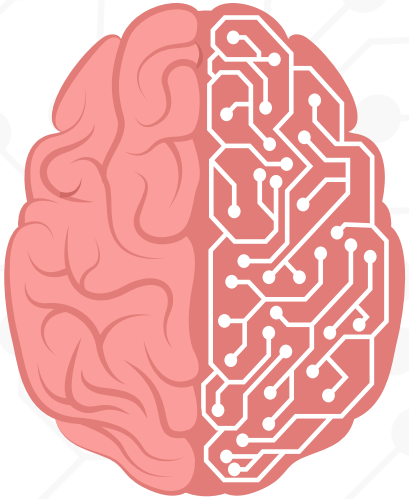
Fibrinolytics for Acute Ischemic Stroke in Patients taking DOACs: tP-YAY or tP-NAY?

Markus Reedy, PharmD
PGY1 Pharmacotherapy Resident
University of the Incarnate Word Feik School of Pharmacy



Financial Disclosures

- This speaker has no financial conflicts of interest to disclose

Learning Objectives for Pharmacists

1. Identify differences between DOACs and fibrinolytics
2. Review inclusion and exclusion criteria for the use of fibrinolytics in patients presenting with an acute ischemic stroke
3. Interpret primary literature to compare DOAC patients who were given tPA vs non-DOAC patients who were given tPA
4. Using a patient case, develop a treatment plan for a patient taking a DOAC presenting with an acute ischemic stroke

Learning Objectives for Pharmacy Technicians

1. Highlight differences between DOACs and fibrinolytics
2. Define inclusion and exclusion criteria for the use of fibrinolytics in patients presenting with an acute ischemic stroke
3. Examine primary literature comparing DOAC patients given fibrinolytics vs non-DOAC patients given fibrinolytics

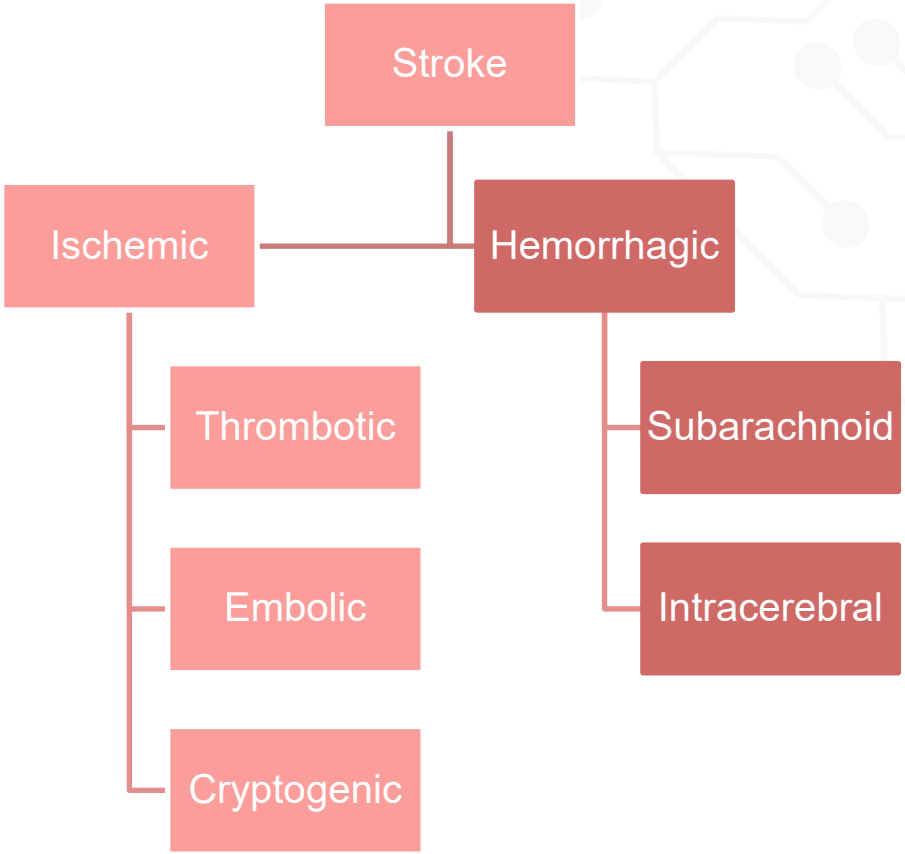
Abbreviations

Abbreviation	Meaning	Abbreviation	Meaning
DOAC	Direct oral anticoagulant	**PK**	Pharmacokinetics
AIS	Acute Ischemic Stroke	**INR**	International Normalized Ratio
tPA	Alteplase	**PT**	Prothrombin Time
TNK	Tenecteplase	**aPTT**	Activated Partial Thromboplastin Time
MOA	Mechanism of Action	**TT**	Thrombin time
AE	Adverse Effects	**ECT**	Ecarin clotting time
VTE	Venous Thromboembolism	**ECA**	Ecarin chromogenic assay
A. fib	Atrial Fibrillation	**dTT**	Diluted thrombin time
sICH	Symptomatic Intracranial Hemorrhage	**PG**	Prostaglandins
VHD	Valvular Heart Disease	**NIHSS**	National Institutes of Health Stroke Scale
PAI-1	Plasminogen Activator Inhibitor -1	**mRS**	Modified Rankin scale
MRI	Magnetic resonance imaging	**CT**	Computerized tomography

Overview of Stroke

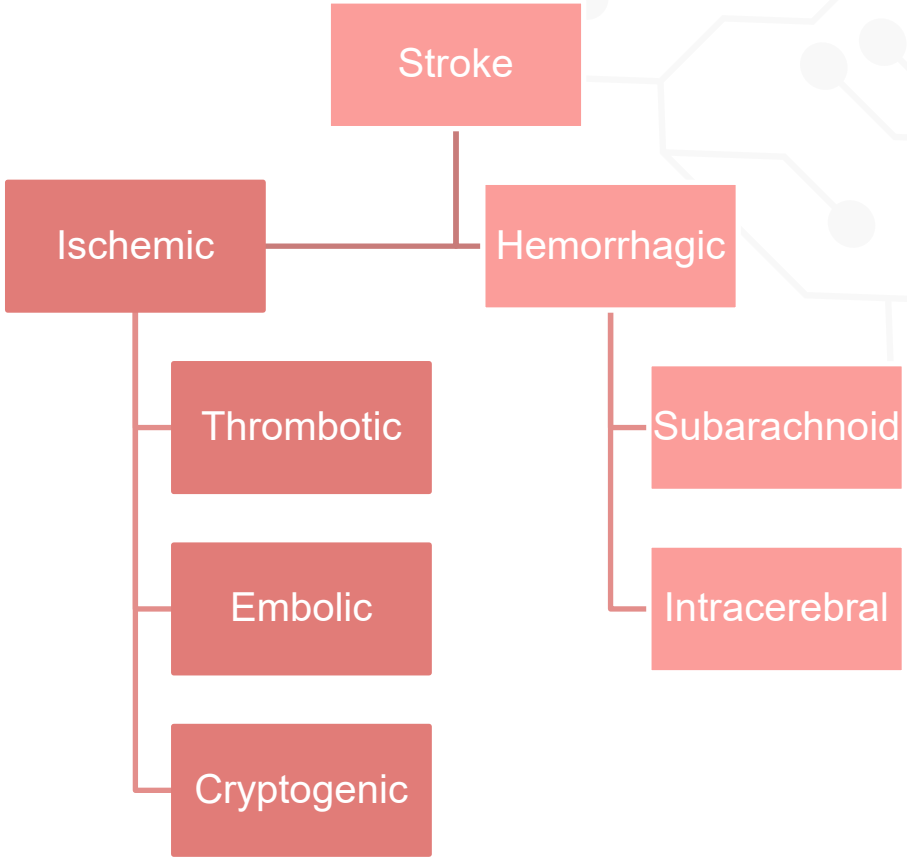
Types of stroke, pathophysiology, risk factors, signs and symptoms

Types of Stroke



Neurol Clin. 2008;26(4):871-vii

Types of Stroke



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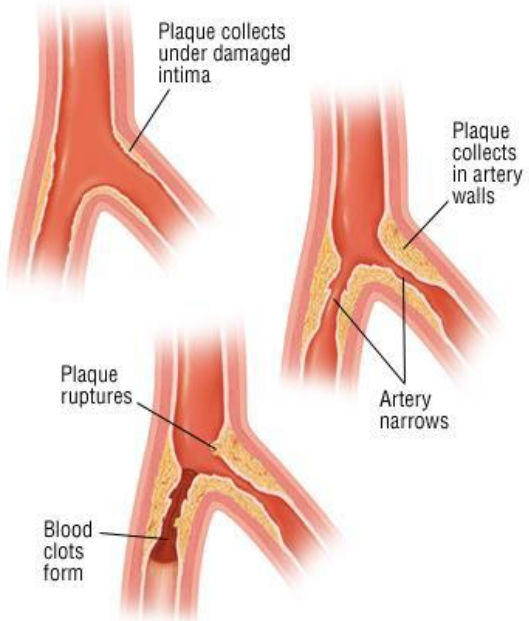
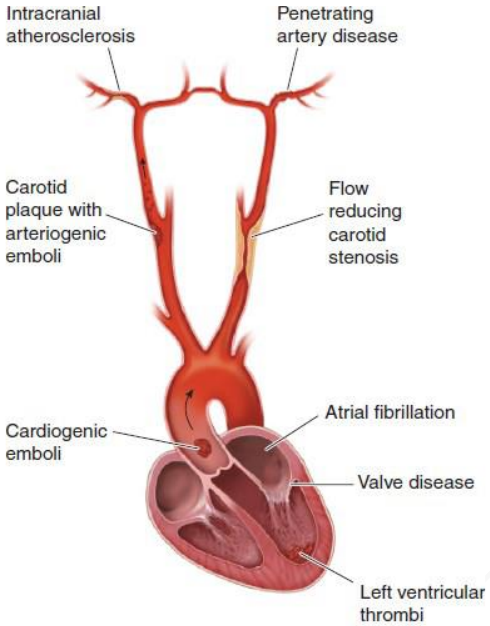
Types of Ischemic Strokes

