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TX Yay or Nay: An Overview of the Clinical Utility of Tranexamic Acid

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Disclosures

- The presenter was a speaker for Haemonetics in the past 24 months. This relevant financial relationship has ended and been mitigated.
- The presenter will discuss off-label use of tranexamic acid.

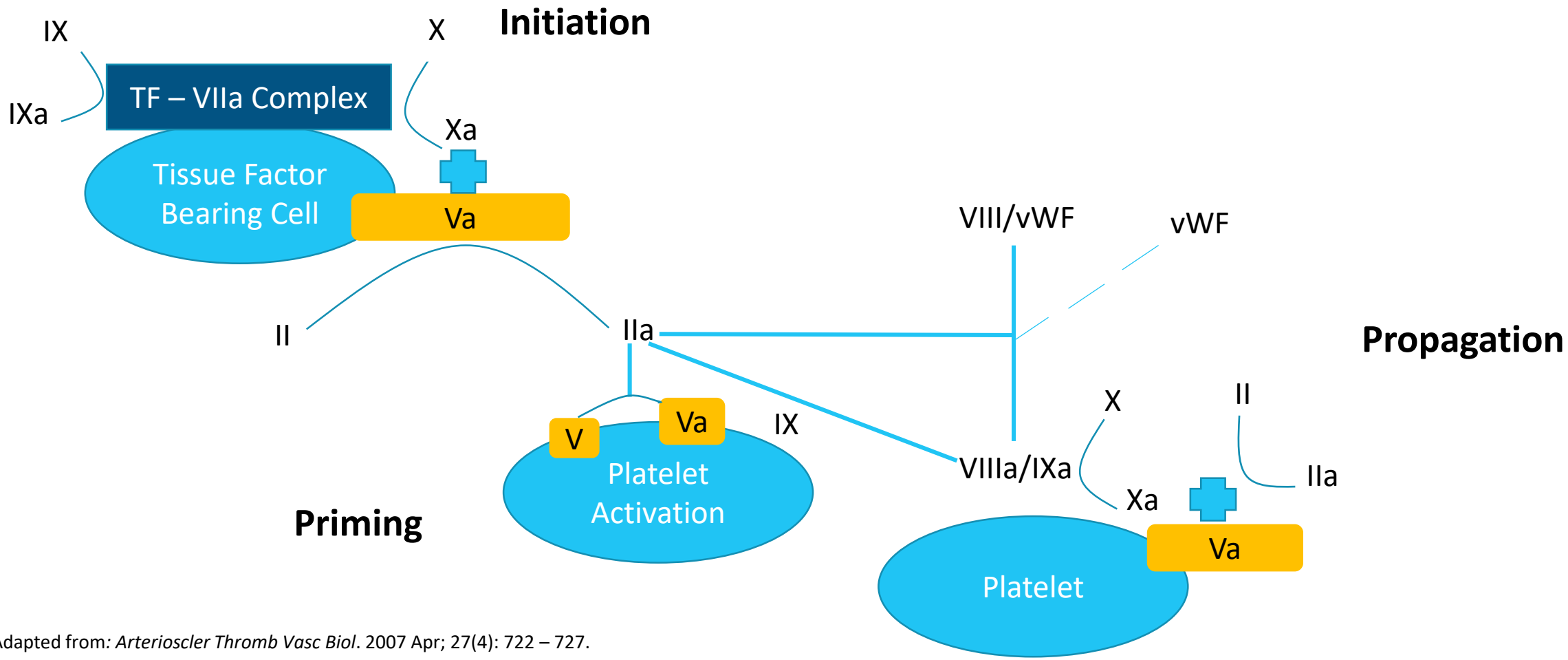
Note: This program may contain the mention of suppliers, brands, products, services or drugs presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand, product, service or drug.

Learning Objectives

At the end of this session, participants should be able to:

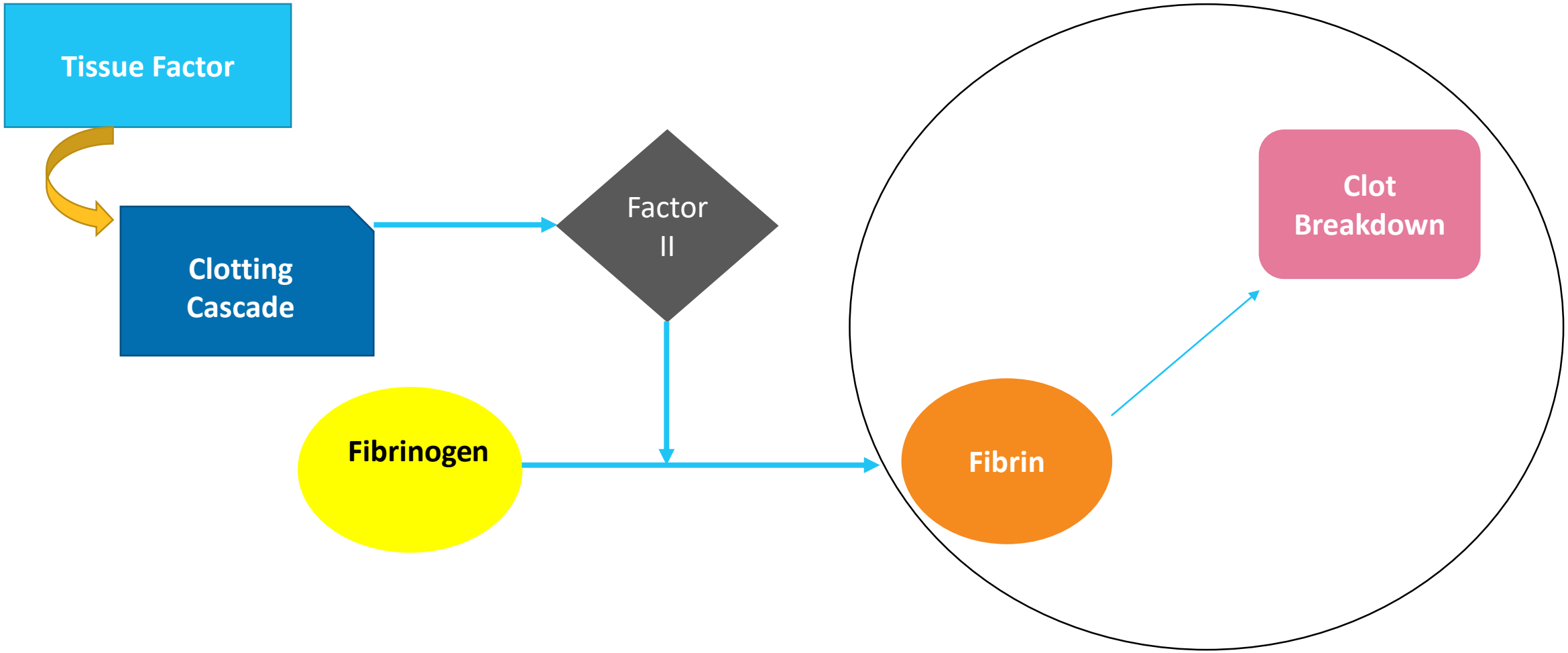
1. Recall the mechanism of action of tranexamic acid (TXA) and how it is incorporated into hemostasis
2. Identify pros and cons to administration of TXA in patients experiencing variable disease states presented
3. Recognize strategies for administration processes that will improve efficiencies

Cell-based Model of Coagulation



Adapted from*: Arterioscler Thromb Vasc Biol*. 2007 Apr; 27(4): 722 – 727.

