

### Stages of Hemostasis

<b>1. Vessel Spasm</b>	Response to inflammation. Initiated by endothelial injury. Reflex vessel restriction by the smooth muscle layer reducing blood flow. Only last 1 minute. Thromboxane A2 released from platelets contribute to vasoconstriction. This happens locally at the site of the injury
<b>2. Formation of Platelet Plug</b>	Platelets are attracted to damaged vessel wall by the release of von willebrand factor. Once they encounter vWF they activate and change from disk shaped to star shaped then flat sphere like shaped. Then they adhere to collagen and aggregation occurs. Aggregation is mediated by the release of granules- ADP and TXA2 (more of these = more aggregation). Glycoprotein IIb and IIIa receptors bind fibrinogen and link platelets together. This leads to the platelet plug formation.
<b>3. Blood Coagulation</b>	Results in conversion of inactive soluble fibrinogen to insoluble fibrin. <i>Vitamin K</i> is necessary for synthesis of factors <b>VII, IX, X, prothrombin, protein C</b> . <i>Calcium</i> is required by activated factor <b>X</b> to convert prothrombin to thrombin. Involves intrinsic, extrinsic and common pathway. Regulated by natural anticoagulants (Antithrombin II, Protein C-inactivates factor V and VIII, plasmin-breaks down fibrin).
<b>4. Clot Retraction</b>	Serum is squeezed out of the clot and the edges of the vessels are joined. Failure of clot retraction is indicative of low platelet count.
<b>5. Clot Dissolution</b>	Needed for permanent tissue repair. Process known as fibrinolysis (getting rid of clot). Plasmin digests fibrin, factors V, VIII, XII, prothrombin. Plasminogen is activated to plasmin by enzymes (one is factor XII or Hageman factor).

These 5 stages are the holy grail of wound healing.

vWF is produced by endothelial cells, platelets and connective tissue. disorder?

### Hemostasis

**Definition:** The process which causes the bleeding to stop. Maintains blood fluidity and prevents blood from leaving the vascular compartments

**Main Factors:** 1. Cell membrane  
2. Platelets 3. Coagulation cascade

*Abnormal function of hemostasis:* thrombosis (inappropriate clotting) or bleeding/hemorrhaging \*insufficient clotting)

### Coagulation Cascade

### Blood Testing for Coagulability (cont)

**PTT-** Tests *intrinsic*  
**Partial thromboplastin time** pathway. Used to monitor *heparin*.  
Normal range is 30-50 seconds.

### Hypercoagulability (increased platelet function)

Hypercoagulability results in platelet adhesion and formation of clots which leads to disruption of blood flow.

### Increased Clotting Activity

### Increased Clotting Activity (cont)

**Secondary:** *Acquired*. Stasis due to bed rest (slows normal blood flow and allows accumulation of clotting factors)cancer, birth control, smoking and obesity, MI.

**Antiphospholipid Syndrome:** AKA Hughes syndrome. Autoimmune hypercoagulable state caused by antiphospholipid antibodies. Provokes blood clots in arteries in veins. Can be primary or secondary (due to lupus).

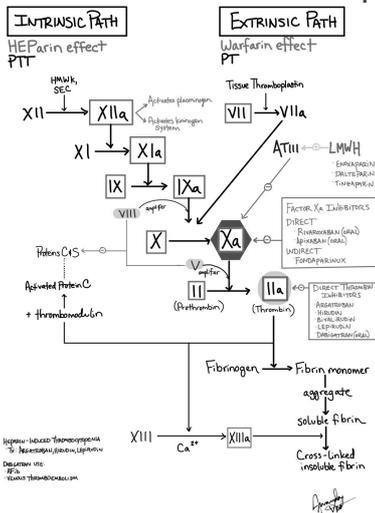
### Bleeding Disorders

### Bleeding Disorders (cont)

**Thrombocytopenia:** Low circulating platelets. Due to decreased production by bone marrow (aplastic anemia, leukemia, HIV) or increased pooling of platelets in the spleen, or decreased platelet survival or nutritional deficiencies (B12, iron, folic acid),

Types: idiopathic, thrombotic or hemolytic uremia syndromes or heparin induced.

**Decreased platelet function:** Caused by aspirin, uremia (increased urea in blood coats the platelets causing glycoproteins not to function) or genetic disorders



**Primary:** *Genetics.* Mutations in factor V and prothrombin genes. Results in inability of factor Va to be deactivated by protein C. Examples: Factor V Leiden disorder where clotting persists and predisposes to DVT. Other disorders are inherited deficiencies of antithrombin III, protein C/S.

**Platelet** normal range:  
**Disorders:** 150,000- 400,000/ml. Signs of disorders include:  
 Petechia, purpura, ecchymosis, bleeding from mucous membrane

**Blood Testing for Coagulability**

**PT-** Tests *extrinsic* and *common* pathway.  
**Prothrombin time** Looking at time to clot. Used to monitor *warfarin*. Normal is 11-13 seconds. PT is increased with warfarin



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### Bleeding Disorders (cont)

Genetic disorders:  
Bernard Soulier-  
GpIIb disorder so  
vWf has nowhere  
to bind, Von  
Willebrand  
Disease-no vWF to  
bind platelets.  
Leads to decreased  
platelet adhesion  
\*Vasopressin can  
stimulate release of  
vWF for tx.  
Glanzmann  
thrombocytopenia-  
GpIIb-IIIa so  
platelets cant bind  
together

**Coagulation Cascade Disorders:** Deficiencies or impairments of one or more coagulation factors due to defective synthesis, inherited disease or increased consumption. Prevents fibrinogen from converting to fibrin. Will see bleeding in deep tissues like hematomas. Elevated PTT and PT.

