Day Five: Von Willebrand Disease and Fibrinonolysis

Von Willebrand Disease

- Most common inherited bleeding disorder.

    - Incidence 1.3 / 100 to 1 /33,000

    - Could be low estimate since some cases are undiagnosed since they are so mild.

- Von Willebrand disease is due to either quantitative or qualitative deficiencies of the Von Willebrand factor

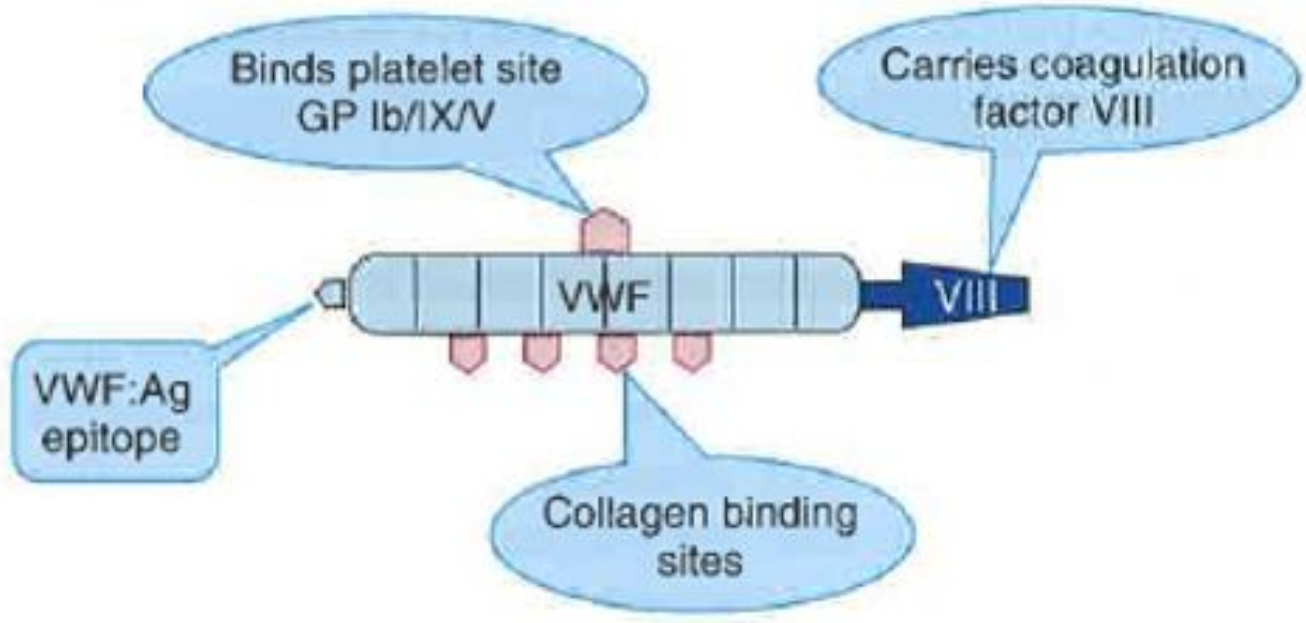
-Von Willebrand Factor

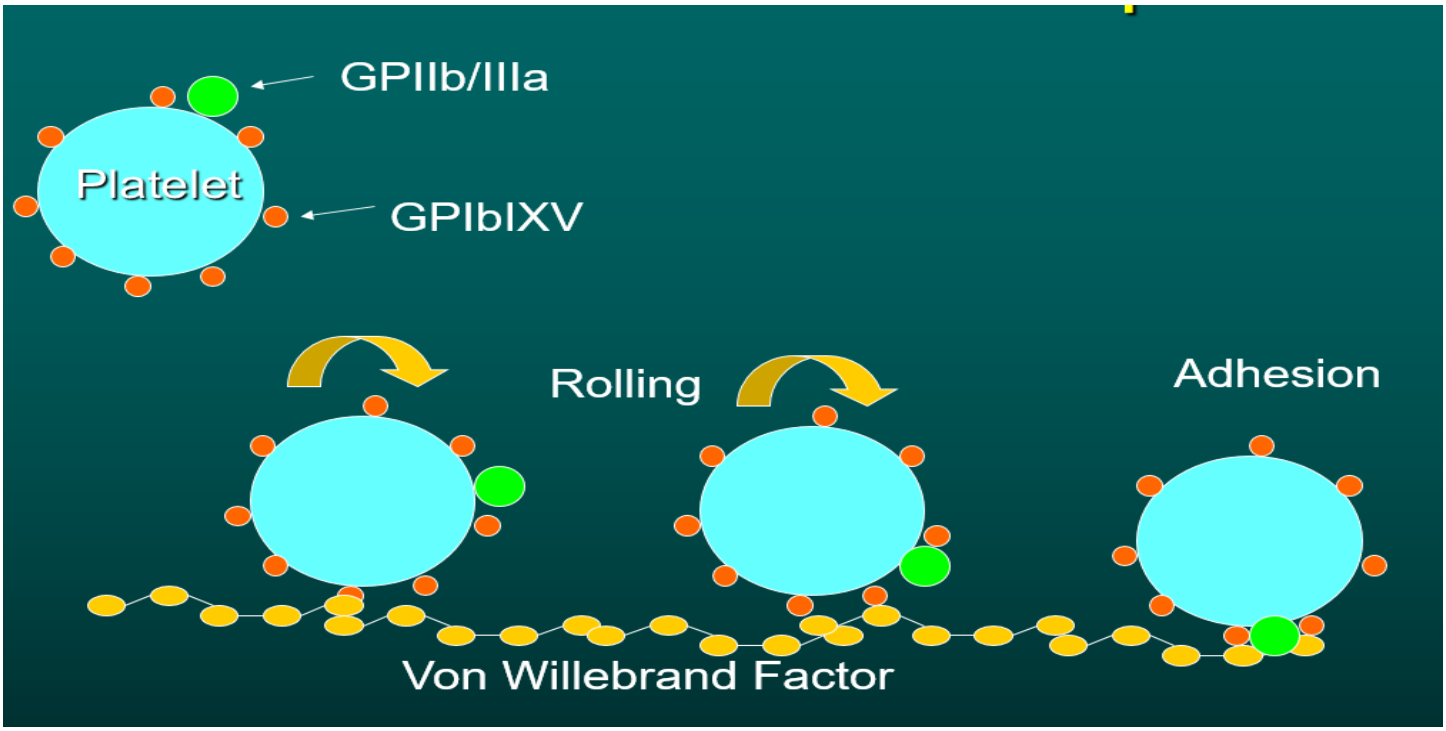
- VWF mediates the adhesion of platelets to injured endothelium in situations of high shear stress. It accomplishes this by binding to glycoprotein Ibα [GPIbα] on the platelet surface and the sub-endothelium. → Acts as a "glue"
- VWF is the protective carrier of fVIII [cascade] → Two values correspond
- VWF is a globular protein synthesized in the endothelial cells and megakaryocytes.

Lab tests:

Platelet Count: normal (except ↓ in 2B and 2M)
Bleeding Time/Platelet Function Screen: ↑ (bleeding time is no longer utilized testing)
aPTT: slightly ↑
VWF Ag: ↓ (except normal in 2M and 2N)
    - Measured by immunoassay
Ristocetin cofactor: ↓ (normal in 2N)
    -Assay that measures binding of VWF to GPIb. This is mediated by ristocetin and reagent platelets. Ristocetin should induce platelet plug formation
