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ILLUSTRATED REVIEW

Alteplase or tenecteplase for thrombolysis in ischemic stroke: An illustrated review

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Abstract

Intravenous thrombolysis is a standard of care treatment for patients with acute ischemic stroke. Tissue plasminogen activator (tPA) has been the main thrombolytic agent used since the publication of the seminal National Institutes of Neurological Disorders and Stroke trial in 1995. There is now mounting evidence to support the routine use of Tenecteplase (TNK) to treat acute ischemic stroke. TNK is a genetically modified tPA with higher fibrin specificity, longer half-life, and reduced systemic coagulopathy. In this illustrated review, we compare the indications, doses, mechanisms of action, efficacy and safety of TNK and tPA. We provide an overview of published clinical trials studying TNK in acute ischemic stroke, including dose-escalation studies and head-to-head comparisons with tPA. Finally, we summarize current acute stroke guideline recommendations and suggest treatment algorithms to manage the two main complications of intravenous thrombolysis: symptomatic intracerebral hemorrhage and angioedema.

KEYWORDS
fibrinolytic agents, hemorrhagic stroke, pharmacological mechanisms of action, stroke, treatment outcome

Essentials

- Thrombolysis, traditionally with Alteplase, is a standard of care treatment for ischemic stroke.
- Tenecteplase is a genetically modified version of Alteplase.
- Tenecteplase has theoretical benefits over Alteplase: better recanalization and reduced bleeding.
- Growing evidence support the routine use of Tenecteplase 0.25mg/kg for acute ischemic stroke.

Annie Zhu and Phavalan Rajendram contributed equally to this work

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Capsule 1: Introduction to acute ischemic stroke revascularization treatment

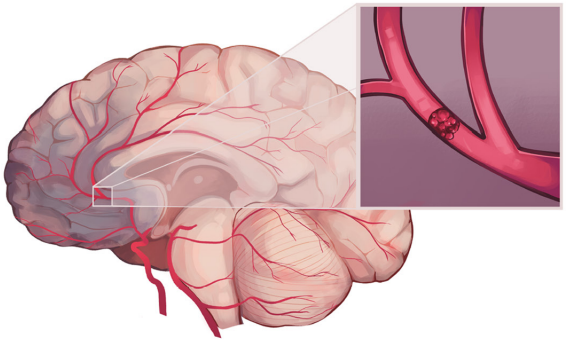
Stroke in numbers

2nd
leading cause of death and 3rd leading cause of death and disability combined in the world.[1]

12.2 million
incident cases of stroke and 101 million prevalent cases globally.[1]

40 seconds
is how often someone in the United States has a stroke. Stroke is the 5th leading cause of death (4th if excluding COVID).[2]

$45.5 billion
is the estimated average annual cost of stroke and it is rising.[3]



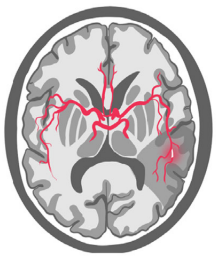
Ischemic stroke is caused by an interruption in cerebral blood flow.

Acute ischemic stroke revascularization treatment includes ***intravenous thrombolysis (IVT)*** and ***endovascular thrombectomy (EVT)***.[4-10]