TXA is a Narrow Spectrum Hemostatic Agent



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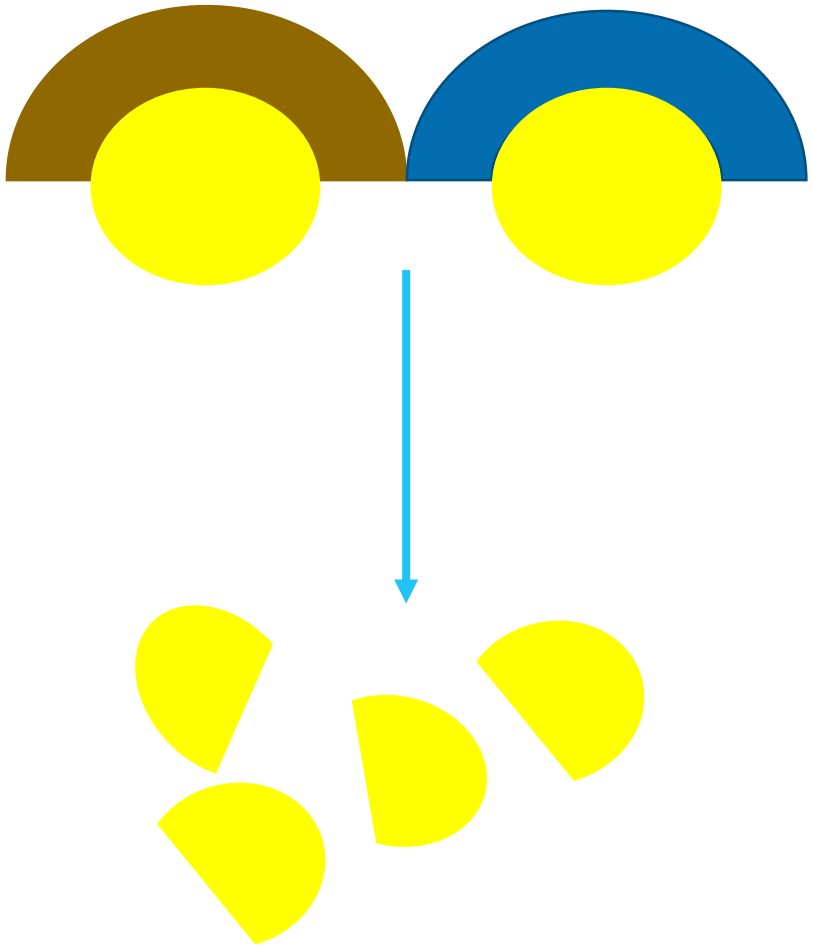
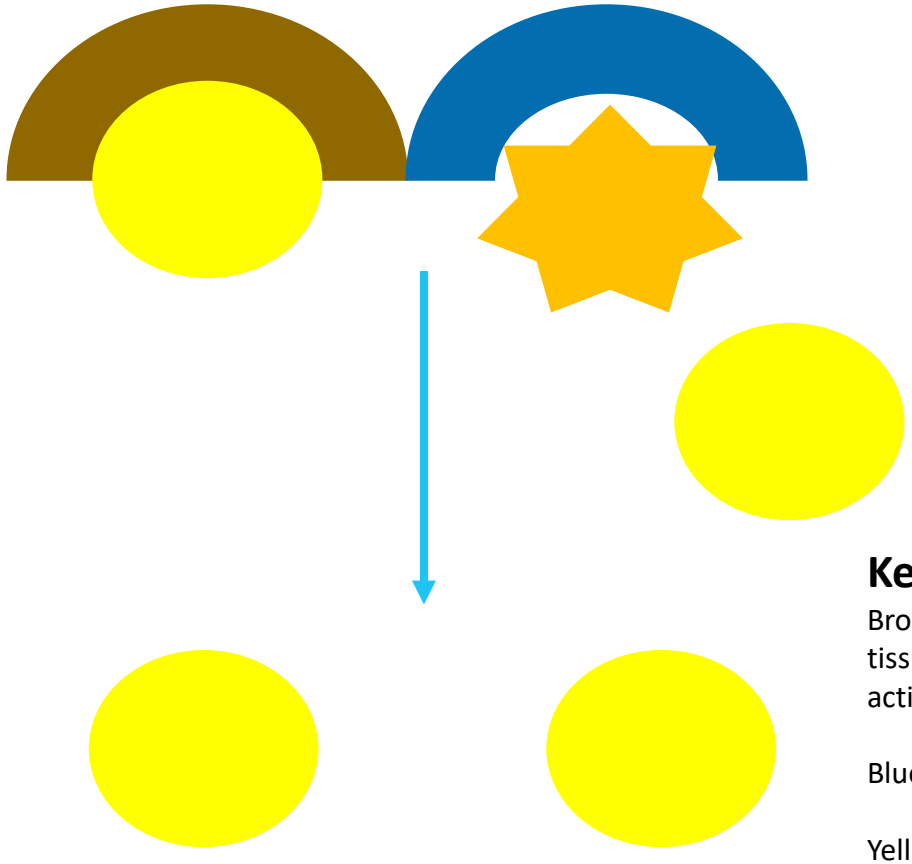
Fibrinolysis & TXA's Mechanism of Action





Key:

Brown = endogenous tissue plasminogen activator (tPA)

