BRIGHAM HEALTH
BRIGHAM AND WOMEN'S
Department of Medicine

Dana-Farber
Cancer Institute

HARVARD
MEDICAL SCHOOL
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Education

Bleeding and Clotting Emergencies in the ICU

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Conflicts of Interest

Scientific Ad Boards and Consulting:

- Abbott
- Anthos
- Bristol-Myers Squibb
- Janssen
- Perosphere Technologies
- Sanofi

Agenda

Coagulopathy:

pathological condition that reduces the ability of the blood to coagulate, can lead to uncontrolled bleeding

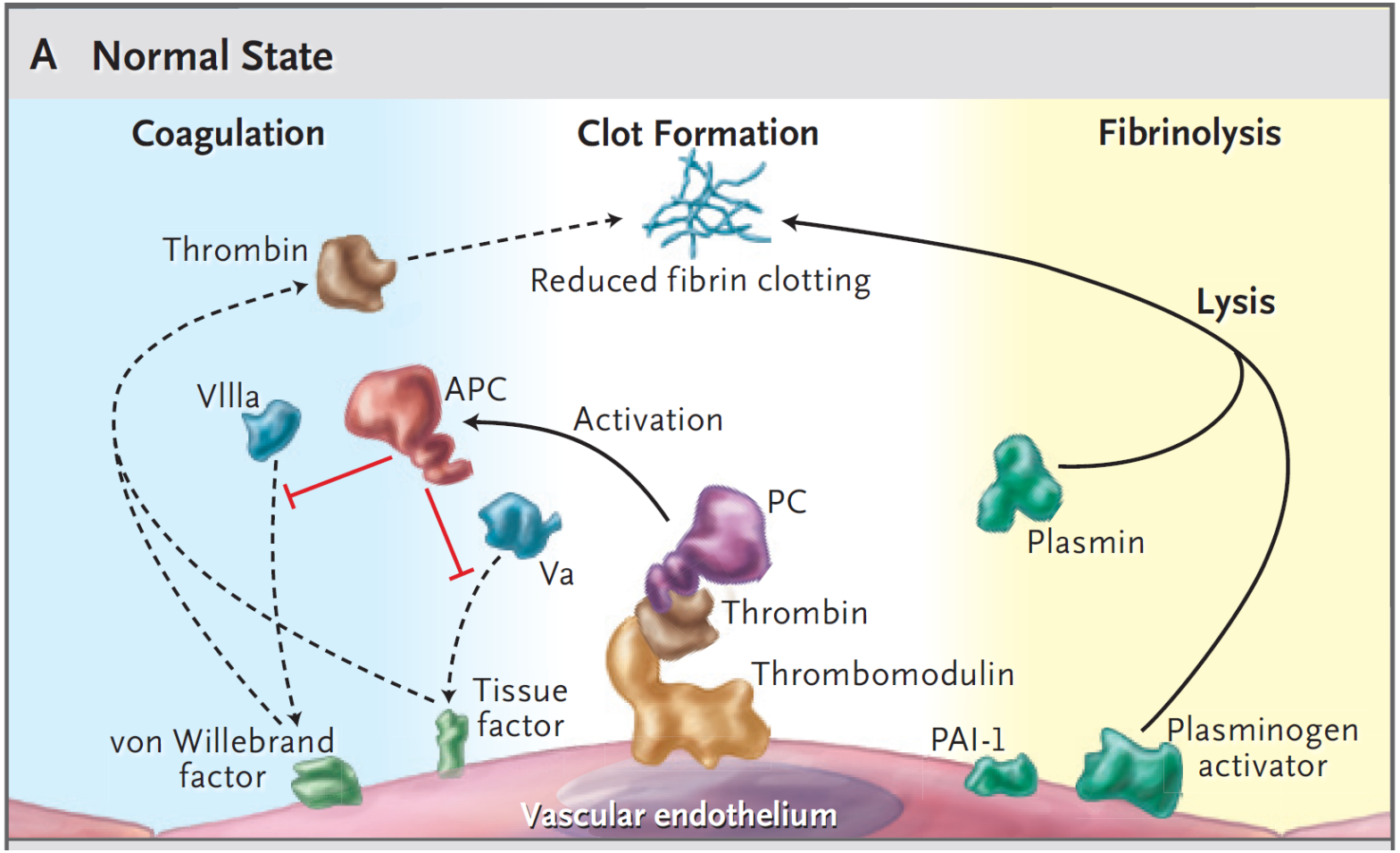
- review of coagulation tests
- available hemostatic products
- DIC
- Cirrhosis
- antifibrinolytics

Treat the bleeding patient not numbers. An elevated PT or PTT does not mandate treatment if there is no bleeding.

Thrombosis

- Pathologic activation of coagulation leading to unwanted blood clots
  - Heparin induced thrombocytopenia

Normal Hemostatic Balance



Requirements for Hemostasis

- **Factors needed to stop bleeding:**
  - **Vasoconstriction**
    - Includes closing holes in vessels
  - **Platelets and vWF**—primary hemostasis
  - **Soluble coagulation factors**—secondary hemostasis, aka the clotting cascade

