LOUISIANA
EMERGENCY RESPONSE NETWORK
Right Place. Right Time. Right Care.

Acute Ischemic Stroke Management

Tashfin Huq, MD, RPNI
Board Certified Vascular Neurologist
Stroke Medical Director
Primary Stroke Center
Thibodaux Regional Health System
LERN Region 3 Stroke Champion

Morbidity and Mortality

Mortality Data:	Worldwide: According to the Global Burden of Disease Study, stroke is the second leading cause of death globally, responsible for approximately 11% of all deaths[1].	United States: Stroke is the fifth leading cause of death in the United States, causing around 150,000 deaths annually[2].
Morbidity Data:	Worldwide: Stroke is a major cause of disability worldwide. According to the World Health Organization, stroke is a leading cause of long-term disability, with survivors often experiencing motor, sensory, and cognitive impairments[3].	United States: In the United States, stroke is a leading cause of serious long-term disability, with up to 80% of stroke survivors experiencing some form of impairment[4].

Healthcare Expenditure Data

Worldwide:

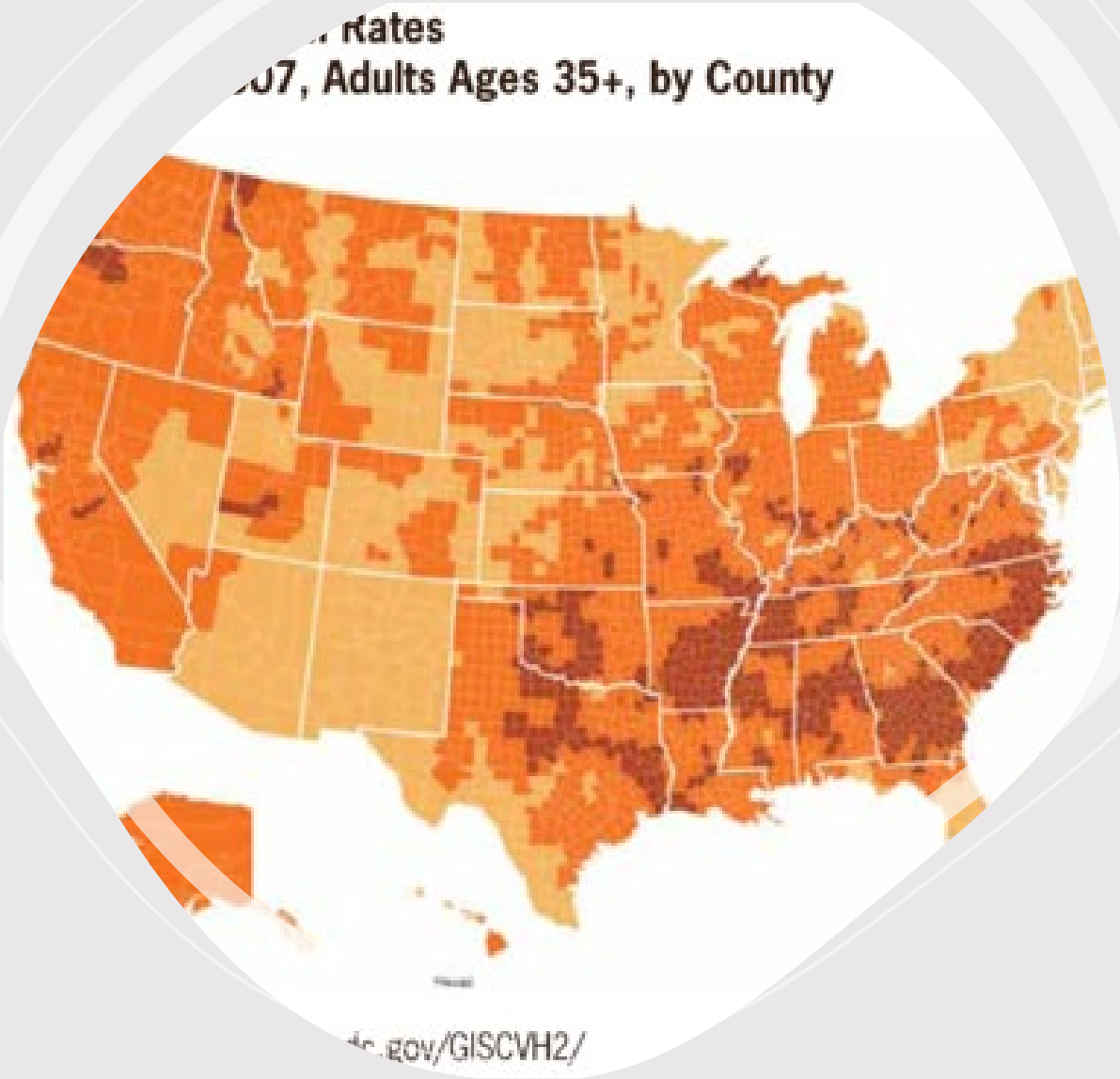
Stroke places a significant economic burden on healthcare systems globally.

According to a study published in The Lancet, the estimated global economic cost of stroke is expected to reach $180.3 billion annually[5].

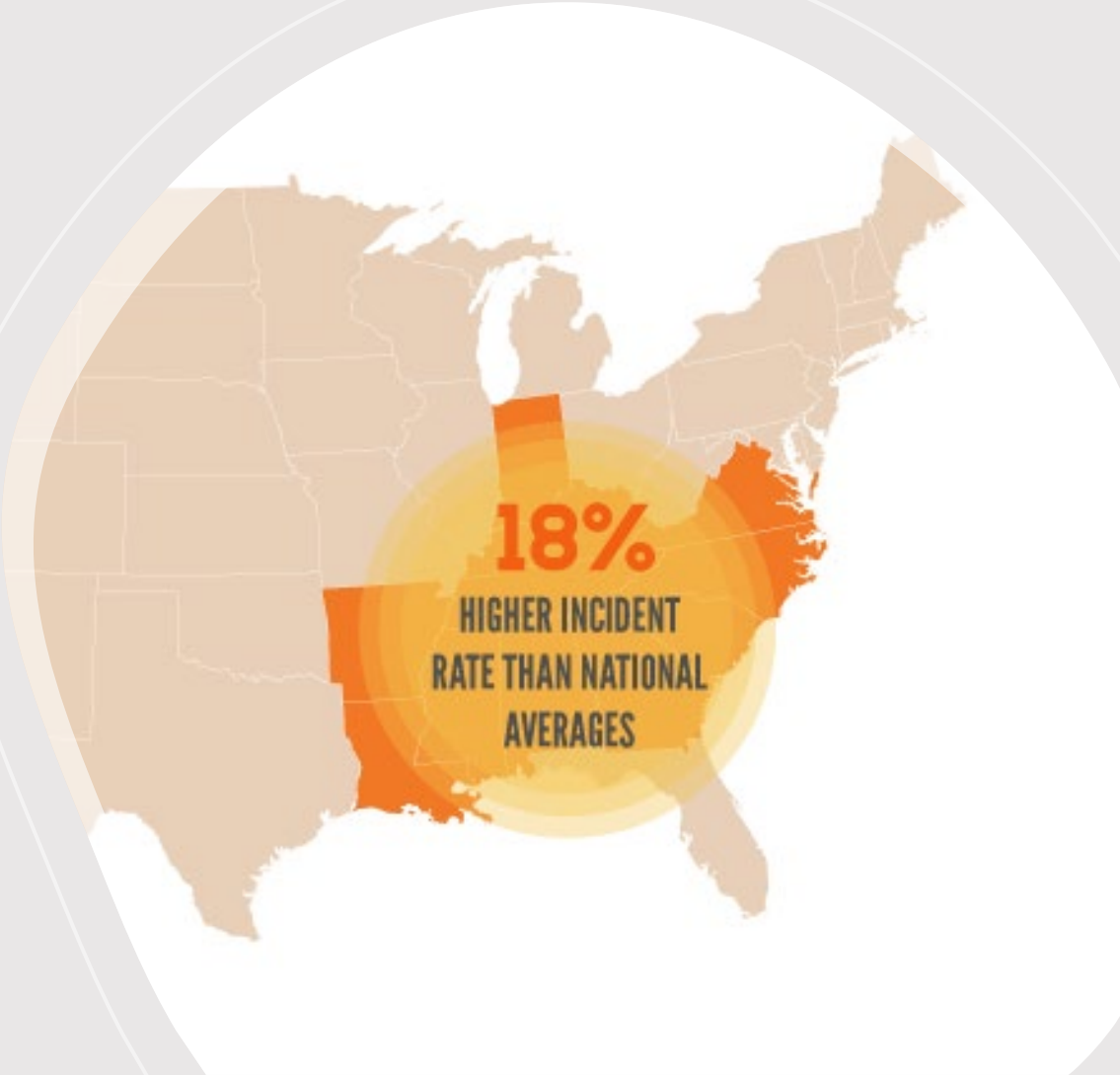
United States:

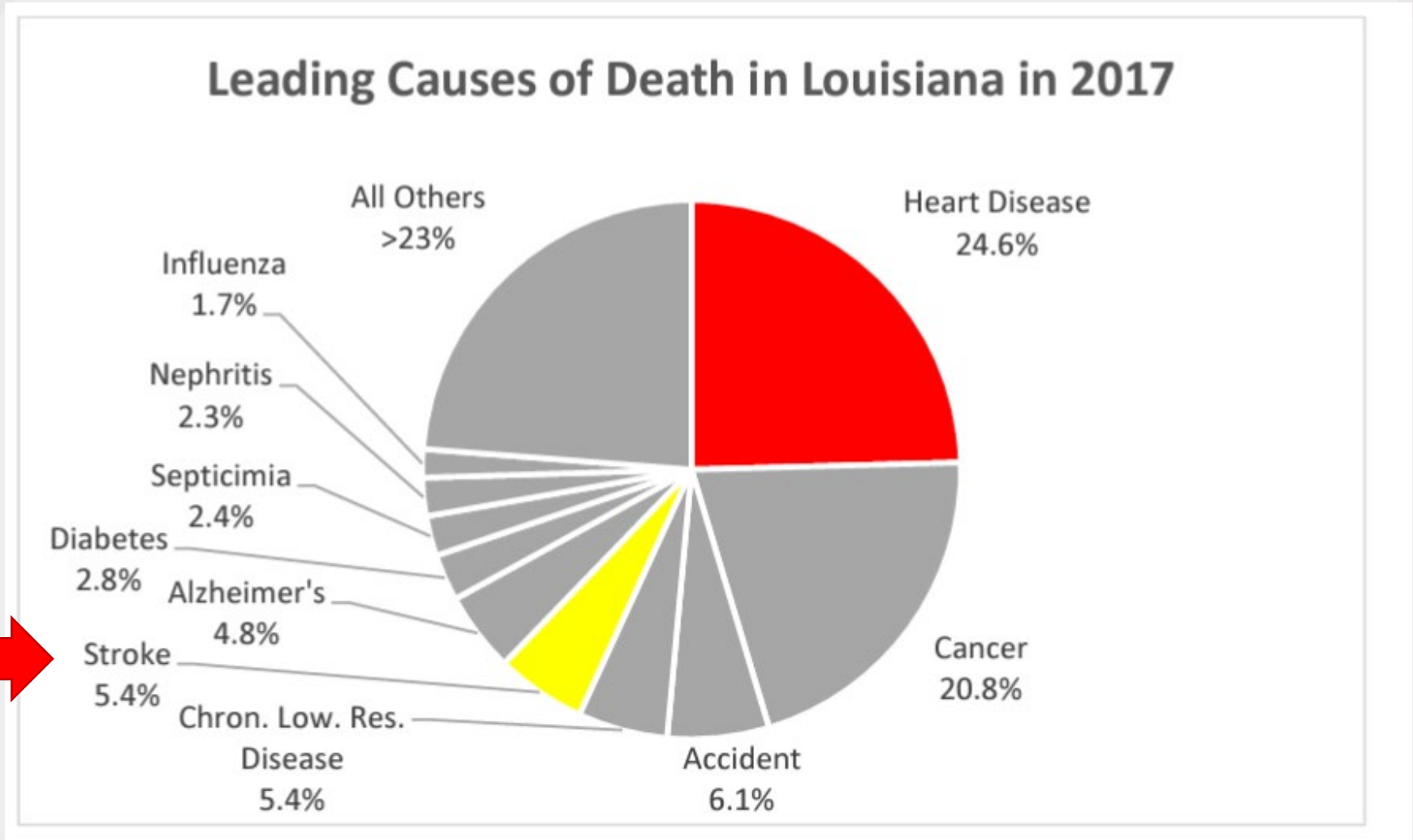
Stroke is a leading contributor to healthcare costs in the United States.

