

# Updates in Management of Acute Ischemic Stroke



A presentation for HealthTrust Members  
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## Disclosures

- The presenter has no financial relationships with any commercial interests pertinent to this presentation.
- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.

# Objectives

## Pharmacist

- Identify the pharmacist's role in the management of patients with acute ischemic stroke (AIS)
- Discuss the updated recommendations for the use of systemic fibrinolytic therapy for AIS
- Review the updated recommendations for adjunctive and/or alternative pharmacologic and nonpharmacologic therapies for AIS

## Technician

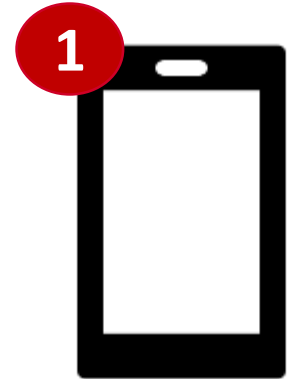
- Recall the difference between hemorrhagic and ischemic strokes
- Identify brand and generic drug names for medications used to treat strokes

# Abbreviations

AIS: acute ischemic stroke	DWI: diffuse weighted imaging	mRS: modified rankin scale
ASPECTS: Alberta Stroke Program Early CT score	ED: emergency department	MT: mechanical thrombectomy
AVM: atrioventricular malformation	EMS: emergency medical services	NIHSS: National Institute of Health Stroke Scale
BA: basilar artery	HTN: hypertension	PAI-1: plasminogen activator inhibitor
BP: blood pressure	ICA: internal carotid artery	sICH: symptomatic intracerebral hemorrhage
CPSS: Cincinnati Prehospital Stroke Score	LAPSS: LA Prehospital Stroke Screen	TNK: tenecteplase
CT scan: computerized tomography scan	LMWH: low molecular weight heparin	tPA: alteplase
CTA: CT angiogram	M1: middle cerebral artery segment 1	
DAPT: dual antiplatelet therapy	M2: middle cerebral artery segment 2	
DOAC: direct oral anticoagulant	MCA: middle cerebral artery	
DTN time: door to needle time	MI: myocardial infarction	

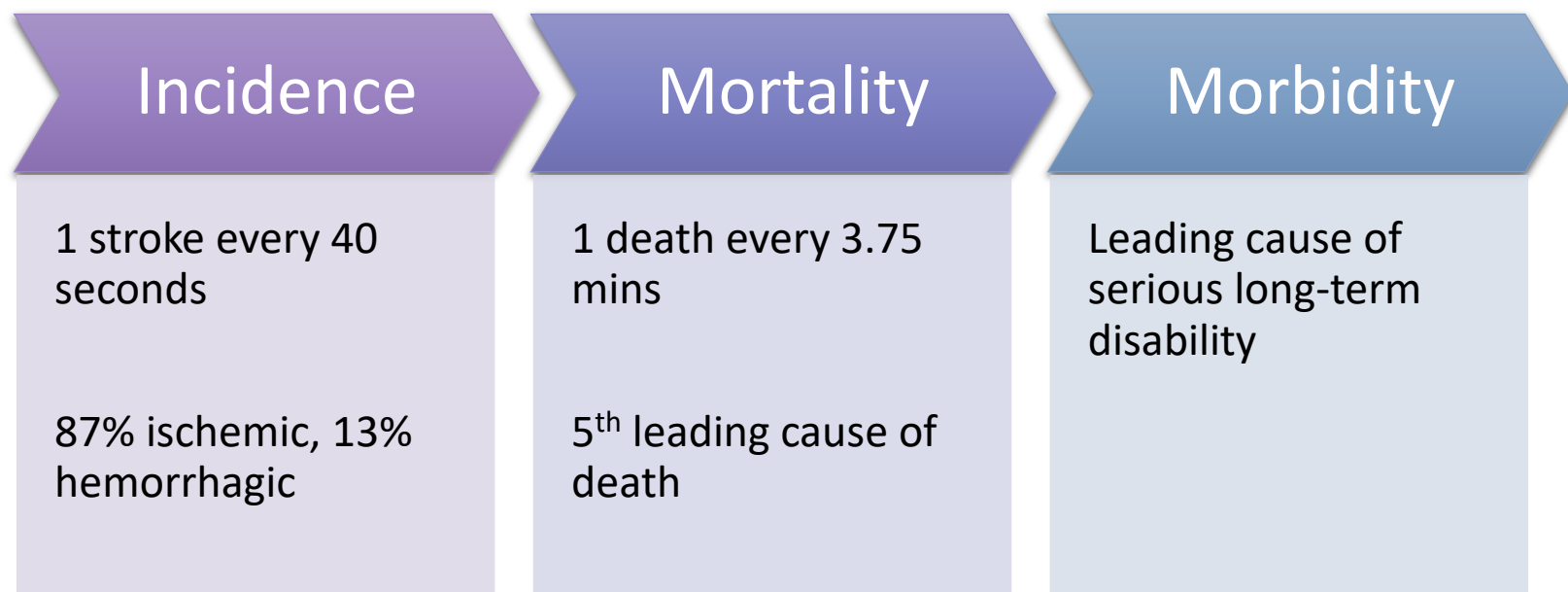
# Key Symbols

Stroke guideline updates and new recommendations



Highlighting the pharmacist's role

# Stroke Epidemiology in the US



# AHA/ASA Guideline

## 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

**A Guideline for Healthcare Professionals From the American Heart  
Association/American Stroke Association**

*Reviewed for evidence-based integrity and endorsed by the American Association of Neurological  
Surgeons and Congress of Neurological Surgeons*

*Endorsed by the Society for Academic Emergency Medicine*

2013 AIS  
Guideline

2018 AIS  
Guideline



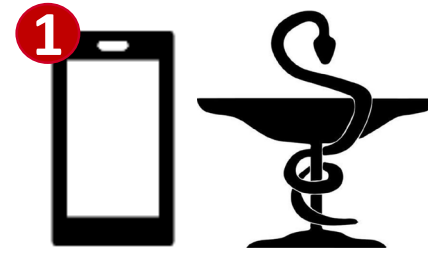
2015 AIS Update:  
Endovascular Treatment

