT interpretation

The CT predicts only left arm weakness. However, the exam shows a much more Severe deficits

Hence, a mismatch between clinical deficit And infarct volume by imaging



CT Perfusion Scan

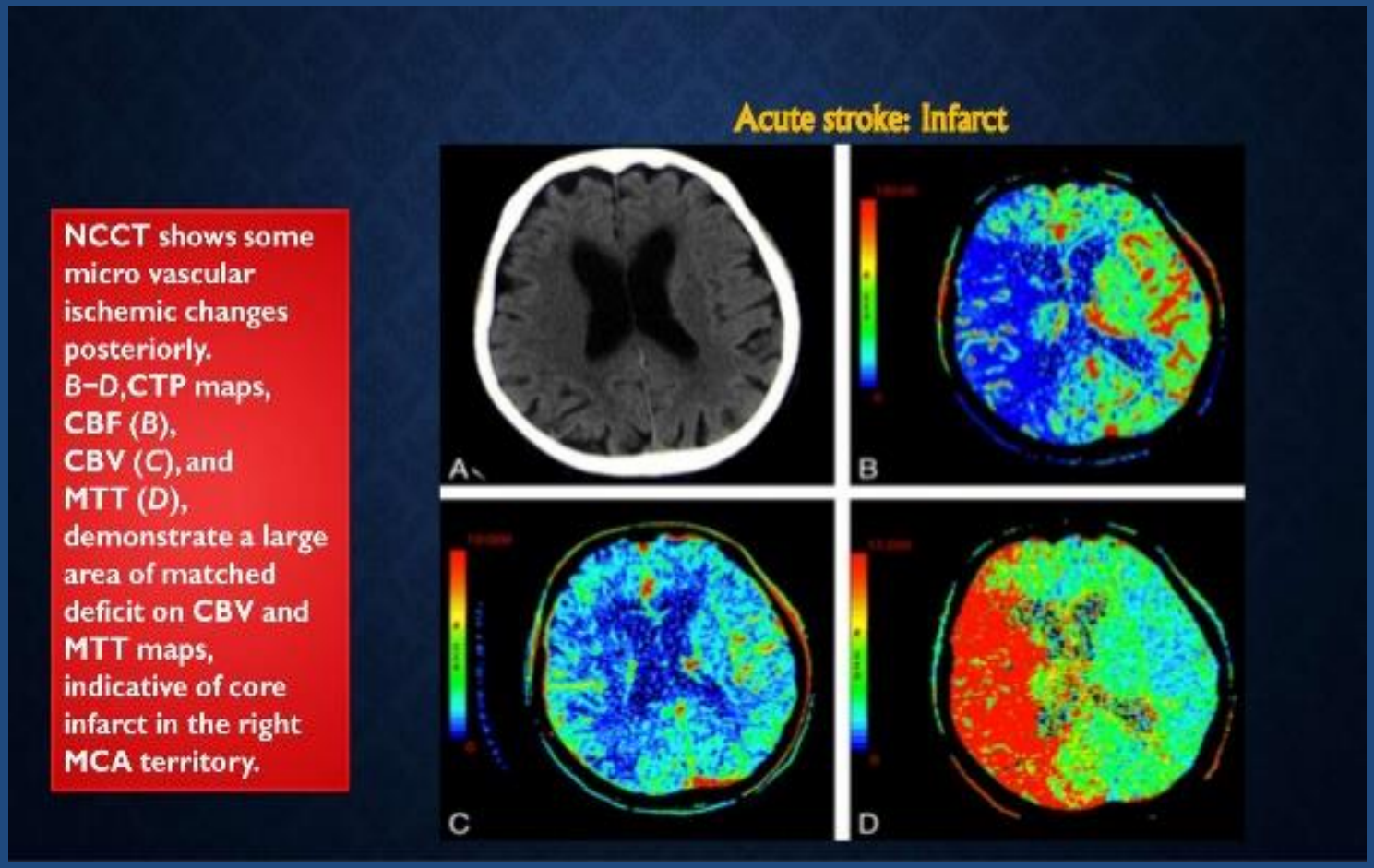


c Core, 23 ml

Volume of Per

Mismatch volume, 105 ml
Mismatch ratio, 5.6

CT Perfusion Scan



CT Perfusion Scan

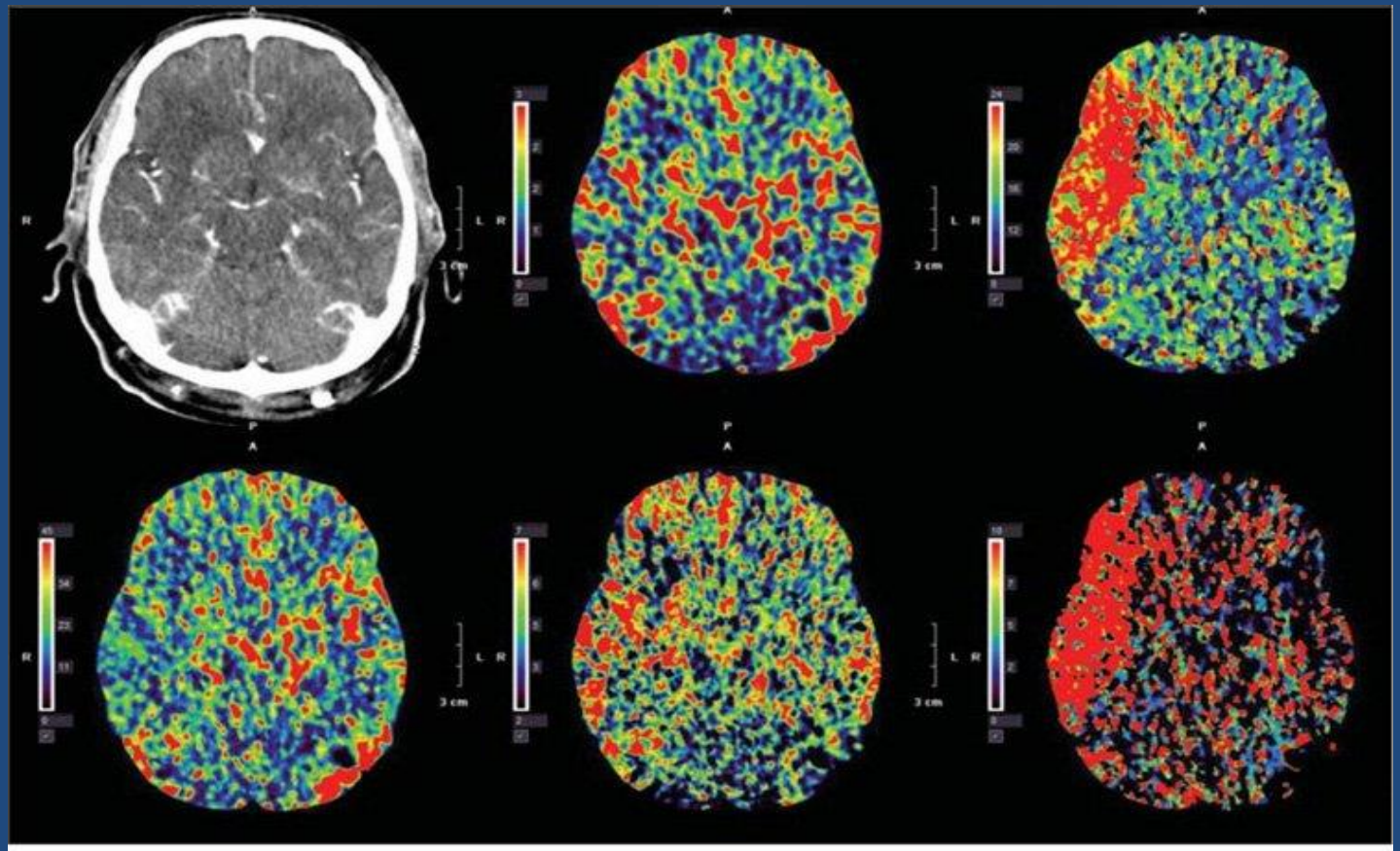


Fig. 4 – CTP imaging study showing an acute stroke of the right MCA territory with salvageable penumbra. The upper right panel indicates increased TTP (red area on perfusion map), whereas the upper middle panel indicates no significant CBV loss as seen by the minimal blue coloring in the right MCA territory. This patient underwent thrombectomy on the basis of CTP imaging findings and National Institutes of Health Stroke Scale score.