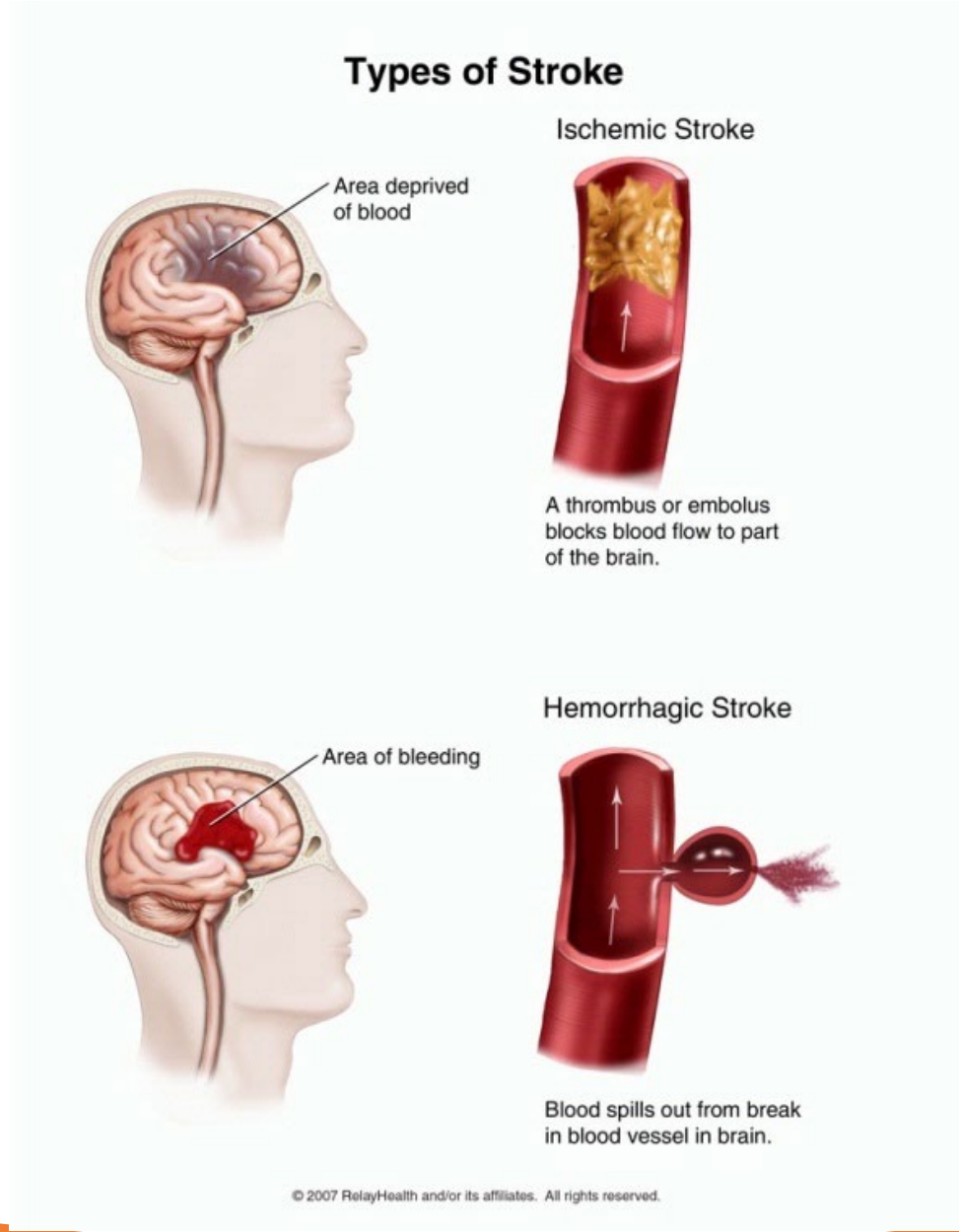
According to the American Heart Association, the total direct and indirect costs of stroke in the US are estimated to be around $105 billion annually, including healthcare expenses and lost productivity[6].


Rates
07, Adults Ages 35+, by County
.gov/GISCVH2/


THE STROKE BELT


18%
HIGHER INCIDENT
RATE THAN NATIONAL
AVERAGES

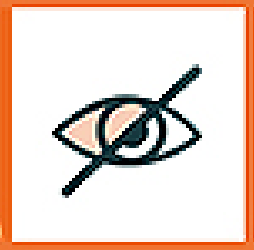

Leading Causes of Death in Louisiana in 2017
All Others
>23%
Heart Disease
24.6%
Influenza
1.7%
Nephritis
2.3%
Septicimia
2.4%
Diabetes
2.8%
Alzheimer's
4.8%
Stroke
5.4%
Chron. Low. Res.
Disease
5.4%
Accident
6.1%
Cancer
20.8%


Types of Stroke
Ischemic Stroke
Area deprived of blood
A thrombus or embolus blocks blood flow to part of the brain.
Hemorrhagic Stroke
Area of bleeding
Blood spills out from break in blood vessel in brain.
© 2007 RelayHealth and/or its affiliates. All rights reserved.

B E F A S T

BALANCE

LOSS OF BALANCE,
HEADACHE
OR DIZZINESS

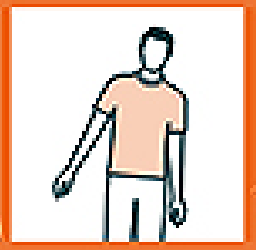


EYES

BLURRED VISION

FACE

ONE SIDE OF THE
FACE IS DROOPING



ARMS

ARM OR LEG
WEAKNESS

SPEECH

SPEECH DIFFICULTY

TIME

TIME TO CALL
FOR AMBULAN
IMMEDIAT

CALL 911 IMM

LOUISIANA
EMERGENCY RESPONSE NETWORK

NINDS Time Goals

ED Arrival
10 MIN

ED Arrival
25 MIN

ED Arrival
45 MIN

Activate Emergency Response (EMS)
Identify signs and symptoms of possible stroke

CRITICAL EMS ASSESSMENTS AND ACTIONS

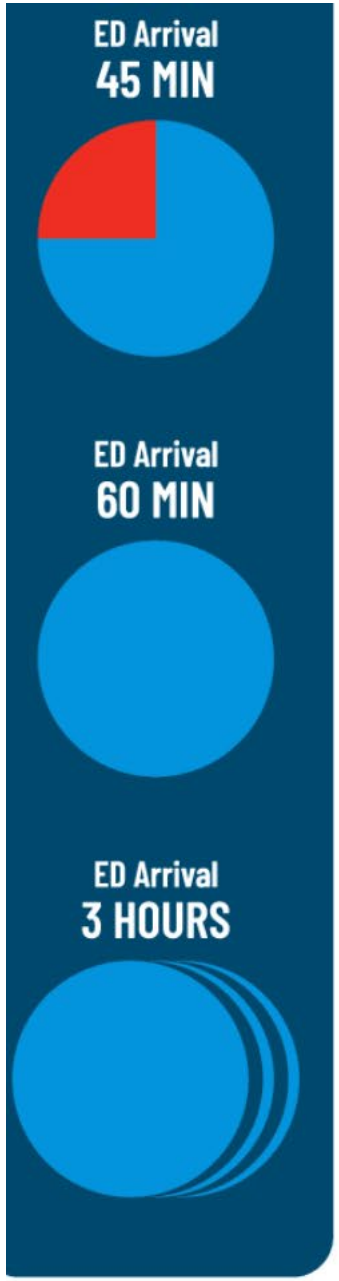
1. SUPPORT ABC'S
   Give oxygen if needed
2. PREHOSPITAL STROKE ASSESSMENT
3. ESTABLISH TIME OF SYMPTOM ONSET
   When they were last normal
4. TRIAGE TO STROKE CENTER
5. ALERT HOSPITAL
   Consider direct transfer to CT scan
6. CHECK GLUCOSE IF POSSIBLE

IMMEDIATE GENERAL ASSESSMENT AND STABILIZATION

- ASSESS ABC'S, VITAL SIGNS
- PROVIDE OXYGEN IF HYPOXEMIC
- IV ACCESS AND LAB ASSESSMENTS
- CHECK GLUCOSE; TREAT IF INDICATED
- NEUROLIGIC SCREENING ASSESSMENT
- ACTIVATE STROKE TEAM
- ORDER EMERGENT CT SCAN OR MRI OF BRAIN
- OBTAIN 12-LEAD ECG

IMMEDIATE NEUROLOGIC ASSESSMENT BY STROKE TEAM OR DESIGNEE

- REVIEW PATIENT HISTORY
- ESTABLISH TIME OF SYMPTOM ONSET OR LAST KNOWN NORMAL
- PERFORM NEUROLOGIC EXAMINATION
  NIH Stroke Scale or Canadian Neurological Scale



TEAM OR DESIGNEE

- PERFORM NEUROLOGIC EXAMINATION
  NIH Stroke Scale or Canadian Neurological Scale

Hemorrhage shown by CT Scan?

No Hemorrhage

Probable acute ischemic stroke
Consider fibrinolytic therapy

Check for fibrinolytic exclusions and repeat neurologic exam

ASK: Are deficits rapidly improving to normal?

Is patient a candidate for fibrinolytic therapy?

Yes

Review risks and benefits with patient and family

- If acceptable:
  > If acceptable:
  > Give rtPA
  Not anticoagulants or antiplatelet treatment for 24 hours

- Begin post-rtPA stroke pathway
- Aggressively Monitor:
  > BP per protocol
  > For neurologic deterioration
- Emergent admission to stroke unit or intensive care unit

