Expanded Use of IV Thrombolytics in Acute Ischemic Stroke

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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, Alteplase >3 hours for AIS

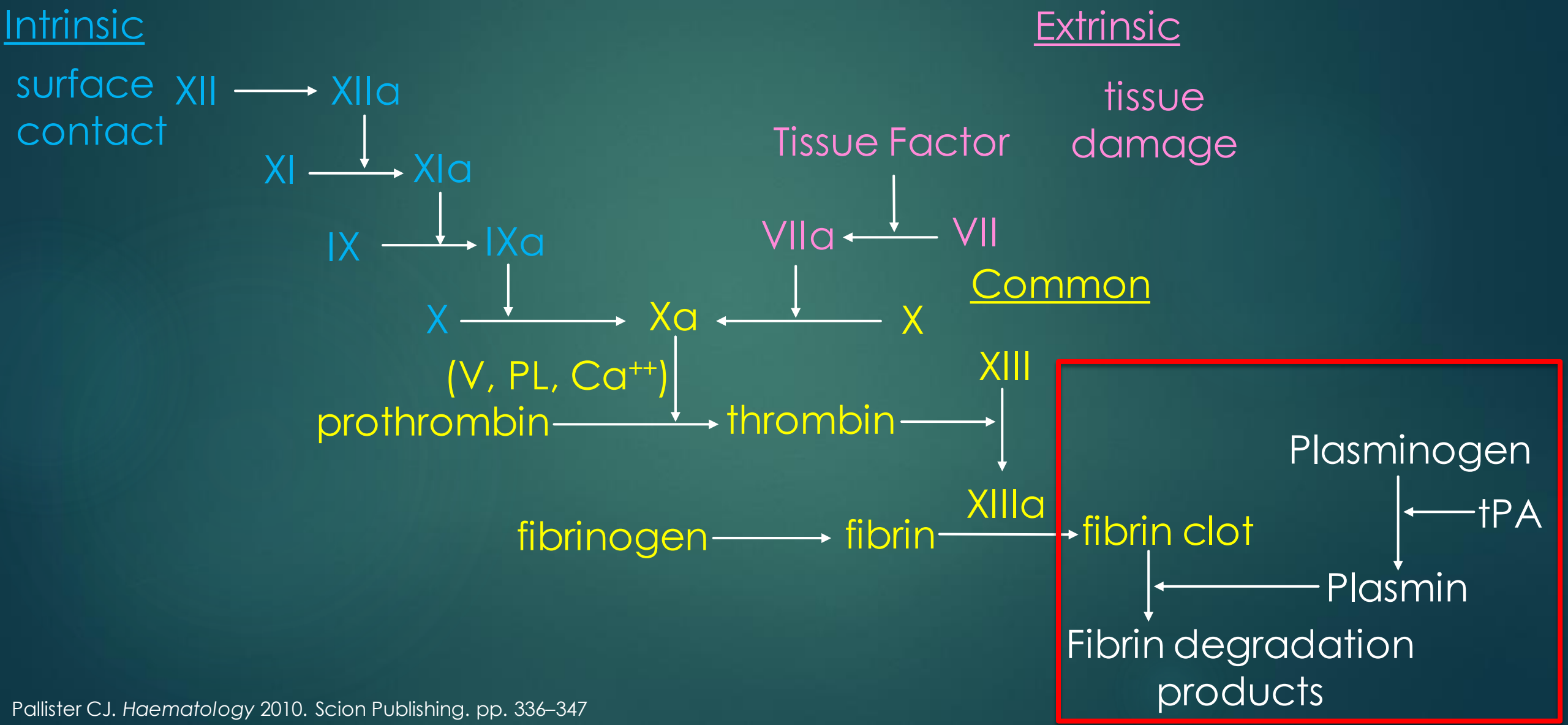
*A commercial interest is any entity producing, marketing, re-selling, or distributed health care goods or services consumed by, or used on, patients

AIS, Acute Ischemic Stroke

Objectives

- Identify thrombolytic treatment options for an acute ischemic stroke (AIS)
- Evaluate literature for timing of thrombolytic use in AIS
- Summarize AIS guideline recommendations