CT Perfusion Scan

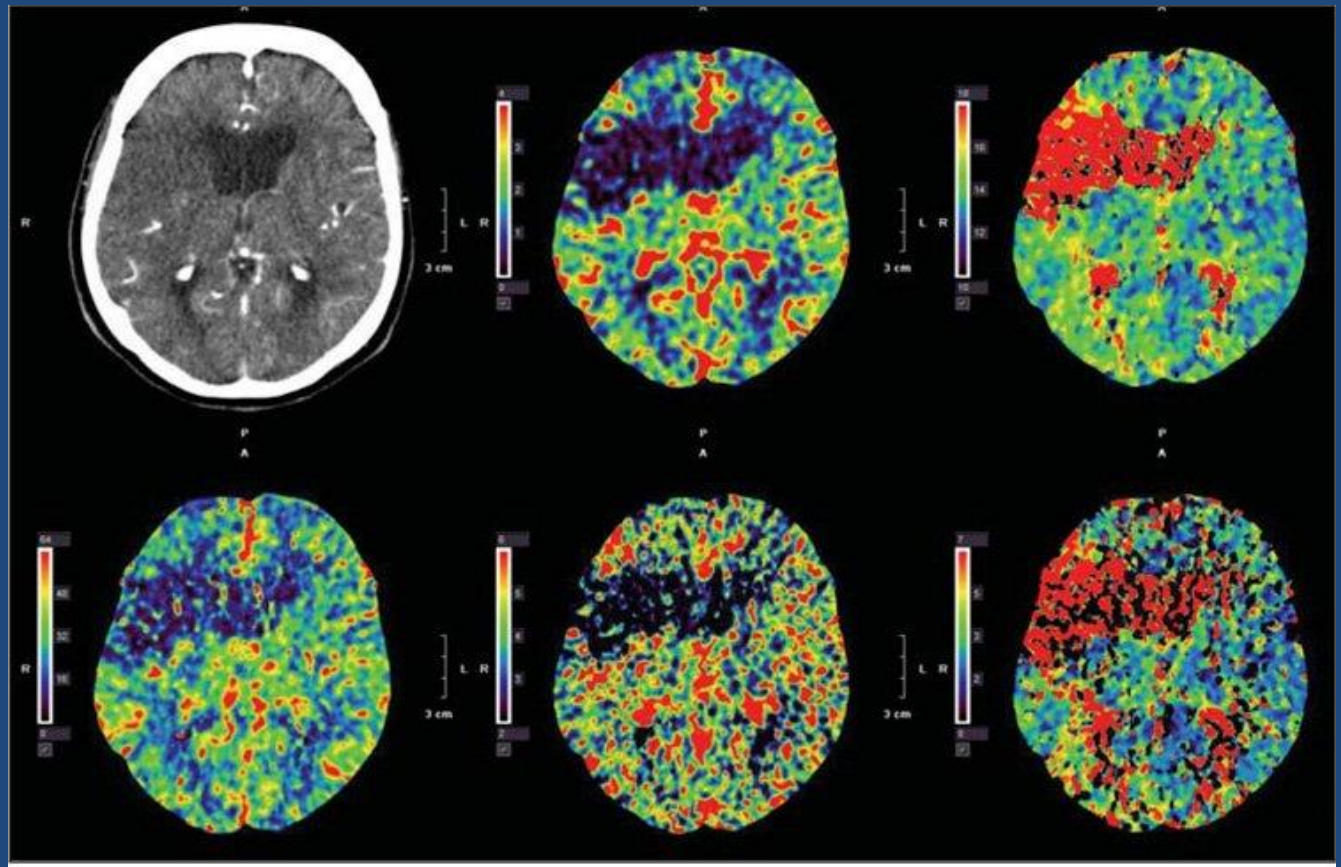


Fig. 3 – CTP imaging study showing a right-sided middle cerebral artery (MCA) stroke without any salvageable penumbra. Of the six-image panel, the upper right image represents time to peak (TTP), which indicates a delay in blood flow to the region of the brain seen as bright red on the color map. The upper middle component of the six-image panel represents cerebral blood volume (CBV). Notice the dark blue within that image, which highlights significant core infarct and large volume loss. Regions of irreversibly infarcted tissue show matched areas of decreased CBF and TTP. No stroke intervention was offered for this patient.