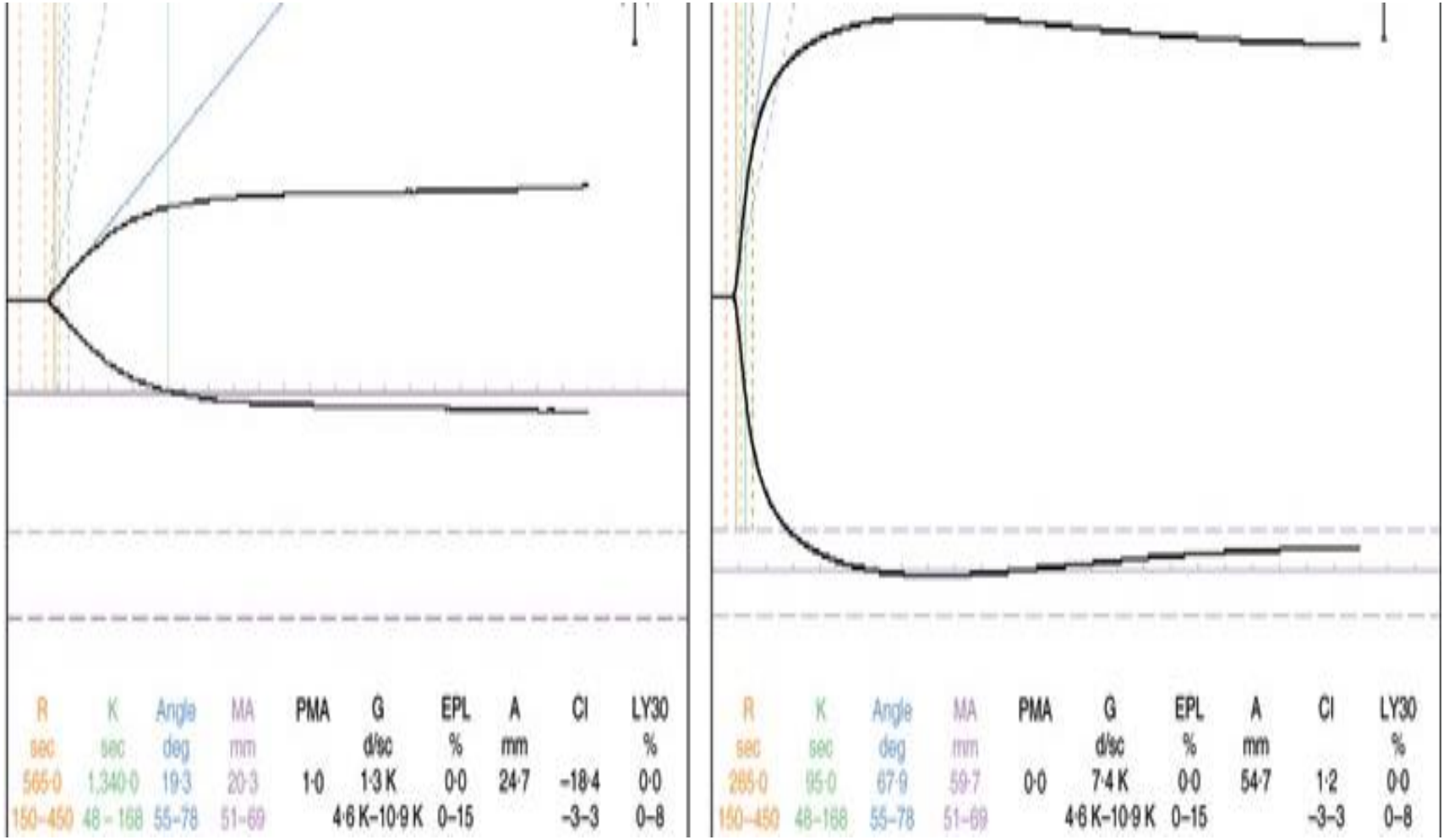
Blue = plasminogen

Yellow = fibrin and fibrin degradation

Red = Orange

Adapted from: Wu. *PLoS ONE*. 2020 May 26; 15(5): e0233640.

Identifying Fibrinolysis Phenotypes



Source: Computer generated by presenter, do not reproduce without permission

Fibrinolysis Phenotypes

Hyperfibrinolysis	Physiological Fibrinolysis	Fibrinolytic Shutdown
Increases in endogenous tPA; down regulation of plasminogen activator inhibitor; patients would benefit from anti-fibrinolytic therapy like TXA	Normal hemostatic properties with balance of clot stability and breakdown; no intervention is needed in this phenotype	Endogenous tPA resistance; upregulation of plasminogen activator inhibitor; patients at risk for organ failure and venous thromboembolism

tPA, tissue plasminogen activator

Source: Moore. *Nat Rev Dis Primers*. 2021 Apr 29;7(1):30.

Pros & Cons of Empiric TXA Use

Variable	Pro	Con
Efficacy		✓
Safety		✓
Cost	✓	

Administration & Dosing

- Wide variability in reported doses but most consider the 1 g diluted in 100 cc of normal saline administered over 10 minutes +/- 1 g over 8 hours

- Package insert discourages rapid undiluted administration for fear of hypotension
  - This data was derived from elderly and cardiothoracic patients already at risk for hypotension

- U.S. military recommends administration of 2 g undiluted rapid push
  - Does this translate to non-tactical settings?

Sources: *J Spec Oper Med.* 2020 Fall; 20(3):36 – 43.
J Spec Oper Med. 2020 Winter; 20(4): 85 – 91.

Case 1

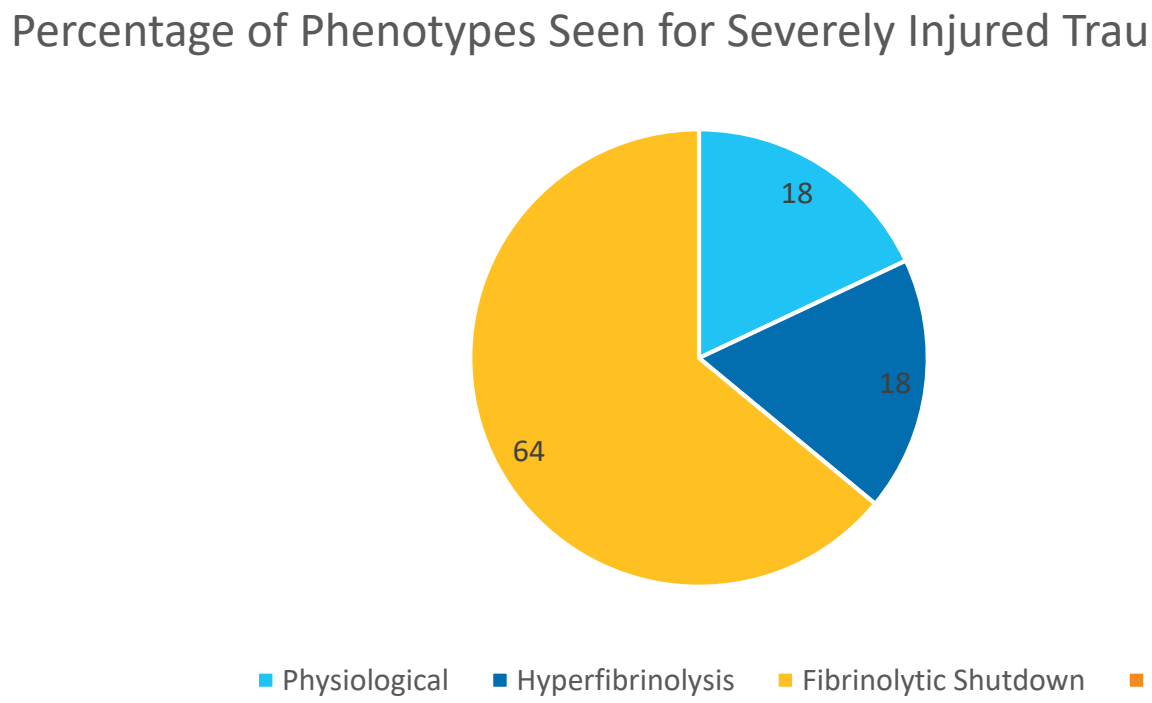
- TC is a 42-year-old male with no known past medical history who was involved in a motor vehicle collision going at highway speeds
- He is transported quickly by EMS to the local trauma center and is being evaluated
- Vitals include: BP 74/63, O2 saturation of 93%, HR 150
- +FAST
- He is receiving 1 unit of PRBC (~250 cc)
- For access the patient has an 18 g antecubital while more access is trying to be obtained
- The trauma surgeon is asking if we should administer TXA
  - If planning on administering, what dose would you choose?
    - How would you administer?

