OB/GYN Webinar Series 2017-2018

Vermont Child Health Improvement Program
UNIVERSITY OF VERMONT LARNER COLLEGE OF MEDICINE

OB/GYN Webinar Series 2017-2018

Tuesday, May 8th, 12pm- 1pm EST

Recordings: Vchipwebinars.wordpress.com

Presented by:

The University of Vermont
LARNER COLLEGE OF MEDICINE

THE University of Vermont
MEDICAL CENTER

VERMONT
DEPARTMENT OF HEALTH

Today's Webinar

- **Tranexamic Acid for Postpartum Hemorrhage**

  Kelley McLean, MD

  University of Vermont Medical Center

  Maternal Fetal Medicine

- **Women's Health Initiative**

  Alexandra Frey

  Vermont Blueprint for Health

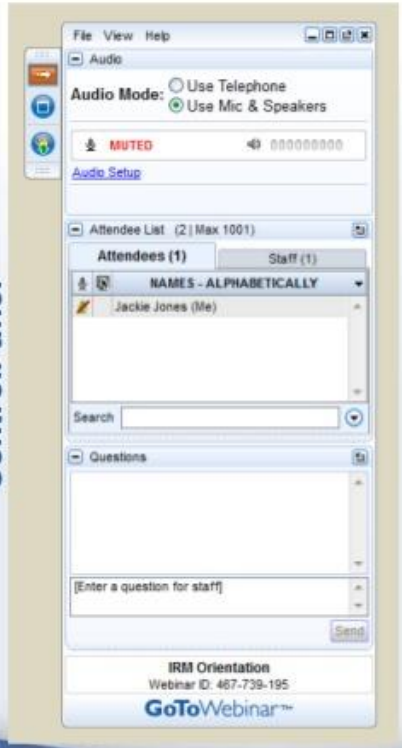
Chat Box

GoToWebinar® Attendee Controls

Grab Tab

- Click **arrow** to expand and collapse control panel
- Click **hand icon** to raise/lower hand

ControlPanel



Audio Pane
Use **Audio Setup** wizard to configure and test audio.

Attendee List
(if selected to display by organizer)

Question Pane
Enter questions here.

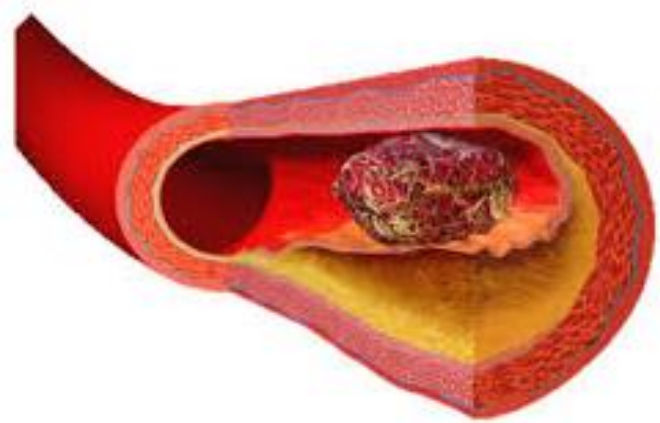
Tranexamic Acid: the Rebirth of an Old Drug

Kelley McLean
Assistant Professor, Maternal Fetal Medicine
University of Vermont Larner College of Medicine
VCHIP Webinar, May 2018

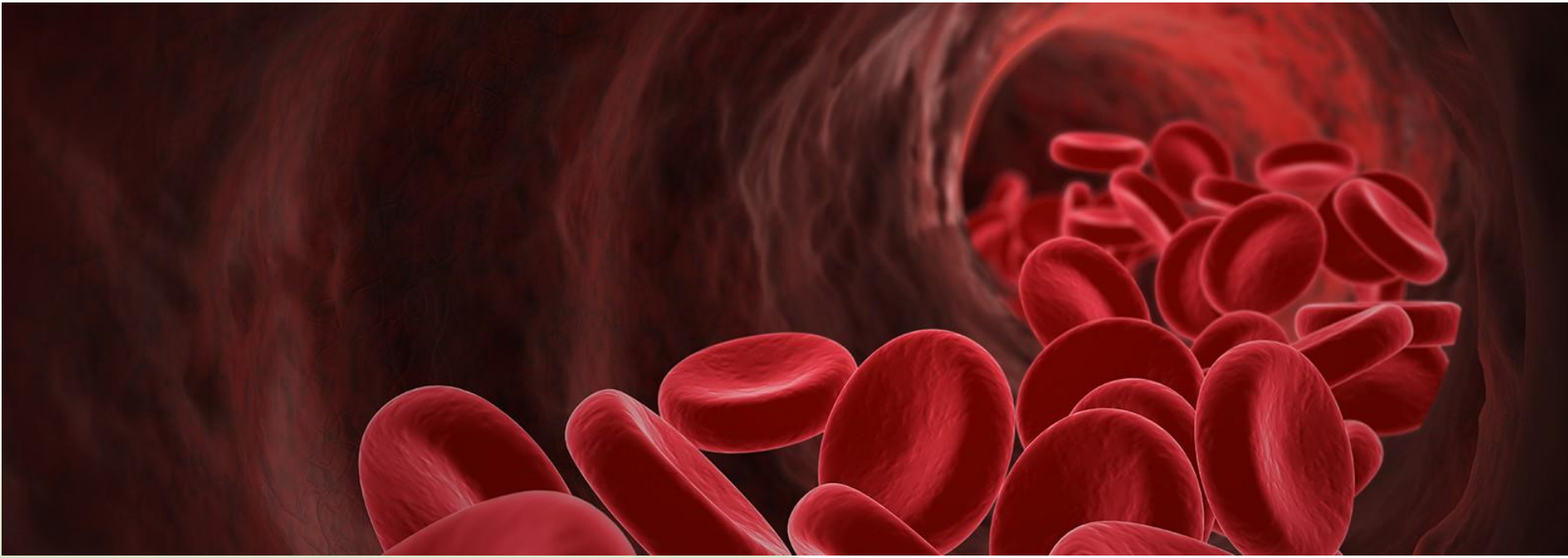
The University of Vermont

Learning Objectives:

1. Understand how tranexamic acid works
2. Review the history of use since its introduction in the 1960s
3. Review indications for use in obstetrics