ORIGINAL ARTICLE

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

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November 11, 2017 | DOI: 10.1056/NEJMoa1706442

Previous randomized trials that involved patients with acute stroke[1-6] showed that endovascular thrombectomy had a clinical benefit when it was performed within 6 hours after the onset of stroke symptoms[7] and that the benefit diminished as the interval between the time that the patient was last known to be well and thrombectomy increased.[8] For the purposes of determining eligibility for thrombolysis or thrombectomy, the time that the patient was last known to be well has typically been considered to be the time of stroke onset, including among patients who wake up with stroke symptoms or have an uncertain time of stroke onset. There is limited information on the effect of thrombectomy that is performed more than 6 hours after the time that the patient was last known to be well, particularly among patients with ischemic brain tissue that has not yet undergone infarction and may be salvaged with reperfusion. Patients with brain tissue that may be salvaged with reperfusion can be identified by the presence of a clinical deficit that is disproportionately severe relative to the volume of infarcted tissue on imaging studies (see Section S3 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[9]

DAWN Trial

Background:

- The effect of endovascular thrombectomy that is performed more than 6 hours after the onset of ischemic stroke is uncertain
- Brain tissue that has not yet undergone infarction may be salvaged with perfusion
- Brain tissue that may be salvageable can be identified by the presence of a clinical deficit that is disproportionately severe relative to the volume of infarct tissue on imaging studies

DAWN Trial

Methods:

- Multi-center, prospective, randomized, open label trial with blinded assessment of end points
- Patients must have occlusion of the intracranial internal carotid artery or proximal middle cerebral artery who had last been known to be well 6 to 24 hours earlier
- Exclusion include >1/3 infarct volume of MCA territory by initial CT or MRI
- Patients are allowed, if indicated, to receive t-PA within 4.5 hours

DAWN Trial

Methods:

- There must be a mismatch between the severity of the clinical deficit and the infarct volume (mismatch between NIHSS and infarct volume)
- Infarct volume was assessed with the use of DW MRI/CT perfusion and was measured with automated software (RAPID)
- Patients were randomly assigned in a 1:1 ratio to thrombectomy plus standard care (the thrombectomy group) or to standard care alone (the control group).

DAWN Trial

Methods:

- Randomization was performed with the use of a central web based procedure
- 26 centers randomized patients in the USA, Canada, Europe, and Australia
- At least 40 mechanical thrombectomy procedure had to be performed at each center annually

DAWN Trial

Methods:

- Thrombectomy was performed with the use of Trevo device: a retrievable self-expanding stent that is used to remove occlusive thrombi and restore blood flow

- The end points (MRS) was obtained by a local certified assessor, who were unaware of the treatment assignment

DAWN Trial

Methods:

- The coprimary end points were the mean score for disability on the utility-weighted modified Rankin scale (which ranges from 0 [death] to 10 [no symptoms or disability]) and

- The rate of functional independence (a score of 0, 1, or 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating more severe disability) at 90 days.

DAWN Trial

Results:

- At 31 months, enrollment was halted because the results of an interim analysis met the pre-specified criterion for trial discontinuation

- From Sept. 2014 to Feb. 2017, 206 patients were enrolled in the study: 107 assigned to thrombectomy and 90 to control

Table 1. Characteristics of the Patients at Baseline.*

Variable	Thrombectomy Group (N=107)	Control Group (N=99)
Age — yr	69.4±14.1	70.7±13.2
Age ≥80 yr — no. (%)	25 (23)	29 (29)
Male sex — no. (%)	42 (39)	51 (52)
Atrial fibrillation — no. (%)	43 (40)	24 (24)
Diabetes mellitus — no. (%)	26 (24)	31 (31)
Hypertension — no. (%)	83 (78)	75 (76)
Previous ischemic stroke or transient ischemic attack — no. (%)	12 (11)	11 (11)
NIHSS score†		
Median	17	17
Interquartile range	13–21	14–21
10 to 20 — no. (%)	78 (73)	72 (73)
Treatment with intravenous alteplase — no. (%)	5 (5)	13 (13)
Infarct volume — ml		
Median	7.6	8.9
Interquartile range	2.0–18.0	3.0–18.1
Type of stroke onset — no. (%)‡		
On awakening	67 (63)	47 (47)
Unwitnessed stroke	29 (27)	38 (38)
Witnessed stroke	11 (10)	14 (14)
Occlusion site — no. (%)§		
Intracranial internal carotid artery	22 (21)	19 (19)
First segment of middle cerebral artery	83 (78)	77 (78)
Second segment of middle cerebral artery	2 (2)	3 (3)
Interval between time that patient was last known to be well and randomization — hr		
Median	12.2	13.3
Interquartile range	10.2–16.3	9.4–15.8
Range	6.1–23.5	6.5–23.9
Time from first observation of symptoms to randomization — hr		
Median	4.8	5.6
Interquartile range	3.6–6.2	3.6–7.8

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. There were no significant differences between the two treatment groups with respect to the baseline characteristics, except for a history of atrial fibrillation (P=0.01), treatment with intravenous alteplase (P=0.04), and the onset of stroke on awakening (P=0.03).

† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a more severe deficit.

‡ A patient with the onset of stroke on awakening had last been known to be well before going to bed and had the first observation of symptoms on awakening. In a patient with an unwitnessed stroke, the time that the patient had last been known to be well and the first observation of symptoms were different and the first observation of symptoms did not occur on awakening. In a patient with a witnessed stroke, the time that the patient had last been known to be well and the first observation of symptoms were the same; all patients with a witnessed stroke had a time from first observation of symptoms to randomization of more than 6 hours.

§ Patients who had occlusion of the intracranial internal carotid artery may also have had occlusion of the first segment of the middle cerebral artery.

