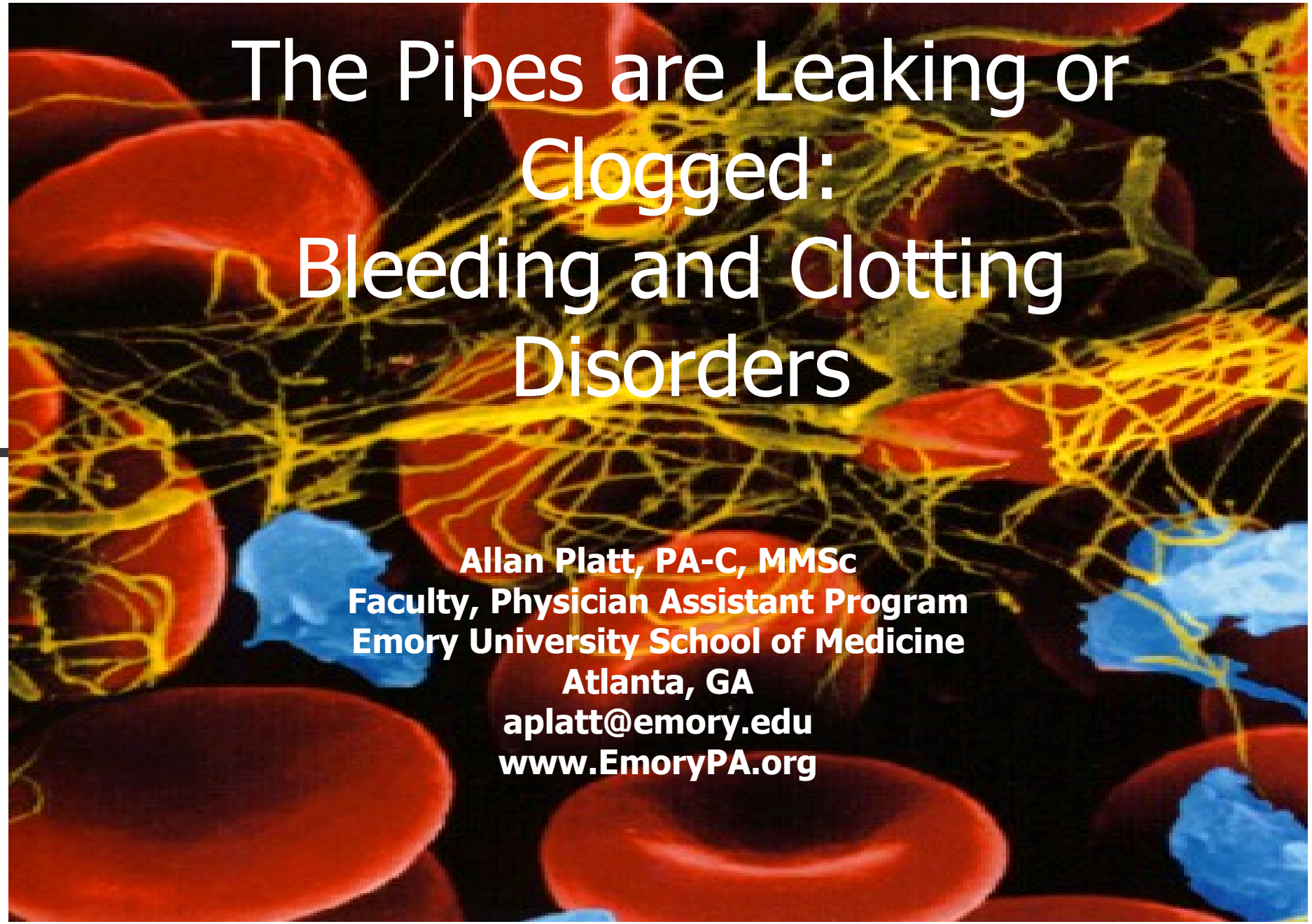

The Pipes are Leaking or Clogged: Bleeding and Clotting Disorders

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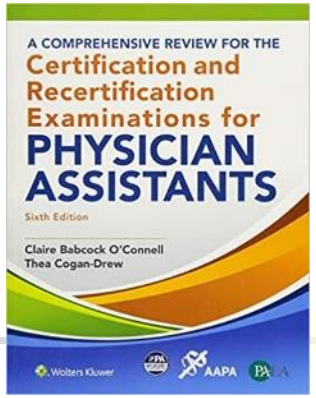
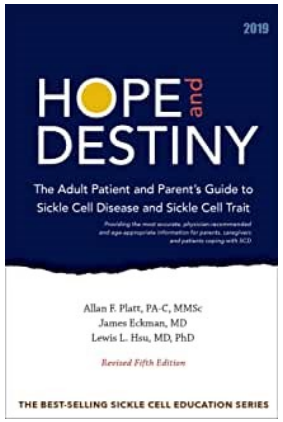
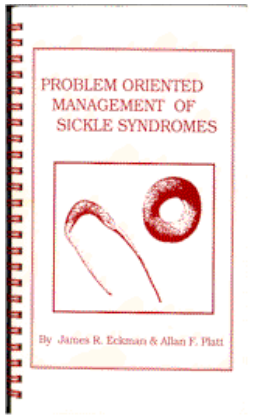
Disclosures

- Author of Chapter 4 – Hematology in **A Comprehensive Review for the Certification and Recertification Examinations for Physician Assistants Sixth Edition** by Claire O'Connell (Author)

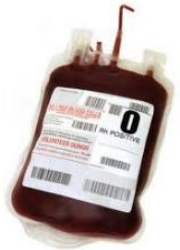


- Co-Author of **Hope and Destiny 5th Edition: The Adult Patient and Parent's Guide to Sickle Cell Disease and Sickle Cell Trait** by Allan F. Platt Jr. P.A.-C. M.M.Sc., James Eckman M.D., et al. | May 12, 2019





- Sickle cell advisory board to a NIH funded project
- Webmaster of SCInfo.org website and monthly e-newsletter editor
- I do promote donating blood!!!



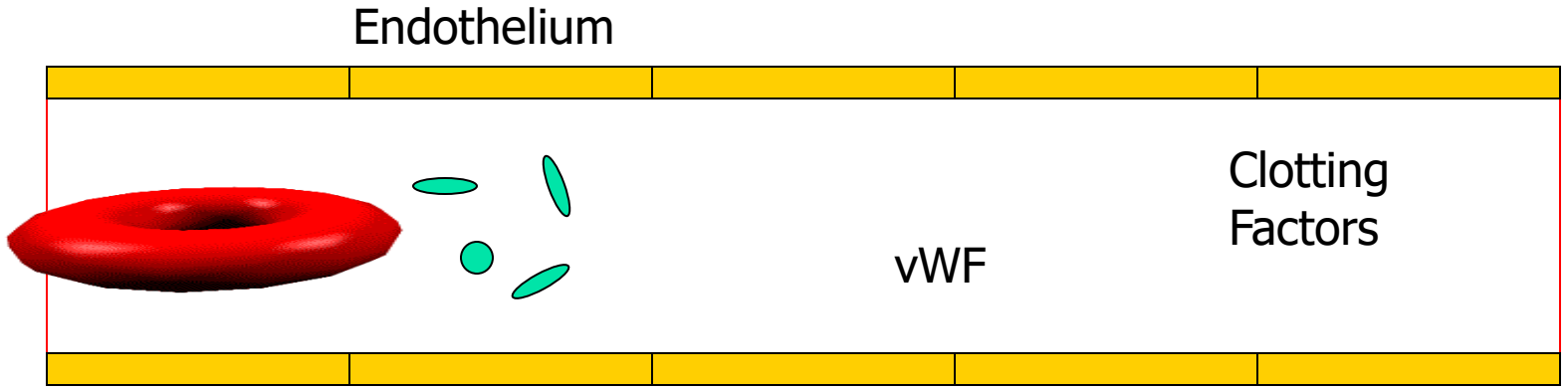
Objectives

Participants should be able to:

- Recognize common laboratory patterns for common bleeding disorders seen in primary care
- Diagnose common bleeding and clotting disorders
- Formulate a treatment plan or referral for common bleeding and clotting disorders

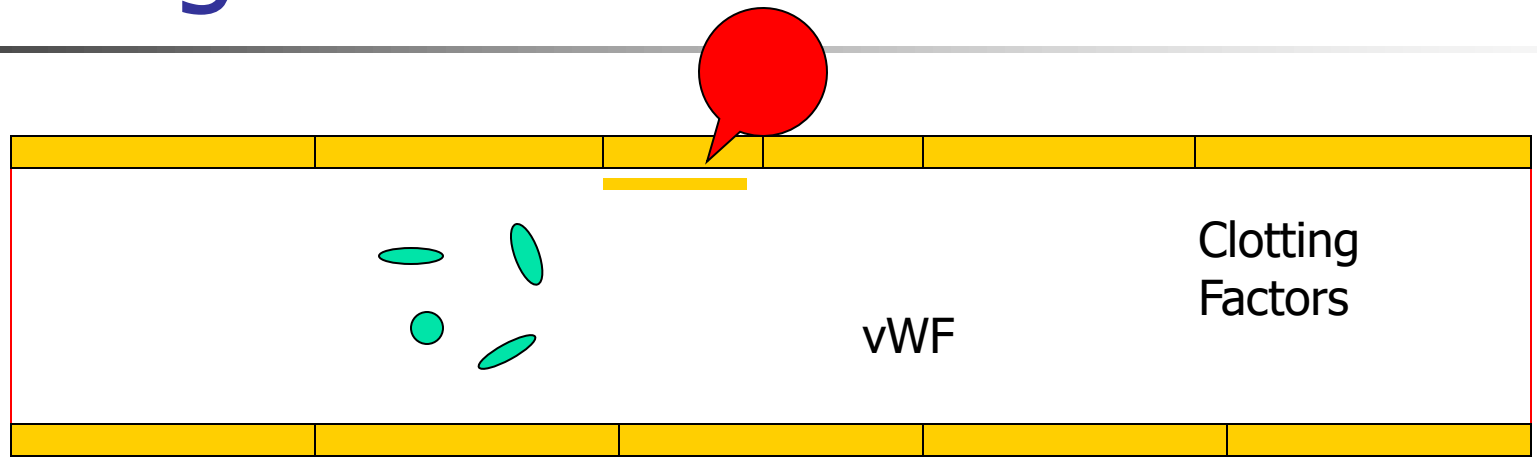
Bleeding: think PVC Pipes

Keep Blood in the Tubing
PVC-pipes



- Platelets Adequate number that work right
- Von Willebrand Factor (vWF)
- Clotting Factors
- Pipes - Intact and healthy endothelium

Clotting Process



- Break in vessel wall – smooth muscle contracts
- Platelets with (vWF) stick to collagen and Activate
- More platelets are attracted
- Clotting Factors activate to form Fibrin
- Clot contracts

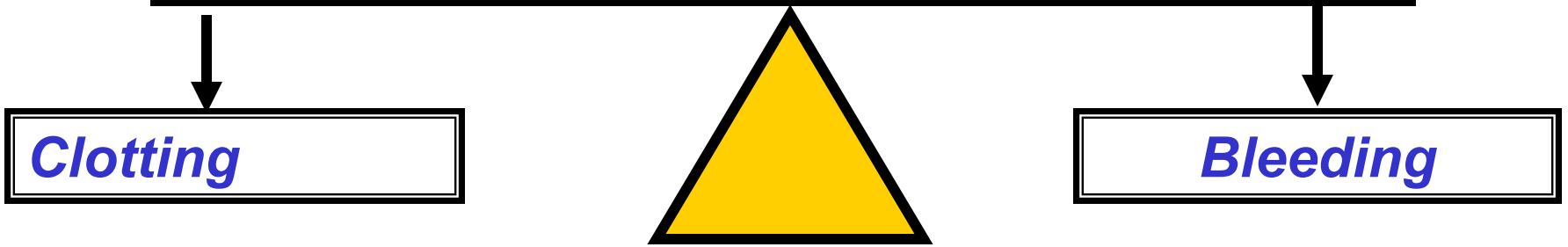
Balance

Procoagulation

- Fibrinogen-Fibrin
- Prothrombin-Thrombin
- Factors V, VII, VIII, IX, X, XIII
- Tissue Factor
- Collagen
- vWF
- Activated Platelets
- Plasminogen Activator Inhibitor (PAI-1)
- Thrombin-Activatable Fibrinolysis Inhibitor (TAFI)

Anticoagulation

- Plasminogen
- Protein C, Protein S
- Thrombomodulin
- Heparin sulfate
- Antithrombin
- Tissue Plasminogen Activator (tPA)
- Tissue Factor Pathway Inhibitor (TFPI)
- Alpha-2-antiplasmin
- Nitric Oxide (NO)
- Prostacyclin

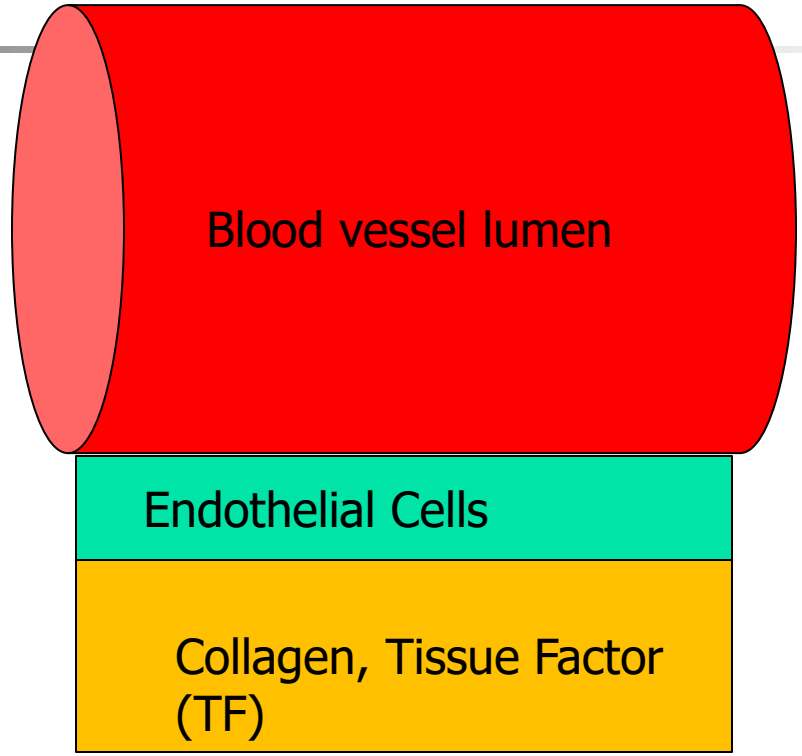


Von Willebrand Factor - vWF

- Super glue of platelets to stick to damaged walls
- Stabilizes and transports Factor VIII
- Made by Endothelial Cells
- Most common genetic bleeding disorder