No

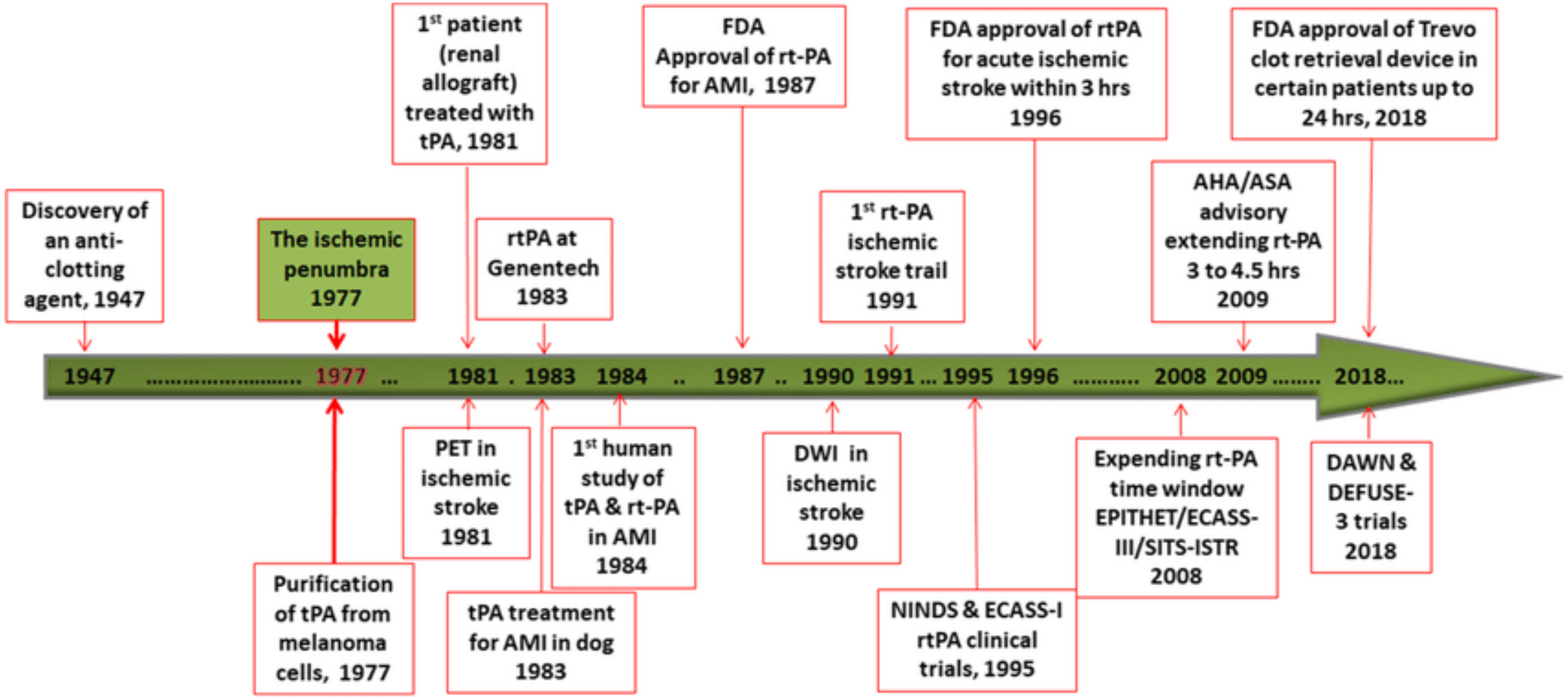
Consultation

Consult neurologist or neurosurgeon and consider transfer if not available

- Begin stroke or hemorrhage pathway
- Admit to stroke or intensive care unit

Hemorrhage

Initiate Intracranial hemorrhage protocol


1st patient (renal allograft) treated with tPA, 1981
FDA Approval of rt-PA for AMI, 1987
FDA approval of rtPA for acute ischemic stroke within 3 hrs 1996
FDA approval of Trevo clot retrieval device in certain patients up to 24 hrs, 2018
Discovery of an anti-clotting agent, 1947
The ischemic penumbra 1977
rtPA at Genentech 1983
1st rt-PA ischemic stroke trail 1991
AHA/ASA advisory extending rt-PA 3 to 4.5 hrs 2009
1947 ..... 1977 ... 1981 . 1983 1984 .. 1987 .. 1990 1991 ... 1995 1996 ..... 2008 2009 ..... 2018...
PET in ischemic stroke 1981
1st human study of tPA & rt-PA in AMI 1984
DWI in ischemic stroke 1990
Expending rt-PA time window EPITHET/ECASS-III/SITS-ISTR 2008
DAWN & DEFUSE-3 trials 2018
Purification of tPA from melanoma cells, 1977
tPA treatment for AMI in dog 1983
NINDS & ECASS-I rtPA clinical trials, 1995

National Institute of Neurological Disorders and Stroke (NINDS) Trial Design[6,13,14]

INCLUSION CRITERIA[6,13a]	• Ischemic stroke with a clearly defined time of onset (allowing for treatment initiation within 3 hours) • A deficit measurable on the National Institute of Health Stroke Scale (NIHSS) • A baseline computed tomography (CT) scan of the brain that showed no evidence of intracranial hemorrhage			
ENROLLMENT	**PART 1** **January 1991 - October 1994**[14] **Total (n=291)**		**PART 2** **November 1992 - October 1994**[14] **Total (n=333)**	
RANDOMIZATION[6b]	**Activase (n=144)**	**Placebo (n=147)**	**Activase (n=168)**	**Placebo (n=165)**
PRIMARY ENDPOINT	**AT 24 HOURS**[6] Proportion of patients with ≥4-point improvement in the NIHSS, or complete recovery (NIHSS=0)		**AT 90 DAYS**[c] Favorable outcome defined as minimal or no disability using 4 stroke assessment scales[6]: 1. Barthel index (score ≥95) 2. Modified Rankin Scale (score ≤1) 3. Glasgow Outcome Scale (score=1) 4. NIHSS (score ≤1)	

- Compared the use of IV tPA within three hours of stroke onset to a placebo group.

- The primary outcome assess the degree of disability at three months post-stroke, measured (mRS).

- mRS is a standardized scale that rates the level of disability and dependence in stroke patients, ranging from 0 (no symptoms) to 6 (death).

- NINDS trial demonstrated a significant benefit of IV tPA treatment.

- Patients who received tPA within three hours of stroke onset had better functional outcomes compared to those in the placebo group.

- 30% improvement in the chances of having minimal or no disability at three months, with a corresponding decrease in the risk of dependency or death.

- IV tPA in acute ischemic stroke is time-sensitive.

- Benefit significantly decreased beyond 3-hour time window, and there was an

- Increased risk of hemorrhagic transformation in patients treated after 3-hr window.

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%

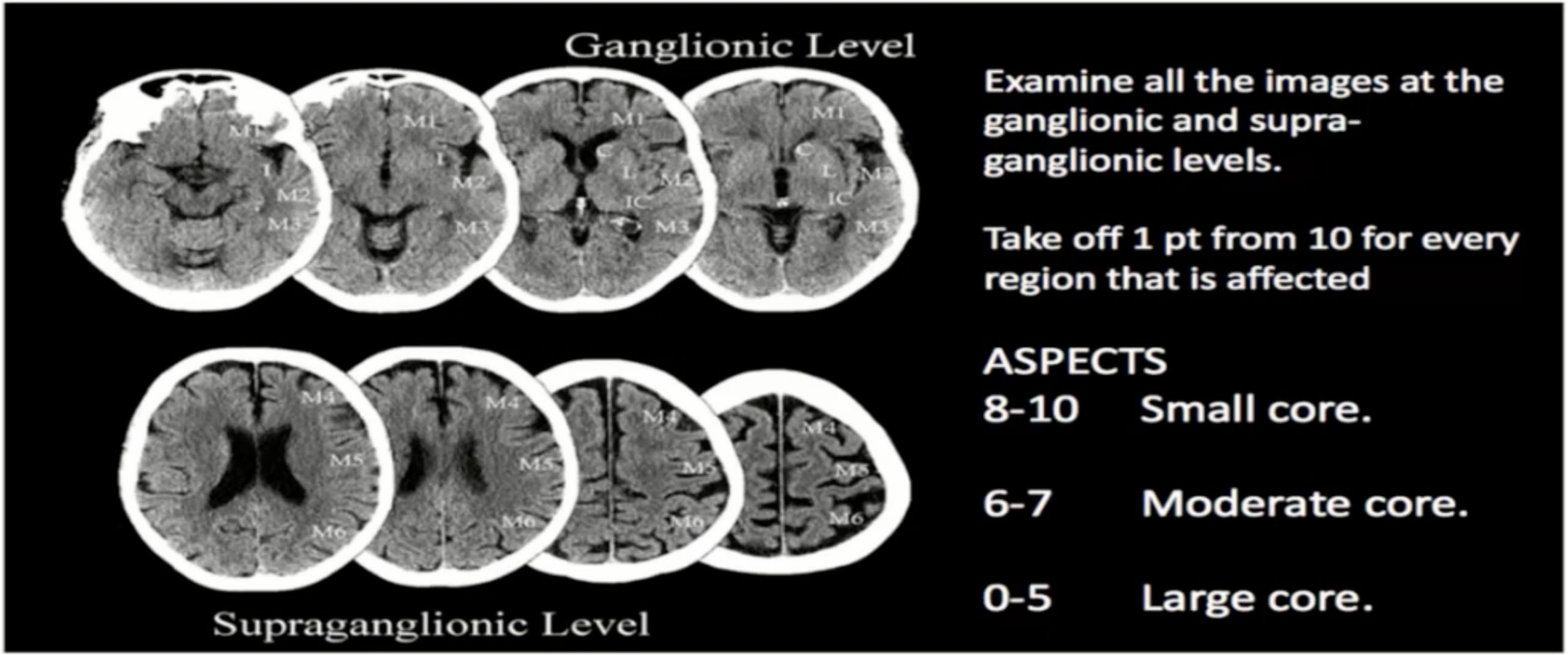
ECASS III trial: Investigated the use of IV tPA up to 4.5 hours after stroke onset, extending the treatment window for eligible patients and changing the standard of care.

IMS-III trial: Compared standard medical management to mechanical thrombectomy using intra-arterial treatment devices, showing no additional benefit of mechanical thrombectomy in acute ischemic stroke.

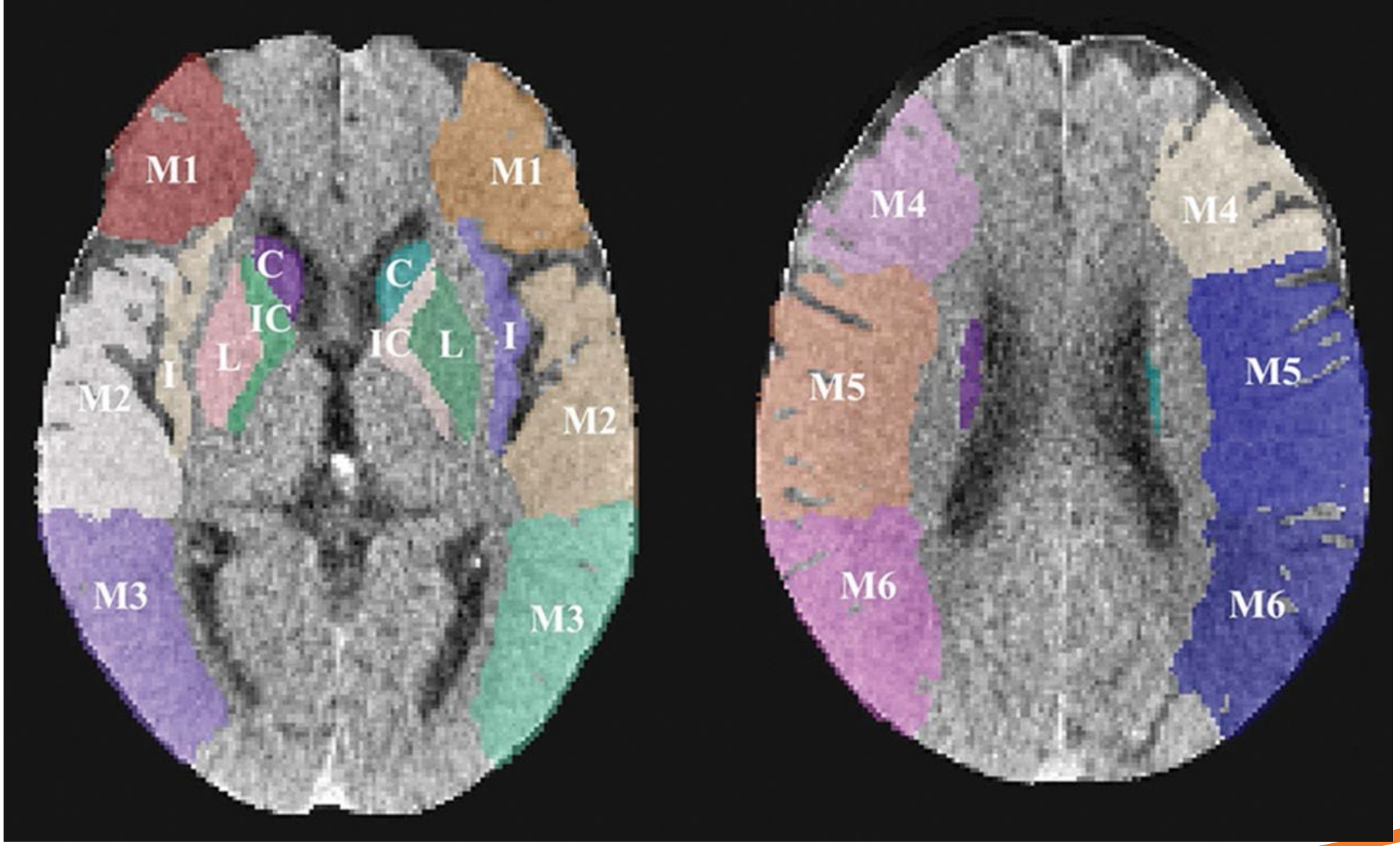
IST-3 trial: Explored the use of IV tPA beyond the three-hour time window, showing benefit in certain patients up to 6 hours after stroke onset.

