# UPDATE ON STROKE: TNKase® (TENECTEPLASE)

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## Objectives

1. Review research done to support use of Tenecteplase in acute stroke management
2. Discuss advantages and contraindications of Tenecteplase use across patient populations
3. Explain administering and monitoring of Tenecteplase

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## Disclosures

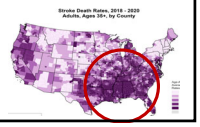
- TNKase® (Tenecteplase) is not FDA approved for the treatment of Acute Ischemic Stroke.

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## Stroke Statistics

- 5th leading cause of death in the U.S
- Nearly 800,000 people in the United States have a stroke annually
  - Of those, over 600,000 thousand are new strokes
- Someone in the United States has a stroke every 40 seconds
- Someone dies of a stroke every 3.5 minutes
- In 2017 and 2018
  - stroke related cost were close to **$53 billion** dollars
- Stroke is the leading cause of preventable adult long-term disability




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## Types of Stroke

- **Ischemic Stroke (~87% of strokes)**
  - Accounts for 87% of strokes

Arterial occlusion of either large or small perforating arteries

Large vessel occlusion (LVO) is the most severe form of ischemic stroke resulting in devastating neurologic disability; treated by both tissue plasminogen activator (tPA) drugs (alteplase or TNK) and thrombectomy; unsuccessful reperfusion may require extreme treatment by hemicraniectomy to prevent herniation and death

Small vessel occlusions (lacunar stroke) can be treated by tPA drugs

- **Hemorrhagic Stroke (~13% of strokes)**
  - **Non-structural hemorrhages: Intracerebral or Intraparenchymal Hemorrhage**

Mostly caused by poorly controlled blood pressure; use of **DOACs** is an important contributor

- Adequate blood pressure control while on anticoagulants is important

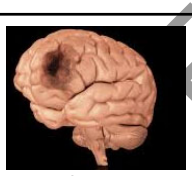
  - **Structural hemorrhages: Aneurysmal Subarachnoid Hemorrhage (aSAH) and Vascular Malformations** (VM)

Weakened or abnormal blood vessels that rupture causing brain hemorrhage;

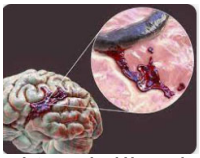
aSAH is much more common than VM and is associated with hypertension and smoking, as well as genetic causes

VM are most seen in the form of arteriovenous malformations (AVM)

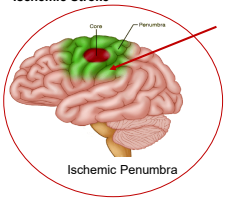
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Ischemic Stroke



Intracerebral Hemorrhage




Ischemic Penumbra



Subarachnoid Hemorrhage

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## Stroke Care Improving Over Time


The New York Times

- 1937: 3rd leading cause of death in the U.S
- 1995: National Institute of Neurological Disorders and Stroke
  - (NINDS rt-PA Stroke Study + for AIS treatment with alteplase)
    - AIS treated with IV-tPA in the first 3hrs had better outcomes at 3mths

As compared with patients given placebo, patients treated with t-PA were at least 30% percent more likely to have minimal or no disability at three months on the assessment scales

- 1996: FDA Approved the use of IV Alteplase in acute ischemic stroke < 3 hours from onset
- 2008: 4th leading cause of death in the U.S
- 2014 – now: 5th leading cause of death in the U.S.

**Alteplase: Treatment for Acute Ischemic Stroke since 1996**

ACTIVASE® ALTEPLASE

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## Thrombolytics in Acute Stroke Treatment

ACTIVASE® ALTEPLASE

Tissue plasminogen activator (tPA)

- Activase and Tenecteplase
  - Causes conversion of plasminogen to plasmin (main enzyme that dissolves blood clots)
- Binds to fibrin on the clot's surface (*Fibrin is the main component of a clot)*
  - ➢ Activates fibrin-bound plasminogen
    - ➢ Plasmin is cleaved from the plasminogen associated with the fibrin
      - ➢ Fibrin molecules are broken apart by the plasmin and the clot dissolves

TNKASE® TENECTEPLASE




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## Review of Literature : TNK and Stroke

**Several trials comparing Alteplase to Tenecteplase**

- Dose escalation trials
- Tempo-1
- EXTEND-IA TNK
- EXTEND-IA TNK 2
- TNK-SB
- TAAIS trial
- ATTEST
- NOR-TEST
- NOR-TEST 2
- TASTE-A
- Twist
- ACT
- TRACE

