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Treating tPA-Associated ICH

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Disclosures

- I have received research funding from Pfizer, Portola, and Octapharma, and consulting from CSL Behring, Octapharma, Phillips, Portola, and NControl.

Presenter

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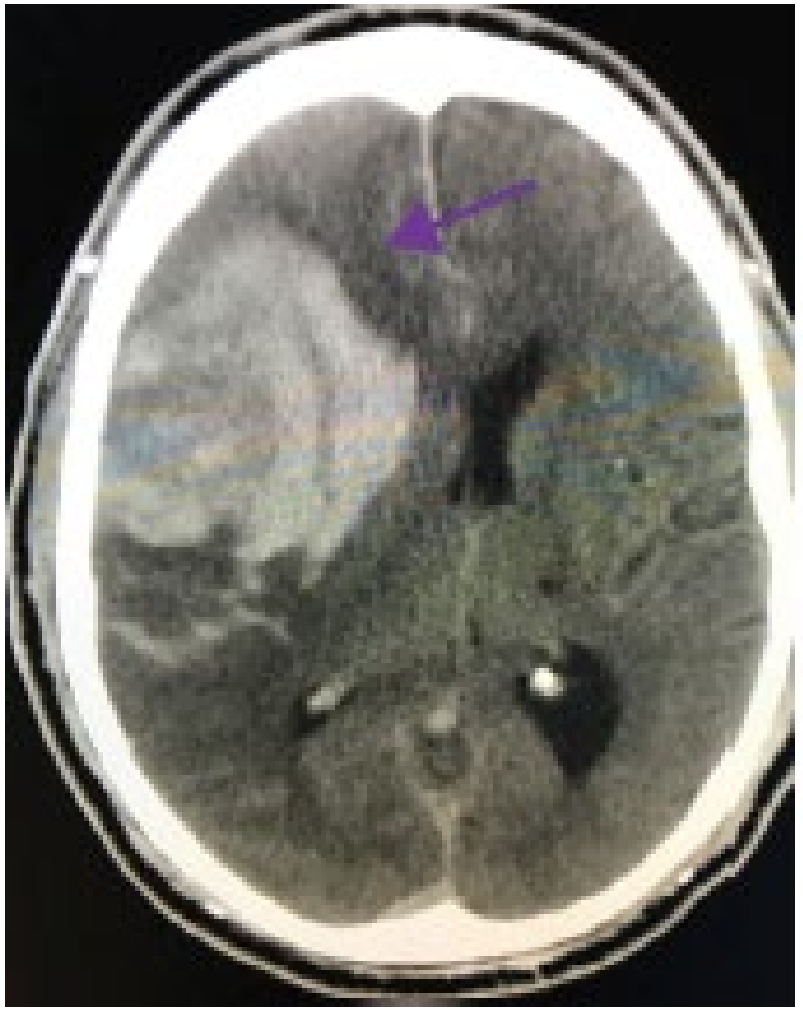
MGH 1811

VE RI TAS

Outline

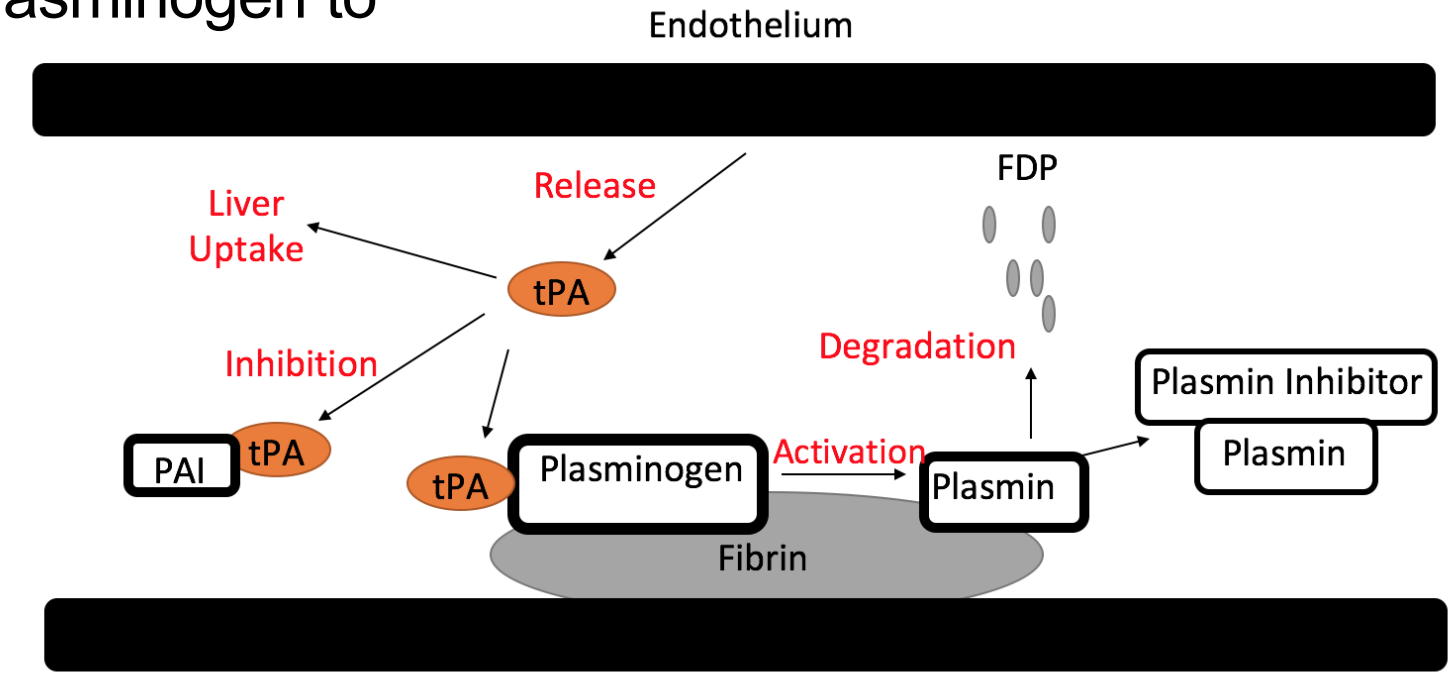
- Alteplase (tPA)
- tPA-Associated ICH – Not all the same
- Is there something to reverse?
- Options for treatment
- Supportive care



