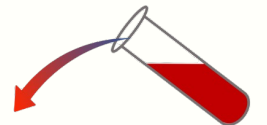


# Acquired Bleeding Disorders



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**Sylvester Comprehensive Cancer Center,**  
**University of Miami Health System**  
**gas199@Miami.edu**



**WORLD  
THROMBOSIS  
DAY**  
13<sup>th</sup> October

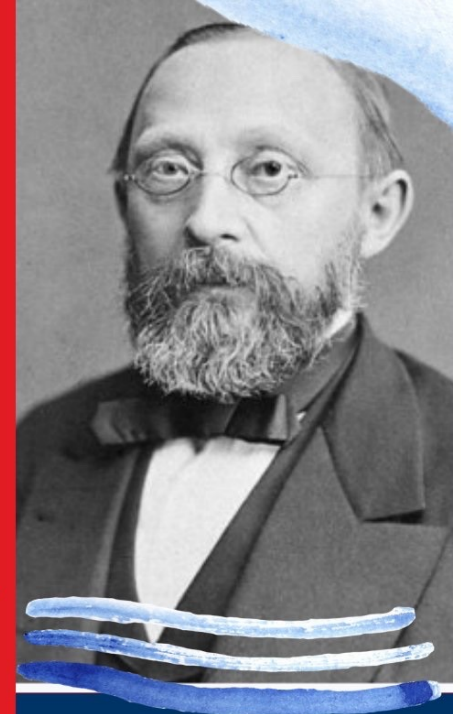
Adobe Stock | #288811782

Why

# OCT 13?

WTD takes place every year on 13 October, the birthday of Rudolf Virchow who was a pioneer in the pathophysiology of thrombosis.

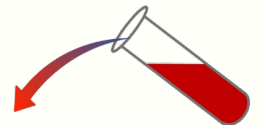
A German physician, pathologist, biologist and anthropologist, Virchow developed the concept of "thrombosis" and advanced our understanding of this condition



WORLD THROMBOSIS DAY  
13 OCTOBER

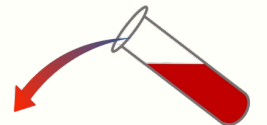
WorldThrombosisDay.org | #WTDay22

October 12 2023



# Disclosures

- Research Support (Past 5 years):
  - Amgen
  - Janssen Scientific Affairs
  - Sobi/Dova Pharmaceuticals
  - Anthos Therapeutics
- Advisory Boards (Past 5 years)
  - Janssen Scientific Affairs
  - Sobi/Dova Pharmaceuticals
  - Sanofi
  - Novartis
  - Agios Pharmaceuticals.



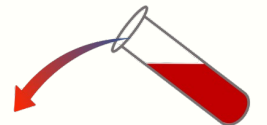
# Hematology Consult for “Bleeding”

Are we working up the patient, the laboratory tests, or the surgeon?

- Is the patient symptomatic, or is the surgeon symptomatic?
- Are we consulting for a bleeding patient or a scary lab value?
- aPTT of 55” can be from von Willebrand Disease (bleeding), moderate hemophilia (bleeding), Factor XI deficiency (possible risk for post-op bleeding), or Anti-phospholipid antibody syndrome (prothrombotic).

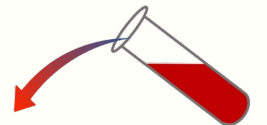


<https://depositphotos.com/stock-photos/surgeons.html>



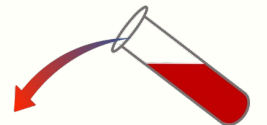
# During the year, we will have additional presentations on specific topics.

- Thrombocytopenia, platelet function abnormalities, anticoagulation, vascular causes of bleeding.
- Here we will focus on the overall approach to acquired bleeding episodes, and more common disorders.



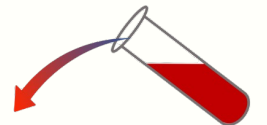
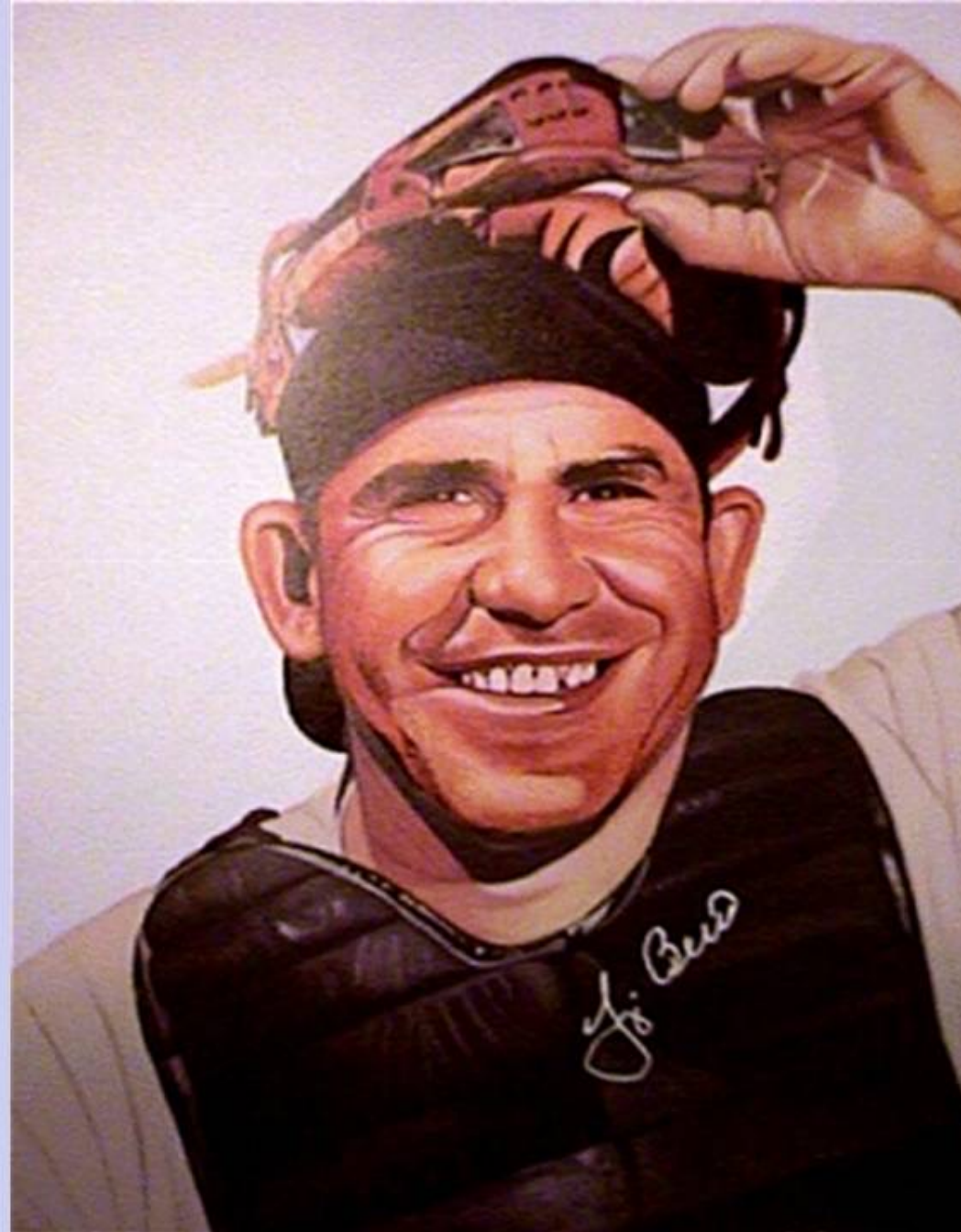
# Pattern of Bleeding/History:

- Clinical Presentations Help Define Differential Diagnosis
- Mucocutaneous versus deep bleeding?
- Immediate versus late bleeding?
- Local versus systemic?
- Acquired versus congenital?
- Family history?



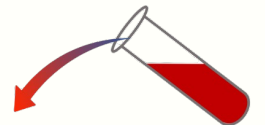
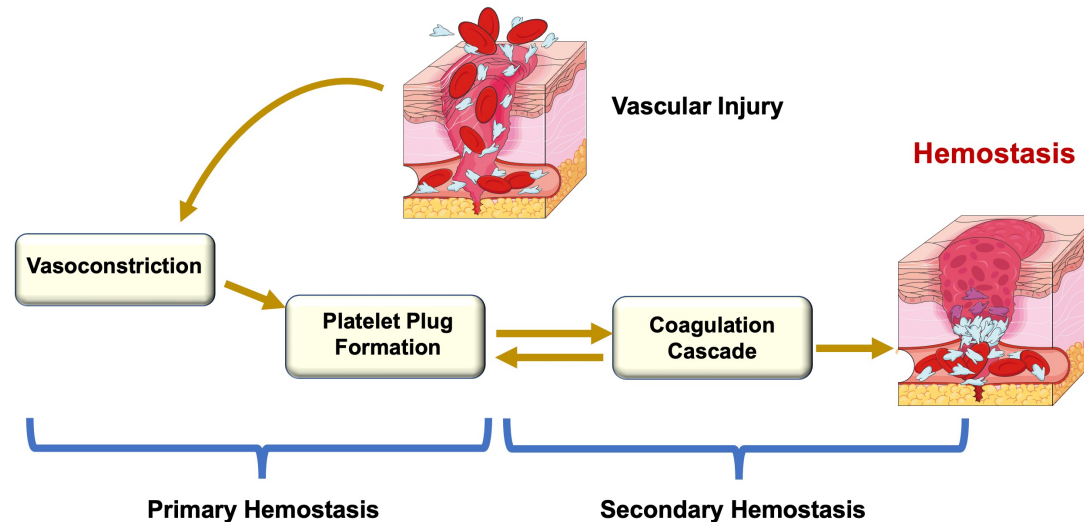
**You can  
observe  
a lot  
just by  
watching.**

**Yogi Berra**



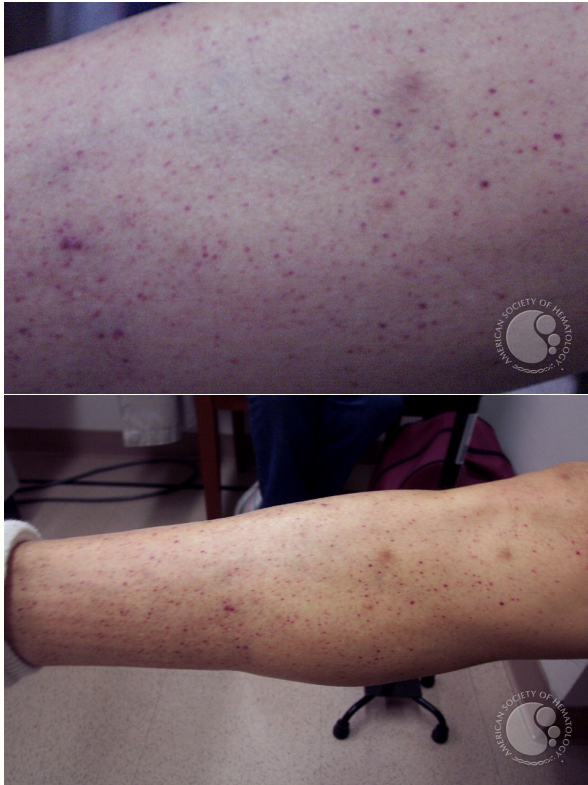
# Clinical Features of Bleeding Disorders

	Primary Hemostasis	Secondary Hemostasis
<b>Defect</b>	<b>Thrombocytopenia Platelet Function Disorders Vascular Defects</b>	<b>Coagulation Factor Disorders</b>
<b>Site of Bleeding</b>	<b>Skin: Petechiae/Purpura/Ecchymoses, Mucous membranes, Epistaxis, gum, vaginal, GI</b>	<b>Deep: Soft tissues, joints, muscles</b>
<b>Bleeding after surgery or trauma</b>	<b>Immediate, usually mild</b>	<b>Delayed (1-2 days), often severe</b>