Endogenous tPA During Hemorrhagic Shock

- Bleeding remains the #1 cause for preventable mortality in trauma patients
- Hypotension seems to drive the release of endogenous tPA, resulting in hyperfibrinolysis
- Some trauma models show reductions in plasminogen activator inhibitor as well
- Therefore TXA in this patient population where we see most benefit from empiric use
  - Shock
  - Those requiring massive transfusion protocol

Source: Moore. *Nat Rev Dis Primers*. 2021 Apr 29;7(1):30.

Majority of Trauma Patients Should Not Benefit From Empiric TXA Use Based on TEG® Findings



Source: Adapted from: Moore. *J Trauma Acute Care Surg.* 2015 Jun; 78(6 Suppl 1): S65 – 69.

TXA Mania

- Large, randomized controlled trial
  - 274 hospitals
  - >20k patients
  - Empiric use in polytrauma cohort
    - Including TBI
  - 1 g TXA over 10 minutes
    - 1 g TXA over 8 hours

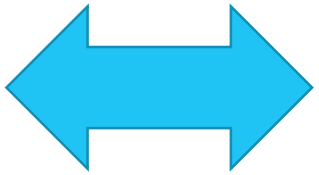
CRASH – 2 Trial

Source: *Lancet*. 2010; 376(9734): 23–32.

CRASH-2 Results

All cause mortality with TXA (14.5% vs. 16.0%; RR 0.91; 95% CI 0.85 – 0.97)

Death due to bleeding with TXA (4.9% vs. 5.7%; p=0.007)



No difference in transfusion requirements (50.4% vs. 51.3%; p=NS)

No difference in vascular occlusive events (1.7% vs. 2.0%, p=NS)

Source: *Lancet.* 2010; 376(9734): 23 – 32.

CRASH-2 Comments

- If TXA did not reduce blood transfusions how did it reduce mortality?
- Do these results still apply when trauma center availability is so prevalent in the U.S.?
- There was no difference in the “dead and dependent” secondary outcome so were the survivors from the TXA group associated with poor neurological outcomes?
- Was the population really sick enough? The greatest benefit seen was in the subgroup of patients with systolic blood pressures <75 mmHg

Source: *Lancet.* 2010; 376(9734): 23–32.

Case 1 Revisited

- While we do not have a repeat BP after the 1 unit of blood, the +FAST could indicate active hemorrhage and shock
  - At this point the patient might benefit from TXA based on subgroup analysis of the CRASH-2 study
  - With limited access we do not want to tie a line up with TXA running so a bolus option is supported by military and pre-hospital data
    - Doses supported in the literature are 1–2 g IV push
      - There is likely no benefit to continuing TXA (especially for 8 hours) if source control is obtained; therefore would recommend just the bolus and if concerned for ongoing fibrinolysis could consider serial fibrinogens or viscoelastic testing

Case 2

- LM is a 28-year-old male who presents after a slip and fall from standing because of intoxication and icy steps
- No other external trauma is noted and his FAST is negative but CT shows SDH
- His vitals are all normal for age
- His traditional coagulation tests are all normal
- A rapid TEG is drawn with the following values:
  - **ACT – 152 seconds (86 – 118 seconds)**
  - **R Time – 1.1 minutes (0.3 – 0.8 minutes)**
  - K Time – 0.9 (normal)
  - Alpha angle – 76 degrees (normal)
  - Maximum amplitude – 71 (normal)
  - **Ly% at 30 minutes – 0.3% (0.8 – 3%)**

CRASH-3

- Large, randomized controlled trial
  - 175 hospitals in 29 countries
  - >12k patients randomized
  - Empiric use in isolated TBI patients
    - Blunt and penetrating
  - 1 g TXA over 10 minutes
    - 1 g TXA over 8 hours

CRASH – 3 Trial

Source: *Lancet.* 2019; 394 (10210): 1713–1723.

CRASH-3 Results

28-day, in-hospital head injury associated mortality, RR 0.94 (95% CI 0.86 – 1.02)

Mortality in mild to moderate TBI (GCS 9 – 15), 5.8% vs. 7.5%, RR 0.78 (95% CI 0.64 – 0.95)

Disability rating scale

Vaso-occlusive events, 1.6% in both groups, seizures 3.2% in TXA vs. 3.0% in placebo, p=NS

Source: *Lancet.* 2019; 394 (10210): 1713 – 1723.

CRASH-3 Comments

- Did not assess fibrinolytic phenotype prior to TXA administration
- Controversy on primary outcome “head injury associated mortality”
- Without surveillance of vaso-occlusive events could there be a falsely low incidence rate?
- Potential type I error with the “positive” subgroup analysis findings and likely deserves further exploration prior to routine implementation

Source: *Lancet.* 2019; 394 (10210): 1713 – 1723.

Case 2 Revisited

- This patient has suffered an isolated TBI
- The trauma surgeons are asking for TXA in hopes of preventing hematoma expansion
- Nothing empirically stood out as to why this patient should receive TXA
- Traditional coagulation tests were normal but some abnormalities were noted on TEG
- This patient's TEG profile can be interpreted as clotting factor dysfunction, normal fibrinogen and platelet function, and fibrinolytic shutdown indicating no clot breakdown
- This patient would not benefit from TXA and it's likely this could contribute to VTE risk if given

Final Comments on TXA Use in Trauma

- Reasonable to consider empiric administration to those presenting in shock or high risk for massive blood transfusion activation
- Viscoelastic data highlighting fibrinolytic phenotype can prevent erroneous administration or possibly reduce occlusive events
- Unclear role for TXA use in developed countries with abundance of access to trauma centers where source control can be obtained

Aneurysmal Subarachnoid Hemorrhage (aSAH)

- Type of stroke which has arterial bleed within the subarachnoid space which is a common devasting cerebrovascular disease
- Rebleeding leads to increased mortality and poor neurological outcomes (rates as high as 20% with highest incidence within 24 hours after rupture)
- High clinical focus on preventing rebleeding and source control of hemorrhage
- Must balance cerebral ischemic with ongoing hemorrhage
- TXA remains controversial for use in aSAH

Source: *Front Neurol.* 2022 Jan 24; 12:710495.