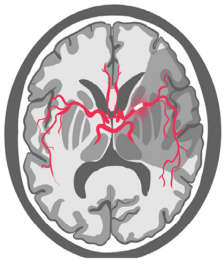
Treatment indications

≤ 4.5 HRS

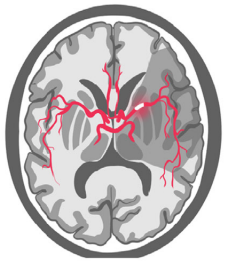
> 4.5 HRS



IVT



IVT & EVT



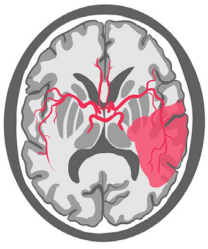
EVT

FOCUS OF REVIEW

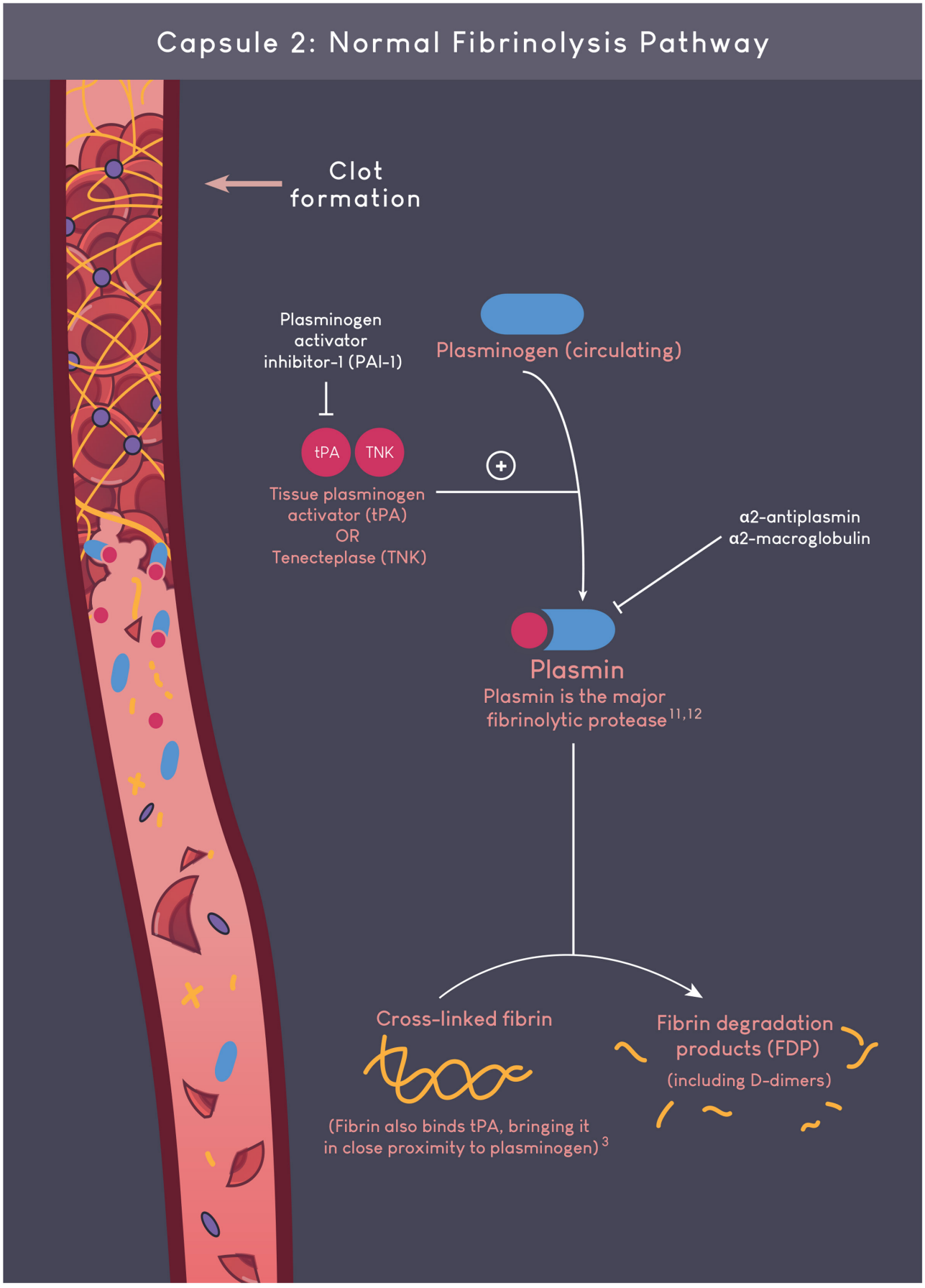
Comparing mechanisms of action, effectiveness, and safety of IVT therapies: **Alteplase (tPA) and Tenecteplase (TNK)**