# “Code Stroke” Overview





# Education

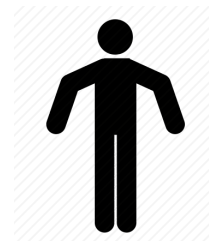


## BE-FAST



B

Balance: dizzy, trouble walking/ balancing



A

Arm weakness or drift



E

Eyes: vision changes



S

Speech: slurred speech, unable to talk



F

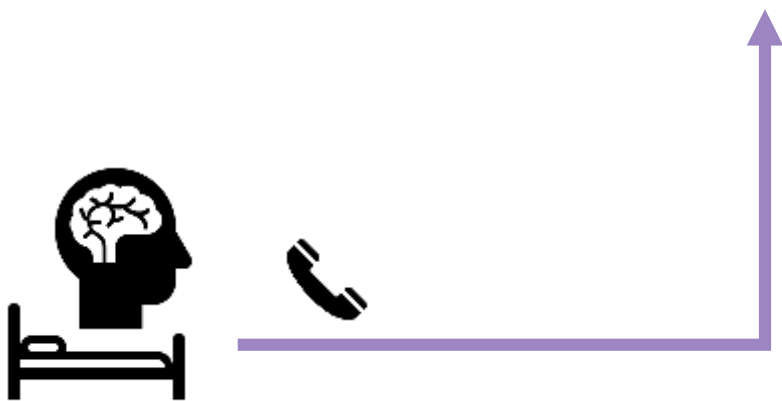
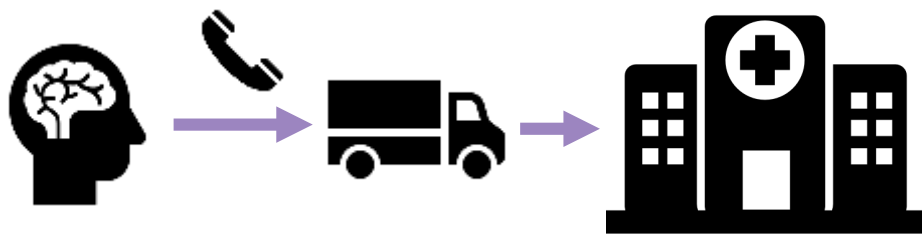
Facial droop, numbness

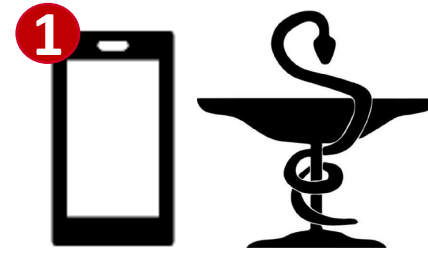


T

Time to call 911!!

# “Code Stroke” Overview





# Prehospital Care

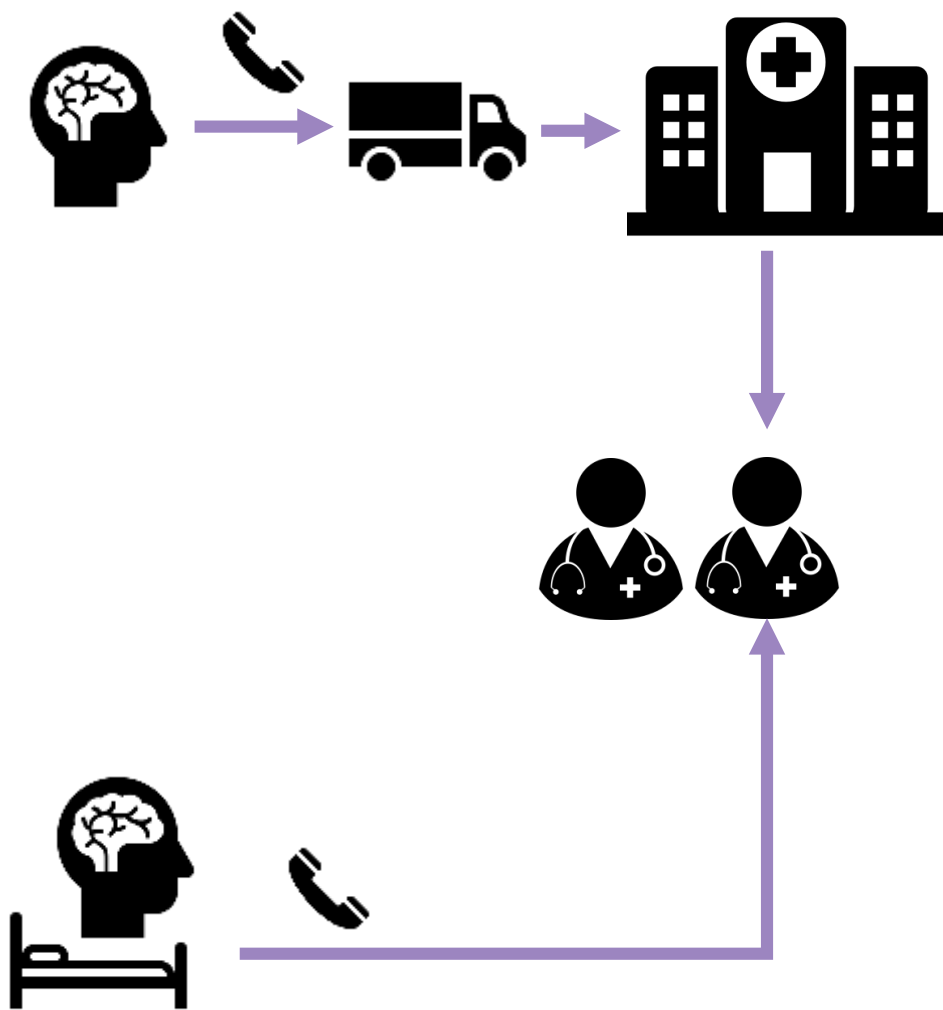
## Cincinnati Prehospital Stroke Score (CPSS)

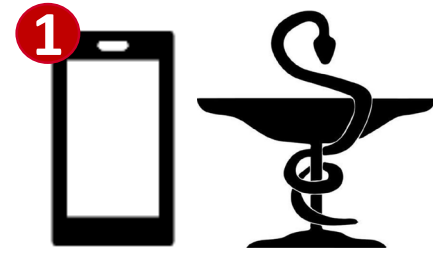
Facial Droop  
Arm Drift  
Speech

## LA Prehospital Stroke Screen (LAPSS)

Age >45  
History of seizure  
New onset (within 24 hrs.)  
neurologic symptoms  
Ambulatory at baseline  
Blood glucose  
Asymmetry: facial droop,  
arm drift, grip