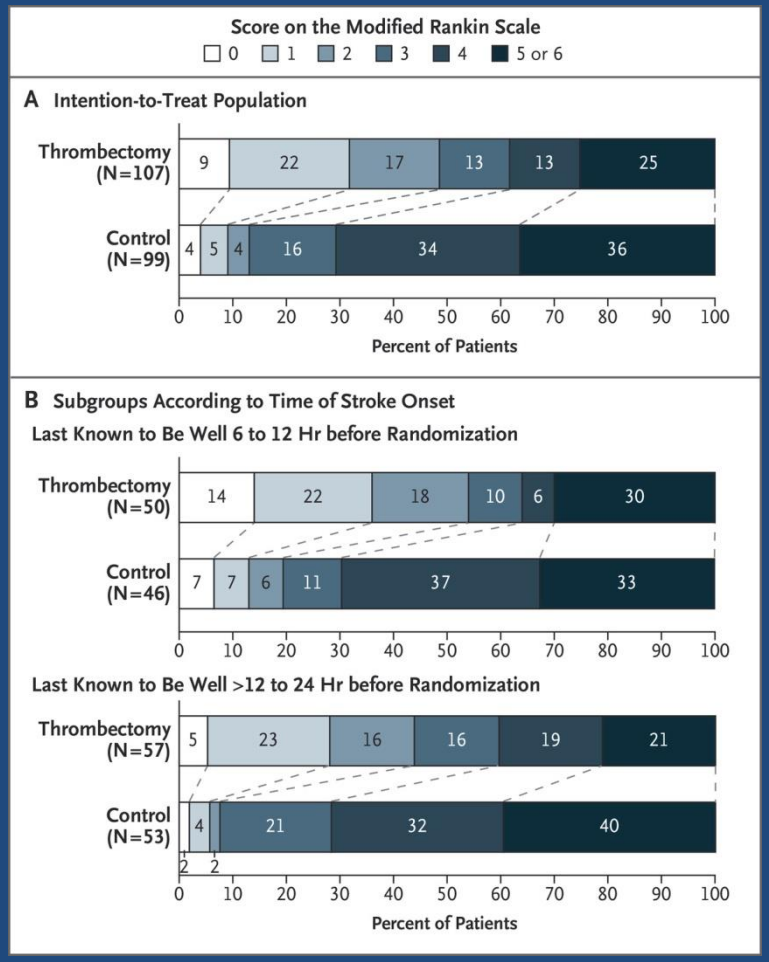
Results

Table 2. Efficacy Outcomes.*

Outcome	Thrombectomy Group (N=107)	Control Group (N=99)	Absolute Difference (95% CI)†	Adjusted Difference (95% Credible Interval)‡	Posterior Probability of Superiority
Primary end points					
Score on utility-weighted modified Rankin scale at 90 days§	5.5±3.8	3.4±3.1	2.1 (1.2–3.1)	2.0 (1.1–3.0)	>0.999
Functional independence at 90 days — no. (%)¶	52 (49)	13 (13)	36 (24–47)	33 (21–44)	>0.999
				Risk Ratio (95% CI)	**P Value**
Secondary end points					
Early response — no. (%)‖	51 (48)	19 (19)	29 (16–41)	3 (2–4)	<0.001**
Recanalization at 24 hr — no. (%)††	82 (77)	39 (39)	40 (27–52)	2 (2–4)	<0.001**
Change from baseline in infarct volume at 24 hr — ml††					0.003‡‡
Median	1	13			
Interquartile range	0–28	0–42			
Infarct volume at 24 hour — ml††					<0.001‡‡
Median	8	22			
Interquartile range	0–48	8–68			
Grade of 2b or 3 on mTICI scale — no. (%)§§	90 (84)	NA			

* Plus–minus values are means ±SD. CI denotes confidence interval, and NA not applicable.
† Absolute differences are reported in percentage points, except for the absolute difference in the score on the utility-weighted modified Rankin scale, which is reported in points.
‡ Adjusted differences were estimated with the use of a Bayesian general linear model with adjustment for infarct volume at baseline.
§ The utility-weighted modified Rankin scale ranges from 0 (death) to 10 (no symptoms or disability).
¶ Functional independence was defined as a score of 0, 1, or 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating more severe disability.
‖ Early response was defined as a decrease in the NIHSS score of 10 points or more from baseline or an NIHSS score of 0 or 1 on day 5, 6, or 7 of hospitalization or at discharge if it occurred before day 5.
** The P value was calculated with the use of Fisher's exact test.
†† For details on the assessment of this end point, see Section S2 in the Supplementary Appendix.
‡‡ The P value was calculated with the use of the nonparametric Wilcoxon test.
§§ The modified Thrombolysis in Cerebral Infarction (mTICI) scale ranges from 0 to 3, with a grade of 2b or 3 indicating reperfusion of more than 50% of the affected territory.

Results


Score on the Modified Rankin Scale
0
1
2
3
4
5 or 6
A Intention-to-Treat Population
Thrombectomy (N=107)
9
22
17
13
13
25
Control (N=99)
4
5
4
16
34
36
0 10 20 30 40 50 60 70 80 90 100
Percent of Patients
B Subgroups According to Time of Stroke Onset
Last Known to Be Well 6 to 12 Hr before Randomization
Thrombectomy (N=50)
14
22
18
10
6
30
Control (N=46)
7
7
6
11
37
33
0 10 20 30 40 50 60 70 80 90 100
Last Known to Be Well >12 to 24 Hr before Randomization
Thrombectomy (N=57)
5
23
16
16
19
21
Control (N=53)
4
21
32
40
2
2
0 10 20 30 40 50 60 70 80 90 100
Percent of Patients