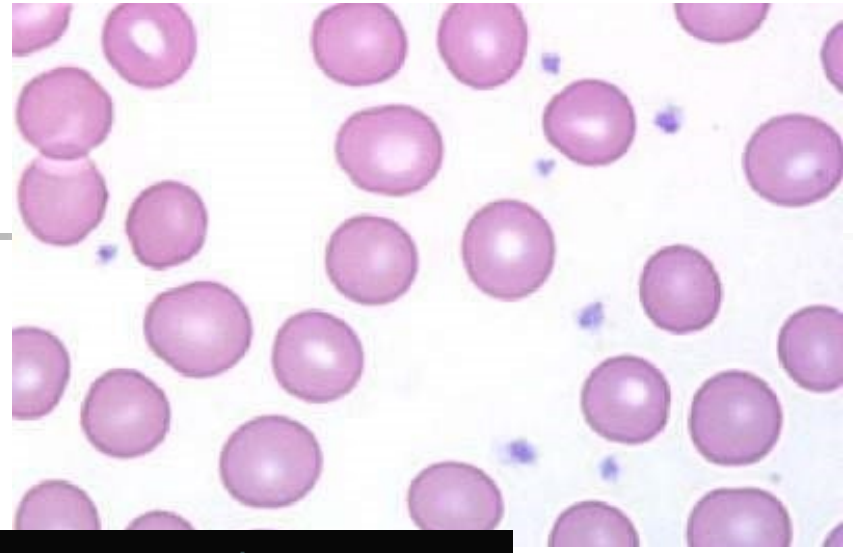
Endothelium

- Covers collagen, Tissue Factor (TF)
- vWF
- tPA
- Nitric Oxide (NO)
- Prostacyclin –Cox2 mediated
- ADPase
- TF Pathway Inhibitor (TFPI)
- Heparin
- Thrombomodulin – Binds free thrombin



Platelets

- Made in the bone marrow
- Thrombopoeitin made in liver stimulates production
- Fragments of megacaryocytes
- No nucleus
- 67% in circulation
- 33% in spleen storage
- Life 8 – 10 days



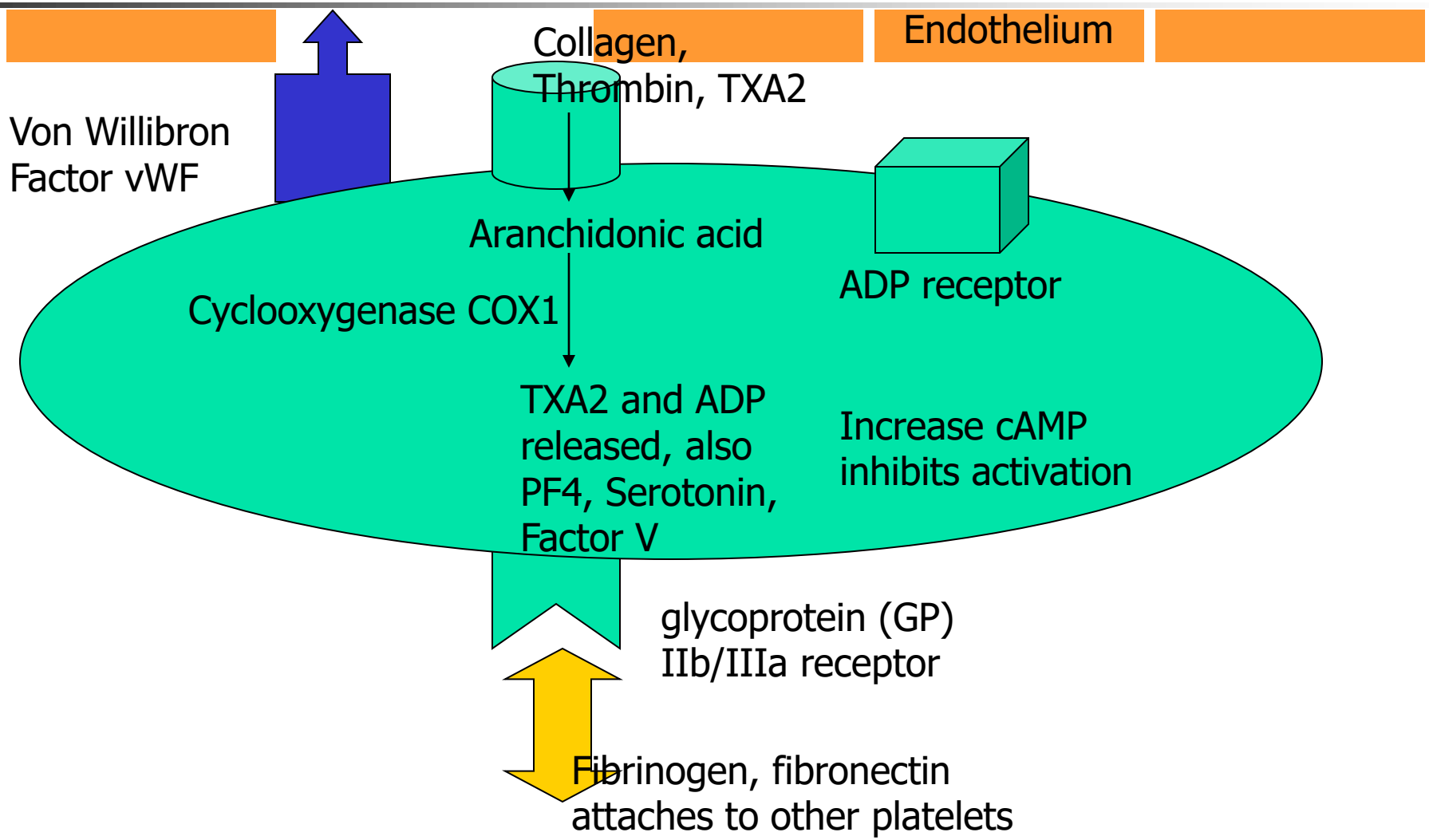
Platelet Package

- Role: coagulation, inflammation, atherosclerosis, antimicrobial host defense, angiogenesis, wound repair, and tumorigenesis
- Alpha granules - P-selectin, GPIIb/IIIa, GPIb, von Willebrand factor (vWF), clotting factors I (fibrinogen), V, IX, and XIII.
- Dense granules - calcium, potassium, serotonin, ATP and ADP
- Actin and Myosin
- Growth factors VEGF angiopoietin
- Thromboxane A_2 (TXA_2)

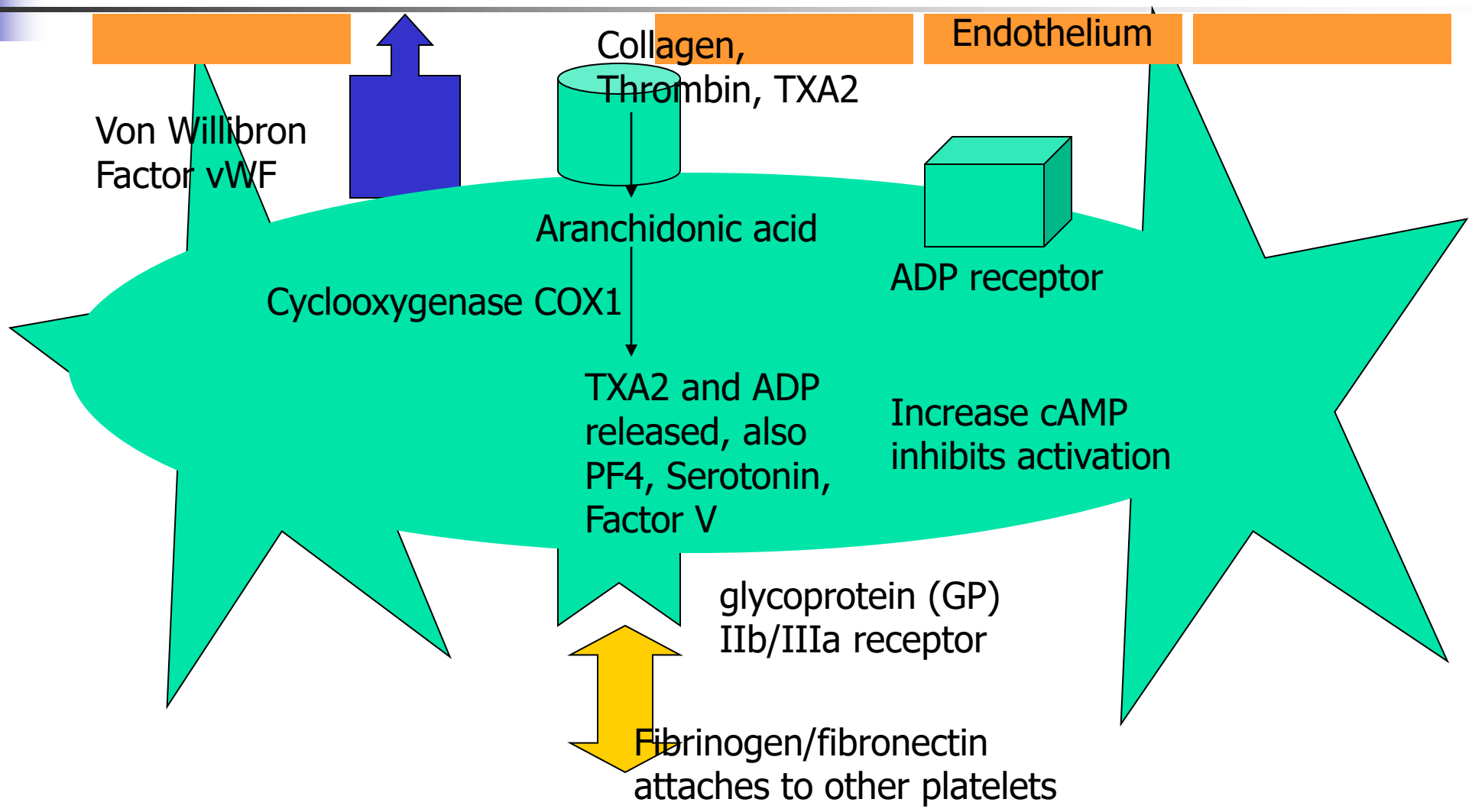
- What activates a Platelet? collagen, epinephrine, TXA_2, and thrombin