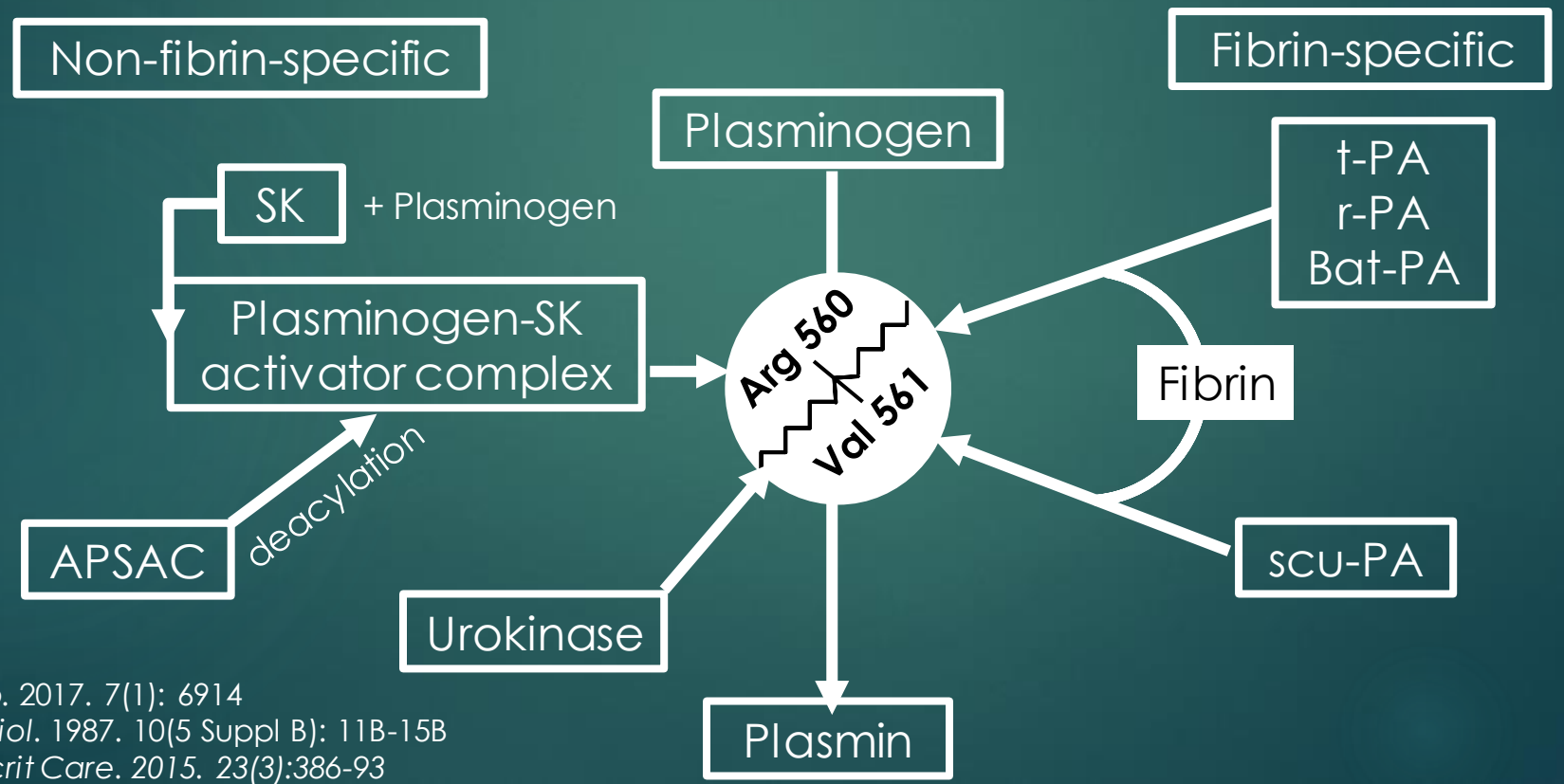
Mechanism of Thrombolytics



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



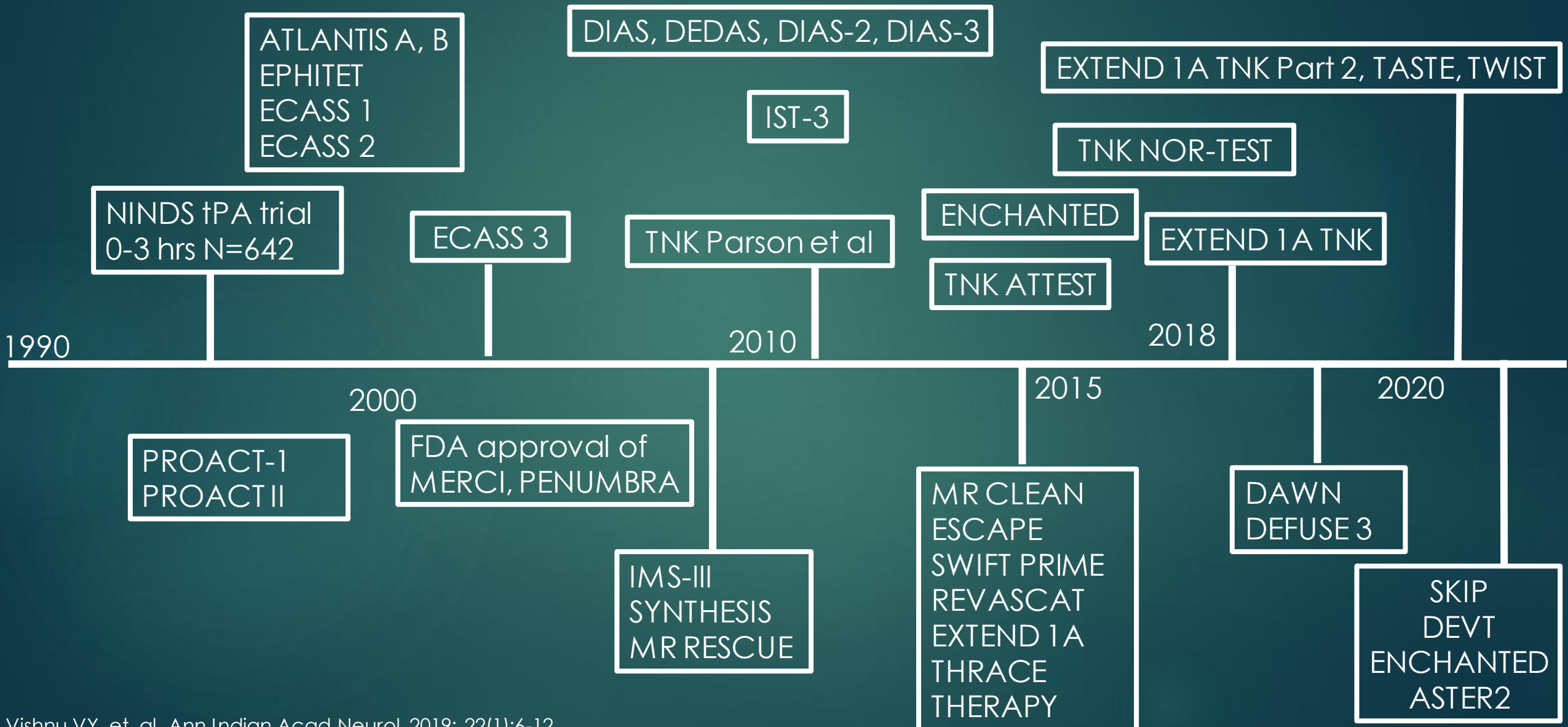
Bannish BE. et. al. *Sci Rep.* 2017. 7(1): 6914
Collen D. *J Am Coll Cardiol.* 1987. 10(5 Suppl B): 11B-15B
Kramer AH. et. al. Neurocrit Care. 2015. 23(3):386-93

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

AIS Candidate for IV Thrombolytic

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

Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke

- Alteplase vs Placebo
- Hemorrhagic transformation occurred significantly more frequently in patients receiving treatment at least 6 hours after symptom onset.

del Zoppo, GJ et. al. Ann Neurol . 1992 Jul;32(1):78-86.