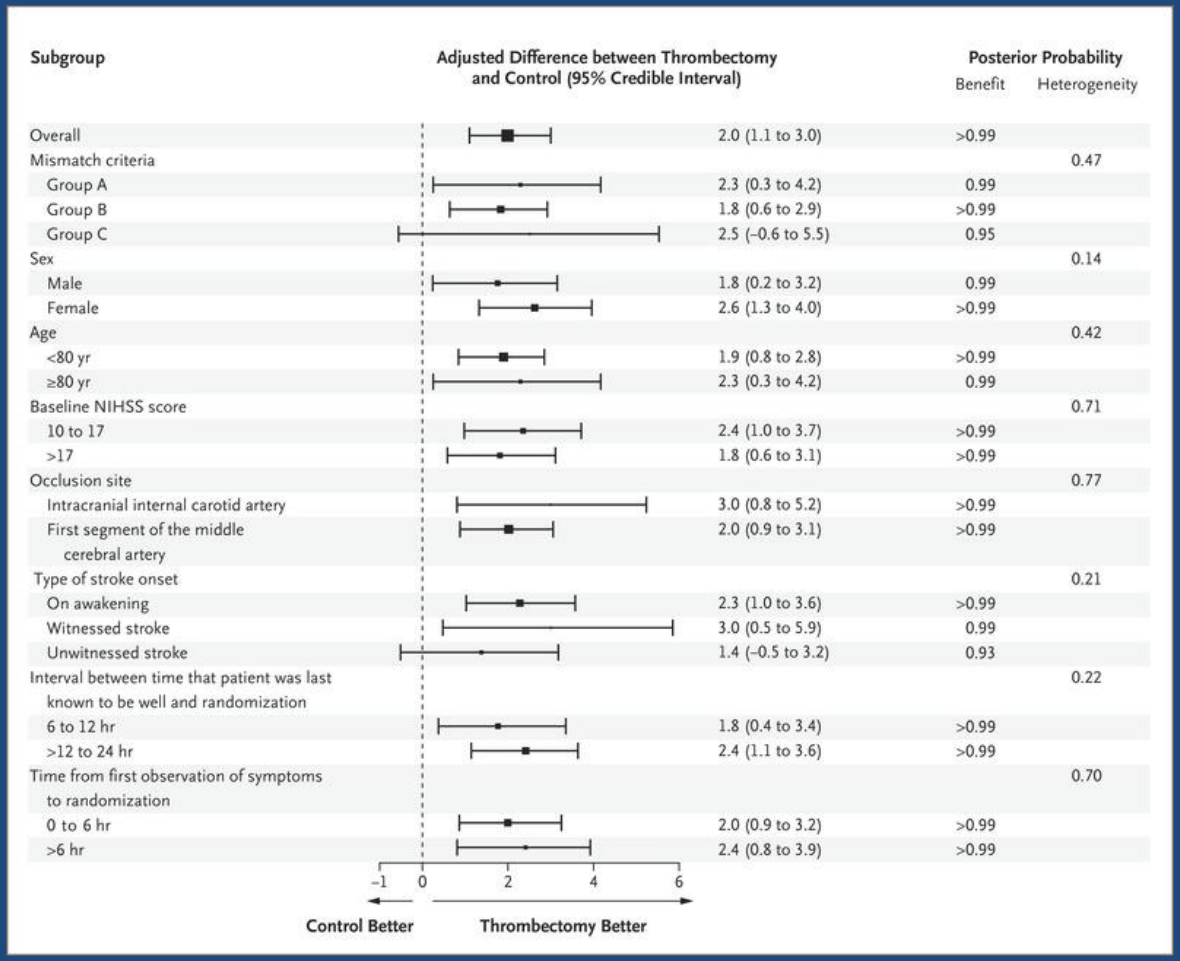

Subgroup
Adjusted Difference between Thrombectomy and Control (95% Credible Interval)
Posterior Probability
Benefit
Heterogeneity
Overall 2.0 (1.1 to 3.0) >0.99
Mismatch criteria 0.47
Group A 2.3 (0.3 to 4.2) 0.99
Group B 1.8 (0.6 to 2.9) >0.99
Group C 2.5 (−0.6 to 5.5) 0.95
Sex 0.14
Male 1.8 (0.2 to 3.2) 0.99
Female 2.6 (1.3 to 4.0) >0.99
Age 0.42
<80 yr 1.9 (0.8 to 2.8) >0.99
≥80 yr 2.3 (0.3 to 4.2) 0.99
Baseline NIHSS score 0.71
10 to 17 2.4 (1.0 to 3.7) >0.99
>17 1.8 (0.6 to 3.1) >0.99
Occlusion site 0.77
Intracranial internal carotid artery 3.0 (0.8 to 5.2) >0.99
First segment of the middle cerebral artery 2.0 (0.9 to 3.1) >0.99
Type of stroke onset 0.21
On awakening 2.3 (1.0 to 3.6) >0.99
Witnessed stroke 3.0 (0.5 to 5.9) 0.99
Unwitnessed stroke 1.4 (−0.5 to 3.2) 0.93
Interval between time that patient was last known to be well and randomization 0.22
6 to 12 hr 1.8 (0.4 to 3.4) >0.99
>12 to 24 hr 2.4 (1.1 to 3.6) >0.99
Time from first observation of symptoms to randomization 0.70
0 to 6 hr 2.0 (0.9 to 3.2) >0.99
>6 hr 2.4 (0.8 to 3.9) >0.99
−1
0
2
4
6
Control Better
Thrombectomy Better

Table 3. Safety Outcomes.*

Outcome	Thrombectomy Group (N=107)	Control Group (N=99)	Absolute Difference (95% CI)	Risk Ratio (95% CI)
	no. (%)		*percentage points*	
Stroke-related death at 90 days	17 (16)	18 (18)	−2 (−13 to 8)	1 (1 to 2)
Death from any cause at 90 days	20 (19)	18 (18)	1 (−10 to 11)	1 (1 to 2)
Symptomatic intracranial hemorrhage at 24 hr†	6 (6)	3 (3)	3 (−3 to 8)	2 (1 to 7)
Neurologic deterioration at 24 hr‡	15 (14)	26 (26)	−12 (−23 to −1)	1 (0 to 1)
Procedure-related complications	7 (7)	NA		
Distal embolization in a different territory	4 (4)	NA		
Intramural arterial dissection	2 (2)	NA		
Arterial perforation	0	NA		
Access-site complications leading to intervention	1 (1)	NA		

* There were no significant differences between the two treatment groups with respect to safety outcomes, except for neurologic deterioration (P=0.04). All safety outcomes were adjudicated by an independent clinical-events committee.
† Symptomatic intracranial hemorrhage was defined according to European Cooperative Acute Stroke Study III criteria as the presence of extravascular blood in the cranium that was associated with an increase in the NIHSS score of 4 points or more or death and was judged to be the predominant cause of neurologic deterioration.
‡ Neurologic deterioration was defined as an increase in the NIHSS score of 4 or more points within 5 days after stroke that was not attributed to intracranial hemorrhage or malignant cerebral edema.

DAWN Trial

Results:

- Symptomatic hemorrhage was the same in the 2 groups: 6% vs. 3% in the Thromb and Cont respectively (P=0.50)

- Mortality was the same in the two groups: 19 and 18% (P=1.00)

DAWN Trial

Conclusion:

- Among patients with acute stroke who had last been known to be well 6 to 24 hours earlier and who had a mismatch between clinical deficit and infarct, outcomes for disability and functional independence at 90 days were better with thrombectomy plus standard care than with standard care alone.

DAWN Trial

Conclusion:

- For every 2 patients who underwent thrombectomy, 1 additional patient had a better score for disability at 3 months

- For 2.8 patients who underwent thrombectomy, 1 additional patient had functional independence at 3 months

ORIGINAL ARTICLE

Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

Gregory W. Albers, M.D., Michael P. Marks, M.D., Stephanie Kemp, B.S., Soren Christensen, Ph.D., Jenny P. Tsai, M.D., Santiago Ortega-Gutierrez, M.D., Ryan A. McTaggart, M.D., Michel T. Torbey, M.D., May Kim-Tenser, M.D., Thabele Leslie-Mazwi, M.D., Amrou Sarraj, M.D., Scott E. Kasner, M.D., Sameer A. Ansari, M.D., Ph.D., Sharon D. Yeatts, Ph.D., Scott Hamilton, Ph.D., Michael Mlynash, M.D., Jeremy J. Heit, M.D., Greg Zaharchuk, M.D., Sun Kim, M.D., Janice Carrozzella, M.S.N., et al., for the DEFUSE 3 Investigators*

January 24, 2018
DOI: 10.1056/NEJMoa1713973

Abstract

DEFUSE 3 Trial

Background:

- CT perfusion and MRI D/P sequence can estimate the volume of irreversibly injured ischemic tissue and the volume of brain that is ischemic but not yet infracted

- These techniques may identify patients who will have a favorable response to ET even when therapy is initiated beyond 6 hours

DEFUSE 3 Trial

Background:

- DEFUSE 3 trial was designed to test the hypothesis that patients who were likely to have salvageable ischemic brain tissue as defined by perfusion imaging and who underwent ET therapy 6 to 16 hours after they were last known normal, would have better functional outcome than patients treated with standard medical therapy