Hemostasis and Thrombosis in Pregnancy



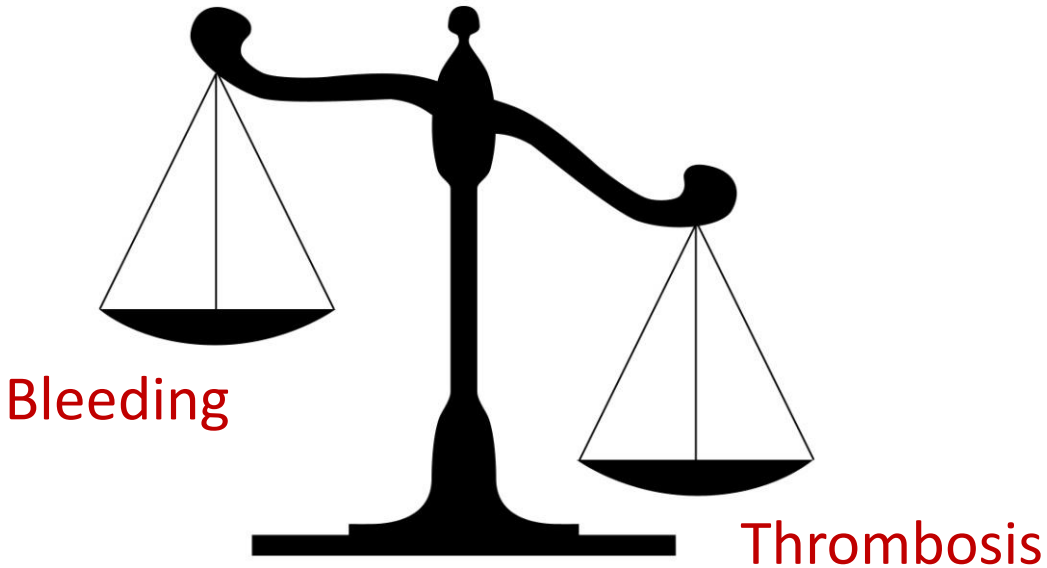
The University of Vermont

Pregnancy: Hemorrhagic *and* Thrombotic risk

- Pregnancy presents a paradoxical challenge to the hemostatic system
  - Risk of hemorrhage at the time of placentation and in the 3rd stage of labor
  - Risk of thrombosis in the uteroplacental circulation
- Multitude of adaptations allow a hemostatic balance to avoid hemorrhage, while maintaining blood fluidity
  - Increase in most coagulation factors
  - Overall decrease in coagulation inhibitors
  - Decrease in fibrinolysis

Pregnancy & Postpartum: Systemic Changes in Hemostasis

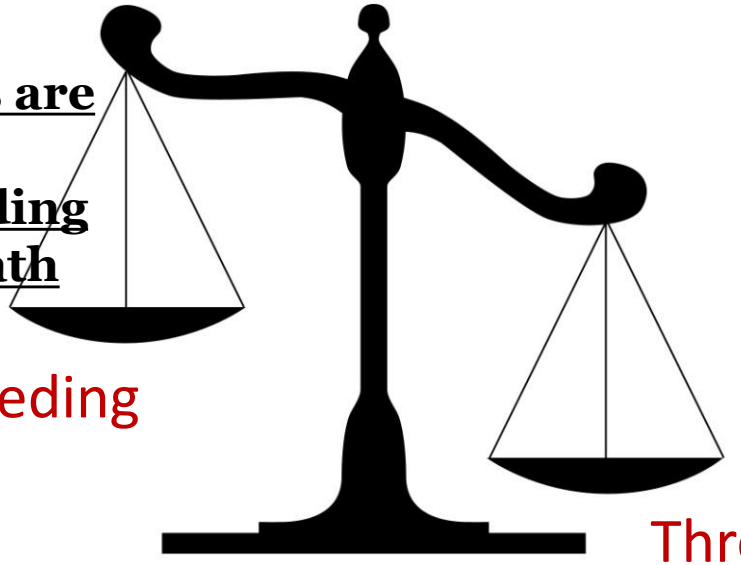
- Relative shift away from the non-pregnant anti-coagulant state to a more pro-coagulant state



Pregnancy & Postpartum: Systemic Changes in Hemostasis

- Relative shift away from the non-pregnant anti-coagulant state to a more pro-coagulant state

However….<u>VTE events are rare</u>, and <u>hemorrhage is the leading causes of maternal death worldwide</u>



A Complex Hemostatic Balance

Current Commentary

The National Partnership for Maternal Safety

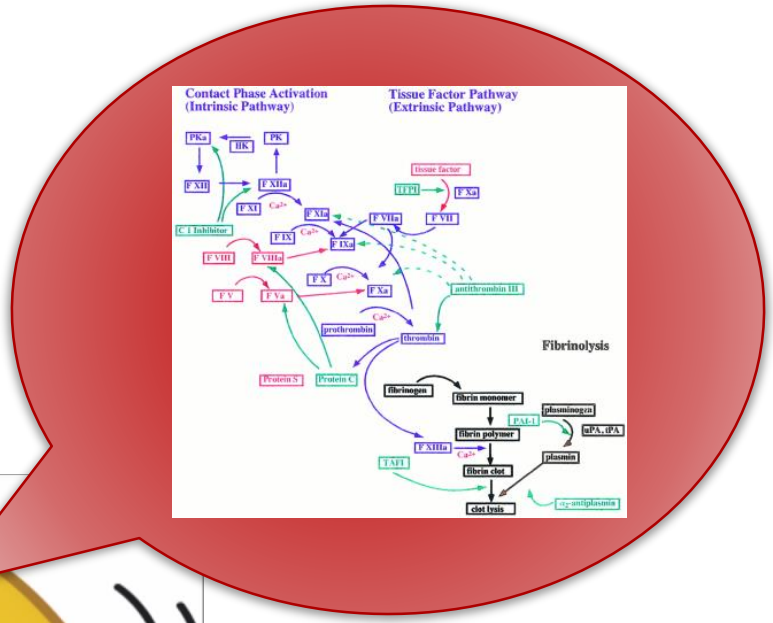
Mary E. D'Alton, MD, Elliott K. Main, MD, M. Kathryn Menard, MD, and Barbara S. Levy, MD

- Identified 3 "priority bundles" for the most common preventable causes of maternal death and severe morbidity:
  - **Obstetric hemorrhage**
  - Severe hypertension in pregnancy
  - **Peripartum venous thromboembolism**

