# To bleed or not to bleed…

Physiology of primary hemostasis

and

Approach to the patient with a bleeding diathesis

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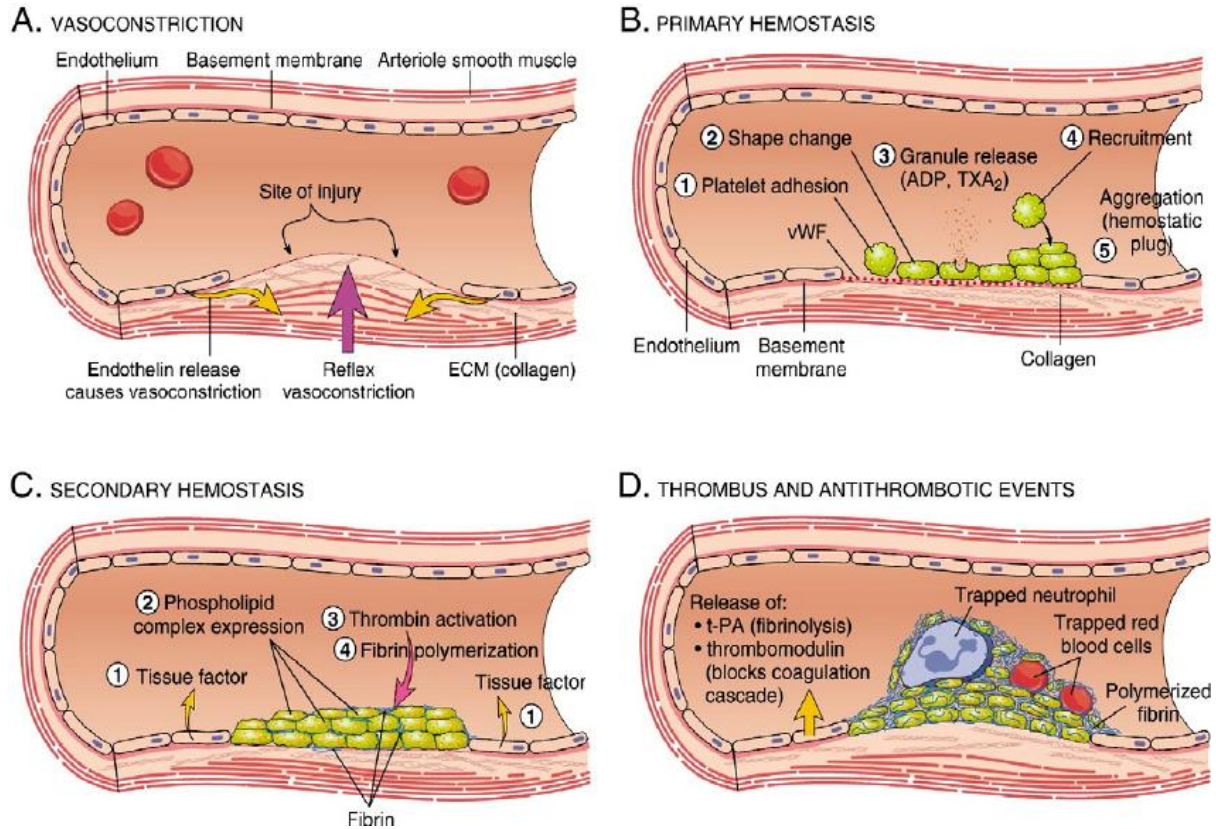
# Physiology of primary hemostasis

