Thrombolysis in Acute Ischemic Stroke

ERICA N KRANTZ, PHARMD, BCCCP

ASCENSION VIA CHRISTI ST. FRANCIS
November 2021

Disclosures

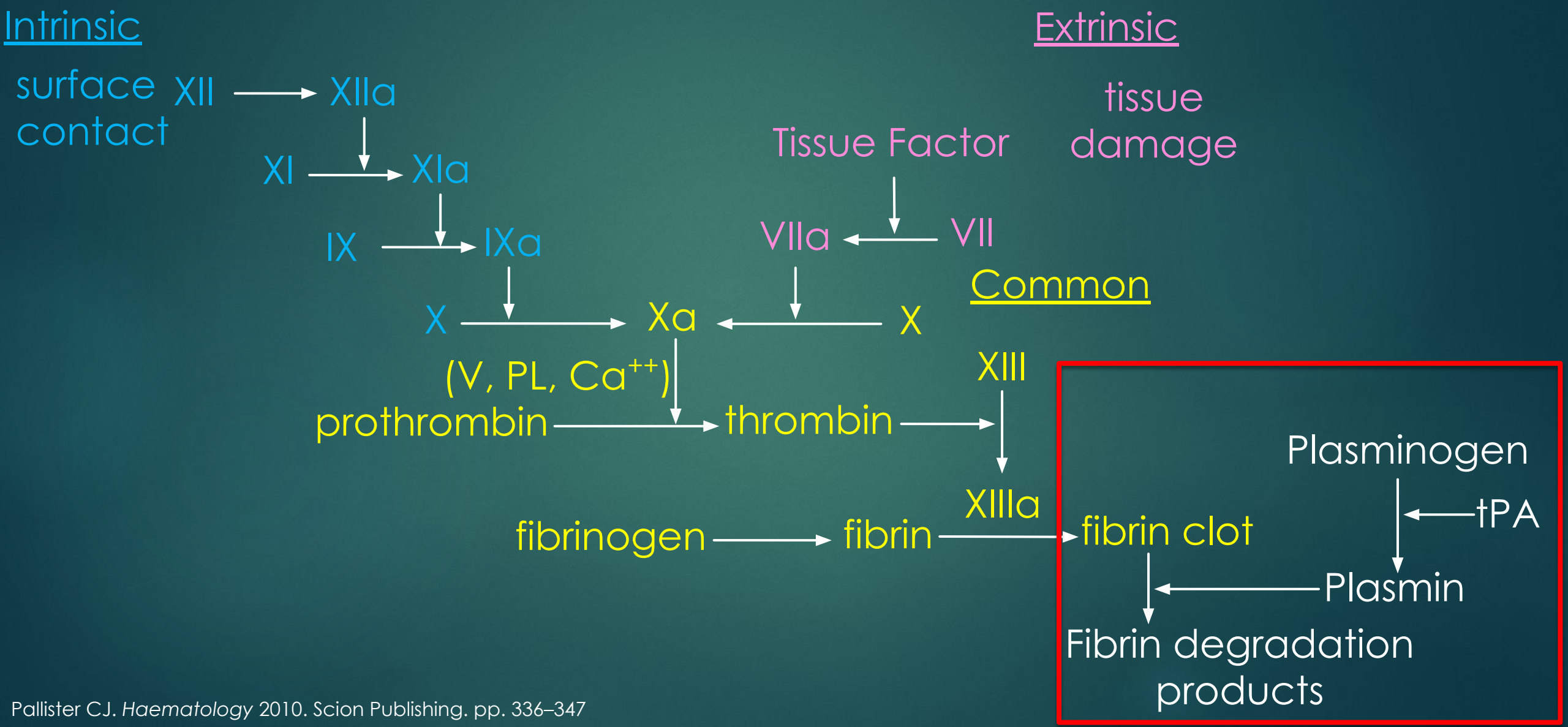
- I have no relevant financial relationships with any ACCME-defined commercial interest* to disclose
- I intend to reference the following off-label or investigational use of drugs or products in my presentation: Tenecteplase

*A commercial interest is any entity producing, marketing, re-selling, or distributed health care goods or services consumed by, or used on, patients

Objectives

- Identify thrombolytic treatment options for an acute ischemic stroke (AIS)
- Evaluate literature for tenecteplase use in AIS
- Summarize AIS guideline recommendations
- Develop a hospital implementation strategy to switch AIS treatment