Yaghi S et al, Stroke 2017

tPA

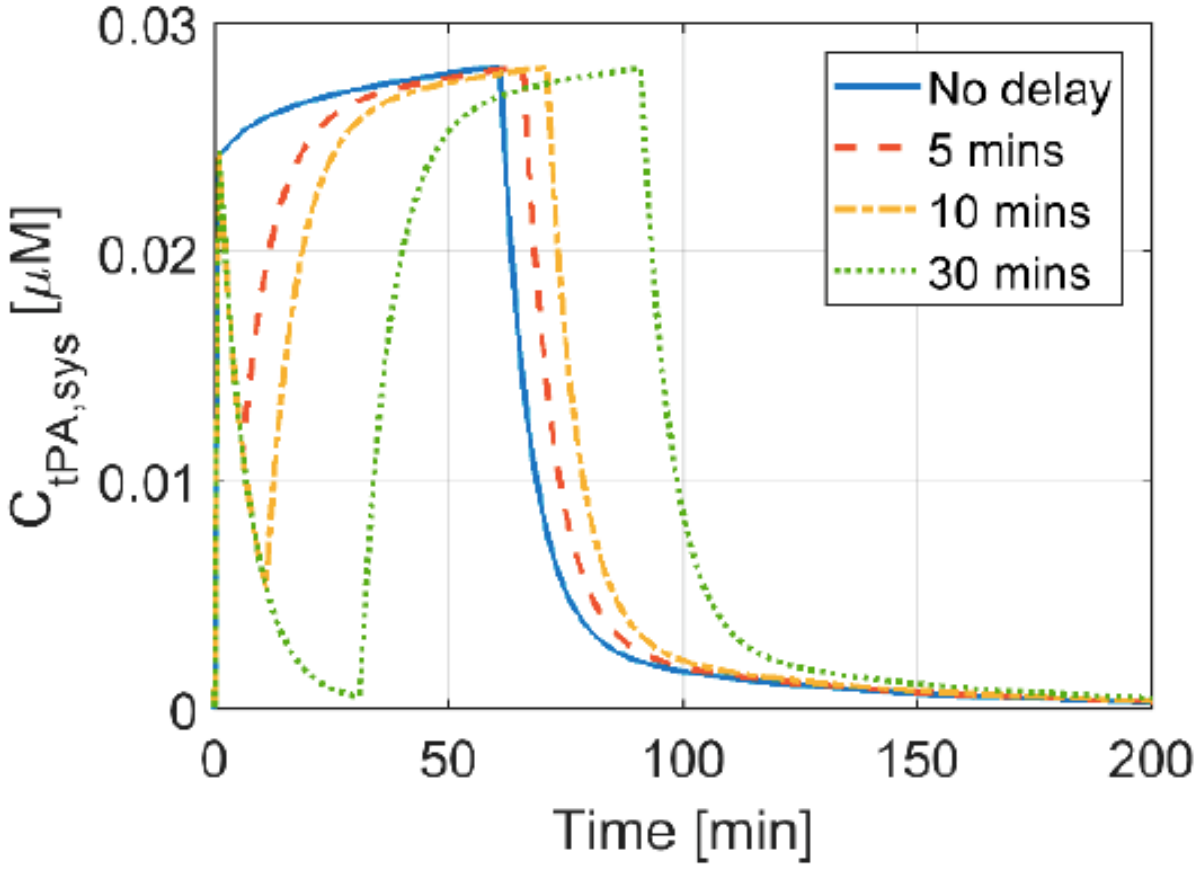
- Tissue plasminogen activator
- Catalyzes the conversion of plasminogen to plasmin
- Recombinant products
  - Alteplase
  - Retevase
  - Tenecteplase



Source: Wikipedia

How long does it last?