**Petechiae: <3 mm**



imagebank.hematology.org

**Purpura: 3–10 mm/Ecchymosis: >10 mm**

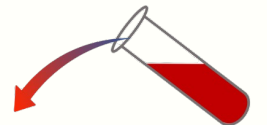


imagebank.hematology.org



[https://commons.wikimedia.org/wiki/File:Upper\\_Arm\\_Bruise.jpg](https://commons.wikimedia.org/wiki/File:Upper_Arm_Bruise.jpg)

**Flat, not warm, not tender!**



# Hematoma

## Muscle



Hoffbrand AV, Pettit JE: Color atlas of clinical hematology, ed 4, London, 2010, Mosby



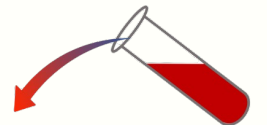
[https://commons.wikimedia.org/wiki/File:CT\\_of\\_Morel-Lavallee\\_lesion.jpg](https://commons.wikimedia.org/wiki/File:CT_of_Morel-Lavallee_lesion.jpg)

## Subcutaneous

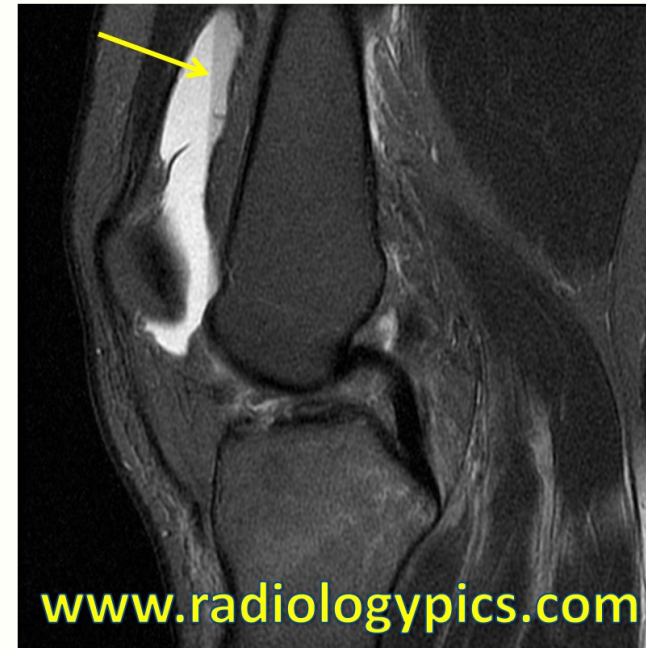
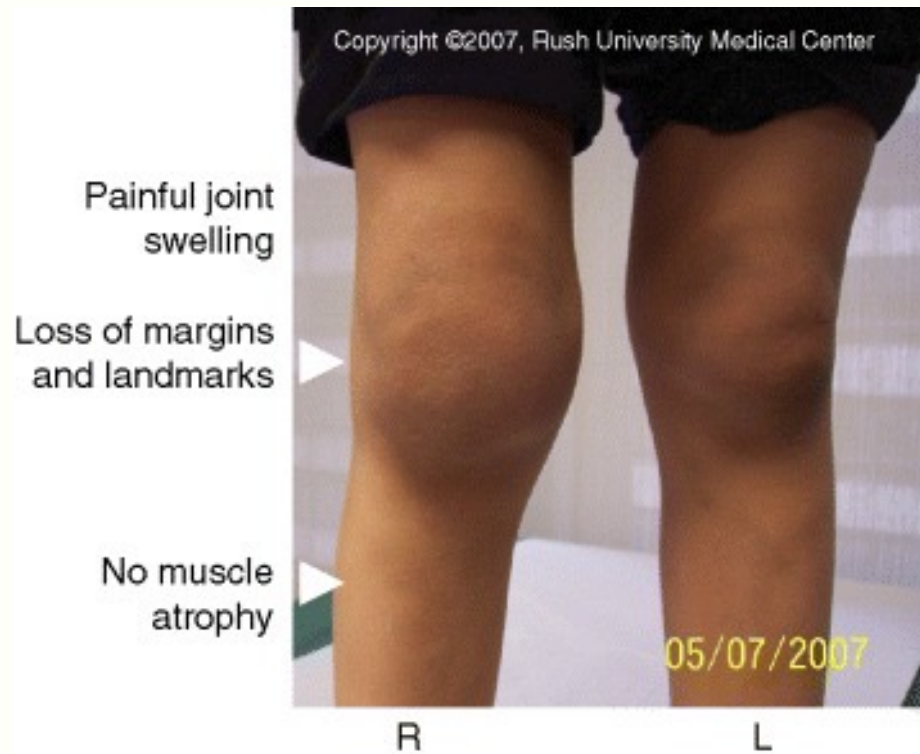


[https://commons.wikimedia.org/wiki/File:Hematoma\\_at\\_backside.jpg#filelinks](https://commons.wikimedia.org/wiki/File:Hematoma_at_backside.jpg#filelinks)

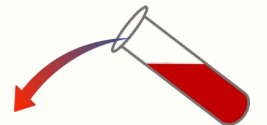
**Raised, tender, painful, warm**



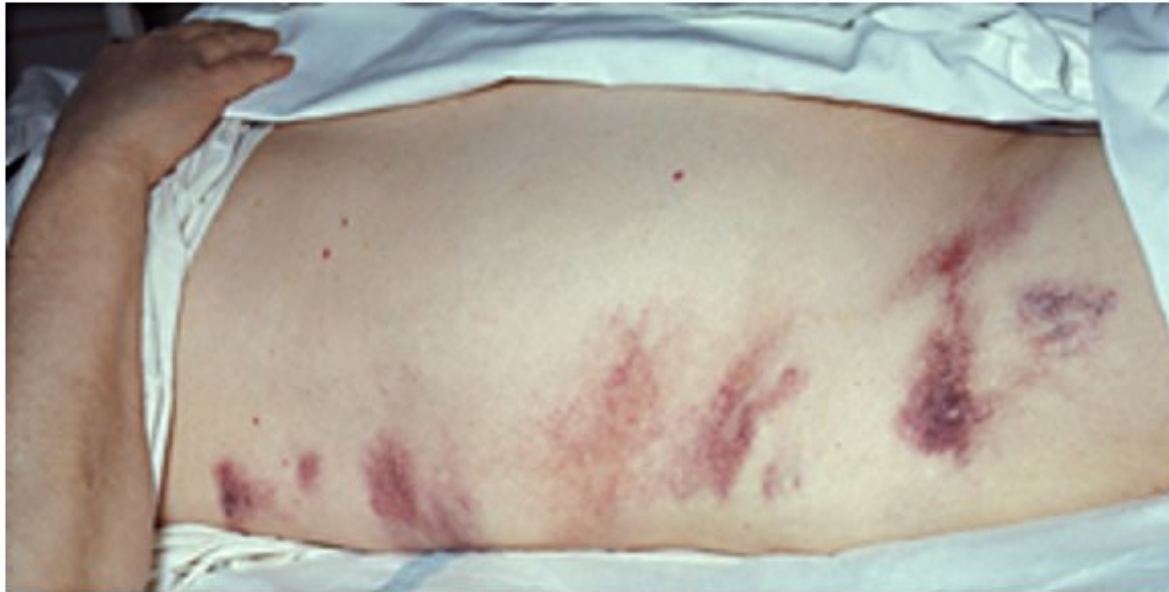
# Hemarthrosis: Joint Bleed. From Severe Factor Deficiency



[https://www.researchgate.net/profile/Steven\\_Pipe/publication/6016957/figure/fig5/AS:267796365967398@1440859038152/Figure-1-Acute-hemarthrosis-The-right-R-knee-is-swollen-warm-and-painful-to-touch.png](https://www.researchgate.net/profile/Steven_Pipe/publication/6016957/figure/fig5/AS:267796365967398@1440859038152/Figure-1-Acute-hemarthrosis-The-right-R-knee-is-swollen-warm-and-painful-to-touch.png)

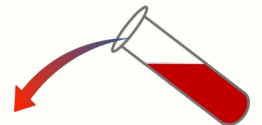


# A deep bleed may appear to “spread” with time, as the deep blood products migrate to the skin.



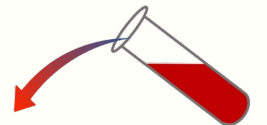
- Grey-Turner’s Sign:
- Appears to be “bruising.”
- A sign of retroperitoneal hematoma.
- Grey Turner's sign usually take 24–48 hours to develop.

[https://en.wikipedia.org/wiki/Grey\\_Turner%27s\\_sign#/media/File:Hemorrhagic\\_pancreatitis\\_-\\_Grey\\_Turner's\\_sign.jpg](https://en.wikipedia.org/wiki/Grey_Turner%27s_sign#/media/File:Hemorrhagic_pancreatitis_-_Grey_Turner's_sign.jpg)



# Vascular Bleeding Disorders

- Defects in blood vessels
- Clinical Manifestations:
  - Often petechiae, purpura, and bruising
- Causes:
  - Vasculitis: Inflammatory, Scurvy, immunoglobulin A–associated vasculitis (Henoch-Schönlein purpura).
  - Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)
  - Ehlers-Danlos syndrome: Deficiencies of vascular and perivascular collagen
- Diagnosis:
  - Coagulation tests normal.
  - Positive markers of inflammation.
  - Specific tests are available for some.

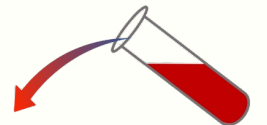


# Mimics of Bleeding: Hypersensitivity Vasculitis



- Hypersensitivity vasculitis, or cutaneous small vessel vasculitis:
  - Allergic reaction
  - Reaction to an infection
  - Idiopathic
- Lesions of vasculitis tend to be diffuse, while thrombocytopenia/ITP tend to be more in dependent areas.

<https://arapc.com/vasculitis-nutshell/>

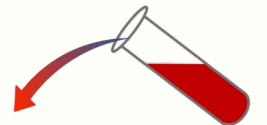


# Mimics of Bleeding: Henoch-Schonlein Purpura



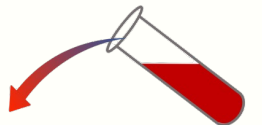
[https://www.medicinenet.com/image-collection/henoch-schonlein\\_purpura\\_picture/picture.htm](https://www.medicinenet.com/image-collection/henoch-schonlein_purpura_picture/picture.htm)

- Immunoglobulin A–associated vasculitis (Henoch-Schönlein purpura).
- Inflammation of small blood vessels.
- Immune complex vasculitis affecting small vessels with dominant IgA deposits.
- Most commonly occurs in children.
- “Leaking” blood vessels in the skin, intestines, kidneys, and joints.
- “Palpable purpura”
- Usually one or more of:
  - Abdominal pain
  - Arthralgia or arthritis
  - Renal involvement (proteinuria, red blood cell casts, or hematuria)
  - Proliferative glomerulonephritis or leukocytoclastic vasculitis with predominant deposition of IgA on histology



# *Thrombocytopenia*

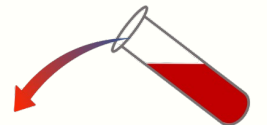
*Thrombocytopenia, including ITP, are to be discussed in separate talks in the next few weeks.*





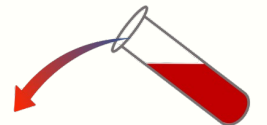
# Acquired Bleeding Disorders:

- Anticoagulant Therapy
- Liver disease
- Vitamin K deficiency
- Disseminated intravascular coagulation
- Uremic coagulopathy
- Acquired hemophilia
- Acquired von Willebrand disease
- Acute Promyelocytic Leukemia