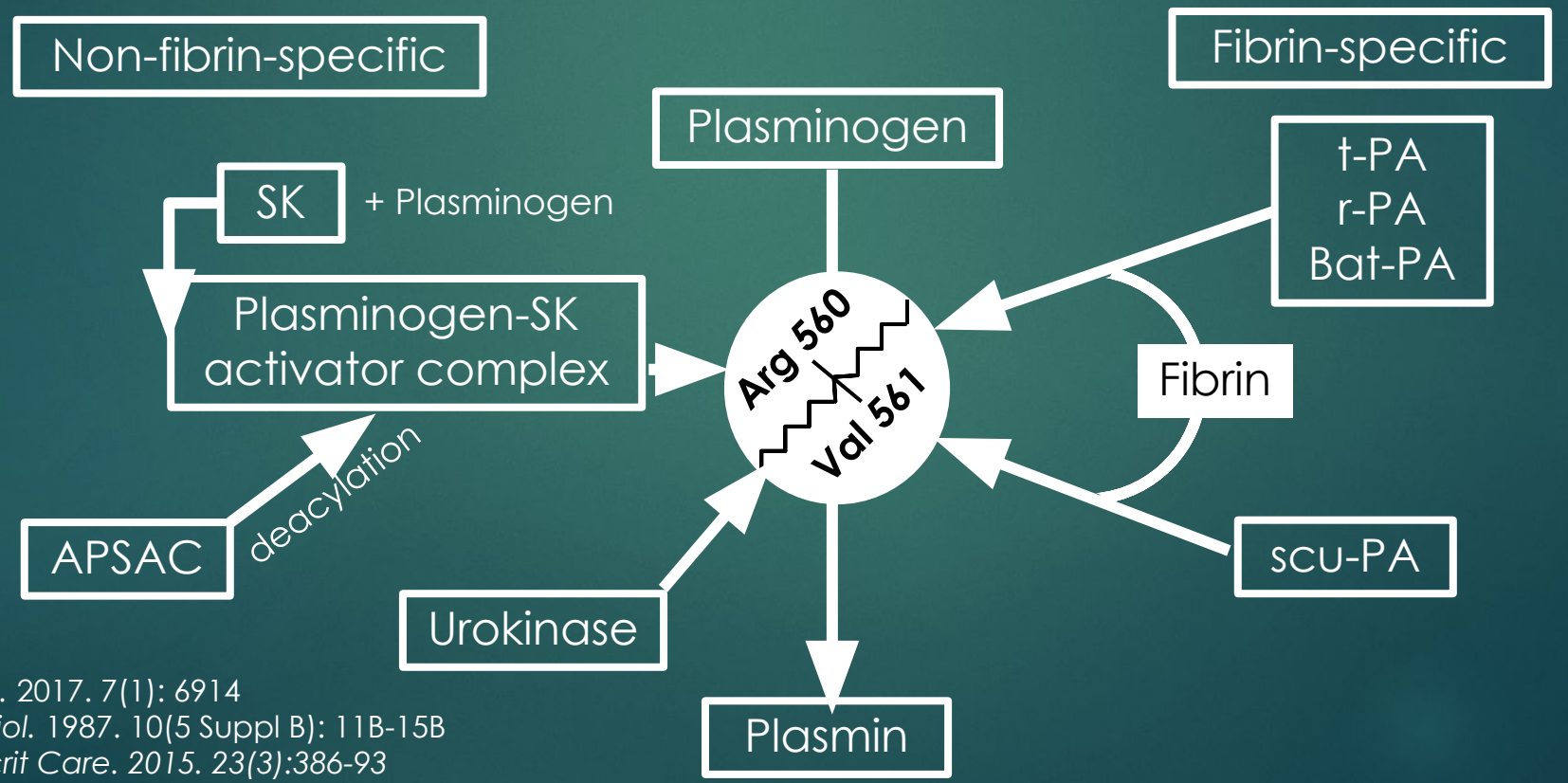
Mechanism of Thrombolytics



Pallister CJ. *Haematology* 2010. Scion Publishing. pp. 336–347

Mechanism of Thrombolytic Drugs

- The plasmin(ogen) molecule has lysine binding sites, which bind to fibrin



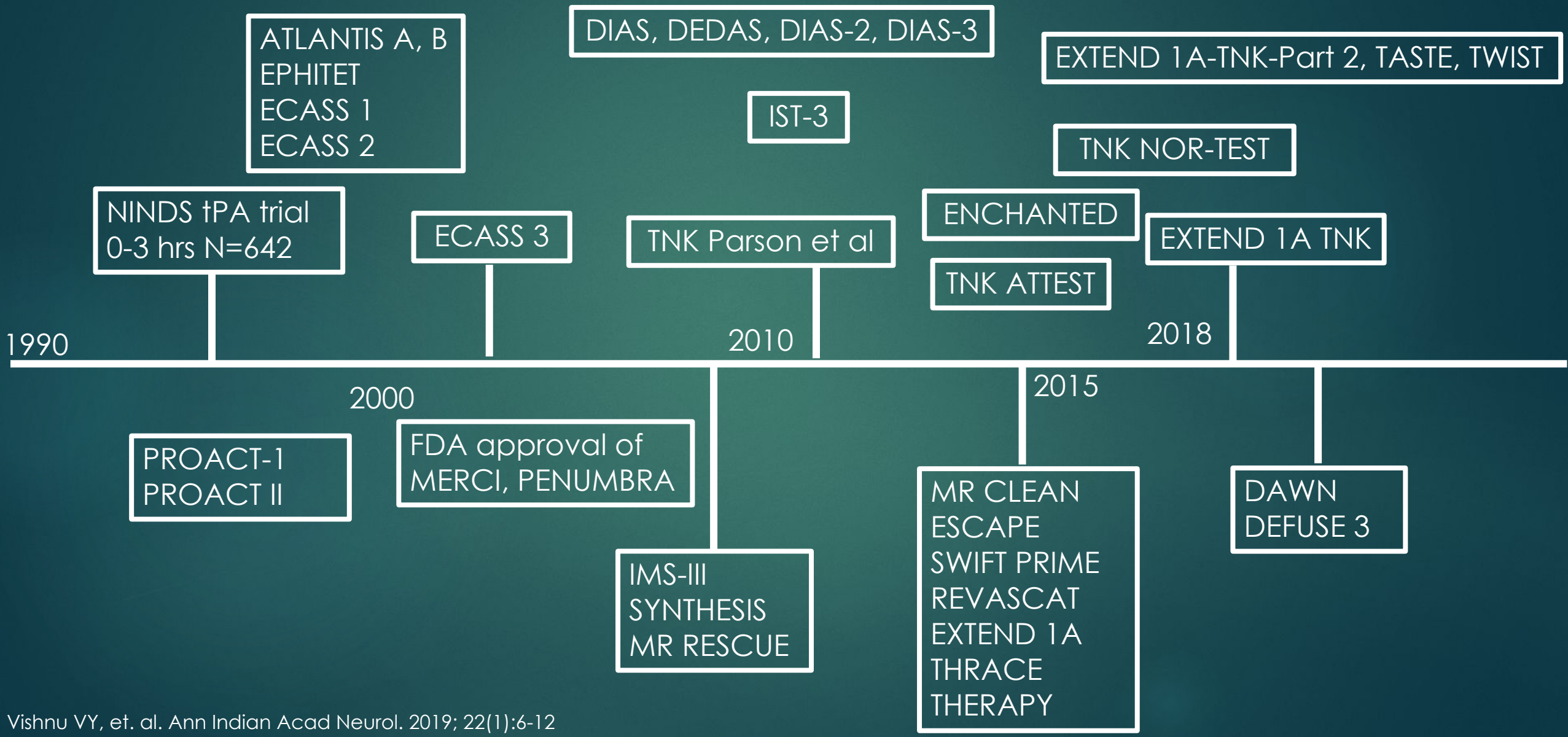
Bannish BE. et. al. *Sci Rep.* 2017. 7(1): 6914
Collen D. *J Am Coll Cardiol.* 1987. 10(5 Suppl B): 11B-15B
Kramer AH. et. al. Neurocrit Care. 2015. 23(3):386-93