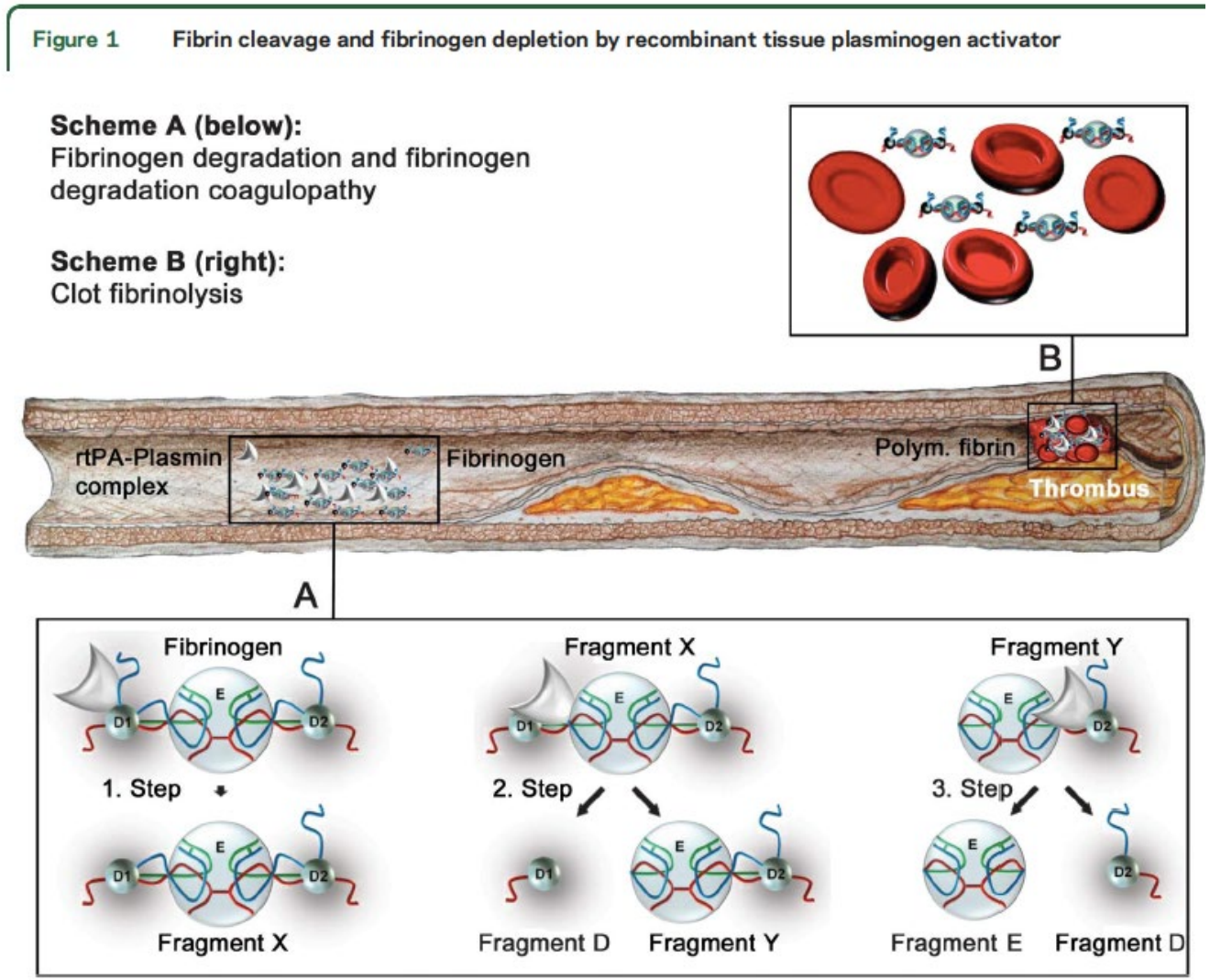
- Alteplase: Given as IV bolus then 1 hour infusion
- Half life = 5-10 minutes
- After the end of infusion:
  - Approximately 50% cleared within 5 minutes
  - Approximately 80% cleared within 10 minutes
- Tenecteplase half life: 20 minutes



Gu B et al, Pharmaceutics 2019

Effects of tPA

- Fibrinogen degradation – reduced fibrinogen!
- Fibrinogen degradation products are created