- Thrombotic



- Embolic



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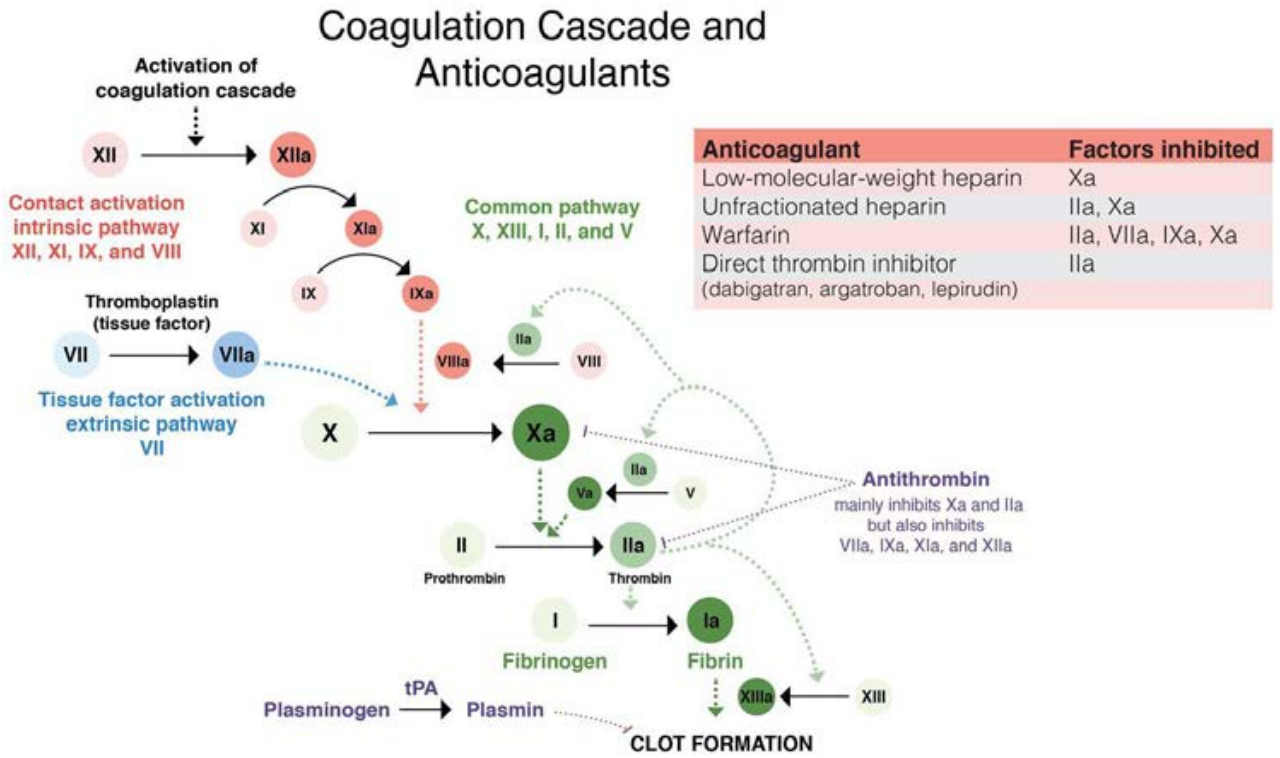
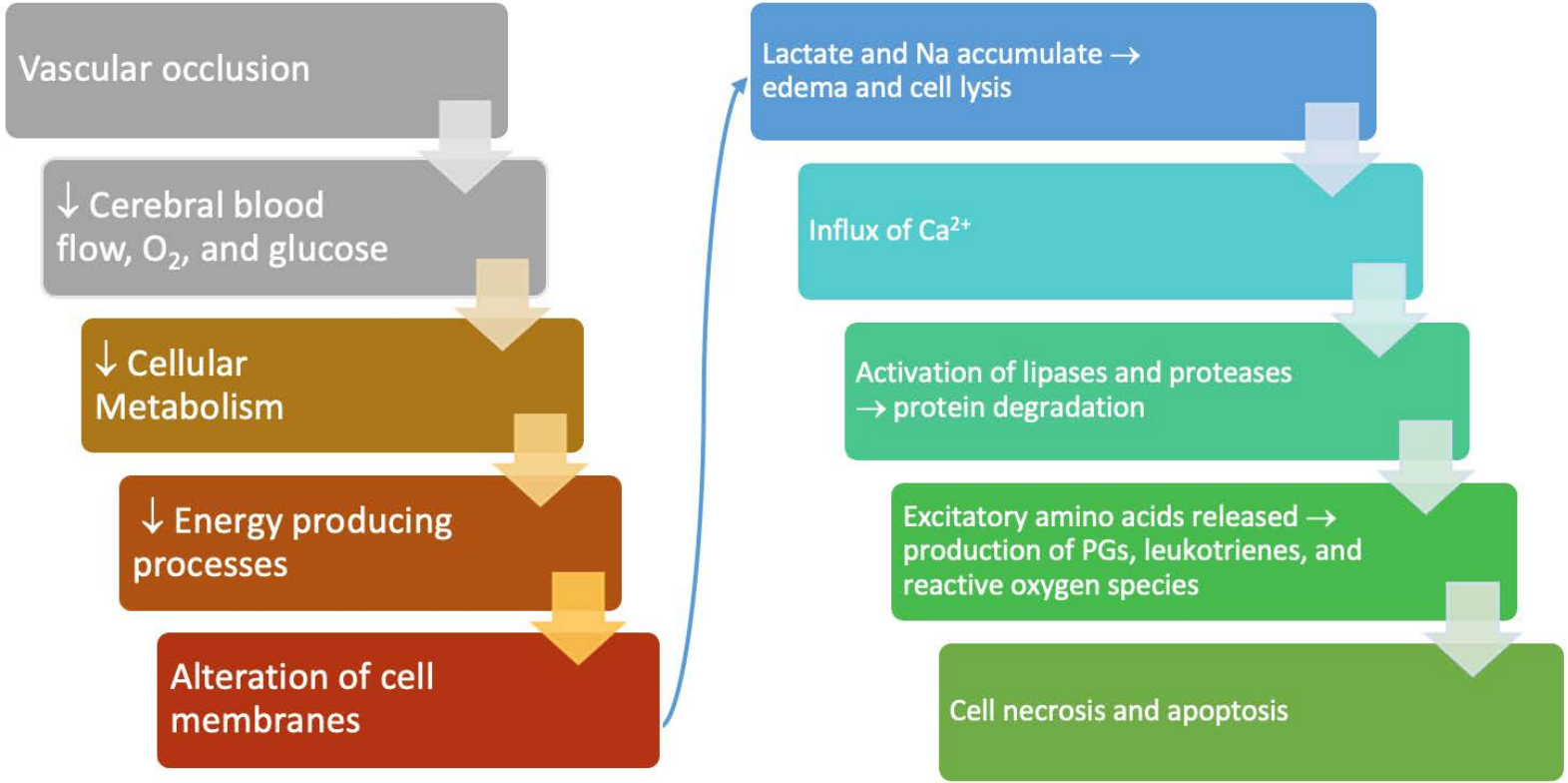
The Coagulation Cascade



Blood. 2016;128(1):104-109.