Collagen Binding Assay: ↓ (normal in 2N)
Ristocetin Dose Response: ↓ (normal in 2N)
FVIII: normal to ↓ (severely decreased in type 2N)

TREATMENT: sometimes transfusion (more severe cases), Desmopressin acetate (DDAVP)
    -Desmopression acetate used as antidiuretic hormone in diabetes mellitus, side effect is release of VWF from storage organelles





There are several types of VWF disorders. There are three main groups 1, 2, 3.

- **Type 1** is a **quantitative** disorder with an accompanying decrease of FVIII, VWF amount and activity. [70%-80%]

  Range asymptomatic to severe. Most detected by problems after surgery or menorrhagia

  Failure to secrete or cleared more quickly than normal

- **Type 2** VWF **qualitative** deficiencies with functional abnormalities. [20%-30%]

  2A: Mutation impaired ability to coalesce and form large VWF leads to Increased VWF degradation of HMW multimers ↓ & low ristocetin cofactor [10% - 15%]

  2B: Mutations leads to increased binding of VWF to GPIb "Gain of function"
  [Platelets coated with VWF are cleared at an increased rate leading to loss of HMW + ↓ PLT]
  If the GPIa is defective it is call platelet-type or pseudo VonWillebrand [<5%]

  2M: Decreased functionality with normal multimers. Impaired ability to bind PLT receptor