	MR CLEAN[17]	ESCAPE[18]	SWIFT PRIME[19]	EXTEND-IA[20]	REVASCAT[21]
No of patients	500	316	196	70	206
Age (years)	≥18	≥18	18–80	≥18	18–85
NIHSS inclusion criteria	≥2	>5	8–29	None	≥6
Treatment Arm	IV rt-PA + IA UK/rt-PA/device	Stent retriever ± IV rt-PA	Stent retriever ± IV rt-PA	Stent retriever ± IV rt-PA	Stent retriever ± IV rt-PA
Control Arm (Standard care)	± IV rt-PA	± IV rt-PA	± IV rt-PA	± IV rt-PA	± IV rt-PA
IV rt-PA use	87%	72.7%	100%	100%	68%
Median time from stroke onset to groin puncture (min)	260	200	224	210	269
Use of Stent retriever	81.5%	86.1%	89%	77%	95%
Rate of recanalization [TICI 2b/3a]	59%	72.4%	88%	86%	66%
Functional Independence (mRS 0–2)	32.6% vs. 19.1%	53.0% vs. 29.3%	60.0% vs. 35%	71% vs. 40%	43.7% vs. 28.2%
Mortality/sICH	No significant difference in death or sICH	Mortality at 90 days: 10.4% (treatment arm) vs. 19% (control arm). No significant difference in sICH	No significant difference in death or sICH	No significant difference in death or sICH	No significant difference in death or sICH

1. Pre-stroke modified Rankin Score (mRS) of 0 to 1 (functional independence)
2. Patients ≥ 18 years
3. Stroke severity on NIHSS ≥ 6
4. Computed tomography (CT) brain without evidence of large infarct suggested by Alberta Stroke Program Early CT Score (ASPECTS) of ≥ 6
5. Imaging proven causative occlusion of the Internal carotid artery (ICA) or proximal segment (M1) of middle cerebral artery (MCA).
6. Treatment can be initiated (groin puncture) within 6 hours of symptom onset.



http://www.aspectsinstroke.com


M1
M1
C
C
IC
IC
L
L
I
I
M2
M2
M3
M3
M4
M4
M5
M5
M6
M6

MR CLEAN trial: Demonstrated the benefit of mechanical thrombectomy in acute ischemic stroke caused by large vessel occlusion within 6 hours of stroke onset, leading to changes in stroke guidelines.

REVASCAT trial: Similar to MR CLEAN, showed the efficacy of mechanical thrombectomy in acute ischemic stroke within 6 hours of symptom onset.

SWIFT PRIME trial: Investigated the use of mechanical thrombectomy within 6 hours of stroke onset, demonstrating improved functional outcomes and changing stroke management guidelines.

ESCAPE trial: Similar to SWIFT PRIME, showed the benefit of mechanical thrombectomy within 6 hours of symptom onset, leading to changes in stroke protocols.

EXTEND-IA trial: Investigated the use of mechanical thrombectomy up to 6 hours after stroke onset, showing improved outcomes in selected patients.

DAWN trial: Evaluated the use of mechanical thrombectomy up to 24 hours after stroke onset in selected patients, expanding the treatment window for this intervention.

DEFUSE 3 trial: Investigated the use of thrombectomy up to six hours after stroke onset in selected patients, leading to expanded treatment guidelines for thrombectomy.

Summary of DAWN and DEFUSE -3 Eligibility Criteria

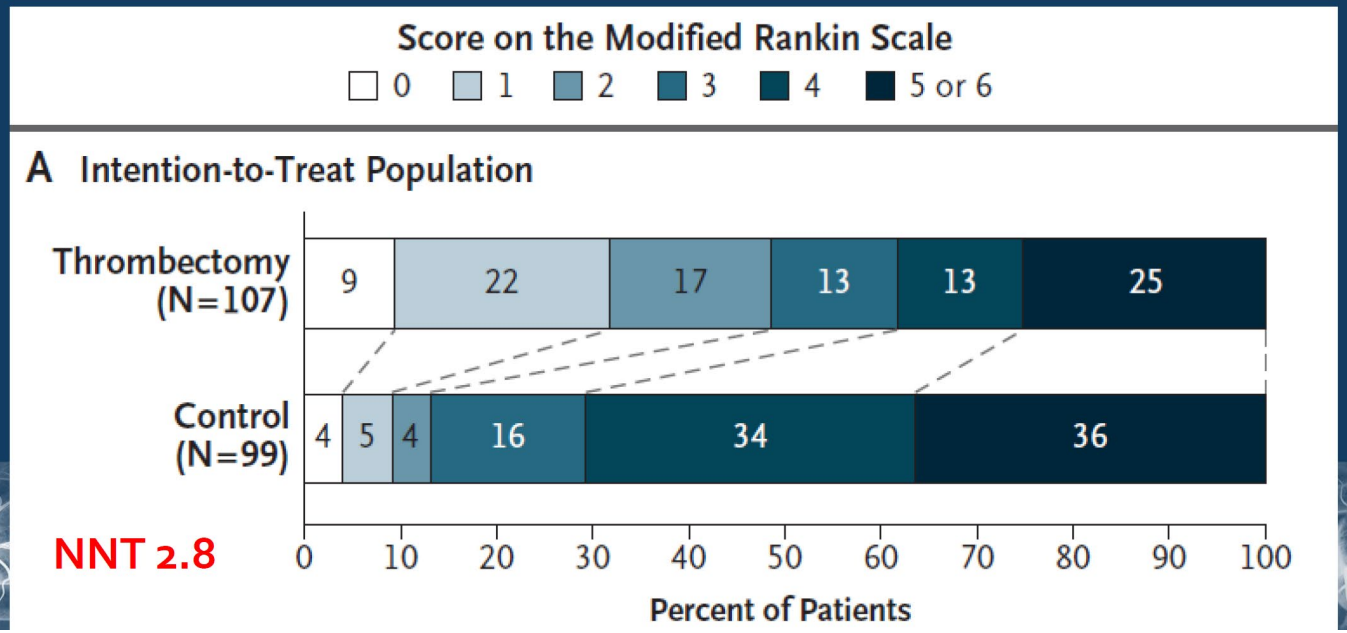
DAWN Criteria (6 to 24 hours)[25]	DEFUSE-3 (6 to 16 hours)[26]
• Age ≥ 18 years • NIHSS ≥ 10 • Prestroke mRS ≤ 1 • Occlusion of the intracranial ICA and/or MCA-M1 segment as evidenced by MRA or CTA • Clinical Imaging Mismatch (CIM) defined as one of the following on MR-DWI or CTP: ➢ 0 – < 21 cc core infarct, NIHSS ≥ 10, age ≥ 80 years ➢ 0 – < 31cc core infarct, NIHSS ≥ 10, age < 80 years ➢ 31 – ≤ 51cc core infarct, NIHSS ≥ 20, age < 80 years	• Age 18–90 years • Baseline NIHSS ≥ 6 • Only slight or no prestroke disability: baseline mRS score ≤ 2 • Cervical/Intracranial ICA occlusion (with/without tandem MCA lesions) or M1 segment on CTA/MRA • Target Mismatch profile: ➢ Infarct volume (ischemic core) < 70 cc ➢ Ratio of volume of ischemic tissue to initial infarct volume ≥ 1.8 ➢ Absolute volume of potentially reversible ischemic (penumbra) > 15 cc

DAWN - DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo; DEFUSE 3 - The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; NIHSS - National Institute of Health Stroke Scale; mRS - Modified Rankin Scale; MCA - Middle Cerebral Artery; ICA -Internal Carotid Artery; MRA - Magnetic Resonance Angiography; CTA - Computed Tomography Angiography; MR-DWI - Magnetic Resonance-Diffusion Weighted Imaging; CTP - Computed Tomography Perfusion

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

Dawn Trial

Type of stroke onset — no. (%)‡	Thrombectomy Group	Control Group
On awakening	67 (63)	47 (47)
Unwitnessed stroke	29 (27)	38 (38)
Witnessed stroke	11 (10)	14 (14)



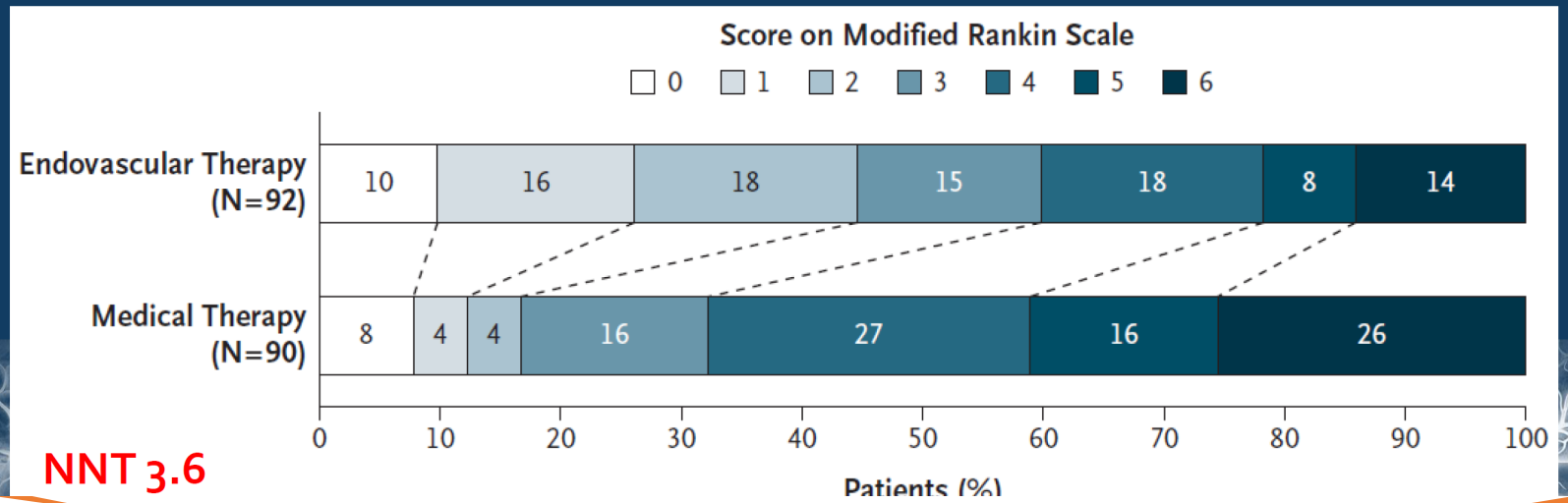
NNT 2.8

LOUISIANA EMERGENCY RESPONSE NETWORK

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

DEFUSE 3 Trial

Stroke onset witnessed — no. (%)	Endovascular Therapy	Medical Therapy
Yes‡	31 (34)	35 (39)
No		
Symptoms were present on awakening	49 (53)	42 (47)
Symptoms began during wakefulness	12 (13)	13 (14)