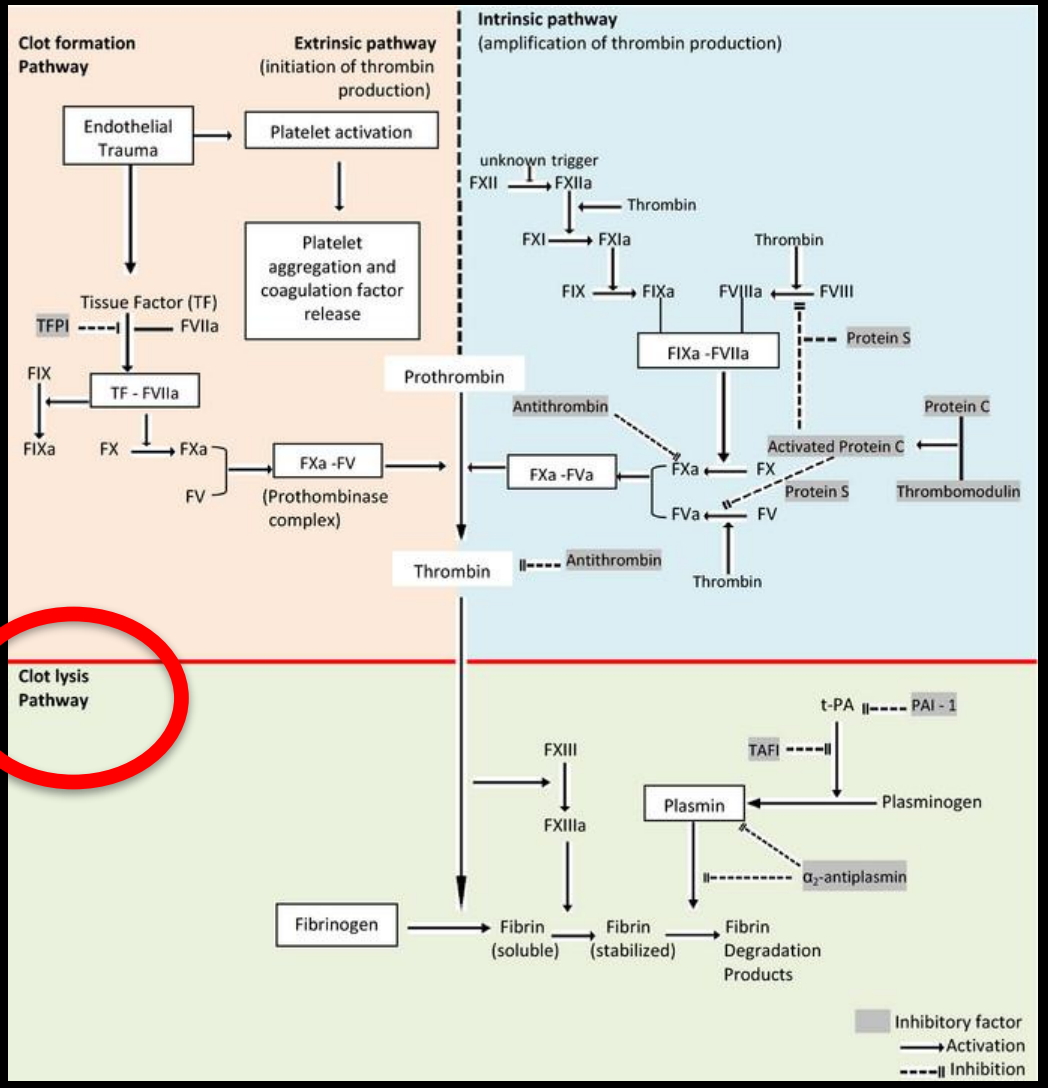
Bottom Line:

- Any intervention to treat obstetric hemorrhage should be considered in the context of a high thrombotic risk, and *vice versa*