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3960550/#!po=8.92857

Platelet Activation



Activated Platelet



Platelet

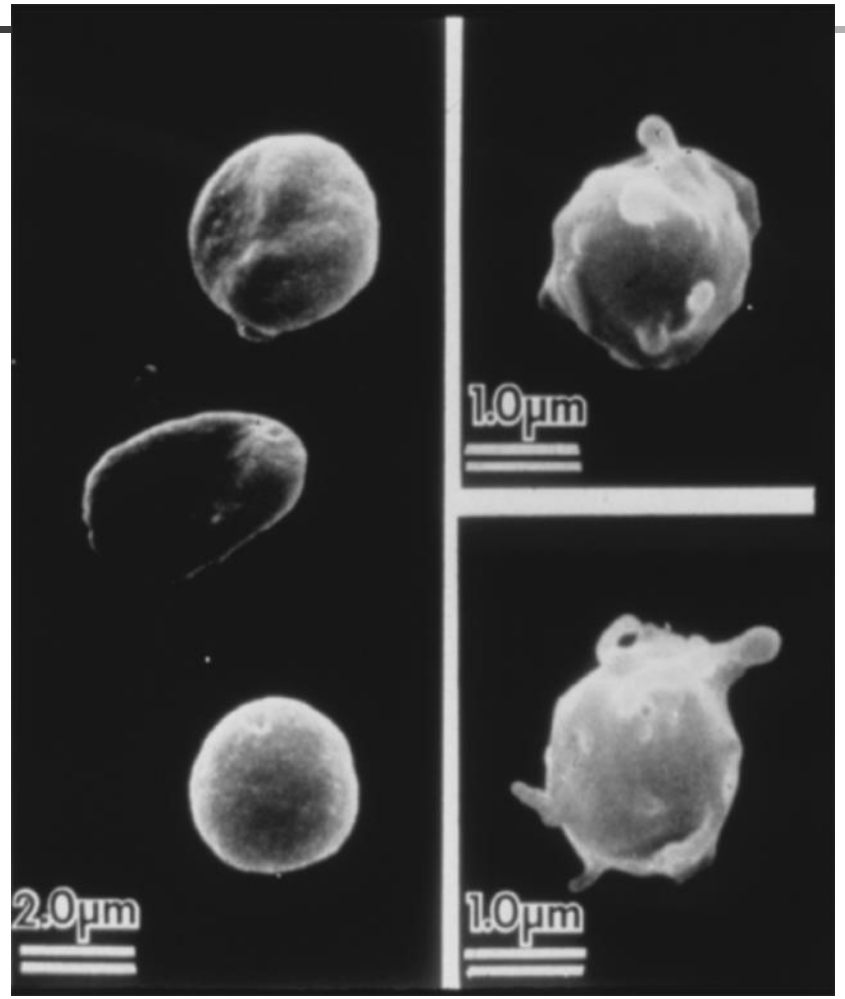
- Calm

- Activated - Spitting Spider Monkey

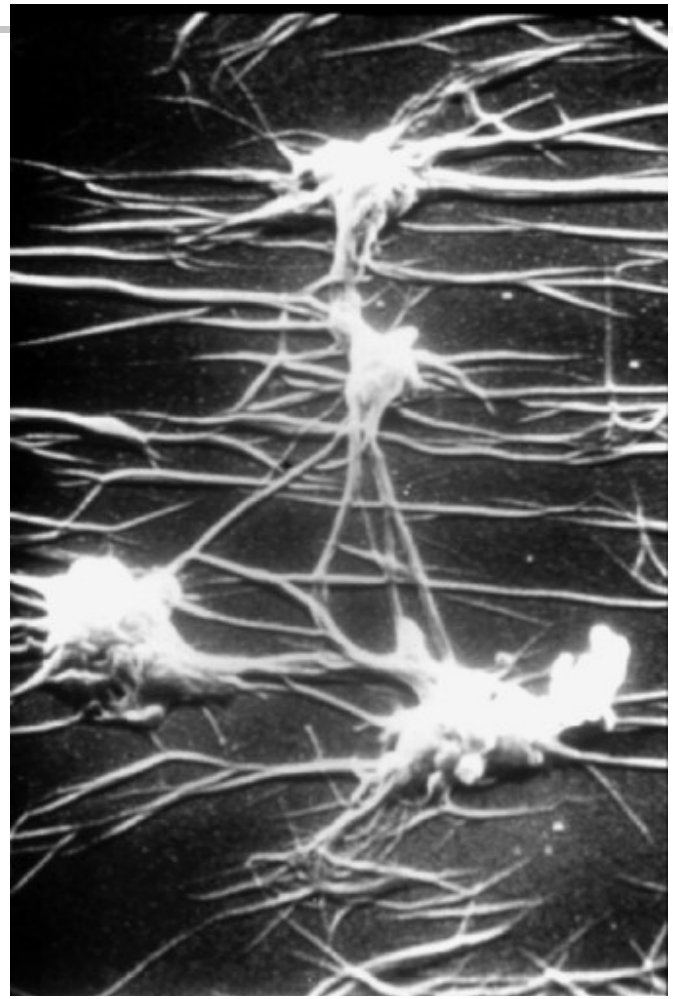
The Shape of Platelets

Flowing Platelets

Activated Platelets

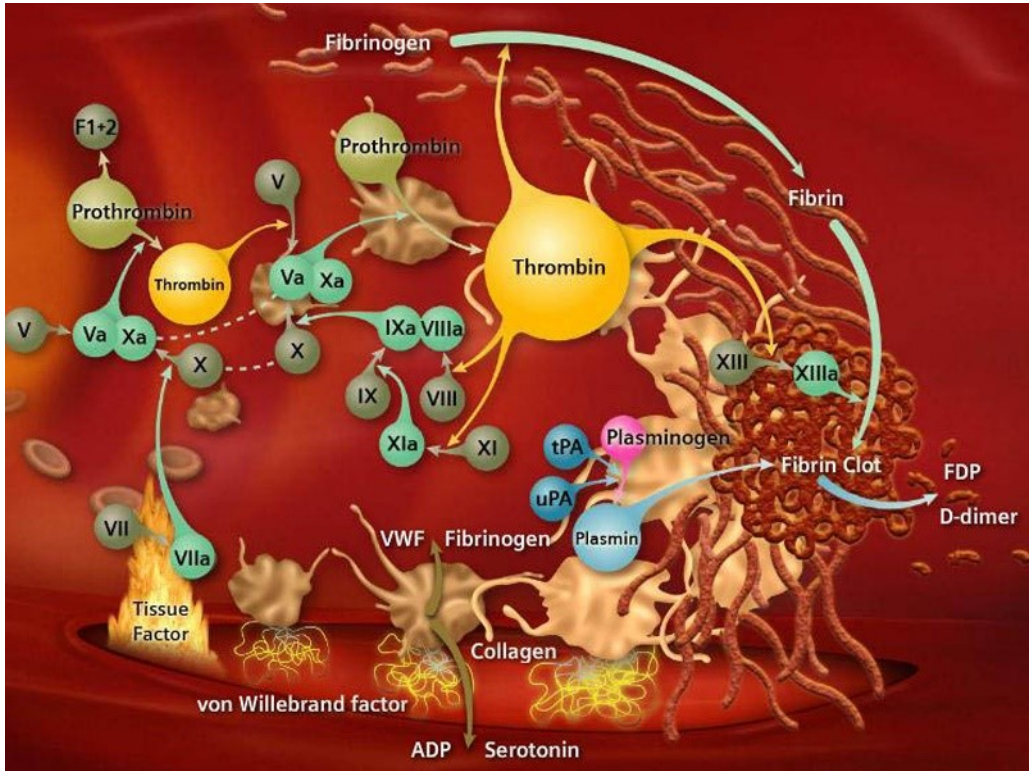


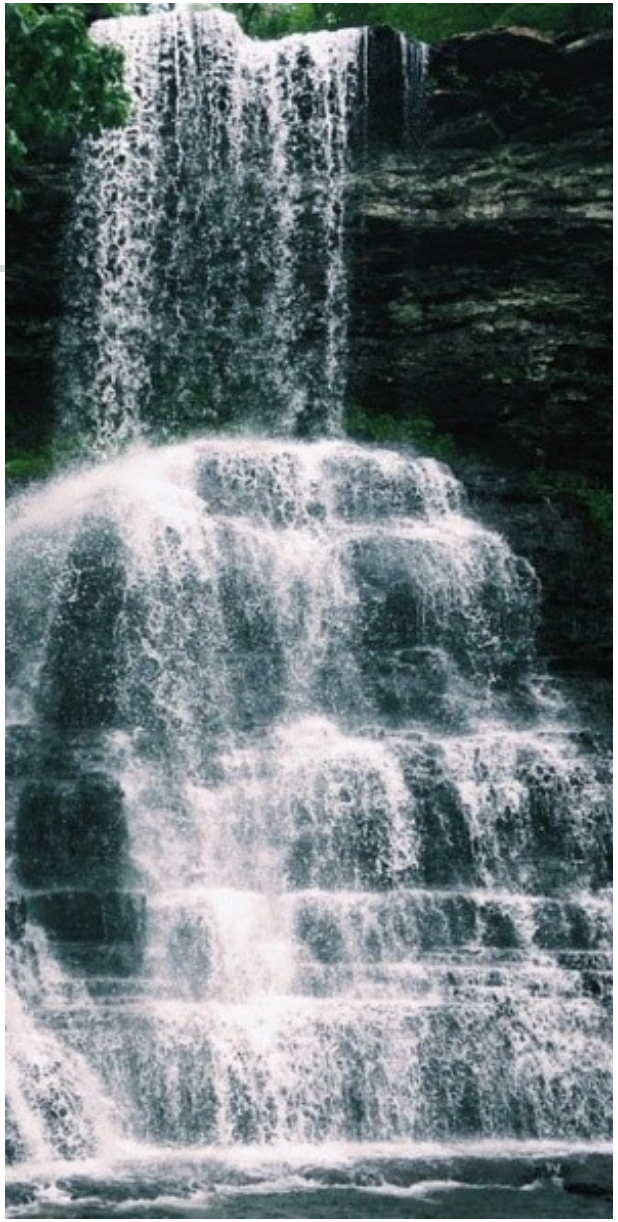
Aggregated - Active Platelets



Courtesy of Helena Diagnostics

Cascades


Fibrinogen
F1+2
Prothrombin
Prothrombin
V
Thrombin
Va
Xa
Thrombin
Fibrin
V
Va
Xa
X
X
IXa
VIIIa
IX
VIII
XIa
XI
XIII
XIIIa
tPA
Plasminogen
Fibrin Clot
FDP
D-dimer
uPA
Plasmin
VII
VIIa
VWF
Fibrinogen
Tissue
Factor
Collagen
von Willebrand factor
ADP
Serotonin



Clotting Cascade - Factors

Intrinsic Pathway –
Inside the cut
Endothelial Injury

Test = aPTT

XII to XII active

XI to XI active

IX to IX active

VIII to VIIIactive

vWF stabilizes Factor VIII

Extrinsic Pathway – outside the cut in the plasma

Vitamin K - Liver dependant

Test = PT

VII to VIIactive + Tissue factor III

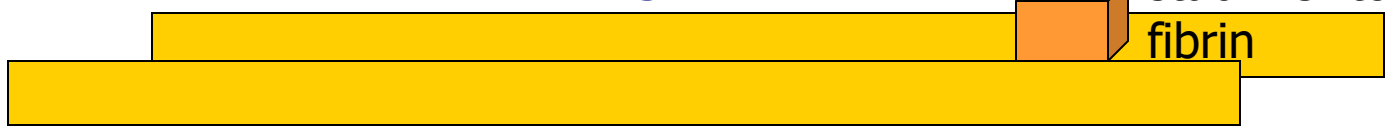
Common Pathway

X to Xactive with V present

II Prothrombin to Thrombin

I Fibrinogen to Fibrin

XIII to XIIIactive stabilizer to crosslink fibrin



Built in Clot Blockers and Busters

Intrinsic Pathway –
Inside the cut
Endothelial Injury

Test = aPTT

XII to XII active

XI to XI active

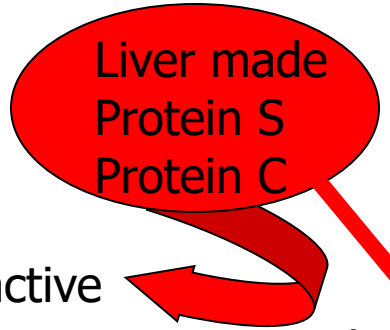
IX to IX active

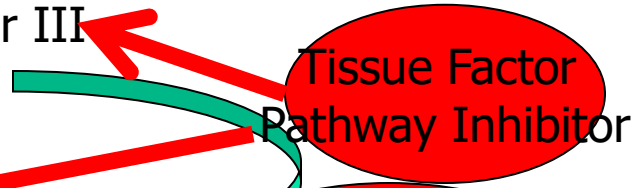
VIII to VIIIactive

Extrinsic Pathway –
outside the cut in the
plasma – Tissue Factor

Test = PT

VII to VIIactive Tissue
Factor III





Common Pathway

X to Xactive with V present

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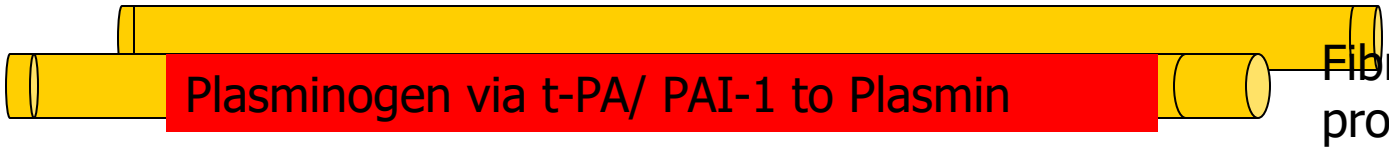

Fibrin split
products, D-Dimer

Built In Clot Blockers and Busters

Intrinsic Pathway –
Inside the cut
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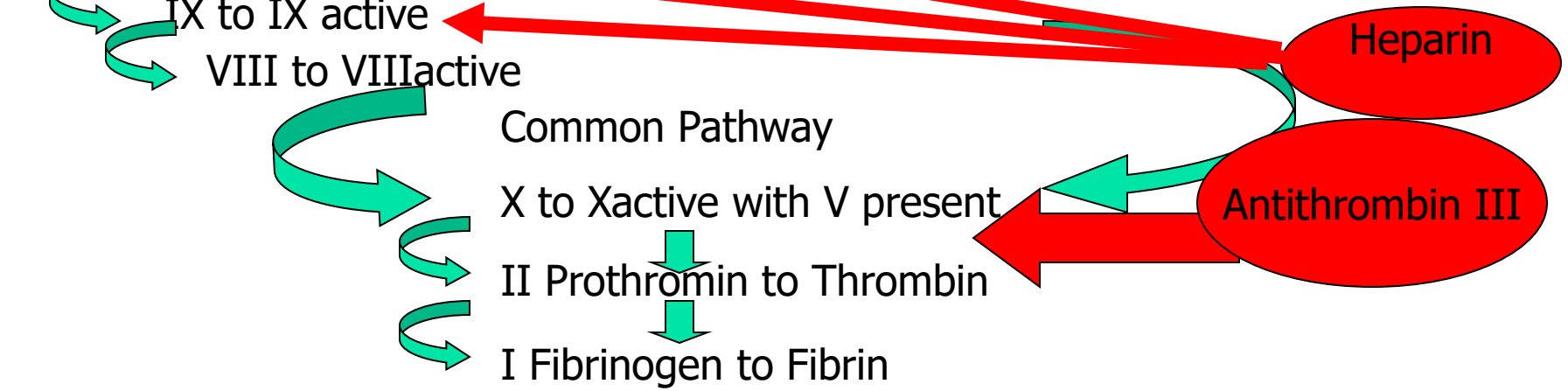


Fibrin split
products, D-Dimer

Bleeding History

- 1. Abnormal bleeding from the mucus membranes such as the mouth, nose or vagina suggests platelet defects or von Willebrand's disease (vWD).
- 2. Abnormal bleeding into joint spaces and soft tissues implies a defect in the clotting factors.
- 3. Purpuric lesions are usually caused by vascular wall defects.