Pharmacokinetics

	Streptokinase	Alteplase	Tenecteplase
Half-life	18 minutes	4-8 minutes	25 minutes
Plasminogen activation	Indirect binding	Direct binding	Direct binding
Fibrin selective	No	Yes	Yes
Development of Allergy	Yes	No	No
Intravenous Administration	Infusion	Infusion	Bolus

Ali R, et. al. Scientific World Journal. 2014; 2014: 586510
Activase (alteplase) [prescribing information] San Francisco, CA: Genentech; February 2018
TNKase (tenecteplase) [prescribing information]. South San Francisco, CA: Genentech; August 2018

Stroke Study Timeline



Vishnu VY, et. al. Ann Indian Acad Neurol. 2019; 22(1):6-12

TW is a 66 year old male presenting to the emergency room with the inability to walk due to left leg weakness that started 2 hours ago. Which thrombolytic agent should be selected for his stroke?

A. Streptokinase
B. Alteplase
C. Tenecteplase
D. More information is needed

TW is a 66 year old male presenting to the emergency room with the inability to walk due to left leg weakness that started 2 hours ago. Which thrombolytic agent should be selected for his stroke?

A. Streptokinase
B. Alteplase
C. Tenecteplase
D. More information is needed

AIS Candidate for TPA

Inclusion

- Ischemic stroke
- Clearly defined time of onset
- Deficit measurable on NIHSS
- CT with no evidence of ICH

Exclusion

- Stroke or serious head trauma ≤ 3 months
- Major surgery within 14 days
- History or signs of hemorrhage
- SBP >185 mm Hg or DBP >110 mm Hg
- Rapidly improving or minor symptoms
- Seizure at the onset of stroke
- Blood glucose <50 mg/dL or >400 mg/dL
- Anticoagulants ≤48 hours of stroke onset

N Engl J Med. 1995; 333(24):1581-7
Hacke W, et. al. N Engl J Med. 2008; 359(13):1317-29

AIS, Acute Ischemic Stroke; TPA, tissue plasminogen activator; NIHSS, National Institutes of Health stroke scale; ICH, intracranial hemorrhage; SBP, systolic blood pressure; DBP, diastolic blood pressure

Tissue Plasminogen Activator for AIS

Conclusions based on TPA for AIS and ECASS III:

- Thrombolysis with alteplase 4.5 Hours after AIS significantly improved clinical outcomes
  - Decreased disability at 3 months

N Engl J Med. 1995; 333(24):1581-7
Hacke W, et. al. N Engl J Med. 2008; 359(13):1317-29

AIS, Acute Ischemic Stroke; tPA, tissue plasminogen activator; ECASS, European Cooperative Acute Stroke Study

Tenecteplase in Acute Ischemic Stroke

Study	Comparison	Outcome	Findings
Phase IIb/III 2010	• Alteplase • 0.1 mg/kg TNK • 0.25 mg/kg TNK • 0.4 mg/kg TNK	Neurologic improvement at 24 hours NIHSS score improvement between baseline and 24 hr	All TNK doses combined 79.3 ± 28.8 Alteplase 55.4 ± 38.7 All TNK doses combined 8.0 ± 5.5 Alteplase 3.0 ± 6.3
Parsons M, et. al. 2012	• Alteplase • 0.1 mg/kg TNK • 0.25 mg/kg TNK	Reperfusion % at 24 hours	TNK 79.3 ± 28.8 Alteplase 55.4 ± 38.7
ATTEST 2015	• Alteplase • 0.25 mg/kg TNK	% salvaged penumbra	TNK 68% Alteplase 68%
NORTEST 2017	• Alteplase • 0.4 mg/kg TNK	Excellent functional outcome	Intent to treat: TNK 64% Alteplase 63%. Per protocol: TNK 64% Alteplase 64%
EXTEND-IA	• Alteplase • 0.25 mg/kg TNK	Reperfusion of >50% ischemic territory/absence of thrombus	TNK 22% Alteplase 10%
EXTEND-IA Part 2	• 0.25 mg/kg TNK • 0.4 mg/kg TNK	Reperfusion of >50% ischemic territory/absence of thrombus	0.4 mg/kg 19.3% 0.25 mg/kg 19.3%

TNK, Tenecteplase; standard alteplase 0.9 mg/kg

Haley EC Jr, et. al. Stroke. 2010; 41:707-11
Huang X, et. al. Lancet Neurol. 2015; 14(4):368-76
Parsons M, et. al. N Engl J Med. 2012; 366(12):1099-107
Logallo N, et. al. Lancet Neurol. 2017; 16(10):781-88
Campbell BC, et. al. Int J Stroke. 2018; 13(3):328-34
Campbell BC, et. al. Int J Stroke. 2020;15(5): 567-72

EXTEND-IA TNK

- Prospective, randomized, open-label blinded endpoint trial comparing Tenecteplase 0.25 mg/kg to Alteplase 0.9 mg/kg

- Outcome: Reperfusion of >50% of the involved ischemic territory *or* an absence of retrievable intracranial thrombus
  - Modified Treatment in Cerebral Ischemia classification

Campbell BC et. al. N Engl J Med 2018; 378:1573-1582

EXTEND-IA TNK

- Included:
  - Within 4.5 hours of stroke onset
  - Eligible for thrombolytics
  - Occlusion in ICA, MCA (M1 or M2) or basilar artery
  - Endovascular thrombectomy expected to commence within 6 hours of stroke onset
  - ~~CT-perfusion mismatch for anterior circulation strokes.~~
- Excluded:
  - ICH
  - mRS >3
  - Rapidly improving symptoms
  - Extensive noncontrast CT hypodensity (>one-third of the MCA or basilar artery territory)

ICA, Internal carotid artery; MCA, middle cerebral artery; M1, first segment of the middle cerebral artery; M2, the second segment of the middle cerebral artery; ICH, intracranial hemorrhage; mRS, modified rankin scale