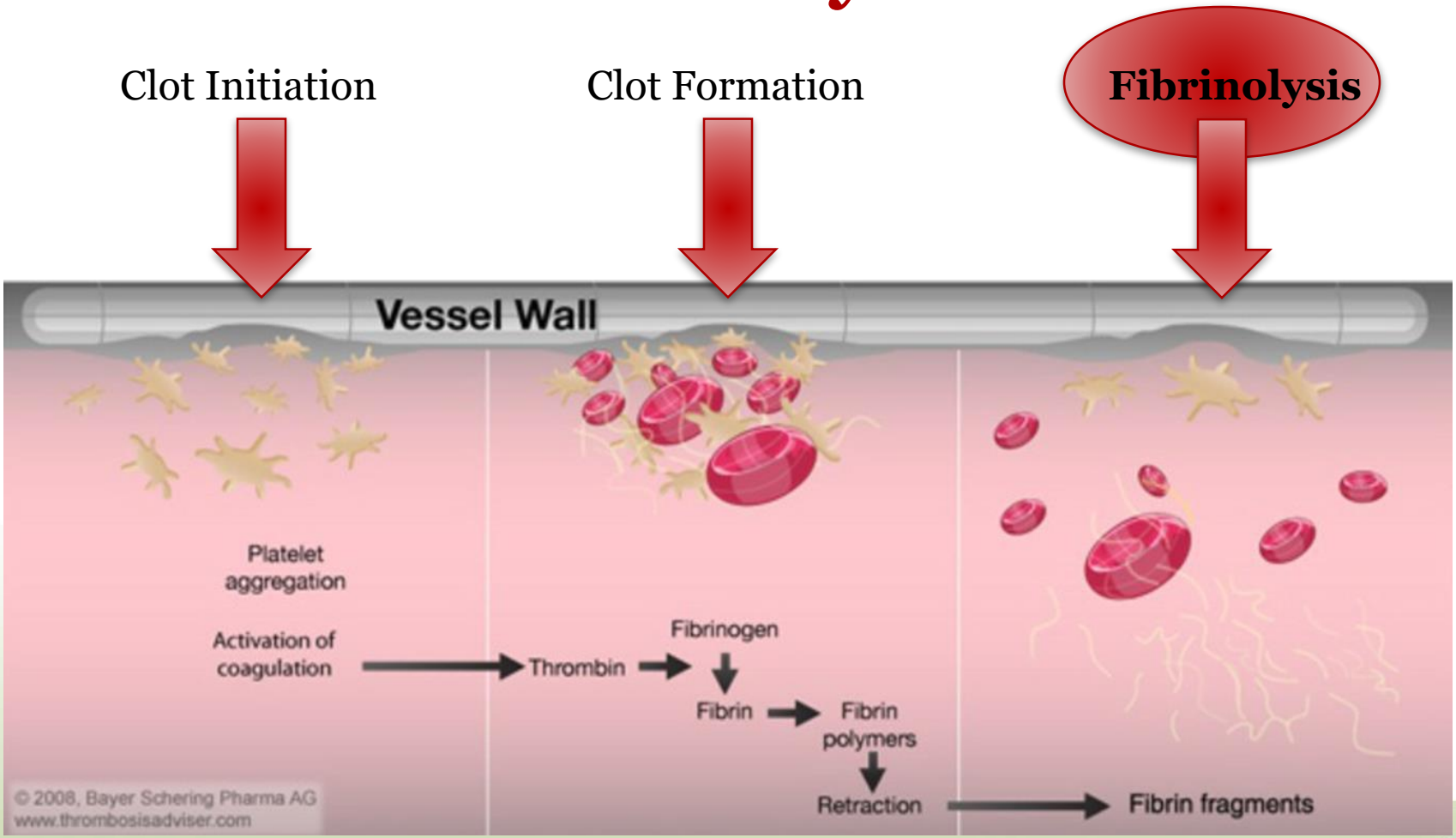
Tranexamic Acid: An Antifibrinolytic


Contact Phase Activation
(Intrinsic Pathway)
Tissue Factor Pathway
(Extrinsic Pathway)
PKa
HK
PK
F XII
F XIIa
F XI
F XIa
F IX
F IXa
F VIIIa
F VIII
C 1 Inhibitor
F VIII
F X
F Xa
F V
F Va
antithrombin III
prothrombin
thrombin
Protein S
Protein C
Fibrinolysis
fibrinogen
fibrin monomer
plasminogen
PAI-1
fibrin polymer
uPA, tPA
F XIIIa
plasmin
fibrin clot
TAFI
clot lysis
α2-antiplasmin

Hemostasis:

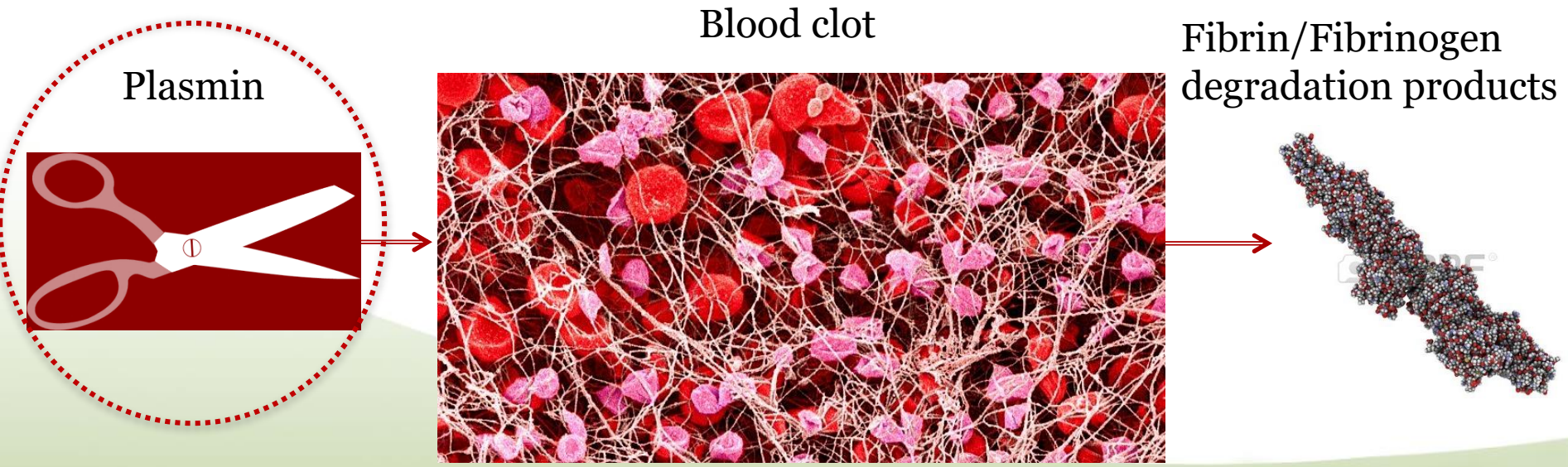

Clot formation Pathway
Extrinsic pathway (initiation of thrombin production)
Intrinsic pathway (amplification of thrombin production)
Endothelial Trauma
Platelet activation
Platelet aggregation and coagulation factor release
Tissue Factor (TF)
TFPI
FVIIa
TF - FVIIa
FIX
FIXa
FX
FXa
FV
FXa -FV
(Prothombinase complex)
Prothrombin
unknown trigger
FXII
FXIIa
Thrombin
FXI
FXIa
FIX
FIXa
FVIIIa
FVIII
FIXa -FVIIa
Protein S
Antithrombin
Protein C
Activated Protein C
FXa -FVa
FXa
FX
FVa
FV
Protein S
Thrombomodulin
Thrombin
Antithrombin
Thrombin
Clot lysis Pathway
t-PA
PAI - 1
TAFI
FXIII
FXIIIa
Plasmin
Plasminogen
α2-antiplasmin
Fibrinogen
Fibrin (soluble)
Fibrin (stabilized)
Fibrin Degradation Products
Inhibitory factor
Activation
Inhibition

Hemostasis: Coagulation + Fibrinolysis



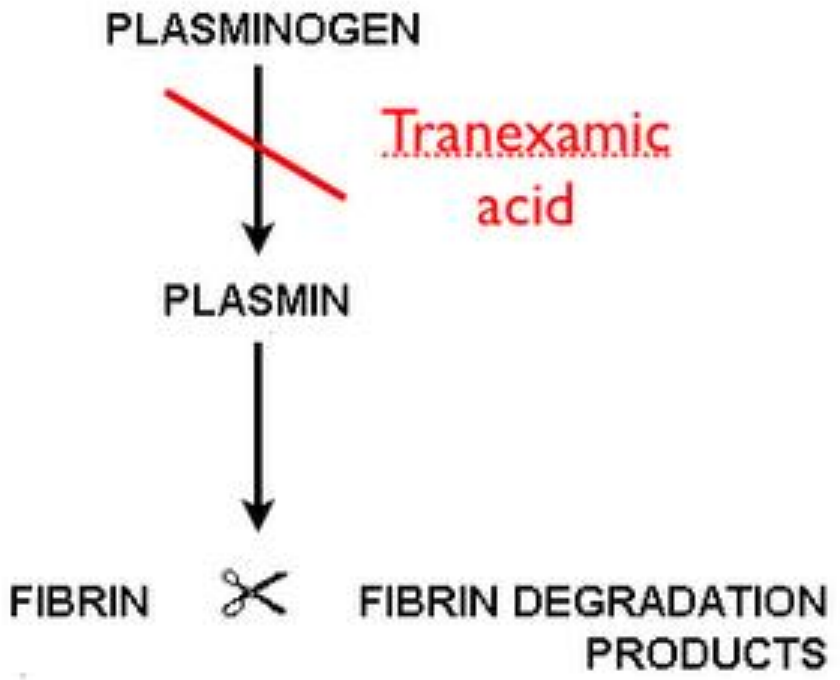
Summary of Fibrinolysis:

- Blood clots are cleared as a result of a short enzyme cascade system (fibrinolysis), which results in the degradation of the fibrin network of the blood clot through plasmin as the key enzyme:



http://www.gettyimages.com/detail/photo/blood-clot-sem-high-res-stock-photography/548001443

Tranexamic Acid (TXA): Action



Tranexamic Acid: A 55 year-old Drug

- 1962: 2 independent research groups (Japan and Sweden) discovered 4-amino-methyl-cyclohexane-carbonic acid (AMCHA)
  - Of the 2 stereoisomers, only the trans-form was antifibrinolytic: *(trans-4-aminomethylcyclohexanecarboxylicacid)*
  - Trans-AMCHA or tranexamic acid (TXA) was born!
    - TXA is 10 x more effective then EACA, and is well-tolerated

Tengborn et al., Thrombosis Research, 2015

Pharmacokinetics

- Studies from the 1960s in Sweden:
  - IV: Highest TXA plasma concentration reached within 1hr
    - Renal clearance, with a ½-life of 80min
  - Oral: Maximum plasma concentration reached within 3 hours
  - Crosses the placenta
  - Present in breast milk at concentrations 100x lower than in plasma

Dosing

- Dosing was originally based on in vitro studies performed in the 1960s (Sweden)
  - fibrinolytic activity of tissue extracts in the presence of varied concentrations of TXA

- Dosing of IV* TXA has varied in more recent studies:
  - 2010: CRASH2 Trial: massive bleeding in severe trauma (n= >20,000)
    - 1gram IV, followed by infusion of 1gram over 8hours
  - 2011: French RCT postpartum hemorrhage (n=144)
    - 4grams IV over one hour, then 1gram/hour x 6 hours
  - 2017: WOMAN Trial: International RCT, postpartum hemorrhage (n= >20,000)
    - 1gram IV over 10min, repeated after 30min if bleeding continued in the 1st 24hrs

*Oral dosing has been more consistent at 10-20mg/kg 3-4 x per day: In the U.S., the FDA recommends 1.3 grams TID for 3-5 days for menorrhagia

Adverse Reactions & Contraindications

- Mild adverse reactions:
  - Hypotension with rapid IV injection
  - Blurred vision
  - Dizziness
  - Diarrhea, nausea, vomiting
  - Allergic dermatitis

- Rare severe adverse reactions (<1%) reported in case reports or post-marketing studies:
  - Allergic skin reaction, anaphylactic shock, anaphylactoid reaction, cerebral thrombosis, DVT, PE, renal cortical necrosis, retinal artery occlusion, retinal vein occlusion, seizure, ureteral obstruction, visual disturbances (including impaired color vision and vision loss)

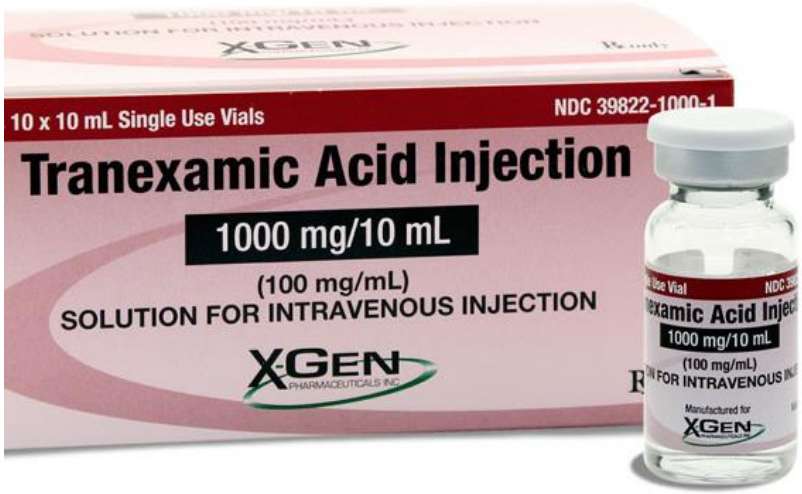
- Precautions: "Use with caution"
  - Renal impairment
  - Current thromboembolic disease

- Contraindications:
  - Hypersensitivity to TXA , **active DIC***, subarachnoid hemorrhage

FDA-Approved & Off Label Use

- FDA Approved Use:
  - Treatment of cyclic heavy menstrual bleeding (oral)
  - Short-term use in hemophilia patients to reduce or prevent hemorrhage and reduce need for replacement therapy during and following tooth extraction (oral, IV)

- Off Label Use:
  - Postpartum hemorrhage
  - Reduction of blood loss associated with cesarean delivery
  - Post-operative bleeding associated with cervical conization
  - Trauma-associated hemorrhage
  - Bleeding associated with dental procedures in patients on oral anticoagulant therapy (topical mouth rinse)
  - Hereditary angioedema (long-term prophylaxis; acute treatment)
  - Perioperative blood loss in total hip or knee arthroplasty, hip fracture surgery
  - Intracranial hemorrhage associated with thrombolytics
  - Prevention of bleeding associated with cardiac surgery, craniosynostosis surgery, extracorporeal membrane oxygenation (ECMO), spinal surgery (eg, spinal fusion), or transurethral prostatectomy