# “Code Stroke” Overview

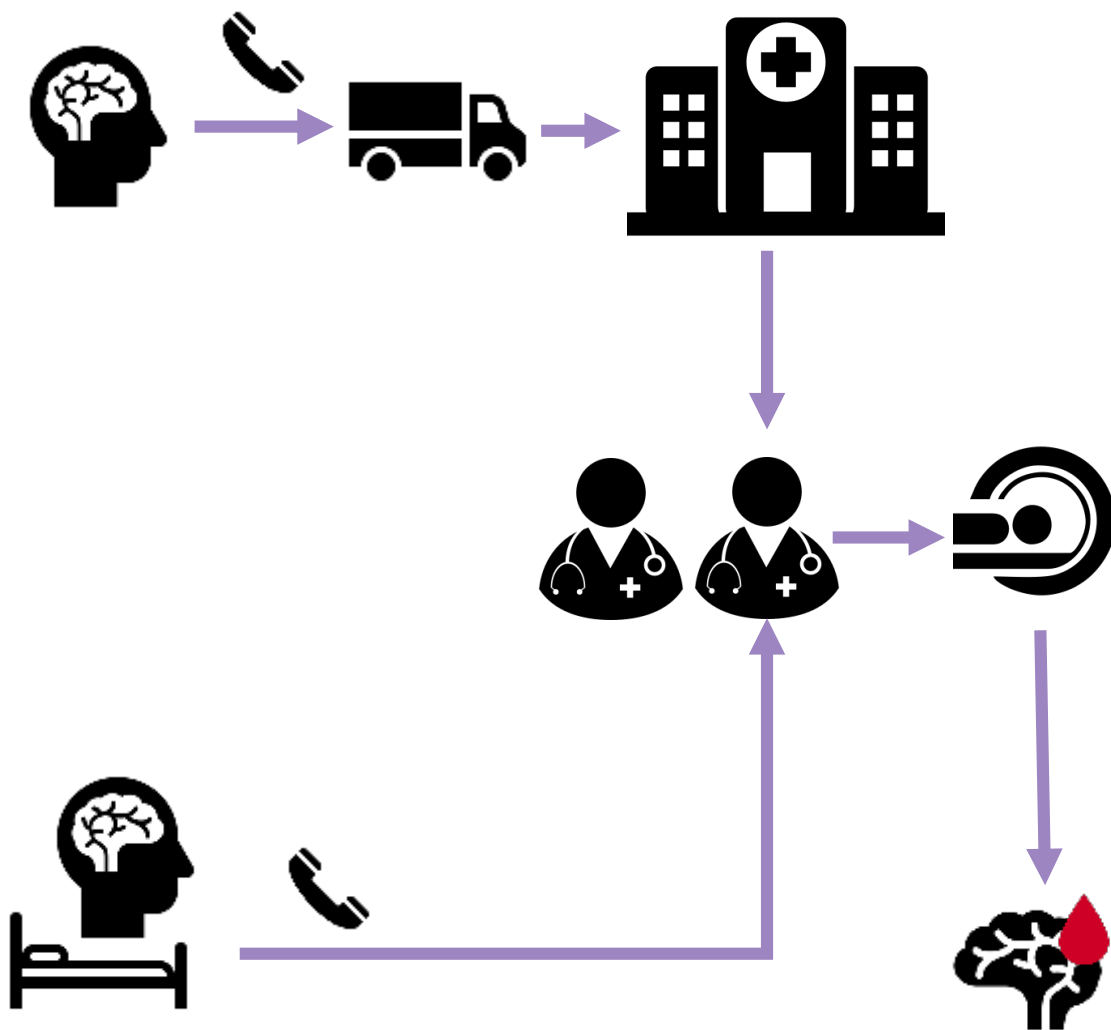




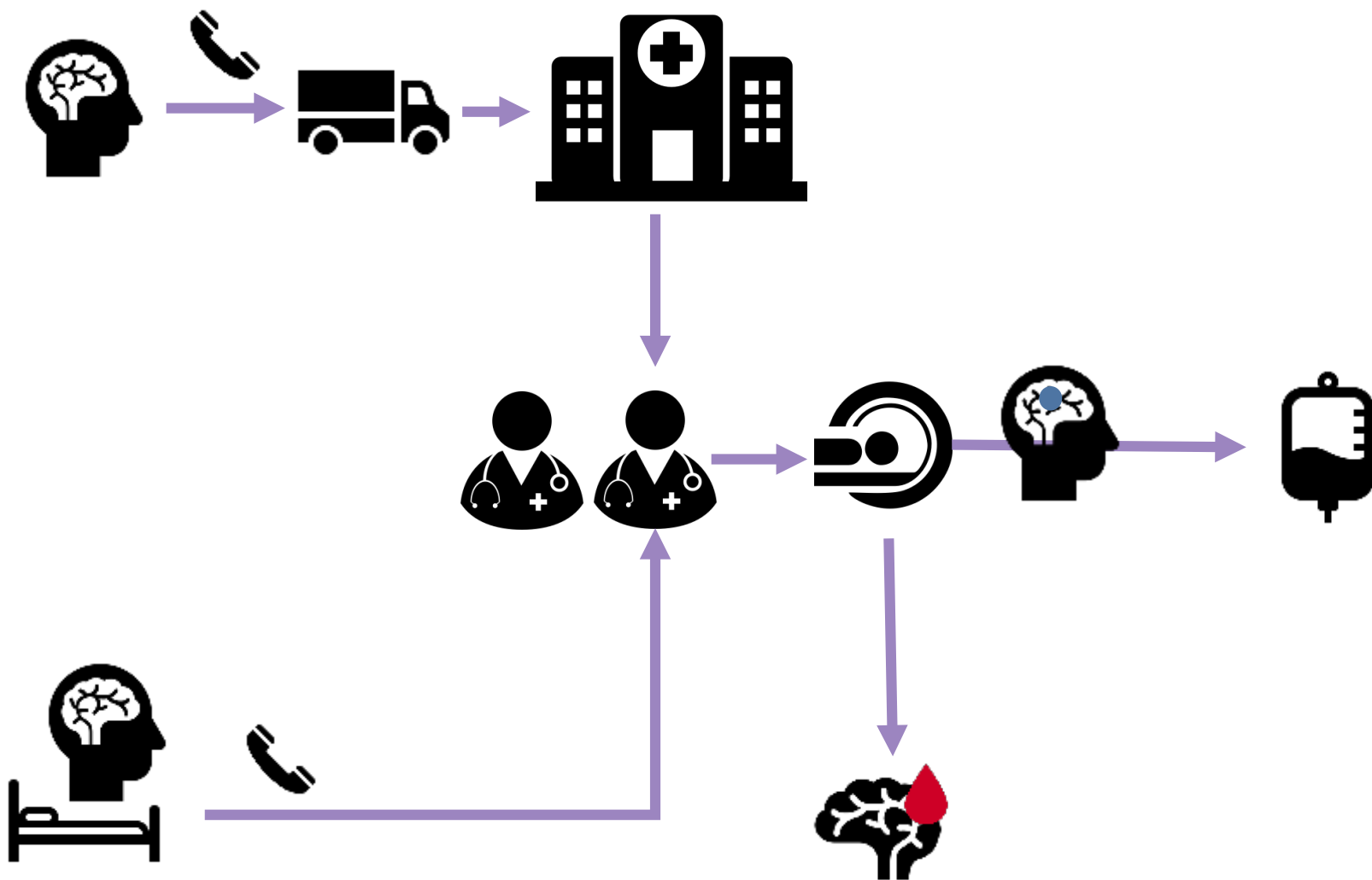
# Initial Evaluation

- Assessment of ABC's
- Vital signs, physical exam
  - Blood glucose
- Neurological exam, NIHSS
- Symptom onset, “last known normal”
- History: co-morbidities, medications
- Diagnostic imaging

# “Code Stroke” Overview



# “Code Stroke” Overview



# Fibrinolytic Therapy

tPA (Activase<sup>®</sup>): 0.9 mg/kg, max 90 mg