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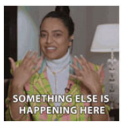
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## Review of Literature : TNK and Stroke

| Study | Year | Purpose | N | Design | TNK Dose | Results |
|---|---|---|---|---|---|---|
| A Pilot Dose-Escalation Safety Study of Tenecteplase in Acute Ischemic Stroke | 2005 | Determine best dose of TNK in AIS | 88 | Dose Escalation | 0.1, 0.25, 0.4, 0.5 mg/kg | Doses ≤ 0.4mg were safe.<br>0.5mg/kg arm stopped b/c sICH |
| **ATTEST**<br>Alteplase versus tenecteplase for thrombolysis after ischaemic stroke a phase 2, randomised, open-label, blinded endpoint study | 2015 | Assess safety and efficacy of TNK vs Alteplase within 4.5hrs of onset | 71 | RCT, open-label, single center, blinded outcome | 0.25mg/kg | No difference in salvageable penumbra at 24-48 hrs. or safety |
| **NOR-TEST**<br>Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial | 2017 | Investigate the safety and efficacy of alteplase vs Tenecteplase<br><br>.4mg/kg Tenecteplase<br>0.9mg/kg alteplase | 1100 | RCT, open-label blinded outcome | 0.4mg/kg | Tenecteplase was not shown to be superior to alteplase for treatment of acute ischemic stroke<br><br>Safety was similar |
| **EXTEND-IA TNK**<br>Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke | 2018 | Compare TNK to Alteplase in establishing reperfusion prior to thrombectomy when given within 4.5 hrs of LKWT | 202 | RCT, open-label, blinded outcome | 0.25mg/kg | Better outcomes at 90 days with TNK and sICH rate the same<br>TNK associated with better reperfusion |
| **(EXTEND-IA TNK) 2**<br>Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke<br>The EXTEND-IA TNK Part 2 Randomized Clinical Trial | 2020 | Determine if 0.4mg/kg TNK is more effective than 0.25mg/kg TNK in establishing reperfusion if given within 4.5 hrs of symptoms<br>Large Vessel Occlusion | 300 | RCT, open-label blinded outcome | 0.25, 0.4mg/kg | No differences.<br>0.40-mg/kg dose of tenecteplase did not significantly improve reperfusion over 0.25-mg/kg |
| **ACT**<br>Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (ACT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial | 2022 | Determine non-inferiority of TNK vs alteplase | 1600 | RCT, open-label | 0.25mg/kg | TNK 0.25mg/kg is comparable to alteplase |

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## TNKase® (Tenecteplase)




ACUTE ISCHEMIC STROKE

FDA approved as a single-bolus thrombolytic in myocardial infarction since 2000







- Currently, not FDA approved for Acute Ischemic Stroke







Majority of clinical trials to evaluate treatment in AIS were done outside of the United States

TNKASE®
TENECTEPLASE

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## Ongoing Trials: TNK and Stroke

- Timeless
- Tempo 2
- Eternal

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## Why the switch to TNKase® (Tenecteplase)

- Wasn't shown to be inferior to Alteplase in clinical trials
  - 2022 Prospective registry-based study: 10 hospital network: ↓ DTN, favorable clinical outcomes at discharge, and ↓ hospital cost
- Advantages in workflow
  - Longer half life-Single bolus over 5 seconds
    - Alteplase ~ 5min vs Tenecteplase ~ 90-130 mins
  - No intravenous infusion pump needed
    - Alteplase 10% over 1 minute , 90% over 1 hour
  - 1-time saline flush after administration
    - Alteplase 50ml saline bag to run at the same rate of the infusion
  - Shorter time to prepare
- Cost less than alteplase
- Off label use in many facilities

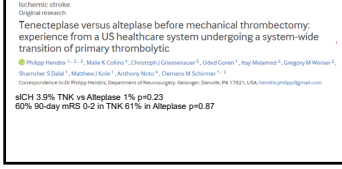
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## Review of Literature : TNK and Stroke



Functional Outcome, Recanalization, and Hemorrhage Rates After Large Vessel Occlusion Stroke Treated With Tenecteplase Before Thrombectomy

sICH 2.5%
47% 90-day independence mRS 0-2



Ischemic stroke
Original research
Tenecteplase versus alteplase before mechanical thrombectomy: experience from a US healthcare system undergoing a system-wide transition of primary thrombolytic

sICH 3.9% TNK vs Alteplase 1% p=0.23
60% 90-day mRS 0-2 in TNK 61% in Alteplase p=0.87

Routine Use of Tenecteplase for Thrombolysis in Acute Ischemic Stroke

sICH 1.8% vs 2.7%
61% vs 57% 90-day independence

BRIEF REPORT

Switching to Tenecteplase for Stroke Thrombolysis

Real-World Experience and Outcomes in a Regional Stroke Network

sICH 1.8% TNK vs 3.4% Alteplase-non-significant difference
TNK greater odds of a favorable outcome

Prospective Observational Cohort Study of Tenecteplase Versus Alteplase in Routine Clinical Practice

sICH 1.7% TNK vs 2.8% Alteplase
Non-inferior favorable outcome at discharge

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## Stroke Risk

Stroke can happen to anyone at anytime!