Matosevic B et al, Neurology 2013

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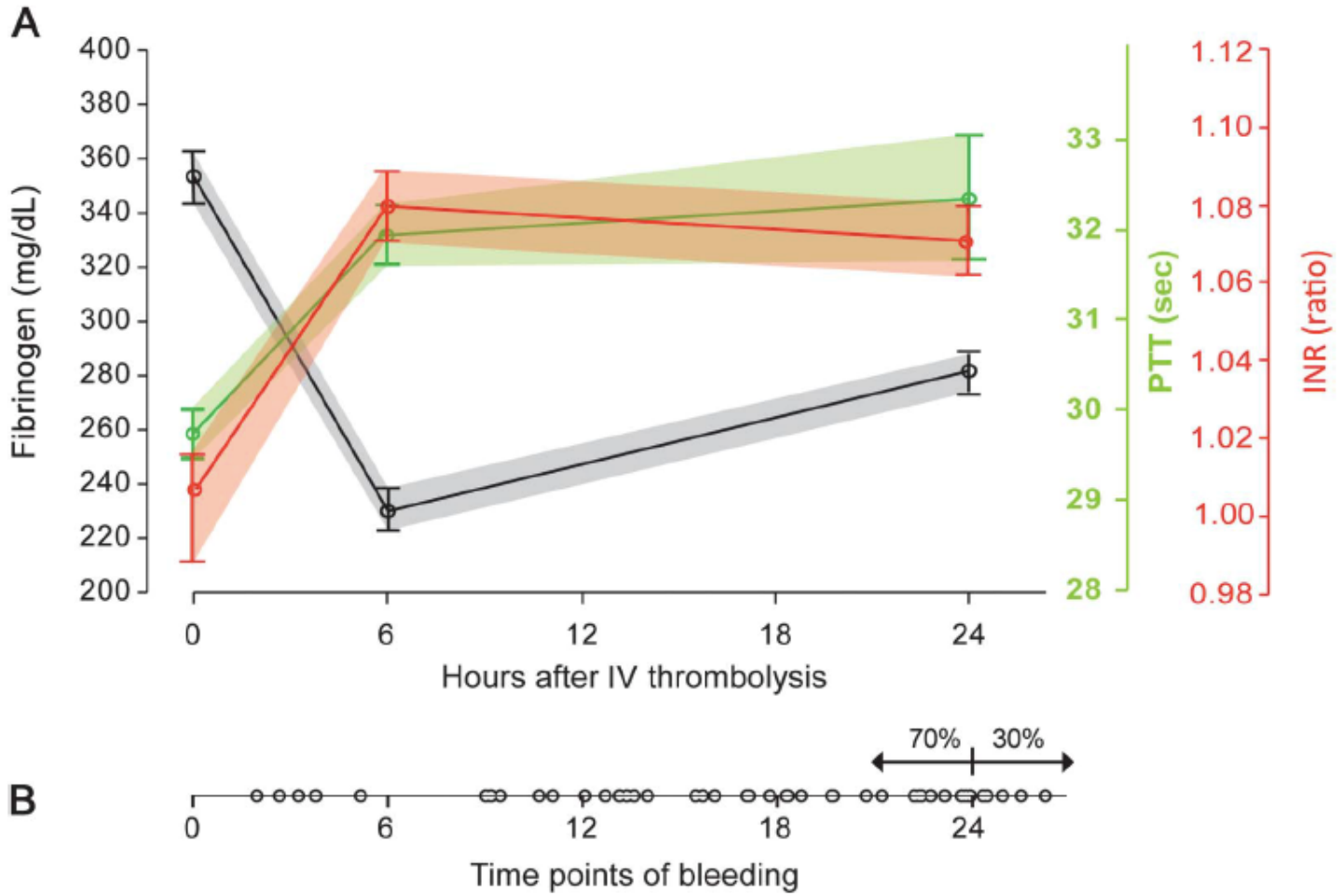
Effects of tPA last longer than the drug itself

Figure 2 Changes after stroke thrombolysis and time points of the clinical manifestation of major bleeding complications



Matosevic B et al, Neurology 2013

Coagulopathy and tpa-ICH

- More severe coagulopathy may be associated with higher ICH risk
- Reduction in fibrinogen and increased FDPs are also associated with increased risk of sICH.
- Hypofibrinogenemia (fibrinogen<200 mg/dL) is associated with increased risk.
- Goal of treatment: Treat coagulopathy (rather than “reverse” tPA).