NNT 3.6

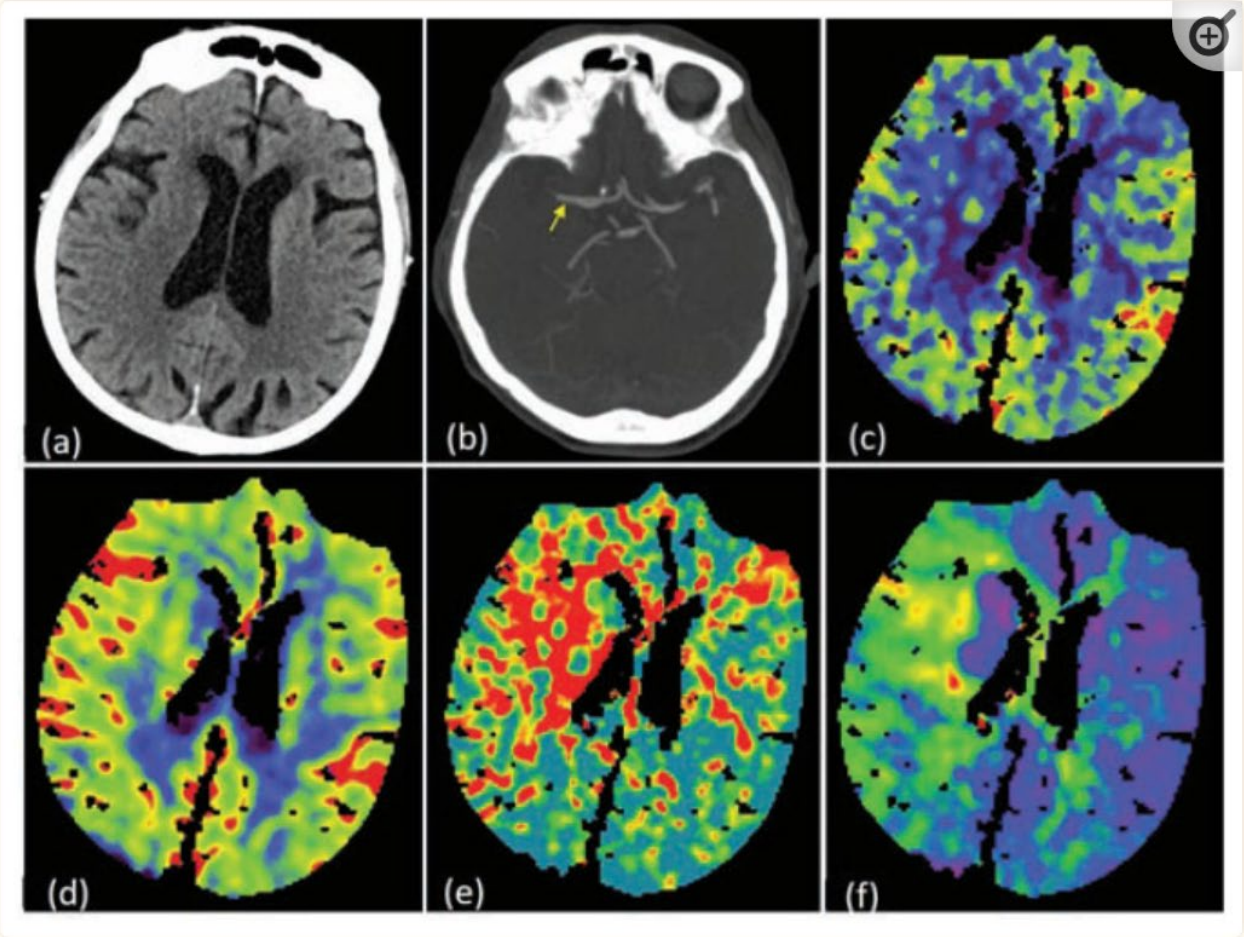


Figure 1

75-year old female presented with sudden onset left sided weakness with left facial droop. Time of onset of symptoms was 3.5 hours prior to coming to the hospital. Patient did not receive IV rt-PA as she was on Xarelto due to underlying atrial fibrillation. NIHSS score on admission was 7. NCCT head was negative for any intracranial bleed or early signs of ischemia (a). CTA head and neck showed occlusion (yellow arrow) of the right proximal M1 segment of MCA (b). CT perfusion study showed a large penumbra [reduced regional cerebral blood flow (c) with preserved regional cerebral blood volume (d), elevated mean transmit time (MTT) (e) and elevated Tmax (f)].

Advances in Acute Ischemic Stroke Treatment: Current Status and Future Directions

G. Bathla, P. Ajmera, P.M. Mehta, J.C. Benson, C.P. Derdeyn, G. Lanzino, A. Agarwal and W. Brinjikji

AJNR Am J Neuroradiol published online 18 May 2023
http://www.ajnr.org/content/early/2023/05/18/ajnr.A7872

Patient with sudden onset of focal neurological deficit

Indications for IV rtPA:
- clinical picture consistent with acute stroke
- last seen well less than 4.5 hours ago

NO → No thrombolysis

YES

Absolute contraindications for IV rtPA:
- arterial blood pressure more than 185 systolic or 110 diastolic despite treatment
- high risk of bleeding
  - INR>1.6
  - PT>15
  - platelet count<100,000
  - hereditary or acquired bleeding disorders
  - use of therapeutic doses of IV or oral anticoagulants within the last 48 hours
- extensive hypodensity on initial brain CT
- evidence of intracranial haemorrhage on initial brain CT
- recent extensive trauma (including surgery, arterial or lumbar puncture)
- high risk of intracranial pathology, eg glioblastoma

YES → No thrombolysis

NO

Relative contraindications for IV rtPA:
- NIHSS>25
- blood sugar<2 mmol/L or >18 mmol/L with persistence of symptoms on treatment
- recent minor trauma or surgery
- low risk intracranial structural lesions, eg meningioma, small asymptomatic aneurysm
- seizure at onset
- previous intracranial haemorrhage
- pregnancy or postpartum
- recent myocardial infarction

YES → Possible thrombolysis

NO

Thrombolysis

Contraindications for use of IV t-PA 0-3 hrs

AHA/ASA 2013 guidelines	2015 FDA guidelines
Prior stroke within 3 months	Removed
Seizure at onset	Removed
Bleeding Diathesis Platelet count < 100,000/mm Abnormal PTT on heparin Anticoagulant with INR > 1.7 Current use of DOAC	Bleeding diathesis remains a contraindication, but all laboratory values and specific examples removed
History of ICH	Warning for recent ICH
SBP > 185/110 mmHg	Remains a warning, but specific BP values removed
Blood glucose < 50 mg/dL (2.8mmol/L)	Removed
Severe Stroke	Removed
Mild or rapidly improving symptoms	Removed
Symptoms suggestive of SAH	Confirmed SAH

American Heart Association Guideline 2019[1]	US Food and Drug Administration (FDA) Package Insert 2015[14]
Indications	
Diagnosis of ischemic stroke with disabling neurologic deficit (regardless of severity)	Same
Symptom onset[b] within 4.5 hours	Within 3 hours
Wake-up stroke with diffusion-weighted imaging-FLAIR mismatch on MRI[c]	Not mentioned
Age ≥18 years	Warning for age >77 years with risk factors for intracranial hemorrhage
Contraindications[d]	
Severe head trauma within 3 months	Contraindicated
Ischemic stroke within 3 months	Removed[e]
Previous intracranial hemorrhage	Warning for recent intracranial hemorrhage (contraindicated if active intracranial hemorrhage)
Suspected subarachnoid hemorrhage	Contraindicated
Suspected infective endocarditis	Not listed
Suspected aortic arch dissection	Not listed
Recent intracranial or intraspinal surgery (within 3 months)	Contraindicated
Intracranial intraaxial neoplasm	Not listed
Gastrointestinal malignancy or gastrointestinal bleeding within previous 21 days	Warning

American Heart Association Guideline 2019[1]	US Food and Drug Administration (FDA) Package Insert 2015[14]
Contraindications[d]	
Active internal bleeding	Contraindicated
Systolic blood pressure (BP) >185 mm Hg or diastolic BP >110 mm Hg that cannot be lowered safely	Contraindicated for severe uncontrolled hypertension (BP values removed[e]); warning for BP >175/110 mm Hg
Bleeding diathesis International normalized ratio (INR) >1.7 Heparin within 48 hours with abnormal activated partial thromboplastin time Low-molecular-weight heparin full treatment dose within previous 24 hours Platelets <100,000/mm^3 Current use of direct thrombin inhibitor or factor Xa inhibitor with abnormal coagulation tests[f]	Contraindicated for bleeding diathesis (laboratory values removed[e])
CT showing acute hemorrhage	Contraindicated
CT showing extensive hypodensity (eg, >1/3 of the cerebral hemisphere)	Removed[e]

Stroke of unknown time of onset

- Almost 33% of all patients with ischemic stroke have unknown time of stroke onset
  - Most have symptoms noted upon awakening
  - Others have unwitnessed stroke onset and the patient cannot provide a time of symptom onset
- Historically, excluded from IV lytic

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

The WAKE UP Trial – RCT IV alteplase vs placebo

- Stroke symptoms upon waking up, or were unable to report the time of onset, and it was at least 4.5 hours since LSN
- MRI showed an acute ischemic lesion on diffusion-weighted imaging but no parenchymal hyperintensity with standard window settings on FLAIR
- Excluded if hemorrhage (n=87)
- Excluded if >1/3 MCA territory on DWI (n=45)
- Excluded if thrombectomy planned (n=15)
- Excluded if NIHSS >25
- Excluded if standard contraindication to IV alteplase

The WAKE UP Trial: *Thomalla G, Simonsen CZ, Boutitie F, et al.* ***MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset.*** *The New England journal of medicine. 2018; 379(7):611-622.* PMID: 29766770

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

The WAKE UP Trial – RCT IV alteplase vs placebo

- Of the 1362 patients screened:
  - 455 were excluded for FLAIR lesion
  - 137 were excluded because the DWI was negative
- The median NIHSS score on arrival was 6.
- 89% of patients had wake up strokes.
- The median time between symptoms noted and alteplase was 3.1 hours.
- The median time between LSN and alteplase was 10 hours.

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

The WAKE UP Trial – RCT IV alteplase vs placebo

Table 2. Primary and Secondary Efficacy Outcomes (Intention-to-Treat Population).*

Outcome	Alteplase Group (N=254)	Placebo Group (N=249)	Effect Variable	Adjusted Value (95% CI)†	P Value
Primary efficacy end point					
Favorable outcome at 90 days — no./total no. (%)‡	131/246 (53.3)	102/244 (41.8)	Odds ratio	1.61 (1.09 to 2.36)	0.02
Secondary efficacy end points					
Median score on modified Rankin scale at 90 days (IQR)§	1 (1–3)	2 (1–3)	Common odds ratio	1.62 (1.17 to 2.23)	0.003¶
Correlation between treatment response at 90 days and deficit level at baseline — no./total no. (%)‖	72/246 (29.3)	44/244 (18.0)	Odds ratio	1.88 (1.22 to 2.89)	0.004¶
Global Outcome Score at 90 days**			Odds ratio	1.47 (1.07 to 2.04)	0.02¶
Median score on Beck Depression Inventory at 90 days (IQR)††	6.0 (2.0–11.0)	7.0 (2.0–14.0)	Mean difference ($\log_e$)	−0.04 (−0.22 to 0.15)	0.69¶
Total score on EQ-5D at 90 days‡‡	1.9±2.1	2.4±2.4	Mean difference	−0.52 (−0.88 to −0.16)	0.004¶
Score on visual analog scale on EQ-5D at 90 days§§	72.6±19.7)	64.9±23.8	Mean difference	7.64 (3.75 to 11.51)	<0.001¶
Median infarct volume at 22–36 hr (IQR) — ml ¶¶	3.0 (0.8–17.7)	3.3 (1.1–16.6)	Mean difference ($\log_e$)	−0.16 (−0.47 to 0.15)	0.32¶

- No safety concern
- 2.4% sICH (ns)
- NNT <9
- THAWS trial also used MRI, but low dose alteplase and terminated early with no difference in outcome

Intravenous thrombolytic treatment and endovascular thrombectomy for ischemic wake-up stroke (Review)

Summary of findings 1. Intravenous thrombolytic treatment compared to standard medical care for wake-up stroke

Intravenous thrombolytic treatment compared to standard medical care for wake-up stroke

Patient or population: people with stroke upon awakening
Setting: hospital emergency department
Intervention: intravenous thrombolytic treatment
Comparison: standard medical care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with standard medical care	Risk with intravenous thrombolytic treatment			
Independent functional outcome at end of follow-up assessed with: mRS 0 to 2 at follow-up: 90 days	584 per 1000	660 per 1000 (590 to 736)	RR 1.13 (1.01 to 1.26)	763 (5 RCTs)	⊕⊕⊕⊕ HIGH
Symptomatic intracranial haemorrhage at follow-up: mean 90 days	5 per 1000	19 per 1000 (5 to 67)	RR 3.47 (0.98 to 12.26)	754 (4 RCTs)	⊕⊕⊕⊕ HIGH
Death at follow-up: mean 90 days	99 per 1000	67 per 1000 (43 to 106)	RR 0.68 (0.43 to 1.07)	763 (5 RCTs)	⊕⊕⊕⊕ HIGH

Cochrane Database of Systematic Reviews 2021, Issue 12. Art. No.: CD010995

LOUISIANA EMERGENCY RESPONSE NETWORK

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

Patients with wake-up stroke should be evaluated with same urgency as a patient presenting within the window for IV alteplase, because those with DWI+/FLAIR- pattern can benefit from treatment.