Metanalyses of TXA Use in aSAH

- 10 RCTs, 2,810 patients (1410 with TXA and 1400 without TXA)
- TXA did not reduce overall mortality (RR 1.0, 95% CI 0.81 – 1.22)
- **Reduced rebleeding rate (RR 0.53, 95% CI 0.39 – 0.71)**
- **Hydrocephalus was higher in TXA group (1.13, 95% CI 1.02 – 1.24)**
- No difference in delayed cerebral ischemia (1.18, 95% CI 0.89 – 1.56)

Source: *Front Neurol.* 2022 Jan 24; 12:710495.

Final Comments on TXA Use in aSAH

- No indication for empiric use at this time
- If it prevents rebleeding there does not seem to be mortality or functional outcomes benefit in this cohort
- Rebleeding may be offset by increased cerebral ischemic but remains unclear
- Again, if viscoelastic testing suggests ongoing hyperfibrinolysis may consider

Postpartum Hemorrhage (PPH)

- Severe hemorrhage defined as ≥ 2,000 mL of blood loss
- Pathophysiology of PPH likely to due to hyperfibrinolysis and dysfibrinogenemia
- Ongoing coagulopathy can lead to more coagulopathy, etc.
- TXA suggested as an ideal agent in this situation to block progression and restore hemostasis

Source: *J Thromb Haemost.* 2022 Dec 22; S1538-7836(22)07652-8.

TXA in PPH

- Large randomized controlled trial
  - Double-blind, placebo controlled
    - 16-years of age or older
    - 193 hospitals in 21 countries
    - 1 g IV

WOMAN's Trial

Source: *Lancet.* 2017 May 27; 389(10084): 2105-2116.

WOMAN's Trial Results

MISCONCEPTIONS!

1) WOMAN's outcomes were not "positive"
   - Composite mortality and hysterectomy (NS), all-cause mortality (NS)

2) Death due to bleeding was (maybe) statistically significant but by a small margin (reduction by 0.4%, 1.5% vs. 1.9%, **p=0.045, 95% CI 0.65-1.0**)

3) Death due to bleeding is NOT an appropriate outcome

Source: *Lancet.* 2017 May 27; 389(10084): 2105-2116.

Final Comment on TXA Use in PPH

- One of the few disease states where 1 g bolus without subsequent maintenance infusion
- More evidence that delayed initiation does not benefit and possibly harms (>3 hours after insult)
- Cost-effective models show that administration of TXA to PPH may prevent procedural costs, LOS, blood transfusions with minimal adverse effects
- Minimal harm but likely limited (if any)

Sources: *Lancet.* 2017 May 27; 389(10084): 2105-2116.
Lancet. 2010; 376(9734): 23 – 32.

Epistaxis

- Commonly seen within every ED
- Damage to mucosal lining, vessel walls, coagulopathy
- Treatment consists of vasoconstriction, cautery with silver nitrate, topical medications
- Anterior packing occurs after treatment failure
- TXA soaked gauze is frequently utilized in EDs to mitigate need for nasal packing

Source: *Ann Emerg Med.* 2021 Jun; 77(6): 631 - 640.

NOPAC Trial

- Randomized controlled trial with 26 centers in the UK
  - 496 patients randomized (254 in TXA cohort and 242 in control)
  - 200 mg in 4 mL applied to a cotton wool dental roll
  - Primary outcome: Use of anterior nasal packing during the ED visit
    - Hospital admission, transfusion requirements, recurrent epistaxis, thrombotic events

TXA for Epistaxis

Source: *Ann Emerg Med.* 2021 Jun; 77(6): 631 - 640.

NOPAC Trial Results

- No difference between groups in primary endpoint (43.7% TXA group vs. 41.3%, p=NS)
- No difference in thrombotic rates (only 1 thrombotic event in either cohort)
- More numerical adverse reactions with TXA group but this was non statistical (3.5% vs. 1.2%)
- No difference in secondary outcomes, as well

Source: *Ann Emerg Med.* 2021 Jun; 77(6): 631 - 640.

Final Comments on TXA Use in Epistaxis

- Low risk given that “rhino rockets” will occur with or without TXA
- Ensure this does not delay surgical options
- Education that this likely will not prevent significant bleeding

Hemoptysis

- Hemoptysis can be minimal to severe with life-threatening hemorrhage
- Interventional procedures are the mainstay of therapy for life-threatening bleeding with minimal data on the use of medications to obtain hemostasis
- Paucity of evidence on the use of inhaled TXA to reduce blood loss
- Minimal regimens evaluated but the most studied regimen has been 500 mg nebulized every 8 hours
- Diluted with 5 mL of normal saline and nebulized over 7–12 minutes

Chest. 2018 Dec; 154(6): 1379 – 1384.

Case 3

- LP is a 58-year-old with a past medical history significant for liver failure, alcohol use disorder and hypertension
  - He denies taking any daily prescription medications
- He presents with a chief complaint of vomiting blood, and after examination he has dried blood on his pants, discoloration around his mouth, bloated abdominal area
- His BP is 93/58, Hgb 5.8 g/dL, platelets of 109k, and an INR 1.6
- The medical team believes this is a variceal bleed exacerbated by alcohol-related liver failure
  - They want to know what dose of TXA to administer to the patient

HALT-IT Trial

- Large, randomized controlled trial
  - 164 hospitals in 15 countries
  - >12k patients randomized
  - Empiric use in gastrointestinal bleeds
    - Upper and lower both enrolled
  - 1 g TXA over 10 minutes
    - 125 mg/hr for 24 hours

TXA for GIB

Source: *Lancet.* 2020; 395 (10241): 1927-1936.

HALT-IT Trial Results

- ⟷ Death due to bleeding within 5 days of randomization (3.7% vs. 3.8%; p=NS)
- ↑ Risk of deep vein thrombosis or pulmonary embolism in TXA group (RR 1.85, 95% CI 1.15 – 2.98); seizures in TXA group (0.6% vs. 0.4%, RR 1.73, 95% CI 1.03 – 2.93)
- ⟷ Transfusion of blood products (RR 0.99, 95% CI 0.97 – 1.02)
- ⟷ Surgical, endoscopic, or radiological intervention (RR 1.0, 95% CI 0.99 – 1.01)

Source: *Lancet.* 2020; 395 (10241): 1927-1936.