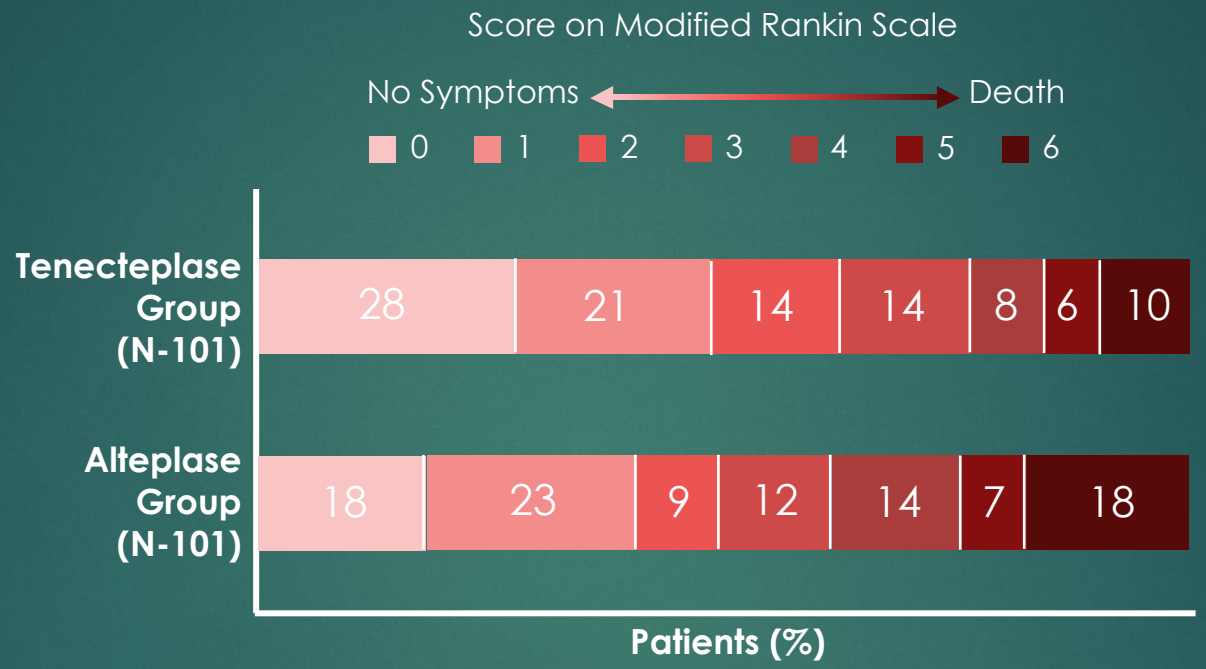
Campbell BC, et.al. JAMA. 2020; *323*(13), 1257-65

EXTEND-IA TNK

	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect size (95% CI)	P Value
Primary efficacy outcome				
Substantial reperfusion at initial angiographic assessment – no. (%)	22 (22)	10 (10)		
Difference – percentage points			12 (2-21)	0.002
Adjusted incidence ratio			2.2 (1.1-4.4)	0.03
Adjusted odds ratio			2.6 (1.1-5.9)	0.02
Secondary outcomes				
Score on the modified Rankin scale at 90 days – Median (IQR) on ordinal analysis	2 (0-3)	3 (1-4)	1.7 (1.0-2.8)	0.04
Early neurologic improvements – no. (%)	72 (71)	69 (68)		
Adjusted incident ratio			1.0 (0.9-1.2)	0.70
Adjusted odds ratio			1.1 (0.6-2.1)	0.70
Safety Outcomes				
Death – no. (%)	10 (10)	18 (18)		
Adjusted risk ratio			0.5 (0.3-1.0)	0.049
Adjusted odds ratio			0.4 (0.2-1.1)	0.08
Symptomatic intracerebral hemorrhage – no. (%)	1 (1)	1 (1)		
Risk ratio			1.0 (0.1-15.9)	0.99
Odds ratio			1.0 (0.1-16.2)	0.99

Campbell BC et. al. N Engl J Med 2018; 378:1573-1582

EXTEND-IA TNK



- Modified Rankin Scale Scores at 90 days in intent to treat - median (IQR)
  - Tenecteplase: 2 (0-3)
  - Alteplase: 3 (1-4)
  - OR (95% CI): 1.7 (1.0 to 2.8); p=0.04

Campbell BC et. al. N Engl J Med 2018; 378:1573-1582

EXTEND-IA TNK

- Conclusion: Tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within 4.5 hours after symptom onset

Campbell BC et. al. N Engl J Med 2018; 378:1573-1582

EXTEND-IA TNK Part 2

- Randomized, open-label blinded endpoint trial comparing Tenecteplase 0.4 mg/kg to 0.25 mg/kg
- Outcome: Reperfusion of >50% of the involved ischemic territory *or* an absence of retrievable intracranial thrombus
- A prespecified analysis pooled data from part 2 of the trial with the original trial data that compared 0.25 mg/kg of tenecteplase to alteplase to evaluate non-inferiority

Campbell BC, et.al. JAMA. 2020; *323*(13), 1257-65

EXTEND-IA TNK Part 2

- Included:
  - Within 4.5 hours of stroke onset
  - Eligible for thrombolytics
  - Occlusion in ICA, MCA (M1 or M2), or basilar artery
  - Endovascular thrombectomy intended to be performed
- Excluded:
  - mRS >3
  - Extensive noncontrast CT hypodensity (>⅓ of the MCA or basilar artery territory)

Campbell BC, et.al. JAMA. 2020; *323*(13), 1257-65

ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified rankin scale; CT, computed tomography