Contraindication to treatment

Acute hemorrhage



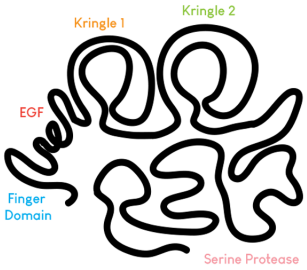
→ ⊘ IVT & EVT


Capsule 2: Normal Fibrinolysis Pathway
Clot formation
Plasminogen activator inhibitor-1 (PAI-1)
Plasminogen (circulating)
tPA
TNK
Tissue plasminogen activator (tPA) OR Tenecteplase (TNK)
α2-antiplasmin
α2-macroglobulin
Plasmin
Plasmin is the major fibrinolytic protease[11,12]
Cross-linked fibrin
(Fibrin also binds tPA, bringing it in close proximity to plasminogen)[3]
Fibrin degradation products (FDP)
(including D-dimers)

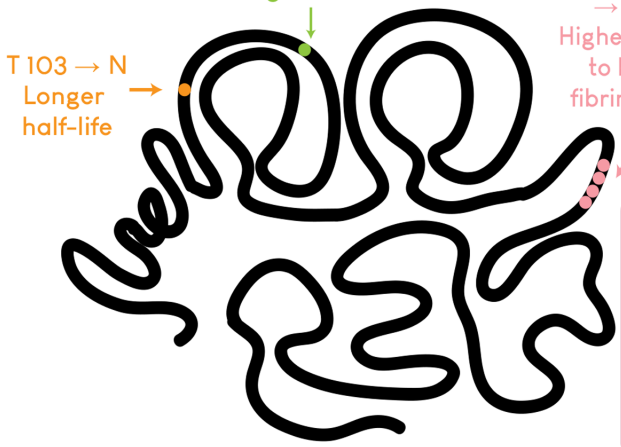
Capsule 3: Pharmacokinetics of thrombolysis

Amino acid structure [13,14]

tPA



TNK



A - Alanine, H - Histidine, K - Lysine, N - Asparagine, Q - Glutamine, R - Arginine, T - Threonine

TNK is a genetically modified version of tPA created in 1994 [16]

Comparison of tPA vs TNK [11,19-21]

	tPA	TNK
Half-life	4 minutes	20 minutes
Fibrin specificity	Intermediate - can act on clot-bound and systemic plasminogen	High - acts primarily on thrombus
PAI-1 Resistance	Low	Intermediate
Fibrinogen depletion	Intermediate	Low
Laboratory markers	↑ PTT ↑ D-Dimer	↑ D-Dimer

TNK has...

- ↑Fibrin specificity
- ↑Half-life
- ↓Systemic Coagulopathy

TNK has theoretical benefit in recanalization and bleeding risk over tPA

Capsule 4: tPA and TNK for acute ischemic stroke

tPA

- 0.9mg/kg (max 90mg)
- 10% IV bolus & infusion over 60 minutes [4-5,22-24]
- Other doses studied: 0.6/mg (max 60mg) approved in Japan [25-29]

TNK

- 0.25mg/kg (max 25mg)
- Single bolus
- Other doses studied: 0.1 - 0.5 mg/kg [30-36]

Advantages of TNK

- Easier to administer
- Less room for dosing errors without infusion
- Increased efficiency – faster treatment, better for inter-hospital transfers
- More practical with infectious precautions

Disadvantages of TNK

- Inability to stop infusion if the patient's clinical status changes or new information arises

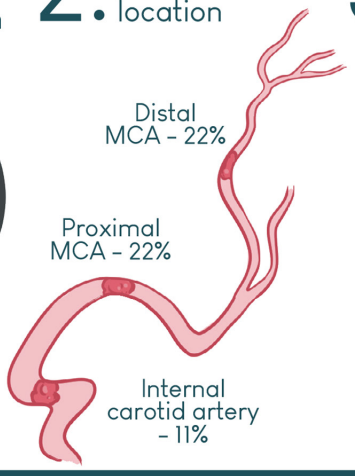
Capsule 5: Effectiveness of thrombolysis for recanalization

IVT has successful recanalization in 30% of patients [37-39]

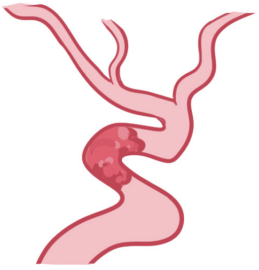
Factors associated with increased probability of recanalization with alteplase