Pathophysiology of Ischemic Stroke



J Neurol Neurosurg Psychiatry. 2004;75(3):353-361

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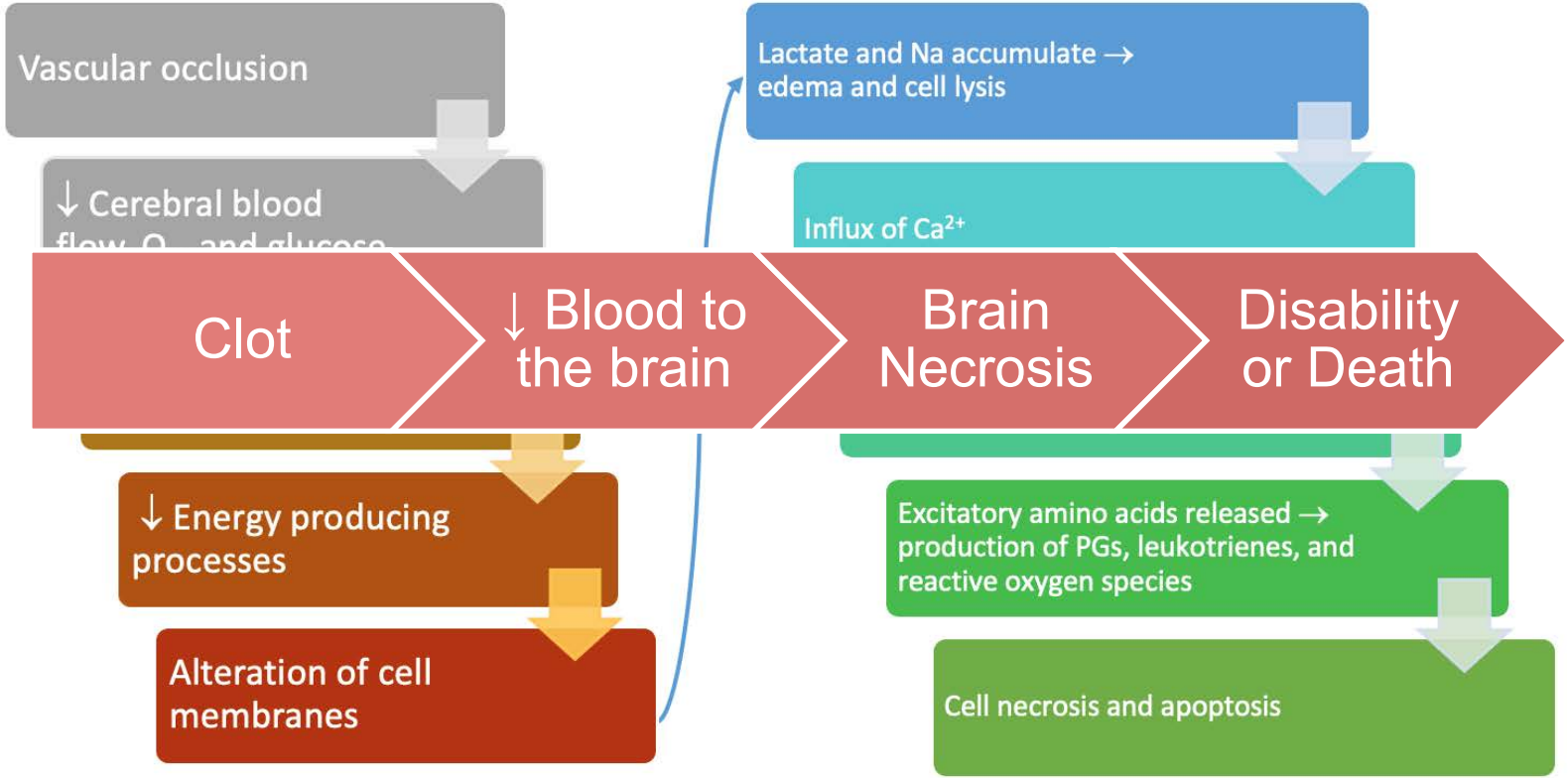


J Neurol Neurosurg Psychiatry. 2004;75(3):353-361

Acute Ischemic Stroke: Risk Factors

Non-Modifiable	Modifiable
• Age • Race • Sex • Low Birth Weight • Genetics	• Smoking • Hypertension • Diabetes • Dyslipidemia • A. Fib • Other Cardiac Diseases

Neurol Clin. 2008;26(4):871-vii

Signs and Symptoms of an Acute Ischemic Stroke

- Numbness or Weakness of the face, arms, or legs
- Confusion
- Trouble speaking
- Trouble seeing
- Trouble walking, dizziness, balance problems
- Severe headache

Arch Neurol. 2005;62(3):393-397.

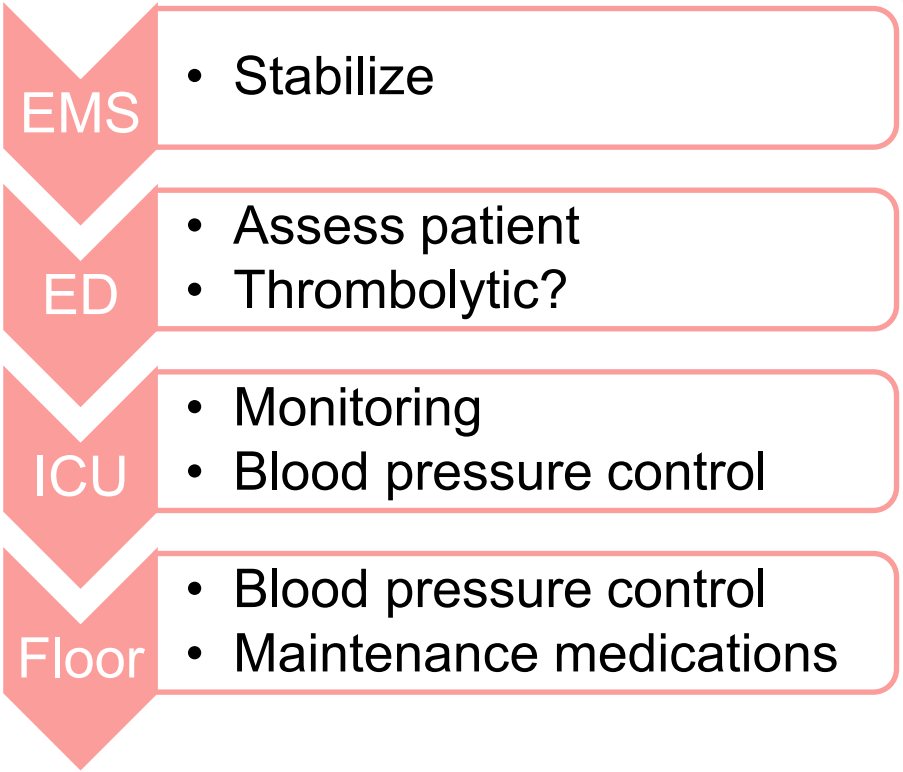
Knowledge check:
What does the ”T” in F.A.S.T stand for?

a) Taylor Swift
b) Taylor’s Version
c) Thrombolytic
d) Time

Management of Acute Ischemic Stroke

Timeline of events and assessment of fibrinolytic candidates

Management of an Acute Ischemic Stroke



Stroke. 2019;50(12):e344-e418.

Stroke Management Goals

Goal	Time
Door to MD/Stroke Team	≤ 15 minutes
Door to CT	≤ 20 minutes
Door to CT interpretation	≤ 45 minutes
Door to drug	≤ 45 minutes (up to 60 minutes)
Door to stroke unit	≤ 3 hours

Stroke. 2019;50(12):e344-e418.

Emergency Medical Services and in the ED

★ TIME!!! ★

- When did symptoms start?
- What is the PMH?

Airway, Breathing, Circulation

- Oxygen Saturation ≥94%

Stroke. 2019;50(12):e344-e418.

Emergency Medical Services and in the ED

Rule Out Other Causes

- Hypoglycemia
- Seizures
- Drug overdose or toxicities
- CNS tumor/abscess
- Infection
- Electrolyte disturbances

Stroke. 2019;50(12):e344-e418.

Emergency Medical Services and in the ED

Labs

- BMP
- CMP
- CBC
- Cardiac Markers
- IV dextrose for BG < 60mg/dL

Blood Pressure

- Fluids if hypotensive
- Anti-hypertensives:
  - If SBP >220mmHg (all patients)
  - Or < 185/110 (tPA candidates)

Stroke. 2019;50(12):e344-e418.

Emergency Medical Services and in the ED

Imaging

- Non-contrast Head CT
- MRI

NIHSS Score

- Evaluates patient acuity
- Helps treatment decision
- Predicts patient outcomes

Stroke. 2019;50(12):e344-e418.

NIHSS Score

- 11 item scale
- Each item is 3 - 5 points
- 0 is normal
- Higher score = worse outcomes

Item Number	Item Name	Scoring Guide	Patient Score
1B	LOC Questions	0=answers both correctly 1=answers one correctly 2=answers neither correctly	_____
1C	LOC Commands	0=performs both tasks correctly 1=performs one task correctly 2=performs neither task	_____
2.	Gaze	0=normal 1=partial gaze palsey 2=total gaze palsey	_____
3.	Visual Fields	0=no visual loss 1=partial hemianopsia 2=complete hemianopsia 3=bilateral hemianopsia	_____
5a.	Left Arm Motor	0=no drift 1=drift before 10 seconds 2=falls before 10 seconds 3=no effort against gravity 4=no movement	_____
5b.	Right Arm Motor	0=no drift 1=drift before 10 seconds 2=falls before 10 seconds 3=no effort against gravity 4=no movement	_____
6a.	Left Leg Motor	0=no drift 1=drift before 5 seconds 2=falls before 5 seconds 3=no effort against gravity 4=no movement	_____
6b.	Right Leg Motor	0=no drift 1=drift before 5 seconds 2=falls before 5 seconds 3=no effort against gravity 4=no movement	_____
8.	Sensory	0=normal 1=abnormal	_____
9.	Language	0=normal 1=mild aphasia 2=severe aphasia 3=mute or global aphasia	_____
11.	Neglect	0=normal 1=mild 2=severe	_____
		Score (out of 31):	_____

* Scoring from Original Scale

Stroke. 2019;50(12):e344-e418.