Bleeding History

- HX - History of melena, abdominal pain, Aspirin or non-steroidal anti-inflammatory agents (NSAIDs) use, past peptic ulcer disease , then consider GI bleeding, platelet dysfunction.
- - In females the menstrual history quantifying the amount of bloodloss ,or possible pregnancy should be obtained.
- - History of alcohol abuse - consider liver disease.
- - Family history of blood cell or bleeding disorder: consider Hemophilia, von Willebrand Disease

Bleeding History

- - History of weight loss, Cancer, HIV, rheumatoid arthritis, thyroid disease, renal disease -then consider secondary cause
- - History of fever and chills, cough, dyspnea, then consider Infection.
- - History of prolonged bleeding after dental extractions, epistaxis, gum bleeding, easy bruising, then consider low or dysfuctional platelets.
- - History of bleeding into joints, then consider hemophilia.
- - History of Lupus - Lupus anticoagulant

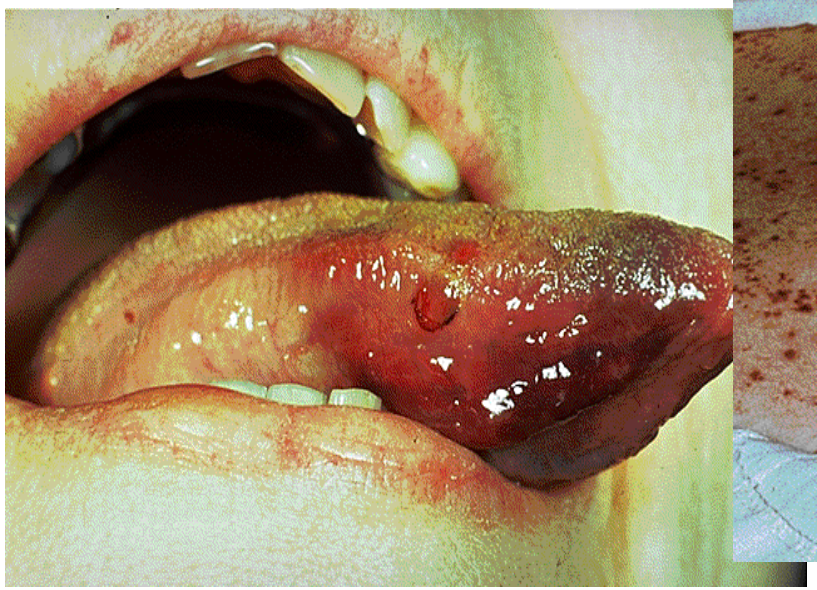
Physical Exam

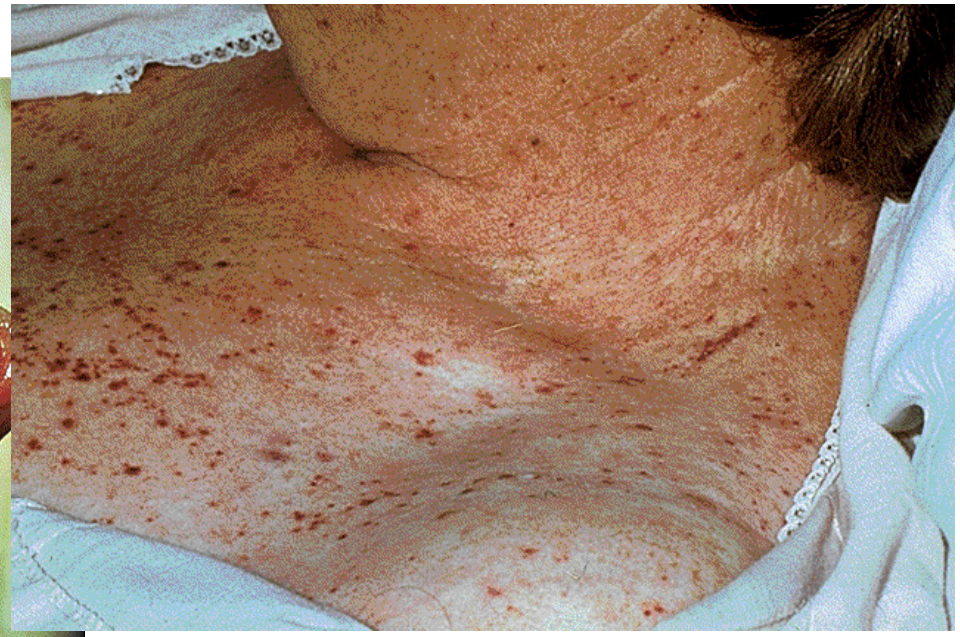
- PHYSICAL EXAM
- GENERAL INSPECTION- clubbing in TB or lung cancer
- Skin- Hypothyroid, SLE, Bruises, lesions, petechiae or purpura.
- Weight - Loss in Cancer, HIV, Chronic disease
- VITAL SIGNS- Pulse: Tachycardia from increased cardiac output
- Respirations: Tachypnea from decreased oxygen transport
- BP: Orthostatic if volume depleted
- Temp: Fever in infections and drug or transfusion reactions,

Physical Exam 2

- HEENT- Eye: Jaundice if hemolysis, pallor in palpebral conjunctiva
- LUNG- consider infection, lesion, rub
- CV - new murmer or CHF , Listen for Bruits
- ABDOMINAL- Liver/spleen size, masses, tenderness, surgical scars
- RECTAL- Stool guaiac,
- PELVIC/BREAST- Uterine abnormality, Pap smear, Breast nodule
- LYMPHNODES- consider lymphoma, leukemia, infection, connective tissue disease
- EXTR- Homan's or calf tenderness/swelling

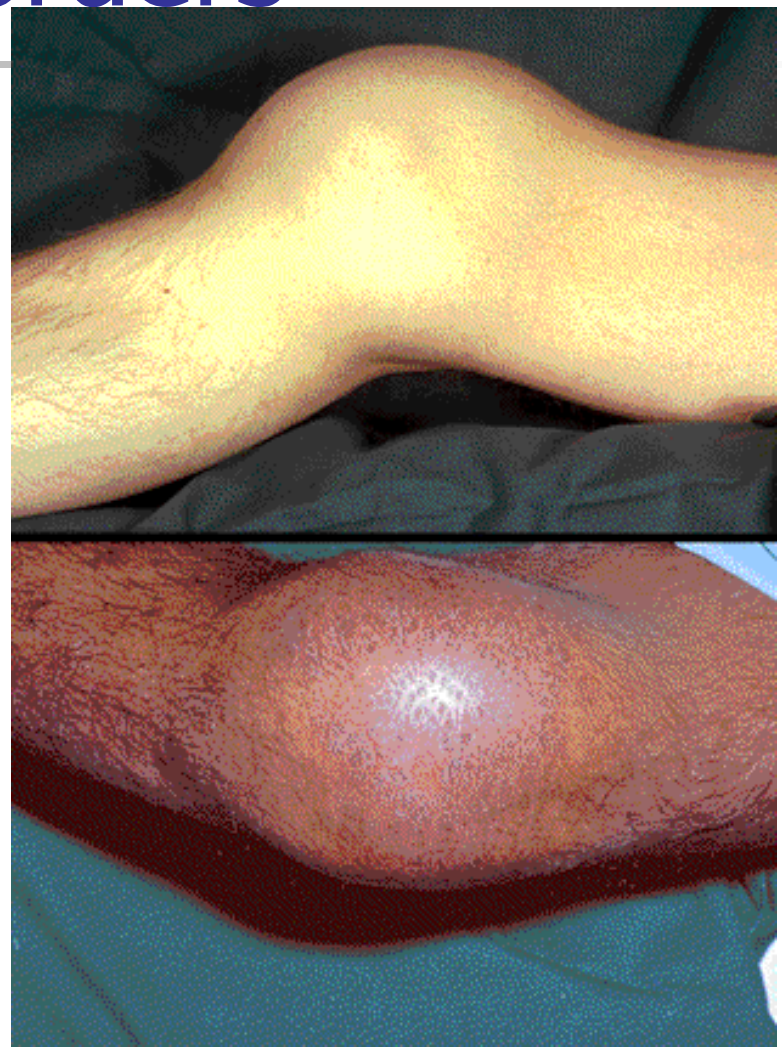
Platelet Problems or Von Willebrand Disease (vWD)





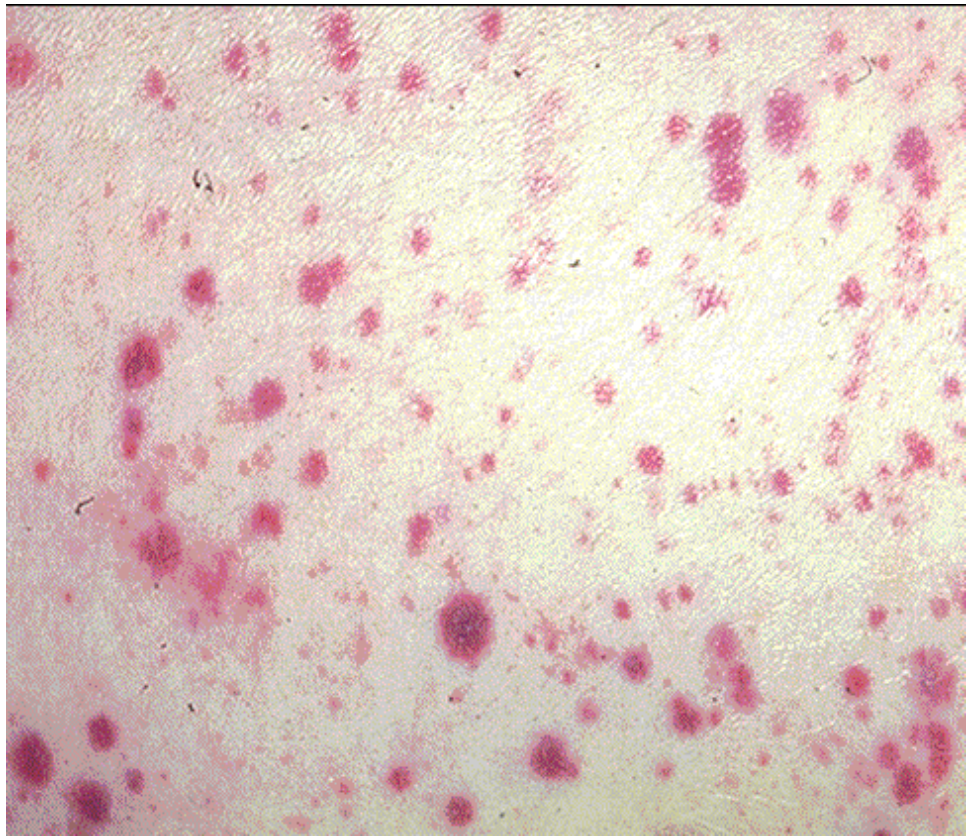
Clotting Factor Disorders

Hemarthrosis



Vascular Wall Defects

Purpura



Testing Bleeding: PVC-Pipes

- Platelets – CBC platelet count
  - Do they work – PFA (Bleeding time)
- vWF – abnormal PFA and aPTT (Factor VIII depends of vWF) do vWF analysis
- Clotting Factors – PT and aPTT if either abnormal – do Mixing study – if corrects do Factor levels VIII, IX. If both PT and aPTT abnormal do TT Thrombin time
- CMP, UA (Renal or Hepatic causes)
- Pipes – Vasculitis C-Reative Protein, Biopsy

Tests to Order – Screen for Clotting ability

- **--PT** -Prothrombin Time - +/- 2 of control = 11 - 16 sec. Extrinsic system monitor for coumadin therapy. INR is International Normalization Ratio, 1 is normal, 2- 3 for Coumadin Therapy, 2.5 - 3.5 if heart valve
- -**aPTT** - activated Partial Thromboplastin Time- 25 - 38 sec. Intrinsic system. Used to monitor Heparin therapy (if abnormal do Factor analysis and consider vWD)
- Mixing Study (add normal plasma to patient plasma re do PT and aPTT) – if PT or aPTT **do not** correct then there is a inhibitor present and not a factor deficiency.
- **TT** – Thrombin Time measures the common pathway – **Need only if both PT and aPTT are prolonged**

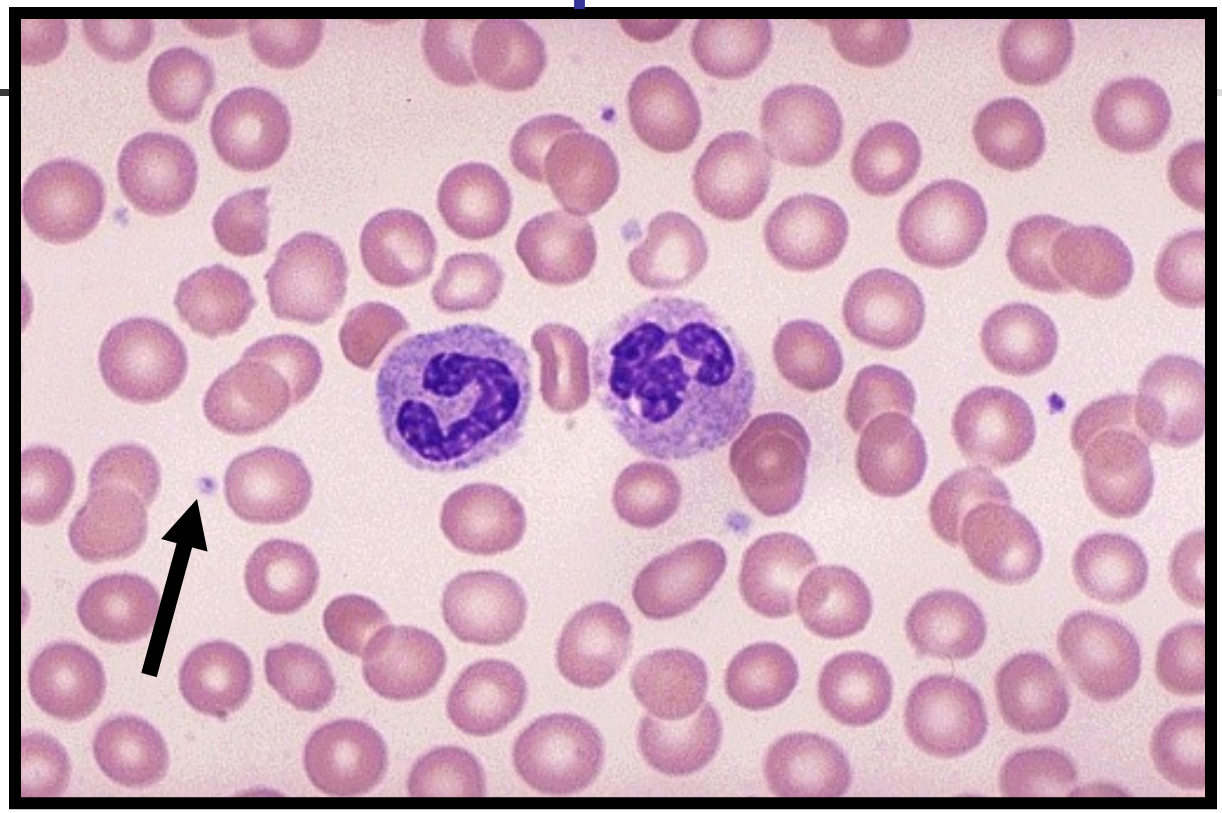
Bleeding Work-up

- First pass – CBC, CMP, UA, Platelet Function Analysis (PFA), PT, aPTT
- CMP– Abnormal Liver enzymes or Renal Failure (BUN/Creat)
- UA – Abnormal Renal function – Proteinuria or Hematuria
- CBC Platelets Low - Thrombocytopenia
  - Peripheral Smear and/ or Bone Marrow Biopsy
  - Are they under attack – Platelet antibody studies, HIT assay if on heparin
  - Is the spleen enlarged?

- Platelet Function Analysis abnormal
  - Von Willebrand analysis
  - Aspirin or other platelet inhibitors
  - Platelets not working right – Platelet Aggregometry, Chem profile (BUN, Creat), Urinalysis – Uremia
  - Dietary/Herbal history – Fish oil, chocolate, red wine garlic…..

- PT or aPTT abnormal
  - Von Willebrand analysis (If aPTT abnormal and PFA abnormal)
  - Mixing study – if corrects then measure Factors, if not: Inhibitor is present
  - Both abnormal then do TT Thrombin Time for common pathway and also consider DIC.

Normal Peripheral Blood Smear



Size:

Platelet 2μm.

Approximately ¼ size of RBC.