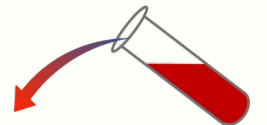
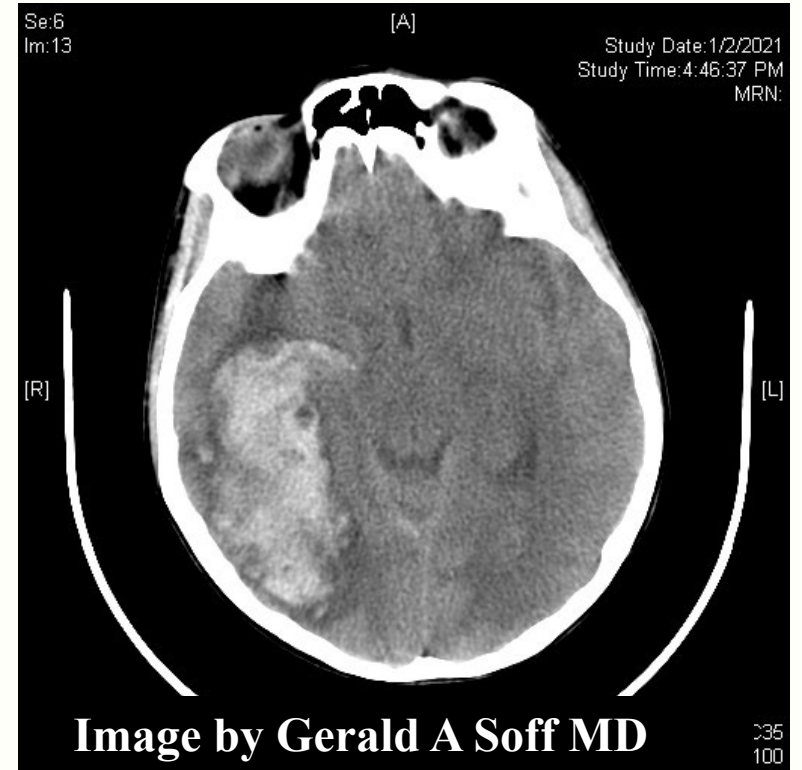
# Synergy Of Risks

- Some patients with mild-moderate hereditary bleeding tendency do not have clinical manifestations, until an added hemostatic challenge is added, such as:
  - Surgery
  - Trauma
  - Dental extraction
  - Menstruation/pregnancy
- Examples:
  - Von Willebrand Disease
  - Factor XI Deficiency



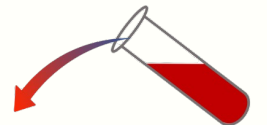
# Managing Anticoagulant-Related Bleeding

- Bleeding is a common side effect of anticoagulant use.
- However, most bleeding events are not life threatening and can be managed conservatively.
  - 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. Tomaselli et al. J Am Coll Cardiol 2017;70:3042–67.
  - Hanigan et al. American College of Cardiology 2019. Managing Anticoagulant-related Bleeding in Patients with Venous Thromboembolism



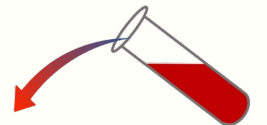
# Management of Vitamin K Antagonist-Related Bleeding (Warfarin)

- “In the setting of a life-threatening bleed related to vitamin K antagonist (VKA) use, rapid reversal of the VKA drug effects and replenishing clotting factors is a priority.”
- “To achieve that goal, administer vitamin K 10 mg intravenously along with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) to achieve a sustained reduction of the international normalized ratio (INR).”
- Prothrombin complex concentrate (PCC) is preferred! (See below).
- “Generally, a goal INR of  $\leq 1.3-1.5$ , depending on the site of the bleed, is targeted.”
  - Hanigan and Barnes. American College of Cardiology 2019. Managing Anticoagulant-related Bleeding in Patients with Venous Thromboembolism. [ <https://www.acc.org/latest-in-cardiology/articles/2019/10/07/14/29/managing-anticoagulant-related-bleeding-in-patients-with-venous-thromboembolism> ]



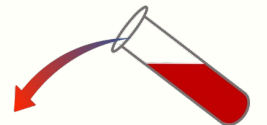
# Prothrombin Complex Concentrate (PCC) is Preferred For Vitamin K Antagonist-Related Bleeding (Warfarin)

- The INR of a unit of FFP is approximately 1.5.
- Transfusion of even very large amounts of FFP into a patient with an elevated INR will not correct the INR to below 1.6.
- “If any clinician orders FFP transfusions with a goal INR below this, it probably won’t happen.”
- <https://thetraumapro.com/2013/01/29/whats-the-inr-of-fresh-frozen-plasma/>
- Toward rational fresh frozen plasma transfusion: the effect of plasma transfusion on coagulation test results. Am J Clin Pathol 126(1):133-139, 2006.
- Effect of fresh frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion 46(8):1279-1285, 2006.

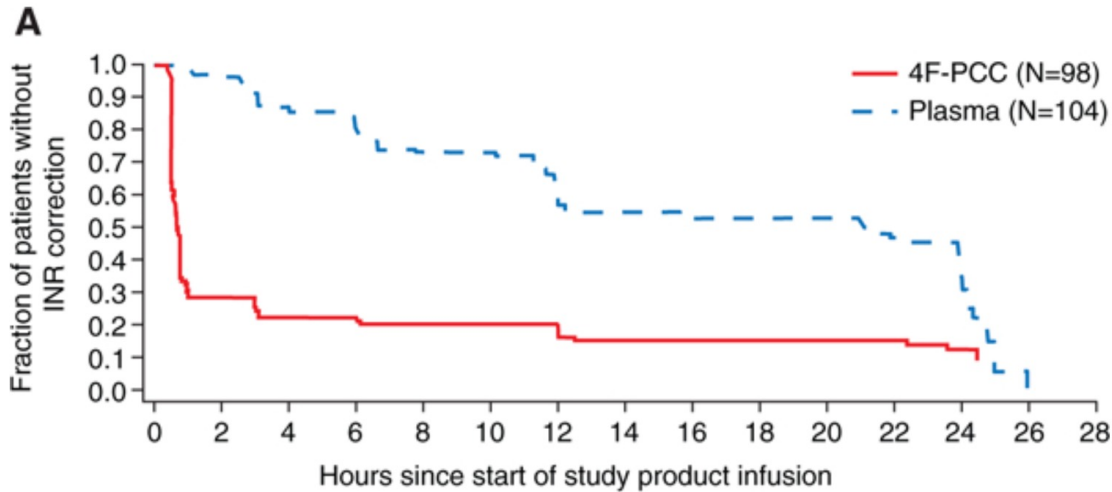


# Limitations of FFP Use to Reverse VKA-Associated Bleeding

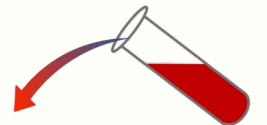
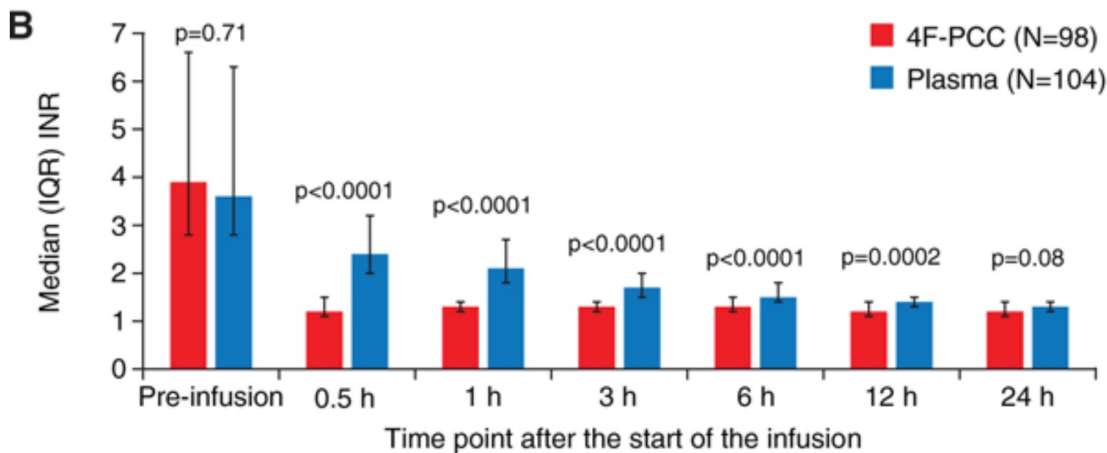
- Need for blood typing.
- Thawing may result in administration delays.
- Large volume requirement that leads to prolonged infusion times.
- Protein load in plasma limits amount of replacement possible.
- Potential for transfusion-associated circulatory overload (TACO).
- Risk of transfusion-related acute lung injury (TRALI).
  - Hanigan and Barnes. American College of Cardiology 2019. Managing Anticoagulant-related Bleeding in Patients with Venous Thromboembolism. [ <https://www.acc.org/latest-in-cardiology/articles/2019/10/07/14/29/managing-anticoagulant-related-bleeding-in-patients-with-venous-thromboembolism> ]



# Prothrombin Complex Concentrate Versus Plasma for Management of Vitamin K Antagonist-Related Bleeding (2)

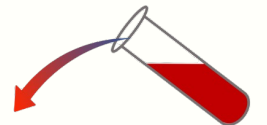


- Prothrombin complex concentrate (Kcentra ®) provides more factors/volume and has less risk of infusion-related infection than plasma.
  - Sarode et al. *Circulation*. 2013, 10; 128(11): 1234–1243.  
doi:10.1161/CIRCULATIONAHA.113.002283.
- Weight/INR based dose versus fixed dose?



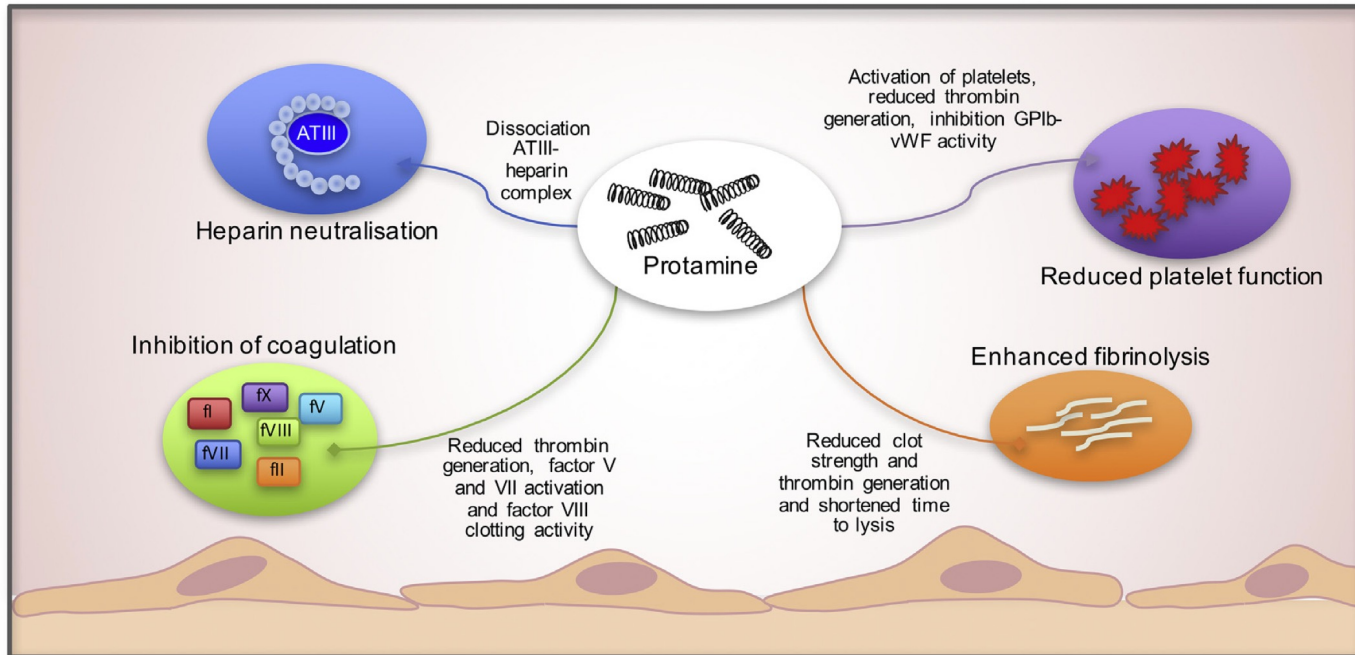
# Protamine: Reversal of IV Unfractionated Heparin

- Highly cationic peptide.
- Binds heparin or low molecular weight heparin (LMWH).
- Protamine:Heparin complex is cleared by the reticuloendothelial system.
- Need to estimate the amount of residual heparin.
- Excess protamine has anticoagulant and anti-platelet activity.