Acute Ischemic Stroke Treatment: Assessing for tPA Eligibility

Time of symptom onset:	History of anticoagulation:	Blood glucose:	Blood Pressure:
• ≤ 3 hours • ≤ 4.5 hours in select patients	• INR ≤ 1.7 • PT ≤ 15 seconds • No DOAC use within 48 hours	• Not hypoglycemic • BG >70	• SBP < 185 • DBP < 110

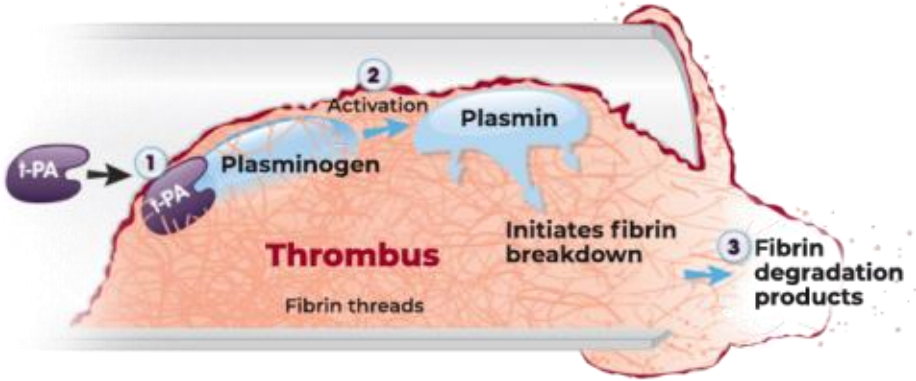
Stroke. 2019;50(12):e344-e418.

Knowledge Check:
NIHSS correlates with which of the following?

a) Functional outcomes of patient's who have had a stroke
b) Stroke severity
c) The risk of having a stroke in a patient with A. fib

Review of Fibrinolytics

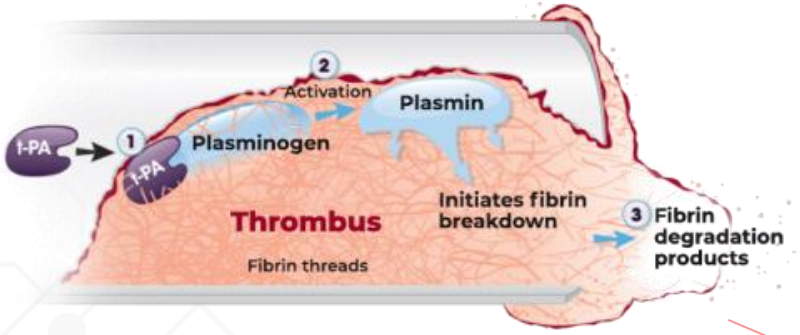
Drug	Alteplase (Activase)	Tenecteplase (TNKase)
$T_{1/2}$	5 min	10 – 24 min
Dosing	0.9mg/kg (max 90mg) • 10% IVB over 1 min • Remaining continuous IV over 60 minutes	0.25mg/kg (max 25mg) once as single IV bolus over 5 seconds
Adverse events	**BLEEDING**	



1 Recombinant t-PA (alteplase) bind to fibrin in thrombus
2 converting entrapped plasminogen to plasmin that
3 initiates local fibrinolysis.

Lancet. 2012;379(9834):2364-2372.

Fibrinolytics and the Coagulation Cascade



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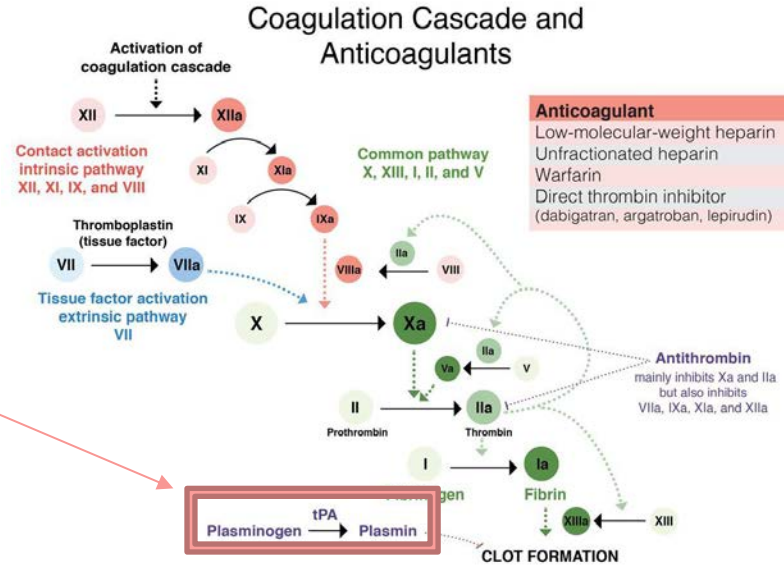
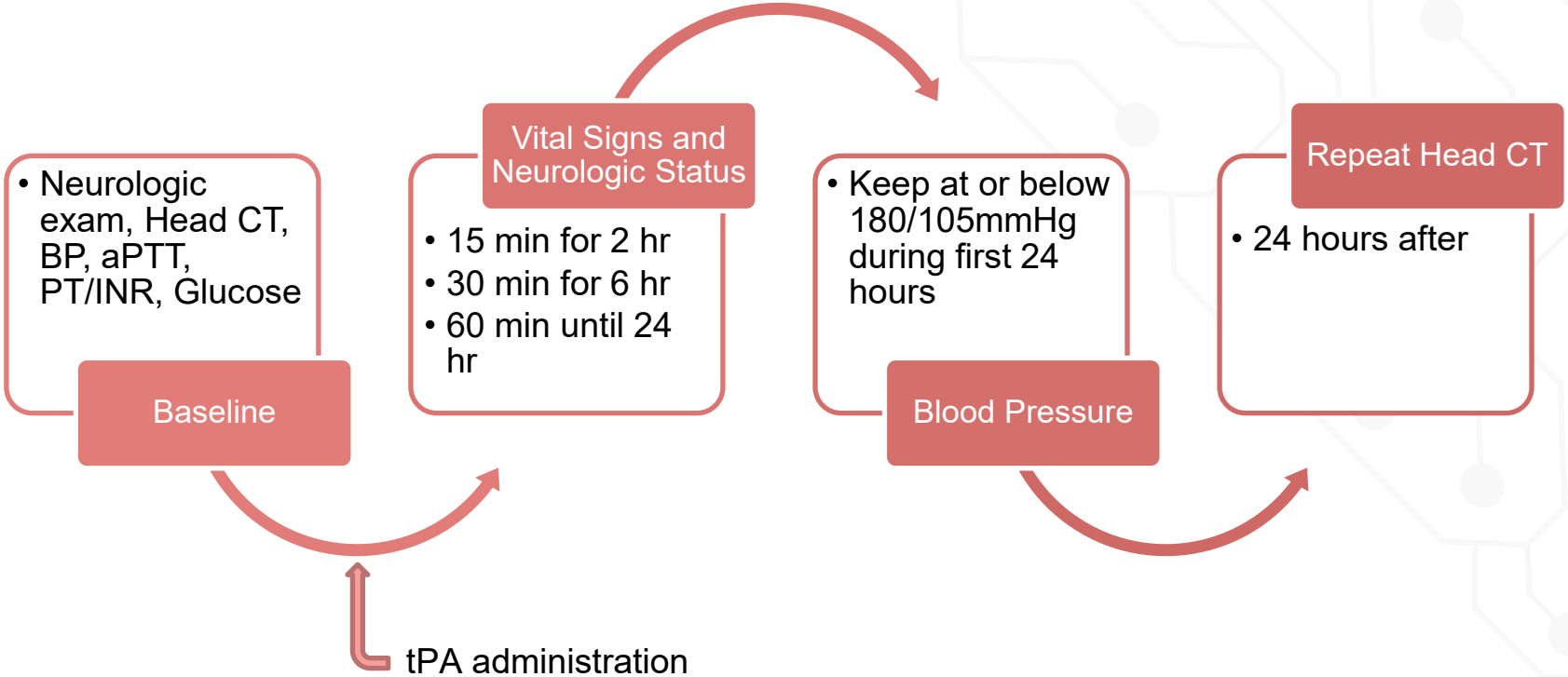


Anticoagulant	Factors inhibited
Low-molecular-weight heparin	Xa
Unfractionated heparin	IIa, Xa
Warfarin	IIa, VIIa, IXa, Xa
Direct thrombin inhibitor (dabigatran, argatroban, lepirudin)	IIa

Blood. 2016;128(1):104-109.

Lancet. 2012;379(9834):2364-2372.

Monitoring of Fibrinolytics



Lancet. 2012;379(9834):2364-2372.

Let’s Talk Fibrinolytic Outcomes

tPA Outcomes: The Good, The Bad, The Ugly

Emberson J et al. 2014 Meta-analysis: The Good

6756 Patients

tPA vs Placebo

Primary Outcome

Proportion of patients with mRS 0– 1

Time Frame	Results	Odds Ratio	NNT
≤ 3 Hours	33% v 23%	1.75 (95% CI 1.35-2.27)	**10!!**
3-4.5 Hours	35% v 30%	1.26 (95% CI 1.05-1.51)	20
>4.5 Hours	33% v 31%	1.15 (95% CI 0.95-1.40)	50

Lancet. 2014;384(9958):1929-1935.

Emberson J et al. 2014: The Bad and The Ugly

Safety Outcomes

Outcomes	Results	Odds Ratio	NNH
sICH	6.8% v 1.3%	5.55 (95% CI 4.01-7.70)	**18!!**
Fatal ICH within 7 days	2.7% v 0.4%	7.14 (95% CI 3.98-12.79)	44
Death at 90 days	17.9% v 16.5%	1.11 (95% CI 0.99-1.25)	-

Lancet. 2014;384(9958):1929-1935.