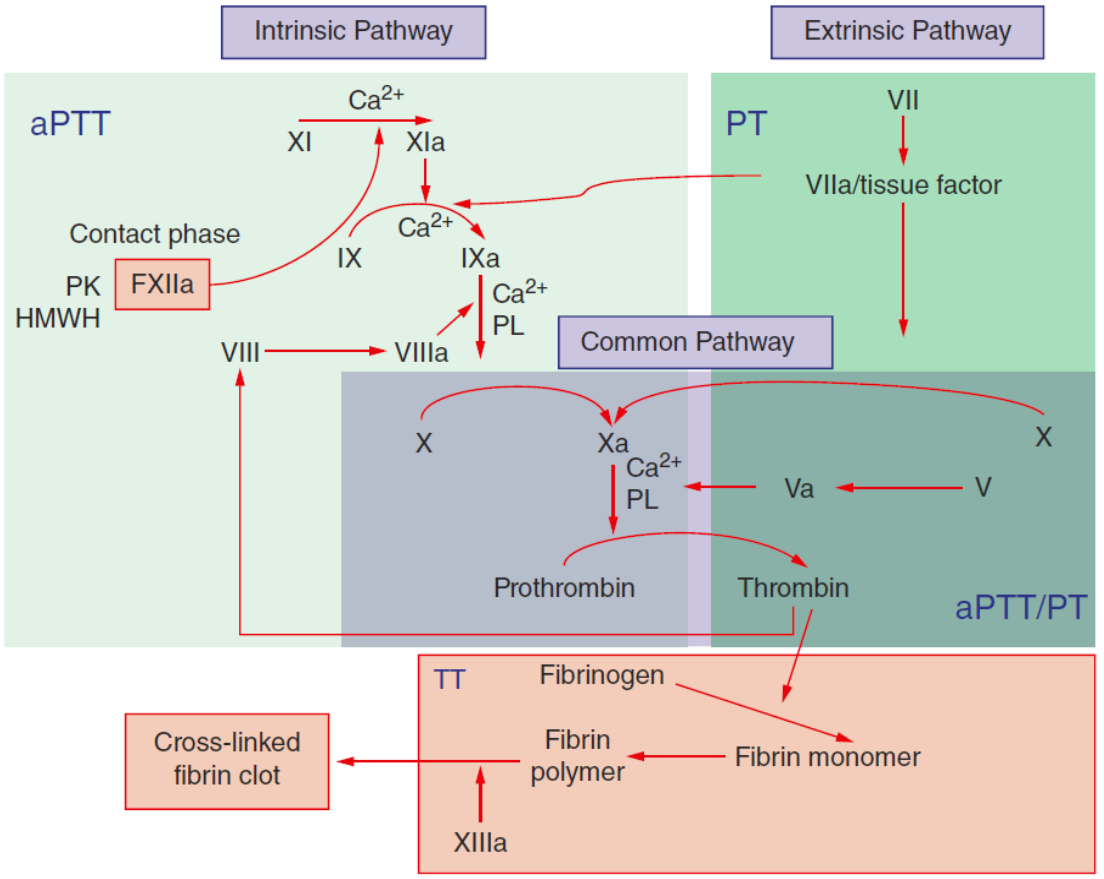
Ideally: normal body temperature, normal pH, normal Ca++

Approach to evaluation of coagulopathy

- **History**
  - Acquired versus inherited
- **Physical**
  - Type and location of bleeding
    - Diffuse oozing
    - Ecchymosis, petechiae
    - Surgical site
- **Laboratory tests**
  - CBC and review of peripheral smear
  - PT
  - PTT
  - Fibrinogen and D-dimer

Interpretation of lab tests

- **Elevated PT only**
  - **Factor VII** is low
  - Warfarin
  - Rivaroxaban, edoxaban
- **Elevated aPTT only**
  - **FXII, FXI, FIX, FVIII**
    - Lupus anticoagulant
    - Rare: specific factor inhibitor
    - heparin
- **Both PT and aPTT elevated**
  - Fibrinogen
  - Drug effect: heparin, DTI
  - Rare: **FX or FV** deficiency or inhibitor



Harrison's Textbook of Medicine

Vitamin K

Management of Coagulopathy

- **Establish diagnosis**
  - **Production**
    - Cirrhosis
    - Shock liver
    - Vitamin K
  - **Dilution**
    - Trauma
    - Massive hemorrhage
  - **Consumption**
    - DIC
    - Snake bite, TPA
- **Supportive care**

Management of Coagulopathy

- Severity of bleeding, need for procedures drives treatment decisions

- **In general**
  - Fibrinogen > 100-200 mg/dL
  - Platelets >20-30 x 10^9/L
  - Need for “normal” aPTT or PT?

Plasma

- **FFP or TP**
  - Contains all clotting and anti-clotting factors at **normal plasma concentration**
  - 70 kg person has 2.8 liters plasma
  - “Normal” PT and aPTT require factor levels >30%
  - Each bag of plasma approx 250 ml (180-300)
  - To obtain a 30% level when starting at <1% will require **4 to 6 bags of FFP** or approximately 20 ml/kg
    or **1000-1500 ml of plasma**

Cryoprecipitate

- Contains:
  - **Fibrinogen**
  - **vWF and FVIII**
  - **FXIII**

  - Obtained from 1 unit whole blood
    - Cold insoluble fraction of high mw proteins as thawing FFP
    - resuspended in 15 ml plasma = 1 unit cryo
    - Minimum **80** IU FVIII and **150** mg fibrinogen per unit

  - BWH: One order of cryo = 2 bags* = **10 units of cryo**
    - should increase **fibrinogen** level by 50-100 mg/dL

Adverse effects of FFP and cryo

- FFP: volume and infusion time
- Allergic
- TRALI—USA now uses only male donors for plasma
- TACO—Transfusion associated circulatory overload
- ABO type specific
- Pathogens--processed, pasteurized, solvent-detergent treated products
- Are lyophilized concentrates the future?

Factor Concentrates

- Benefits of factor concentrates:
  - low volume,
  - no cross matching
  - acellular
  - no alloimmunization
  - viral free
  - increasingly used in algorithms for bleeding

- For PCCs, most data are for warfarin reversal
- Limited single arm studies of prospective data for 4F-PCC in Xa inhibitor DOAC

Fibrinogen Concentrate

- RiaSTAP FDA approved for use in 2009, now others
- Fibrinogen concentrate made from pooled plasma
  - Heat treated, lyophylized
- Labeled indication for hypo- or afibrinogenemia, not dysfibrinogenemia
- Other off label use:
  - Acquired hypofibrinogenemia
  - Obstetric hemorrhage including post-partum hemorrhage
  - Post-operative hemorrhage
  - Trauma-associated hemorrhage
  - Increasingly used in Europe due to concerns for CJD from plasma

Kcentra (4F-PCC)

- non-activated 4 Factor Prothrombin Complex Concentrate
  - Contains vitamin K-dependent coagulation Factors II, VII, IX, and X and antithrombotic Proteins C and S* (and small amount of heparin)

Pre-treatment INR	2–< 4	4–6	> 6
Dose* of Kcentra (units† of Factor IX) / kg body weight	25	35	50
Maximum dose‡ (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

- Dose: 25-50 units/kg
- Volume 25 units/ml
  - Volume for 70kg * 50 units/kg Kcentra = 140 mls
- Administer with vitamin K for sustained reversal of warfarin
- Off-label use for DOAC reversal, intra-op bleeding, liver disease

Kcentra (prothrombin complex concentrate) [prescribing information Kankakee, IL. CSL Behring LLC; 12/13.

rVIIa: NovoSeven RT, SEVENFACT

- Recombinant Factor VIIa
  - Black box warning: serious arterial and venous thrombotic and thromboembolic adverse events
  - Older patients most at risk OR 2.4-3 (Levy NEJM 2010)
- Dose
  - Hemophilia A and B withinihibitors, congenital FVII deficiency
    - NovoSeven 40-90 mcg/kg bolus initial dose
    - SEVENFACT 75 mcg/kg bolus initial dose
  - Uncontrolled bleeding associated with trauma or surgery in which no clear surgical source of bleeding can be identified
    - Low dose—1 mg vial approximately 10-14 mcg/kg

FEIBA: Factor Eight Inhibitor Bypassing Activity

Developed for hemophilia A patients with inhibitors to factor VIII

- *Activated* prothrombin complex concentrate (activated 4PCC)
  - Vitamin K-dependent clotting Factors 2, 9 and 10 mainly in non-activated form and Factor 7 in the **activated** form
  - Dose: 25-50units/kg
- Potentially lower thrombotic risk than rVIIa?
  - "Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity." Aledort, JTH, 2004
    - 24 thrombotic AE per 100,000 infusions rVIIa (stroke)
    - 8.24 thrombotic AE per 100,000 infusions FEIBA (MI)

FEIBA NF (Anti-Inhibitor Coagulant Complex) [package insert]. Village, CA. Baxter Healthcare CorporationWestlake; 2/2011.