# Formation of the platelet plug

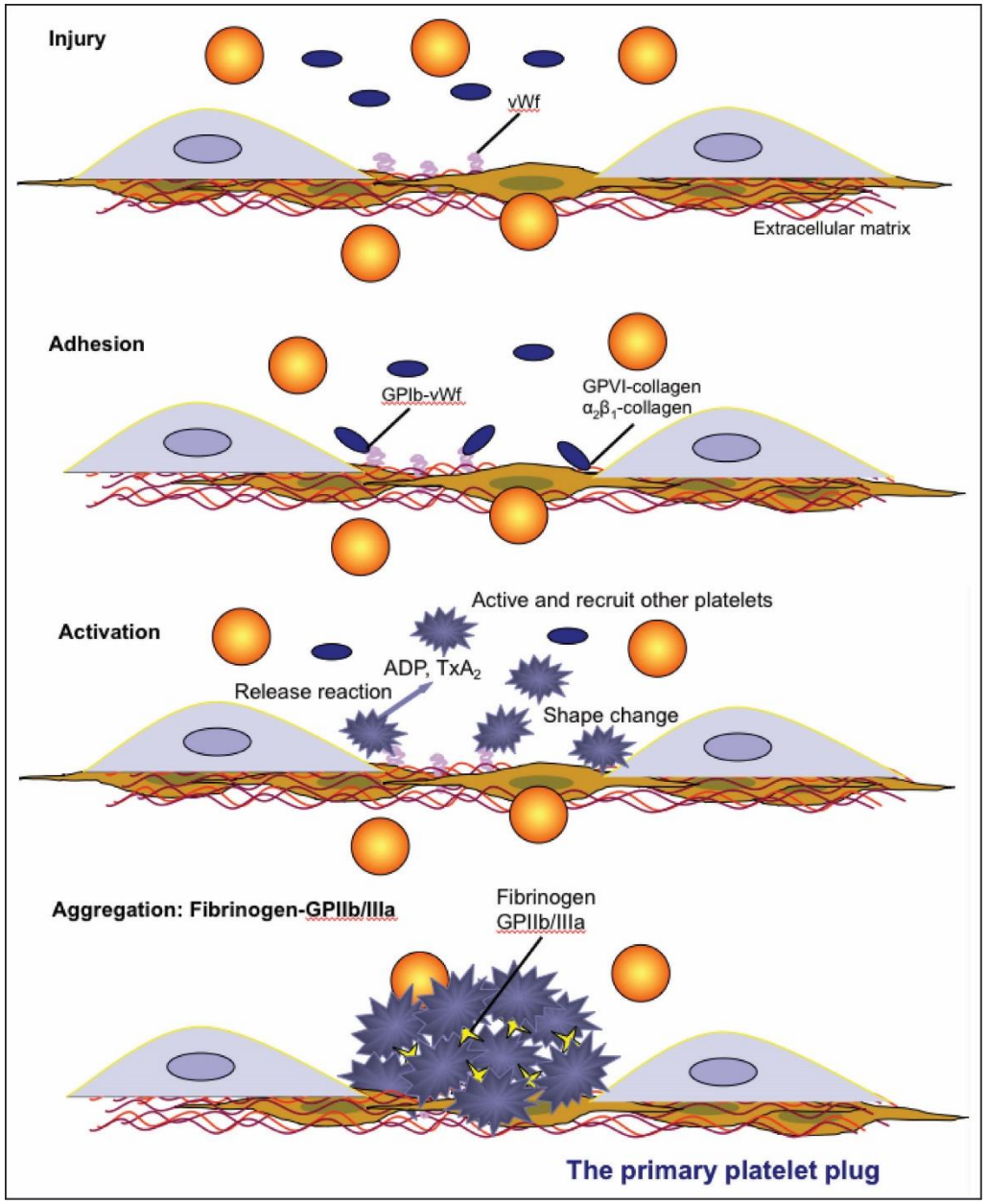
- Intact endothelium prevents adherence of PLt by the production of NO and prostacyclin
- Injury of endothelium-> exposure of subendothelial elements ( collagen, microfibrils…)
- **4 major phases leading to platelet plug**
- Adhesion : deposition on the subendothelial matrix
- Aggregation: platelet to platelet cohesion
- Secretion: release of platelet granule proteins
- Procoagulant activity: enhancement of thrombin generation


A. VASOCONSTRICTION
Endothelium
Basement membrane
Arteriole smooth muscle
Site of injury
Endothelin release causes vasoconstriction
Reflex vasoconstriction
ECM (collagen)
B. PRIMARY HEMOSTASIS
2 Shape change
3 Granule release (ADP, TXA2)
4 Recruitment
1 Platelet adhesion
vWF
Aggregation (hemostatic plug)
5
Endothelium
Basement membrane
Collagen
C. SECONDARY HEMOSTASIS
2 Phospholipid complex expression
3 Thrombin activation
4 Fibrin polymerization
1 Tissue factor
Tissue factor
1
Fibrin
D. THROMBUS AND ANTITHROMBOTIC EVENTS
Release of:
• t-PA (fibrinolysis)
• thrombomodulin (blocks coagulation cascade)
Trapped neutrophil
Trapped red blood cells
Polymerized fibrin