HALT-IT Comments

- Again, viscoelastic testing was not utilized to guide decision on TXA
- Most patients had systolic blood pressures >90 (87%)
- Dosing was altered from previous studies
- Mixed patient sample with both upper and lower gastrointestinal bleeds
- “3–hour” rule

Source: *Lancet.* 2020; 395 (10241): 1927-1936.

Meta-Analyses on TXA Use in Gastrointestinal Bleeds

- High – dose (>2 grams in 24 hours) cohort had 5 studies
  - Mortality (RR 0.98; 95% CI 0.88 – 1.09)
  - Rebleeding (RR 0.92; 95% CI 0.82 – 1.04)
  - Surgical intervention (RR 0.92; 95% CI 0.76 – 1.09)
  - Transfusion requirements (RR 1.0; 95% CI 0.99 – 1.01)
  - **DVT and PE rates were higher in the TXA groups (RR 2.01; 95% CI 1.08 – 3.72) and (RR 1.78; 95% CI 1.06 – 3) respectively**

- Low – dose (≤ 2 grams in 24 hours) cohort had 7 studies
  - Mortality (0.62; 95% CI 0.36 – 1.09)
  - Transfusion requirements (1.03; 95% CI 0.93 – 1.13)
  - **Rebleeding (RR 0.5; 95% CI 0.33 – 0.75)**
  - **Surgical Intervention (RR 0.58, 95% CI 0.38 – 0.88)**

Source: *Critical Care Medicine.* 2022; 50: E313-9. https://doi.org/10.1097/CCM.0000000000005362.

Final Comments on TXA Use in Gastrointestinal Bleeds

- Current data does not suggest benefit for empiric use but high heterogeneity between patient populations and dosing strategies
- Upper GIB typically more arterial bleeding vs. venous bleeds with lower GIB
- High dose >2 g per day likely not beneficial in comparison to low dosing ≤ 2 g
- Role for viscoelastic testing unclear but likely could stratify TXA responders vs. non-responders

Source: *Critical Care Medicine.* 2022; 50: E313-9. https://doi.org/10.1097/CCM.0000000000005362.

Case 3 Revisited

- There is no current data to suggest this patient is coagulopathic
- This patient's bleed is likely due to increased portal pressure
- Patients with liver dysfunction display "rebalanced hemostasis"
- HALT-IT trial found no difference in empiric TXA use to prevent mortality in gastrointestinal bleeds but increased rates of thrombosis (higher doses utilized)
- Checking viscoelastic data is recommended here by the Society of Critical Care Medicine's guidelines on acute or acute on chronic liver failure

Personal Recommendation on TXA Use

- Reasonable to administer empirically to any patient at risk for massive blood transfusion with active exsanguination or hemorrhagic shock
- Viscoelastic testing data to suggest in a hyperfibrinolytic state
- The 1 g IV over 8 hours dosing scheme is antiquated and likely has no role today
- 1-2 g IV push is reasonable and likely does not cause hypotension

Conclusion

- The decision to utilize TXA is complicated and precision data should be incorporated into identifying ideal candidates
- Upregulation of endogenous tPA occurs in those in shock and might be ideal target for empiric TXA use
- If viscoelastic testing is available, clinicians may be able to differentiate hyperfibrinolysis from other fibrinolytic phenotypes
- The majority of large randomized controlled data does not support empiric TXA use

Assessment Question 1

Tranexamic acid may be incorporated into hemostasis protocols due to the following mechanism of action:

A. Provides clotting factor supplementation

B. Increases maximum clot velocity

C. Supports platelet function to produce adhesion

D. By halting ongoing fibrinolysis and preventing clot breakdown

Assessment Question 1 – Correct Response

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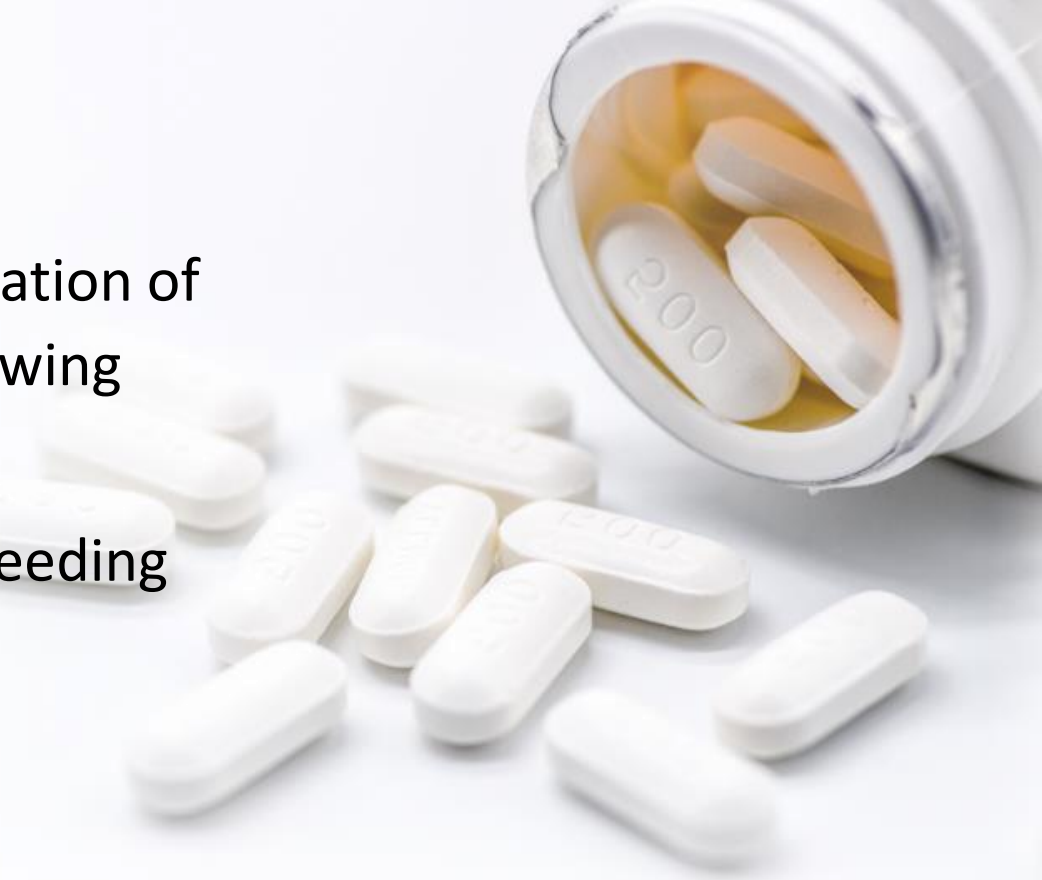
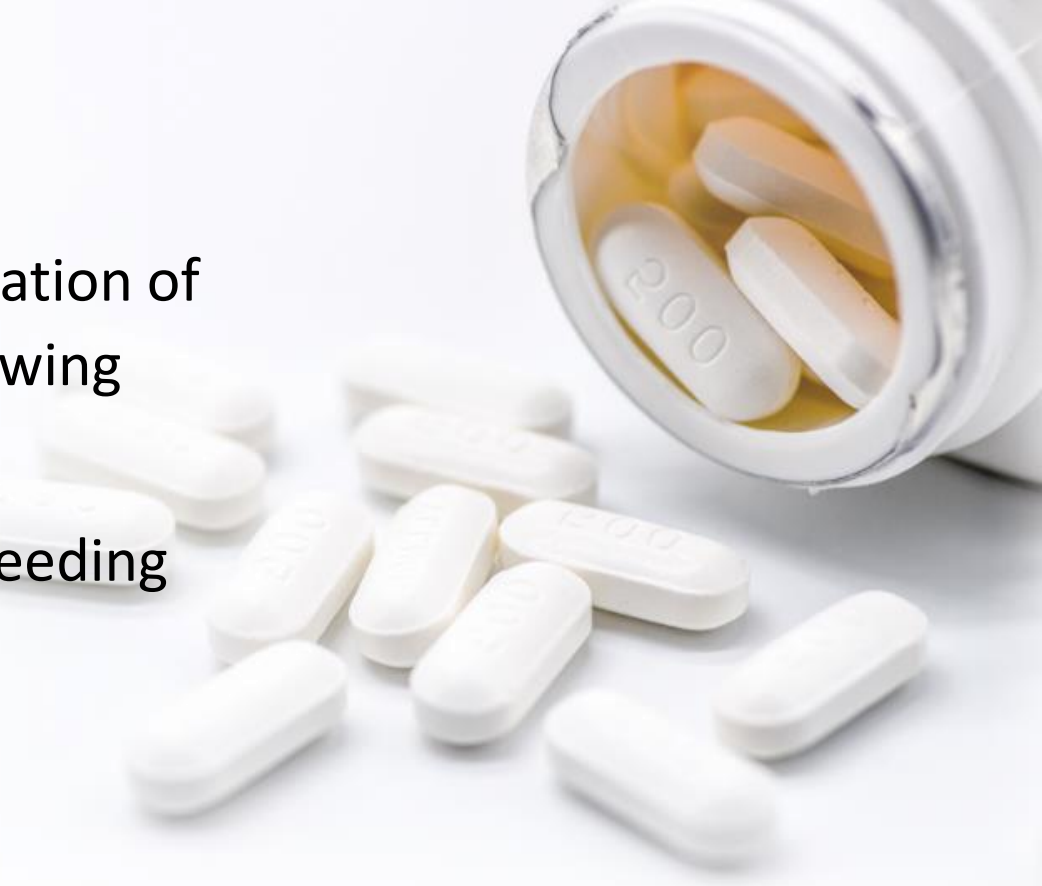
Assessment Question 2