Appearance:

Reddish granules throughout

See http://patients.uptodate.com/topic.asp?file=lab_med/6606

Tests – Bleeding too much

- **Thrombin Time (fibrinogen), Reptilase Time (heparin)**
- **Platelet Function Analysis (PFA) do platelets work?**
- **Platelet Aggregometry do platelets stick together (IIb- IIIa)**
- **-Bleeding Time - (normal 3-8 minutes) is a measure of platelet function and an intact coagulation cascade.**

Do if suspect vWD (abnormal PFA and aPTT)

- **Von Willebrand Antigen Measurement**
- **Ristocetin Cofactor Activity (von Willebrand Activity)**
- **Factor VIII Activity**
- **Von Willebrand Multimer Analysis**

Coag Test Summary

PT	aPTT	Differential diagnosis
Prolonged	Normal	Factor VII deficiency or inhibitor, vitamin k deficiency, liver disease, warfarin therapy
Normal	Prolonged	Factor VIII, IX, XI, XII deficiency or inhibitor; von Willebrand disease; lupus anticoagulant; heparin therapy
Prolonged	Prolonged	Prothrombin, fibrinogen, Factor V or X deficiency; liver disease; disseminated intravascular coagulation; combined heparin and warfarin therapy Need TT Thrombin Time

Clotting Tests for bleeding

Test/Disease	PT	aPTT	PFA	Platelet Ct
vWD	Normal	Increased	Abnormal	Normal
Hemophilia A/B heparin, lupus	Normal	Increased	Normal	Normal
DIC	Increased	Increased	Abnormal	Low
Uremia	Normal	Normal	Abnormal	Normal
Aspirin NSAIDs	Normal	Normal	Abnormal	Normal
Early: Liver Dz Vit K def, F VII coumadin	Increased	Normal	Normal	Normal
Late Liver Dz	Increased	Increased	Normal	Low
ITP, TTP, HUS, HIT	Normal	Normal	Normal	Low

Platelet Function Analyzer: PFA-100

- Advantages
  - Sensitive screen for abnormalities of primary hemostasis (vWF and platelets)
  - Response to aspirin therapy
  - Response to DDAVP
  - Performed on whole blood (more representative)
- Limitations
  - Not specific for any disorder
  - Affected by many antiplatelet factors (even chocolate Omega -3 , red wine)
  - Affected by low plt count, low hematocrit, and low WBC count
  - Poor positive predictive value for pre-procedural bleeding

Platelet Abnormalities: Abnormal Platelet Function

1. Acquired
   - Drugs (Aspirin, NSAIDs)
   - Diet (Omega 3 - Fish oil, chocolate, …)
   - Uremia (renal failure)
   - Leukemia and Myeloproliferative Disorders
   - Mechanical (cardiopulmonary bypass)
2. Congenital
   - Bernard-Soulier (abnormal adhesion)
   - Glanzmann's Thrombasthenia (abnormal aggregation)
   - Storage Pool Disease (abnormal release response)
   - Platelet-type von Willebrand's Disease

Bleeding Differential Diagnosis

- C - Cirrhosis/Liver Disease and Coumadin
- A - Aspirin and other NSAIDs
- L - Leukemia
- F - Factor Deficiency - Hemophilia

- D - Disseminated Intravascular Coagulation
- I - Idiopathic Thrombocytopenic Purpura (ITP)
- P - Platelet Deficiency (TTP, HUS, DIC, Heparin- HIT)
  - Platelet Dysfunction (vWD)
- S - Scurvy: Vitamin C Deficiency

PVC pipes

- **Platelets**
  - Not enough below 50,000 – production, destruction, sequestration
  - Not working –ASA, NSAIDs, Uremia, Congenital
- **Von Willebrands Disease**-Type 1 most common
- **Clotting Factors**
  - Most common: VIII, IX
  - Vitamin K Deficiency, Liver Disease
- **Pipes** - Vasculitis, Scurvy, Ehlers-Danlos, Heritary Hemorrhagic Telangiectasias, Steroids
  - Palpable Purpura – Sepsis, Meningococcemia, Henoch-Schonlein purpura, Drugs

Thrombocytopenia

- Production
  - Nutritional B12 or Folate Deficiency
  - Liver failure – low thrombopoietin
  - Congenital – Alports syndrome, Fanconi anemia, Wiscott-Aldrich syndrome
  - Infection – EB virus, Zika, Parvo, Hep C, RMSF
  - Marrow damage – aplastic anemia, chemotherapy, drugs, maligancy – myeloma or leukemia, radiation, mylodysplasia
- Destruction
  - Immune – (Positive Platelet Associated Antibody test or HIT assay) ITP, Drug, HIV, SLE, HIT
  - Non-Immune- DIC, TTP, Preeclampsia, HELLP syndrome Anti-phospholipid syndrome
- Sequestration- Liver, spleen, marrow -myelofibrosis, cancer http://www.aafp.org/afp/2012/0315/p612.html

Platelets - How low can you go?

- 150,000 - 350,000 cu/mm Normal
- 80 – 100K – need for surgery
- 40 – 50K for procedures like LP
- 10 – 40K –At risk if trauma or surgery
- < 10,000K spontaneous bleeding
- if > 1 million - Clotting too much

There is a song for that

Friends With Low Platelets | Garth Brooks Parody | ZDoggMD.com

https://www.youtube.com/watch?v=-rwcIRfHcAE

Thrombocytopenia Testing

- Liver Spleen size – Ultrasound or CT
- Bone Marrow Biopsy
- Platelet antibodies (direct and indirect)
- HIT assay if on heparin
- ADAMTS 13 (TTP)
- Blood smear (morphology)
- Antibody response to *Escherichia coli O157:H7*

ITP - Immune Thrombocytopenic Purpura

- In children linked to viral infection
  - platelet-associated antibodies
  - 80% rapid remission, and does not recur
    - Treatment: steroids and IVIG
  - 10% to 20% develop chronic ITP
    - Splenectomy works in 70%
    - Thrombopoietin receptor agonist *Eltrombopag*
- Adults linked to HIV and Hepatitis C
  - 50% develop chronic ITP
  - Same treatments

TTP, HUS, DIC, get HEELP!

- TTP – Thrombotic Thrombocytopenia Purpura with ADAMTS-3 and big vWF
- HUS – Hemolytic Uremic Syndrome with E.Coli 0157:h7
- DIC – Disseminated Intravascular Coagulation – Sepsis, Burns, Trauma
- All of these need ICU/expert care: PUNT to Hematologist

HELLP- Pregnancy

- Hemolysis (high indirect Bilirubin, LDH)
- Elevated Liver Enzymes (AST, ALT)
- Low Platelets
- severe preeclampsia (BP increased and proteinuria) increased maternal and fetal mortality
- 1 per 1000 pregnancies up to 20% with preeclampsia/eclampsia at 28 – 36 weeks gestation
- Rx Support and Deliver Baby

Thrombocytopenia – Not HIT

Issue/ Disease	Acute ITP	Chronic ITP	TTP	HUS	DIC	HELLP
Age	Children	Adults	Adults	Children	Any	Pregnant
Cause	Immune Post viral	Immune HIV Hep C, SLE	ADAMTS-3 and big vWF	Infections E.Coli 0157:h7	Sepsis, burns trauma	Pre-ecclampsia
PT/PTT	normal	normal	normal	normal	abnorm	+/-
Fever	no	no	yes	yes	depends	+/_
Hemolysis*	no	no	yes	yes	no	yes
Organ failure	no	no	CNS > Renal	Renal > CNS	All possible	Liver
Treatment	None – IVIG, Steroids	Steroids Splenectomy,	Plasma Exchange, No Plts	Support, No Plts	Support, Fix cause	Deliver ($MgSO_4$)

Hemolysis*- Microangiopathic: increased indirect Bilirubin/LDH/Shistocytes/Reticulocytes/Low Haptoglobin

Von Willebrand Disease

- Most common inherited bleeding disorder
- Found in approximately 1% of the population
- Most individuals are asymptomatic unless a significant bleeding event occurs
- Blood Group O individuals have significantly lower vWF than other groups (30% lower)
- vWF stabilizes Factor VIII so any decrease in vWF will increase aPTT and platelet function analysis will be abnormal

Von Willebrand Disease

- Measure vWF antigen (vWF:Ag)
  - How much protein is present?
- Measure vWF activity (Ristocetin Cofactor)
  - How well is the protein working?
- Measure Factor VIII activity
  - How well is vWF stabilizing Factor VIII?
- Evaluate pattern of von Willebrand multimers by electrophoresis
  - Important for classification of disease (6 types) and therapeutic management
- Treat most common cause with DDAVP

Hemophilia A,B, C

- US 13,320 cases of hemophilia A (VIII) 3,640 cases of hemophilia B (IX) and rare hemophilia C (XI).
- prolonged aPTT with a normal PT
- Bleeding into joints
- Treat with Recombinant Factor replacement (No longer plasma exposure)
- Three types of Hemophilia A – Genetic, vWD, Inhibitor to factor VIII acquired or developed
- Hemophilia C - Ashkenazi Jews 10% carrier

Renal Failure and clotting

- Early stages of CKD - Low protein C and antithrombin III, (anticlotting system) Increased fibrinogen, von Willebrand factor, factor VIII (pro thrombotic) Increased plasminogen activator inhibitor-1 (PAI-1), low tissue plasminogen activator (t-PA) So Clots stay
- End stage CKD - accumulating uremic toxins decrease platelet function, inhibiting their adhesion, aggregation and releasing platelet factors, such as serotonin or thromboxane A_2
- Damage to endothelial cells produce large amounts of prostacyclin (PGI_2) and nitric oxide (NO) inhibitor of platelet aggregation platelet adhesion.

Liver Disease

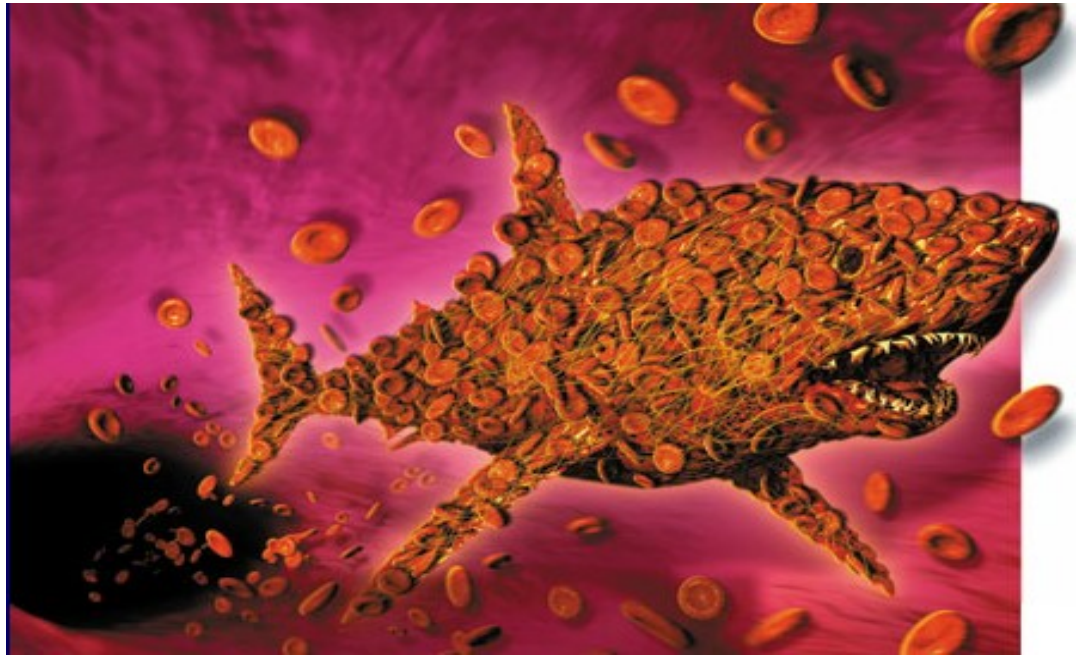
- The liver is THE site for coagulation factor synthesis (except Factor VIII)
- Liver failure leads to multi-factorial coagulopathy
  - Decreased coagulation factors
  - Decreased anti-coagulation factors
  - Decreased fibrinogen
  - Decreased platelets
  - Increased D-dimers (interfere with clot formation)
- Bleeding from liver failure is a major cause morbidity and mortality
- Give Vitamin K or Fresh Frozen Plasma

Bleeding Therapy Summary

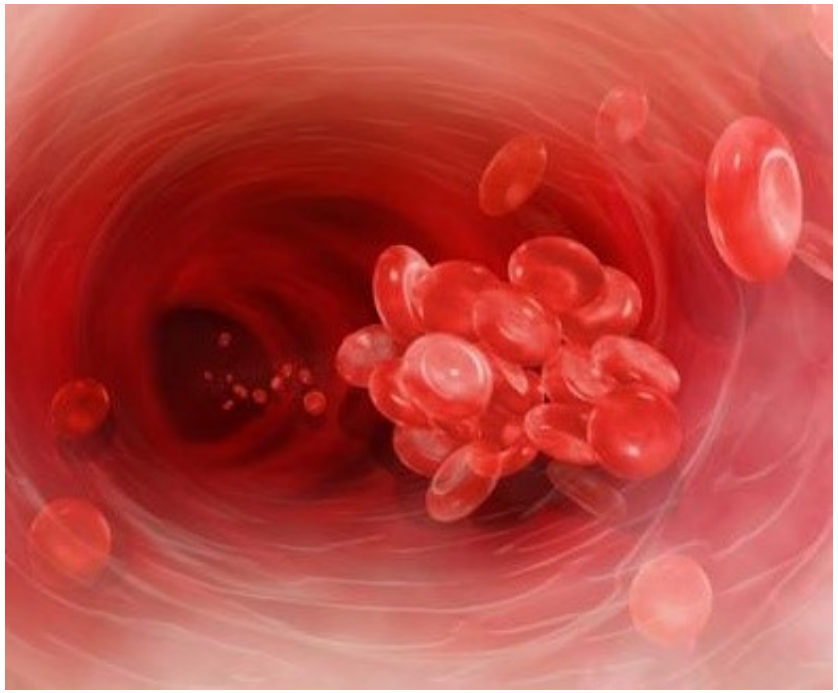
- Low platelets immune attack – Corticosteroids, splenectomy
- CKD – Dialysis, Renal transplant
- Low platelets – Transfuse platelets (not if HIT, TTP, HUS +\- ITP) Thrombopoietin receptor agonist *Eltrombopag*
- vWD – DDAVP nose spray
- Hemophilia A – Factor VIII, DDAVP, Tranexamic acid
- DIC/Multiple clotting factors low – FFP or Cryo
- Liver Disease, Coumadin excess – Vitamin K or FFP
- HIT – Stop heparin and use non hepraniod anticoagulant
- Reverse UF heparin – protamine
- Heavy Menstrual Bleeding - Tranexamic acid