DEFUSE 3 Trial

Methods:

- A multi-center, randomized, open-label, with blinded outcome assessment of thrombectomy within 6-16 hours from the symptoms onset

- Neurointerventionists were preapproved to participate on the basis of training and experience

DEFUSE 3 Trial

Methods:

- Patients were assigned in a 1:1 ratio to ET or Standard medical treatment with the use of web-based dynamic randomization system

- Randomization was stratified according to age, core infarct volume, time from symptoms onset to enrolment, baseline score of NIHSS and trial site

DEFUSE 3 Trial

Methods:

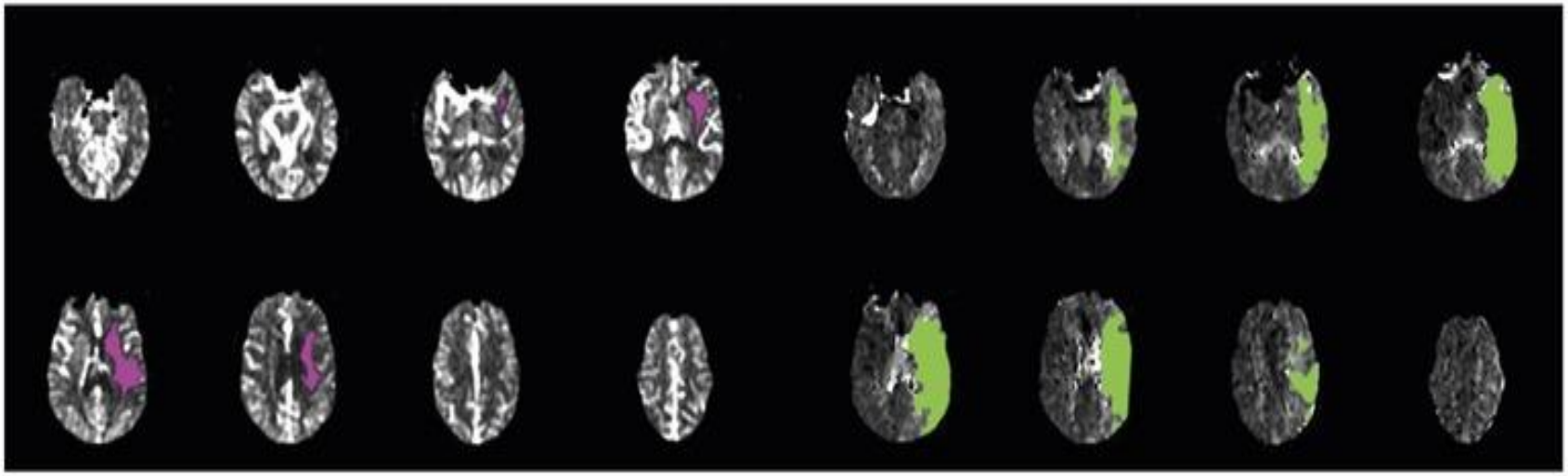
- ET was performed with any FDA approved thrombectomy device at the discretion of the NI
- GA was discouraged
- IV t-PA within 4.5 hours was allowed

DEFUSE 3 Trial

Inclusion criteria include:

- ✓ Proximal MCA or ICA occlusion

- ✓ Infarct volume (ischemic core)< 70ml, a ratio of volume of ischemic tissue to infarct core of >1.8 and an absolute volume of penumbra of> 15 ml [RAPID software was used to calculate the volume of ischemic core and penumbra regions from CT perfusion and MRI D/P scans]



Volume of Ischemic Core, 23 ml

Volume of Perfusion Lesion, 128 ml

Mismatch volume, 105 ml
Mismatch ratio, 5.6

DEFUSE 3 Trial

Methods:

- The primary outcome was the MRS (range 0-6, with higher score indicating greater disabilty) at day 90
- Primary outcome was assessed by a certified rater who was unaware of the trial group assignment

DEFUSE 3 Trial

Results:

- 38 US centers participated in the study
- The NIH, induced by the DAWN trial results, asked the investigators to hold enrollment and perform early interim analysis
- The results of interim analysis dictated early termination of enrollment
- From May 2016 to May 2017, a total of 182 patients underwent enrollment; 92 to the ET and 90 to the SMT

DEFUSE 3 trial

Table 1. Baseline Characteristics of the Patients and Features of Thrombectomy.*

Characteristic	Endovascular Therapy (N = 92)	Medical Therapy (N = 90)
Median age (IQR) — yr	70 (59–79)	71 (59–80)
Female sex — no. (%)	46 (50)	46 (51)
Median NIHSS score (IQR)†	16 (10–20)	16 (12–21)
Stroke onset witnessed — no. (%)		
Yes‡	31 (34)	35 (39)
No		
Symptoms were present on awakening	49 (53)	42 (47)
Symptoms began during wakefulness	12 (13)	13 (14)
Treatment with intravenous t-PA — no. (%)§	10 (11)	8 (9)
Imaging characteristics¶		
Qualifying imaging — no. (%)		
CT perfusion imaging	69 (75)	64 (71)
Diffusion and perfusion MRI	23 (25)	26 (29)
Median volume of ischemic core (IQR) — ml	9.4 (2.3–25.6)	10.1 (2.1–24.3)
Median volume of perfusion lesion (IQR) — ml‖	114.7 (79.3–146.3)	116.1 (73.4–158.2)
Occlusion site on baseline CTA or MRA — no. (%)		
Internal carotid artery	32 (35)	36 (40)
Middle cerebral artery**	60 (65)	54 (60)
Median ASPECTS on baseline CT (IQR)††	8 (7–9)	8 (7–9)
Process measures — hr:min		
Median time from stroke onset to qualifying imaging (IQR)	10:29 (8:09–11:40)	9:55 (7:59–12:20)
Median time from stroke onset to randomization (IQR)	10:53 (8:46–12:21)	10:44 (8:42–13:04)
Median time from qualifying imaging to femoral puncture (IQR)	0:59 (0:39–1:27)	NA
Median time from femoral puncture to reperfusion (IQR)	0:38 (0:26- 0:59)	NA

* Patients in the endovascular-therapy group received endovascular therapy plus standard medical therapy. Patients in the medical-therapy group received standard medical therapy alone. There were no significant differences between the two groups for any baseline characteristic. CT denotes computed tomography, CTA computed tomographic angiography, IQR interquartile range, MRA magnetic resonance angiography, and MRI magnetic resonance imaging.

† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a greater deficit.

‡ Patients with witnessed onset underwent randomization a median of 9.5 hours after stroke onset.