  2N: Mutation in the FVIII binding site with the half-life of fVIII shortened [Normandy]

- **Type 3:** Severe with **undetectable** VWF, FVIII, & Ristocetin activity
  Autosomal recessive

HMW multimers have more hemostatic function than LMW multimers, due to the increased number of subunits and binding sites per multimers in the HMW forms

	Normal	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3	PLT-vWD
vWF:Ag	N	↓/↓↓	↓	↓	↓	N/↓	absent	↓
vWF:Rco	N	↓/↓↓	↓↓/↓↓↓	↓↓	↓↓	N/↓	absent	↓↓
FVIII	N	N/ ↓	N/ ↓	N/ ↓	N/ ↓	↓↓	1-9 IU/dl	N/↓
RIPA	N	often N	↓	often N	↓	N	absent	often N
PFA-100® CT	N	N/↑	↑	↑	↑	N	↑↑↑	↑
BT	N	N/↑	↑	↑	↑	N	↑↑↑	↑
Pl-Count	N	N	N	↓/N	N	N	N	↓
vWF multimers	N	N	abnormal	abnormal	N*	N*	absent	abnormal
								

Bernard-Soulier Syndrome

- Rare autosomal recessive bleeding disorder

- Missing the other part of the chain

- Missing or abnormal GPIb/IX/V receptor, results in abnormal adhesion

- Heterozygous: near normal

- Homozygous: moderate to severe bleeding and results in thrombocytopenia with giant platelets on peripheral smear

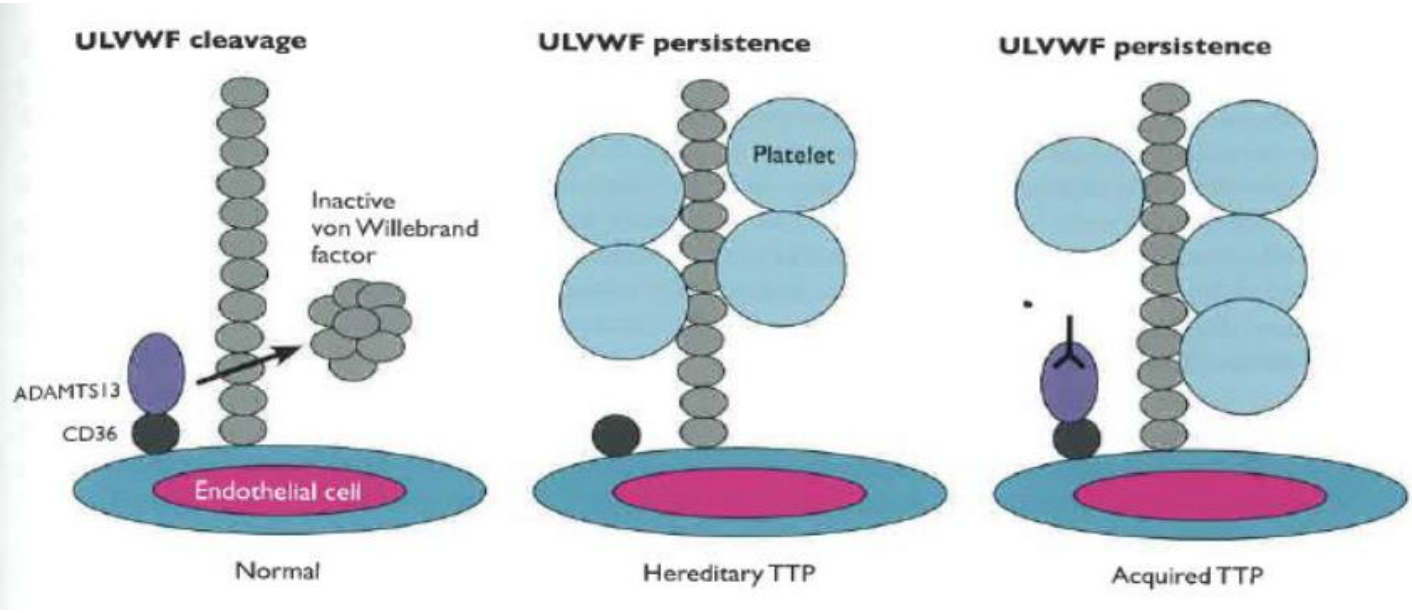
Platelet Count: ↓ 40 to 100 k

Platelet MCV: ↑ (Giant Platelet Syndrome)