Emberson J et al. 2014: Takeaways

tPA is beneficial!

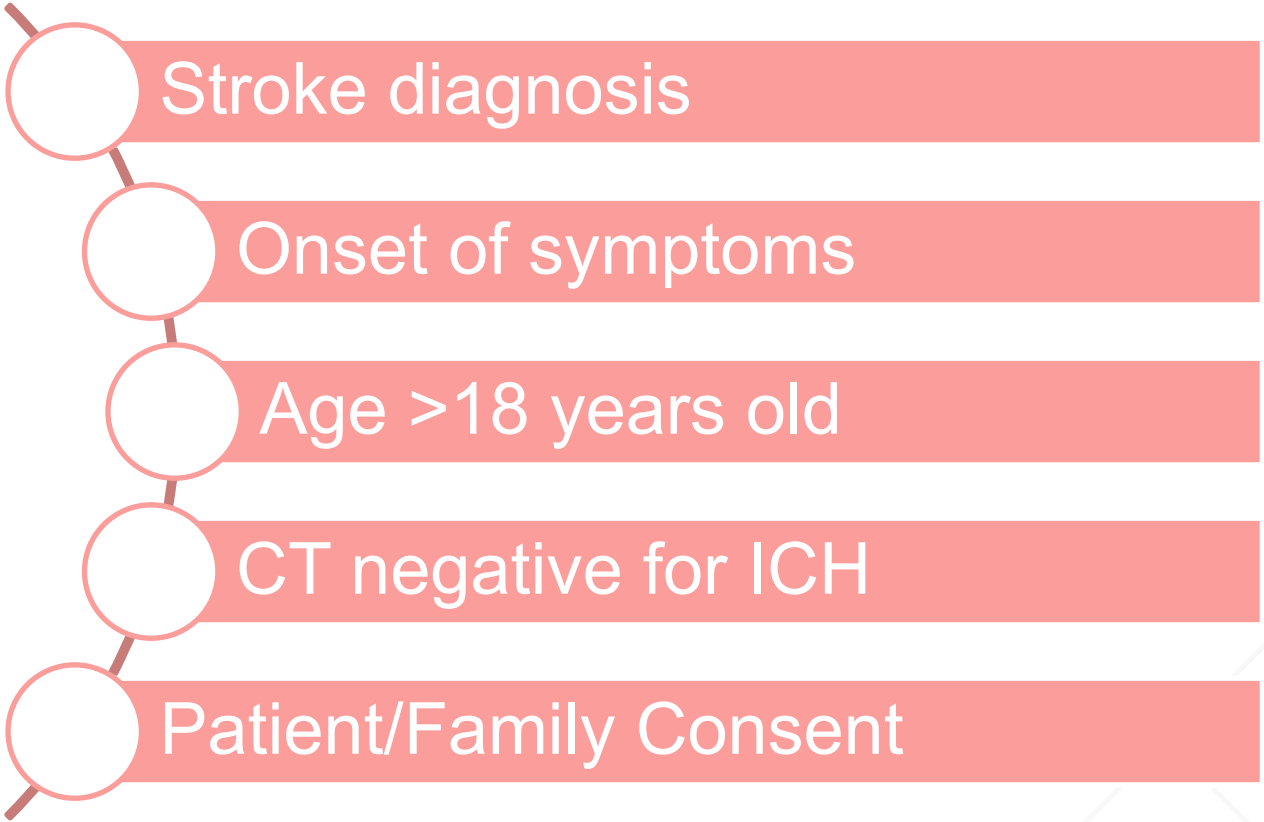
Regardless of the risk of ICH, age, severity, or treatment delay

No effect on mortality

Time from stroke onset to treatment matters

Lancet. 2014;384(9958):1929-1935.

tPA Inclusion Criteria



Stroke. 2019;50(12):e344-e418.

tPA Exclusion Criteria: ≤ 3 hours

Head

- Trauma or stroke within 3 months
- ICH or History of ICH
- Intracranial or Intraspinal surgery
- Multilobar infarctions on CT

Bleeding

- Arterial puncture in previous 7 days
- Active internal bleed
- Platelets < 100,000/mm^3

Stroke. 2019;50(12):e344-e418.

tPA Exclusion Criteria: ≤ 3 hours

Medications

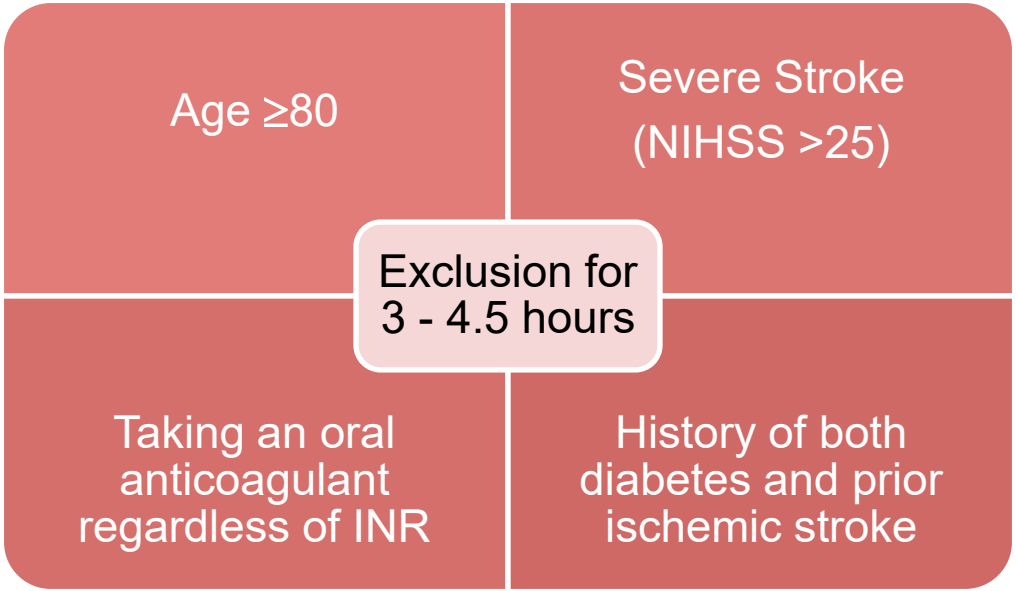
- Heparin within 48 hours with an elevated aPTT
- Anticoagulant use with INR >1.7, PT >15 seconds, or aPTT >40 seconds
- **Current use of DOAC within 48 hours**

Other

- Blood Glucose < 50mg/dL
- SBP >185mmHg or
- DBP >110mmHg

Stroke. 2019;50(12):e344-e418.

tPA Exclusion Criteria: 3 – 4.5 hours



Stroke. 2019;50(12):e344-e418.

Knowledge check:
Which of the following statements is true?

a) tPA has a mortality benefit
b) tPA has the highest benefit when given ≤ 3 hours from stroke onset
c) tPA is only beneficial in patients with stroke onset >4.5 hours

How did we reach these tPA exclusions?

And why do we exclude patients taking DOACs?

NINDS & ECASS III Trials

NINDS Exclusion Criteria	ECASS III Exclusion Criteria
• Stroke or serious head trauma within previous 3 months • Major surgery within 14 days • History of ICH or suspected SAH • SBP >185mmHg or DBP >110mmHg • Rapidly improving or minor symptoms • GI or GU bleeding within previous 21 days • Arterial puncture at noncompressible site within previous 7 days • Seizure at onset of stroke • Anticoagulants or anti-thrombotics within 48 hours preceding onset of stroke • Elevated PTT/PT or platelets <100k • Glucose <50 or >400 mg/dl	• ICH on CT or MRI • Symptoms of SAH even without signs on CT • Major ischemic infarct on CT or MRI • NIHSS score >25 • Seizure at onset of stroke • Unknown onset of symptoms or greater than 4.5 hours prior to drug administration • Symptoms minor or rapidly improving • Stroke or head trauma within 3 months • History previous stroke and diabetes • Heparin within past 48 hours and PTT greater than upper level of normal • Oral anticoagulant therapy • Platelets <100k • SBP >185, DBP >110 • Blood glucose <50 or >400mg/dl • Major surgery or trauma within 3 months • Other disorders associated with increased risk of bleeding

N Engl J Med. 1995;333(24):1581-1587.

N Engl J Med. 2008;359(13):1317-1329.

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3 Additional Questions...

What year was the NINDS trial published?

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When was the first DOAC approved?

3 Additional Questions...

What year was the NINDS trial published?

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What year was the ECASS III trial published?

2008

When was the first DOAC approved?

2010 (Dabigatran)

How are these exclusion criteria affecting patients taking DOACs?