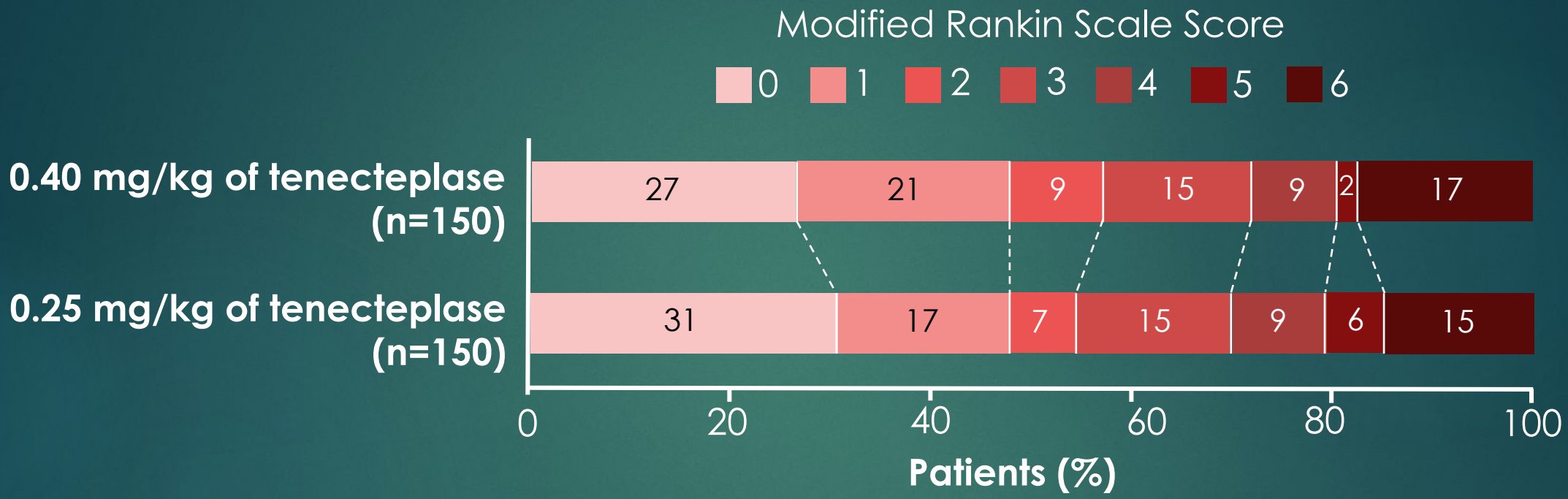
EXTEND-IA TNK Part 2

	0.4 mg/kg TNK (n = 150), No (%)	0.25 mg/kg TNK (n = 150), No (%)	Unadjusted Risk Difference (95% CI,), %	Effect size (95% CI)	P Value
Primary Efficacy Outcome					
Substantial reperfusion at initial angiogram	29 (19.3)	29 (19.3)	0.0 (-8.9 to 8.9)	Adjusted RR, 1.03 (0.66 to 1.61)	0.89
Secondary Outcomes					
mRS score at 90 days, median (IQR)	2 (0 to 4)	2 (0 to 4)	NA	Adjusted generalized OR, 0.96 (0.74 to 1.24)	0.73
Functional independence (mRS score of 0-2 or no change)	88 (59)	84 (56)	2.7 (-8.5 to 13.9)	Adjusted RR, 1.08 (0.90 to 1.29)	0.40
Freedom from disability (mRS score of 0-1 or no change)	74 (49)	74 (49)	0.0 (-11.3 to 11.3)	Adjusted RR, 1.04 (0.84 to 1.29)	0.69
Safety					
Death	26 (17)	22 (15)	2.7 (-5.6 to 11.0)	Adjusted RR, 1.27 (0.77 to 2.11)	0.35
Symptomatic intracranial hemorrhage	7 (4.7)	2 (1.3)	3.3 (-0.5 to 7.2)	RR, 3.50 (0/74 to 16.62)	0.12
Parenchymal hematoma	4 (2.7)	6 (4.0)	-1.3 (-5.4 to 2.7)	RR, 0.67 (0.19 to 2.32)	0.52

TNK, Tenecteplase; mRS, modified rankin scale; IQR, interquartile range; NA, not applicable; RR, risk ratio; OR, odds ratio

Campbell BC, et.al. JAMA. 2020; *323*(13), 1257-65

EXTEND-IA TNK Part 2



	No. of Patients						
Modified Rankin Scale Score	**0**	**1**	**2**	**3**	**4**	**5**	**6**
0.4 mg/kg	40	32	14	22	13	3	26
0.25 mg/kg	46	26	10	23	14	9	22

Campbell BC, et.al. JAMA. 2020; *323*(13), 1257-65

EXTEND-IA TNK Part 2

Outcome	0.9 mg/kg Alteplase (n=101)	Pooled tenecteplase (n=401)	Effect size (95% CI)	P-value
Primary Outcome				
Substantial reperfusion at initial angiogram – no. (%)	10/101 (9.9%)	80/401 (20.0%)	Adjusted Risk Ratio 1.90	0.04 (superiority)
Secondary Outcomes				
Score on the modified Rankin scale at 90 days			Adjusted Common Odd Ratio 1.50	
Median score (IQR) on ordinal analysis	3 (1-4.5)	2 (0-4)	(1.01-2.22)	0.04
Independent outcome (mRS 0-2 or no change) – no. (%)	52/101 (51%)	237/401 (59%)	Adjusted Risk Ratio 1.15 (0.94-1.40)	0.18
Excellent outcome (mRS 0-1 or no change) – no. (%)	43/101 (43%)	200/401 (50%)	Adjusted Risk Ratio 1.17 (0.93-1.47)	0.18
Early neurological improvement – no. (%)	69/101 (68%)	267/401 (67%)	Adjusted Risk Ratio 0.98 (0.85-1.14)	0.82
Safety Outcomes				
Death – no. (%)	18/101 (18%)	58/401 (14%)	Adjusted Risk Ratio (0.87 (0.56-1.34)	0.52
Symptomatic intracranial hemorrhage – no. (%)	1/101 (1.0%)	10/401 (2.5%)	Risk Ratio 2.52 (0.33-19.49)	0.38
Parenchymal hematoma – no. (%)	5/101 (5.0%)	16/401 (4.0%)	Risk Ratio 0.81 (0.30-2.15)	0.67

mRS, modified rankin scale; IQR, interquartile range;

Campbell BC, et.al. JAMA. 2020; *323*(13), 1257-65

EXTEND-IA TNK Part 2

- Conclusion: 0.4 mg/kg tenecteplase dose does not confer an advantage over the 0.25 mg/kg dose in patients with large vessel occlusion ischemic stroke in whom endovascular thrombectomy is planned

Campbell BC, et.al. JAMA. 2020; *323*(13), 1257-65

American Heart Association (AHA) Guidelines

AHA Guidelines

- In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible
- Give IV alteplase within 3-4.5 hours of ischemic stroke symptom onset or patient last known well
  - 0.9 mg/kg, maximum dose 90 mg over 60 minutes
  - Initial 10% of dose given as bolus over 1 minute