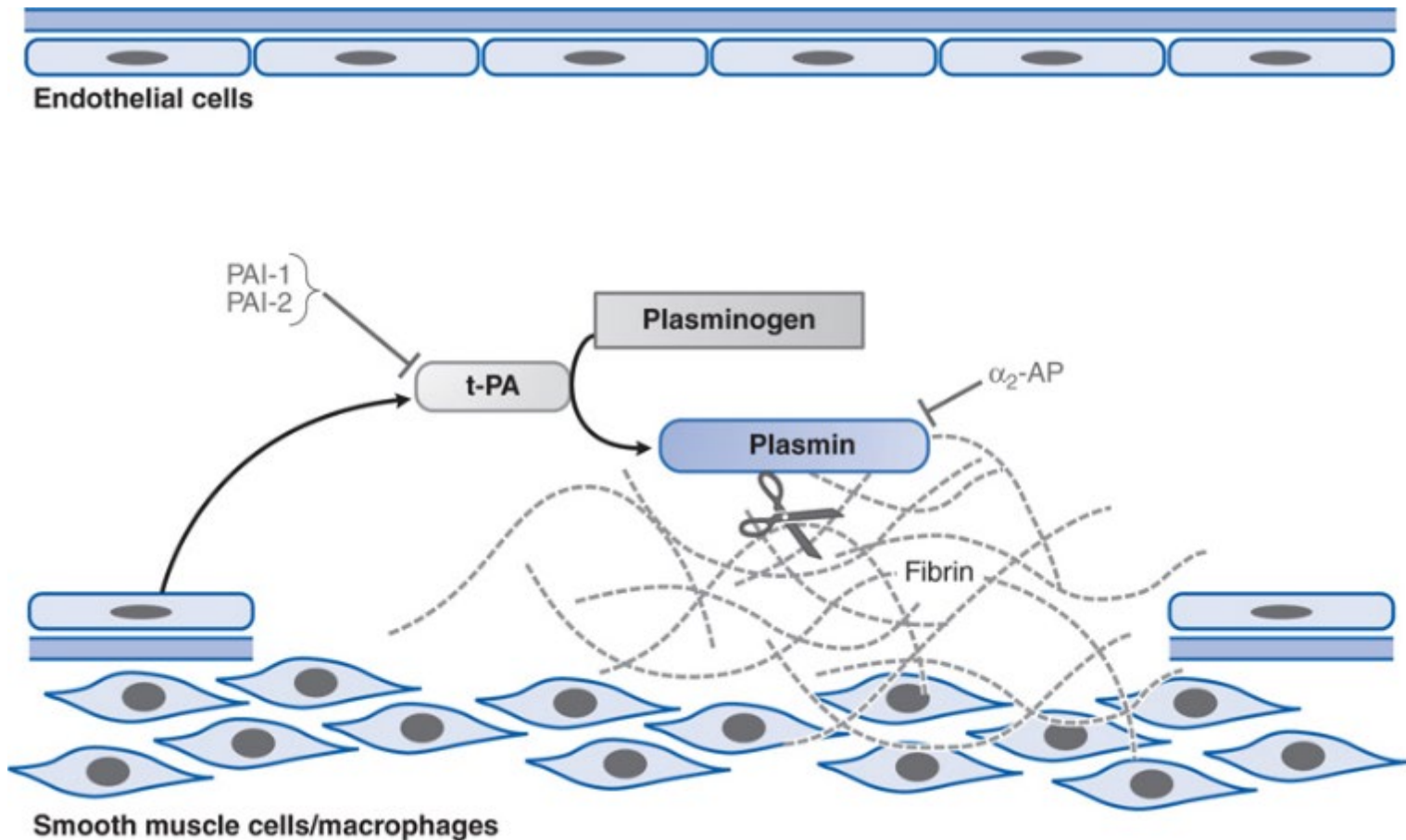
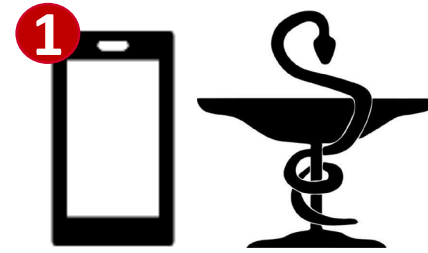


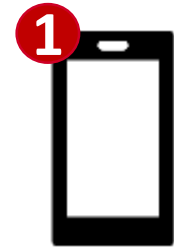
Figure 1: Fibrinolysis. Accessed from <https://basicmedicalkey.com/drug-therapy-of-thromboembolic-disorders/>





# Alteplase: Inclusion Criteria

- Symptom onset within 3 hours
- Symptom onset within 3-4.5 hours, with additional criteria
- AIS with measurable neurologic deficit
- Age  $\geq 18$  years