- Hypertension # 1 controllable risk factor for stroke
  - May be able to prevent up to 80% of strokes with good BP control
    - Better management of blood pressure, especially in the African American community
- Diabetes
  - Too much glucose over time can lead to clots or fatty deposits in blood vessels
- Atrial Fibrillation (clot travels to the brain)
  - Paroxysmal atrial fibrillation is a significant contributor
  - Patients with LVO cortical stroke and no evidence of atherosclerosis or frank AF should be provided with a loop recorder for long term monitoring
- Atherosclerosis (hardening of the arteries)
  - Plaque builds up over time, rupture, leads to clots blocking blood vessels in the brain
  - Smoking accelerates plaque progression

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## Stroke Risk

Risk of Stroke After Cardiac Procedures

- Stroke after CABG ≈1.3%
  - Usually occur in the first 7 to 10 days
- Percutaneous Coronary Intervention- stroke risk is ≈ 0.2% to 0.5%
  - Peak of risk in the first week
    - Highest risk within the first 48 hours
    - Compressible site, so treatment with tPA is important and can be successful although clot morphology may limit reperfusion (e.g., calcified material)

**Patients with stroke shown to have poorer outcomes

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## Understanding Your Role

- Recognize
  - Medical Emergency
  - 1.9 million brain cells die each minute during a stroke

***BEFAST***

**B**alance: Sudden onset of loss of balance, dizziness
**E**yes: Vision changes
**F**ace: Facial asymmetry
**A**rms: Weakness
**S**peech: Trouble speaking
**T**ime: Time to get help!



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## Time Interval Goals

- Door to Needle ≤45 mins
  - Door to ED Doctor ≤ 5mins
  - Door to Stroke Team ≤10mins
  - Door to CT/CTA* ≤20mins
  - Door to CT/CTA* Interpretation ≤35 mins



*The new Ideal Foundations" AHA/AHA Scientific Statement suggests that all patients with suspected ischemic or hemorrhagic stroke should undergo BOTH noncontrast CT/CTA immediately upon recognition of neurologic deficit

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## Understanding Your Role

- Time last seen without any deficits (Last Known /symptom onset)
  - Are symptoms consistent?
- Patient Medical History
- Vascular risk factors
- Medications
- Allergies

**Time from onset to treatment has an impact on outcomes

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## What Happens Next

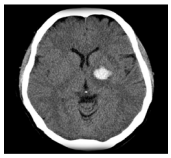
All Hands-On Deck!!

- IV access
- Stroke Scale Assessment
- Obtaining history from patient/family, witness, and/or medical record
- Pharmacist checking medication history in the system
- Lab draws
  - Glucose
- Non-contrast CT of the brain
  - Looking for any blood
  - Advanced Imaging to look at larger vessels in the brain

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## What Happens Next





- Imaging read
- Decision to treat or not to treat-based exclusion criteria
- TNK mixed
- Administered
- Monitoring begins

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## FDA Approved Inclusion and Exclusion Criteria for Alteplase – Note: most programs also use these for TNK

**Inclusion criteria**

- Clinical diagnosis of ischemic stroke causing neurological disability (can treat an NIHSS score of 0)
- Noncontrast CT negative for hemorrhage
- Within 3.0 hours of symptom onset or baseline (note: Guidelines suggest treatment out to 4.5 hours consistent with 2008 ECASS-3 findings that demonstrated efficacy)

*There are no restrictions by age on the label!*

**Exclusion criteria**

- Current intracranial hemorrhage, subarachnoid hemorrhage or active internal bleeding
- Recent (within 3 months) intracranial or intraspinal surgery or serious head trauma
- Structural vascular conditions that may increase the risk of hemorrhage (i.e., known aneurysm, VM, or brain neoplasm)
- Bleeding diathesis including medication induced anticoagulation
- Severe uncontrolled blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg) - use continuous infusion dihydropyridine calcium channel blocker agents