Powers WJ, et.al. Stroke 2018; 49:e46-e110.
Powers WJ, et.al. Stroke. 2019; 50(12): e344-e418

IV, Intravenous

AHA Guidelines

- Consider tenecteplase as an alternative to alteplase
- For IV fibrinolysis who are also eligible to undergo mechanical thrombectomy
  - IV bolus of 0.25-mg/kg, maximum 25 mg
- Minor neurological impairment and no major intracranial occlusion
  - IV bolus 0.4-mg/kg, maximum 40 mg
  - Not superior or noninferior to alteplase

Powers WJ, et.al. Stroke 2018; 49:e46-e110.
Powers WJ, et.al. Stroke. 2019; 50(12): e344-e418

IV, Intravenous

AHA Guidelines

- The administration of IV defibrinogenating agents or IV fibrinolytic agents other than alteplase and tenecteplase is not recommended.
- Patients eligible for IV alteplase should receive IV alteplase even if mechanical thrombectomy is being considered.

Powers WJ, et.al. Stroke 2018; 49:e46-e110.
Powers WJ, et.al. Stroke. 2019; 50(12): e344-e418

IV, Intravenous

AHA Guidelines

- Strong evidence for use of thrombectomy initiated within 6 hours of stroke onset, irrespective of:
  - patient age
  - NIHSS score
  - or receipt of intravenous thrombolysis
- Recommendation based on MR CLEAN, ESCAPE, SWIFT PRIME, EXTEND-IA and REVASCAT

Benjamin EJ, et.al. Circulation. 2019; 139(10): e56-e528

Implementation of TNK for AIS

KRISTINA WILLOUR, RN, SCRN

TNK, Tenecteplase; AIS, Acute Ischemic Stroke

Implementation of TNK for AIS

1. Risk Assessment
2. Approval through involved members and committees
3. Orderset update
4. Policy update
5. Availability
6. Education
7. Implementation
8. Monitoring

TNK, Tenecteplase; AIS, Acute Ischemic Stroke

Implementation of TNK for AIS - Risk Assessment

- Off label use
- High risk, time sensitive
- No vendor return policy
- No vendor educational materials

- Potential decrease risk of bleeding due to increase fibrin specificity
- Potential decrease in treatment times
- Ease of transfer
- Potential improvement within systems of care from arrival to reperfusion
- Cost savings

Implementation of TNK for AIS - Approval

- Approval through involved members and committees
  - Stakeholders
  - Acute Stroke Response Team
  - Neuro Critical Care Team members
  - Pharmacy and Therapeutics Committee (P&T)
  - Med Executive

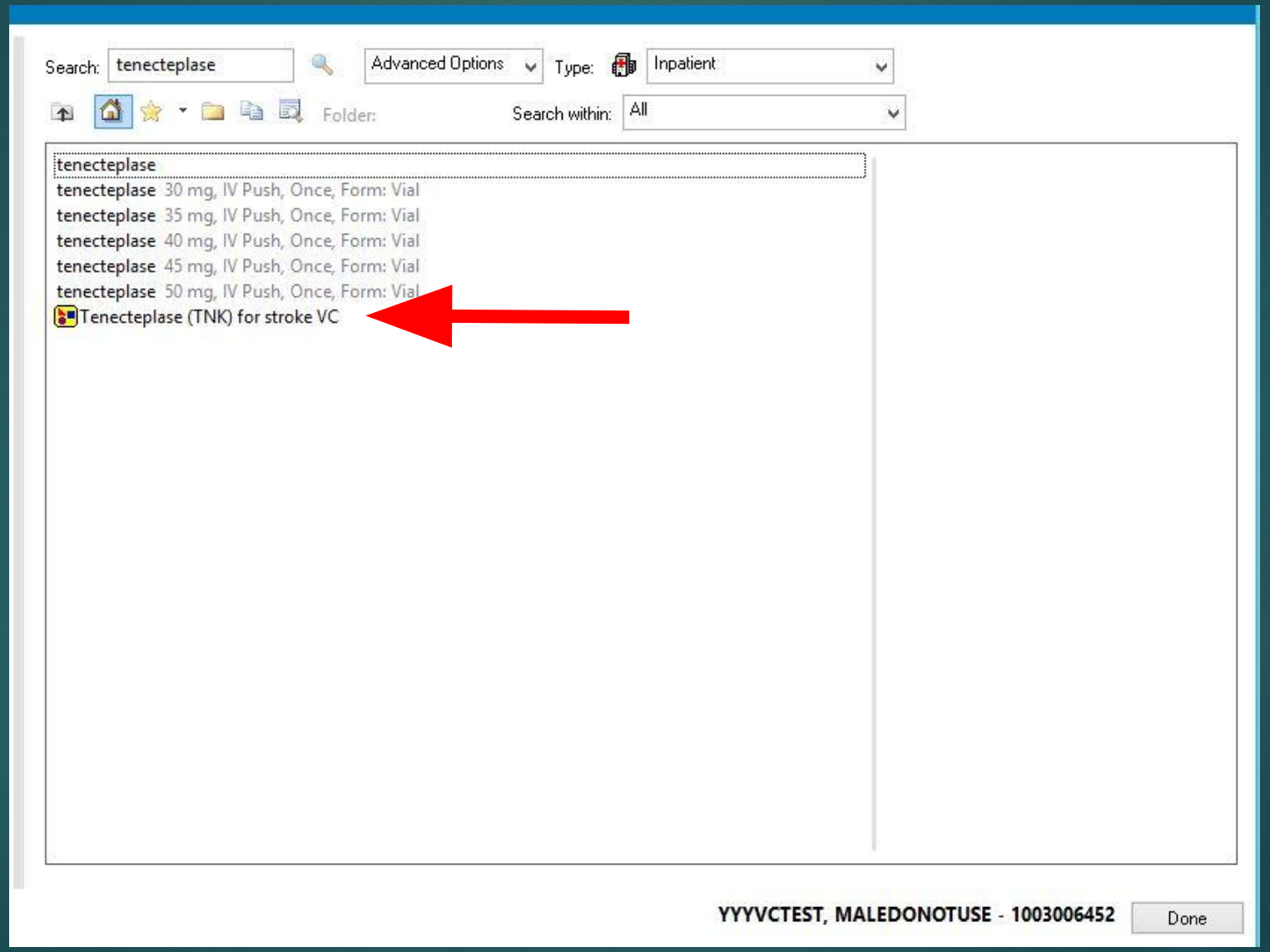
TNK, Tenecteplase; AIS, Acute Ischemic Stroke