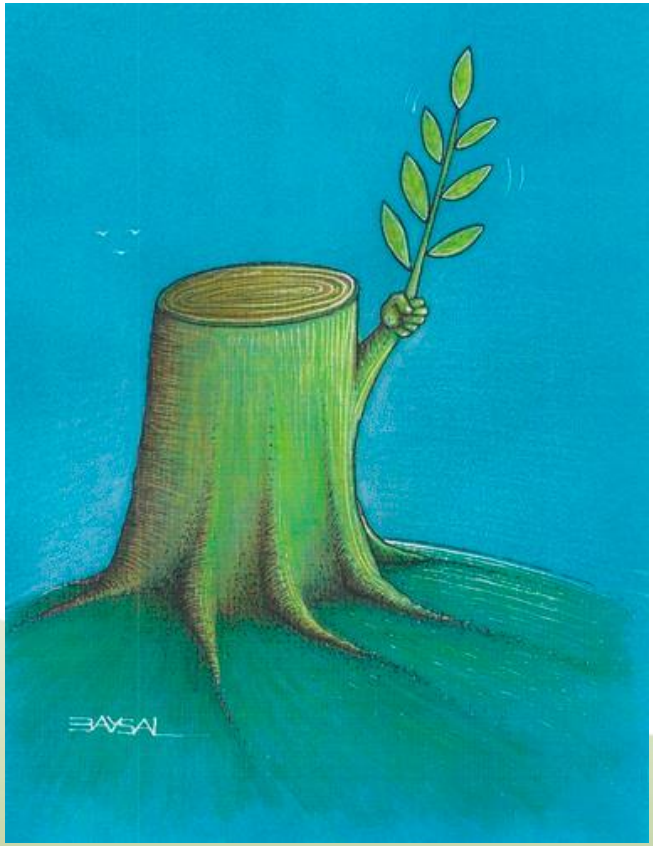
Cost of one vial: $24

Average 2012 Amount Paid for Childbirth

	CONVENTIONAL DELIVERY	CAESAREAN
United States	**$9,775**	**$15,041**
Switzerland	4,039	5,186
France	3,541	6,441
Chile	2,992	3,378
Netherlands	2,669	5,328
Britain	2,641	4,435
South Africa	2,035	3,449

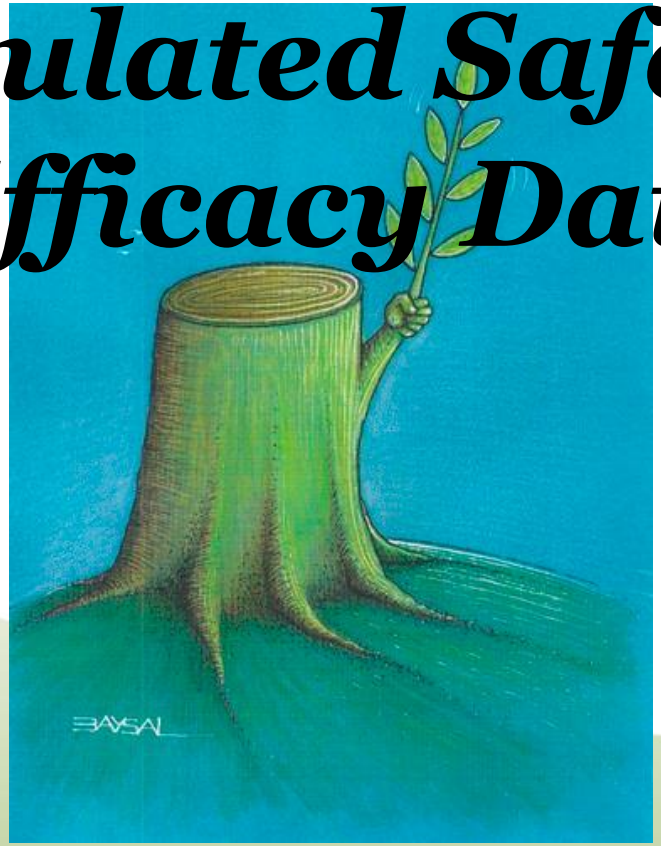
International Federation of Health Plans, from New York Times, June 30, 2013

TXA: Why the Rebirth?



TXA: Why the Rebirth?

Accumulated Safety and Efficacy Data

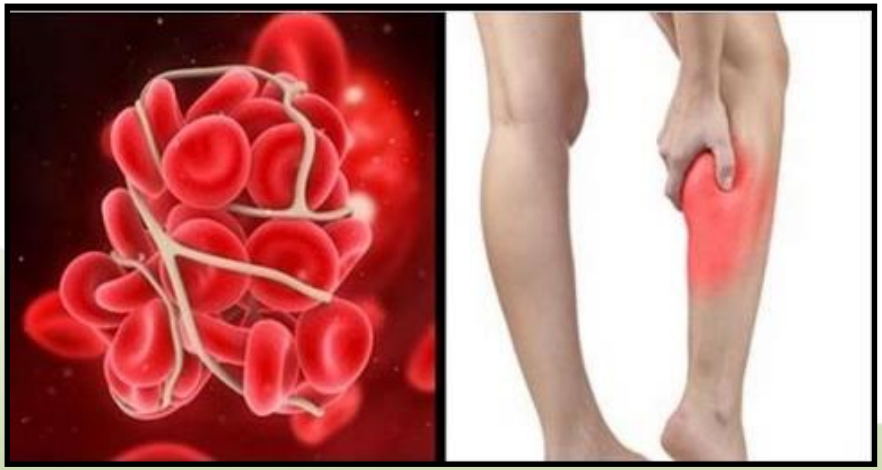


Safety and Efficacy Data

- Approx. 70% of publications in the last 55 years with "tranexamic" in the title were published in the previous 15 years
  - 1,080 articles published since 2015
    - Wide range of areas: trauma, ortho, cardiovascular, obstetrics, neurosurg, pharmacology, etc.
- Efficacy of TXA in the reduction of blood loss has been made clear through these studies
- Studies were not powered to assess safety
  - Case reports of thrombosis (arterial and venous)
  - Case reports and post-marketing reports of renal cortical necrosis, ureteral obstruction, seizures

Million Dollar Question…

- If tranexamic acid stabilizes blood clots to treat and/or prevent hemorrhage, is the risk of DVT/PE and other venous and/or arterial thrombosis increased?
  - Given the relative infrequency of thrombotic events, very large studies are needed to evaluate thrombotic risk with tranexamic acid….



CRASH-2: Recap

- **C**linical **R**andomisation of an **A**ntifibrinolytic in **S**ignificant **H**aemorrhage (**CRASH-2**) trial
  - RCT on the effect of TXA on death and vascular occlusive events in bleeding trauma patients, published in 2010
  - 20,211 adult trauma patients with significant bleeding, or at risks of significant bleeding, within 8h of their injury, randomly allocated to receive TXA or matching placebo (1g over 10min followed by 1g over 8hr infusion)
    - Sig reduction in death to bleeding (RR-0.85, 95% CI -.76-0.96)
      - Reduced all-cause mortality (RR= 0.91, 95% CI 0.85-0.97)
      - No increase in vascular thrombosis

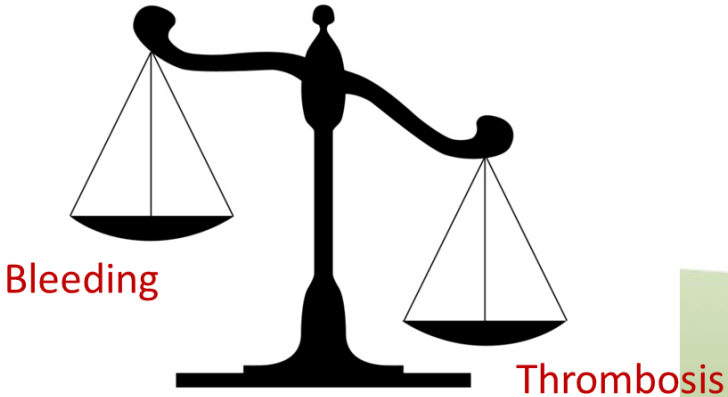
CRASH-2 Collaborators, Lancet, 2010

TXA for Obstetric Bleeding

- High risk of thrombosis in severe trauma with hemorrhage- the lack of increased risk for arterial and/or venous thromboses in the CRASH-2 trial was promising….