# Platelet activation

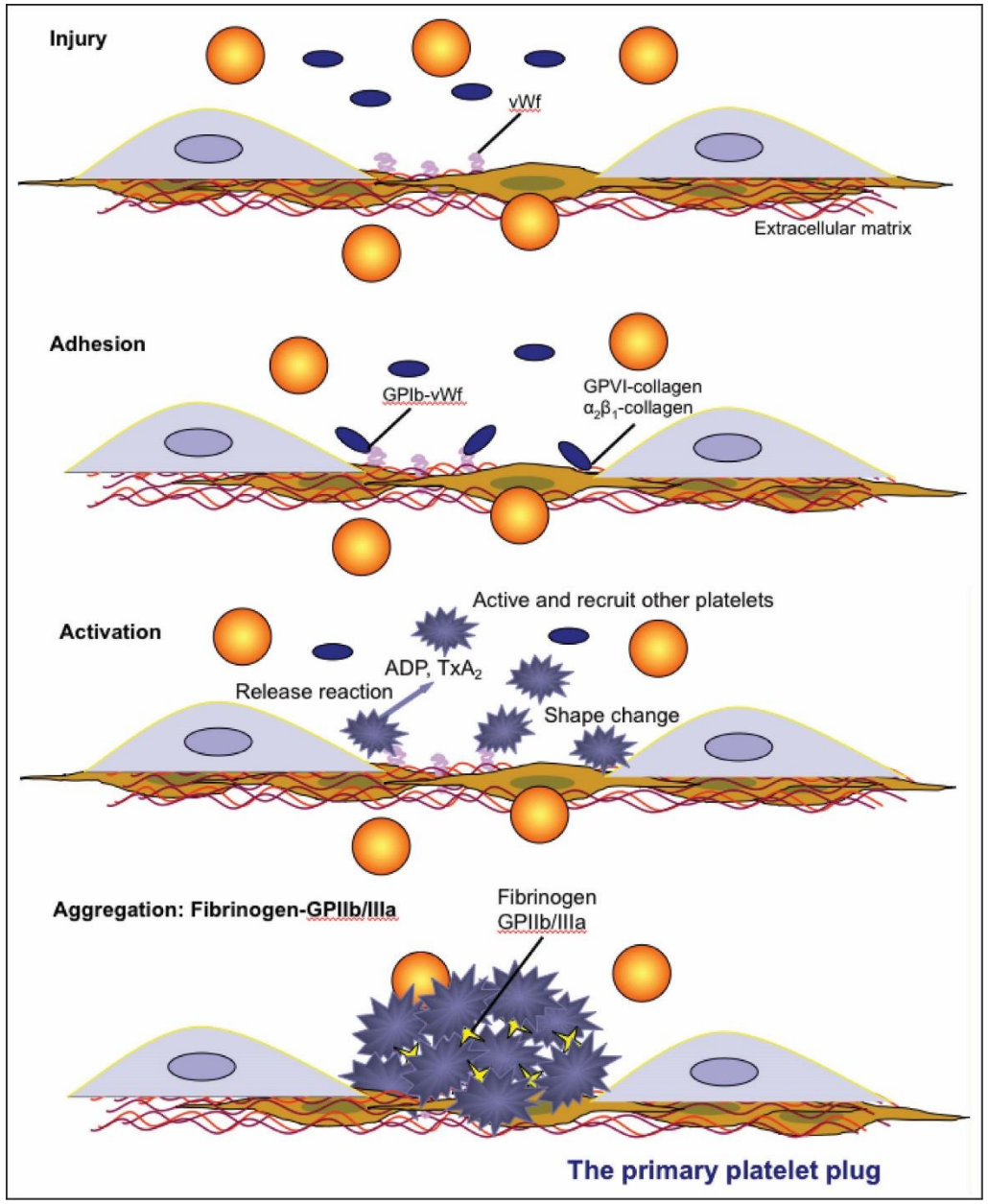
- Physiologic platelet activators: ADP epinephrin thrombin and collagen

- Collagen: GPIa/IIa ( adhesion) and GPVI ( activation)
- Thrombin: mediated by protease activated receptors ( PAR 1 high affinity, PAR-4 low affinity)
- ADP: binds to $P2Y_1$ (calcium mobilization PLT shape change rapidly reversible aggregation )and $P2Y_{12}$ (Plt secretion and more stable aggregation)