Clotting too much

Clotting Too much – Thrombosis - Pulmonary Embolus, Deep Vein Thrombophlebitis, Stroke, Myocardial Infarction



PVC Pipe Clog vs Clot



Increased Clotting Presentation

Deep Vein Thromboplebitis (DVT)

Calf swelling, pain

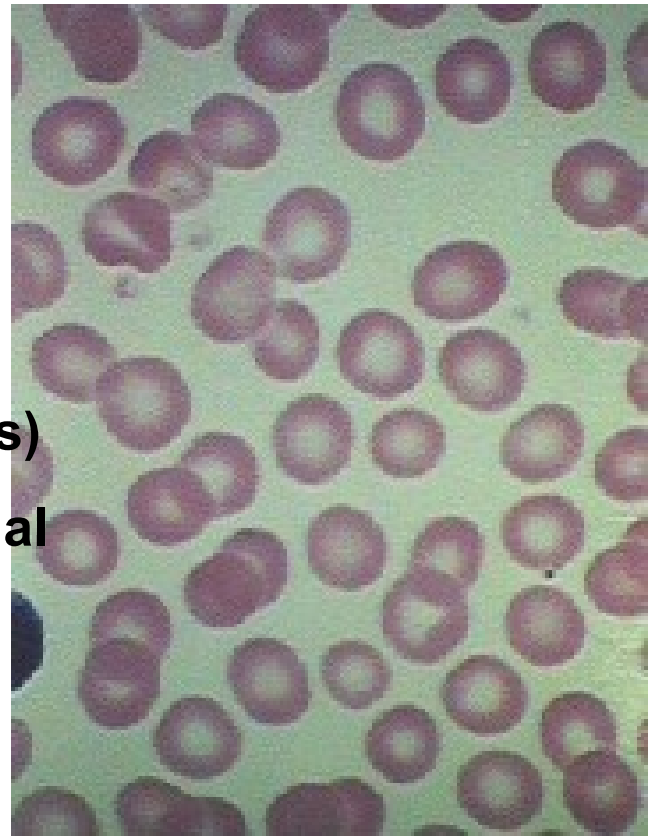
Pulmonary Embolus (PE)

Myocardial Infarction, Angina

Stroke, or Transient Ischemic Attacks (TIAs)

High Risk – post operative, pregnancy, atrial fibrilation, congestive heart failure

Elevated platelets



Increased Clotting History

- History of recurrent clots, PEs... consider protein S,C, or Antithrombin III deficient, Factor V Leiden, hyperhomocysteine, prothrombin 20210 mutation
- Pregnancy - Increased blood viscosity, fibrinogen and factor VIII. Post Partum - Hypercoaguable state
- Polycythemia vera - increased viscosity
- Sickle cell disease and possibly trait

Increased Clotting History

- Smoking, Resent Surgery, Diabetes, Congestive Heart Failure, Cancer, Atrial Fibrillation are all high risk
- Autoimmune diseases such as systemic lupus erythematosis, and medications such as procainamide, chlorpromazine, and quinidine.
- Oral contraceptives - Estrogen

Labs for clotting

- Best screening test for hypercoagulable state:

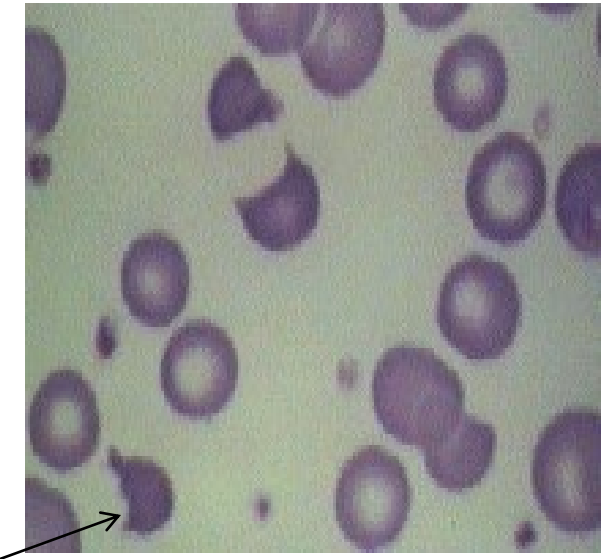
  NONE!!!

If clotting is going on: CBC, CMP, UA, d-Dimer

If on Heparin: HIT assay

Tests – Is Clotting going on

- D-Dimer elevation – from thrombolysis (break apart)
  - Also used to know when to stop Coumadin therapy
- Fibrin Split products
- Peripheral smear may show shistocytes (helmet cells)



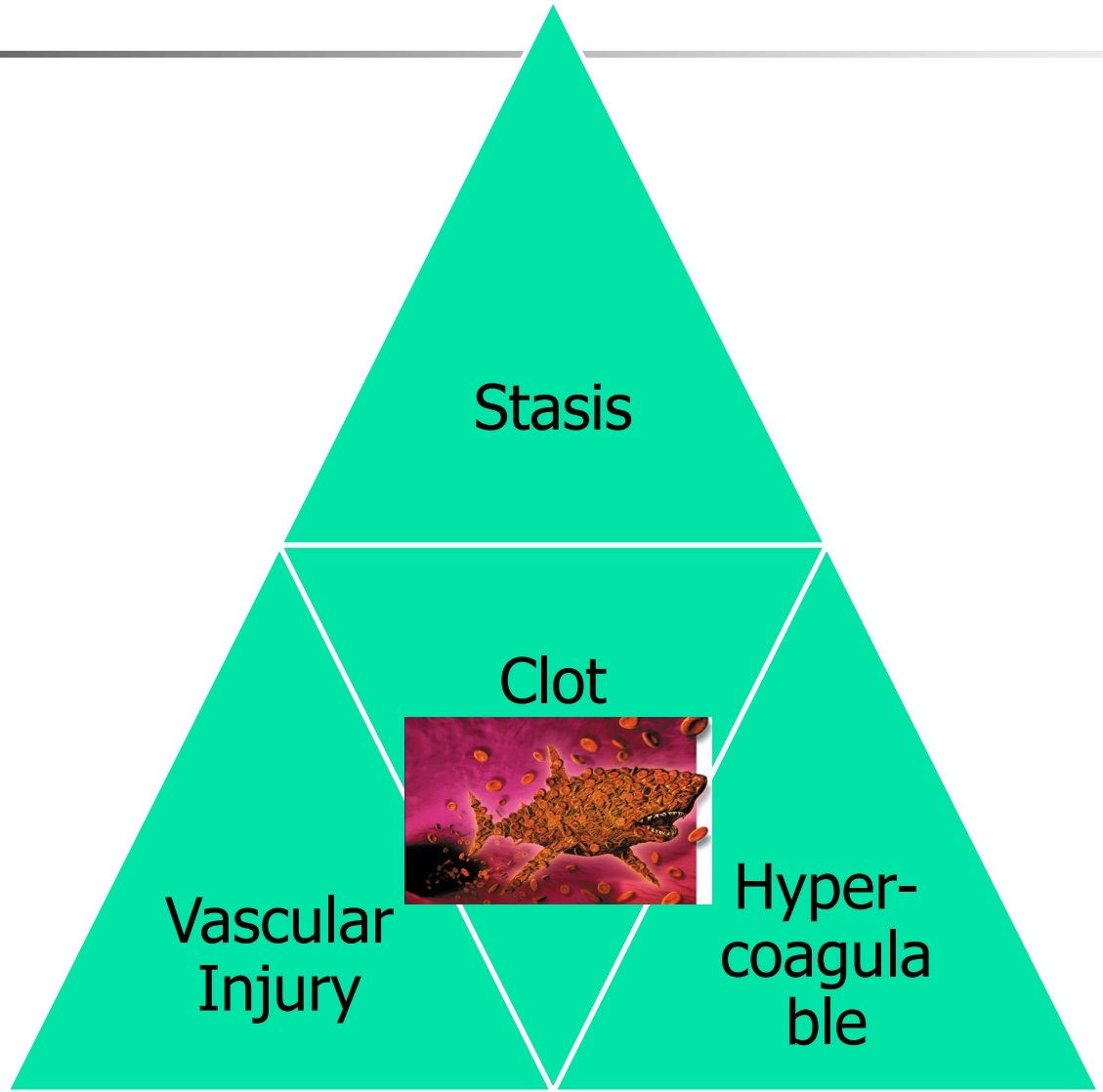
Tests – Clotting too much

- Fasting homocysteine level/ MTHFR gene
- Factor V Leiden assay
- Protein S, C, antithrombin III assay
- Lupus anticoagulant
- Anticardiolipin antibodies
- Anti Beta-GPI antibodies
- Prothrombin 20210 mutation test
- Fibrinogen level
- HIT Assay if Heparin exposure

Prevalence and Relative Risk of Clotting problem DVT/PE

- Hyperhomocyteinemia/ MTHFR gene (10% -15%) RR=3
- Factor V Leiden (5% Most common genetic) RR=7-80
- Platelet GPIIb/IIIa Human Platelet Antigen -HPA-1b (2 - 3%) RR = 4
- Prothrombin 20210 mutation (1- 2%) RR=2-5
- Protein C deficiency (0.2 – 0.5%) RR=7
- Protein S deficiency (0.1%) RR= 8.5
- Antithrombin III deficiency (0.2 – 0.5%) RR=8

Virchow's Triad



Hypercoagulability – PVCs

- **Platelets**
  - Too many (over 1 million)
  - Overactive
- **Vascular Injury**
- **Clotting Factors**
  - Anti-clotting factors deficient/ not working
  - Too many factors/triggers/COVID-19
- **Stasis and Surgery**

Differential Diagnosis - Hycoagulability

- The mnemonic is: 5 Ps HAD CAUSED CLOTs

- P - Pregnancy - Increased blood viscosity, fibrinogen and factor VIII. Post Partum - Hypercoaguable state
- P – Prothrombin 20210 mutation,
- P - Protien S, C, or Antithrombin III deficient – Inherited
- P - Polycythemia vera - increased viscosity
- P – Paroxysmal Nocturnal Hemoglobinuria
- S- Smoking

Differential Diagnosis - Hycoagulability

- H – HIT Heparin Induced Thrombocytopenia
- H – H Hyperhomocyteinemia (MTHFR gene)
- A – Antithrombin III Deficiency
- D – Dysfibrinogenemia

- C – CHF or Congestive Heart Failure
- A – Antiphospholipid Antibody Syndrome - SLE
- U – Uremia – Chronic Renal Failure
- S – Surgery – Orthopedic is greatest risk
- S – Stasis from any immobility
- E – Estrogen
- D - Diabetes

Differential Diagnosis

- C - Cholesterol elevation, Cancer - procoagulant effects, COVID-19
- L – Leiden Factor V mutation – Activated Protein C resistance
- O – Obesity and Cholesterol elevation
- T - Trauma, Travel (immobility) - Stasis of blood flow and release of tissue thromboplastin in trauma
- T – Thyroid disease hyper or hypo
- T- Thrombotic Thrombocytopenic Purpura- TTP
- S - Sepsis

Pregnancy and OCP Estrogen

- Increases in fibrinogen, vWF, and factors VII, VIII, and X; decreased protein S
- OCP + Smoking = increased platelet reactivity, mediated in part by increased thromboxane synthesis
- Acquired activated protein C resistance
- Protein S levels decrease

Cancer

- mucinous adenocarcinomas
- promyelocytic leukemia
- malignancies of lung, breast, GI, and any metastatic solid tumor

- Trousseau syndrome = migratory thrombophlebitis with noninfectious vegetations on the heart valves (marantic endocarditis)

Nephrotic Syndrome

- Decreased antithrombin and plasminogen (renal loss)
- Increased platelet activation and increased fibrinogen
- Increased renal vein thrombosis, DVT/PE
- Albumin below 2.0 g/dL

COVID and clotting

- Increased D-dimer and fibrinogen levels
- Disseminated intravascular coagulation (DIC); 71% of patients who did not survive hospitalization reported to have developed DIC compared to 0.6% of survivors
- Low Platelets
- Elevated PT/INR
- Thromboprophylaxis using unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH)

Vinayagam S, Sattu K. SARS-CoV-2 and coagulation disorders in different organs. *Life Sci*. 2020;260:118431. doi:10.1016/j.lfs.2020.118431

Heparin-induced thrombocytopenia (HIT)

- Due to an antibody against heparin
- Occurs in 1-3% of adult patients receiving heparin for 1 week or more. heparin binds to platelet factor 4 (PF4), forming a highly reactive antigenic complex on the surface of platelets
- An unexpected fall in platelet count occurring 4-14 days after heparin exposure
- Platelet count usually falls by 50%
- Mean platelet count 60,000 – 100,000/uL
- Platelets become activated and induce clotting
- Associated with thrombosis - 10-30% develop arterial or venous thromboses (usually DVTs or PEs)
- Of those forming a clot, 30% will die or require amputation
- Platelet counts should be monitored while patient is on heparin therapy
- HIT Assay
- STOP all Heparin products (Flush, LMWH, Heparin) and give Direct Thrombin Inhibitor.

Leiden Factor V mutation – Activated Protein C resistance

- Factor V Leiden mutation - 5% of the US population.
- Factor V Leiden mutation – present in 30-50% of patients with recurrent DVT
- Most common hereditary cause of thrombosis.
- Consider lifelong anticoagulation after VTE/DVT

Thrombocytosis

- >450,000 x 10^9/L
- Causes
  - Polycythemia vera -Jak2 mutation
  - Essential
  - Reactive – infection, inflammation, post-op
  - Iron Deficiency
  - CML
  - Genetic
  - Malignancy
- Treat with low dose aspirin to prevent VTE
- Plateletpharesis or Hydroxyurea
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3200282/

Who ya gonna Call?