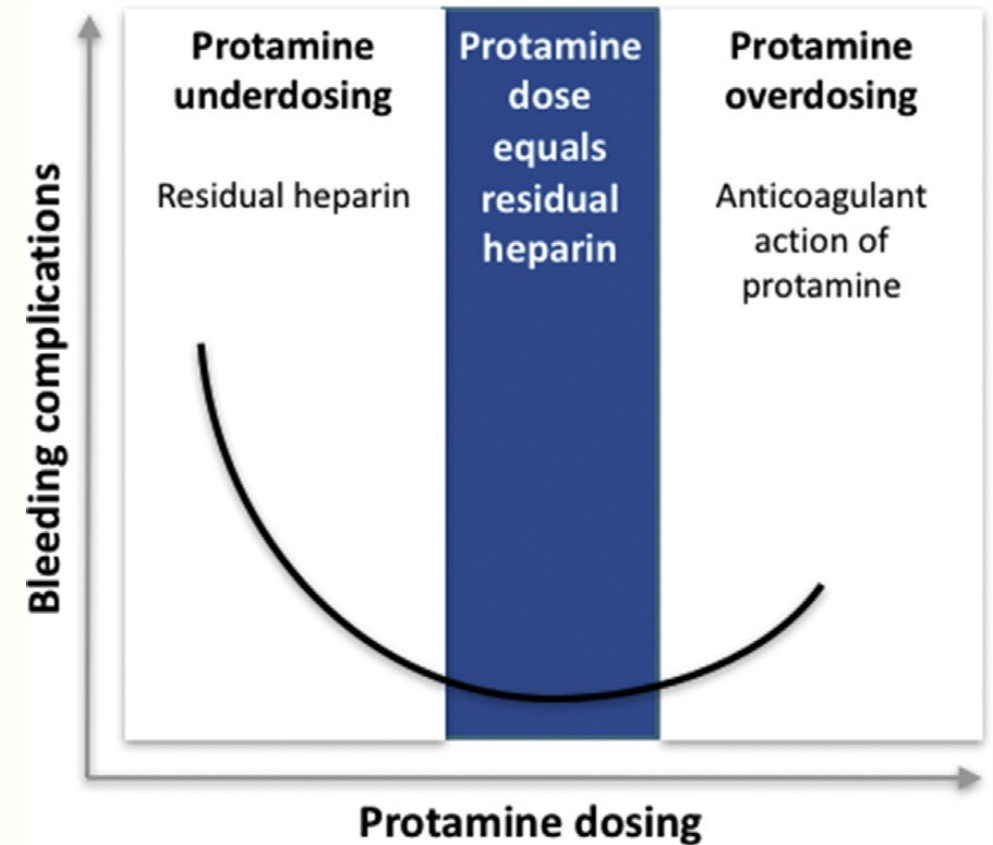


# Overview of the Hemostatic Actions of Protamine

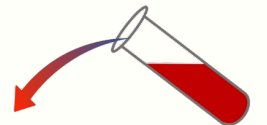


- Neutralizes heparin,
- Interferes with platelet function
- Interferes with activation of coagulation factors
- Potentiates fibrinolysis

# Hypothetical relation of protamine dosing with bleeding complications



Boer C et al. *British Journal of Anaesthesia*, 120 (5): 914e927 (2018)



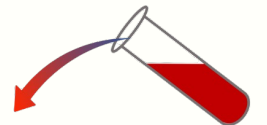
## Reversal of IV Unfractionated Heparin

Time Elapsed	Dose of Protamine (mg) to Neutralize 100 units of IV Unfractionated Heparin
Immediate	1-1.5
30-60 min	0.5-0.75
>2 h	0.25-0.375

## Reversal of Enoxaparin\*

Time Elapsed	Dose of Protamine (mg) to Neutralize Enoxaparin
≤8 hours	1 mg of protamine per mg of enoxaparin
> 8 hours prior	0.5 mg of protamine per mg of enoxaparin

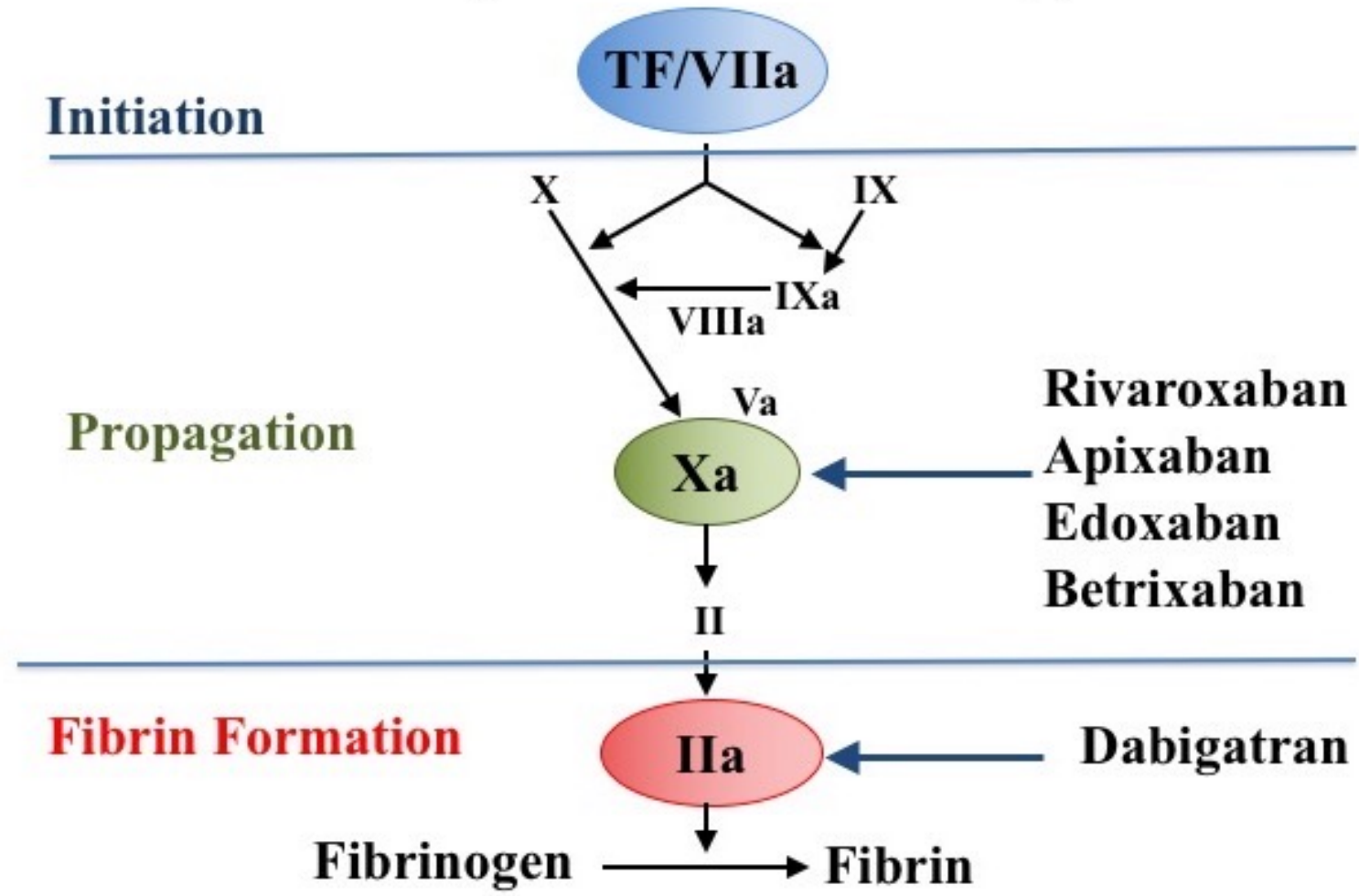
\* Neutralizes about 60-75% of activity



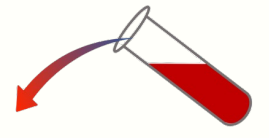
**Steps In Coagulation**

**Coagulation Pathway**

**Inhibitory Drugs**

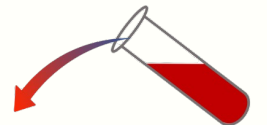


➤ Adapted from Soff, Arteriosclerosis, Thrombosis, and Vascular Biology 2012, 32:569-574.

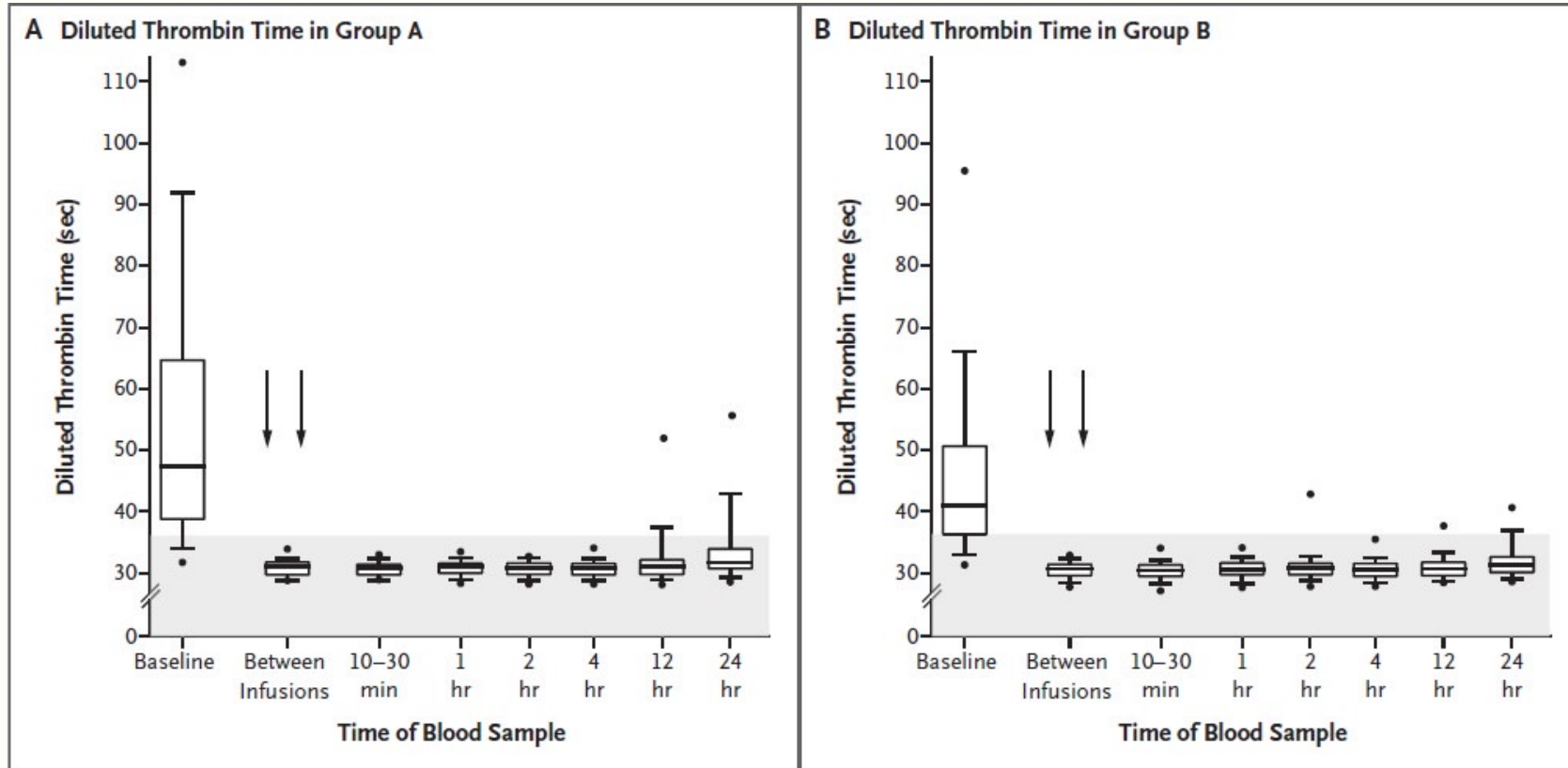


# Idarucizumab for Dabigatran Reversal

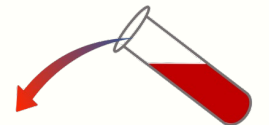
- Humanized anti-dabigatran Ab
- Final analysis of 503 patients in need of reversal
  - Serious bleeding (group A): n=301
  - Emergent procedure (group B): n=202
- Fixed dose of 5 g IV
  - Two separate boluses of 2.5 g given no more than 15 min apart.
  - Pollack CV *et al*, N Engl J Med 2017.