§ Treatment with intravenous tissue plasminogen activator (t-PA) was allowed if begun within 4.5 hours after symptom onset.

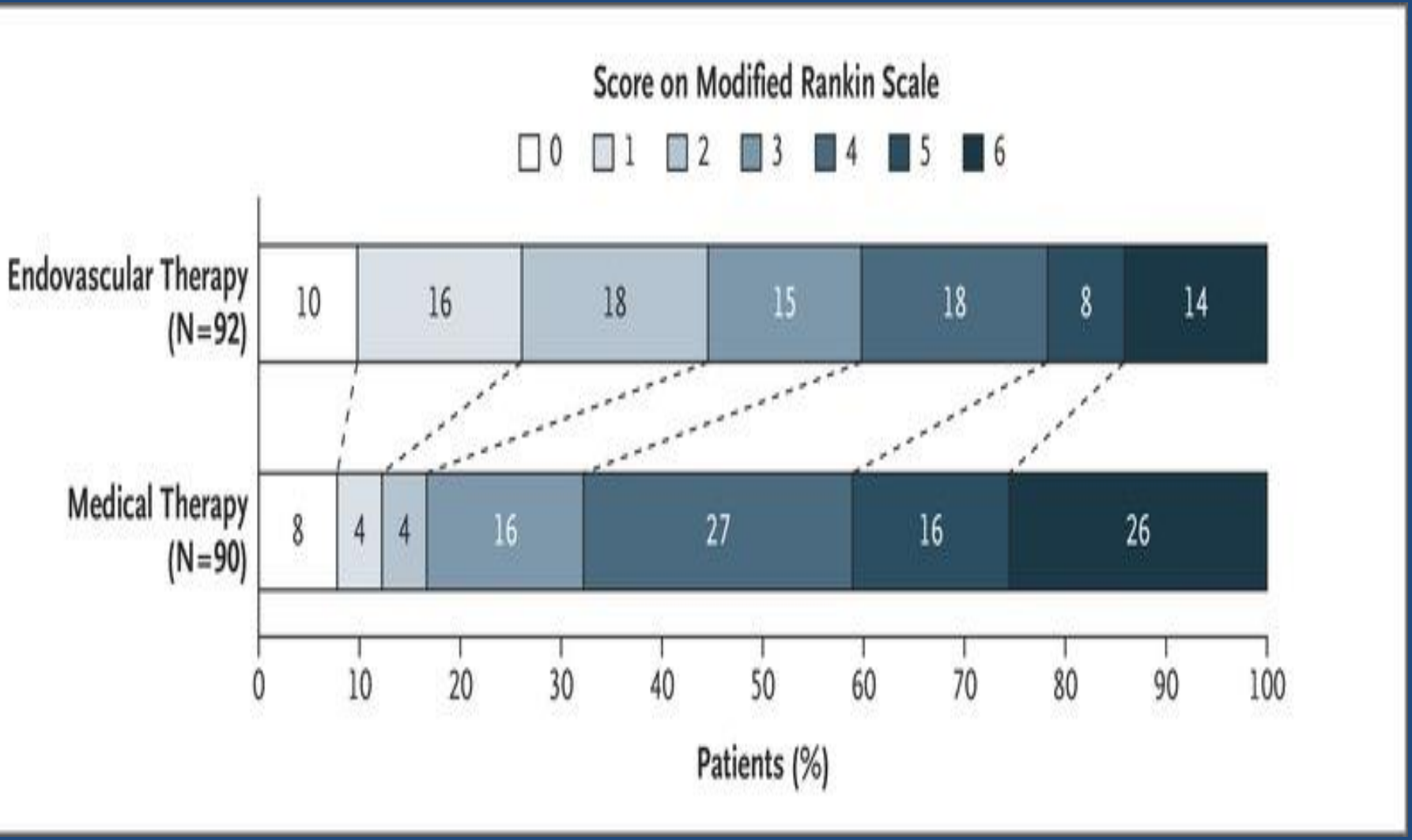
¶ Values are those reported by the central imaging laboratory.

‖ Shown is the volume of tissue for which there was delayed arrival of an injected tracer agent exceeding 6 seconds. Data were missing for two patients in the medical-therapy group owing to technically inadequate perfusion studies. These two patients were enrolled on the basis of alternative neuroimaging inclusion criteria (see the Supplementary Appendix).

** All middle-cerebral-artery occlusions involved the M1 segment, except in one patient in the medical-therapy group who had an occlusion involving the M2 segment.

†† The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is a tool that is used to estimate the volume of infarcted tissue. Scores range from 0 to 10, with lower scores indicating a larger area. Baseline scores were available for 76 patients in the endovascular-therapy group and 66 patients in the medical-therapy group. Baseline scores are not reported for patients in whom the qualifying imaging study was an MRI.

DEFUSE 3 Trial



DEFUSE 3 Trial

Table 2. Clinical and Imaging Outcomes.

Outcome	Endovascular Therapy (N=92)*	Medical Therapy (N=90)	Odds Ratio or Risk Ratio (95% CI)†	P Value
Primary efficacy outcome: median score on modified Rankin scale at 90 days (IQR)‡	3 (1–4)	4 (3–6)	2.77 (1.63–4.70)§	<0.001
Secondary efficacy outcome: functional independence at 90 days — no. (%)¶	41 (45)	15 (17)	2.67 (1.60–4.48)	<0.001
Safety outcomes — no. (%)				
Death at 90 days	13 (14)	23 (26)	0.55 (0.30–1.02)	0.05
Symptomatic intracranial hemorrhage‖	6 (7)	4 (4)	1.47 (0.40–6.55)	0.75
Early neurologic deterioration	8 (9)	11 (12)	0.71 (0.30–1.69)	0.44
Parenchymal hematoma type 2	8 (9)	3 (3)	2.61 (0.73–14.69)	0.21
Imaging outcomes**				
Median infarct volume at 24 hr (IQR) — ml	35 (18–82)	41 (25–106)	—	0.19
Median infarct growth at 24 hr (IQR) — ml	23 (10–75)	33 (18–75)	—	0.08
Reperfusion >90% at 24 hr — no./total no. (%)	59/75 (79)	12/67 (18)	4.39 (2.60–7.43)	<0.001
Complete recanalization at 24 hr — no./total no. (%)	65/83 (78)	14/77 (18)	4.31 (2.65–7.01)	<0.001
TICI score of 2b or 3 — no./total no. (%)	69/91 (76)	—	—	

* An intervention was attempted in 90 patients (98%), of whom 88 had an attempted mechanical thrombectomy and 2 had carotid stenting alone. In one of these two cases, the interventionalist elected not to perform a thrombectomy. The other patient did not have an occlusion on the baseline angiogram but was treated with carotid stenting for presumed dissection. The 2 patients with no intervention had carotid-artery occlusions, one in the common carotid and the other in the internal carotid, and the interventionalist decided that treatment was not feasible. Revascularization of the carotid artery with angioplasty, stenting, or both was performed in 13 patients (14%).