ECASS I

- 1.1 mg/kg alteplase vs placebo
- Stroke symptom onset within 6 hours
- Primary end points: 90 day Barthel Index (BI) and mRS

- 17.4% protocol violations in intention to treat group

- Conclusion:
  - Per protocol group: mRS improved in alteplase group
  - No difference in mortality or overall hemorrhage rates
  - Increased large parenchymal hemorrhage rates in alteplase group

Hacke, W. et. al. JAMA .1995 Oct 4;274(13):1017-25.

mRS, modified Rankin Scale

ECASS II

- 0.9 mg/kg alteplase vs placebo
- Stroke symptom onset within 6 hours
- Primary Outcome: favorable 90 day mRS
  - 40.3% alteplase vs 36.6% placebo (p=0.277)

- Hemorrhage rates:
  - 8.8% alteplase vs 3.4% placebo

- Conclusion:
  - No statistically significant difference between groups
  - Trend towards alteplase improving outcomes

Hacke, W. et. al. Lancet. 1998 Oct 17;352(9136):1245-51.

mRS, modified Rankin Scale

ECASS III and TPA for AIS Studies

Conclusions based on TPA for AIS and ECASS III:

- Thrombolysis with alteplase 3-4.5 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

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
- Consider tenecteplase as an alternative to alteplase
- Off label use
  - Alteplase > 3 hours of symptom onset
  - All tenecteplase use