Neurochecks q15mins x 2h, then q30mins x 6h, then q1h there after

Supplemental oxygen to keep O2 says >94%

Check BP q15mins x2h, then q30mins x 6h, then q6 x 16h

SBP goal <180/105

Bedside swallow test (30 mL water PO) before anything else PO

Keep glucose 140-180mg/dL, consider insulin get if Glu persistently >200 (hyperglycemia worsens outcomes, increases risk of ICH after ischemic strokes)

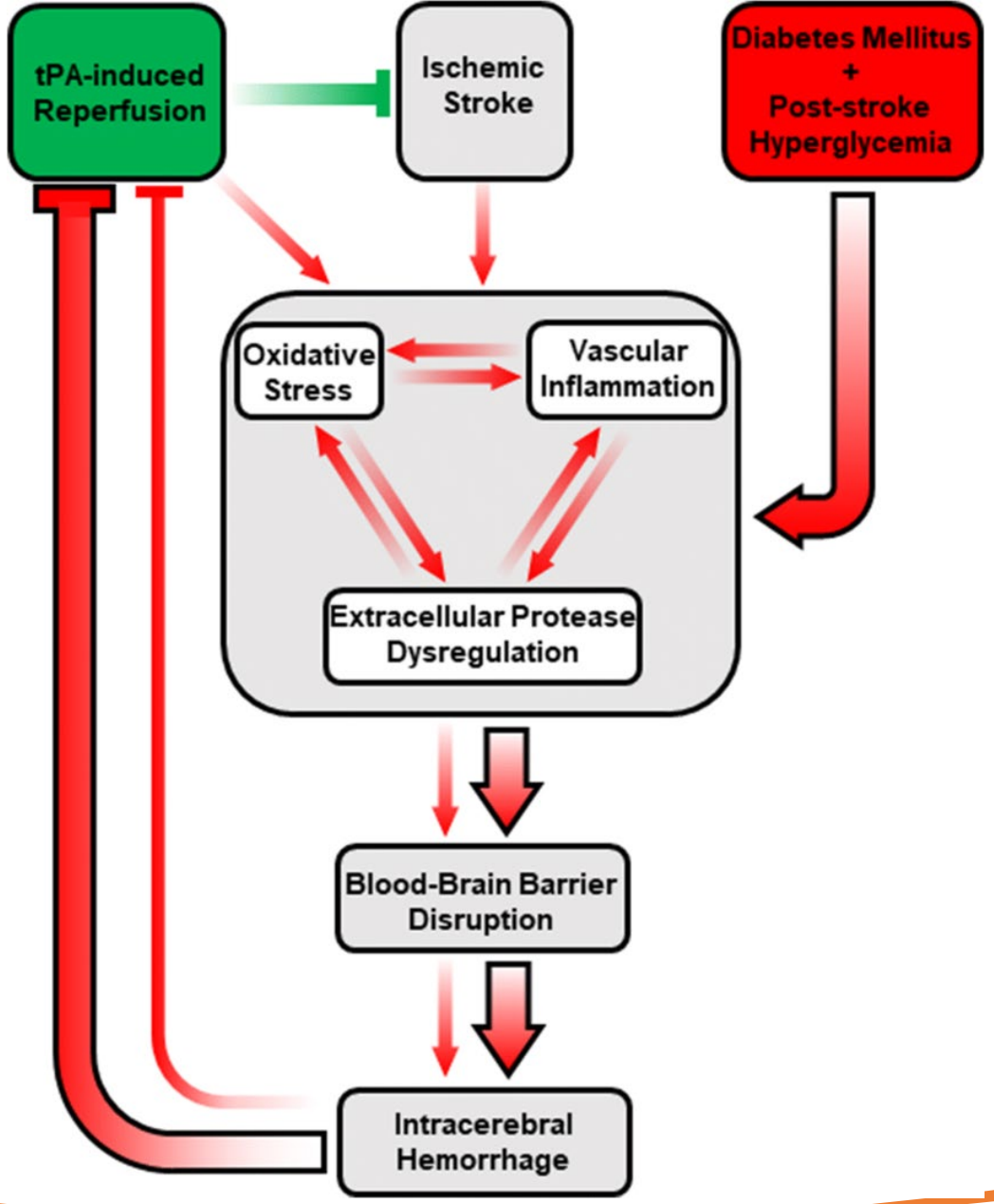
Administer IV fluids (NS at 1.5 mL/Kg/hr), to goal of euvolemia

Bedside telemetry / cardiac monitoring to detect atrial fibrillation, continue x at least 72h

Treat fever source, avoid hyperthermia

Avoid indwelling urinary catheter, NGT, intra-arterial catheters x 4 hours; avoid urinary catheters unless absolutely needed

No anticoagulant / antiplatelet therapy x 24h


tPA-induced Reperfusion
Ischemic Stroke
Diabetes Mellitus + Post-stroke Hyperglycemia
Oxidative Stress
Vascular Inflammation
Extracellular Protease Dysregulation
Blood-Brain Barrier Disruption
Intracerebral Hemorrhage

Academic medicine has improved patient outcomes, including a

dramatic decline in stroke mortality over the last 65 years.

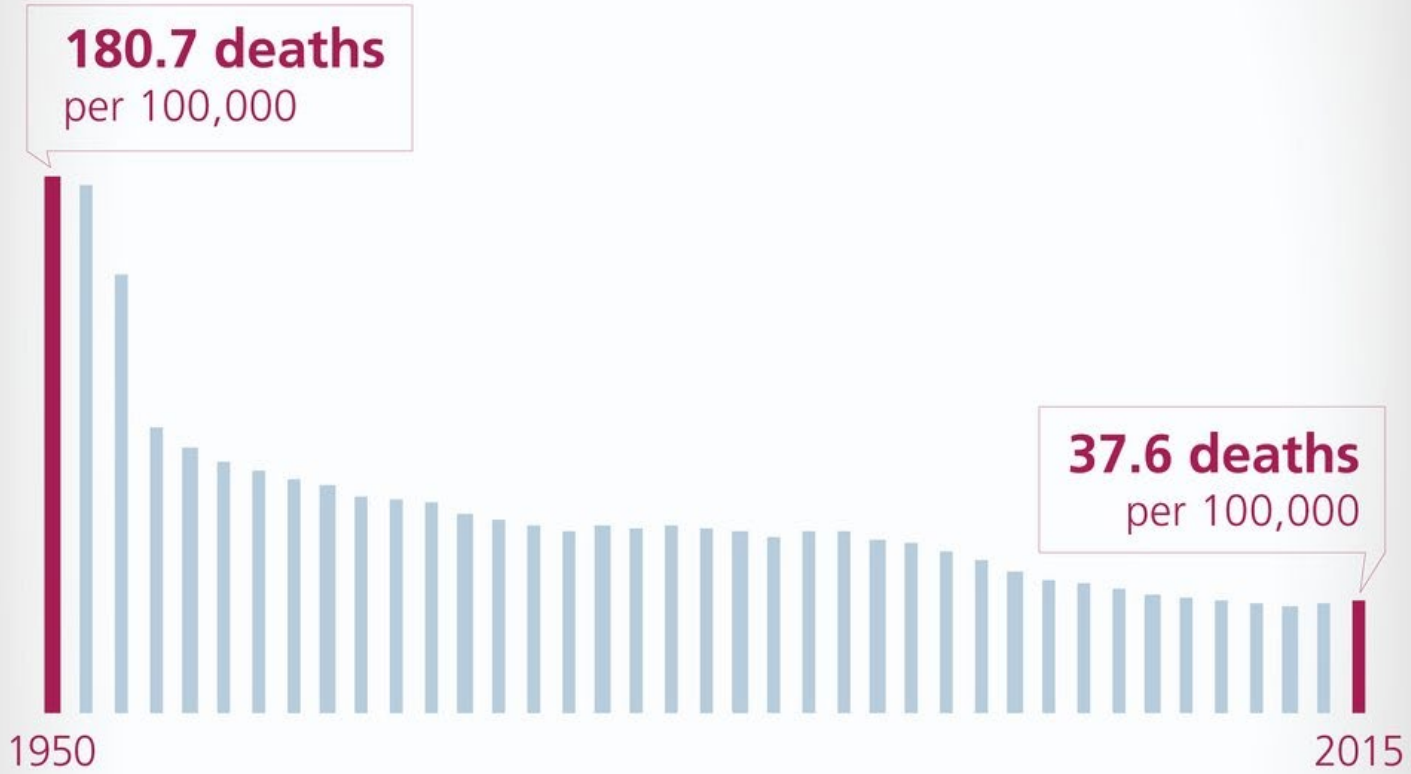


Table 2. Protocol for Management of Postthrombolysis Intracerebral Hemorrhage.[1,48-50]

Suspect ICH (new headache, nausea, vomiting, etc)

- ☐ Discontinue r-tPA infusion
- ☐ STAT blood draw: PT, PTT, platelet count, fibrinogen, type & cross
- ☐ STAT noncontrast CT head

Hemorrhage confirmed?

- ☐ Administer 6-8 units of cryoprecipitate, followed by 6-8 units platelets
- ☐ Consult neurosurgeon & alert to ICH
- ☐ Consult hematologist & alert to current coagulation status
- ☐ Administer ε-aminocaproic acid 4-5 gm IV over 1 hour, followed by 1 gm PO or IV hourly until bleeding is controlled
- ☐ Fibrinogen levels should be rechecked every Q 4 hours & cryoprecipitate transfused PRN to maintain fibrinogen levels > 150 mg/dL
- ☐ Blood pressure monitoring Q 15 minutes
- ☐ Periodic blood work (CBC, PT/PTT) to re-assess coagulation status & need for blood transfusion
- ☐ Consider repeat CT head to assess for ICH growth
- ☐ Consensus decision regarding surgical and/or medical therapy

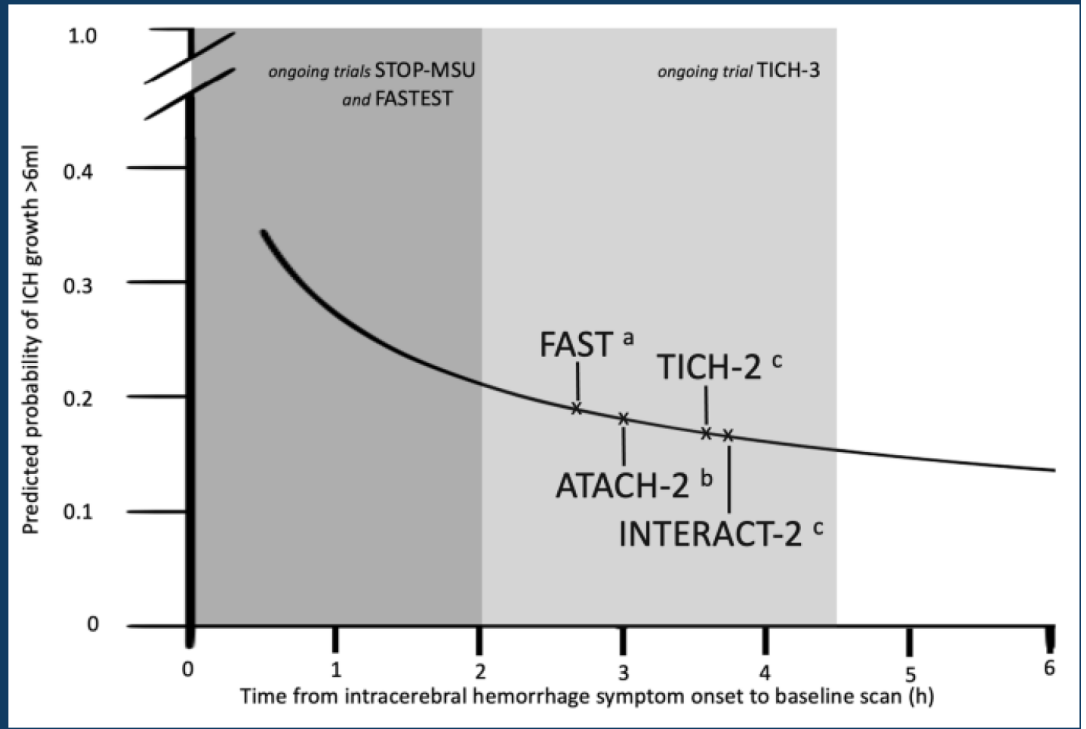
Abbreviations: ICH, intracerebral hemorrhage; r-tPA, recombinant tissue-type plasminogen activator; STAT, at once; PT, prothrombin time; PTT, partial thromboplastin time; IV, intravenous; PO, orally; Q, every; PRN, as needed; CBC, complete blood count.

Management of Symptomatic "ICH" Occurring Within 24h After Administration of IV Alteplase
Stop alteplase infusion
CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match
Emergent nonenhanced head CT
Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <150 mg/dL
Tranexamic acid 1000 mg IV infused over 10 min OR ε-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h) (Potential for benefit in all patients, but particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available in a timely manner.)
Hematology and neurosurgery consultations
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control

Figure 19. Management of symptomatic Intracranial Bleeding Occurring Within 24 Hours After Administration of IV Alteplase for Treatment of Acute Ischemic Stroke. CPP, cerebral perfusion; ICP, intracranial pressure; MAP, mean arterial pressure. Addapted for AHA/ASA 2019 update to 2018 Guidelines for the early management of acute ischemic stroke.