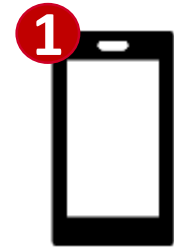


# Alteplase: Inclusion Criteria

- Symptom onset within 3 hours
- Symptom onset within 3-4.5 hours, with additional criteria
- AIS with measurable neurologic deficit
- Age  $\geq 18$  years
- Mild but disabling stroke symptoms
- Sickle cell patients are eligible for tPA

*tPA may be reasonable in patients with:*

- Mild stroke between 3-4.5 hours
- 1-10 previous cerebral microbleeds
- $>10$  previous cerebral microbleeds, if potential for substantial benefit



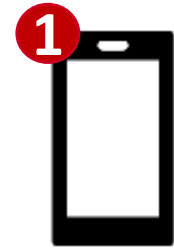
# Alteplase: Exclusion Criteria

## Absolute

- Modifiable: BP >185/110; blood glucose <50mg/dL
- Intracranial hemorrhage (current, or history of)
- Active internal bleeding
- AIS or severe head trauma within 3 mo
- Warfarin with INR >1.7 or PT>15 secs
- DOAC use within 48 hours
- Acute bleeding diathesis
- Recent intracranial or intraspinal surgery
- Intracranial neoplasm, AVM, or aneurysm
- CT with multilobar infarction

## Relative

- Minor symptoms
- Rapidly improving symptoms
- Pregnancy
- Seizure + postictal neurologic impairments
- Recent major surgery/trauma, hemorrhage, or MI
- Within 3-4.5 hours: Age >80 years, severe stroke (NIHSS >25), any oral anticoagulant, history of both diabetes + prior AIS



# Alteplase: Exclusion Criteria

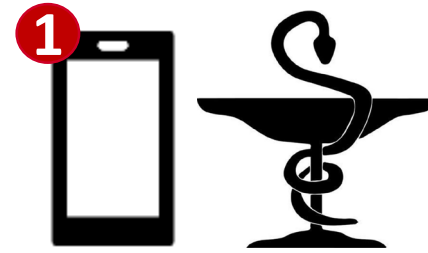
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- Acute bleeding diathesis
- Recent intracranial or intraspinal surgery **Intra-axial intracranial neoplasms**
- Intracranial neoplasm, AVM, or aneurysm **Reasonable for unruptured aneurysm <10mm**
- CT with multilobar infarction

## Relative

- Minor symptoms
- Rapidly improving symptoms
- Pregnancy
- Seizure + postictal neurologic impairments
- Recent major surgery/trauma, hemorrhage, or MI
- Within 3-4.5 hours: ~~Age >80 years, severe stroke (NIHSS >25), any oral anticoagulant, history of both diabetes + prior AIS~~, and imaging evidence of ischemia in >1/3<sup>rd</sup> MCA territory
- **Any DOAC; or warfarin with INR >1.7**

Treatment dose of LMWH



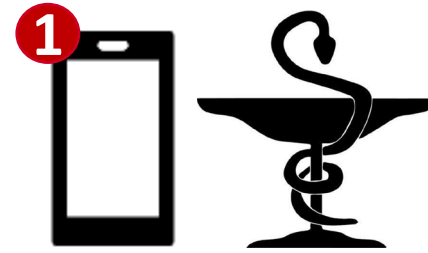
# Goal DTN Time



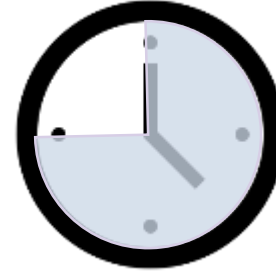
DTN time: within 60 minutes of from hospital arrival

Primary goal: DTN time within 60 minutes in  $\geq 50\%$

Secondary goal: Reasonable to aim for DTN times within 45 minutes in  $\geq 50\%$



# Goal DTN Time



~~DTN time: within 60 minutes of from hospital arrival~~

Primary goal: DTN time within 60 minutes in  $\geq 50\%$

Secondary goal: Reasonable to aim for DTN times within 45 minutes in  $\geq 50\%$



# Improving DTN Time

	Rech MA, et al.	Jacoby JS, et al.
Study	Retrospective, n=125 PharmD vs no PharmD	Retrospective, n=100 PharmD vs no PharmD
Median DTN	48 min vs 73 min	46 min vs 58 min
DTN Goal Achieved	≤60min: 71% vs 29% ≤45min: 44% vs 9%	≤60min: 71% vs 61% ≤45min: 49% vs 25%
Other factors that may affect DTN	More pts over weekend/ overnight in no PharmD group (statistical analysis: did not significantly affect DTN) No difference in HTN No difference in time to imaging	<b>Arrival by EMS and tPA reconstitution in ED associated with lower DTN</b> No difference in HTN
Safety	N/A	No PharmD: 2 errors (reconstitution, infusion rate)



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Safety	N/A	No PharmD: 2 errors (reconstitution, infusion rate)

## Pharmacist independently associated with improved DTN

Sources: Rech MA, et al. Ann Pharmacother 2017;51(12):1084-89.

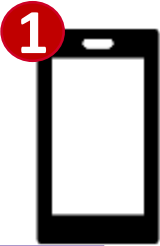
Jacoby JS, et al. Neurohospitalist 2018;8(2):60-65.



# Alternative Fibrinolytic Therapy

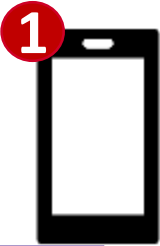
TNK (TNKase<sup>®</sup>): optimal dose and indication not determined

Designation	Amino Acid Substitution	Effect Compared to tPA
T	Thr-103 → Asn	↓ decreased clearance ↓ fibrin binding
N	Asn-117 → Gln	↓ decreased clearance Restores fibrin binding
K	Lys-His-Arg-Arg (296-299) → Ala-Ala-Ala-Ala	↑ fibrin specificity by 15 fold ↑ resistance to PAI-1 degradation by 80 fold