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

IV, Intravenous

Extending the Thrombolytic Administration Window

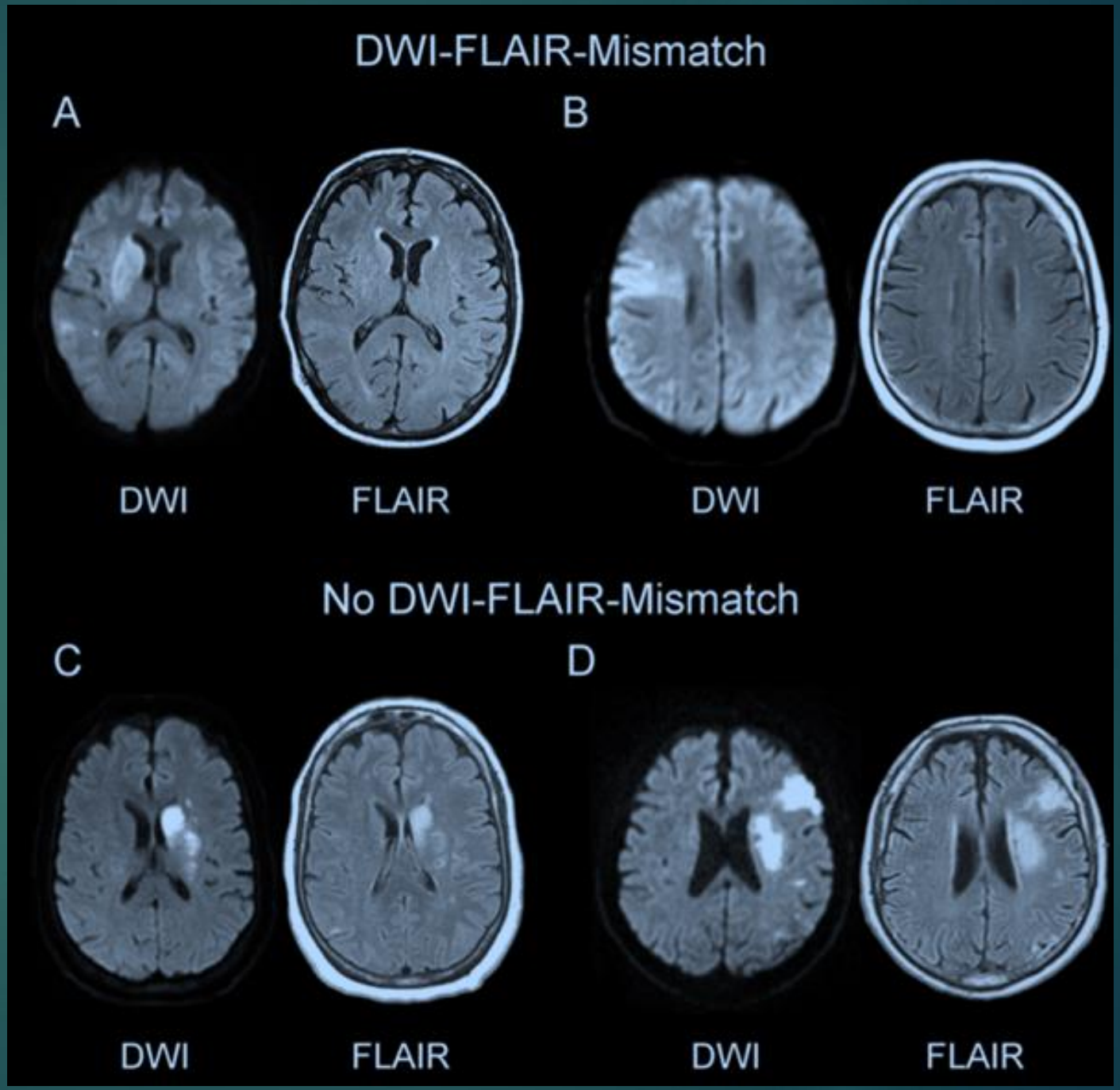
MRI Imaging

- Stroke patients within 4.5 hours of symptom onset have:
  - Diffusion-weighted imaging (DWI)
    - Visible ischemic lesions
  - FLAIR
    - absence of a clearly visible hyperintense signal in the same area

Thomalla G. et. al. Lancet Neurol 2011;10:978-86.

FLAIR, fluid-attenuated inversion recovery

MRI Imaging



Thomalla G, et. al. N Engl J Med. 2018;379(7):611-622

FLAIR, fluid-attenuated inversion recovery; DWI, Diffusion-weighted imaging

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset (WAKE-UP)

- Multicenter, randomized, double-blind, placebo controlled trial
  - Alteplase 0.9 mg/kg vs placebo
- Primary outcome:
  - Favorable clinical outcome (mRS 0 or 1)
- Primary safety endpoint:
  - Death
  - Composite death or dependent mRS (4-6)

Thomalla G, et. al. N Engl J Med. 2018;379(7):611-622

mRS, modified Rankin Scale

WAKE-UP

Inclusion	Exclusion
• Stroke onset unknown • LKW >4.5 hrs from treatment initiation • 18-80 years old • Disabling neurologic deficit • MRI DWI-FLAIR mismatch	• Planned or anticipated endovascular reperfusion treatment • Severe stroke (NIHSS >25) • Significant bleeding • Subarachnoid hemorrhage • Any exclusion from receiving alteplase • Poor MRI imaging

- Intent To Treat study design
  - Sample size: 370 Patients per group
  - Power: 80%
  - Two-sided alpha: 5%

Thomalla G, et. al. N Engl J Med. 2018;379(7):611-622

LKW, last known well; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; DWI, Diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale

WAKE-UP Baseline Characteristics

Variable	Alteplase Group (N=254)	Placebo Group (N=249)
Mean Age ± SD - yr	65.3±11.2	65.2±11.9
Reason for unknown time of symptom onset - no. (%)		
Nighttime sleep	227 (89.4)	222 (89.2)
Daytime sleep	12 (4.7)	11 (4.4)
Aphasia, confusion, or other	15 (5.9)	16 (6.4)
LKW to symptom recognition, Median time (IQR) - hr	7.2 (4.7 - 8.7)	7.0 (5.0-9.0)
Median NIHSS Score (IQR)	6 (4-9)	6 (4-9)

SD, standard deviation; LKW, last known well; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale

Thomalla G, et. al. N Engl J Med. 2018;379(7):611-622

WAKE-UP Primary Outcome

Favorable outcome at 90 days - no/total no. (%)	Alteplase Group	Placebo Group	Odds Ratio (95% CI)	P Value
Intention to Treat	131/246 (53.3)	102/244 (41.8)	1.61 (1.09 to 2.36)	0.02
Per Protocol	116/217 (55)	91/207 (44.4)	1.54 (1.02-2.32)	0.04