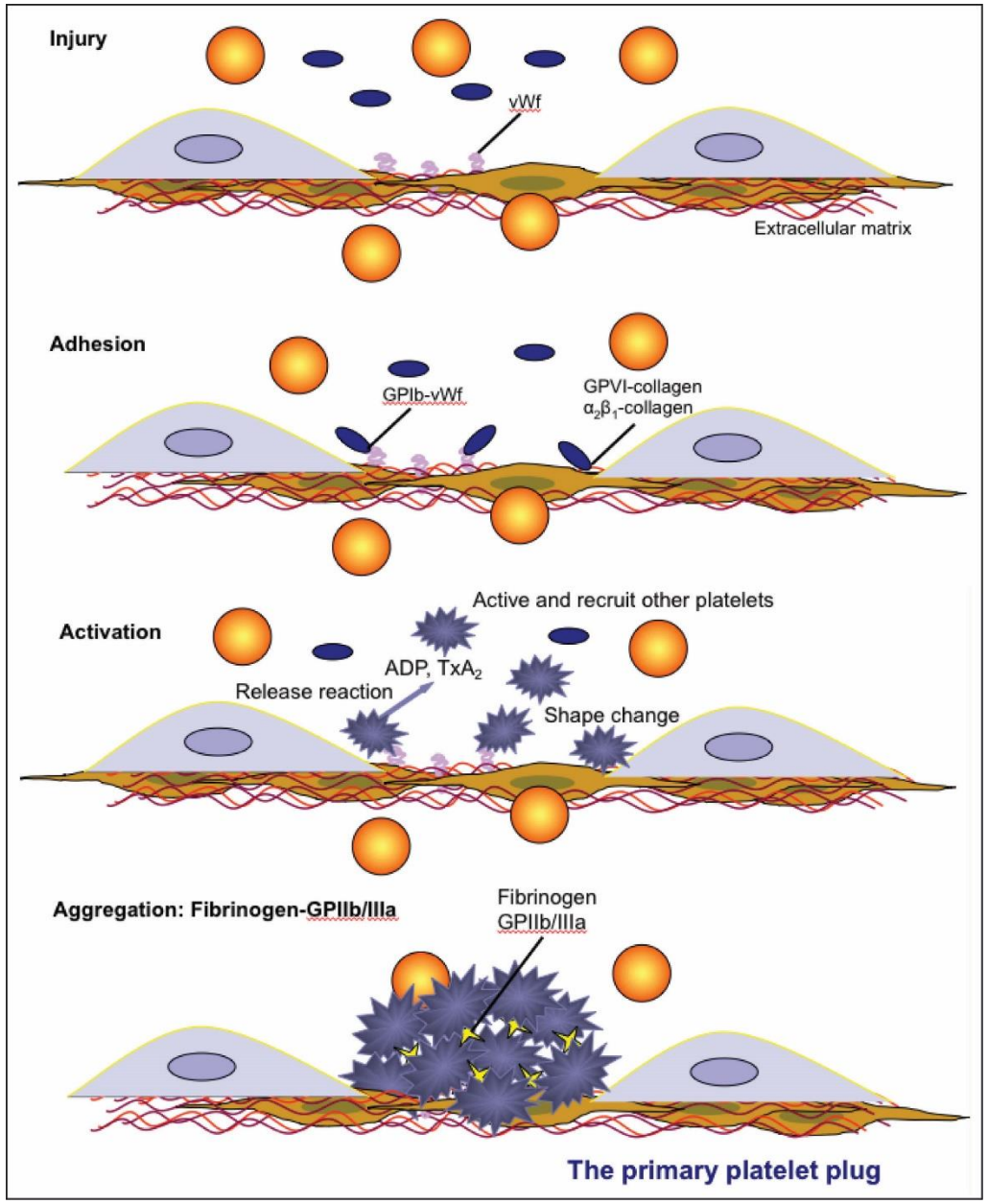
# Platelet adhesion

- Activation-> shape changes
- Binding of GPIb/IX/V complex to VWF in the subendothelial matrix
- Binding of GPIa/IIa to the collagen fibrils