1. Longer time from treatment to recanalization on imaging

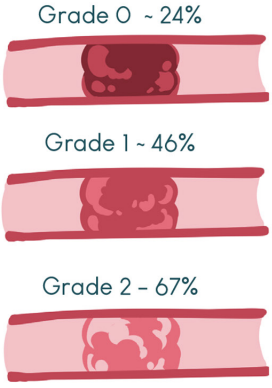
2. More distal thrombus location



3. Clot burden/ Clot length



4. Higher residual flow grades (i.e., permeability)



EVT has successful recanalization in 70% of patients (with or without thrombolysis) [8]

For patients with large vessel occlusion, eligible for IVT and EVT, is there any benefit to giving IVT?

No conclusive evidence to support direct to EVT (i.e., skipping thrombolysis). IVT remains standard of care in those eligible. [40-43]

Capsule 6: Take home messages from major TNK trials

Is TNK as effective as tPA?

Depends on the dose!

0.1 mg/kg

TNK 0.25mg/kg has better reperfusion and clinical outcomes compared to TNK 0.1mg/kg [34]

0.25 mg/kg

TNK 0.25mg/kg has similar or higher reperfusion compared to tPA 0.9mg/kg [35-36, 44-45]

Most likely the correct dose!

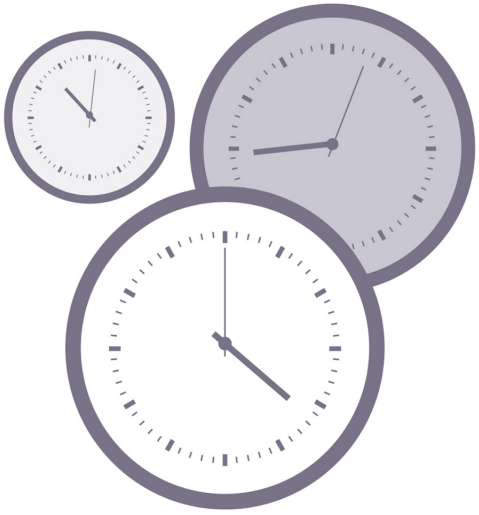
0.4 mg/kg

TNK 0.4mg/kg associated with increased symptomatic intracerebral hemorrhage [30,46-47]

Can TNK be used in the extended window?

Feasible, but effectiveness unclear yet [36,48]

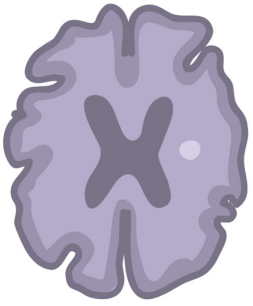
Most studies on late window IVT have used tPA



Can TNK be used with EVT?

Yes! TNK is associated with higher and earlier reperfusion than tPA [36,46]

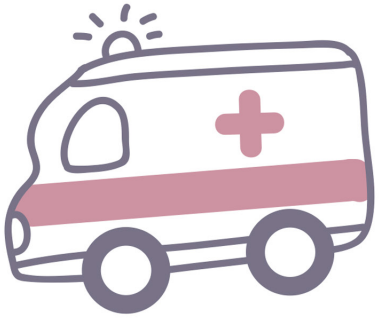
Can TNK be used for minor strokes?



Feasible and safe [32]
Phase III RCT ongoing (TEMPO-2: NCT02398656)

Can TNK be given in the ambulance?

Yes! Faster and better reperfusion [44]



Capsule 7: Current guideline recommendations

American Heart Association & American Stroke Association Guidelines [22]

- "It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy."
- "Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion."

Canadian Best Stroke Practice Recommendations [23]

- No specific mention of TNK in the guidelines published in 2018, but the acute stroke guidelines have been updated and are under submission. In the updated version, "tPA" has been replaced with the more general term "thrombolysis," which refers to tPA or TNK.