Taking a look into the guidelines

Review of Oral Anticoagulants

Drug	MOA	PK	
		Peak (hr)	$T_{1/2}$ (hr)
Apixaban (Eliquis)	Factor Xa Inhibitor	~3 - 4	~12
Rivaroxaban (Xarelto)	Factor Xa Inhibitor	~2 - 4	~5 - 9
Edoxaban (Savaysa)	Factor Xa Inhibitor	~1 - 2	~10 - 14
Dabigatran (Pradaxa)	Direct Thrombin Inhibitor	~1	~12 - 17
Warfarin (Coumadin, Jantoven)	Vitamin K antagonist	~4	~40

Prescribing Practices of DOACs

DOACs vs Warfarin

- Similar/Superior efficacy
- ↓ Bleeding
- Easier monitoring

2014 - 2019

- DOACs Rx: ↑ 30%
- Warfarin Rx: ↓ 40%

Ischemic stroke risk

- 1 – 2% annual risk

J Am Heart Assoc. 2021;10(24):e022644.

Int J Stroke. 2014;9(1):71-78.

AHA/ACC 2019 Guidelines for Early Management of Acute Ischemic Stroke

IV tPA should not be administered to patients taking DOACs

- Unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal or

The patient has **not received a dose of these agents for >48 hours**

- Assuming normal renal metabolizing function

Stroke. 2019;50(12):e344-e418.

Options for DOAC monitoring

aPTT, TT, PT, Anti-Xa level

Qualitative Coagulation Assays: aPTT (25-37 seconds)

Dabigatran	• < 35: Usually not supratherapeutic; could be therapeutic • >35: May be therapeutic or supratherapeutic
Rivaroxaban Apixaban Edoxaban	• May be prolonged at peak concentration

Thromb Haemost. 2018;118(3):437-450.

Qualitative Coagulation Assays: PT (12-15 seconds)

Dabigatran	• Prolonged at peak concentrations
Rivaroxaban Edoxaban	• If normal: levels are not supratherapeutic or therapeutic • Could be a trough level
Apixaban	• May be prolonged at peak concentration

Thromb Haemost. 2018;118(3):437-450.

Qualitative Coagulation Assay: TT (15-19 seconds)

Dabigatran	• 14-19: no levels present • >19: levels are present, unable to determine “therapeutic-ness”
Rivaroxaban Apixaban Edoxaban	• No change

Thromb Haemost. 2018;118(3):437-450.

Qualitative Coagulation Assays: Strengths and Limitations

- Widely Available
- Fast turn-around
- TT useful with Dabigatran

- Not sensitive or specific
- TT not sensitive to Anti-Xa inhibitors
- Reagents affect results

Quantitative Assay: Anti-Xa Level

Calibration

- Calibrated to the specific DOAC for reliable level
- LMWH Anti-Xa is more reliable than UFH for DOAC levels

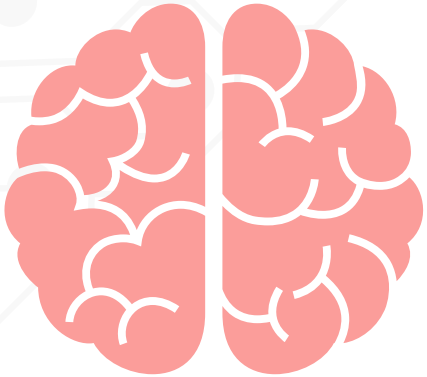
Limitations

- Not readily available
- Long turn-around time
- Concentration levels vary up to 40% with each DOAC

Thromb Haemost. 2018;118(3):437-450.

Knowledge check:
TT can be useful when predicting levels of which DOAC?

a) Apixaban
b) Rivaroxaban
c) Edoxaban
d) Dabigatran



What clinical characteristics should be assessed to determine eligibility of fibrinolytic treatment for an acute ischemic stroke in patients taking DOACs?

Literature Review

Use of Intravenous Recombinant Tissue Plasminogen Activator in Patients With Acute Ischemic Stroke Who Take Non–Vitamin K Antagonist Oral Anticoagulants Before Stroke

Xian Y et al. Circulation 2017

Xian Y et al.

Objective

- Determine if patients who take DOACs and treated with tPA are at a high risk for sICH

Study Design

- Retrospective, observational analysis from GWTG-Stroke Registry

Circulation. 2017;135(11):1024-1035.

Xian et al.

Inclusion Criteria

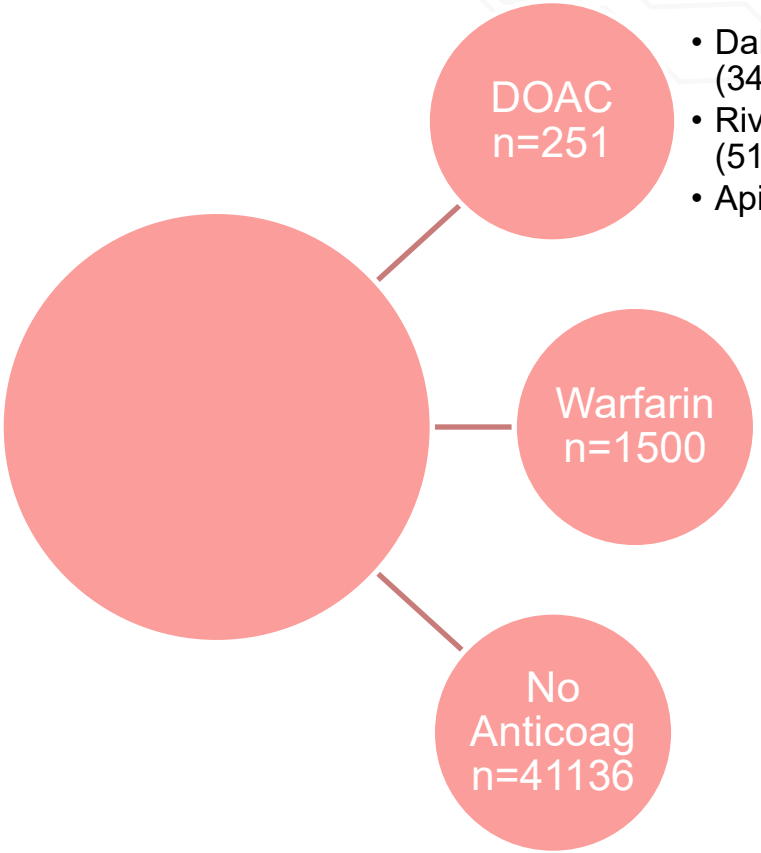
- Acute ischemic stroke treated with tPA
- Presented within 3.5 hours
- If on warfarin, INR <1.7

Exclusion Criteria

- Endovascular treatment
- Received tPA beyond 4.5 hours
- Missing information on anticoagulant or antiplatelet therapy
- Transferred in or out because of hospital care
- Treatment with heparin or another anticoagulant other than DOAC or warfarin

Circulation. 2017;135(11):1024-1035.

Xian et al.



- Dabigatran: 87 (34.7%)
- Rivaroxaban: 129 (51.4%)
- Apixaban: 35 (13.9%)

Circulation. 2017;135(11):1024-1035.

Xian et al. Results:

Baseline	DOAC	Warfarin	No anticoag
Age (median)	74	79	71
NIHSS scores (median)	**12 (6-18)**	**13 (7-19)**	9 (5-15)
INR (median)	1.1 (1.0-1.2)	1.2 (1.1-1.4)	
Time of symptom onset (median, min)	65 (50-88)	69 (54-91)	61 (47-83)
A. fib (n, %)	196 (78.1)	1159 (77.3)	7430 (18.1)
CAD/MI (n, %)	79 (31.5)	505 (23.7)	9705 (23.6)

Circulation. 2017;135(11):1024-1035.

Xian et al. Primary Outcome

Primary Endpoint	DOAC	Warfarin	No anticoag	Adj OR DOAC vs control (95% CI)	Adj OR warfarin vs control
sICH < 36 h	**12/251 (4.8%)**	73/1500 (4.9%)	**1587 (3.9%)**	**0.92 (0.51-1.65)**	0.85 (0.66-1.10)
Life-threatening hemorrhage	1/251 (0.4%)	14/1500 (0.9%)	347 (0.8%)	0.38 (0.05-2.71)	0.78 (0.45-1.37)
Any tPA complication	17/251 (6.8%)	152/1500 (10.1%)	3140 (7.6%)	0.64 (0.39-1.05)	0.90 (0.75-1.08)

Circulation. 2017;135(11):1024-1035.

Xian et al. Conclusions:

Strengths

- Triple group propensity score matching to adjust for baseline differences
- Analysis of patients on DOACs not chosen for tPA

Circulation. 2017;135(11):1024-1035.

Xian et al. Conclusions:

Limitations

- Retrospective, unblinded, observational analysis
- Small sample size for DOAC patients
- NIHSS score missing for 2.1%
- No data on last intake of DOAC
- Only collected INR, missing other coagulation measurements

Circulation. 2017;135(11):1024-1035.

Xian et al. Take away:

DOAC patients were older, had more severe strokes, and more comorbidities

After adjustment, DOAC use before tPA was not associated with increased sICH

Future studies should look at more patients, get timing of last DOAC intake, and collect more coagulation parameters

Circulation. 2017;135(11):1024-1035.

Association of Recent Use of Non-Vitamin K Antagonist Oral Anticoagulants with ICH Among Patients with Acute Ischemic Stroke Treated with Alteplase

Kam W et al. JAMA 2022

Kam W et al. Methods:

Objective

- Evaluate the safety and functional outcomes of tPA in patients taking DOACs prior to stroke and compare outcomes with patients who were not taking anticoagulants

Design

- Retrospective cohort study
- Utilized GWTG-Stroke Registry and ARAMIS Registry

JAMA. 2022;327(8):760-771.