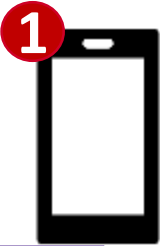
# Tenecteplase for AIS

Study	NOR-TEST	EXTEND-IA TNK
Study	Prospective, randomized, blinded endpoint, superiority	Prospective, randomized, blinded endpoint
Patients	N=1100 AIS eligible for thrombolytic +/- MT Median: NIHSS 4 (2-8), age 77 NIHSS 0-7: 78% vs 73%	N=204 ICA, M1, M2, or BA AIS eligible for thrombolytic + MT within 6 hours Median: NIHSS 17 (12-22), age 71 M1 stroke: ~60%
Intervention	Bolus TNK 0.4 mg/kg (max 40mg) tPA 0.9 mg/kg (max 90mg)	Bolus TNK 0.25 mg/kg (max 25mg) tPA 0.9 mg/kg (max 90mg)
Results	mRS 0-1 at 3mo: 64% vs 63% mRS 0-2 at 3mo: 77% vs 78% sICH at 24hrs: 3% vs 2% Mortality at 3mo: 5% vs 5%	Substantial reperfusion: 22% vs 10% mRS 0-1 at 3mo: 51% vs 43% mRS 0-2 at 3mo: 64% vs 51% sICH: at 24 hrs: 1% vs 1% Mortality: 10% vs 18%
Conclusion	TNK similar functional outcomes and safety outcomes as tPA in mild stroke	TNK +MT higher incidence of reperfusion and functional outcome than tPA +MT in proximal artery stroke



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# Tenecteplase for AIS

Study	NOR-TEST	EXTEND-IA TNK
Conclusion	TNK similar functional outcomes and safety outcomes as tPA in mild stroke	TNK +MT higher incidence of reperfusion and functional outcomes than tPA +MT in proximal artery stroke

Tenecteplase 0.4mg/kg not proven superior or noninferior to tPA

May be considered as alternative in patients with mild neurologic impairment and no major intracranial occlusion (IIb-BR)

# Future of Tenecteplase for AIS

Upcoming Phase 3 Trials			
Study	Patients	Intervention	Comparator
ATTEST-2	AIS within 4.5 hrs, no planned MT	TNK 0.25 mg/kg	tPA 0.9 mg/kg
EXTEND-IA TNK 2	Major occlusion AIS within 4.5 hrs	TNK 0.4 mg/kg + MT	TNK 0.25 mg/kg + MT
NOR-TEST 2	AIS within 4.5	TNK 0.4 mg/kg +/- MT	tPA 0.9 mg/kg +/- MT
TASTE	AIS within 4.5 hrs, no planned MT	TNK 0.25 mg/kg	tPA 0.9 mg/kg
TIMELESS	ICA or MCA AIS within 4-24 hrs	TNK 0.25 mg/kg	Placebo
TEMPO-2	AIS within 12 hrs with minor stroke	TNK 0.25 mg/kg	Antiplatelet
TWIST	Wake up stroke	TNK 0.25 mg/kg	Standard of care

**Bottom line: Expect greater discussion about TNK, but tPA will remain the primary thrombolytic for AIS**

Sources: [Clinicaltrials.gov/](https://clinicaltrials.gov/)

[Anzctr.org.au/](https://anzctr.org.au/)

Craig SA. Lancet Neurol 2017;16(10):762-63.

# Assessment 1: Pharmacists

Which of the following is not an absolute contraindication to thrombolytic therapy?

- A. Severe head trauma within 3 months
- B. Extra-axial intracranial neoplasms
- C. Treatment dose of low molecular weight heparins
- D. Last-known-normal 8 hours prior to presentation

# Response 1: Pharmacists

Which of the following is not an absolute contraindication to thrombolytic therapy?

- A. Severe head trauma within 3 months
- B. Extra-axial intracranial neoplasms**
- C. Treatment dose of low molecular weight heparins
- D. Last-known-normal 8 hours prior to presentation

# Assessment 2: Technicians

Which of the following medications are thrombolytics?

- A. Clopidogrel (Plavix<sup>®</sup>)
- B. Tenecteplase (TNKase<sup>®</sup>)
- C. Alteplase (Activase<sup>®</sup>)
- D. Aspirin
- E. B and C