(Personal communication Dr. Patrice Lindsay, Director of Health Systems and Senior Editor, Canadian Stroke Best Practice Recommendations at the Heart and Stroke Foundation of Canada)

European Stroke Organisation Guidelines [24]

- "For patients with acute ischemic stroke of < 4.5 h duration and not eligible for thrombectomy, we suggest intravenous thrombolysis with alteplase over intravenous thrombolysis with tenecteplase."
- "For patients with acute ischemic stroke of < 4.5 h duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom intravenous thrombolysis is considered before thrombectomy, we suggest intravenous thrombolysis with tenecteplase 0.25 mg/kg over intravenous thrombolysis with alteplase 0.9 mg/kg."

Australian Stroke Foundation Guidelines [49]

- "For patients with potentially disabling ischemic stroke due to large vessel occlusion who meet specific eligibility criteria, intravenous tenecteplase (0.25mg/kg, maximum of 25mg) or alteplase (0.9mg/kg, maximum of 90mg) should be administered up to 4.5 hours after the time the patient was last known to be well."
- "For patients with potentially disabling ischemic stroke without large vessel occlusion who meet specific clinical and brain imaging eligibility criteria, tenecteplase may be used as an alternative to alteplase within 4.5 hours of onset."

Bottom Line:

1. It is reasonable to use TNK in patients who are otherwise eligible for tPA.
2. Several guidelines suggest TNK may be preferable over tPA in patients with large vessel occlusion.
3. Guidelines expected to be updated based on recent publications. [44-45,47]

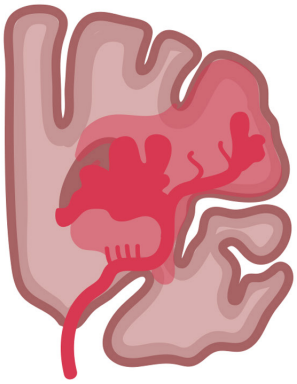
Capsule 8: Safety - Hemorrhagic Transformation

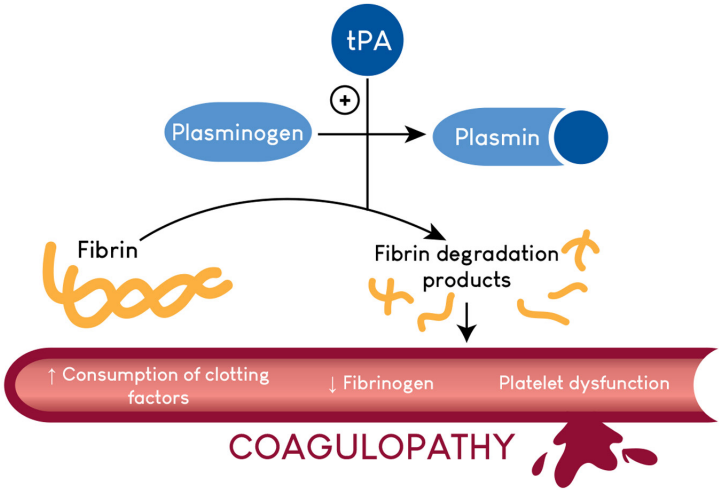
1 %
Risk of major systemic bleeding [50]

2-6%
Risk of symptomatic ICH (sICH) [51-54]

Characteristics of sICH [53]

- Intraventricular
- Large
- Multifocal
- Edema





Mechanism of TNK

Reduced sICH in TNK 0.25 mg/kg compared to tPA [18]

TNK may be associated with less hypofibrinogenemia and hypoplaminogenemia [19]

Management of symptomatic hemorrhagic transformation after thrombolysis [22]

Suspected ICH within 24 hours of thrombolytic adminstration

↓

STOP IV thrombolytic
Assess ABC's
Lower blood pressure (180/105 mmHg)

↓

STAT non-contrast CT Head
STAT bloodwork: CBC, PT/INR, aPTT, fibrinogen, type & cross-match

If fibrinogen < 1.5 g/L
- Give fibrinogen concentrate 4 g
- If fibrinogen not available, consider cryoprecipitate 10 units

If INR > 1.5 before thrombolytic and patient was on warfarin
- Give PCC 1000 IU and Vitamin K 10 mg IV

If platelets < 100 x 10^9/L
- Give Platelets x 1 adult dose (equivalent to 4 units)

Consider the following adjunct therapies on a case-by-case basis. There is currently a paucity of evidence for efficacy or harm:

- Tranexamic Acid: inhibits plasminogen activation and plasmin activity
  - 1,000 mg IV bolus
  - Could be followed by 1,000 mg IV infusion depending on clinical reassessment [11, 12]
- Plasma: if INR > 1.5, fibrinogen > 2.0 g/L and patient not on anticoagulation
  - Plasma 3-4 units (15 ml/kg)

Repeat CBC, INR, aPTT, fibrinogen 10 minutes after products completed to ensure coagulopathy resolved
Consult Neurosurgery and ICU

Capsule 9: Safety - Angioedema

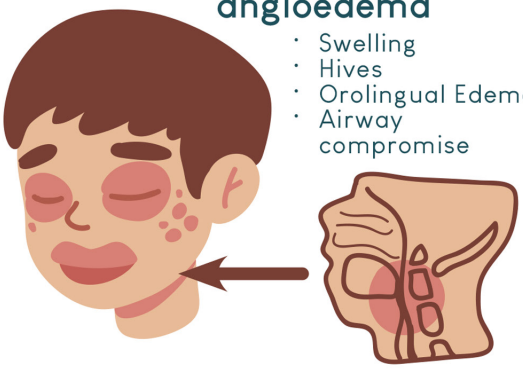
1 -5 %
Incidence of angioedema in patients receiving thrombolysis [55-56]

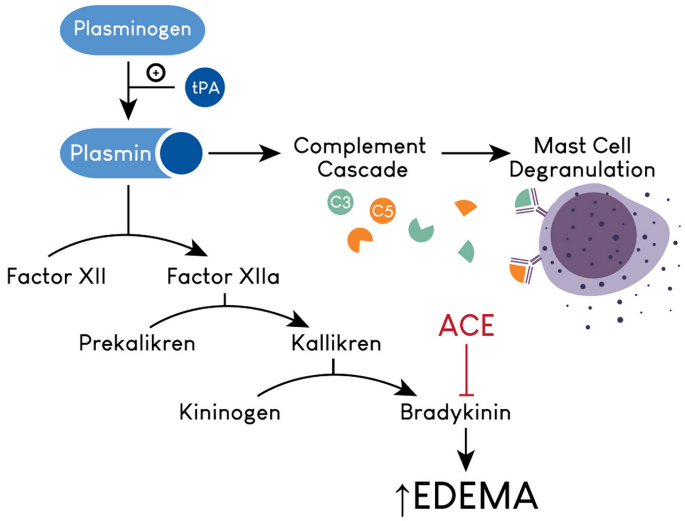
Risk factors

- ACE inhibitors
- Ischemia in insular/ frontal cortex
- Older age [57]

Characteristics of angioedema

- Swelling
- Hives
- Orolingual Edema
- Airway compromise





Mechanism

Thrombolysis can mediate a hypersensitivity reaction by activating complement cascade (histamine) and kinin pathway (bradykinin) [56,58]

Patients on ACE inhibitors are at higher risk [58]

Management of orolingual angioedema [22]

STOP IV thrombolysis

Assess airway

- Edema in larynx, palate, floor of mouth, oropharynx → **Consult ICU and ENT**
  May require intubation or cricothyrotomy
- Edema limited to anterior tongue and lips → **Monitor**

Administer medications

- Diphenhydramine 50 mg IV
- Methylprednisolone 125 mg IV
- Ranitidine 50 mg IV or Famotidine 20 mg IV

Patient on ACE inhibitor

- Hold ACE inhibitors
- Consider FFP or icatibant 3 ml SC [7]

If worsening angioedema or anaphylaxis:

- Epinephrine 0.3 ml IM or 0.5 mL by nebulizer

AUTHOR CONTRIBUTIONS

A.Z. contributed to the study design, manuscript drafting, and illustration. P.R. contributed to the study design and manuscript drafting. E.T. contributed to the study design and manuscript revision. S.B.C. contributed to the study design and manuscript revision. A.Y.X.Y. contributed to the study design, manuscript drafting and revision, and supervision.

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RELATIONSHIP DISCLOSURE

S.B.C. is the principal investigator of the TEMPO-2 trial, which is assessing the use of tenecteplase in the treatment of minor stroke. TEMPO-2 is funded by CIHR and the study drug is provided by Boehringer Ingelheim.

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