Prothrombin complex concentrates and activated factors

Vitamin K-dependent coagulation factors	4-Factor PCC*	Plasma	4F-PCC activated (FEIBA)	3-Factor PCC*	rFVIIa
II	✓	✓ †	✓	✓	
VII	✓	✓ †	✓activated	Low levels	✓activated
IX	✓	✓ †	✓	✓	
X	✓	✓ †	✓	✓	
Protein C	✓	✓			
Protein S	✓	✓			

*Factors in PCCs are ~25x more concentrated than the factors in plasma.
†In plasma, total content of factors relative to volume is low; large volumes are required for reversal.

Zareh M et al. *West J Emerg Med.* 2011;12:386-392. **2**. Bebulin (Factor IX Complex) Prescribing Information. Baxter Healthcare Corporation. July 2012. **3.** Profilnine (Factor IX Complex) Prescribing Information. Grifols Biologicals Inc. August 2011.

Overt DIC scoring system

Platelet Count	
>100 x 10^9/L	0 Points
>50 - <100 x 10^9/L	1 Point
<50 x 10^9/L	2 Points
Increase in Fibrin-related Markers [D Dimers]	
No change	0 Points
Moderate rise	2 Points
Strong rise	3 Points
Prothrombin Time [PT] Prolongation	
3 s or less	0 Points
>3 s but <6 s	1 Point
>6 s	2 Points
Fibrinogen [Clauss] Level	
>1.0 g/L	0 Points
<1.0 g/L	1 Point

Score ≥ 5 DIC

J Thromb Haemost 2007; **5**: 604–6

DIC: Management

- Identify and treat underlying condition
- Supportive care
  - If underlying condition rapidly reversible, watch and wait if patient not bleeding
  - use FFP, cryo, and platelets as needed
  - **Treat bleeding not numbers**
    - Fibrinogen >100-200, plts >20-30k, higher if bleeding
- Stop microvascular thrombosis?
  - consider heparin, tPA, or urokinase
    - Role more established in chronic DIC
    - Low dose 4-5 U/kg IV UFH
    - **No mortality benefit**

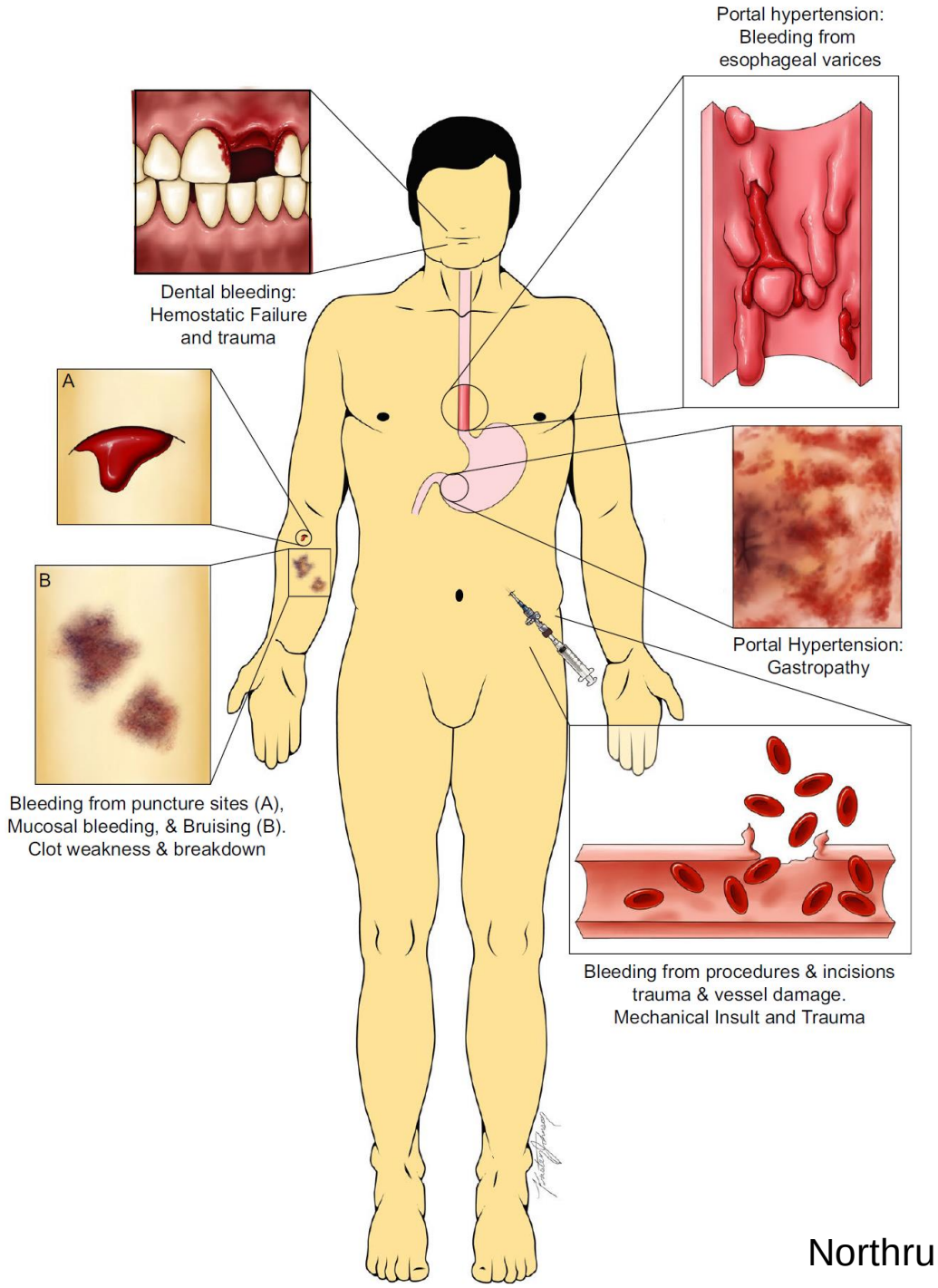
DIC--Management

- Control bleeding, use FFP, cryo, platelets as needed
  - RiaStap, Fibryga: fibrinogen concentrate
  - Kcentra: II, VII, IX, X, proteins S and C (4-PCC)