### Bleeding Disorders (cont)

Hemophilia A- Factor VIII deficiency: X-linked recessive disorder, affects mostly males. Soft tissue bleeding of GI, hip, knee, elbow and ankle joints. Can lead to joint fibrosis and contractures. Tx is factor VIII replacement therapy. Only affects intrinsic pathway.

### Anticoagulants

**Warfarin (Coumadin):** Vitamin K antagonist. Blocks epoxidase reductase, leads to depletion of reduced vit K (which is essential for synthese of factors II, VII, IX, X, protein c/s)  
Uses: Prevention of thrombosis in predisposed patients. AE- bleeding

### Anticoagulants (cont)

**Heparin (IV)/ LMW Heparin (lovenox):** Induces a conformational change in antithrombin III making it more accessible to proteases -> increase inactivation of thrombin

Uses: Prophylaxis and tx of thromboembolic diseases, unfractionated (IV heparin) used with antiplatelet agents for tx of acute coronary syndromes. Lovenox is an efficient cataly-zation of factor Xa inactivation.

AE: bleeding and heparin induced thrombocytopenia

### Novel Oral Anticoagulants

**Apixaban (Eliquis), Rivaroxaban (Xarelto):** Direct inhibitor of free and clot-bound factor Xa which prevents the conversion of prothrombin to thrombin. Prevents clot formation.

### Novel Oral Anticoagulants (cont)

Uses: A- reduces stroke and systemic embolism, prophylaxis of DVT/PE after hip or knee surgery. R- same but prophylaxis of venous thromboembolic events for hip/knee surgery pts.

AE: easy bruising, bleeding, back or muscle pain, hypotension.

**Dabigatran (Pradaxa):** Direct thrombin inhibitor which prevents conversion of fibrinogen to fibrin.

Uses: Prevents thromboembolism in pts with AF, DVT, PE

**Betrixaban (Bevyxxa):** Cofactor-independent direct inhibitor of factor Xa.

Uses: prophylaxis of VTE in moderate to severe restricted mobility patients.

*Rivaroxaban interacts with Aspirin.  
All drugs will have bleeding as a side effect!*



Inhibition of Anticoagulation	Antiplatelet Agents	Antiplatelet Agents (cont)	Antiplatelet Agents (cont)
<p><b>Protamine:</b> Antagonist of heparin.</p> <p><i>Uses:</i> IV administration if there is life threatening hemorrhage/heparin excess</p>	<p><b>Aspirin (ASA)</b> Non selective COX inhibitor. Irreversible inhibition of COX-1= inhibits platelet aggregation for 10 days. Stops conversion of arachidonic acid to thromboxane A2 (potent platelet aggregation inducer).</p> <p><i>Uses:</i> Pain/inflammation/fever, reduces risk of MI/unstable angina, prevents strokes due to blood clots</p> <p><i>AE:</i> hemorrhagic stroke, GI bleeding</p>	<p><i>Uses:</i> Intermittent claudication symptoms (by widening the vessels in teh legs which helps with blood flow).</p> <p><i>AE, DI:</i> heart failure, tachycardia, interacts with NSAIDs and aspirin.</p>	<p><i>Uses:</i> reduces risk of MI/stroke, better than aspirin in decreasing CV outcomes</p> <p><i>AE, DI:</i> upper RTI, joint, chest pain, depression, bleeding. DI- Ibuprofen</p>
Thrombolytic Agents	PDE Inhibitors	ADP Receptor Pathway Inhibitor	GPIIb-IIIa Antagonist
<p><b>Streptokinase:</b> Forms a stable complex with plasminogen which then cleaves other plasminogen molecules into plasmin</p> <p><i>Uses:</i> PE, STEMI, arterial thrombosis, DVT. <i>AE:</i> systemic fibrinolysis, hemorrhage</p>	<p><b>Cilostazol (Pletal)</b> Antiplatelet and vasodilator. Inhibitors phosphodiesterase II -&gt; suppresses cAMP degradation -&gt; increases cAMP in platelets and blood vessels -&gt; inhibition of platelet aggregation and vasodilation</p>	<p><b>ADP Receptor Pathway Inhibitor</b></p> <p><b>Clopidogrel (Plavix)</b> Irreversibly binds to P2Y12 which prevents the binding of ADP receptors on platelets which prevents GPIIb-IIIa activation -&gt; inhibits platelets aggregation</p>	<p><b>Abicixmab (Reopro)</b> Binds to intact platelet GPIIb/IIIa receptor and blocks access of large molecules to receptor through steric hinderance or conformational change. Prevents cell adhesion</p> <p><i>Uses:</i> prevents cardiac ischemic complications in vascular surgeries or pts w/ unstable angina, intended for use with aspirin and heparin</p> <p><i>AE:</i> N&amp;V, hypotension, vision changes, back pain</p>
<p><b>Recombinant Tissue Plasminogen Activator:</b> Binds to newly formed thrombi and makes it a potent activator of plasminogen. Cleaves plasminogen into plasmin which then cleaves fibrin into fibrin degradation products</p> <p><i>Uses:</i> PE,STEMI, Acute ischemia stroke. <i>AE:</i> bleeding</p>			