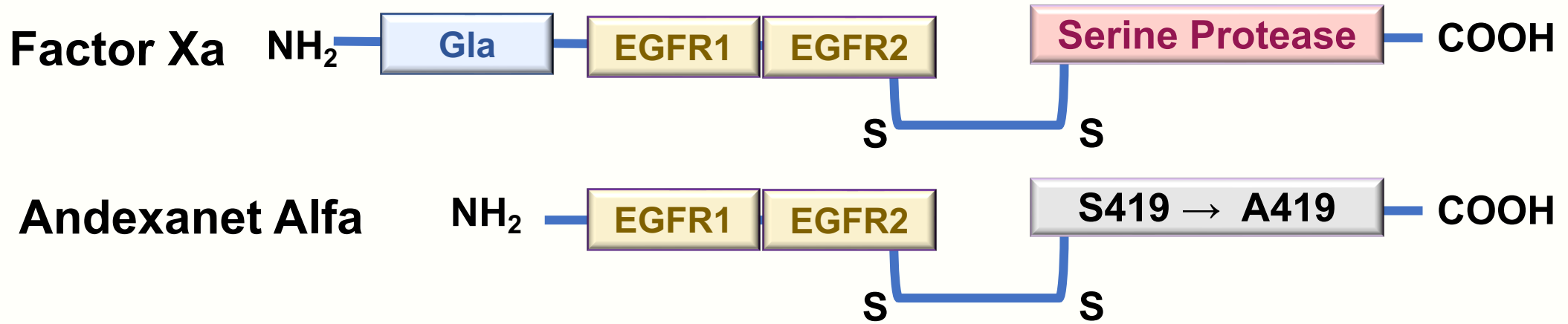
# Dilute Thrombin Time



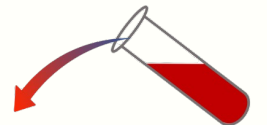
- The median maximum reversal <4 hours was 100%
- Pollack CV et al, N Engl J Med 2017.



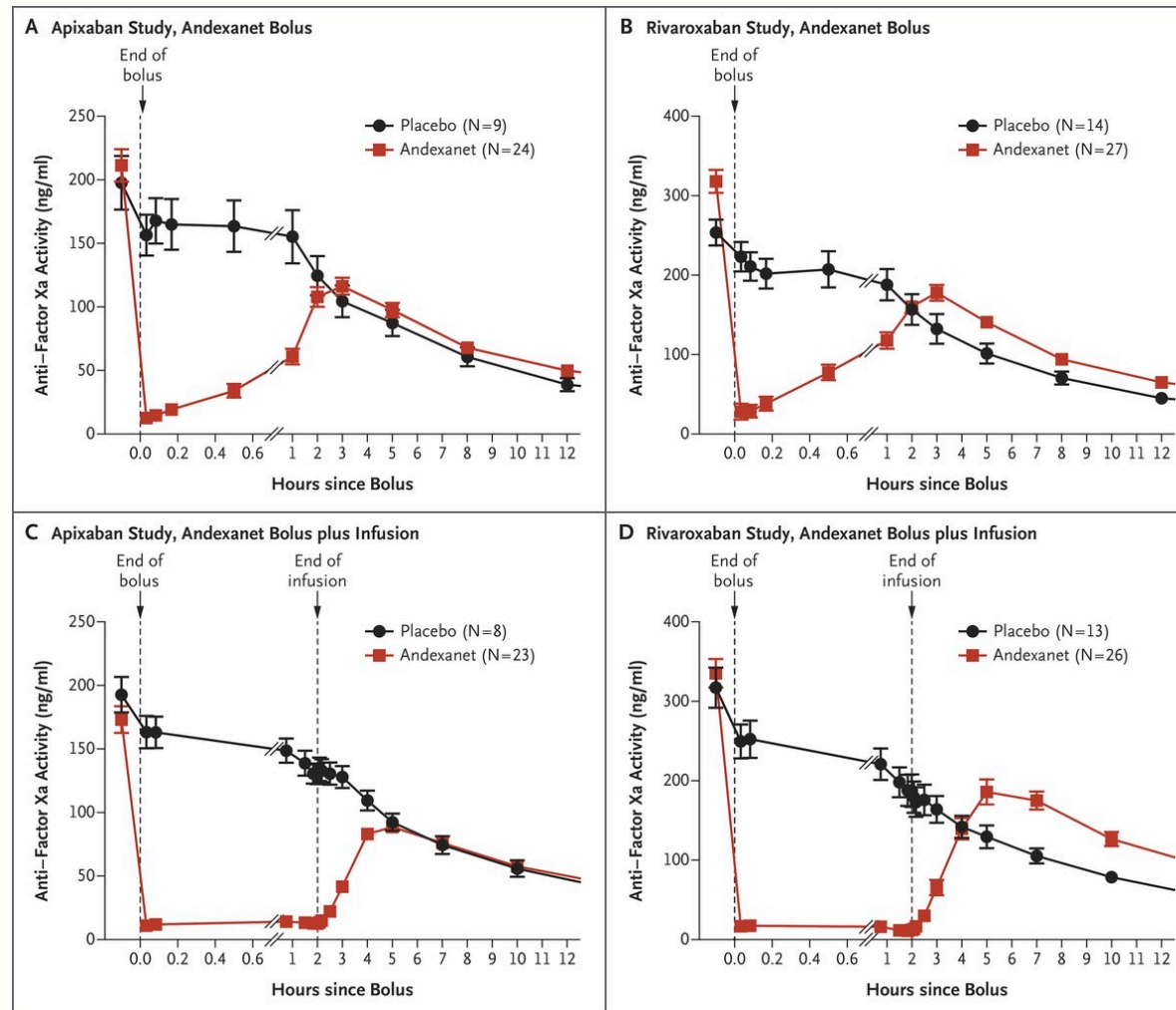
# Reversal of Xa-DOAC's



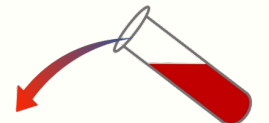
- Xa Decoy (Andexanet Alfa)
- “Decoy” Xa drug neutralizes the effect of anti-Xa agents
  - Inactive mimetic binds the anticoagulant.
  - Serine, the active site of FXa, was substituted with alanine.
  - The Gla domain of FXa was removed to prevent its assembly into the prothrombinase complex.



# Time Courses of Anti-Factor Xa Activity before and after Administration of Andexanet. (Healthy older volunteers)



Siegel DM et al. NEJM 2015;373:2413-2424.

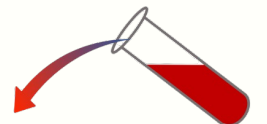


# Dosing Recommendations for Andexanet Alfa

Xa Inhibitor	Last FXa Inhibitor Dose	Last FXa Inhibitor Dose < 8 Hours Prior/Unknown	Last FXa Inhibitor Dose ≥ 8 Hours Prior
Rivaroxaban	≤ 10 mg	Low dose	Low dose
Rivaroxaban	> 10 mg or unknown	High dose	
Apixaban	≤ 5 mg	Low dose	
Apixaban	> 5 mg or unknown	High dose	

	Bolus	2-hour IV infusion
Low dose	400-mg IV	4 mg/min
High dose	800-mg IV	8 mg/min

<https://www.fda.gov/media/113279/download>

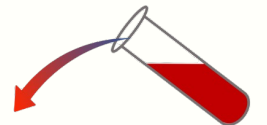




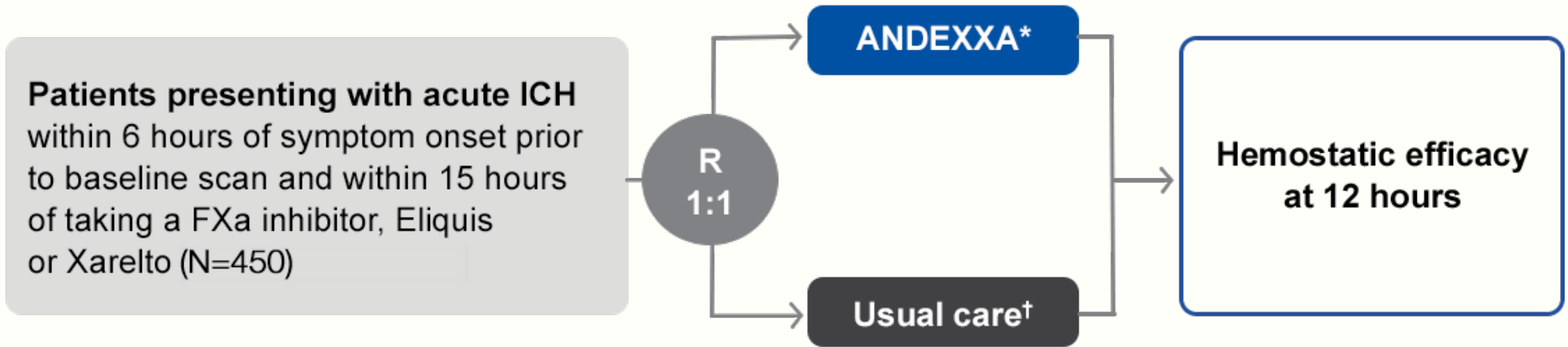
# Reversal of Direct Oral Anticoagulants: Guidance from the Anticoagulation Forum:

Cuker et al. *Am J Hematol*. 2019;94:697–709.

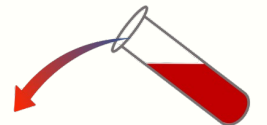
- How should reversal agents be used to manage factor Xa inhibitor-associated bleeding?
- In patients with rivaroxaban-associated or apixaban-associated major bleeding in whom a reversal agent is warranted, we suggest treatment with andexanet alfa dosed according to the US FDA label.
- If andexanet alfa is not available, we suggest treatment with four-factor PCC 2000 units.