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## Mixing TNKASE® (TENECTEPLASE)

**TNKASE® (TENECTEPLASE)**

- Draw up **10ml** of **sterile water** with the syringe
- Inject the **10ml** into the TNKase 50mg vial. Gently SWIRL, do not shake
- Concentrate becomes **5mg/ml**
- Draw up the correct volume based on patient's weight
- Discard any unused solution



****Key Point**

TNKASE® (TENECTEPLASE) IS NOT APPROVED FOR REIMBURSEMENT IF MIXED DOSES ARE NOT USED

**DOSE FOR TNKASE® (TENECTEPLASE)**

- 0.25 MG/KG (MAX DOSE IS 25MG)

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## TNKASE® (TENECTEPLASE) ADMINISTRATION

**TNKASE® (TENECTEPLASE) SHOULD ONLY BE GIVEN IN PATIENTS WITH A LAST KNOWN WELL TIME OF ≤ 4.5 HOURS**

**DOSE FOR TNKASE® (TENECTEPLASE)** 0.25 MG/KG (MAX DOSE IS 25MG)

- Review the inclusion/exclusion criteria with the Physician
- Determine the correct dose based on patient's weight (0.25 MG/KG - MAX DOSE IS 25MG) and verify dose with another nurse or pharmacist
- If the patient's IV contains dextrose, flush the line with a saline solution prior to and after administration. (Dextrose causes precipitation of TNKase).
- Give as an IV bolus over 5 seconds.
- Flush the line after bolus and document it on the MAR

PRIOR TO ADMINISTRATION

Obtain weight
Obtain Neuro Assessment no more than 15 minutes prior to bolus
Obtain BP no more than 15 minutes prior to bolus **BLOOD PRESSURE** GOAL IS **< 185/110**

AFTER ADMINISTRATION **BLOOD PRESSURE** GOAL IS:

- **B/P < 180/105**

**TREAT ELEVATED BLOOD PRESSURE WITH A **NICARDIPINE INFUSION** (TITRATE UP TO 15MG/HR)
IF NICARDIPINE IS NOT IMMEDIATELY AVAILABLE, YOU MAY GIVE A 10MG DOSE OF LABETALOL IV PUSH.

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## Administering and Monitoring

Blood Pressure Control

- Higher blood pressures increases the risk of hemorrhage
- Variability in blood pressure increases the risk of hemorrhage
- BP limits were "guestimations" that originated from the NINDS rt-PA Stroke Study; we still don't know precisely how low or high we should go
  - Pre IV thrombolytic therapy: < 185/110 mm Hg
  - Post IV thrombolytic therapy: < 180/105 mm Hg
    - Once a thrombolytic agent is given, BP should *never again* exceed these limits throughout the entire hospitalization

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## Administering and Monitoring

**Blood Pressure Control**

**Management Originating from the NINDS rt-PA Stroke Trial (1991-1995):**

- Labetalol 10–20 mg IVs over 1–2 min, repeat every 5 minutes to a total dose of 150 mg
  - Doesn't last long
  - Associated with tremendous BP variability
  - If you've had to give it more than once to control BP, switch to a better agent!

**Dihydropyridine Calcium Channel Blockers are supported by the best evidence for adequate BP control!**

- Nicardipine 5 mg/hr IV
  - Titrate up by 2.5 mg/hr every 5–15 min
    - Max dose: 15 mg/hr
- Clevidipine 1–2 mg/h IV
  - Titrate by doubling the dose every 2–5 min until desired BP reached;
    - Max dose of 21 mg/h
- Note: dihydropyridine calcium channel blocker infusions are rapid acting with extremely short half-lives; once they are turned off, they stop working; titrate to maintain BP within safe limits

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## Administering and Monitoring

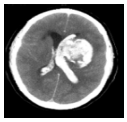
- Monitor BP and Neurological assessment
  - Every 15 min for 2 hours
  - Then every 30 min for 6 hours
  - Then every hour for 16 hours
- Oxygen Saturation
  - Keep 02 sat >94%
- 24 hr follow-up CT or MRI scan before starting antiplatelets or anticoagulants
- Delay placement of foleys, NGTs, or intra-arterial pressure catheters if the patient can be managed without them

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## Administering and Monitoring

- Symptomatic Intracerebral Hemorrhage (sICH)
  - Sudden neurological deterioration
  - Nausea/Vomiting
  - Severe headache
  - Worsening of preexisting symptoms already present



- Bleeding
  - Ecchymosis, petechiae, abdominal and/or flank pain, hemoptysis
  - Gingival oozing
  - Hematemesis