Bleeding Time: ↑

Ristocetin Dose Response: ↓

TREATMENT: Transfusions, Recombinant FVII

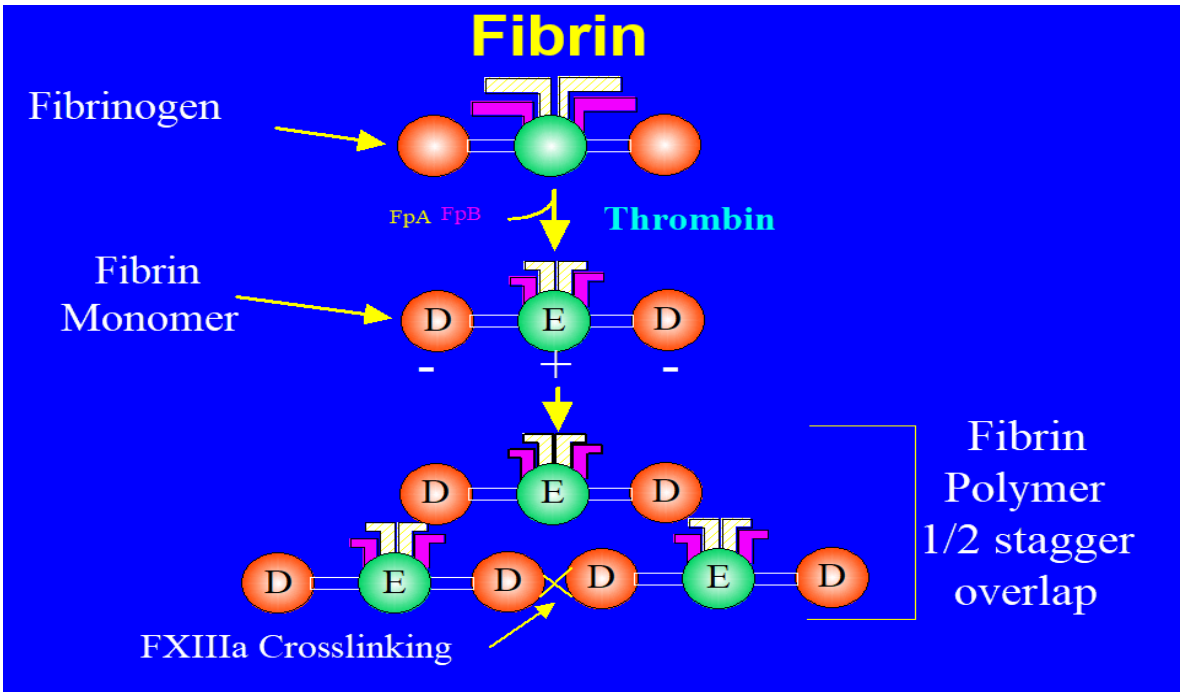


Thrombotic Thrombocytopenia Purpura (TTP)

Categorized as a platelet disorder

- Thrombotic: tendency to clot
- Platelet thrombi are dispersed throughout arterioles and capillaries subsequent to accumulation of large VWF multimers
- Larger VWF multimers have increased binding sites for platelets.
- ADAMTS-13: enzyme responsible for cleaving larger VWF multimers into smaller ones