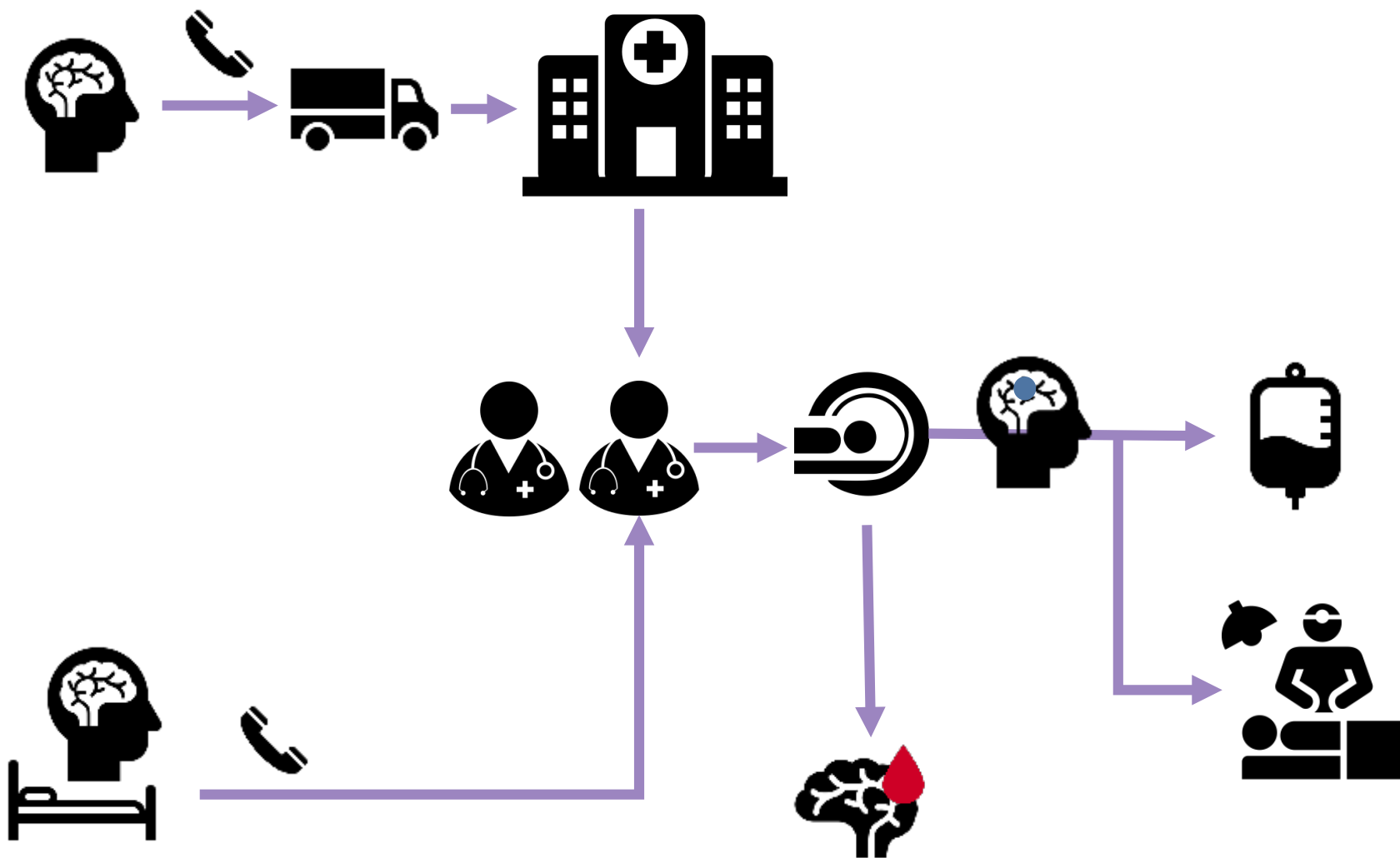


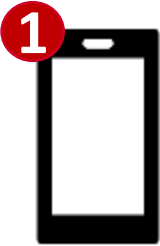
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- B. Tenecteplase (TNKase<sup>®</sup>)
- C. Alteplase (Activase<sup>®</sup>)
- D. Aspirin
- E. B and C

# “Code Stroke” Overview





# Mechanical Thrombectomy

Fibrinolytic therapy received if eligible

Evaluate eligibility for MT ↓ Do NOT delay to assess for improvement following fibrinolytic therapy

2018 Recommendation	Criteria for Endovascular Management
IA	<ul style="list-style-type: none"><li>• Pre-stroke mRS 0 to 1</li><li>• M1, ICA</li><li>• Age <math>\geq</math> 18</li><li>• NIHSS <math>&gt;</math> 6</li><li>• ASPECTS <math>\geq</math> 6</li><li>• Symptom onset within 6 hours</li></ul>
IA	<ul style="list-style-type: none"><li>• LKW 6 – 16 hours (DEFUSE3 criteria)</li></ul>
IIa,B-R	<ul style="list-style-type: none"><li>• LKW 6 – 24 hours (DAWN criteria)</li></ul>
IIb, B-R	<ul style="list-style-type: none"><li>• Consider if M2 or M3, within 6 hours of symptom onset</li></ul>
IIb, B-R	<ul style="list-style-type: none"><li>• Consider if pre-stroke mRS <math>&gt;</math>1, ASPECTS <math>&lt;</math>6, or NIHSS <math>&lt;</math>6 with ICA or M1 stroke within 6 hr onset window</li></ul>
IIb, C-EO	<ul style="list-style-type: none"><li>• Consider if anterior cerebral, vertebral, basilar, or posterior cerebral arteries</li></ul>

Sources: Powers W.J., et al. Stroke 2018;49:e1-e65.  
Gralla J., et al. Stroke 2012;43:280-85.

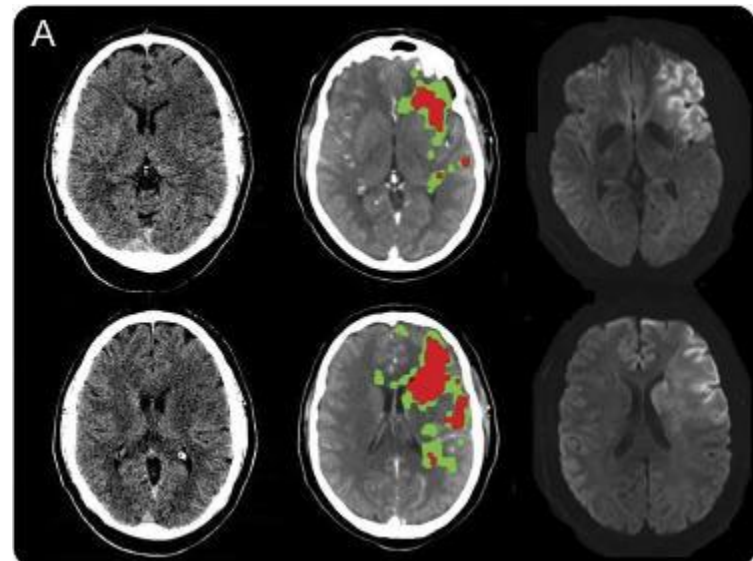
# Determining MT Eligibility

Identification of  
ischemic vessel  
(MCA, ICA) &  
carotid stenosis

CTA or MRA

ASPECTS

CT or DWI (MRI)