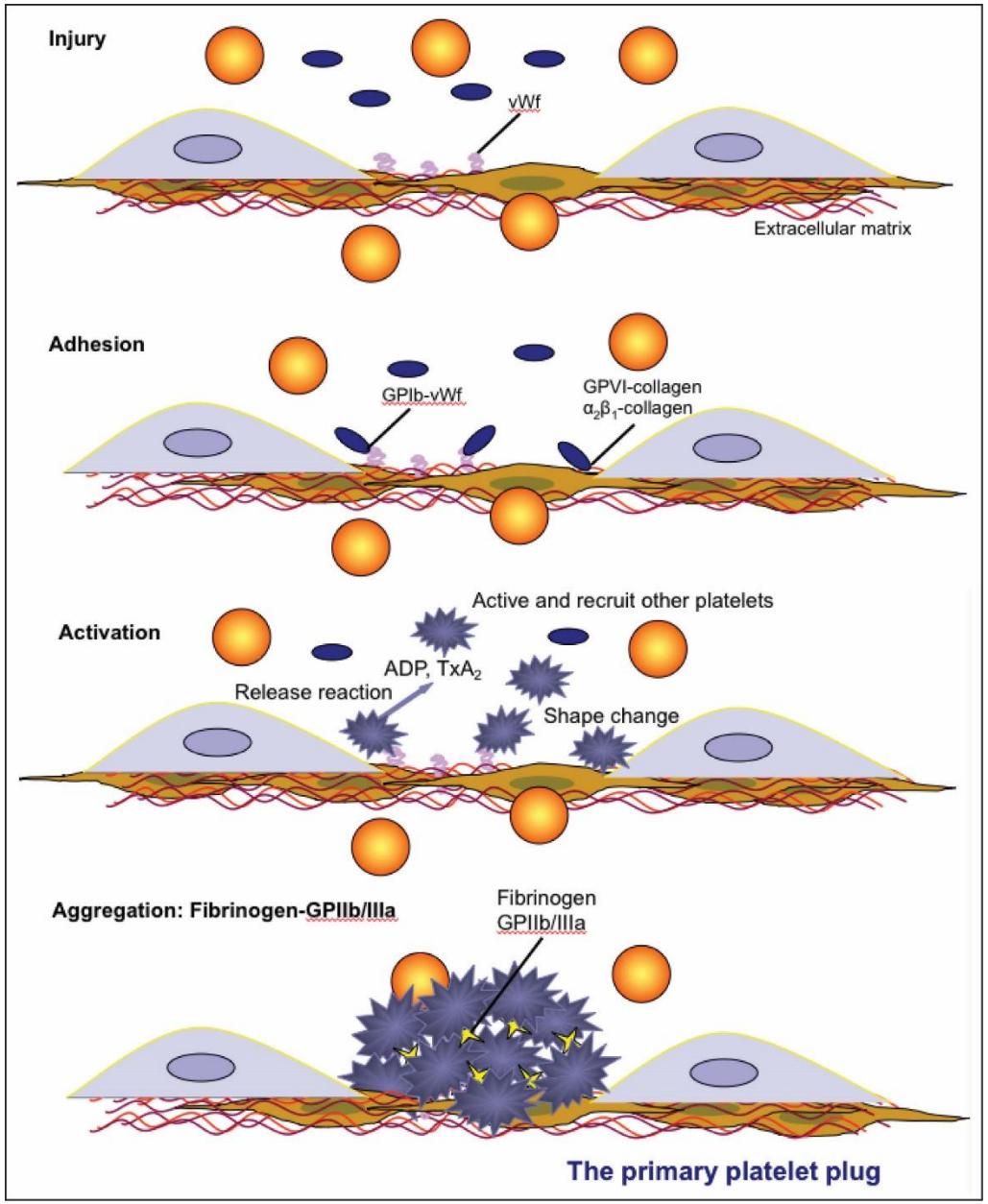
# Platelet aggregation

- Activation: exposure and conformational changes of GPIIb/IIIa
- Binding of VWF and fibrinogen