Yaghi S. et al, Stroke 2017

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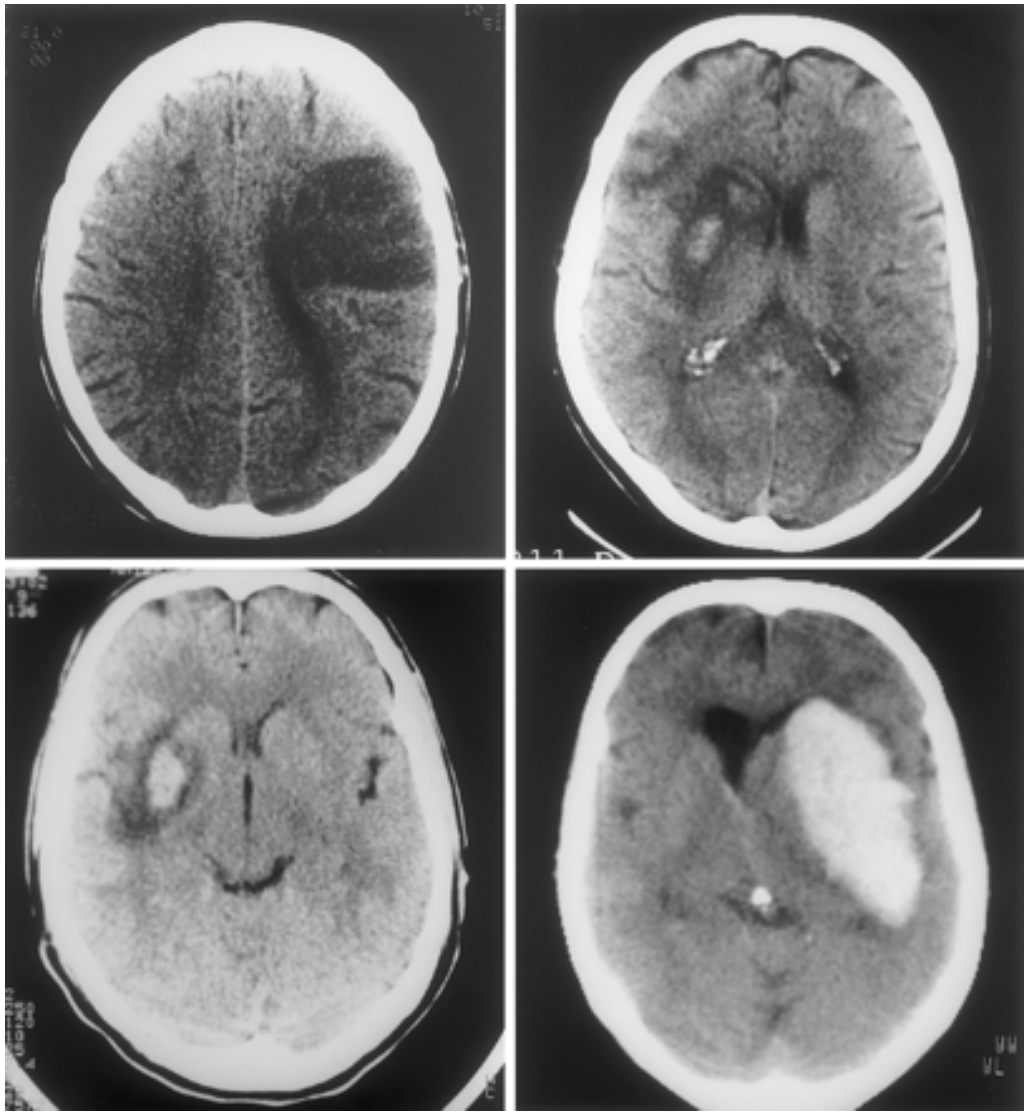
When does post tPA sICH occur?

- Of those who will develop this, it will happen:
  - Within 12 hours in 65-80% of patients
  - Within 12-24 hours in 15-20% of patients
  - Within 24-48 hours in <10% of patients

Is all ICH the same after tPA?

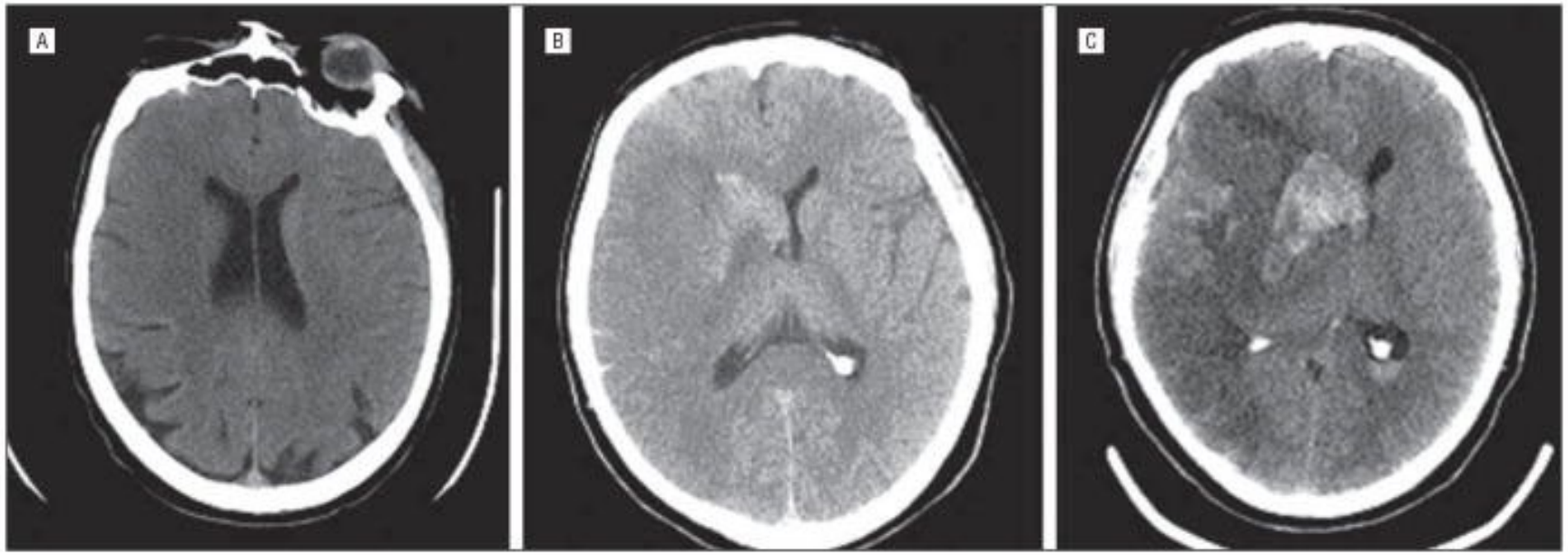
- This shows 4 different types:
  - HI (Hemorrhagic infarct) 1 = small petechiae
  - HI2 = confluent petechiae
  - PH1 (parenchymal hemorrhage) = <30% of the infarcted area
  - PH2 = >30% of the infarcted area with significant space-occupying effect, or clot remote from infarcted area.
- Only PH2 is probably worse for the patient
- HOWEVER: can we prevent the small ones from becoming large?