Clot Busters

tPA (tissue Plasminogen Activator)

Drug Clot Busters tPA – reteplase, alteplase, tenecteplase

Intrinsic Pathway –
Inside the cut
Endothelial Injury

Test = aPTT

XII to XII active

XI to XI active

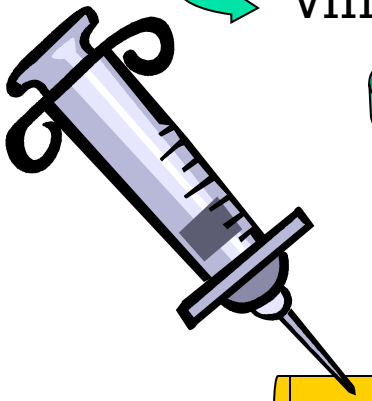
IX to IX active

VIII to VIIIactive

Extrinsic Pathway –
outside the cut in the
plasma – Tissue
Throboplastin

Test = PT

VII to VIIactive



Common Pathway

X to Xactive with V present

II Prothrombin to Thrombin

I Fibrinogen to Fibrin

Fibrin split
products, D-Dimer

Plasminogen via t-PA to Plasmin

Heparin

Protamine reverses Heparin

Intrinsic Pathway –
Inside the cut
Endothelial Injury

Test = aPTT

XII to XII active

XI to XI active

IX to IX active

VIII to VIIIactive

Extrinsic Pathway –
outside the cut in the
plasma – Tissue Factor

Test = PT

VII to VIIactive

Heparin

Antithrombin III

Common Pathway

X to Xactive with V present

II Prothromin to Thrombin

I Fibrinogen to Fibrin

LMW Heparin Danaparoid, Fondaprinux

LMWH

dalteparin – (Fragmin)

tinzapain – (Innohep, Logiparin)

enoxaparin (Lovenox, Clexane)

Intrinsic Pathway –
Inside the cut
Endothelial Injury

Test = aPTT

XII to XII active

XI to XI active

IX to IX active

VIII to VIIIactive

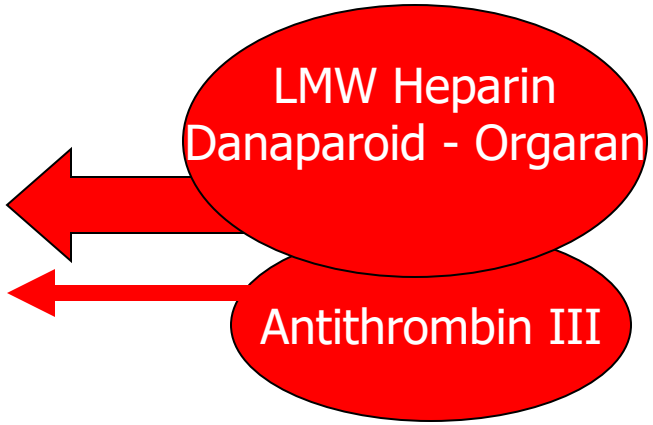
Common Pathway

X to Xactive with V present

II Prothrombin to Thrombin

I Fibrinogen to Fibrin

fondaprinux –(Arixtra) direct Xa blocker, non Heparin



Thrombin Inhibitors

Intrinsic Pathway –
Inside the cut
Endothelial Injury

Test = aPTT

XII to XII active

XI to XI active

IX to IX active

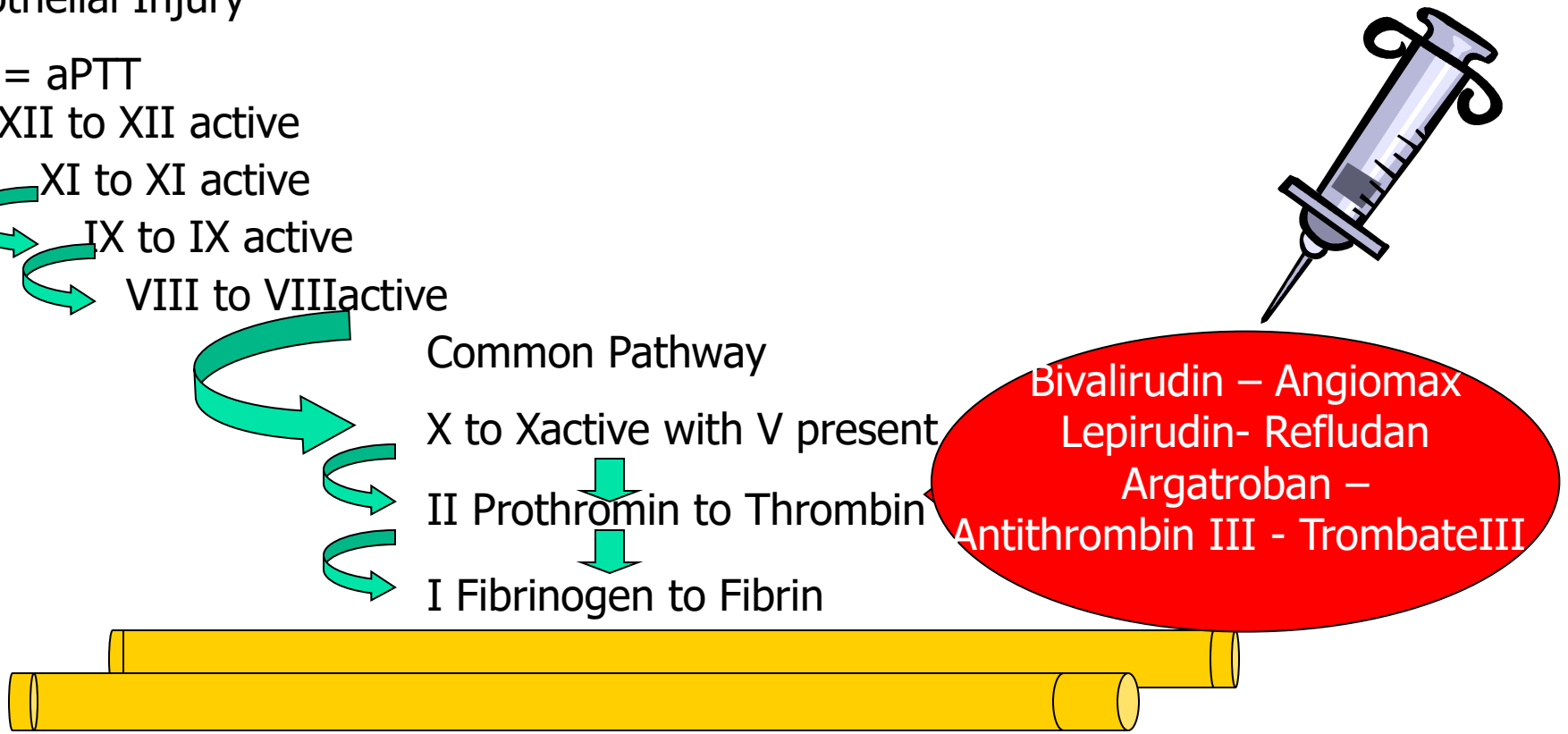
VIII to VIIIactive

Common Pathway

X to Xactive with V present

II Prothrombin to Thrombin

I Fibrinogen to Fibrin



Coumadin

Reverse with Vitamin K

Intrinsic Pathway – Inside the cut
Endothelial Injury

Test = aPTT

XII to XII active

XI to XI active

IX to IX active

VIII to VIIIactive

Extrinsic Pathway – outside the cut in the plasma

Vitamin K - Liver dependant

Test = PT

VII to VIIactive + III Tissue factor

Common Pathway

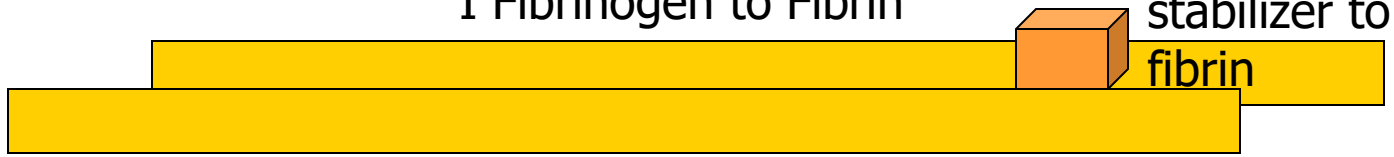
X to Xactive with V present

II Prothromin to Thrombin

I Fibrinogen to Fibrin

Coumadin blocks the liver -Vitamin K dependent factors

XIII to XIIIactive stabilizer to crosslink fibrin

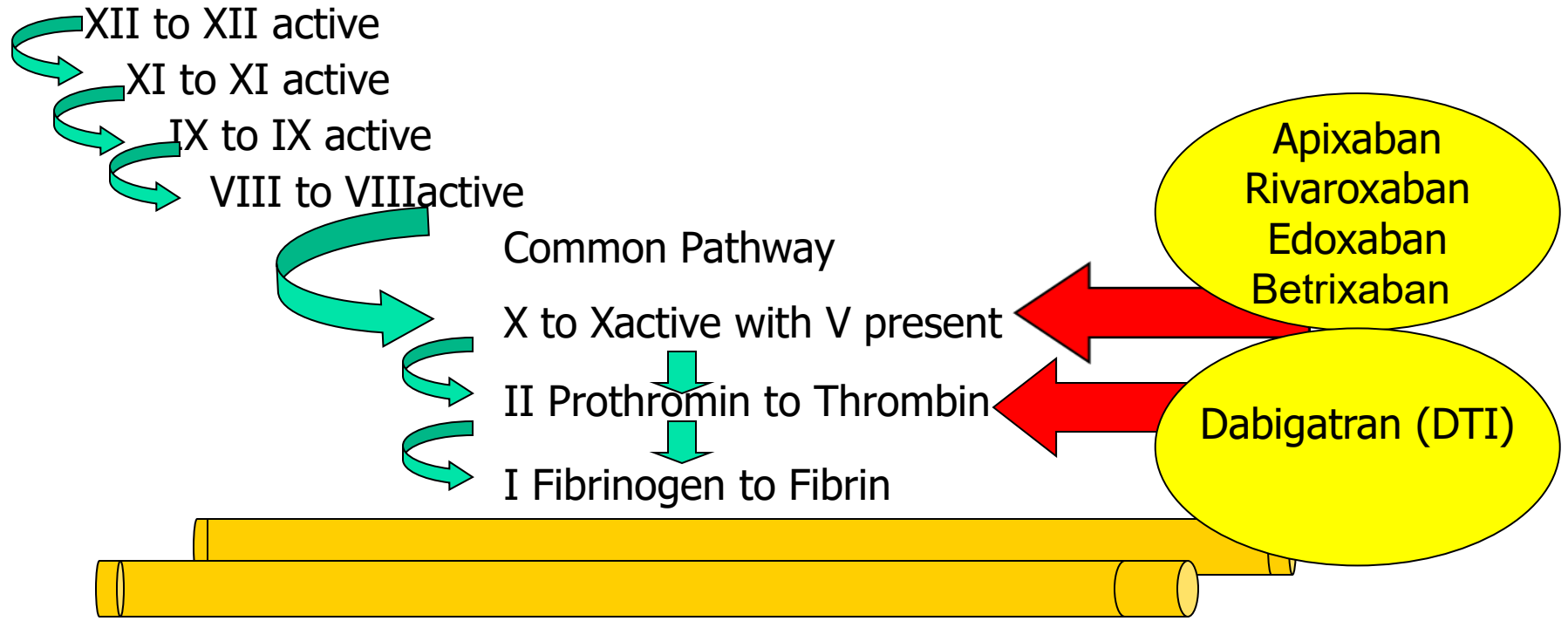


Direct Oral Anticoagulants - Thrombin and Factor Xa inhibiors DOACs

Intrinsic Pathway –
Inside the cut
Endothelial Injury

Test = aPPT

May replace Coumadin with fewer side effects. Risk of MI may be increased



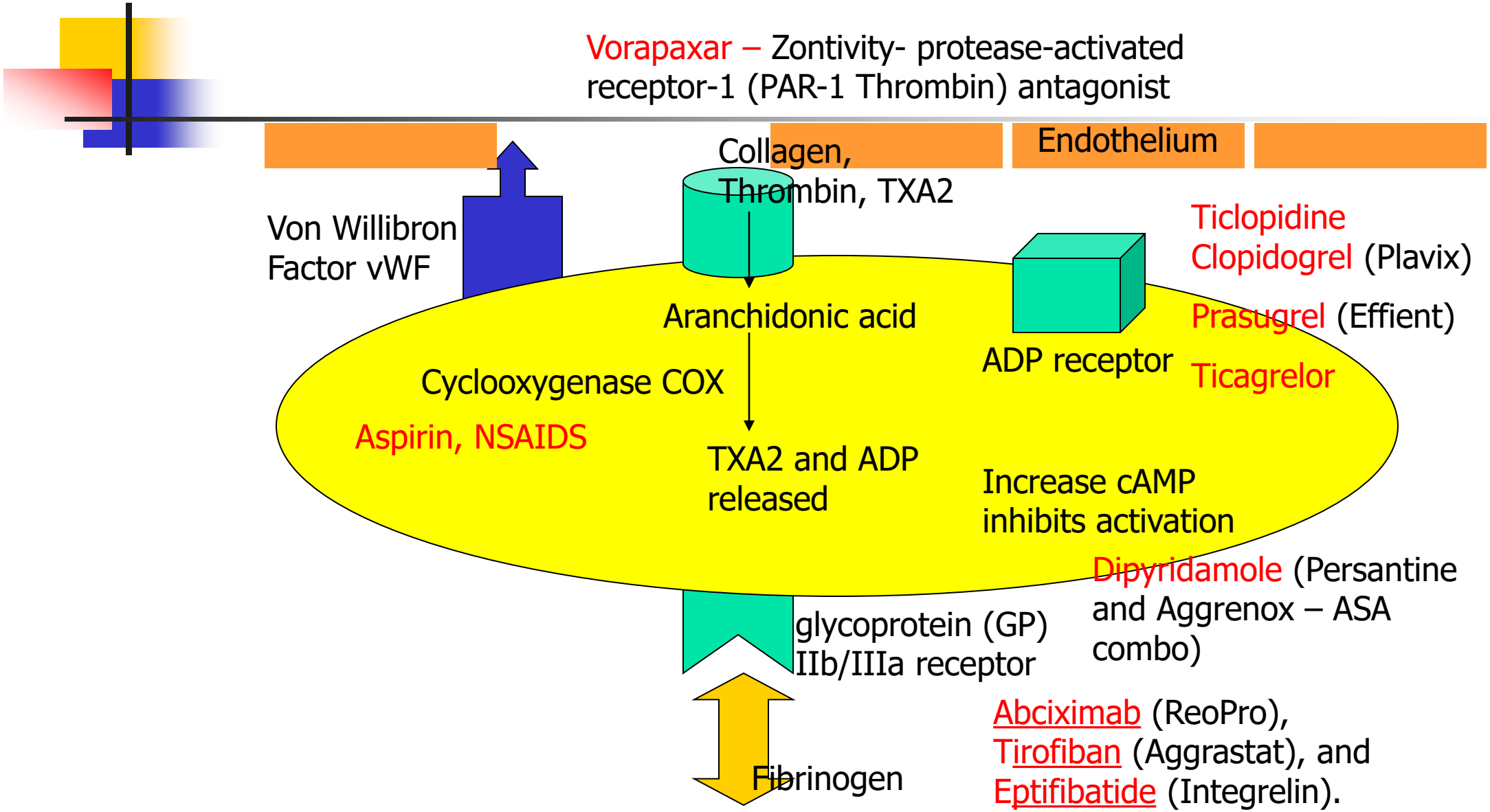
The new oral anticoagulants for VTE – Comparison (Advantages, Disadvantages)