In some patients experiencing hemorrhage, administration of tranexamic acid is recommended in which of the following scenarios:

A. Those without shock symptoms and no signs of bleeding
B. Patients undergoing massive blood transfusions
C. Those in fibrinolytic shutdown
D. In patients with isolated traumatic brain injury

Assessment Question 2 – Correct Response



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Assessment Question 3

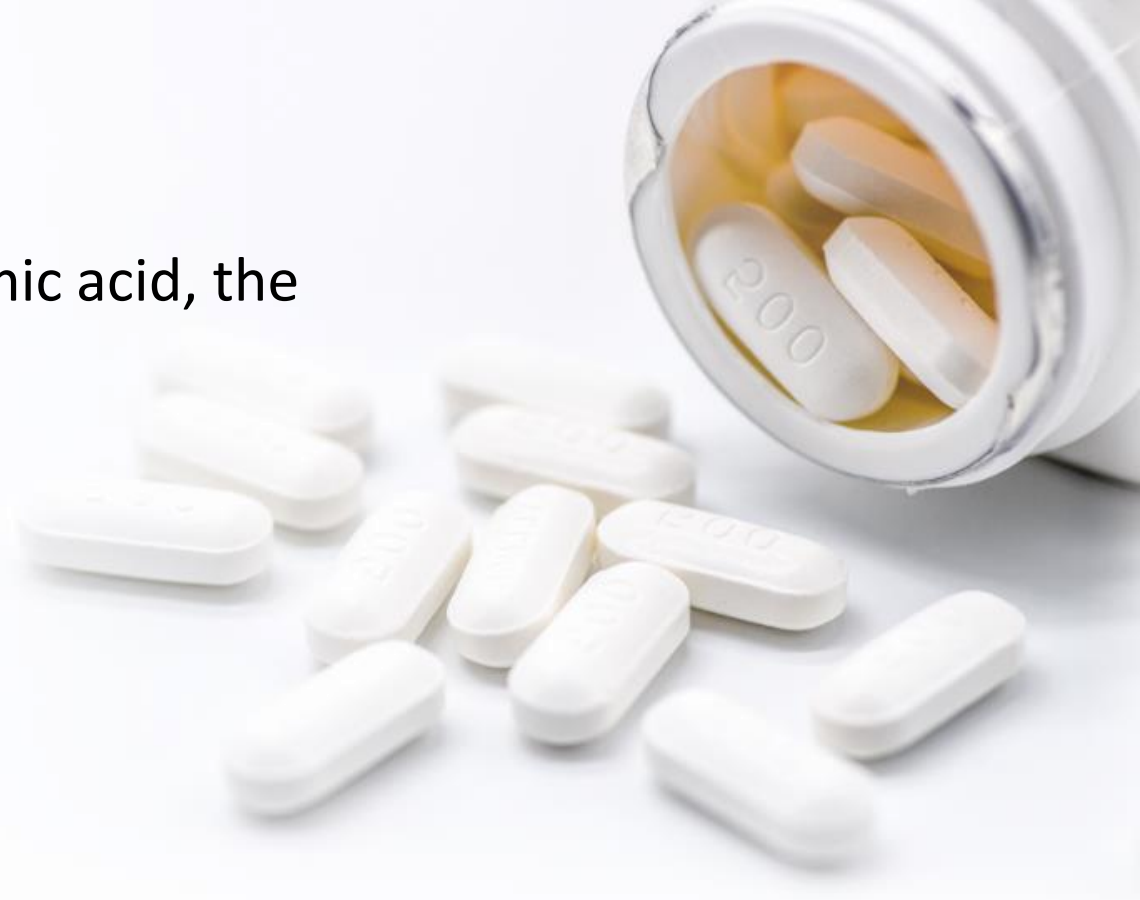
For better efficiency when administering tranexamic acid, the following strategies are available:

A. Undiluted IV push over 5 minutes

B. Bolus dose without 8-hour drip

C. Both A & B

D. Neither A or B



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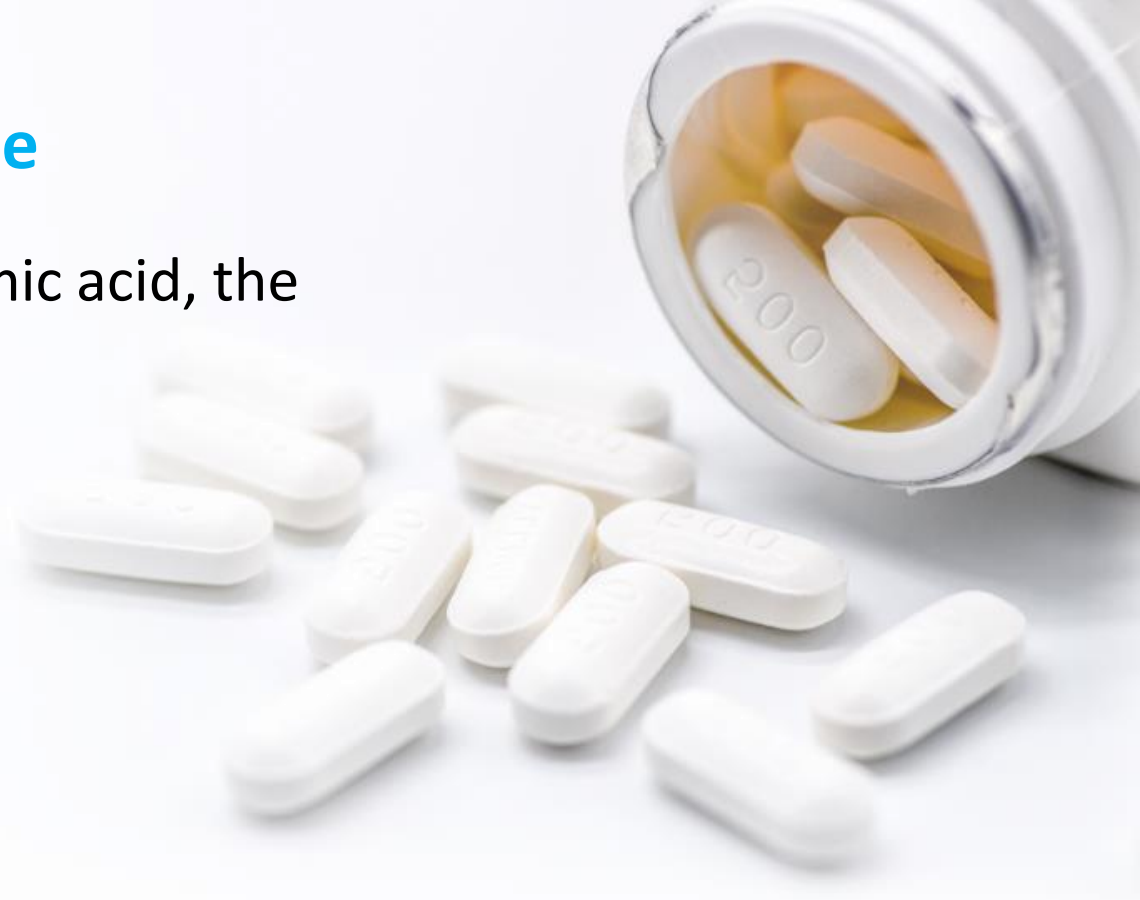

References

- *Arterioscler Thromb Vasc Biol*. 2007 Apr; 27(4): 722 – 727.
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- *Arch Pathol Lab Med.* 2017 Apr; 141(4): 569 – 577.
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- *Lancet.* 2020; 395 (10241): 1927-1936.
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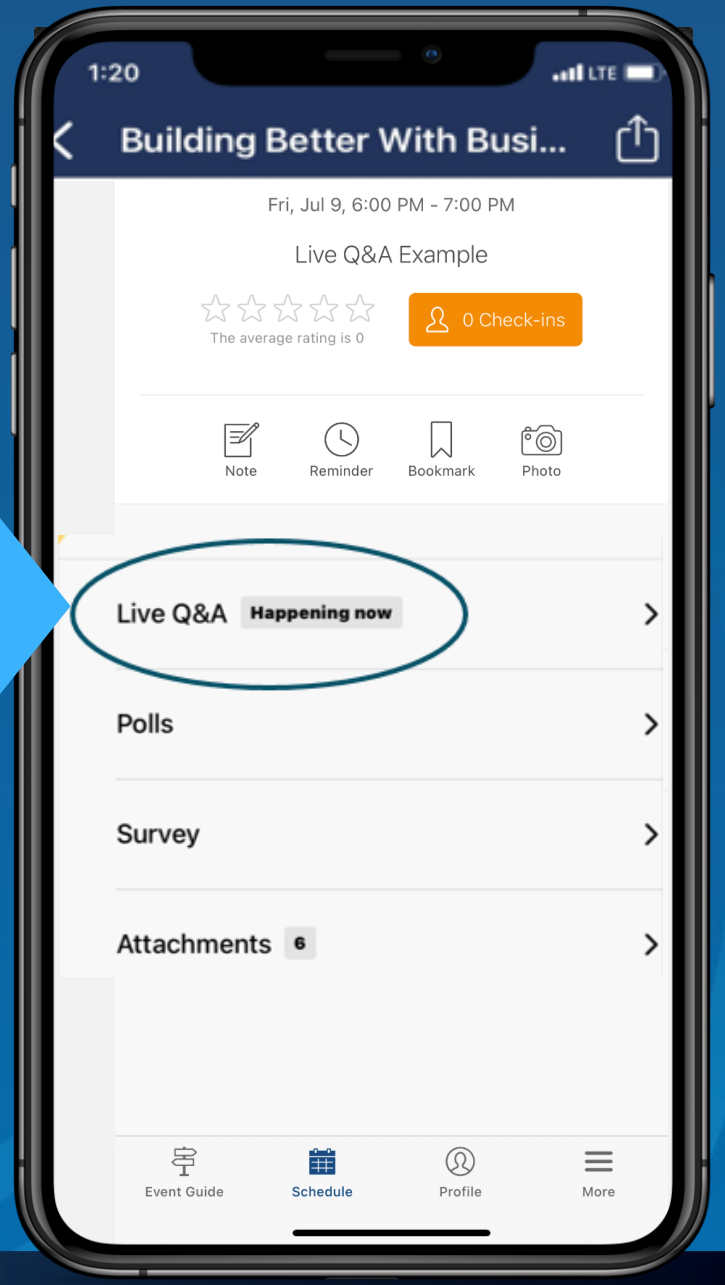
- Send in any time; Qs will be held until the end of the session



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Thank you...

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