Fiorelli et al, Stroke 1999;30:2280-2284

Do patients have ongoing bleeding after sICH?

- Yes - up to 40% can have further bleeding.
- Example: This was a 56 year old male with left sided weakness who received tPA for stroke



1.5 hours | 11 hours | 19 hours

Goldstein JN et al, Arch Neurol 2010

Conclusions

- The half-life of tPA is so short that you can't specifically "reverse" it.
- However, the impact of tPA on the coagulation system can last 24 hours
  - And, many people have ongoing bleeding after tpa-ICH diagnosis
- Therefore, there is probably a window of opportunity to improve hemostasis, and maybe minimize further bleeding.
- Do we have any tools to do this?
- Are there any clinical trials?

First question- whether to "do" anything

- Are there some people with tPA ICH who could benefit from procoagulant treatment and some who cannot? How to know?
- Should we use risk of ongoing expansion?
  - Patients with preexisting (or current) coagulopathy are highest risk
- Should we use opportunity to benefit?
  - Small ICH
    - Don't treat: Lower risk of ongoing bleeding, unclear clinical relevance, concern for thromboembolism
    - Do treat: Large opportunity to benefit? This is the chance to stop a small bleed from becoming a large bleed!
  - Large ICH
    - Don't treat: The damage is done – low opportunity to benefit
    - Do treat: High risk of expansion, opportunity to prevent this.

Second question- how to treat tPA-associated coagulopathy

- There are no clinical trials or high quality large multicenter studies.
- This event is so rare that there are only small single center observational studies.
- Guidance is based on expert opinion
  - (Stroke, 2017).

AHA/ASA Scientific Statement

Treatment and Outcome of Hemorrhagic Transformation After Intravenous Alteplase in Acute Ischemic Stroke

A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

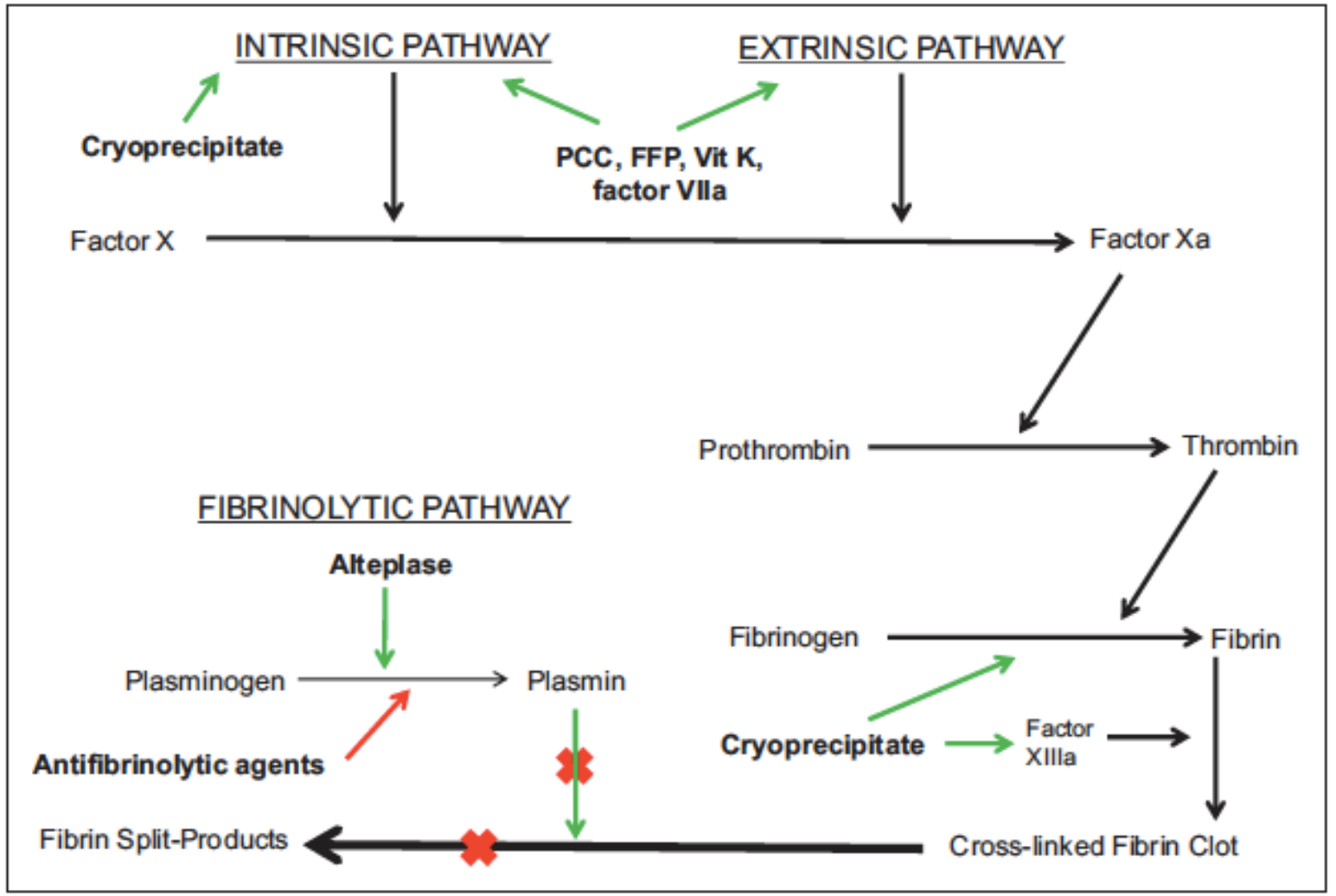
The American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Cerebrovascular Section affirms the educational benefit of this document.