- Role for natural anticoagulant products?
  - **No mortality benefits have been shown for any**
    - Antithrombin
    - Activated protein C (drotrecogin/Xigris)
    - Recombinant thrombomodulin
    - TFPI
    - Other investigational agents: MAPK,IL-10,NAPc2

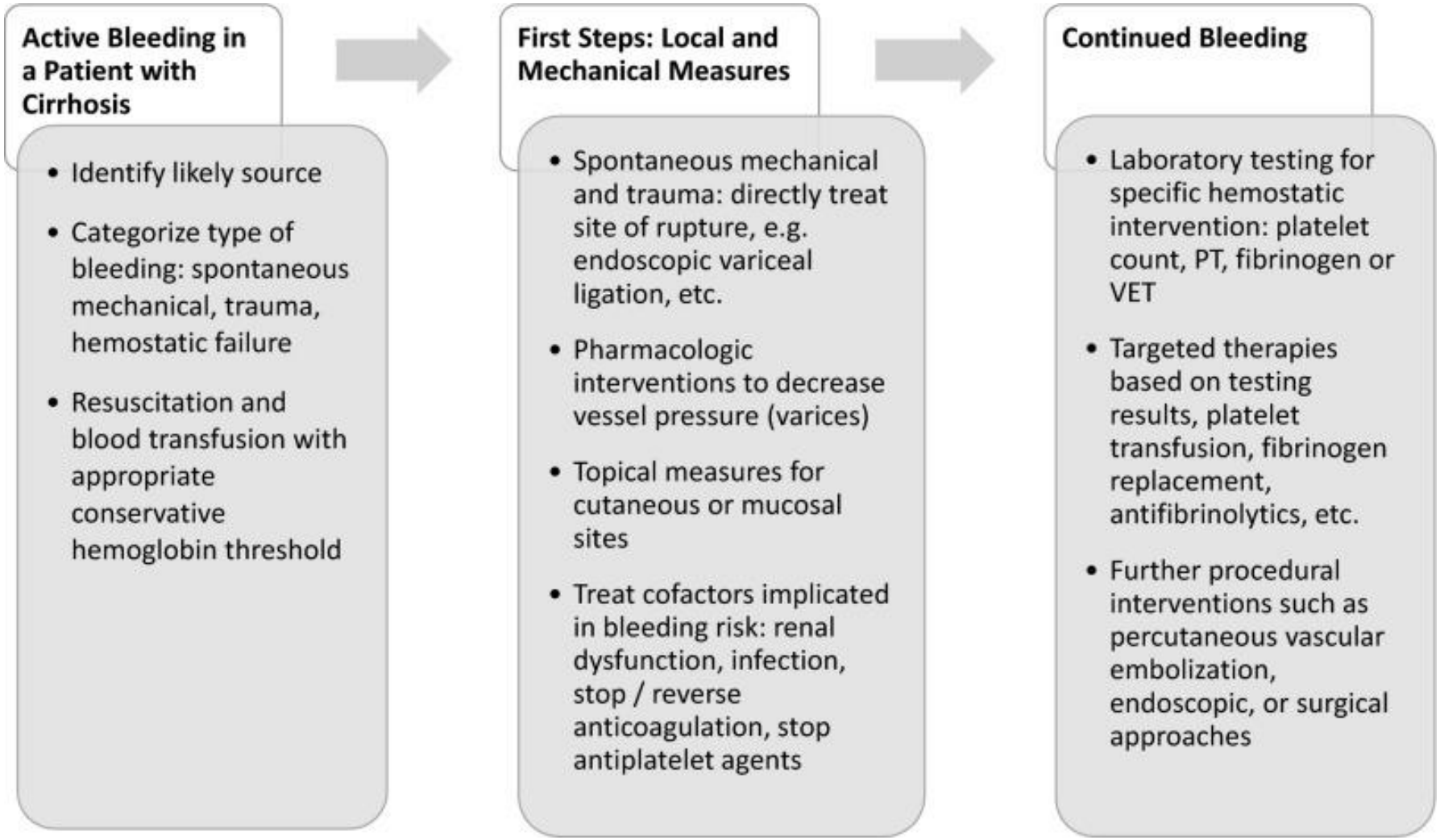
Cirrhosis

- Bleeding can be spontaneous due to mechanical sources such as rupture of varices
- Often acute medical illness on chronic cirrhosis with resultant bleeding due to medical procedures
- Rarely due to end-stage lack of factors→ usually compensated homeostasis