# ANNEXA-I: Prospective, randomized, multicenter, open-label, blinded-endpoint, phase 4 study comparing ANDEXXA to usual care

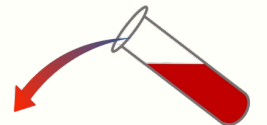


- ANNEXA-I Trial stopped early due to superior efficacy vs usual care.
  - Primary efficacy endpoint: Hemostatic efficacy at 12 hours.
  - (Excellent or good hemostasis was defined as  $\leq 35\%$  hematoma volume expansion at 12 hours,  $\leq 6$ -point National Institutes of Health Stroke Scale (NIHSS) score increase at 12 hours, and no rescue therapy 3-12 hours post-randomization)
  - **Data submitted to FDA, but not yet published.**



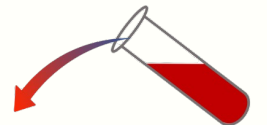
# Coagulopathy of Liver Disease (I)

- Patients with CLD have multiple abnormalities that contribute to hemostatic imbalance.
- Decrease in coagulation factor synthesis:
  - All coagulation factors, except Factor VIII and vWF are made in hepatocytes.
  - Factor VIII is produced in liver sinusoidal cells and vascular endothelial cells.
  - von Willebrand factor: Vascular endothelium and megakaryocytes ( $\alpha$ -granules of platelets).
- Decrease in physiologic anticoagulants:
  - Protein C, Protein S, Antithrombin

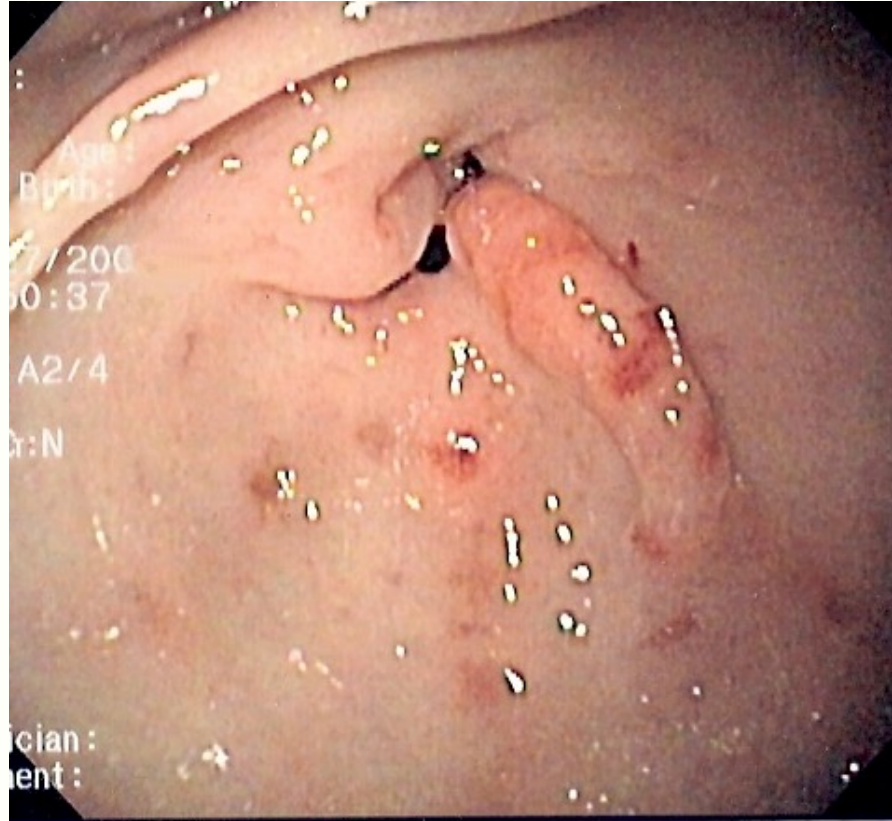


# Coagulopathy of Liver Disease (II)

- Often concomitant Vitamin K deficiency
  - Poor nutrition,
  - Malabsorption of fat-soluble vitamins
- Dysfibrinogenemia characterized by an increased content of sialic acid residues that results in delayed fibrin polymerization.
  - Martinez J et al Blood. 1983;61(6):1196.
- Thrombocytopenia
  - Decreased thrombopoietin (TPO)
  - Splenic sequestration

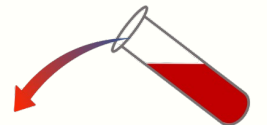


# Liver Disease Associated with Varices, An Anatomical Risk for Bleeding.



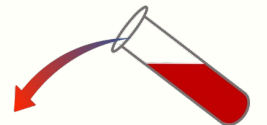
Variceal Bleeding in CLD

- [https://commons.wikimedia.org/wiki/File:Gastric\\_antral\\_vascular\\_ectasia\\_\(before\\_and\\_after\).png](https://commons.wikimedia.org/wiki/File:Gastric_antral_vascular_ectasia_(before_and_after).png)



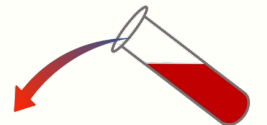
# Laboratory Findings In Coagulopathy of Liver Disease: PT/INR is more sensitive to prolongation in CLD, compared with aPTT

- Prothrombin Time:
  - Factor VII has the shortest half-life of procoagulant factors
  - Acquired Vitamin K deficiency concomitant with CLD.
- Increase in Factor VIII shortens the aPTT
  - “Acute phase reactant”
  - In CLD, this blunts the aPTT prolongation.



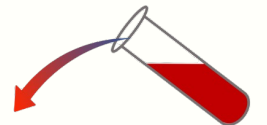
# Management of Coagulopathy of CLD

- Treatment not always necessary.
- Supportive care.
- Try empiric Vitamin K.
  
- In general treatment is reserved for acute bleeding or before procedures
- **FFP** 10-15 ml/kg if bleeding or procedure
- **4-Factor PCC “off label”**
  - **Factors II, VII, IX and X, Protein C, Protein S.**
- **Cryoprecipitate**
  - Keep fibrinogen above 100 mg/dl in the acute setting
- **Platelet transfusions usually not needed**, unless severe thrombocytopenia and bleeding.
  - De Simone & Sarode. Semin Thromb Hemost 2013;39:172–181
  
- **PCC and Cryoprecipitate together have all the essential factors, except for Factor V.**
- **Factor V is present in platelet alpha granules.**



# Thrombopoietin Receptor Agonists in CLD scheduled to undergo a procedure.

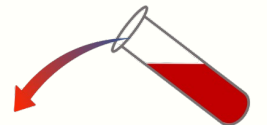
- Avatrombopag (Doptelet ®)
- Lusutrombopag (Mulpleta ®)
  - Thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.
  - Avatrombopag : Begin 10 to 13 days prior to the scheduled procedure.
  - Lusutrombopag: Begin 8 to 14 days prior to the scheduled procedure.



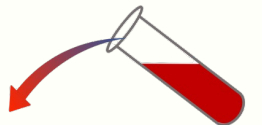


# Liver Disease Does Not Constitute “Auto-Anticoagulation!”

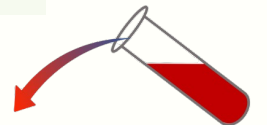
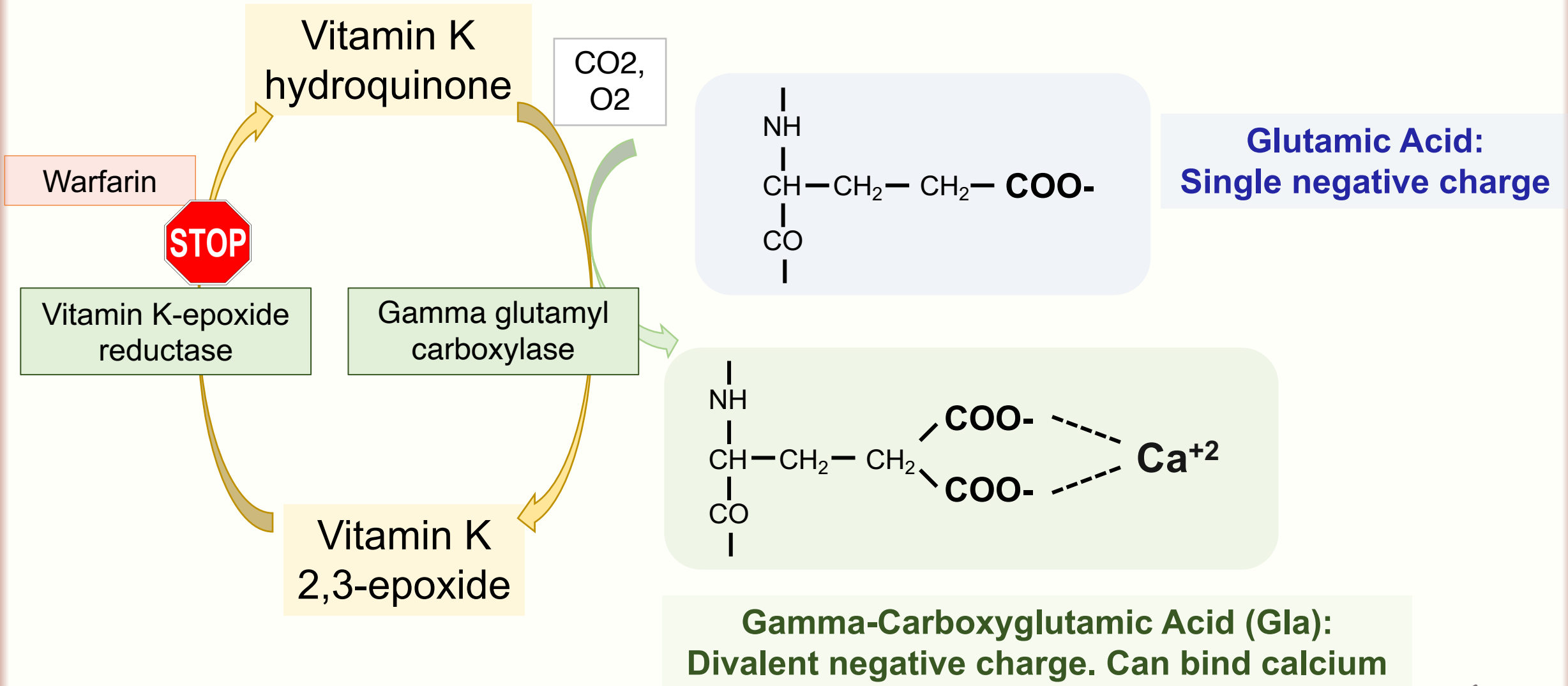
- May have thrombotic tendency at same time as hemorrhagic tendency.
- Decrease in physiologic anticoagulants!
  - Protein C, Protein S, Antithrombin III
- 50% decrease in anticoagulant proteins is associated with thrombotic tendency.
- 50% decrease in procoagulant proteins is not associated with hemorrhagic tendency.



# *Vitamin K Deficiency*

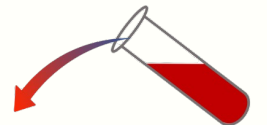


# Vitamin K Mediated $\gamma$ -Carboxylation of Glutamic Acid



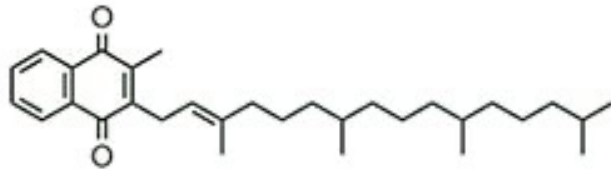
# Vitamin K-Dependent Factors

- Factors II (Prothrombin), VII, IX, X
- Protein C, Protein S
- While both procoagulants and anticoagulants are affected, the net effect of vitamin K deficiency or antagonism is anticoagulation.
- Deficiency of vitamin K-dependent factors prolongs both the PT and aPTT, but effect is greater on PT.