Thomalla G, et. al. N Engl J Med. 2018;379(7):611-622

WAKE-UP Safety Outcomes

Outcome	Alteplase Group (N=251)	Placebo Group (N=244)	Odds Ratio* (95% CI)	P Value
Death or dependency at 90 days	33 (13.5)	44 (18.3)	0.68 (0.39-1.18)	0.17
Death at 90 days	10 (4.1)	3 (1.1)	3.38 (0.92-12.52)	0.07
Symptomatic ICH as defined in ECASS III	6 (2.4)	1 (0.4)	6.04 (0.72-50.87)	0.1
Parenchymal hemorrhage type 2	10 (4.0	1 (0.4)	10.46 (1.32-82.77)	0.03

*Odds ratio adjusted for stratification factors (ie age and symptom severity) at randomization

Thomalla G, et. al. N Engl J Med. 2018;379(7):611-622

ICH, intracranial hemorrhage

WAKE-UP Conclusion

- In unknown LKW with DWI-FLAIR mismatch alteplase improved 90 day functional outcome

- Interpretation is limited by
  - Thrombectomy candidates excluded
  - Study stopped early limits safety outcome interpretation

Thomalla G, et. al. N Engl J Med. 2018;379(7):611-622

LKW, last known well; FLAIR, fluid-attenuated inversion recovery; DWI, Diffusion-weighted imaging

Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke (EXTEND)

- Multicenter, randomized, placebo controlled trial
  - Alteplase 0.9 mg/kg vs placebo
- Primary outcome:
  - mRS of 0 or 1 at 90 days
- Primary safety endpoint:
  - Death within 90 days
  - Symptomatic ICH

Ma, H. et.al N Engl J Med 2019; 380:1795-1803

mRS, modified Rankin Scale; ICH, intracranial hemorrhage`

EXTEND

Inclusion	Exclusion

• Treatment initiated within
  ○ 4.5 and 9 hours of stroke onset OR
  ○ Wake-up strokes with midpoint of sleep <9 hours
• ≥18 years old
• NIHSS 4 - 26
• Hypoperfusion with salvageable regions on perfusion imaging
  ○ CT perfusion or MRI perfusion
	• Considering endovascular thrombectomy
	• Pre-stroke mRS ≥ 2
	• Rapidly improving symptoms
	• Ischemic Core >⅓ MCA territory
	• ICH
	• Any exclusion from receiving alteplase

Ma, H. et.al N Engl J Med 2019; 380:1795-1803

NIHSS, National Institutes of Health Stroke Scale; MRI, magnetic resonance imaging; CT, computed tomography; ICH, intracranial hemorrhage mRS, modified Rankin Scale; MCA, middle cerebral artery

EXTEND Baseline Characteristics

Variable	Alteplase Group (N=113)	Placebo Group (N=112)
Mean Age ± SD - yr	73.7±11.7	71.0±12.7
Time from stroke onset to randomization - no. (%)		
>4.5 to 6 hr	12 (10.6)	11 (9.8)
>6.0 to 9.0 hr	28 (24.8)	28 (25.0)
Awoke with stroke symptoms	73 (64.6)	73 (65.2)
Median NIHSS Score (IQR)	12.0 (8.0-17.0)	10.0 (6.0-16.5)

Ma, H. et.al N Engl J Med 2019; 380:1795-1803

SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range

EXTEND Primary Outcome

Primary Outcome	Alteplase Group	Placebo Group
mRS score 0-1 at 90 days	40/113 (35.4)	33/112 (29.5)

Unadjusted Effect Size (95% CI)	P Value
1.2 (0.82-1.76)	0.35

Adjusted* Effect Size (95% CI)	P Value
1.44 (1.01-2.06)	0.04

*Adjusted for age and clinical severity

Ma, H. et.al N Engl J Med 2019; 380:1795-1803

mRS, modified Rankin Scale

EXTEND Safety Outcomes

Outcome	Alteplase Group (N=113)	Placebo Group (N=112)	Adjusted Effect Size (95% CI)	P Value
Death within 90 days after intervention	13 (11.5)	10 (8.9)	1.17 (0.57-2.40)	0.67
Symptomatic ICH within 36 hr after intervention	7 (6.2)	1 (0.9)	7.22 (0.97-53.54)	0.053