Kam W et al. Methods:

Inclusion Criteria

- Age >18
- Ischemic stroke treated with tPA within 4.5 hours
- DOAC use within 7 days of stroke

Exclusion Criteria

- Taking warfarin
- Received tPA outside standard treatment guidelines
- In-hospital strokes
- Received tPA at outside-hospital
- Missing discharge information

JAMA. 2022;327(8):760-771.

Kam W et al. Outcomes:

Primary Outcome	• sICH within 36 hours after tPA administration
Secondary Safety Outcomes	• Inpatient Mortality • Life-threatening or serious systemic hemorrhage within 36 hours • Any tPA related complication
Secondary Functional Outcomes at Discharge	• Independent ambulation • Discharge location • Free of disabilities (mRS 0-1) • Functionally independent (mRS 0-2)

JAMA. 2022;327(8):760-771.

JAMA. 2022;327(8):760-771.

Kam W et al. Baseline Characteristics

Baseline Characteristics	Taking DOACs (n = 2207)	Not taking DOAC (n = 160,831)
Age, median (IQR), y	**75 (64-82)**	70 (58-81)
Atrial fibrillation or flutter, No. (%)	1614 (73.1%)	23458 (14.6%)
CAD or prior MI, No. (%)	624 (28.3%)	34823 (21.7%)
Heart Failure, No. (%)	421 (19.1%)	13801 (8.6%)
Prior Stroke, No. (%)	**628 (28.5%)**	32825 (20.4%)
Hypertension, No. (%)	1753 (79.4%)	115623 (71.9%)
Smoker, No. (%)	242 (11.0%)	**29045 (18.1%)**
Any antiplatelets, No. (%)	769 (34.8%)	73319 (45.6%)
Antihypertensives, No. (%)	1560 (70.7%)	83665 (52.0%)
Cholesterol reducers, No. (%)	1362 (61.7%)	68844 (42.8%)
National Institutes of Health Stroke Scale score, median (IQR)	**10 (5-17)**	7 (4-14)
Able to ambulate independently at admission, No. (%)	336 (27.0%)	**26740 (32.2%)**
Unable to abulate at admission, No. (%)	**573 (46.1%)**	32650 (39.3%)

Kam W et al. Primary Outcome

Endpoint, No. (%)	Taking DOAC (n = 2207)	Not taking DOAC (n = 160831)	OR (95% CI) Unadj	OR (95% CI) Adj	Adjusted absolute risk difference, % (95% CI)
sICH within 36 hours	**81 (3.7%)**	5129 (3.2%)	1.18 (0.94-1.47)	**0.88** (0.70-1.10)	-0.51 (-1.36-0.34)

JAMA. 2022;327(8):760-771.

Kam W et al. Secondary Outcomes

Endpoint, No. (%)	Taking DOAC (n = 2207)	Not taking DOAC (n=160831)	OR (95% CI) Unadj	OR (95% CI) Adjusted	Adjusted absolute risk difference, % (95% CI)
Life-threatening or serious systemic hemorrhage within 36 hr	16 (0.7%)	898 (0.6%)	1.28 (0.79-2.07)	0.95 (0.57-1.60)	-0.03 (-0.39-0.32)
Able to ambulate independently, No./total (%)	1008/1951 (51.7%)	83807/ 144751 (57.9%)	0.81 (0.74-0.88)	1.25 (1.12-1.40)	5.65 (2.91-8.40)
Free of disabilities (mRS score of 0-1)	372/1382 (26.9%)	34548/ 101554 (34.0%)	0.74 (0.65-0.83)	1.22 (1.06-1.42)	3.71 (0.91-6.52)

JAMA. 2022;327(8):760-771.

Kam W et al. ARAMIS Registry Outcomes

Endpoint, No. (%)	Overall (n = 47)	0 – 24 hr (n = 8)	0 – 48 hr (n=25)	>48 hr (n = 22)
Primary Outcome				
Symptomatic intracranial hemorrhage within 36 hr	2 (4.3%)	0	**2 (8.0%)**	0
Seconday Outcomes				
Life-threatening or serious systemic hemorrhage within 36 hr	0	0	0	0
Any alteplase complication	3 (6.4%)	0	3 (12.0%)	0
Inpatient mortality	2 (4.3%)	0	1 (4.0%)	1 (4.6%)
Able to ambulate independently at hospital discharge, No./total (%)	28/45 (62.2%)	5/8 (62.5%)	12/24 (50.0%)	16/21 (76.2%)

JAMA. 2022;327(8):760-771.

Kam W et al. Conclusions

Strengths

- Large(r) sample size
- Baseline characteristics adjusted via propensity-weighted overlap-weighting method
- Gave information on last intake utilizing ARAMIS registry

JAMA. 2022;327(8):760-771.

Kam W et al. Conclusions

Limitations

- Retrospective, observational analysis
- Selection bias in DOAC cohort
- Specific timing of last DOAC intake only available for small number of patients
- No drug-specific coagulation assays or other coagulation parameters

JAMA. 2022;327(8):760-771.

Kam W et al. Take aways

tPA use for ischemic stroke in patients with DOAC in take within 7 days appears to be safe

Data suggest no increased risk for sICH and favorable functional outcomes

Small number of patients with known last DOAC intake

Still need: more coagulation parameters and more information on timing of last DOAC intake

JAMA. 2022;327(8):760-771.

IV Thrombolysis in Patients With Ischemic Stroke and Recent Ingestion of DOACs

Meinel TR et al. JAMA Neurology 2023

Meinel TR et al. Methods

Objective

- Determine risk of sICH associated with use of IV tPA in patients with recent DOAC ingestion

Design

- Investigator-initiated, international, multicenter, retrospective analysis

JAMA Neurol. Published online January 03, 2023. doi:10.1001/jamaneurol.2022.4782

Meinel TR et al. Inclusion and Exclusion Criteria

Inclusion Criteria

- Age >18
- Ischemic stroke treated with tPA
- Confirmed ingestion of a DOAC within 48 hours

Exclusion Criteria

- Patients with known DOAC ingestion more than 48 hours before stroke

JAMA Neurol. Published online January 03, 2023. doi:10.1001/jamaneurol.2022.4782

Meinel TR et al. Interventions

Taking DOAC (n=832)

- DOAC plasma levels measured (n=225)
- No known DOAC level or use of idarucizumab (n=355)
- Use of idarucizumab (n=252)

Control

- Not taking anticoagulants (n=33207)

JAMA Neurol. Published online January 03, 2023. doi:10.1001/jamaneurol.2022.4782

Meinel TR et al. Baseline Characteristics

Baseline Characteristics	Recent ingestion of DOAC (n = 832)	Not taking DOAC (n = 32,375)
Age, median (IQR), y	**79 (71-85)**	72 (62-80)
Atrial fibrillation, No. (%)	608 (90.1%)	4008 (25.1%)
Arterial HTN, No. (%)	**565 (75.1%)**	20072 (62.2%)
Diabetes, No. (%)	**173 (23.2%)**	6311 (19.6%)
Antiplatelet therapy, No. (%)	88 (11.2%)	10383 (35.7%)
NIHSS score, median (IQR)	**11 (6-17)**	9 (5-16)
Prestroke mRS score, median (IQR)	0 (0-1)	0 (0-0)
Time from symptom onset to hospital admission, median (SD), h	**1.7 (1.0-2.6)**	1.3 (0.8-2.3)
Presence of large vessel occlusion	**454 (59.0%)**	10516 (32.6%)
Time from symptom onset to IVT, median (IQR), min	**153 (110-210)**	138 (98-190)

JAMA Neurol. Published online January 03, 2023. doi:10.1001/jamaneurol.2022.4782

Meinel TR et al. DOAC Sub-group Characteristics

DOAC Characteristics based on selection strategy, No. (%)	DOAC plasma levels measured (n=225)	Neither known levels nor idarucizumab (n=355)	Idarucizumab (n=252)
Dabigatran	15 (6.7%)	75 (21.1%)	252 (100%)
Rivaroxaban	119 (52.9%)	139 (39.2%)	0
Apixaban	73 (32.4%)	90 (25.4%)	0
Edoxaban	18 (8.0%)	50 (14.1%)	0
< 12 hours since intake	39 (17.3%)	73 (20.6%)	130 (51.6%)
12-24 hours since intake	48 (21.3%)	78 (22.0%)	32 (12.7%)
24-48 hours since intake	43 (19.1%)	59 (16.6%)	1 (0.4%)
aPTT, median (IQR), sec	29 (26-33)	30 (27-34)	37 (29-46)
TT, median (IQR), sec	16.6 (15.2-18.3)	14.6 (11.4-17.4)	81.4 (43.9-120.0)
DOAC plasma level, median (IQR), ng/mL	21 (4.6-46)	-	83 (27-134)

JAMA Neurol. Published online January 03, 2023. doi:10.1001/jamaneurol.2022.4782

Meinel TR et al. Primary

Outcomes, % (95%CI)	All DOAC Patients (n=832)	DOAC plasma levels measured (n=225)	Neither known levels nor idarucizumab (n=355)	Not taking DOAC (n=32035)	OR (95% CI) Unadj	OR (95% CI) Adjusted
Primary Outcome						
sICH within 36 hr	**2.5% (1.6-3.8)**	3.1% (1.3-6.3)	3.1% (1.6-5.5)	**4.1% (3.9-4.4)**	0.62 (0.40-0.96)	**0.57 (0.36-0.92)**