Implementation of TNK for AIS - Orderset

- Orderset Update
  - Work with clinical informatics to switch alteplase to tenecteplase to change:
    - Drug
    - Dose
    - Drug rounding
    - Drug dose cap
    - Flush

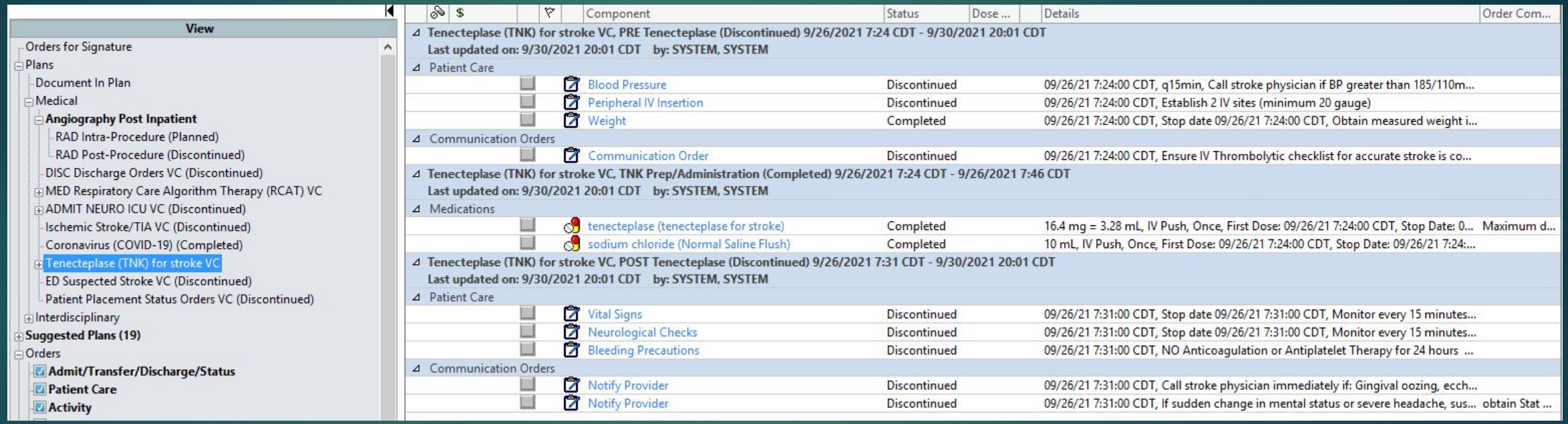
TNK, Tenecteplase; AIS, Acute Ischemic Stroke

Implementation of TNK for AIS - Orderset



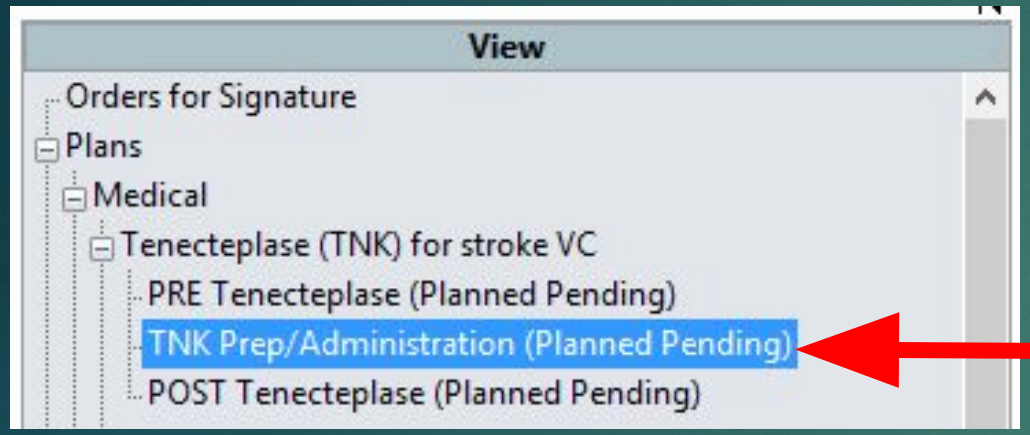
TNK, Tenecteplase; AIS, Acute Ischemic Stroke

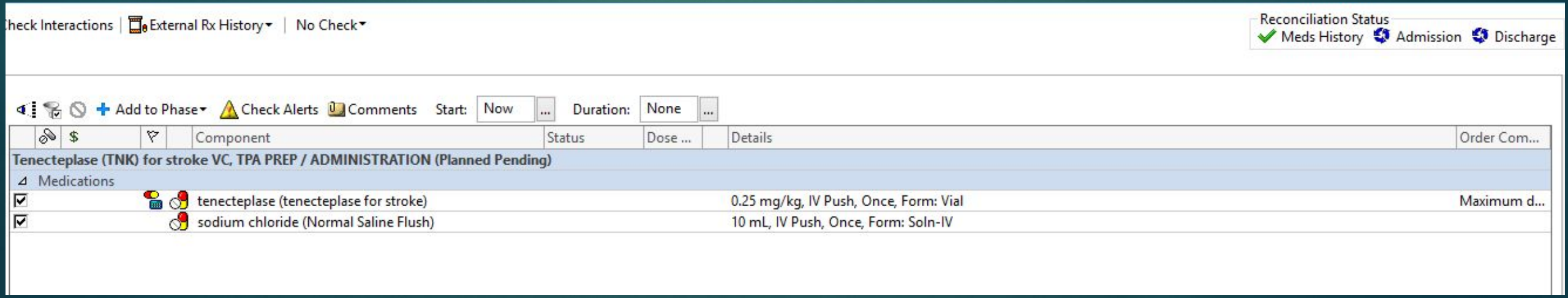
Implementation of TNK for AIS - Orderset