Ma, H. et.al N Engl J Med 2019; 380:1795-1803

ICH, intracranial hemorrhage

EXTEND Conclusion

- Alteplase had no or minor neurologic deficits more often than the placebo group

- Interpretation is limited by
  - Study termination early due to the WAKE-UP trail
  - Imbalanced baseline characteristics
  - Long door-to-needle time

Ma, H. et.al N Engl J Med 2019; 380:1795-1803

Extending Thrombolysis to 4.5–9 h and wake-up stroke using perfusion imaging a systematic review and meta-analysis

- Meta analysis and systematic review
  - Alteplase 0.9 mg/kg vs placebo
  - Had CT perfusion or perfusion-diffusion MRI
- EXTEND, ECASS4-EXTEND and EPITHET trials included
- Primary outcome:
  - Excellent functional outcome (mRS of 0 or 1 at 3 months)
- Primary safety endpoint:
  - Death
  - Symptomatic ICH

Campbell BCV, et. al. Lancet. 2019;394(10193):139-147.

CT, computed tomography; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; ICH, intracranial hemorrhage`

Extending Thrombolysis Meta-analysis Baseline Characteristics

Variable	Alteplase Group (N=152)	Placebo Group (N=152)
Mean Age (SD) - yr	73.2 (13.1)	72.1 (12.3)
Time from stroke onset to randomization - no. (%)		
>4.5 to 6 hr	33 (22)	31 (20)
>6.0 to 9.0 hr	37 (24)	37 (24)
Awoke with stroke symptom	82 (54)	84 (55)
Median NIHSS Score (IQR)	12 (7-17)	11 (7-17)

*In patients with automated perfusion mismatch

Campbell BCV, et. al. Lancet. 2019;394(10193):139-147.

SD, standard deviation; LKW, last known well; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale

Extending Thrombolysis Meta-analysis Primary Outcome

Outcome*	Alteplase Group (N=152)	Placebo Group (N=152)	Odds Ratio (95% CI)	P Value
Excellent functional outcome (mRS score 0 - 1) at 3 months	55/152 (36)	39/151 (26)	2.06 (1.17-3.62)	0.012

*In patients with automated perfusion mismatch

Campbell BCV, et. al. Lancet. 2019;394(10193):139-147.

mRS, modified Rankin Scale

Extending Thrombolysis Meta-analysis Safety Outcomes

Outcome	Alteplase Group (N=152)	Placebo Group (N=152)	Odds Ratio (95% CI)	P Value
Death at 3 months, n (%)	20 (13)	16 (11)	1.28 (0.06-2.73)	0.52
Symptomatic ICH, n (%)	7 (5)	1 (1)	7.29 (0.88-60.18)	0.07

*In patients with automated perfusion mismatch

Campbell BCV, et. al. Lancet. 2019;394(10193):139-147.

ICH, intracranial hemorrhage

Extending Thrombolysis Meta-analysis Conclusion

- Alteplase improved functional outcomes in AIS patients with perfusion mismatch 4.5-9 hours from stroke onset or symptoms on waking
- Increased hemorrhage rates in alteplase group but no difference in mortality

Campbell BCV, et. al. Lancet. 2019;394(10193):139-147.

AIS, acute ischemic stroke

Ongoing Trials

- A Phase III, Prospective, Double-blind, Randomized, Placebo-controlled Trial of Thrombolysis in Imaging-eligible, Late-window Patients to Assess the Efficacy and Safety of Tenecteplase (TIMELESS)

- Randomization to Extend Stroke Intravenous ThromboLysis In Evolving Non-Large Vessel Occlusion With TNK (RESILIENT [EXTEND-IV])

According to the American Heart Association, for treatment of stroke, IV thrombolytic therapy should be administered within what timeframe from symptom onset?

A. 1 - 2 hours
B. 3 - 4.5 hours
C. 4.5 - 6 hours
D. 6 - 12 hours

Conclusion

- Identifying imagine mismatch perfusion might allow for extending the window of administration of IV thrombolytics in AIS
- AHA Guidelines does not discuss imaging based IV thrombolytic treatment
- Further studies need to be completed comparing extending the IV thrombolytic window in patients who receive thrombectomy to thrombectomy alone

AIS, Acute Ischemic Stroke, AHA, American Heart Association

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