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## Administering and Monitoring

**Managing sICH**

- PT (INR), aPTT, CBC, fibrinogen level, and type and cross-match
- Emergent CT of the head
- Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min
  - 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
- Hematology and neurosurgery consultations
- Supportive therapy: BP management, ICP, CPP, MAP, temperature, and glucose control

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## Administering and Monitoring

- Orolingual Angioedema
  - Swelling of the lips
  - Swelling of the gums
  - Swelling of the throat and/or tongue



***More common in African Americans and patients taking ace-inhibitors*

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## Administering and Monitoring

**Managing Orolingual Angioedema**

- Rapid progression of edema may require intubation
- IV methylprednisolone 125 mg
- IV diphenhydramine 50 mg
- Ranitidine 50 mg IV or famotidine 20 mg IV
- If further progression in angioedema, give epinephrine (0.1%) 0.3 mL SQ or by nebulizer 0.5 mL
- Supportive care

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## Things to Remember

- Early recognition –BEFAST
- Stroke is a medical emergency
- Activate the stroke team – physician permission is not needed!
- **Last Known Well Time /Symptom onset**
- NO blood on CT Scan
- Meets inclusion criteria
- If no exclusion criteria
  - TNK bolus
- Close monitoring

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## Case Scenario

- Julie is a 64 yr. old female with a past medical history of CAD, HTN, and high cholesterol
- Presented to the hospital for a diagnostic heart cath for unstable angina
- There were no neurological issues immediately following the procedure at 4:30pm
- Her speech was normal and there were no neurological issues at 5:15pm
- The nurse returns at 5:30pm and notices L sided weakness and slurred speech
- Blood pressure is 170/88 mm Hg; NSR

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## What Would You Do Now?

- Check blood glucose
- Notify primary MD
- Activate Code Stroke
- Be prepared to provide the last known well/symptom onset time to the stroke team
- Be prepared to give a brief history of present illness
  - Diagnostic heart cath
- Current medications
  - No anticoagulants at home
- Transport to CT Scan and obtain BOTH a noncontrast CT and a CTA (arch, neck, head)

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## Question

What last known well time/symptom onset would you report to the stroke team?

- 4:30pm
- 5:15pm
- 5:30pm

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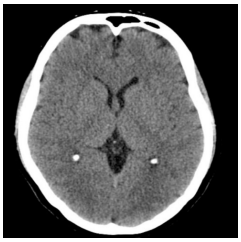
## In the meantime,……

- Neurologist or Advanced Practice Provider
  - Obtaining more history from the stroke team nurse
    - Initial stroke score NIHSS 3
  - Cardiologist that did the procedure reports that
    - Some bleeding noted at groin site
    - Low dose heparin given during the procedure
  - Neurologist or APP arrives at bedside
    - Exam is worse
    - Stroke score now 6 (was 3)
      - Worsening of arm weakness and dysarthria

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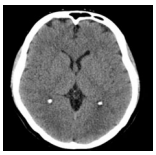
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## CT of the Brain at time of event



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## Do you think Julie can get TNK?



- Yes
- No

- LKWT 5:15pm
- Stroke Team at bedside
- Diagnostic heart cath with some bleeding noted at puncture site and low dose heparin during the procedure
- No blood on Cat Scan
- BP 170/80

**Any Contraindications**?

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## Can Julie receive TNK?

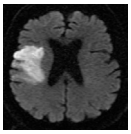
- There are no absolute contraindications
- Cardiologist and Neurologist discussed the case
  - Cardiologist does not think that there are any major risk
- No blood on CT
- Discuss risk, benefits, alternatives with patient/family
- Patient and family agrees to treatment
- Stroke team nurse gives TNK
  - Transport patient to designated stroke unit or ICU
  - Monitor puncture site
  - Initiate Post IV Thrombolytic monitoring

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## TNK Follow Up

- 24-hour MRI did show a stroke



- There was no hemorrhage on repeat imaging
- Julie states that her symptoms have improved

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## In Conclusion

- Stroke is a medical emergency
- Early recognition is important for outcomes
  - BEFAST
  - Educate our colleagues and our community
- TNK has been shown to be effective in establishing reperfusion in at- risk brain tissue and can be given safely
- More clinical trials are needed and are ongoing to evaluate its use in all AIS patients
- Blood pressure control is important pre and post TNK
- Post procedures is not always a contraindication to treatment
  - Provider collaboration is needed

**Early recognition and treatment leads to better outcomes!**

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## Acknowledgments


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