Hematoma expansion – time from onset of ICH

- Multivariate modeling of HE-predictors showed that the predicted probability for HE declined at increasing time from onset to diagnostic imaging.
- The decline was steepest between 0.5 and 3 h, indicating that HE is much more probable within the first 3 h.
- Ongoing bleeding beyond 4 hours of symptom onset is uncommon



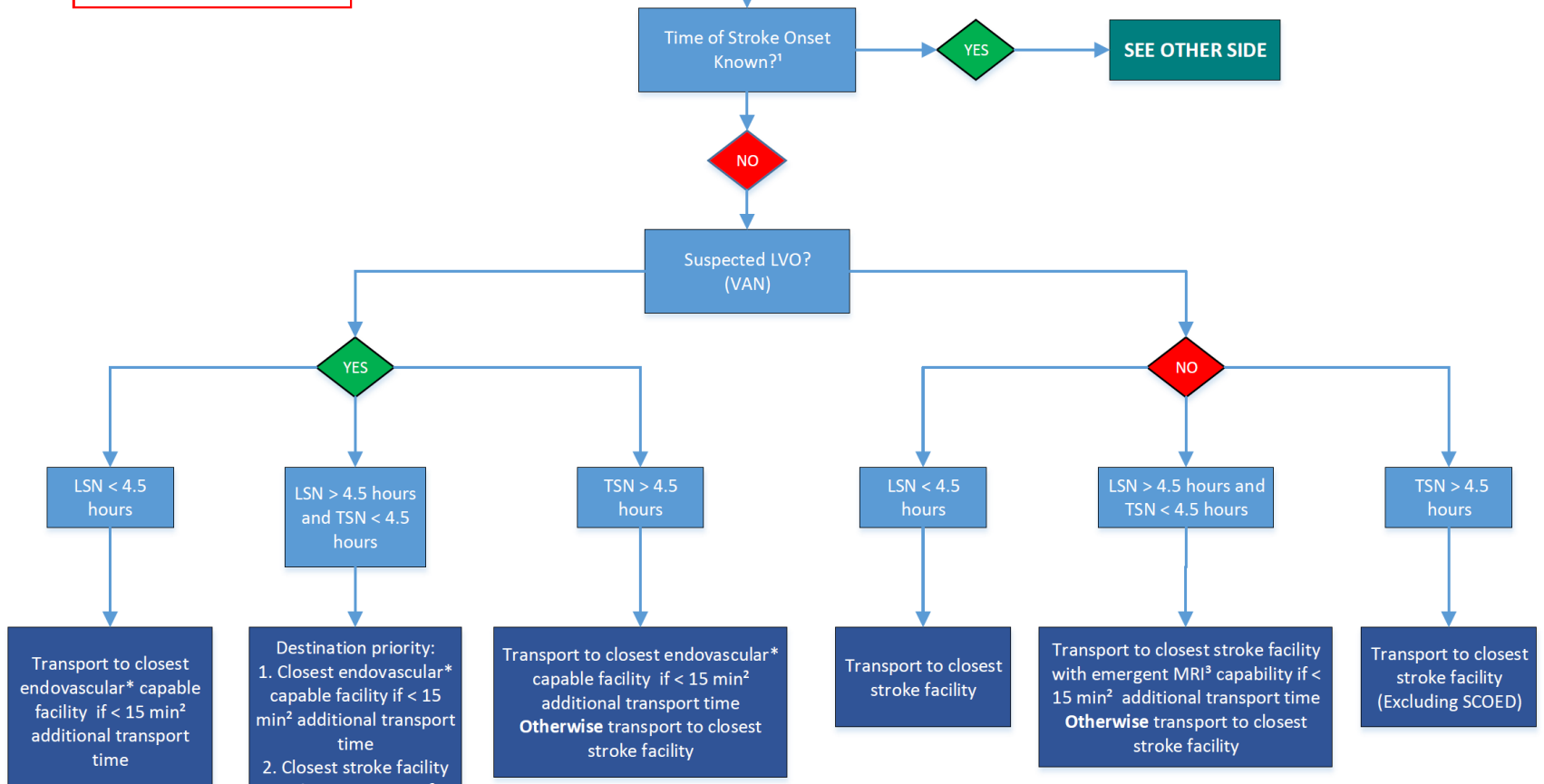
LOUISIANA EMERGENCY RESPONSE NETWORK
Right Place. Right Time. Right Care.

STROKE DESTINATION PROTOCOL

Time of Onset Unknown

SUSPECTED STROKE:
- Determine TSO: TIME OF STROKE ONSET[1]
- Determine LSN: LAST SEEN NORMAL[1]
- Determine TSN: TIME SYMPTOMS NOTED[1]
- Perform VAN assessment

LERN Communication Center
1-866-320-8293

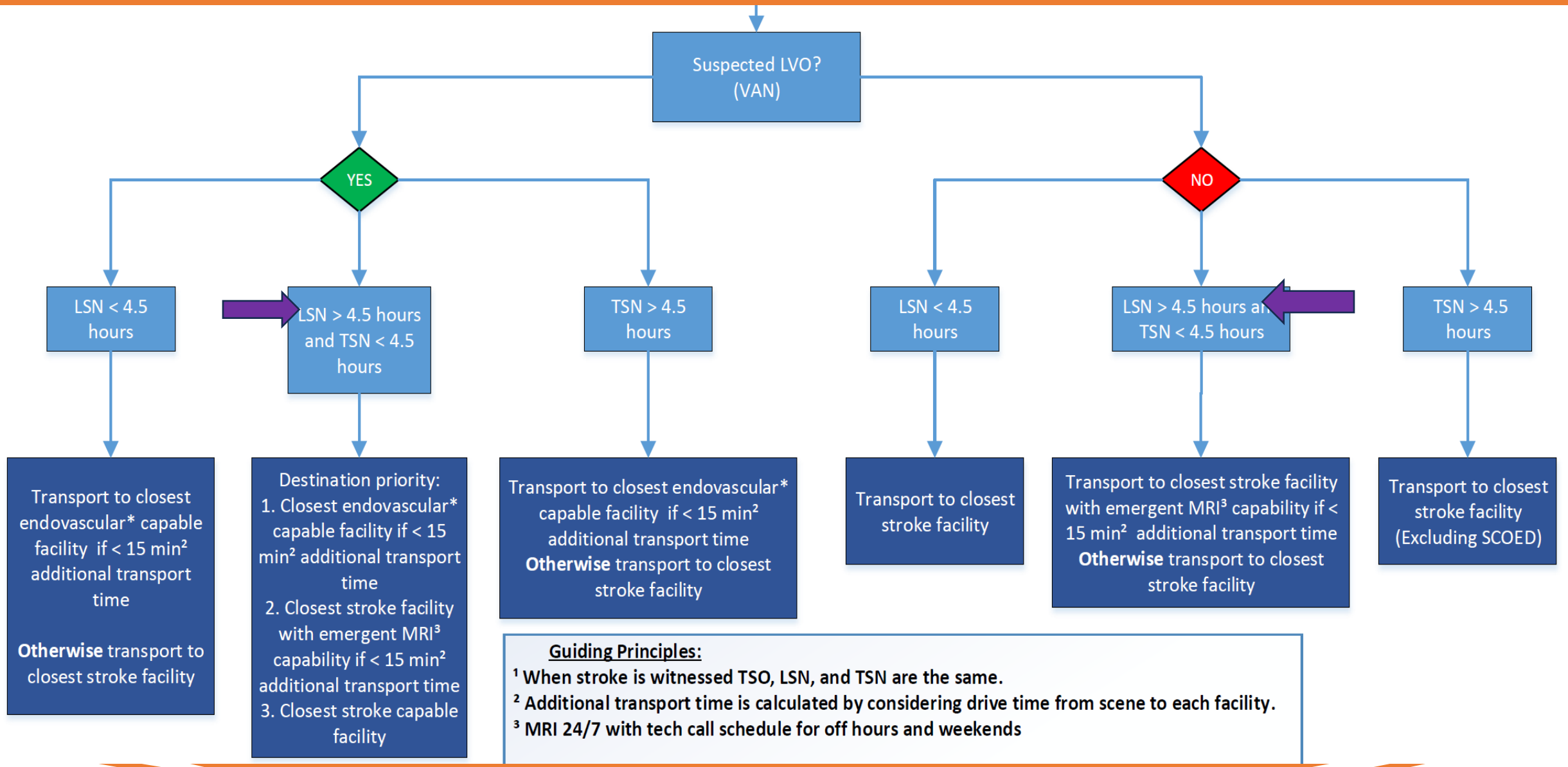


Guiding Principles:

[1] When stroke is witnessed TSO, LSN, and TSN are the same.
[2] Additional transport time is calculated by considering drive time from scene to each facility.
[3] MRI 24/7 with tech call schedule for off hours and weekends

Stroke Facility Definitions: **Endovascular Capable*

*CSC: Comprehensive Stroke Center
*TSC: Thrombectomy Capable Stroke Center
*PSC-E: Primary Stroke Center with Endovascular (May not be 24/7. Contact LCC to verify)
PSC: Primary Stroke Center
ASRH: Acute Stroke Ready Hospital
SCOED: Stroke Capable Off Site ED



Guiding Principles:

[1] **When stroke is witnessed TSO, LSN, and TSN are the same.**

[2] **Additional transport time is calculated by considering drive time from scene to each facility.**

[3] **MRI 24/7 with tech call schedule for off hours and weekends**

NDC 50242-120-47

Tenecteplase
TNKase®
50 mg

For use in myocardial infarction

Kit Contents: Each kit contains one 50 mg vial of TNKase, one 10 mL vial of preservative-free Sterile Water for Injection, USP, one BD® 10 mL syringe with TwinPak™ Dual Cannula Device, and package insert containing full prescribing information.

Vial Contents: The preservative-free single-use vial of TNKase contains 52.5 mg Tenecteplase, 0.55 g L-arginine, 0.17 g phosphoric acid, and 4.3 mg polysorbate 20, under partial vacuum. No U.S. standard of potency.