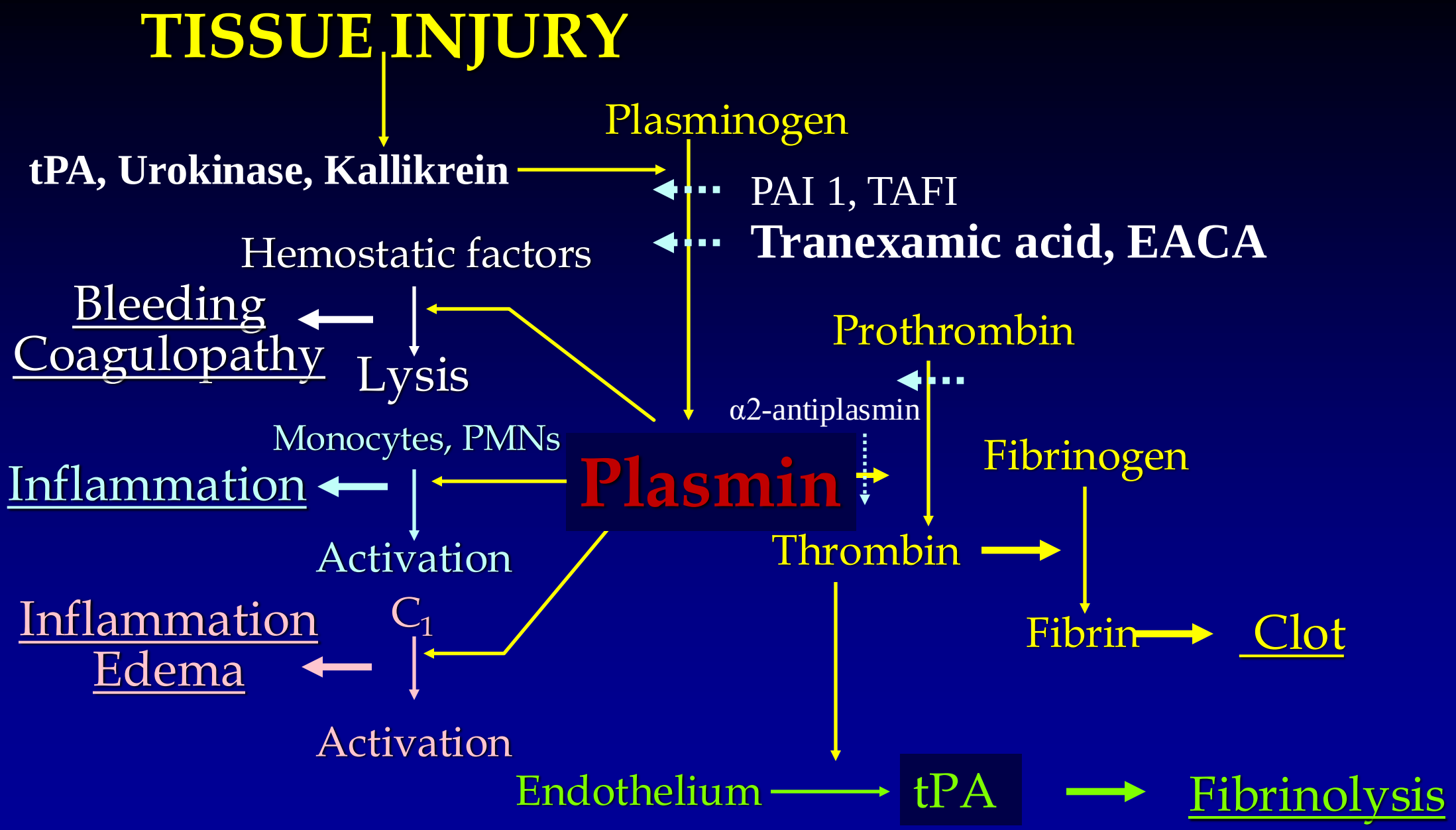


Northrup, JTH 2021

Cirrhosis and active bleeding



Northrup, JTH 2021



Levy JH: Lancet 2010;376(9734):3-4

EACA and TXA are anti-fibrinolytics

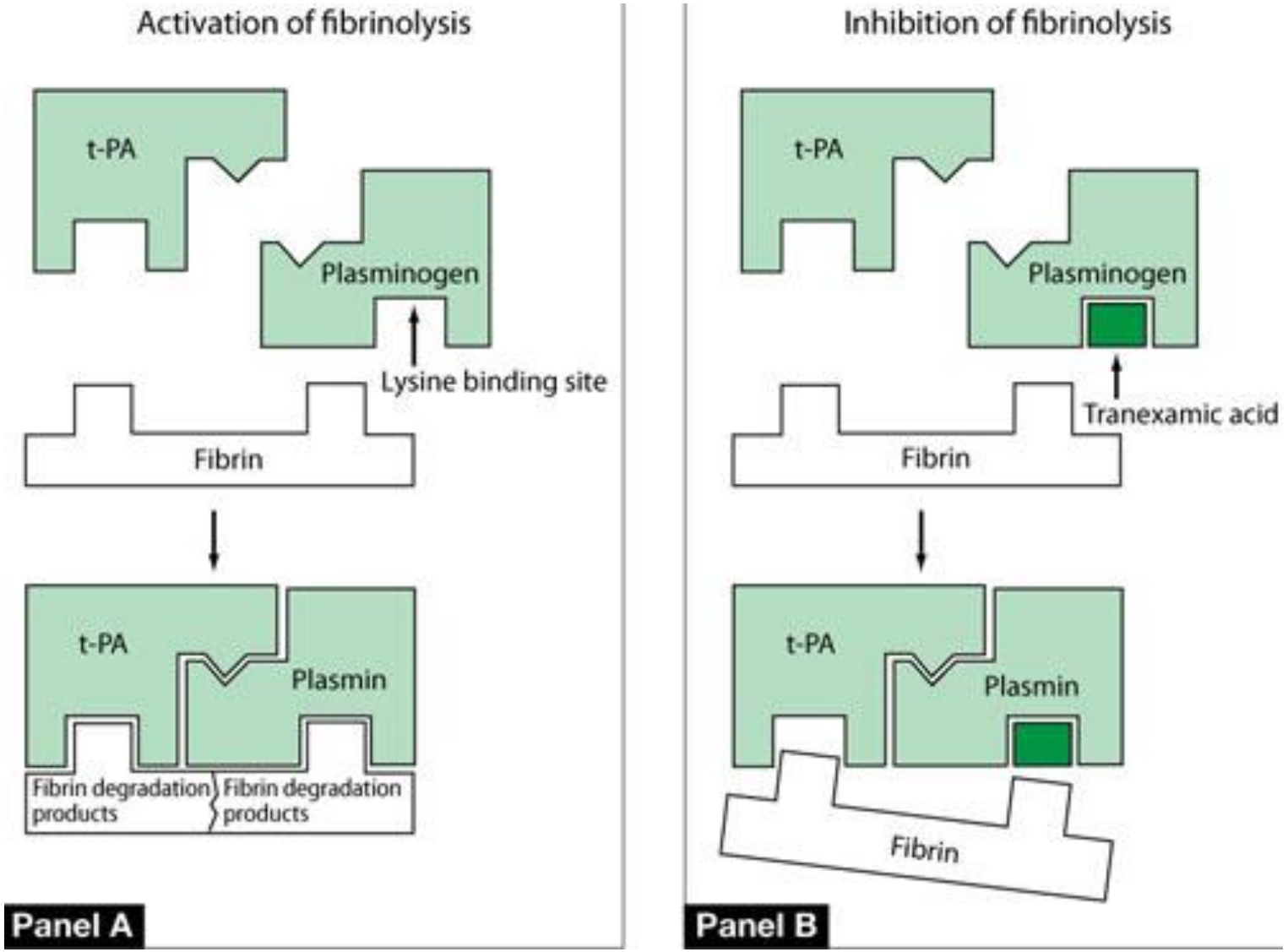


Image from www.obgmanagement.com, Oct. 2010 – Vol. 22, No. 10

Antifibrinolytics

- **CRASH 2 trial** Lancet 2010
  - TXA for trauma: 20,000 randomized to 1gm bolus plus 1 gm over 8 hours vs placebo
  - Early treatment of trauma patients with TXA resulted in better survival, no difference in transfused products
  - Absolute Risk Reduction **1.5%**, 0.8% ARR reduction in death due to bleeding
- **WOMAN trial** Lancet 2017
  - TXA for PPH double blind RCT in **20,000** women
  - Randomized to 1 gm TXA over 10 mins
  - Absolute risk reduction **0.4%** in death due to bleeding; NNT 267
  - No difference in combined outcome of mortality and hysterectomy