Shadi Yaghi, MD, Chair; Joshua Z. Willey, MD, MS, FAHA, Vice Chair; Brett Cucchiara, MD, FAHA; Joshua N. Goldstein, MD, PhD, FAHA; Nicole R. Gonzales, MD; Pooja Khatri, MD, MSc, FAHA; Louis J. Kim, MD; Stephan A. Mayer, MD, FAHA; Kevin N. Sheth, MD, FAHA; Lee H. Schwamm, MD, FAHA; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Quality of Care and Outcomes Research

Options for treatment

- 1. Cryoprecipitate
- 2. Antifibrinolytics
  - Aminocaproic acid (Amicar), tranexamic acid
- 3. Platelets
- 4. Fresh frozen plasma (FFP)
- 5. Prothrombin Complex Concentrate (PCC; Kcentra most commonly in the US)
- 6. Factor VIIa (NovoSeven).

Options for treatment



Yaghi S et al, Stroke 2017

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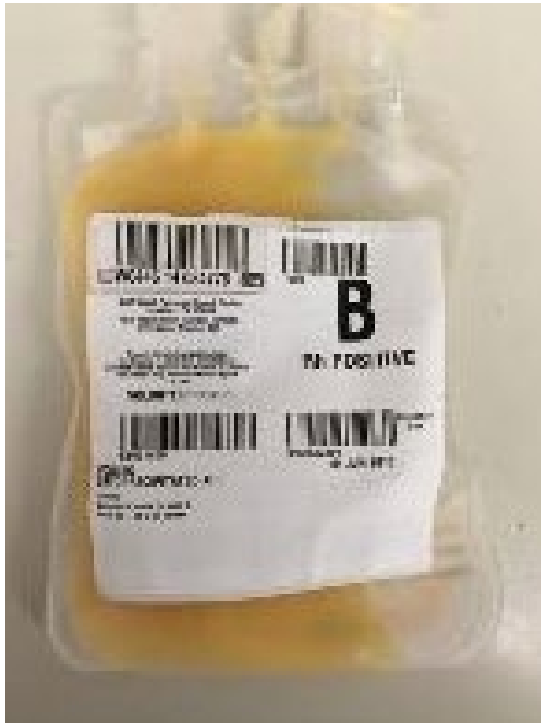
Cryoprecipitate

- Derived from Fresh Frozen Plasma (FFP)
- Contains Fibrinogen!!!!
  - (plus other components of coagulation cascade)
- Options:
  - 1. Administer 10 units empirically
    - Treat presumed hypofibrinogenemia
  - 2. Stat check fibrinogen level
    - Provide cryoprecipitate as needed to treat hypofibrinogenemia
    - Goal fibrinogen >150mg/dL
- Risks:
  - Transfusion reaction, thromboembolic events