US License No.: 1048

℞ only

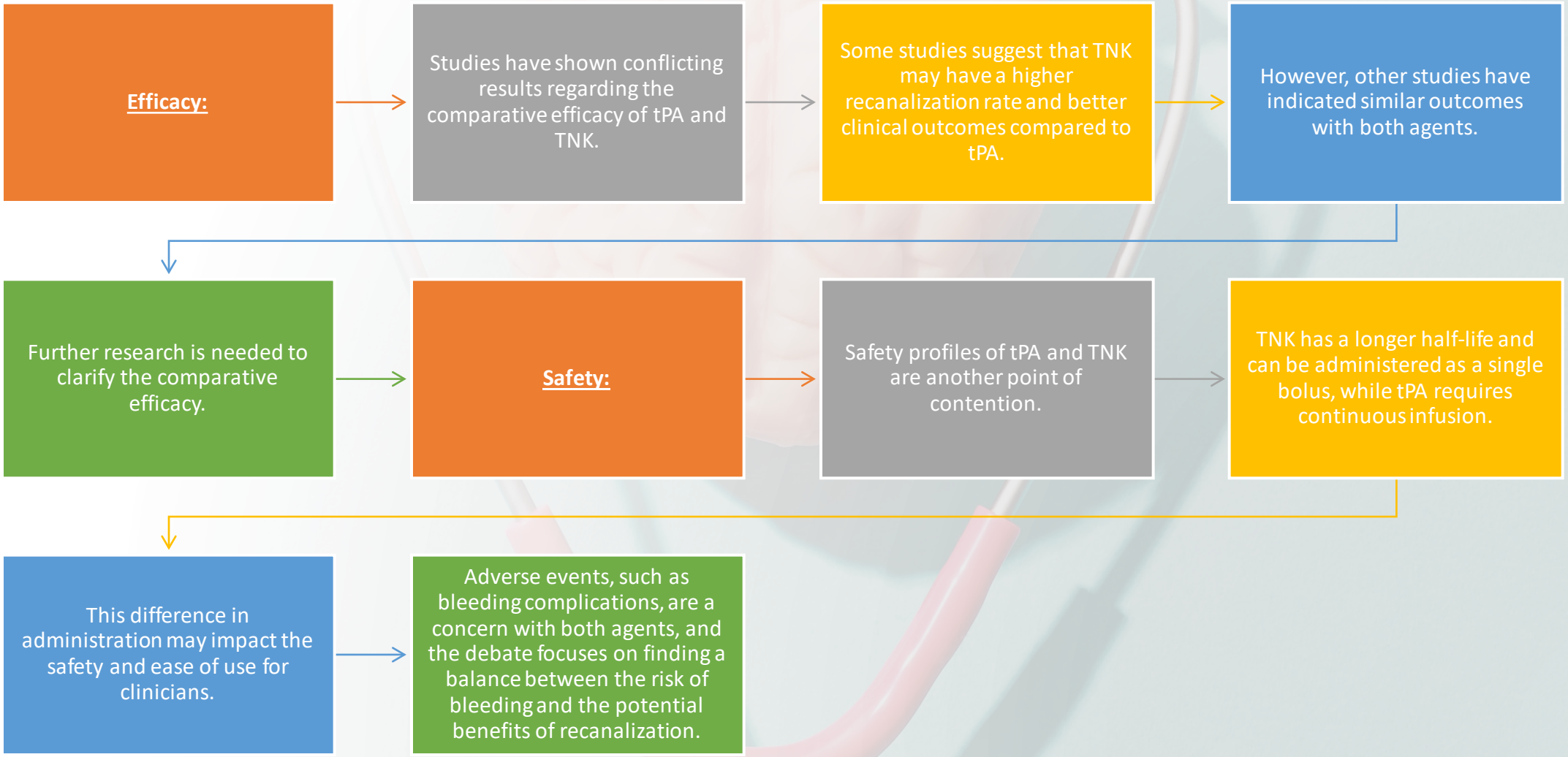
10200128

Genentech

	Alteplase (tPA)	Tenecteplase (TNK)
Mechanism	Recombinant version of naturally occurring tissue plasminogen activator *Binds only semi-selectively to fibrin bound plasminogen	Bioengineered variant of tPA * More fibrin specific * More resistant to degradation by endogenous PAI-1
Half life	5 minutes; Terminal: 72 minutes	Initial: 20–24 minutes; Terminal: 90–130 minutes
Preparation	More complex, approx. 5 mins	Simple, approx. 1 min
Administration	60 minutes (Bolus + infusion)	5-10 seconds (IV Bolus)

Study	Design	Results	Conclusion
A Randomized Trial of Tenecteplase verses Alteplase for Acute Ischemic Stroke (n=75)	Alteplase (0.9 mg/kg) or TNK (0.1 mg/kg or 0.25 mg/kg) less than 6 hours after the onset of ischemic stroke	**Primaries:** Proportion of perfusion – TNK **79.3% vs Alt 55.4% (P=0.004)** Clinical improvement on NIHSS – TNK 8 vs. Alt 3 (P<0.001)	"Tenecteplase was associated with **significantly bette reperfusion** and **clinical outcomes** than alteplase in patients with stroke who were selected on the basis of perfusion imaging"
EXTEND-IA TNK	TNK (0.25 mg/kg; Max 25 mg) or alteplase (0.9 mg/kg; Max 90 mg) within 4.5 hours of to symptom onset	**Primary**: Substantial reperfusion - **22% TNK** vs. **10% tPA** (p=0.002 for noninferiority) **Safety**: Symptomatic ICH 1.0% TNK vs. 1.0% tPA	"Tenecteplase before thrombectomy was associated wi a **higher incidence of reperfusion** and better functiona outcome than alteplase"
ENTEND-IA TNK Part 2	TNK doses 0.40 mg/kg vs 0.25 mg/kg	**Primary**: Substantial reperfusion - 19.3% in the 0.40 mg/kg group vs 19.3% in the 0.25 mg/kg group	"The findings suggest that the 0.40-mg/kg dose of tenecteplase does not confer an advantage over the 0.2 mg/kg dose in patients with large vessel occlusion ischer stroke"
NOR-TEST	IV TNK 0.4 mg/kg (Max 40 mg) or alteplase 0.9 mg/kg (Max 90 mg)	**Primary:** Excellent functional outcome by mRS score 0-1 at 3 months - 354 (64%) TNK and 345 (63%) tPA (p=0.52)	"Tenecteplase was **not superior** to alteplase and showe **similar safety** profile"
Evidence that Tenecteplase Is Noninferior to Alteplase for Acute Ischemic Stroke: Meta-Analysis of 5 Randomized Trials (2019)	Systematic literature search and formal meta-analysis adapted to **noninferiority analysis** Alteplase patients received 0.9 mg/kg dose, TNK dose was 0.1 mg/kg in 6.8%, 0.25 mg/kg in 24.6%, and 0.4 mg/kg in 68.6%	**Primary**: % disability-free (mRS, 0-1) 3 mo outcome = TNK 57.9% vs. ALT 55.4% **Secondary**: Functional independence (mRS, 0-2): TNK 71.9% vs. ALT 70.5%	"Accumulated clinical trial data provides strong eviden that **TNK is noninferior to ALT** in the treatment of acut ischemic stroke. These findings provide formal support the recent guideline recommendation to consider TNK alternative to ALT"

Debate between TPA and TNK



Debate between TPA and TNK

Cost-effectiveness:

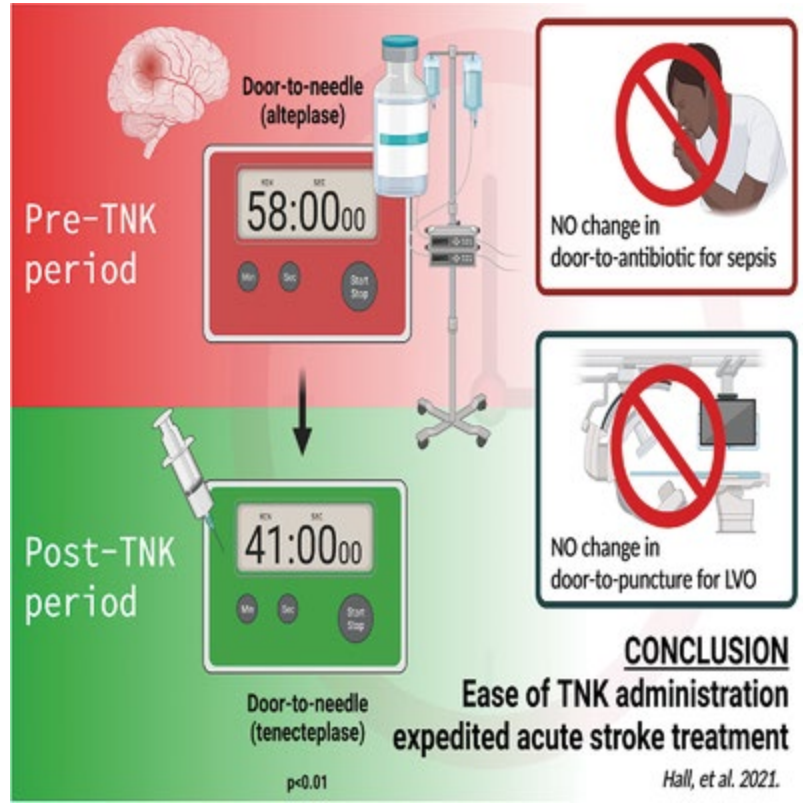
The cost-effectiveness of tPA versus TNK is also an area of debate.

The cost of TNK is generally higher or lower than tPA, which may impact its accessibility and utilization in clinical practice. Cost-effectiveness analyses considering clinical outcomes and healthcare resource utilization will be needed to inform the decision-making process.

Guidelines and regulatory approvals:

The current guidelines, such as those from the American Heart Association/American Stroke Association, recommend the use of tPA as the standard of care for acute ischemic stroke within a specific time window.

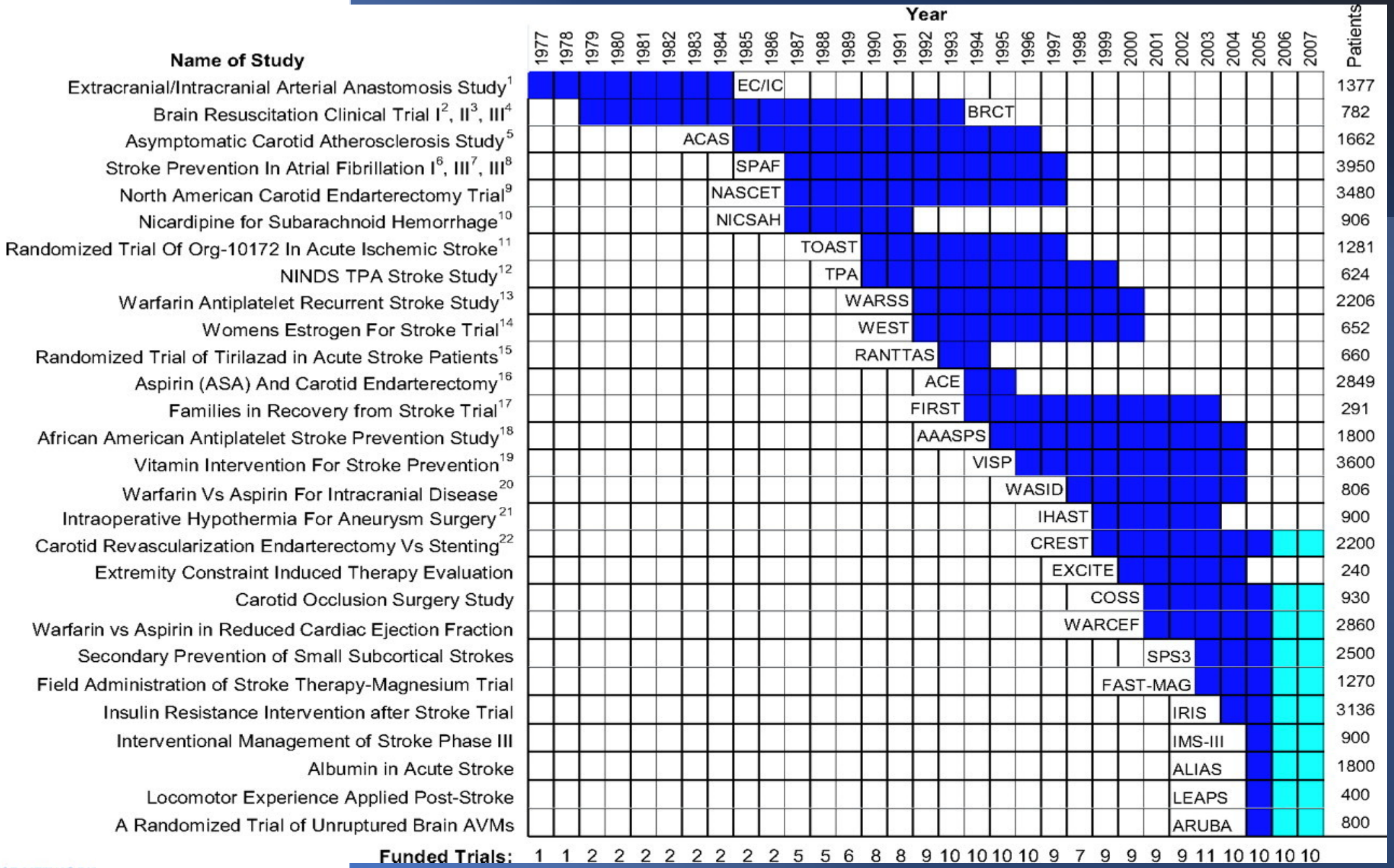
However, there is ongoing research and clinical trials exploring the use of TNK, and these may impact future guideline recommendations.


Door-to-needle
(alteplase)
Pre-TNK
period
58:00 00
NO change in
door-to-antibiotic for sepsis
NO change in
door-to-puncture for LVO
Post-TNK
period
41:00 00
Door-to-needle
(tenecteplase)
p<0.01
CONCLUSION
Ease of TNK administration
expedited acute stroke treatment
Hall, et al. 2021.

CHANCE trial: Explored the use of combination antiplatelet therapy in patients with minor stroke or high-risk transient ischemic attack (TIA), resulting in changes to the standard of care for this patient group.

POINT trial: Studied the use of dual antiplatelet therapy following minor stroke or TIA, showing a decreased risk of recurrent stroke.

EXPRESS trial: Demonstrated the benefits of an integrated care pathway for patients with TIA or minor stroke, changing the standard of care for these patients.



LOUISIANA EMERGENCY RESPONSE NETWORK