Antifibrinolytics

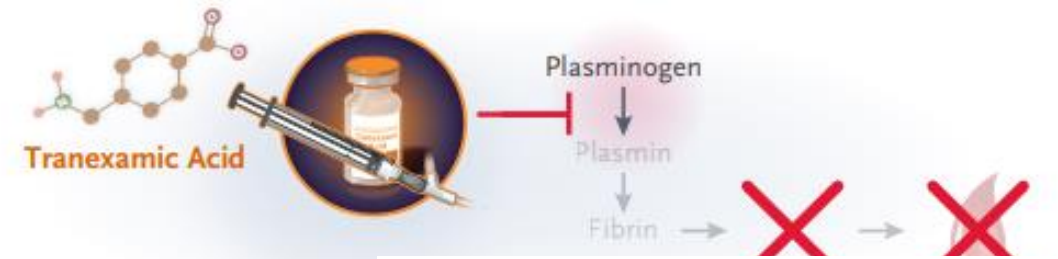
- **TICH-2** Lancet 2018
  - TXA for ICH: **no** difference in mortality or neuro outcomes
- **HALT-IT trial** Lancet 2020
  - GI bleeding
  - **RCT 12,000 patients**
  - loading dose of 1 g tranexamic acid then 3-g infusion over 24 hr
  - **No difference** in mortality
  - Increased VTE 0.8% vs 0.4%
- Why different effects in these trials?
  - Type of bleeding: mucosal ooze vs large holes in vessels?
  - Activation of fibrinolysis in trauma and childbirth
  - heterogeneous GI bleeds?

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Tranexamic Acid in Patients Undergoing Noncardiac Surgery