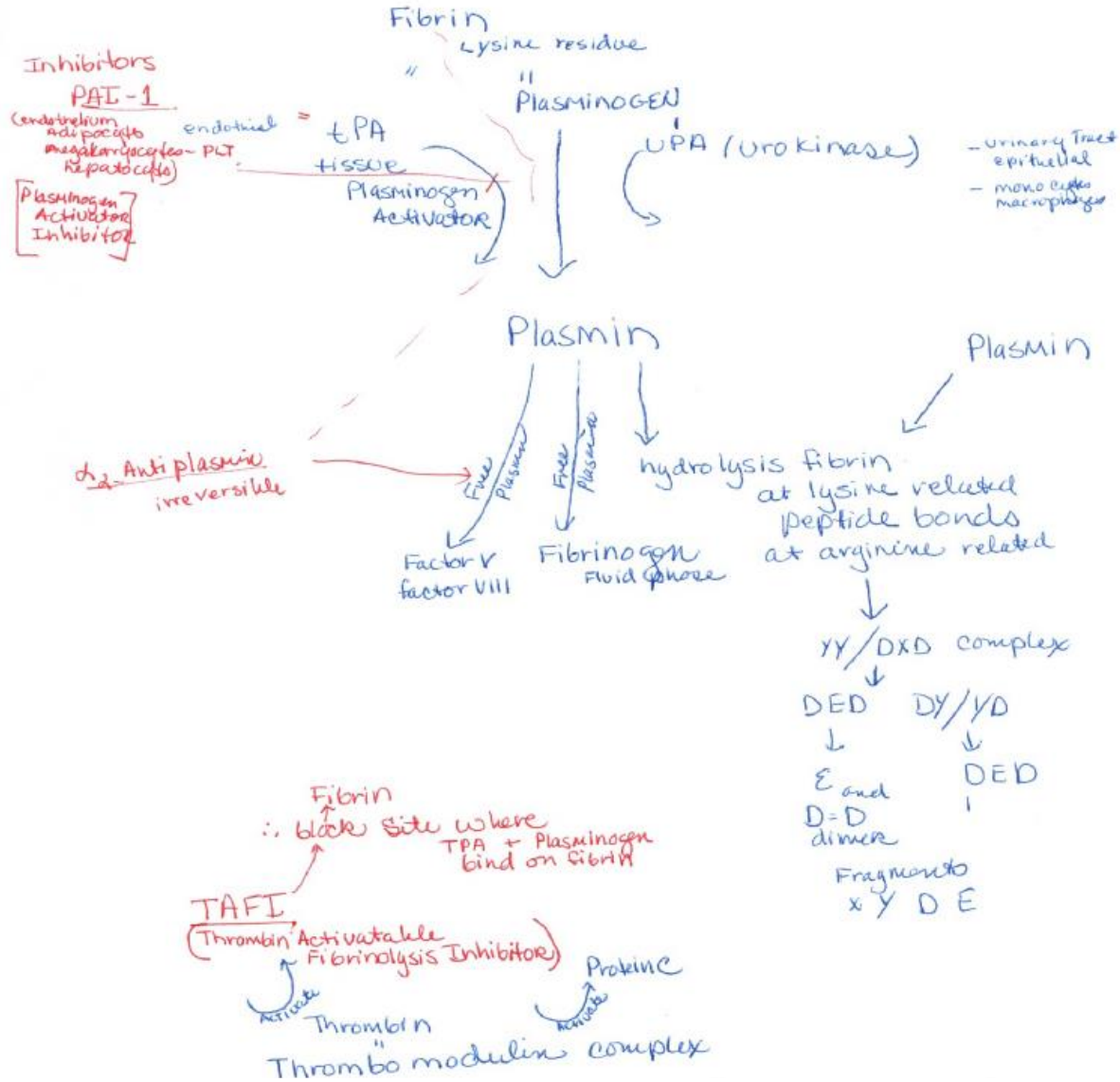
Fibrinolysis



- Fibrinolysis is mediated by plasmin, which degrades fibrin clots into Ddimers and fibrin degradation products (FDP).
- Plasmin can also degrade intact fibrinogen, generating fibrinogen degradation products (FDP) that are detected in FDP assays.

• Patient plasma is mixed with latex particles which are coated with monoclonal anti-FDP antibodies.
• If FDP are present in the patient plasma, the latex particles agglutinate as FDP bind to the antibodies on the particles. these large agglutinated clumps are detected visually by the technologist.
• Various dilutions of patient plasma can be tested to provide an estimation of the FDP titer (semiquantitative result).
• D-dimer is a *specific FDP* that is formed only by plasmin degradation of fibrin, and not by plasmin degradation of intact fibrinogen - can be reliably quantitated

Fragment X = D-E-D
Fragment Y = D-E
D-Dimer = D-D from two separte monomers cross linked by XIIIa


Fibrin
Lysine residue
Plasminogen
Inhibitors
PAI-1
(endothelium adipocytes megakaryocytes PLT Hepatocytes)
Plasminogen Activator Inhibitor
endothelial
tPA
tissue Plasminogen Activator
UPA (Urokinase)
- Urinary Tract epithelial
- mono cytes macrophages
Plasmin
Plasmin
α2- Anti plasmin
irreversible
Free Plasmin
Free Plasmin
hydrolysis fibrin at lysine related peptide bonds at arginine related
Factor V
factor VIII
Fibrinogen
Fluid phase
YY/DXD complex
DED
DY/YD
DED
E and D-D dimer
Fragments
x Y D E
Fibrin
∴ block Site where TPA + Plasminogen bind on fibrin
TAFI
(Thrombin Activatable Fibrinolysis Inhibitor)
Activated
Thrombin
Thrombo modulin complex
Activated
Prokine