JAMA Neurol. Published online January 03, 2023. doi:10.1001/jamaneurol.2022.4782

Meinel TR et al. Secondary Outcomes

Outcomes, % (95%CI)	All DOAC Patients (n=832)	DOAC plasma levels measured (n=225)	Neither known levels nor idarucizumab (n=355)	Not taking DOAC (n=32035)	OR (95% CI) Unadj	OR (95% CI) Adjusted
Any hemorrhage on follow-up imaging within 36 hr	18.0% (15.4-20.9)	20.5% (15.4-26.4)	22.2% (18.0-26.9)	17.4% (16.9-18.0)	1.03 (0.85-1.24)	1.18 (0.95-1.45)
Functional independence at 90 days	45% (41-49)	40% (33-47)	44% (38-50)	57% (56-57)	0.62 (0.53-0.73)	1.13 (0.94-1.36)

JAMA Neurol. Published online January 03, 2023. doi:10.1001/jamaneurol.2022.4782

Meinel TR et al. Conclusions

Strengths

- Confirmed ingestion of DOAC
- Coagulation parameters
- Sensitivity and post-hoc Analyses
- Consistent results across different sensitivity analysis

JAMA Neurol. Published online January 03, 2023. doi:10.1001/jamaneurol.2022.4782

Meinel TR et al. Conclusions

Limitations

- Non-randomized, retrospective, observational analysis
- Selection bias
- Few patients with very recent ingestion
- 51 patients in DOAC group received Tenecteplase

JAMA Neurol. Published online January 03, 2023. doi:10.1001/jamaneurol.2022.4782

Meinel TR et al. Take away

Insufficient evidence of excess harm

COAGULATION PARAMETERS!

Provides options for clinicians to make decisions

Consistent results across sensitivity analysis and post-hoc analysis

Absolute CI vs. Relative CI

JAMA Neurol. Published online January 03, 2023. doi:10.1001/jamaneurol.2022.4782

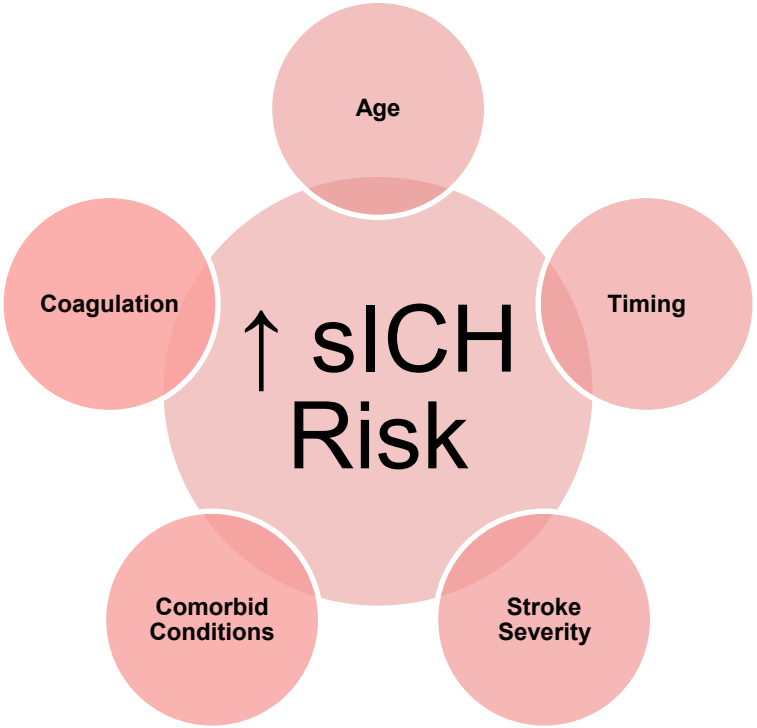
Literature Review Round Up

DOAC Patients	• ↑ risk factors for sICH • Adjusted sICH OR similar to control group
Timing	• No association between time of last intake to stroke
Future Studies	• RCT is ideal but comes with significant limitations • Selection Bias

My Recommendations

Patient Characteristics to Assess for the Use of tPA for Stroke While on a DOAC

Patient Characteristics to Assess



Who I would and would not recommend for tPA

tP-YAY

- Age < 80
- Stroke onset ≤ 3 hours
- NIHSS ≤ 19
- No/Few Comorbidities
- Anti-Xa level < 0.5 U/mL if available
- TT < 60 seconds (dabigatran)

tP-NAY

- Age ≥ 80
- Stroke onset ≥ 3.5 hours
- NIHSS ≥ 20 or Large Vessel Occlusion
- Multiple Uncontrolled Comorbidities

tP-YAY and tP-NAY Examples

tP-YAY

Age: 68

Stroke onset: 1.5 hours

Apixaban intake: 7 hr

NIHSS Score: 9

CT Scan: No Large Vessel Occlusion

History of **controlled HTN** and **Diabetes** (A1c 6%), CrCl 85 mL/min

INR 1.1, aPTT 37 sec, UFH Anti-Xa Level 0.8U/mL

tP-NAY

Age: 80

Stroke onset: 2.5 hours

Apixaban intake: 5 hr

NIHSS Score: 21

CT Scan: No Large Vessel Occlusion

Uncontrolled diabetes (A1c 10%), EF 20%, **CrCl 20 mL/min**, Non-adherence to lisinopril,

INR 1.1, aPTT 37 sec, UFH Anti-Xa Level 0.8U/mL

Post Test Questions

1. TS is a 60-year-old female weighing 113kg who arrives to the emergency department via EMS with concerns for a stroke with left-sided weakness and speech difficulty which was noted to start 60 minutes ago. The team assess TS and finds no contraindications to treatment with alteplase. What is the correct dose and administration of alteplase?

a. Total dose 102mg; 10mg IVB over 1 minute, then 92mg as continuous infusion over 60 minutes
b. Total dose 90mg; 9mg IVB over 1 minute, then 81mg as continuous infusion over 60 minutes
c. Total dose 102mg; 102mg IVB over 1 minute
d. Total dose 90mg; 90mg as continuous infusion over 60 minutes

2. HS is a 72-year-old male weighing 120kg with a PMH of recurrent DVTs (on warfarin) who presents to the emergency department with stroke symptoms that started 3 hours ago. The team assess HS for treatment with alteplase and finds the following: Head CT is negative for ICH, NIHSS score of 9, BMP is within normal limits, and has an INR of 1.5. After assessment, the time since stroke onset is 4 hours and the team wants to administer alteplase. As the pharmacist, will you verify this order?

a. No; alteplase treatment window between 3 – 4.5 hours is contraindicated due to warfarin use regardless of INR
b. No; alteplase treatment window between 3 – 4.5 hours is contraindicated due to NIHSS score of 9
c. Yes; alteplase treatment is appropriate for this patient
d. No; alteplase treatment window between 3 – 4.5 hours is contraindicated due to patient's age

3. Regarding the primary literature reviewed, the baseline characteristics of patients taking a DOAC who received treatment with alteplase for acute ischemic stroke compared to patients not on anticoagulants were:

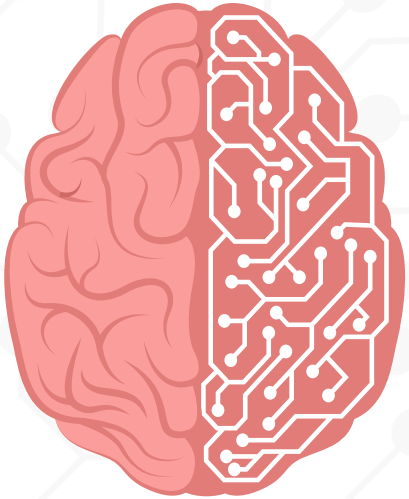
a. Similar to those who were not on anticoagulants
b. At less of a risk to develop sICH due to younger age, lower NIHSS scores, and fewer comorbidities
c. At a higher risk to develop sICH due to younger age, lower NIHSS scores, and fewer comorbidities
d. At a higher risk to develop sICH due to older age, higher NIHSS scores, and more comorbidities

4. TS is a 68-year-old female with a PMH of controlled diabetes, history of controlled HTN, and A. fib on apixaban 5mg PO twice daily. TS takes her daily medications at 7am every morning, and her twice daily medications at 7am and 8pm daily. At 2pm TS develops signs and symptoms of a stroke. TS arrives to the ED at 2:30pm. The stroke team assess TS and finds the following: head CT is negative for ICH, NIHSS score of 10, no suspicion for a large vessel occlusion, BMP is within normal limits, and has an INR of 1.1. The team asks you, the pharmacist, if TS should be treated with alteplase. Based on the treatment algorithm and primary literature, do you recommend alteplase?

a. Yes; tPA has a good functional outcomes and a mortality benefit, every patient should be treated with tPA
b. No; meets absolute contraindication to tPA
c. Yes; patient qualifies due to time of onset < 3 hours, controlled comorbidities, NIHSS < 20, no large vessel occlusion, and no ICH
d. No; time from last ingestion of DOAC to tPA is too short

Fibrinolytics for Acute Ischemic Stroke in Patients taking DOACs: tP-YAY or tP-NAY?

Markus Reedy, PharmD
PGY1 Pharmacotherapy Resident
University of the Incarnate Word Feik School of Pharmacy



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