† The odds ratio is shown for the primary efficacy outcome, and risk ratio is shown for the other outcomes.

‡ Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating greater disability. The protocol required the score to be assessed by a person who was not aware of the trial-group assignments. However, three patients in the endovascular-therapy group and one patient in the medical-therapy group had an assessor who was aware of the trial-group assignments.

§ Shown is the unadjusted common odds ratio. The odds ratio with adjustment for stratification factors is 3.36 (95% CI, 1.96 to 5.77; P<0.001). The proportional-odds assumption was not met when core volume was included in the fully adjusted model; without core volume included, the adjusted odds ratio is 3.24 (95% CI, 1.89 to 5.55).

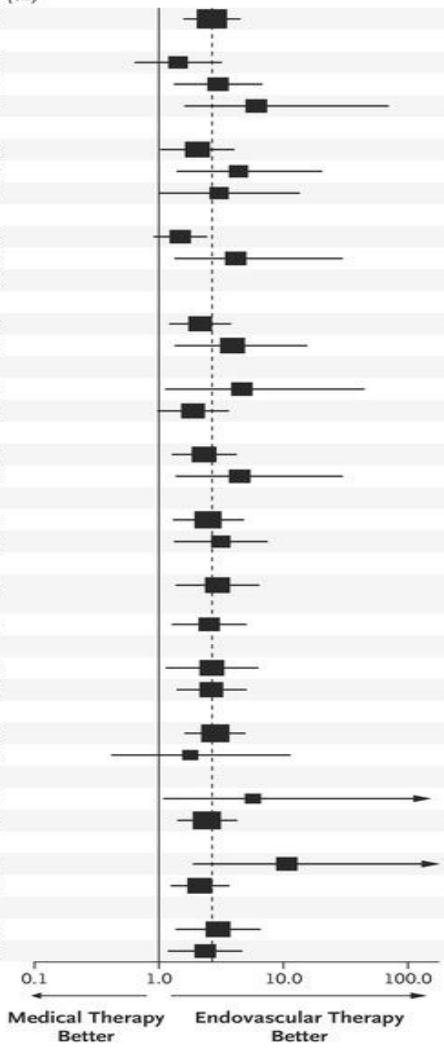
¶ Functional independence was defined as a score on the modified Rankin scale of 0 to 2.

‖ Among the patients with symptomatic intracranial hemorrhage, the hemorrhage was rated as parenchymal hematoma type 2 (dense blood clot exceeding 30% of the infarct volume with substantial space-occupying effect; in two patients in the endovascular-therapy group and three patients in the medical-therapy group), parenchymal hematoma type 1 (blood clot not exceeding 30% of the infarcted area with some mild space-occupying effect; in one patient in the endovascular-therapy group), hemorrhagic infarction type 2 (confluent petechiae within the infarcted area, but without space-occupying effect; in three patients in the endovascular-therapy group), or hemorrhagic infarction type 1 (small petechiae along the margins of the infarct; in one patient in the medical-therapy group).

** Infarct volume at 24 hours was assessed on diffusion-weighted MRI (or CT if MRI was not feasible). Infarct volume and infarct growth at 24 hours were assessed in 90 patients in the endovascular-therapy group and 89 patients in the medical-therapy group (2 patients in the endovascular-therapy group and 1 patient in the medical-therapy group died before imaging).

DEFUSE 3 Trial

Subgroup	No. of Patients	Endovascular Therapy	Medical Therapy	Risk Ratio for Functional Independence at Day 90 (95% CI)	P Value for Interaction
		functional independence (%)			
Overall	182	45	17	2.67 (1.60–4.48)	
Time from stroke onset to randomization					0.21
<9 hr	50	40	28	1.43 (0.65–3.15)	
9–12 hr	72	50	17	3.00 (1.35–6.68)	
>12 hr	60	42	7	6.08 (1.64–69.93)	
Volume of ischemic core					0.47
<10.0 ml	92	42	20	2.04 (1.04–3.99)	
10.0–25.0 ml	44	55	13	4.40 (1.41–20.33)	
>25.0 ml	46	42	14	3.06 (1.01–13.53)	
Baseline NIHSS score					0.20
<13	55	69	46	1.49 (0.92–2.42)	
13–18	55	48	12	4.18 (1.36–29.67)	
>18	72	21	0	—	
Age					1.00
<70 yr	84	59	28	2.15 (1.23–3.76)	
≥70 yr	98	31	8	3.91 (1.36–15.46)	
ASPECTS					0.65
<8	57	32	7	4.66 (1.14–44.44)	
≥8	85	46	24	1.88 (0.99–3.60)	
Site of occlusion					0.69
Middle cerebral artery	113	48	21	2.33 (1.29–4.19)	
Internal carotid artery	68	38	8	4.50 (1.39–29.67)	
Baseline imaging method					0.41
CT	133	39	16	2.50 (1.32–4.75)	
MRI	49	61	19	3.17 (1.35–7.43)	
Determination of time of stroke					0.87
Time that patient was last known to be well	116	38	13	2.96 (1.38–6.36)	
Exact time of symptom onset	66	58	23	2.54 (1.29–5.01)	
Sex					0.71
Female	92	35	13	2.67 (1.15–6.21)	
Male	90	54	20	2.66 (1.41–5.04)	
Race					0.58
White	158	46	16	2.84 (1.64–4.93)	
Other or unknown	24	36	20	1.79 (0.42–11.38)	
Ethnic group					0.61
Hispanic	24	57	10	5.71 (1.11–158.73)	
Non-Hispanic	157	43	18	2.45 (1.43–4.21)	
Atrial fibrillation					0.21
Yes	62	38	4	10.71 (1.91–294.11)	
No	120	48	23	2.14 (1.26–3.64)	
Eligible for DAWN trial					0.96
Yes	112	38	13	3.00 (1.39–6.49)	
No	70	56	24	2.36 (1.20–4.63)	



Acute Ischemic Stroke Treatment in 2017

Conclusion

- IV t-PA, within 4.5 hours from the symptoms onset of acute ischemic stroke, is affective and the standard of care

- Endovascular treatment using stent retriever ± t-PA within 6 hours from the onset of stroke symptoms, is effective and the standard of care

- In selected acute stroke patients within 6-16 hours of last known normal who have a large vessel occlusion in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is *recommended*.

- In selected acute stroke patients within 6-24 hours of last known normal who have large vessel occlusion in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy with a stent retriever is *reasonable*.