BUT…

- Given the uniquely hypercoaguable state of pregnancy and postpartum, another, large, RCT in pregnant women was still needed



WOMAN Trial

- **Wo**rld **M**aternal **An**tifibrinolytic **(WOMAN)** Trial
  - Pragmatic, randomized trial, enrolled >20,000 women between 2010 and 2016 with postpartum hemorrhage in > 20 countries, evaluating TXA vs. placebo

- PPH diagnosis was clinical
  - Study collaborators specified that diagnosis of primary PPH could be based on clinical EBL >500ml after vaginal birth or 1000ml after cesarean delivery, and/or blood loss sufficient to compromise hemodynamic stability
  - "Fundamental eligibility criterion was the clinician's uncertainty about whether to use tranexamic acid in a particular woman with PPH"
  - Patients received all usual care but were also randomly allocated to receive tranexamic acid or placebo
    - 1gram IV over 10min, repeated after 30min if bleeding continued in the 1st 24hrs

WOMAN Trial Collaborators, Lancet, 2017

WOMAN Trial: Recap

- In women diagnosed with PPH, tranexamic acid:
  - Decreased risk of death due to bleeding (1.5% vs. 1.9%)
  - Reduced incidence of laparotomy to control bleeding
  - *No benefit of TXA given >3hours from delivery*
  - Did not result in an increase in adverse effects, including thrombosis

WOMAN Trial
Collaborators, Lancet, 2017

Treatment Timing

- Both CRASH-2 and the WOMAN Trial showed a benefit of “early” treatment (1-3hours), and no benefit if treatment occurred >3hours from injury/birth

Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients

*Angèle Gayet-Ageron, David Prieto-Merino, Katharine Ker, Haleema Shakur, François-Xavier Ageron, Ian Roberts, for the Antifibrinolytic Trials Collaboration**

- Individual patient-level data meta-analysis of RCTS with >1,000 patients that assessed antifibrinolytics in acute severe bleeding between 1946 and 2017: there were only 2…
  - CRASH-2
  - WOMAN

  → 40,138 patients

- TXA significantly increased overall survival from bleeding OR 1.2, 95% CI 1.08-1.33; p=0.001)

- Delay in treatment reduced benefit (p<.0001)
  - With the exception of the first hour, trend of decreasing effectiveness with increasing treatment delay. (Logistic regression model 3 estimated that the treatment benefit decreased by 10% for every 15 min of treatment delay)

Gayet- Ageron, Lancet; Jan 13, 2018

ACOG Practice Bulletin, October 2017: PPH

- "Although the generalizability of the WOMAN trial and the degree of effect in the U.S. is uncertain, given the mortality reduction findings, TXA should be considered in the setting of OB hemorrhage when initial medical therapy fails"
- "Earlier use is likely to be superior to delayed treatment, given that in the stratified analysis it appeared that the benefit was primarily in women treated sooner than 3 hours from the time of delivery"

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

The University of Vermont

World Health Organization Update

- Fall, 2017: WHO convened a panel to replace prior (2012) recommendations re: TXA for PPH
  - strongly recommends early use of IV TXA (within 3 h of birth), in addition to standard with clinically diagnosed PPH following vaginal birth or cesarean birth
  - Supports treatment as done in the WOMAN Trial (1g IV given over 10 min, with a second dose of 1g if bleeding continues after 30 min, or if bleeding restarts within 24 h of completing the first

Vogel et al, Lancet, 2018

Inclusion of TXA in OB Hemorrhage Protocols? YES.

TXA in OB Hemorrhage Protocols

- Every OB hemorrhage protocol and MTP (whether obstetric specific, or institution-wide) should include direction on timing and dosing of tranexamic acid
- While it is unclear if TXA should be given after uterotonics have had a chance to take effect (in the case of atony), *if MTP is being initiated, or even considered, TXA should be given if it hasn't already been*
  - TXA should be readily available, ON THE FLOOR

What WOMAN does not tell us…

1. Will TXA have a similar effect in high-income healthcare settings?

2. Are there subpopulations of pregnant women who should not receive TXA?
   - Recent thrombosis?
   - Women with evidence of DIC at the time of delivery (i.e., massive placental abruption)?

DIC

- Disseminated intravascular coagulation (DIC)* presents an interesting problem- which was not assessed in CRASH-2 or WOMAN, directly.
  - Could the increase in mortality noted with TXA treatment >3hrs in CRASH-2 be due to DIC in a small subset of patients?
- Fibrinolytic "shutdown" has been well-described in DIC in general
  - Gando et. al, 2016 review of DIC:

    "…DIC should not be treated with antifibrinolytic agents that may in fact cause deterioration of microvascular thrombosis."