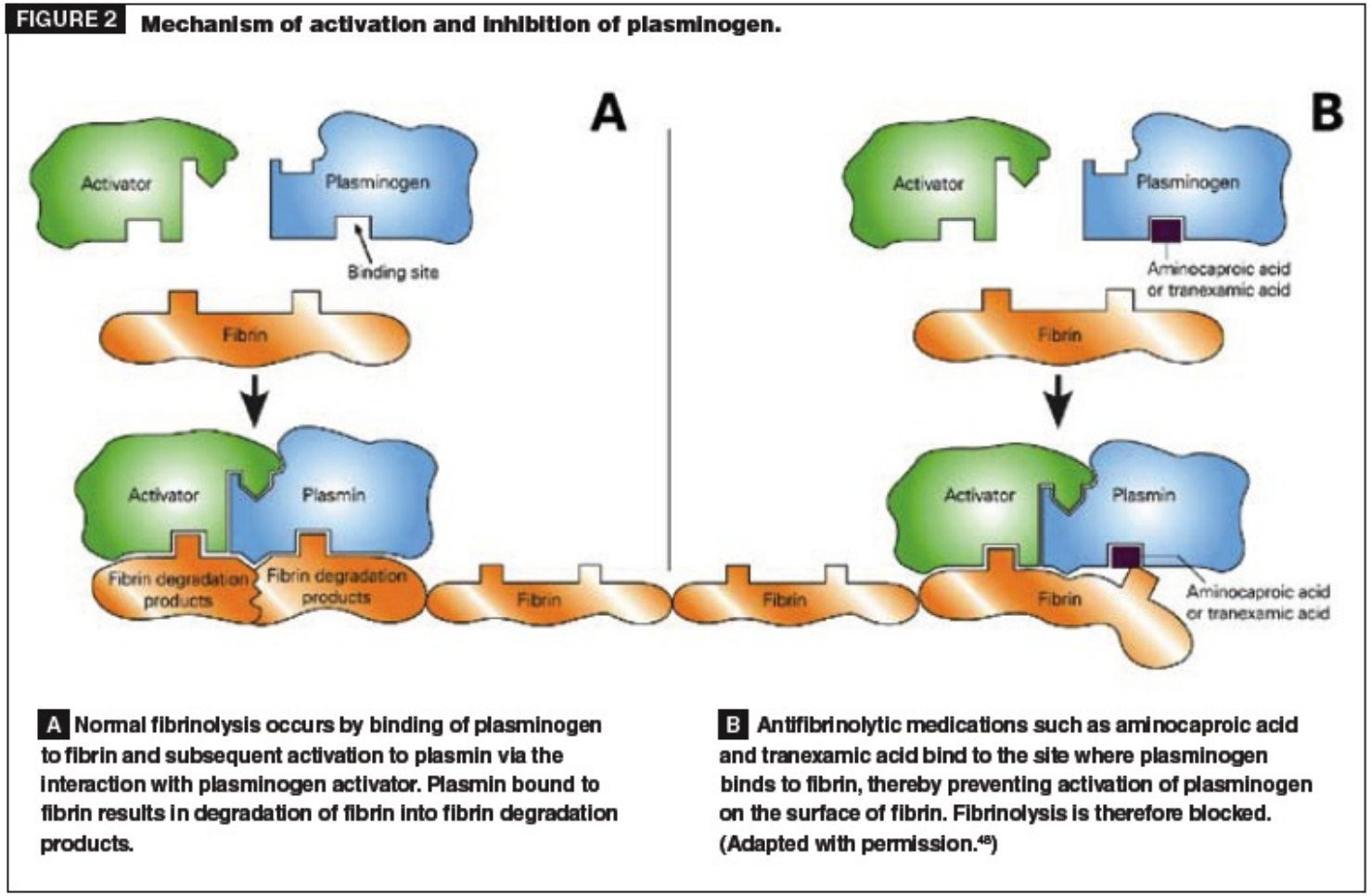


From UTMB

AHA Scientific Statement: Yaghi S et al, Stroke 2017

Antifibrinolytics

- These inhibit plasmin
- Prevent it from binding to fibrin and dissolving it.
- Therefore, they prevent plasmin from dissolving clots
- Since alteplase acts by converting plasminogen to plasmin, increasing plasmin levels, these are the most obvious ”anti tPA” agents.



From: Peripheral Brain, https://pbrainmd.wordpress.com/2015/10/15/1335/

Antifibrinolytics

- Aminocaproic acid (Amicar)
  - Common options:
  - 5g IV bolus
  - 4g IV, then 1g/hour for 8 hours
- Tranexamic acid (TXA)
  - Common dosing: 10mg/kg
- Risks: Thromboembolism

Platelets

- Thrombolysis may lead to platelet inhibition
- Some authorities recommend platelet transfusion to treat this.
  - For patients with thrombocytopenia, platelet transfusion is recommended
  - Otherwise, consider if platelet dysfunction is suspected
  - Consider 8-10 Units
- Risks: Volume overload, transfusion reaction, thromboembolic events

Wikipedia

Prothrombin Complex Concentrates

- Concentrate of vitamin K dependent coagulation factors (II, VII, IX, X), protein C and protein S.
- May help active both intrinsic and extrinsic pathways, facilitated conversion of fibrinogen to fibrin.
- May need to replenish fibrinogen first to provide substrate
- For patients who were on warfarin (coumadin) prior to t-PA, PCC is an excellent choice to restore hemostasis.
- Risks: thromboembolic events

Fresh Frozen Plasma (FFP)

- Plasma collected from donors
- Contains all major components of the coagulation cascade
- Large volume, is limited in rate it can be transfused.
- Consider for those on warfarin prior to tPA, if PCCs are not available.
- Risks: Volume overload, transfusion reaction

Wikipedia

Recombinant activated factor VIIa

- Brand name: NovoSeven
- Activates the coagulation system and promotes hemostasis
- Shown to reduce hematoma expansion in patients with spontaneous ICH (not tPA related)
- Sometimes used off label for multiple types of coagulopathy
- Risk of thromboembolism

Conclusion: Options to treat coagulopathy

- The agents with the most theoretical support:
  - Cryoprecipitate if fibrinogen is low
  - Antifibrinolytics (aminocaproic acid or tranexamic acid)

Supportive care

- How else can we treat sICH:
  - Blood pressure lowering
    - Some evidence from spontaneous ICH that goal SBP<140 can reduce risk in that disease, though unclear if clinically relevant
    - Also, concern for hypoperfusion in the setting of ischemic stroke
  - Anticoagulation reversal
    - If the patient was anticoagulated prior to t-PA administration
  - Surgical ICH evacuation
    - There are minimal data in this setting
    - Consider for cerebellar ICH, for mass effect, for ongoing neurologic deterioration

Question

Thank You