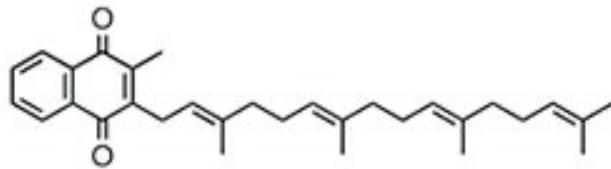


# Vitamin K

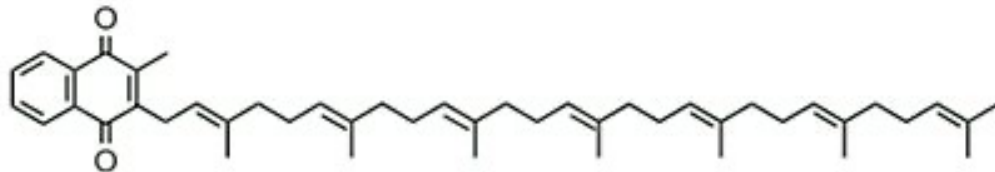
K1



MK-4

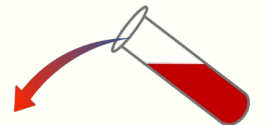


MK-7



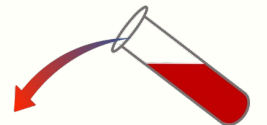
[https://en.wikipedia.org/wiki/Vitamin\\_K](https://en.wikipedia.org/wiki/Vitamin_K)

- Vitamin K1 (phylloquinone), is made by plants, and is found in highest amounts in green leafy vegetables.
- Bacteria in the gut can convert K1 to K2 and then into a range of vitamin K forms.
- It is not clear if the K2-related forms have greater effect on coagulation than K1.
- Vit K deficiency results from decreased dietary intake and/or alteration of gut microbiome.



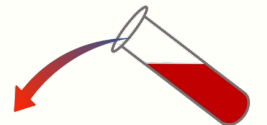
# Vitamin K Deficiency

- Most common causes:
  - Insufficient dietary intake,
  - Inadequate absorption,
  - Decreased storage of the vitamin due to liver disease,
  - Decreased production in the intestines.
- Malabsorption,
  - Especially impaired absorption of fats due to diseases such as cystic fibrosis, celiac disease, chronic pancreatitis or Cohn's disease.
- Antibiotics can decrease K2 production in the intestines.

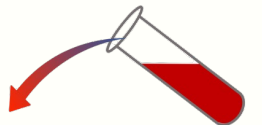


# Vitamin K Deficiency Replacement

- Vit. K: Typically 10 mg PO or IV
  - Excess replacement does not make patient hypercoagulable.
- SC route has unreliable absorption and is no faster than PO administration



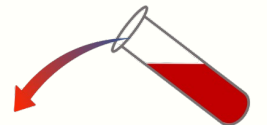
# *Disseminated Intravascular Coagulation*





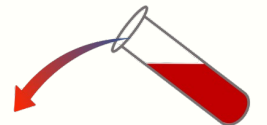
# Disseminated Intravascular Coagulation Is Not A Disease, But a Process

- Systemic, unregulated activation of the coagulation system.
- Multiple causes/mechanisms
- Tissue Factor
  - Shift of Tissue Factor to the circulation
  - Expression of TF by monocytes secondary to bacterial endotoxin
  - Tissue damage/necrosis
- Vascular injury
- Consumptive coagulopathy
- Severe/acute is associated with hemorrhage.
- Low-Grade DIC
  - Cancer: Associated with thrombotic tendency.



# Acute DIC With Hemorrhage

- Sepsis
- Obstetrical catastrophe
- Amniotic fluid embolism, abruptio placentae, HELLP, eclampsia/severe preeclampsia, retained dead fetus, septic abortion
- Trauma with crush injury and/or brain damage
- Intravascular hemolysis
- Snake venom
- Fulminant liver failure
- Pancreatitis
- Acute leukemia/Acute promyelocytic leukemia



# Disseminated Intravascular Coagulation:

Modified from Levi & Scully, *Blood* (2018) 131 (8): 845–854.

Condition	Examples	Impact of precipitating condition
Severe Infectious Diseases	Gram-positive or -negative organisms, malaria, hemorrhagic fevers	Thrombosis may contribute to organ failure (eg acute kidney failure)
Malignancy	Solid tumors (eg, adenocarcinomas)	Primarily thrombotic consequences/VTE
	Acute promyelocytic leukemia or monocytic leukemia	Severe thrombocytopenia and factor deficiency may lead to bleeding
Trauma	Trauma	Primary feature is acute bleeding, followed by thrombosis
	Brain injury	
	Burns	
Obstetrical Complications	Abruptio placentae	Profuse bleeding in combination with thrombotic complications <sup>27,28</sup>
	Amniotic fluid embolism	
	Retain Placental Parts	
Vascular Malformations	Kasabach-Merritt syndrome	Bleeding primarily with severe thrombocytopenia and hypofibrinogenemia
	Giant hemangiomas	
	Other vascular malformations	
	Large aortic aneurysms	
Severe Immunologic Reactions	Transfusion reaction	
Heat stroke		Thrombotic features more common than bleeding
Post–Cardiopulmonary Resuscitation		Thrombosis is a greater risk than bleeding

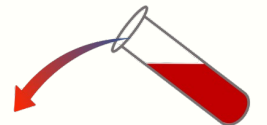
# Disseminated Intravascular Coagulation

## Laboratory findings:

- Prolonged PTT, PT
- Thrombocytopenia
- Fibrinogen decreased
- High D-dimers
  - Non-specific
- Schistocytes
  - Non-specific

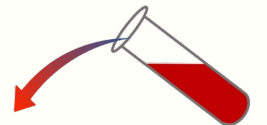
## Treatment:

- TREAT UNDERLYING CAUSE
- Supportive Care:
  - Keep the fibrinogen > 100 mg/dl
  - 10 U cryoprecipitate
  - FFP for bleeding or procedures
  - Avoid inhibitors of fibrinolysis (EACA, tranexamic acid, aprotinin)
- No specific therapy has been validated.



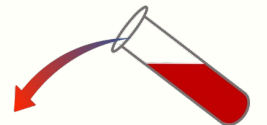
# Uremic Coagulopathy

- Mucocutaneous bleeding
- Multifactorial Pathophysiology:
  - Nitric Oxide (NO): ↑[cGMP]
    - Relaxes smooth muscle cells, vasodilation
    - Inhibits platelet function
  - NO levels increase in renal failure
    - Reduced binding to Hemoglobin
    - Other mechanisms?
    - Anemia contributes to the dysfunction.
- Functional defect is not within the platelets, but uremic plasma inhibits the platelet function.
  - Transfusion of normal platelets will not help.
- PT/PTT not elevated by uremia.



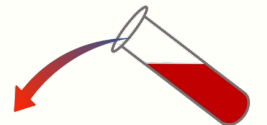
# Uremic Coagulopathy: Treatment

- Acute treatment:
  - Desmopressin (ddAVP)
  - Cryoprecipitate
  - Mechanism of effect not clear. Possibly increase in fibrinogen & vWF allow for improved platelet function without correcting the underlying defect.
- Chronic Management:
  - Supplemental erythropoietin or red cell transfusion to maintain Hgb  $\geq 10$  gm/dL.
  - Dialysis
  - Estrogens



# Acquired Hemophilia

- Antibody directed against FVIII: Acts as an inhibitor
- Isolated prolongation of the PTT
- Mixing study often corrects initially, followed by prolongation after incubation
- Factor VIII levels often very low (undetectable to <5%)
  - “Corrects” with serial dilutions
- Can be seen in anyone but more common in:
  - “Older” individuals (ie >50 YO)
  - Rheumatoid arthritis
  - Cancer
  - SLE
  - Drug Reaction
  - Peripartum
- **Bleeding is similar to severe hemophilia, except patients do not typically experience hemarthrosis.**



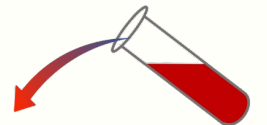
# Acquired Hemophilia: Treatment

## Acute Control of Bleeding

- Low titer inhibitor:
  - FVIII concentrate
- High titer inhibitor:
  - Activated PCC (FEIBA®)
  - rFVIIa
  - rPorcine FVIII

## Elimination of the inhibitor:

- Prednisone +/- cyclophosphamide
- Rituximab

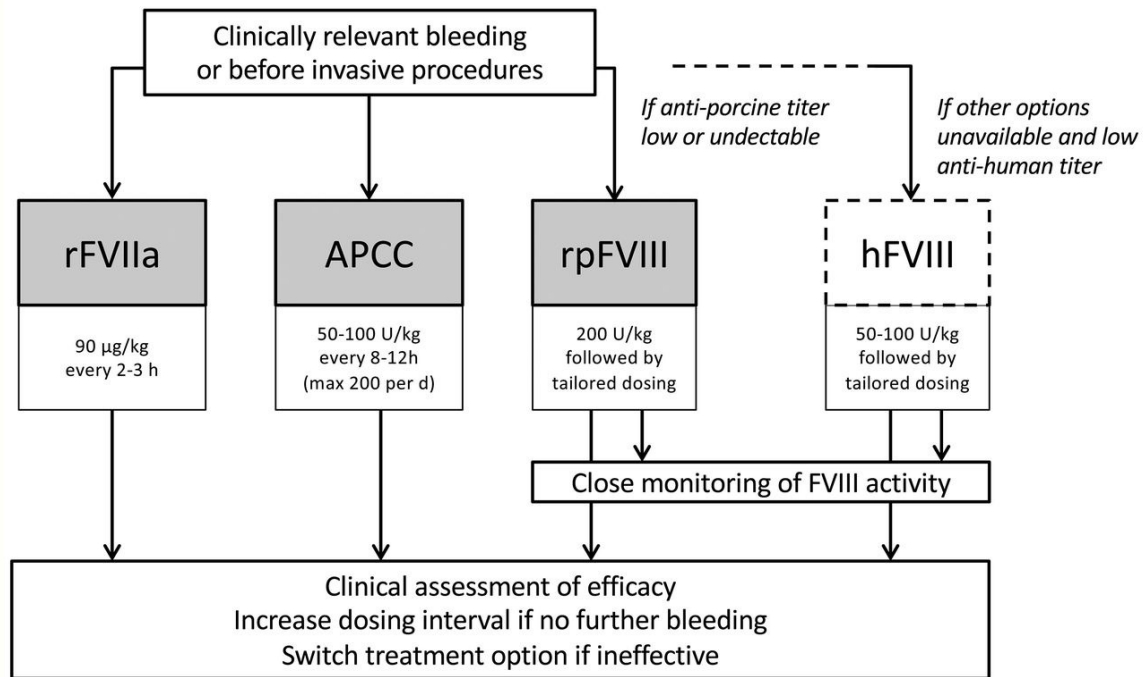




# International Recommendations on Treatment of Acquired Hemophilia A

Tiede et al. Haematologica. 105 , 2020 <https://doi.org/10.3324/haematol.2019.230771>

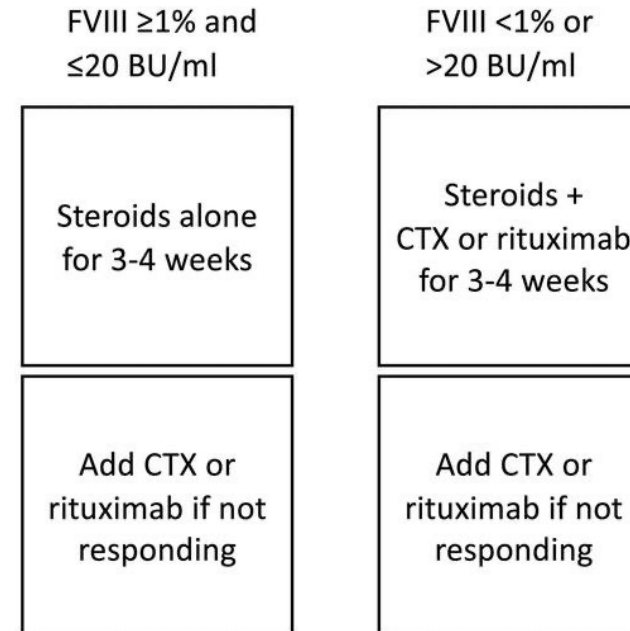
## Acute/Emergent Treatment



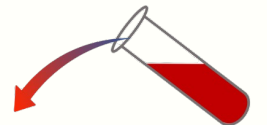
- rFVIIa, recombinant activated factor VII
- APCC, activated prothrombin complex concentrate;
- rpFVIII: recombinant porcine factor VIII
- hFVIII, human (plasma-derived or recombinant)

## Antibody Suppression

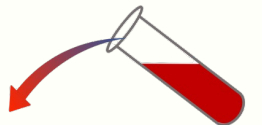
### 2020 Recommendation



- BU: Bethesda unit;
- CTX, cyclophosphamide.