# Expanding the MT Window

## DEFUSE-3 (6-16 hours)

$\leq 90$  yo

NIHSS  $\geq 6$

Infarct core  $< 70$  mL

Ischemic tissue vol to initial  
infarct ratio  $\geq 1.8$

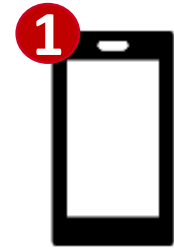
Penumbra  $\geq 15$  mL

## DAWN (6-24 hours)

80 yo + NIHSS  $\geq 10$  + infarct  
 $< 21$  mL

$< 80$  yo+ NIHSS  $\geq 10$  + infarct  
 $< 31$  mL

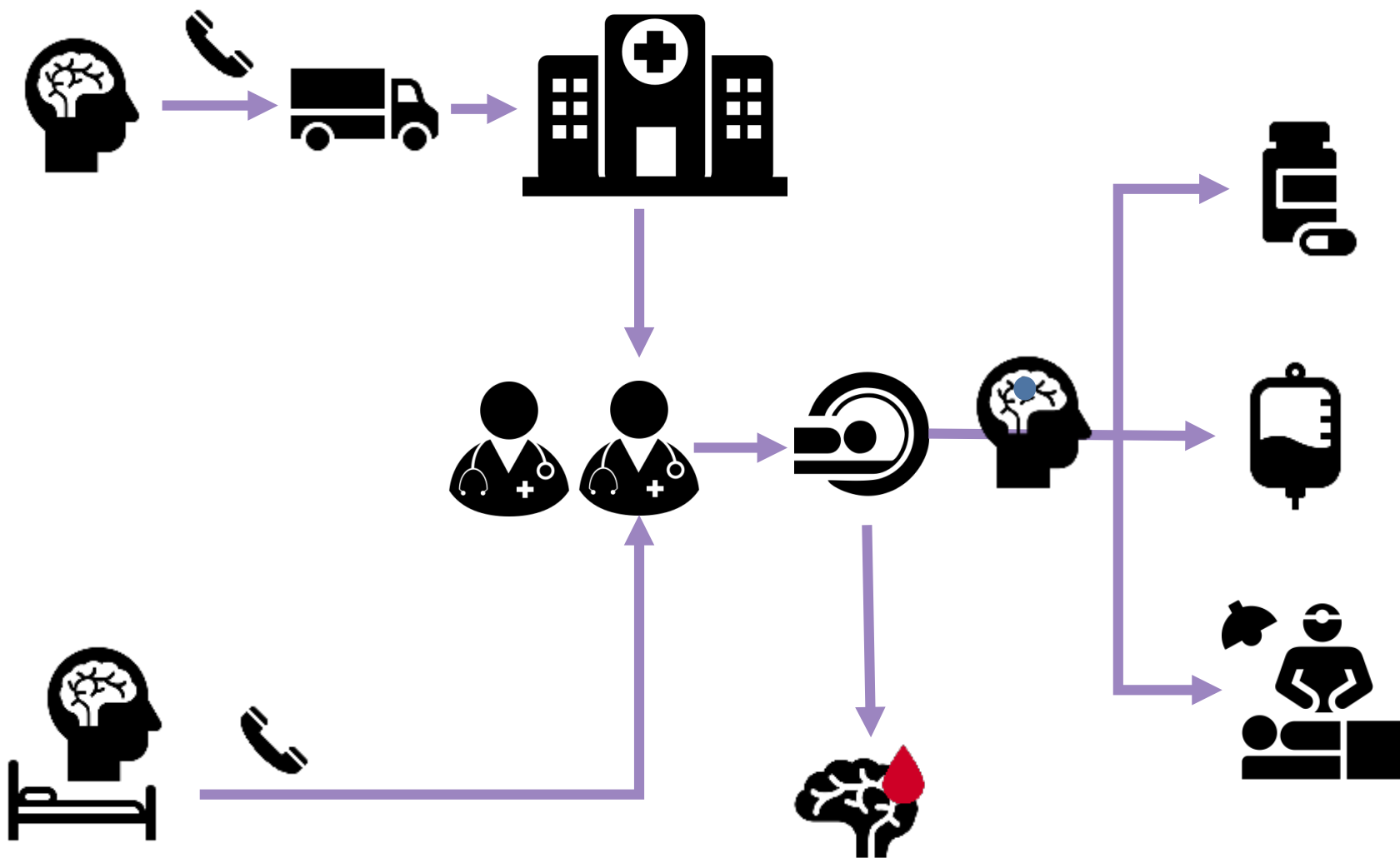
$< 80$  + NIHSS  $\geq 20$  + infarct of  
31 to  $< 51$  mL

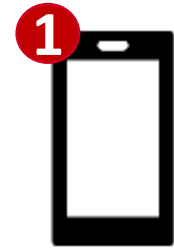


# Pharmacist Role in MT

- If eligible for thrombolytic therapy, do not delay administration of IV thrombolytic for additional imaging and/or MT
  - Facilitate logistics of IV thrombolytic
  - tPA vs. TNK – more to come?
- Blood pressure management: limited data
  - In patients undergoing MT, maintain BP  $\leq 180/105$  during and for 24 hours following procedure
  - In patients undergoing MT with successful reperfusion, maintain BP  $< 180/105$

# “Code Stroke” Overview





# Antiplatelets

Drug	Recommendation
Aspirin	Recommended within 24-48 hours Delay aspirin for 24 hours following IV tPA. May consider earlier initiation based on comorbidities
IV eptifibatide and IV tirofiban	Phase II trials have suggested safety; efficacy not well established. Further clinical trials are needed
IV abciximab	Potentially harmful; not recommended. May be associated with significant increased risk of ICH without improvement in mortality or disability
Aspirin + clopidogrel	In minor stroke, initiating DAPT within 24 hours for 21 days may reduce early secondary strokes for up to 90 days
Tigacrelor	Not recommended over aspirin in acute treatment of minor stroke. May be reasonable alternative if aspirin contraindicated



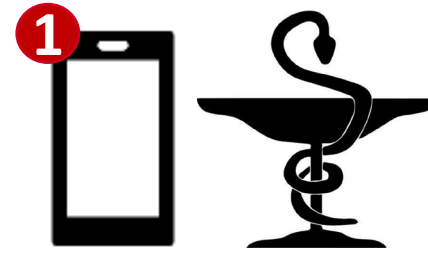
# Anticoagulants

“Not well established”

“Further clinical trials  
needed”

Ongoing studies for factor  
Xa inhibitors – more to  
come?

# Acute Blood Pressure Management



AIS Management	Recommendation
tPA	$\leq 180/105$ for first 24 hours following tPA
MT	$< 180/105$ for first 24 hours might be reasonable
Maximal medical therapy (no tPA or MT)	If BP $< 220/120$ : no benefit to HTN treatment within 48-72 hours If BP $> 220/120$ : benefit of HTN treatment within 48-72 hours uncertain. Might be reasonable to lower BP by 15% during first 24 hours
Emergent co-morbidity*	Lowering BP initially by 15% is probably safe

\*concomitant acute coronary event, acute heart failure, aortic dissection, post thrombolysis sICH, or preeclampsia/eclampsia

# Pharmacist Role Recap

- Education: community, prehospital & hospital services
- Patient evaluation & history
- Facilitating thrombolytic therapy to reduce DTN
  - Management of adverse effects
- Blood pressure management
- Antiplatelet therapy

# Assessment 3: Pharmacists

What is the recommended blood pressure goal in the first 24 hours following mechanical thrombectomy?

- A. <220/120
- B. <180/105
- C. <185/110
- D. <160/100

# Assessment 3: Pharmacists

What is the recommended blood pressure goal in the first 24 hours following mechanical thrombectomy?

- A. <220/120
- B. <180/105**
- C. <185/110
- D. <160/100

# Assessment 4: Technicians

Thrombolytics are used for what type of stroke?

- A. Ischemic
- B. Hemorrhagic

# Response 4: Technicians

Thrombolytics are used for what type of stroke?

- A. Ischemic
- B. Hemorrhagic



Thank you!

Raghad Saadi, PharmD

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