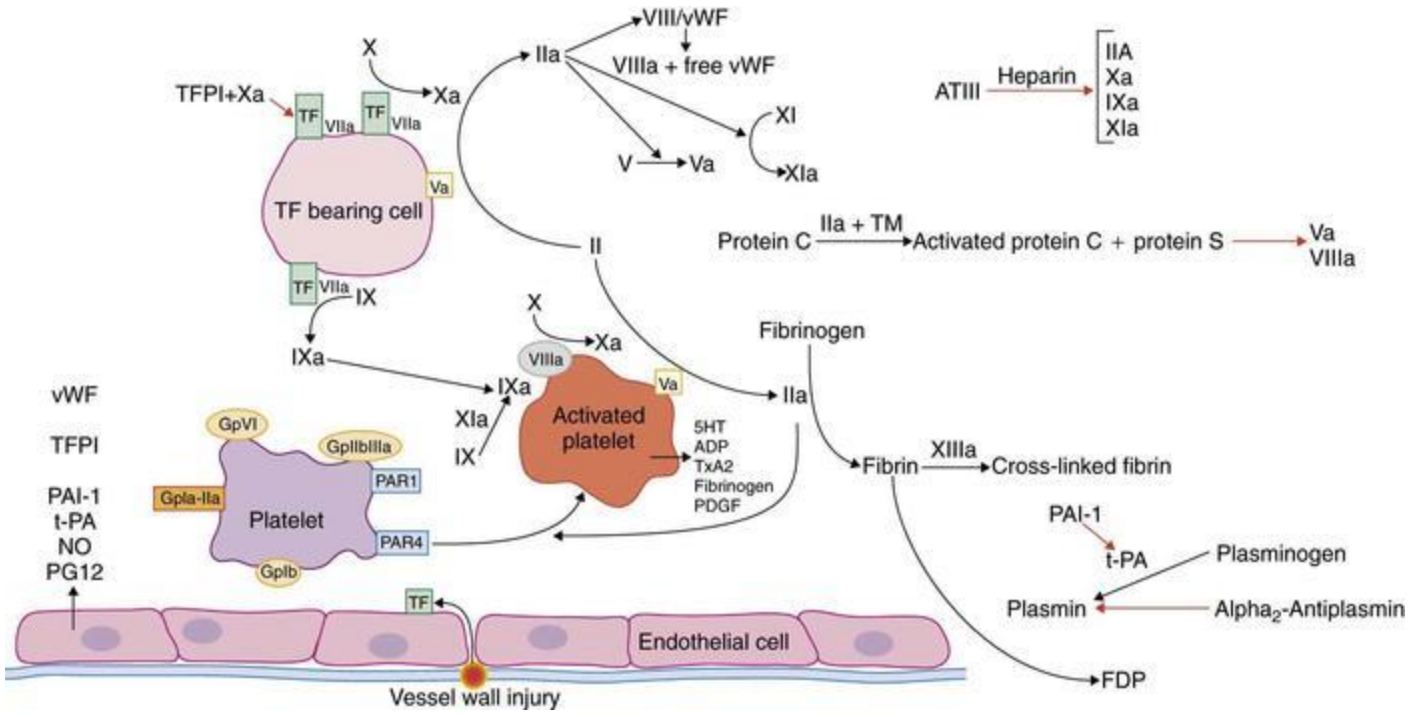
# Platelet secretion

- Alpha  granules : fibrinogen VWF thrombospondin PDGF Platelet factor 4 and P-Selectin
- Dense granules: ADP ATP ionized calcium histamin and serotonin
- -> recruitement of other PLT, promotion of adhesion and aggregation



# Platelet procoagulant activity

- Exposure of procoagulant phospholipids
- Assembly of the enzyme complexes in the clotting cascade



# Approach to the patient with a (so-called) bleeding diathesis

# Careful history

- Emotions vs facts
- Patients with inherited haemostatic problems may report little bleeding tendency Vs others with no inherited or acquired bleeding diathesis who may report exaggerated tendencies
- Clues that provide rationale approach to laboratory investigation
- Standardized bleeding assessment tool?

# Bleeding history (1)

- Past bleeding problems
- History of iron responsive anemia
- Bleeding outcomes after surgical procedure or tooth extraction
- History of transfusion
- Heavy menses
- Dietary habits or antibiotics ( Vitamin K deficiency)
- Thyroid? Liver? Kidney disease?
- Response to trauma
- Hematuria, melena,menorrhagia…

# Bleeding history (2)

- Onset of symptoms?
- What about family history?
- Consistent genetic pattern?
- A negative family history does not exclude an inherited coagulation disorder! 30 to 40% Pt with hemophilia A have a negative family history

# Bleeding history (3)

- Medications:
- Prescribed
- Over the counter
- Plants!
- Combinations!
- Aspirin alone: 3,2 (hospitalisation for bleeding/100pt/year)
- Warfarin alone 5,9
- Aspirin+ warfarin 8,3
- Aspirin+clopidogrel 6,8
- SSRI

## Classes of medications and other substances associated with easy bruising

| |
|---|
| **Medications** |
| **Frequently seen causes** |
| Anticoagulants (eg, heparin, warfarin) |
| Nonsteroidal antiinflammatory drugs (eg, ibuprofen, naproxen) |
| Antiplatelet medications (eg, aspirin, clopidogrel) |
| Corticosteroids (eg, prednisone, hydrocortisone) |
| Antineoplastics – Multiple agents, primarily manifesting via decreased platelet production; also Bruton tyrosine kinase inhibitors, which may affect platelet function |
| **Other** |
| Antibiotics – Most broad-spectrum antibiotics, especially with long-term use |
| Antidepressants – SSRIs and SSNRIs* |
| Quinidine |
| **Other agents** |
| Alcohol |
| **Herbs and supplements** |
| Fish oil |
| Garlic |
| Gingko |
| Vitamin E |

SSRIs: Selective serotonin reuptake inhibitors; SSNRIs: selective serotonin norepinephrine reuptake inhibitors.
* Have been associated with bruising in observational reports but not randomized trials. Please refer to the UpToDate topic on easy bruising for a full discussion.