Devereaux PJ et al. DOI: 10.1056/NEJMoa2201171

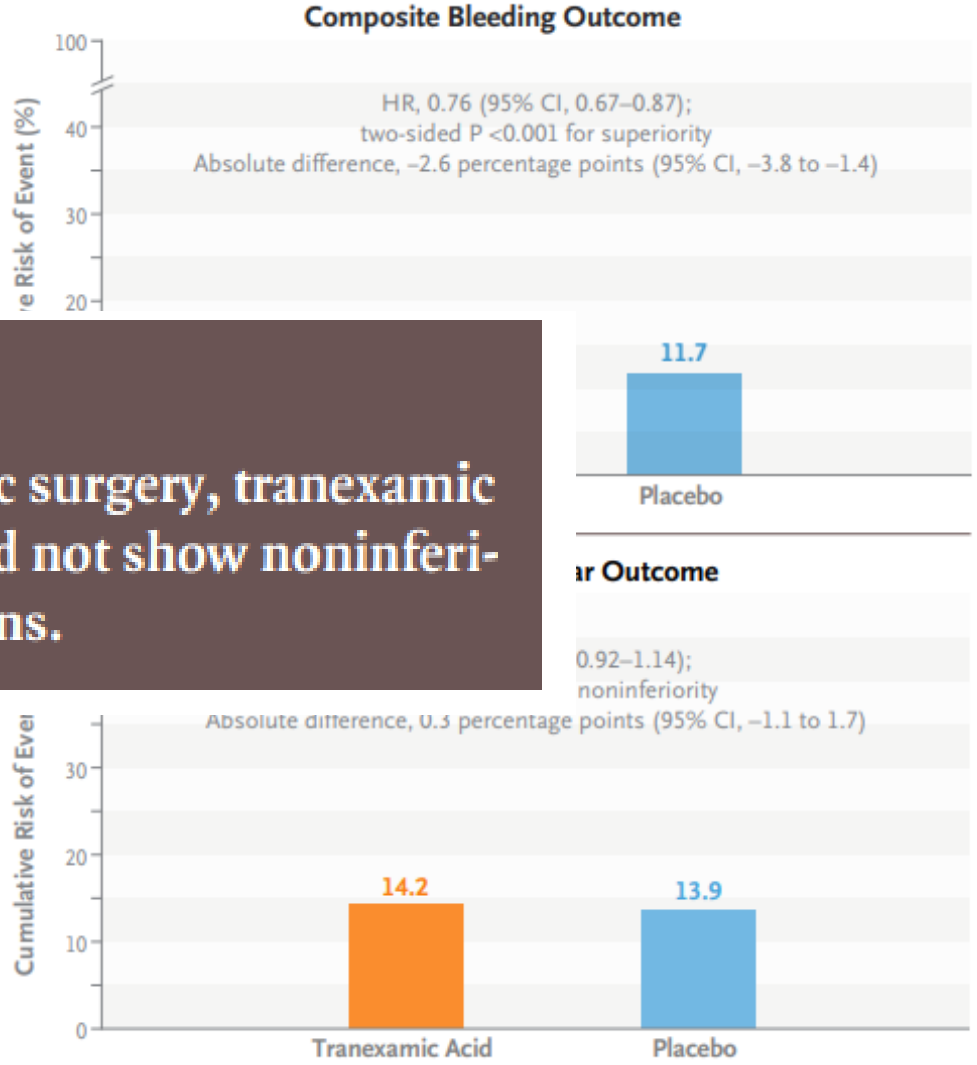


CONCLUSIONS

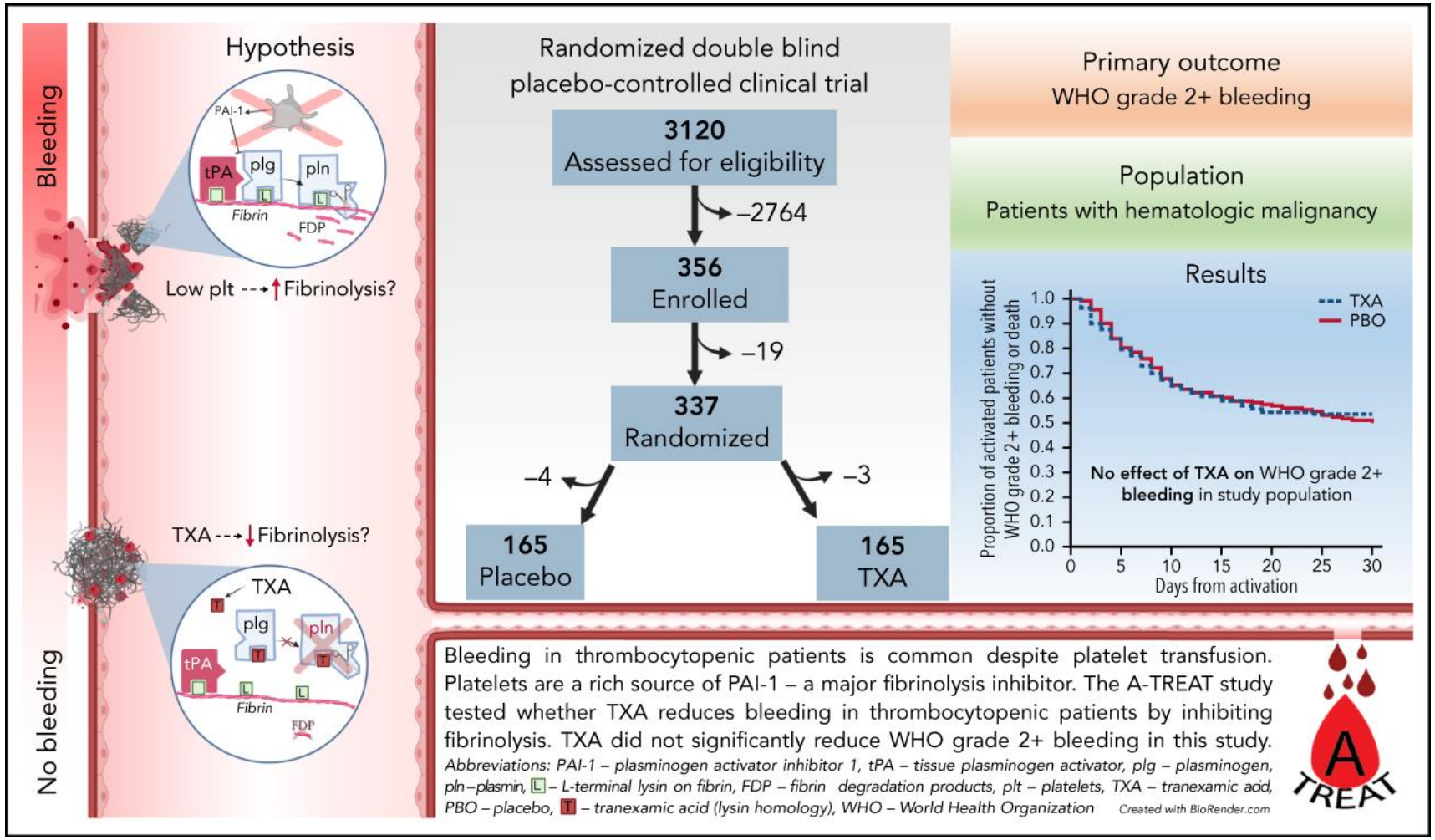
Among patients undergoing noncardiac surgery, tranexamic acid reduced the risk of bleeding but did not show noninferiority to placebo for cardiac complications.

RCT: 9535 patient
cardiovascular cor

- two 1-g IV bolus
  surgery
- **primary efficacy outcome**: composite of life-threatening, major, or critical-organ bleeding 30 days after surgery
- **primary safety outcome**: composite of myocardial injury, nonhemorrhagic stroke, peripheral arterial thrombosis, or symptomatic proximal VTE



Prophylactic tranexamic acid in patients with hematologic malignancy: a placebo-controlled, randomized clinical trial