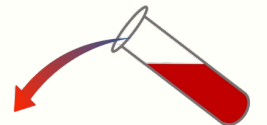


# *Acquired von Willebrand Disease*

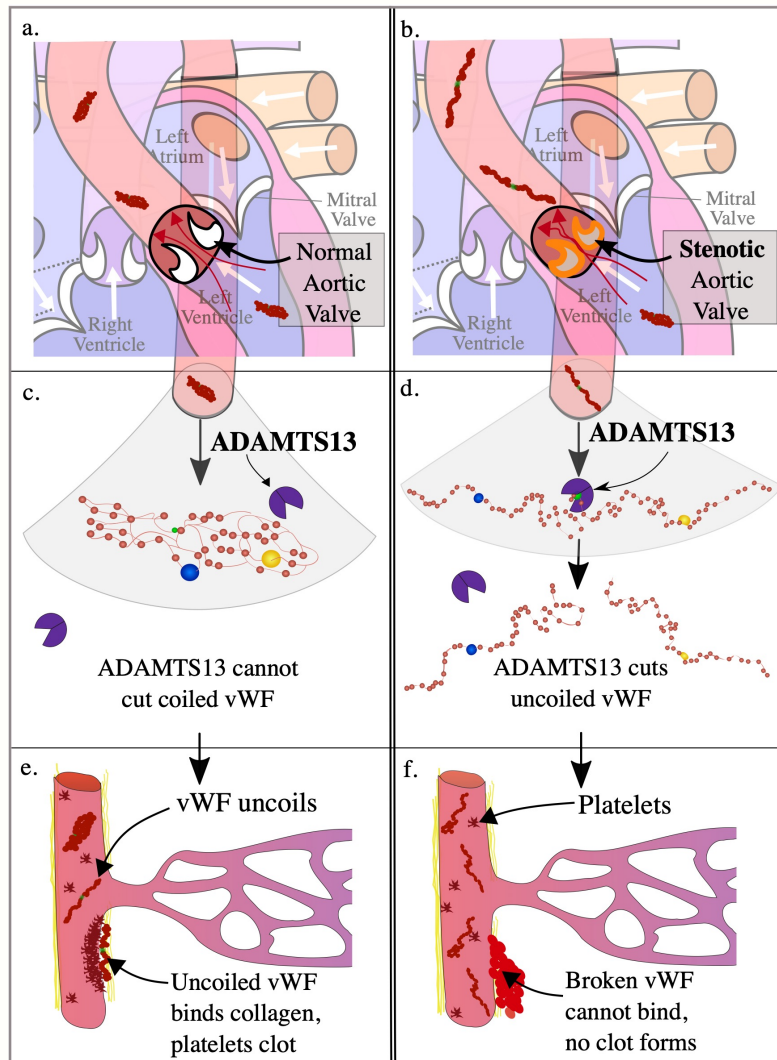


# Acquired vWD: Mechanisms & Associations

- Myeloproliferative neoplasms
  - Adsorption of vWF on platelets
- Wilms tumor:
  - High levels of hyaluronic acid increases viscosity and binds von Willebrand factor (vWF)
- Auto-antibodies:
  - Connective Tissue disorders, idiopathic
- Heyde's syndrome:
  - Acquired vWD-2A deficiency secondary to aortic stenosis.
  - GI Bleeding, from angiodysplastic lesions

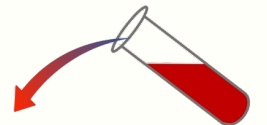


# Heyde's Syndrome Triad

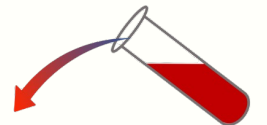


- Aortic stenosis
  - Shear stress on vWF results in “uncoiling”, and increased cleavage by ADAMTS13.
- Selective loss of larger multimers
- Acquired coagulopathy (vWD type 2A)
- Anemia due to bleeding from intestinal angiodysplasia or from an idiopathic site.

By Michael D. Dacre - Own work, CC BY-SA 4.0,  
<https://commons.wikimedia.org/w/index.php?curid=41472958>

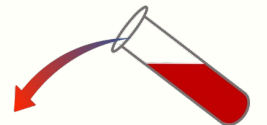


# *Acute Promyelocytic Leukemia*

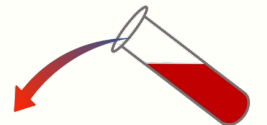
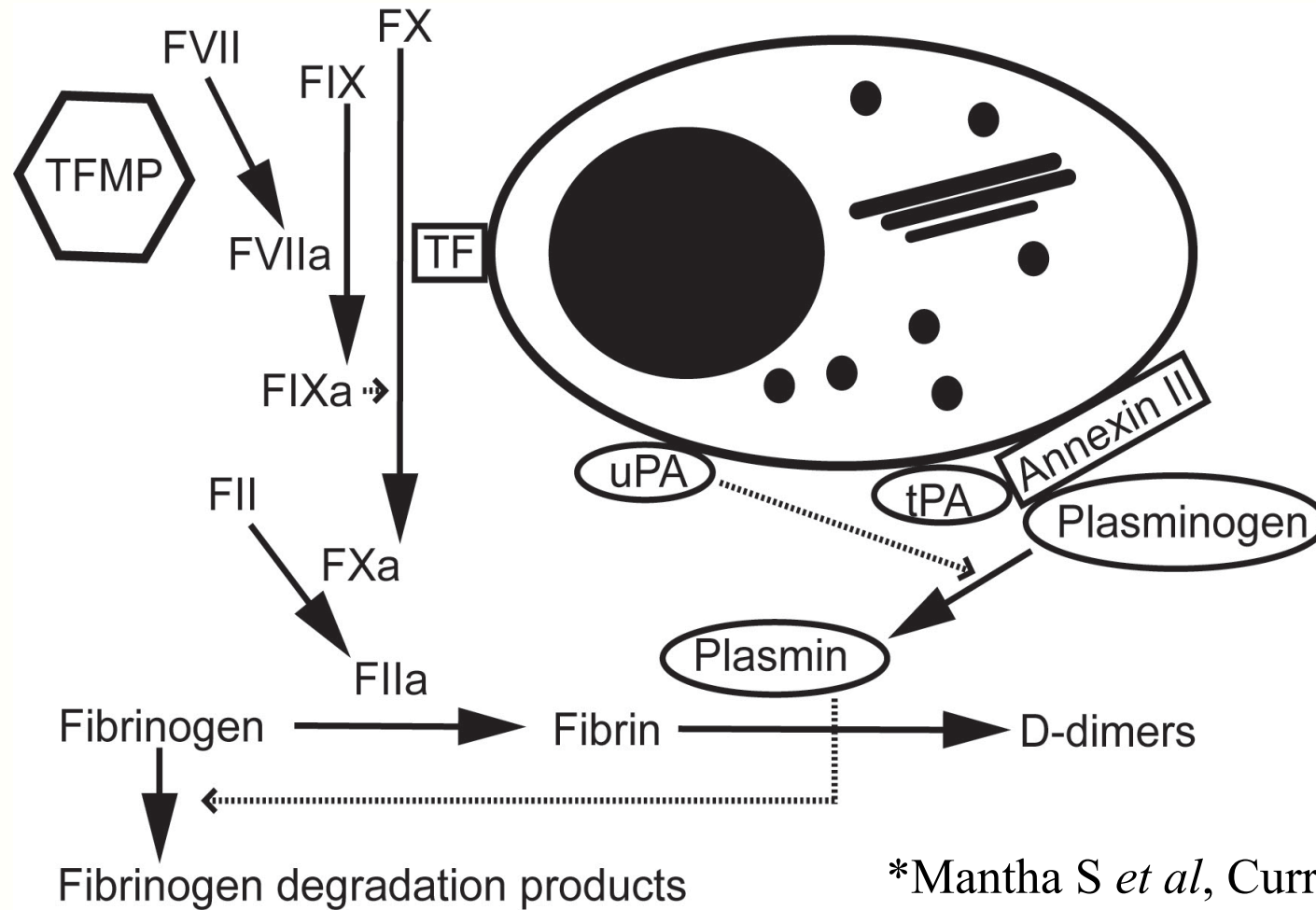


# Acute Promyelocytic Leukemia

- t(15;17)
  - PML-RARA gene rearrangement
- Persistently high rate of early death from hemorrhage
  - 5-10% in different series
- Pathogenesis of coagulopathy multifactorial.
  - No single mechanism is clearly established.
  - Leukemic blasts express tissue factor, leading to DIC
  - Increased plasminogen activators promote primary fibrinolysis.
  - High blast counts correlates with bleeding.
  
- Mantha et al, Blood. 2017 Mar 30; 129(13): 1763–1767.

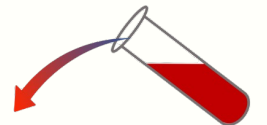


# Acute Promyelocytic Leukemia



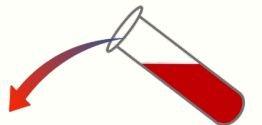
# Acute Promyelocytic Leukemia

- ATRA induces differentiation of cells
  - Decreases expression of tissue factor
  - Early treatment is crucial in decreasing mortality
- Aggressive blood product repletion is warranted



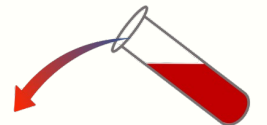


# *Workup of Coagulopathy*



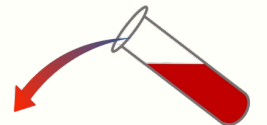
# Workup of Coagulopathy

- Mixing Studies
  - With incubation
- Immediate inhibitors:
  - Anticoagulant contamination
  - Anti phospholipid Antibody
  - Fibrin/Fibrinogen Degradation Products
  - Some Paraproteins
- Inhibitors with Incubation
  - Specific Factor Inhibitors/Antibodies



# Mixing Studies

- Mix patient and normal plasma 1:1
- Perform PT and/or aPTT immediately and after 1 hour incubation at 37°C
- Looking for “Prolongation of the Normal”
- Specific antibodies require time to bind to the antigen target.
- Common inhibitors: heparin, Lupus Anticoagulant, dysproteins, paraproteins, Fibrin Split Products (DIC), specific factor inhibitors



# Mixing Studies

Factor Deficiency

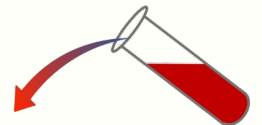
aPTT	Patient	Normal	1:1
Immediate	51"	29"	33"
1 Hour Incubation @ 37°C	52"	29"	32"

Lupus  
Anticoagulant:  
antiphospholipid  
antibody

aPTT	Patient	Normal	1:1
Immediate	51"	29"	48"
1 Hour Incubation @ 37°C	52"	29"	50"

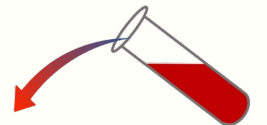
Anti-Factor VIII  
Antibody

aPTT	Patient	Normal	1:1
Immediate	51"	29"	33"
1 Hour Incubation @ 37°C	52"	29"	50"



# A Factor Panel to Differentiate Systemic Coagulopathies

Factor	V	VII	VIII	X
Vitamin K Deficient	NI	↓	NI	↓
Liver Disease	↓	↓	NI or ↑	↓
DIC	↓	↓	↓	↓



Any Questions?