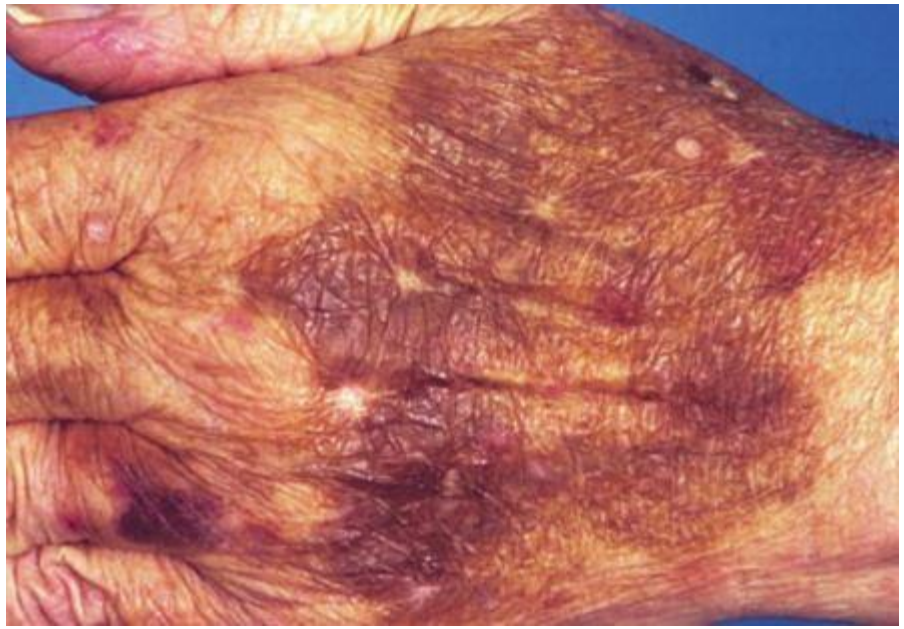
# Clinical manifestations

- Disorders of platelets and blood vessels: rather immediate than delayed
- Petechiae
- Ecchymoses
- Menorrhagia ( 15 to 20% have bleeding diathesis)
- « easy bruising »
- Coagulation disorders:
- large palpable ecchymoses
- Large spreading soft tissue hematomas
- Joints hemorrhages

# Easy bruising

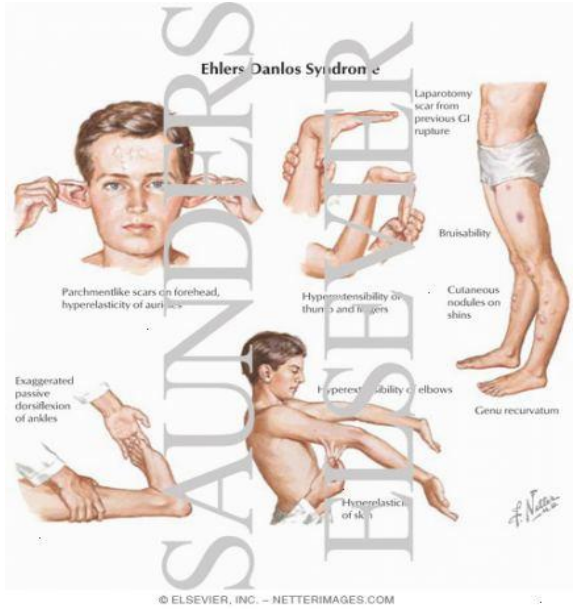
- Bruising with no history of trauma or bruising after minor trauma that would not have caused bruising in the past
- A bruise can result from abnormalities affecting:
- Blood vessels
- Surrounding skin and subcutaneous structures
- Platelet number and function
- Coagulation cascade function
- Frequent 12 to 55% of individuals
- Women>men
- Fair skinned,overweight,female !
- Abuse?
- Location and severity: distal extremities vs multiple areas of the body

# Skin ageing Bateman’s Purpura



# Ehlers Danlos syndrome

- Skin hyper extensibility
- Joint hyperlaxity
- Unusual scars
- Tissue fragility
- More than 7 differents types
- Rare genetic disorder of connective tissue



# Who and how to test

- No laboratory evaluation if:
- Distribution of bruising mainly among distality
- No other evidence of bleeding
- No personal or family history of previous bleeding

- Are Bleeding assessment tests still usefull?