	Dabiagatran (Pradaxa)	**Rivaroxaban** (Xarelto)	**Apixaban** (Eliquis)	**Edoxaban** (Savaysa)
Started immediately upon diagnosis of VTE	no	yes	yes	no
Dosing	twice daily	once daily	twice daily	once daily
Renal clearance	80 %	33 %	25 %	35 %
Efficacy compared to warfarin (recurrent VTE)	same	same	same	same
Safety compared to warfarin in respect to relevant bleeding	same	same/better[1]	better [2]	better [3]
Reversal agent / antidote available for major bleeding [4]	yes - Praxbind	yes - Andexxa	yes - Andexxa	yes - Andexxa
FDA approved for VTE treatment	yes	yes	yes	yes

[1] "Major bleeding" same as with warfarin in DVT trial, but less in PE trial
[2] Less "major bleeding" with apixaban
[3] Less "clinically relevant bleeding" with edoxaban, same "major bleeding"
[4] reversal agents are in early clinical development for all 4 anticoagulants

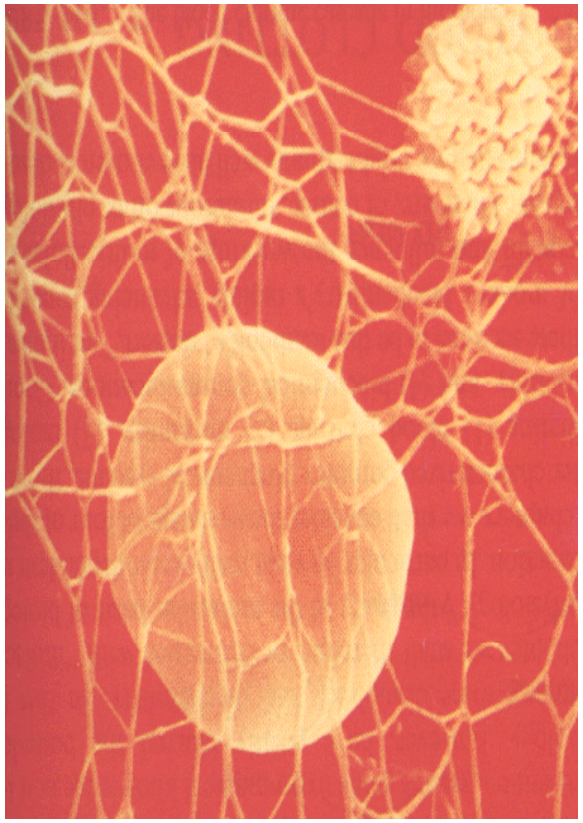
http://professionalsblog.clotconnect.org/2015/01/08/4th-noac-fda-approved-for-dvt-pe-and-atrial-fibrillation-sayasa-edoxaban/

Platelet Activation Blockers



Take Home Points: Stop the Clot Therapy

- **To block Platelets** (MI and Stoke prevention)
- Antiplatelet agents – aspirin or clopidogrel, or aspirin + dipyridamole New agents Prasugrel (Effient),Ticagrelor, Vorapaxar
- 2B3A blockers IV
- **Stop Clotting and Clot prevention-** (DVT, PE, MI, AFib, Genetic….)
- Heparin (Reversed with Protamine)
- LMW Heparin and factor Xa blockers
- Coumadin (Reversed with vitamin K)
- DOACs (Oral with reversal agents)
- **To Bust Clots** (PE, MI,Thrombotic Stroke) tPA -



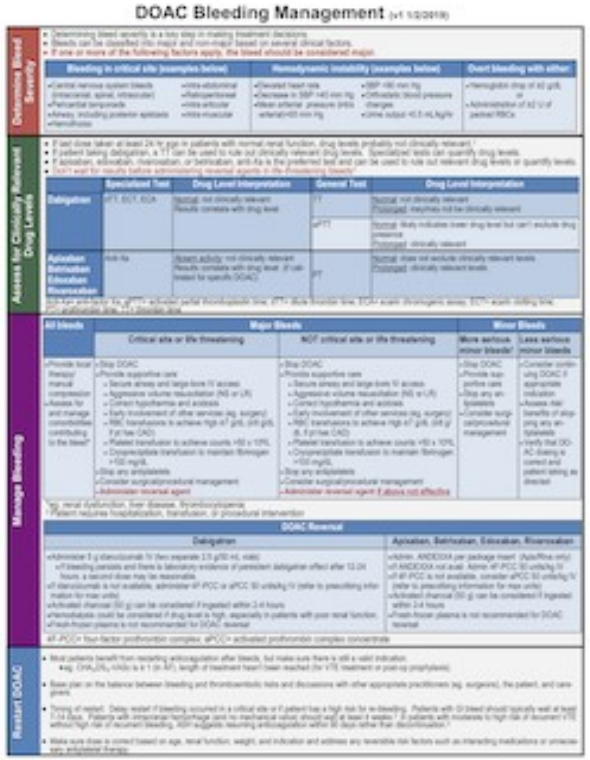
Clot Prevention

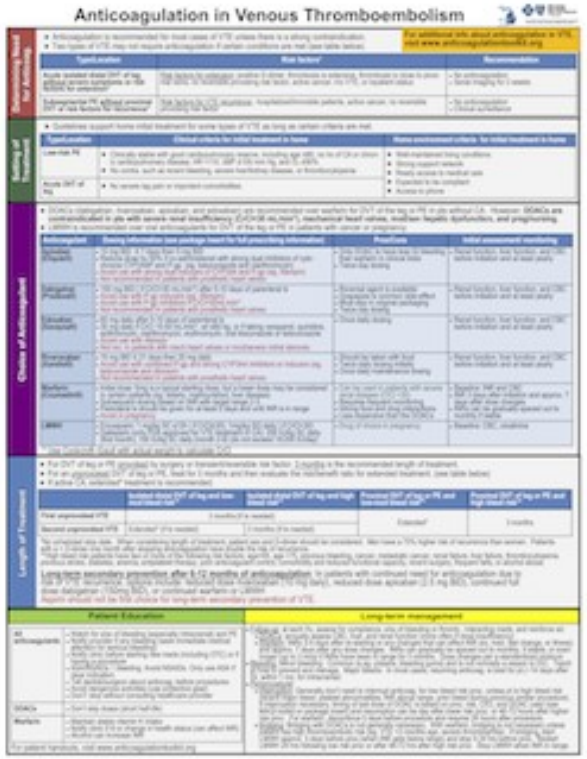
- Healthy diet
- Healthy weight
- Exercise
- No Smoking
- Alcohol in moderation
- Aspirin
- Statins
- LMWH for high risk

The **Double Coronary Bypass**.
From Vortex's menu: Beef Topped with two fried eggs, four slices of American cheese, and 5 slices of bacon, with two grilled cheese sandwiches replacing the buns.

One Page Guides

- https://anticoagulationtoolkit.org/providers





Apps:
CDC anticoagulation manager

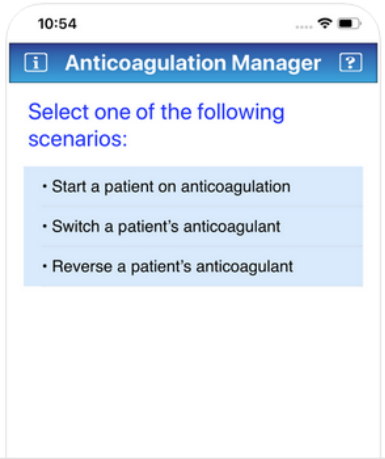
Anticoagulation Manager 17+

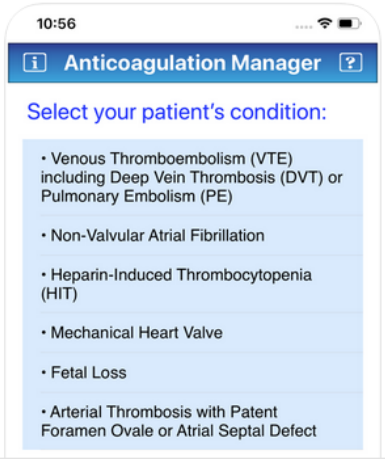
Centers For Disease Control and Prevention

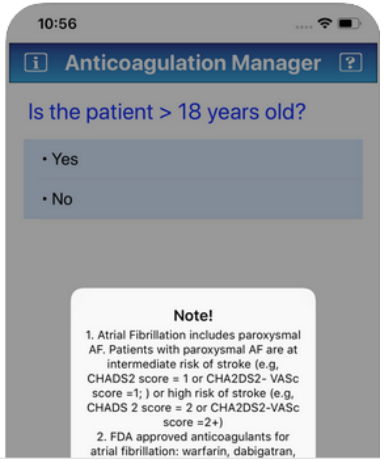
★★⯪☆☆ 2.7, 3 Ratings

Free

Screenshots iPhone iPad







ACC – Anticoag evaluator

AnticoagEvaluator App

AnticoagEvaluator App

FAQ

Newly Updated!

We want to hear from you. Complete a feedback survey here or leave a comment on the app's iTunes or Google Play page.

Use the updated AnticoagEvaluator to make informed decisions on initiation of antithrombotic therapy for patients with atrial fibrillation (AF) who do not have moderate to severe mitral stenosis or a mechanical heart valve. App updates include expanded advice from the 2019 Focused Update to the 2014 ACC/AHA/HRS Guideline for the Management of Patients with AF.

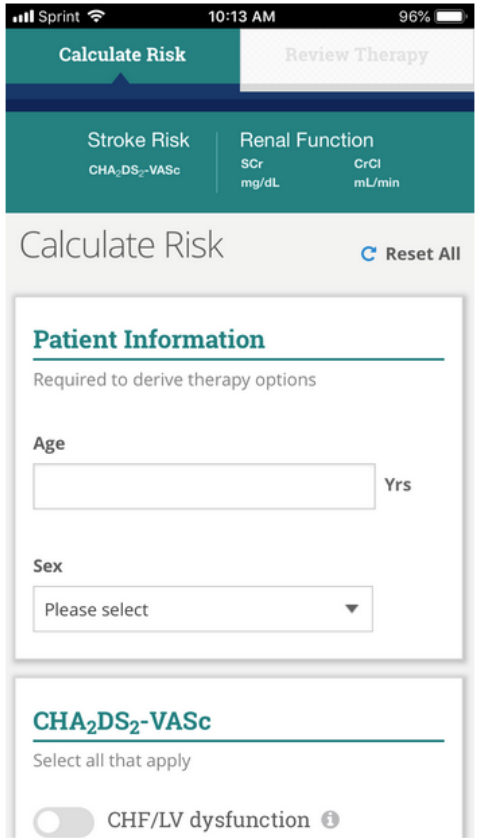
Use the app to:

- Calculate a patient's stroke risk (CHA2DS2-VASc) and renal function (Cockcroft-Gault Equation), and review factors that may contribute to bleed risk (HAS-BLED criteria and concomitant meds)
- Consider updated stroke prevention therapy guidance based on the 2019 ACC/AHA/HRS Focused Update of the 2014 Guideline for the Management of Patients with AF
- Improve safe use of direct oral anticoagulants with adjusted dosage based on prescribing information, fine-tuned for renal and other patient characteristics
- Evaluate suitable therapy for a patient by reviewing:
  - Synthesized individualized risk for antithrombotic therapy options based on clinical trials (i.e.,

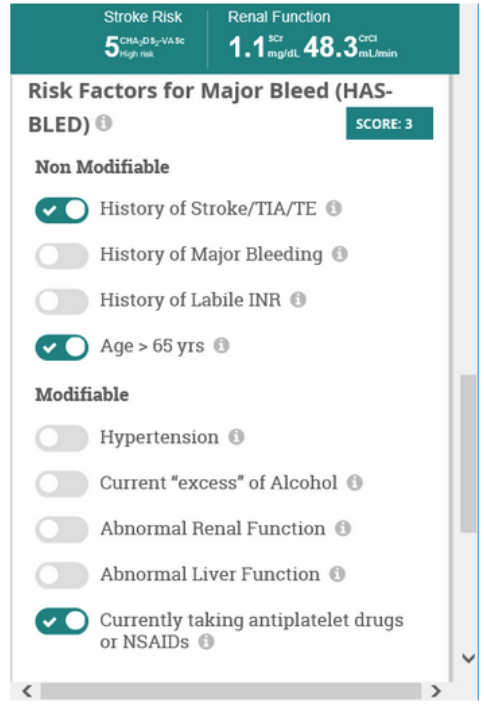
https://www.acc.org/anticoagevaluator

ACC – Anticoag App

App Screenshots



Make informed decisions on antithrombotic therapy initiation for patients with nonvalvular atrial fibrillation.



Calculate a patient's stroke risk and renal function and evaluate bleed risk factors.

Resources

- American Heart Association http://www.americanheart.org
- Thrombophillia Support http://www.fvleiden.org
- Chest – Evidence Based Guidelines for A-Fib 2018 https://journal.chestnet.org/article/S0012-3692(18)32244-X/fulltext
- National Blood Clot Alliance http://www.stoptheclot.org/
- http://www.outcomes-umassmed.org/dvt/best_practice/
- ACC guidelines http://content.onlinejacc.org/article.aspx?articleid=1854230
- Coumadin Rap https://www.youtube.com/watch?v=Mfk05IFfW48

Medscape links

- **Coagulation Disorders**

  Factor VIII disorders

  Factor IX disorders

  Factor XI disorders

  Thrombocytopenia

  - *Idiopathic thrombocytopenic purpura*
  - *Thrombotic thrombocytopenic purpura*
  - *Von Willebrand's disease,*

- *Thrombocytosis*
- *Factor V Leiden*