**There is debate as to whether severe PPH can cause DIC by itself*

Depletion of clotting factors and platelets, with subsequent dilution with IVFs in the context of severe hemorrhage is likely to be fundamentally different than the massive coagulation activation seen with placental abruption, retained POCs, AFE

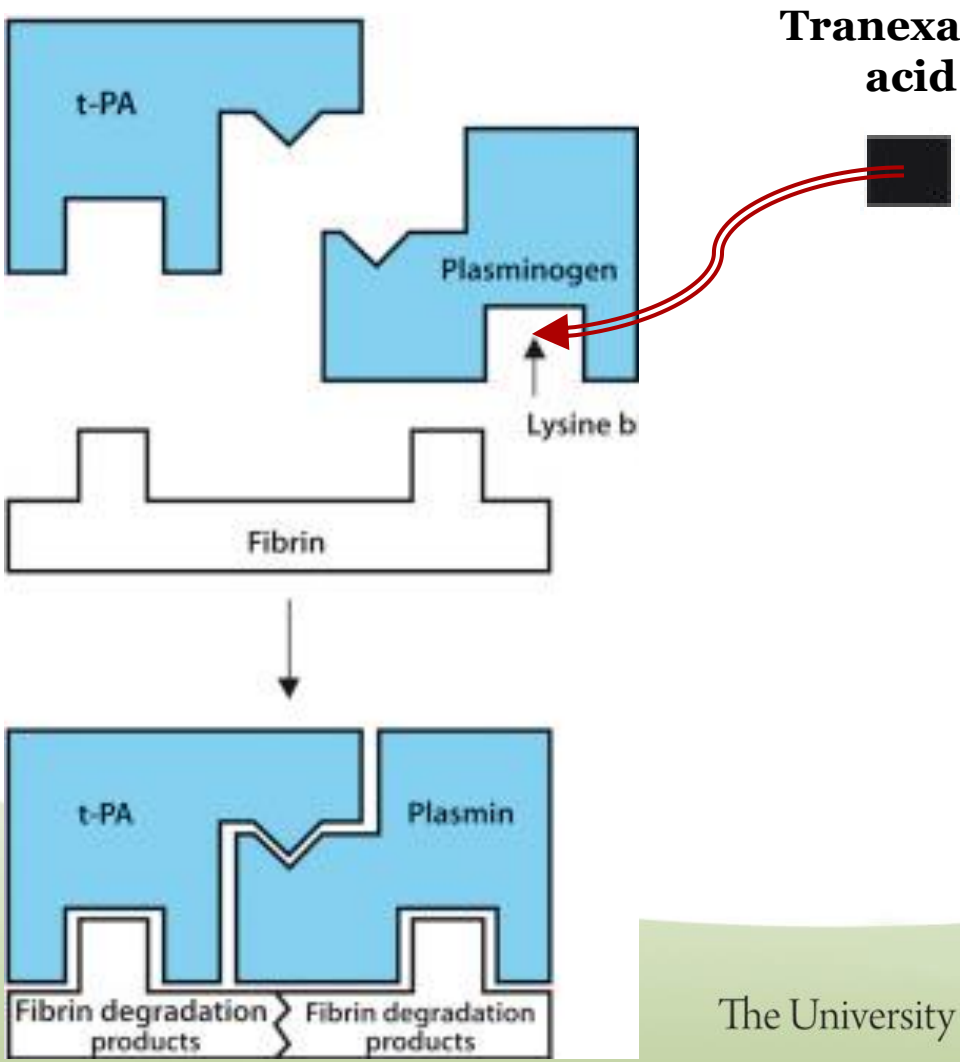
Gando et al. , Nature Reviews, 2016

Finally- What about Prevention?

- >30 studies have evaluated the use of TXA for prevention of obstetric hemorrhage
  - Most have shown a reduction of blood loss at delivery, particularly with cesarean delivery
  - No evidence of increased risk of thromboembolic events
- Despite a substantial number of studies, many are of limited quality:
  - Small sample size (n)
  - Lack of proper randomization and/or masking
  - Use of subjective endpoints (EBL)
- Thromboembolic risk has not been well-assessed when TXA is used prophylactically in the obstetric context
- Good news: Double blind, placebo-controlled RCT is being started by the NICHD/MFMU Network

Pacheco, Obset & Gynecol, 2017

Thank you!!


Tranexamic acid
t-PA
Plasminogen
Lysine b
Fibrin
t-PA
Plasmin
Fibrin degradation products
Fibrin degradation products

References

1. Tengborn L, Blomback M, Berntorp E. Tranexamic acid--an old drug still going strong and making a revival. *Thrombosis research*. 2015;135(2):231-242.

2. Pacheco LD, Hankins GDV, Saad AF, Costantine MM, Chiossi G, Saade GR. Tranexamic Acid for the Management of Obstetric Hemorrhage. *Obstetrics and gynecology*. 2017;130(4):765-769.

3. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. *The Cochrane database of systematic reviews*. 2015(6):CD007872.

4. Straka Z, Vanek T. Topical use of tranexamic acid in cardiac surgery—A review and meta-analysis of four randomized controlled trials. 2013;55(2):e184-e189.

5. https://www.uptodate.com/contents/tranexamic-acid-drug-information

6. CRASH-2 Collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet (London, England)*. 2010;376(9734):23-32.

7. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*. 2017;389(10084):2105-2116.

8. Dennis AT, Griffiths JD. Tranexamic acid for post-partum haemorrhage in the WOMAN trial. *Lancet (London, England)*. 2017;390(10102):1582.

Women's Health Initiative: Participating Medical Practices

Alexandra Frey, BS
Blueprint Project Administrator

The University of Vermont

VCHIP OB Outreach
2018-2019

- **OB VCHIP Webinars:**
  4 – 30min Educational Webinars
  January 2019-April 2019
  and as requested
- **Website Development:**
  Resource for webinar recordings,
  ACOG Updates, Hot Topics Blog,
  Discussion Platform
- **Regional Meetings:**
  NNEPQIN Presentations
  Quarterly VRPHP Nurse Manager Meetings
  Vermont Medical Society Meeting
  Maternal Mortality Review Panel
  Primary Care & Public Health Integration Workgroup
  Alliance for Innovation in Maternal Health
- **Network QA/QI & VCHIP Data Collection & Analysis**
  24 Hour Consultative Service
  Transport/Statistical Conferences
  Vermont Family Based Approach
  UVMMC OB/GYN Projects

How can we better help you?

Visit https://vchipwebinars.wordpress.com
Contact:
Amanda.slater@uvmhealth.org

The University of Vermont

Thank you!

Vermont Child Health Improvement Program
UNIVERSITY OF VERMONT LARNER COLLEGE OF MEDICINE

THE University of Vermont MEDICAL CENTER

The University of Vermont LARNER COLLEGE OF MEDICINE

VERMONT DEPARTMENT OF HEALTH

Marjorie Meyer, MD
Erin Morris, MD
Kelley McLean, MD
Stephen Brown, MD
Carole McBride, PhD
Amanda Slater
Anne Johnston, MD

Breena Holmes, Maternal and Child Health
Ilisa Stalberg, Maternal and Child Health
Rhonda Williams, Chronic Disease Prevention
Bethany Yon, Chronic Disease Prevention
Kim Swartz, Maternal and Child Health
Alexandra Frey, VT Blueprint for Health

Special thank you to Stephanie Winters and Amy Turner for webinar support and coordination!

Vermont Medical Society

The University of Vermont