TNK, Tenecteplase; AIS, Acute Ischemic Stroke

Implementation of TNK for AIS - Orderset





TNK, Tenecteplase; AIS, Acute Ischemic Stroke

Implementation of TNK for AIS - Policy

- Policy Update
  - Formulary update (if needed)
  - High risk/ high alert policy
  - Off label medication use policy
  - Treatment checklist (Indications/ Contraindications)
  - Stroke team policy
  - Stroke team tools/ algorithm

TNK, Tenecteplase; AIS, Acute Ischemic Stroke

Implementation of TNK for AIS - Availability

- Increase purchasing of TNK, decrease purchasing of alteplase
- Automated Dispensing Cabinet (ADC) Updates
  - Ensure alteplase and tenecteplase are not stocked in same cabinet to prevent error
  - Reduce availability of alteplase
  - Increase TNK availability

TNK, Tenecteplase; AIS, Acute Ischemic Stroke; ADC, Automated Dispensing Cabinet

Implementation of TNK for AIS - Education

- Who:
  - Physicians/Advanced Practice Providers
  - Nurses
  - Pharmacists
- What:
  - Situation, Background, Assessment, Recommendations (SBAR)
  - Dosing, reconstitution, administration
  - Orderset and documentation differences
- When:
  - Staff meetings
  - Daily huddles
  - Email communication

TNK, Tenecteplase; AIS, Acute Ischemic Stroke

Implementation of TNK for AIS

- Alteplase orderset scheduled to turn off and TNK orderset to turn on at 0800
- Health care providers were reminded of the go-live date
- First administration occurred on night shift

TNK, Tenecteplase; AIS, Acute Ischemic Stroke

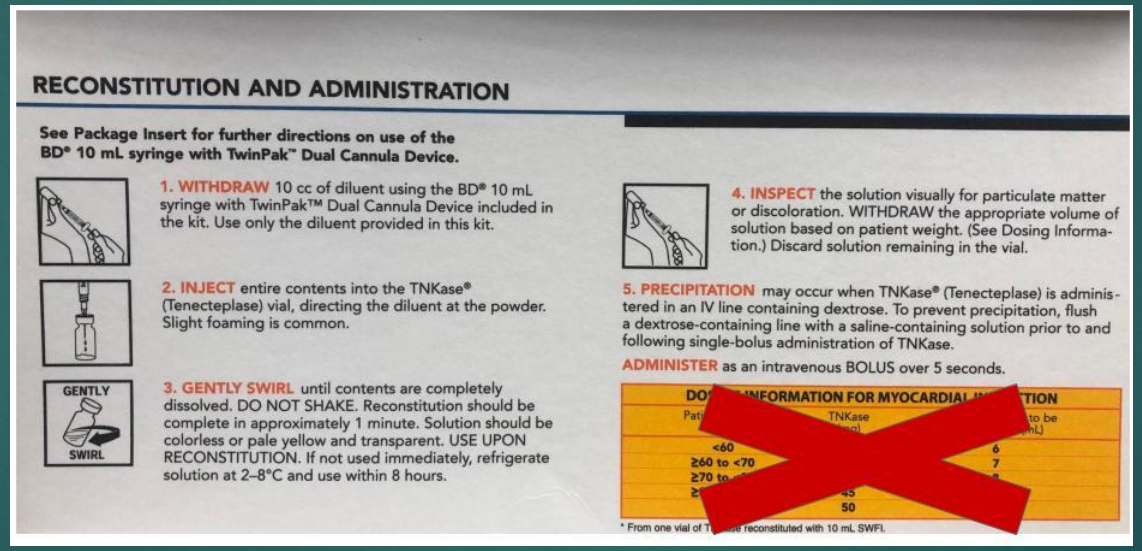
Implementation of TNK for AIS-Monitoring

- Thrombolytic Therapy Metrics
  - Door in door out
  - Hemorrhagic Transformation
  - Endovascular treatment times
  - Recanalization rates
  - 90 day Modified Rankin Score (mRS)
- Provider satisfaction

TNK, Tenecteplase; AIS, Acute Ischemic Stroke; MI, Myocardial Infarction

Implementation of TNK for AIS-Monitoring

- Lessons learned:
  - Travel nurses adds extra layer to education needs
  - MI dosing on TNK box is misleading



RECONSTITUTION AND ADMINISTRATION

See Package Insert for further directions on use of the BD® 10 mL syringe with TwinPak™ Dual Cannula Device.

1. WITHDRAW 10 cc of diluent using the BD® 10 mL syringe with TwinPak™ Dual Cannula Device included in the kit. Use only the diluent provided in this kit.

2. INJECT entire contents into the TNKase® (Tenecteplase) vial, directing the diluent at the powder. Slight foaming is common.

3. GENTLY SWIRL until contents are completely dissolved. DO NOT SHAKE. Reconstitution should be complete in approximately 1 minute. Solution should be colorless or pale yellow and transparent. USE UPON RECONSTITUTION. If not used immediately, refrigerate solution at 2–8°C and use within 8 hours.

4. INSPECT the solution visually for particulate matter or discoloration. WITHDRAW the appropriate volume of solution based on patient weight. (See Dosing Information.) Discard solution remaining in the vial.

5. PRECIPITATION may occur when TNKase® (Tenecteplase) is administered in an IV line containing dextrose. To prevent precipitation, flush a dextrose-containing line with a saline-containing solution prior to and following single-bolus administration of TNKase.

ADMINISTER as an intravenous BOLUS over 5 seconds.

Patient Weight (kg)	TNKase (mg)	Dose to be Administered (mL)
<60		6
≥60 to <70		7
≥70 to		
	45	
	50	

* From one vial of T[illegible] reconstituted with 10 mL SWFI.

TNK, Tenecteplase; AIS, Acute Ischemic Stroke; MI, Myocardial Infarction

Conclusion

- AIS literature supports TNK non-inferiority to alteplase with P&T approval for use
- AHA recognizes TNK as an alternative treatment for AIS
- Implementation of TNK for AIS orderset took time, coordination and significant education

TNK, Tenecteplase; AIS, Acute Ischemic Stroke, P&T, Pharmacy and Therapeutics Committee; AHA, American Heart Association

Thrombolysis in Acute Ischemic Stroke

ERICA N KRANTZ, PHARMD, BCCCP
KRISTINA WILLOUR, RN, SCRN

ASCENSION VIA CHRISTI ST. FRANCIS
November 2021