# Bleeding assessment tools

- Detailed Vs condensed versions
- Very specific although less sensitive
- Useful for detecting mild bleeding disorders?
- High negative predictive value
- Adult vs paediatric BAT

# Bleeding assessment tools

- In very young patients the bleeding history may be negative due to lack of haemostatic challenges
- Always test a young patient with a positive family history even if personnal bleeding history is negative
- If bleeding score is elevated even if VWF levels are normal: test for alternate bleeding disorders

# Bleeding Score

Tosetto A,et al,2006

| | | | | | | |
|---|---|---|---|---|---|---|
| Menorrhagia | – | No | Consultation only | Antifibrinolytics, pill use | Dilatation and curettage, iron therapy | Blood transfusion or replacement therapy or desmopressin or Hysterectomy |
| Postpartum haemorrhage | No bleeding in at least two deliveries | No deliveries or no bleeding in one delivery | Consultation only | Dilatation & Curettage, Iron therapy, Antifibrinolytics | Blood transfusion or replacement therapy or desmopressin | Hysterectomy |
| Muscle haematomas | – | Never | Post-trauma no therapy | Spontaneous, no therapy | Spontaneous or traumatic, requiring desmopressin or replacement therapy | Spontaneous or traumatic, requiring Surgical intervention or blood transfusion |
| Haemarthrosis | – | Never | Post-trauma no therapy | Spontaneous, no therapy | Spontaneous or traumatic, requiring desmopressin or replacement therapy | Spontaneous or traumatic, requiring Surgical intervention or blood transfusion |
| CNS bleeding | – | Never | – | – | Subdural, any intervention | Intracerebral, any intervention |

*Positive BS (4 or more) has a sensitivity of 100% and a specificity of 87%.*

*The positive predictive value is 0.20 and the negative predictive value is 1.*

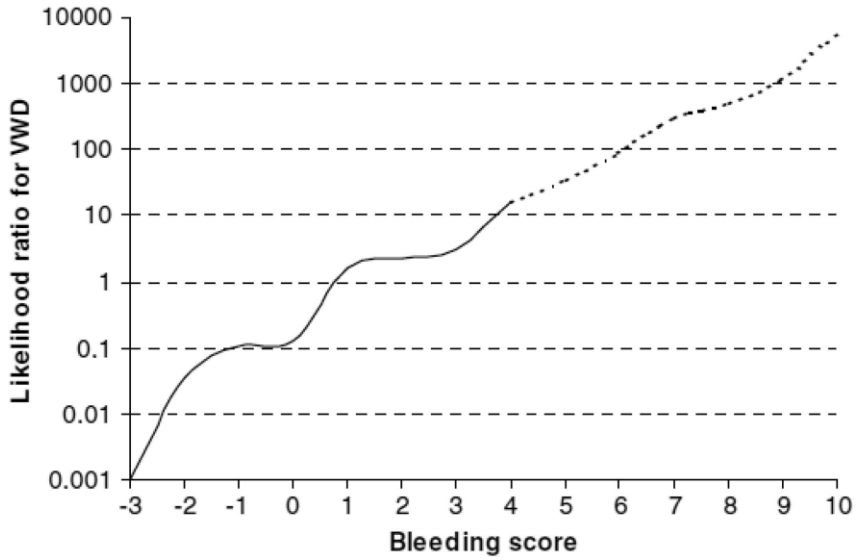
Diagnosis

# Bleeding Score

Tosetto A,et al,2006

| Symptom | −1 | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| Epistaxis | – | No or trivial (<5 episodes) | >5 episodes or >10′ duration | Consultation only | Packing or cauterization or antifibrinolytic | Blood transfusion or replacement therapy or desmopressin |
| Cutaneous | – | No or trivial (<1 cm) | >1 cm and no trauma | Consultation only | | |
| Bleeding from minor wounds | – | No or trivial (<5) | >5 or >5′ | Consultation only | Surgical haemostasis | Blood transfusion or replacement therapy or desmopressin |
| Oral cavity | – | No | Referred at least one | Consultation only | Surgical haemostasis or antifibrinolytic | Blood transfusion or replacement therapy or desmopressin |
| GI bleeding | – | No | Associated with ulcer, portal hypertension, haemorrhoids, angiodysplasia | Spontaneous | Surgical haemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytic | |
| Tooth extraction | No bleeding in at least two extractions | None performed or no bleeding in one extraction | Referred in <25% of all procedures | Referred in >25% of all procedures, no intervention | Resuturing or packing | Blood transfusion or replacement therapy or desmopressin |
| Surgery | No bleeding in at least two surgeries | None performed or no bleeding in one surgery | Referred in <25% of all surgeries | Referred in >25% of all procedures, no intervention | Surgical haemostasis or antifibrinolytic | Blood transfusion or replacement therapy or desmopressin |






Bleeding score >3

Likely to have haemostasis problems

Children 3

Males 4

Women 6

# How to test?

- CBC PTT aPTT
- VW
- PFA
- Platelet aggregation tests