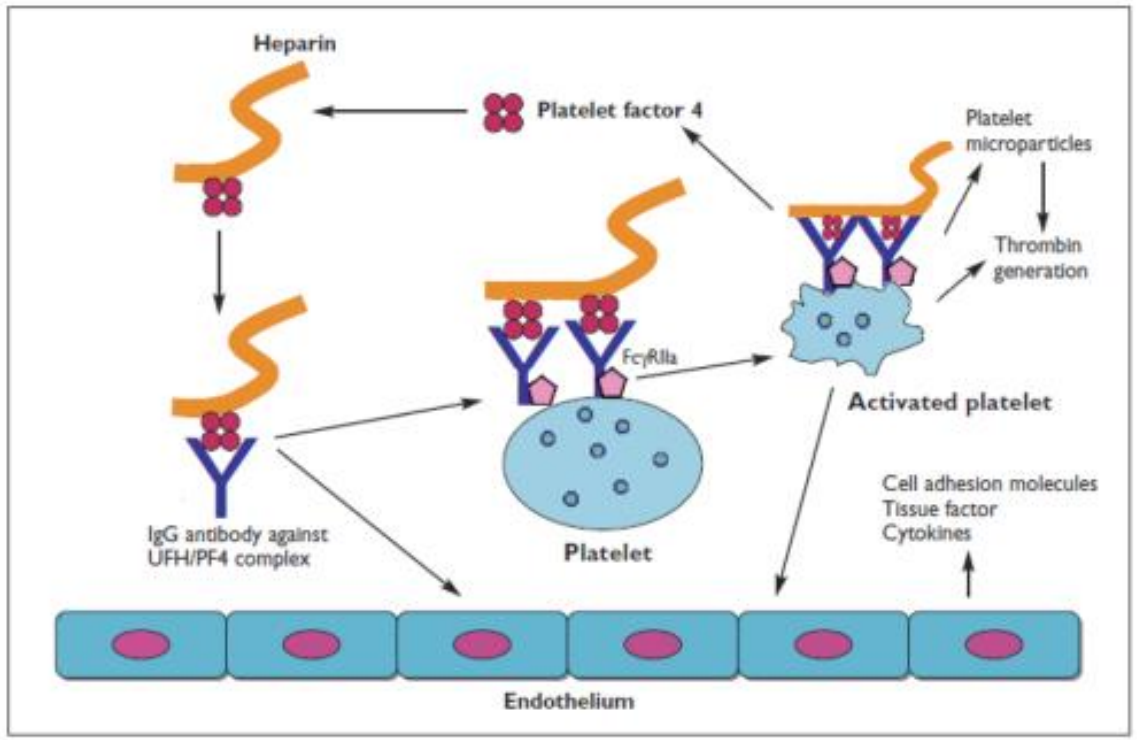


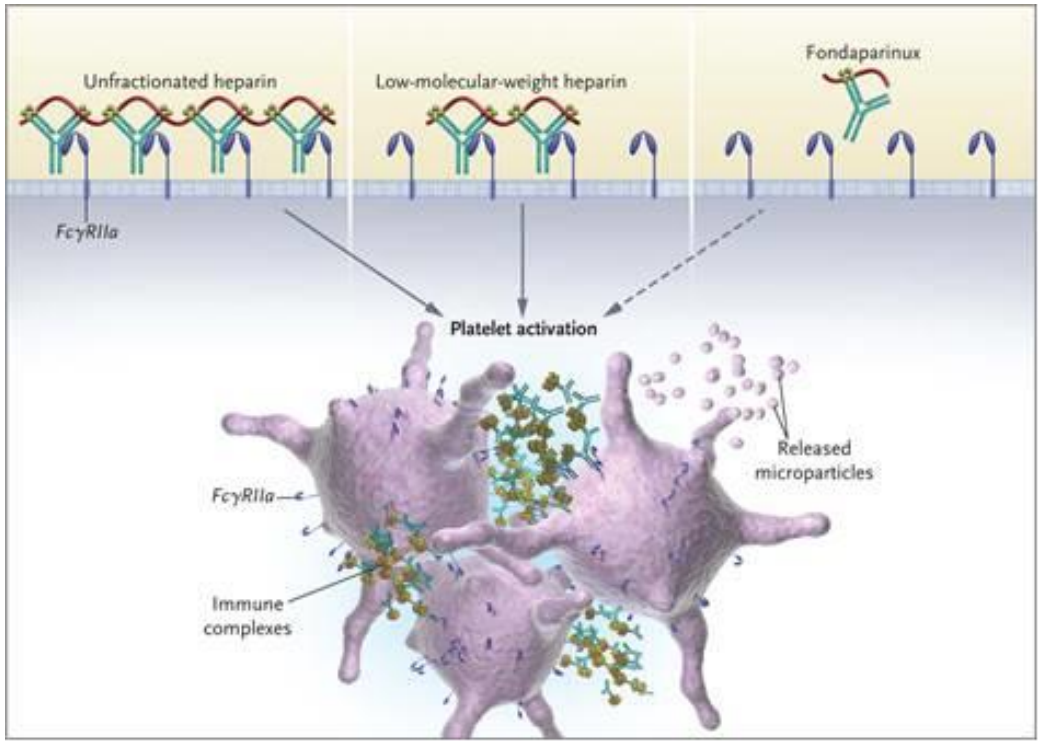
Terry B. Gernsheimer,Siobhan P. Brown,Darrell J. Triulzi,Nigel S. Key,Nahed El Kassar,Heather Herren,Jacqueline N. Poston,Michael Boyiadzis,Brandi N. Reeves,Subodh Selukar,Monica B. Pagano,Scott Emerson,Susanne May, Prophylactic tranexamic acid in patients with hematologic malignancy: a placebo-controlled, randomized clinical trial, Blood, 2022,

When to use what

- **Standard blood products should be used when practical**
  - FFP contains everything, less expensive, safe
  - Cryo contains more than just fibrinogen
- **Concentrates should be reserved for**
  - Patients with significant volume overload
  - Patients with single factor deficiencies or specific issues: warfarin, Xa inhibitor DOAC
  - Local storage use faster than obtaining blood products
- **Antifibrinolytics are in vogue but are the frosting, need the cake**

Heparin Induced Thrombocytopenia





Lefkowitz, An Algorithmic Approach to Hemostasis Testing, 2008; Greinacher, NEJM 2015.

BWH 4T Score Sheet

Brigham and Women's Hospital

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) GUIDELINE

For patients with suspected heparin-induced thrombocytopenia, follow the step-wise approach below

Step 1: Calculate 4 T's Score:

a. **T**hrombocytopenia* (platelet fall from baseline of): ____ pts
*Please consider effects of cardiopulmonary bypass on platelets in applicable patients
☐ Less than 30% (0 pts) ☐ 30-50% (1 pt) ☐ Greater than 50% (2 pts)

b. **T**iming of platelet fall after heparin/LMWH exposure: ____ pts
☐ 4 days or less with no prior exposure in the last 100 days (0 pts)
☐ Greater than 10 days OR ≤1 day and prior exposure in the past 30 to 100 days (1 pt)
☐ 5-10 days OR ≤1 day and prior exposure within the past 30 days (2 pts)

c. **T**hrombosis or other sequelae: ____ pts
☐ None (0 pts)
☐ Suspected thrombosis or non-necrotizing skin lesions (1 pt)
☐ Confirmed thrombosis, skin necrosis, or systemic reaction to UFH bolus (2 pts)

d. Thrombocytopenia from o**T**her causes: ____ pts
☐ None (2 pts) ☐ Possible (1 pt) ☐ Definite (0 pts)

e. Total Score (add a thru d) and determine clinical suspicion ____ pts
☐ Less than 3 Low Suspicion ☐ 3-5 Intermediate Suspicion ☐ Greater than5 High Suspicion

NPV of low-risk score 0.998

HIT: Testing

Heparin /platelet factor 4 ELISA

--immunologic assay detects presence of Ab

--OD > 0.399 considered positive

--repeat in 48 hours if borderline or high clinical suspicio

--high sensitivity (95-99%) but high false +

50% surgical, 20% medical can develop antibodies

--NPV for negative result 95%

Serotonin release assay

--functional assay of ability of complexes to stimulate platelet aggregation/secretion

--gold standard but still not 100% specific or sensitive (88%-100% specificity)

Combined sensitivity PF4 and SRA is 99%

Clinical judgment still required

HIT: Treatment

STOP HEPARIN—all forms including line flush, dialysis; coated lines?

STOP WARFARIN

- If patient on warfarin **and** reverse with Vitamin K

Treat with direct thrombin inhibitors, fondaparinux, DOAC if clinically stable

- When clinically improved and platelet count ≥ 150,000
  - start DOAC or
  - warfarin overlap with DTI for at least 5 days

Warfarin or DOAC rx for at least 3 months—debate about duration if no thrombosis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Question 1

A 68 yo man in the ICU for hypoxemia due to pneumonia develops altered mental status and is found to have ICH. He is on warfarin anticoagulation for a mechanical valve with an INR of 5.3. You reverse the warfarin with:

a. FFP
b. Vitamin K
c. Cryoprecipitate
d. 4F-PCC
e. rVIIa

Question 1

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More TXA

Gernsheimer, T.B., Brown, S.P., Triulzi, D.J., Key, N.S., El Kassar, N., Herren, H., Poston, J.N., Boyiadzis, M., Reeves, B.N., Selukar, S. and Pagano, M.B., 2022. Prophylactic tranexamic acid in patients with hematologic malignancy: a placebo-controlled, randomized clinical trial. *Blood, The Journal of the American Society of Hematology*, *140*(11), pp.1254-1262.

Devereaux, P.J., Marcucci, M., Painter, T.W., Conen, D., Lomivorotov, V., Sessler, D.I., Chan, M.T., Borges, F.K., Martínez-Zapata, M.J., Wang, C.Y. and Xavier, D., 2022. Tranexamic acid in patients undergoing noncardiac surgery. *New England Journal of Medicine*, *386*(21), pp.1986-1997.