Hemostasis & Transfusion medicine

R1 ชญานิศ/ อ.นวลวรรณ

Outlines

01 Hemostasis & Coagulation

02 Disorders of hemostasis

03 Anticoagulation & Pharmacological

04 Blood component transfusion

05 Blood Transfusion reactions

01 Hemostasis and coagulation

- Primary hemostasis
- Secondary hemostasis
- Fibrinolysis

Hemostasis

- Equilibrium between anticoagulation and coagulation is maintained by a complex system of counterbalanced blood proteins and cells.
- Primary hemostasis describes the initiation of the platelet plug and clotting mechanism.

Primary hemostasis

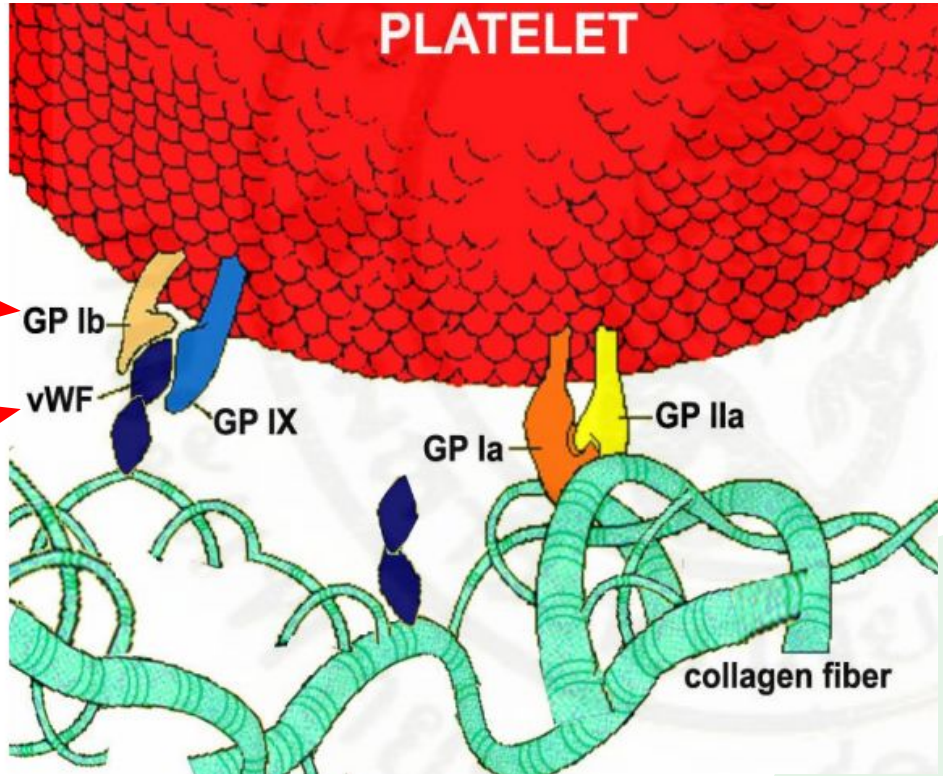
Secondary hemostasis

Primary hemostasis

Platelet adherences, Activations, Stabilization, Inhibition

Platelet adherence

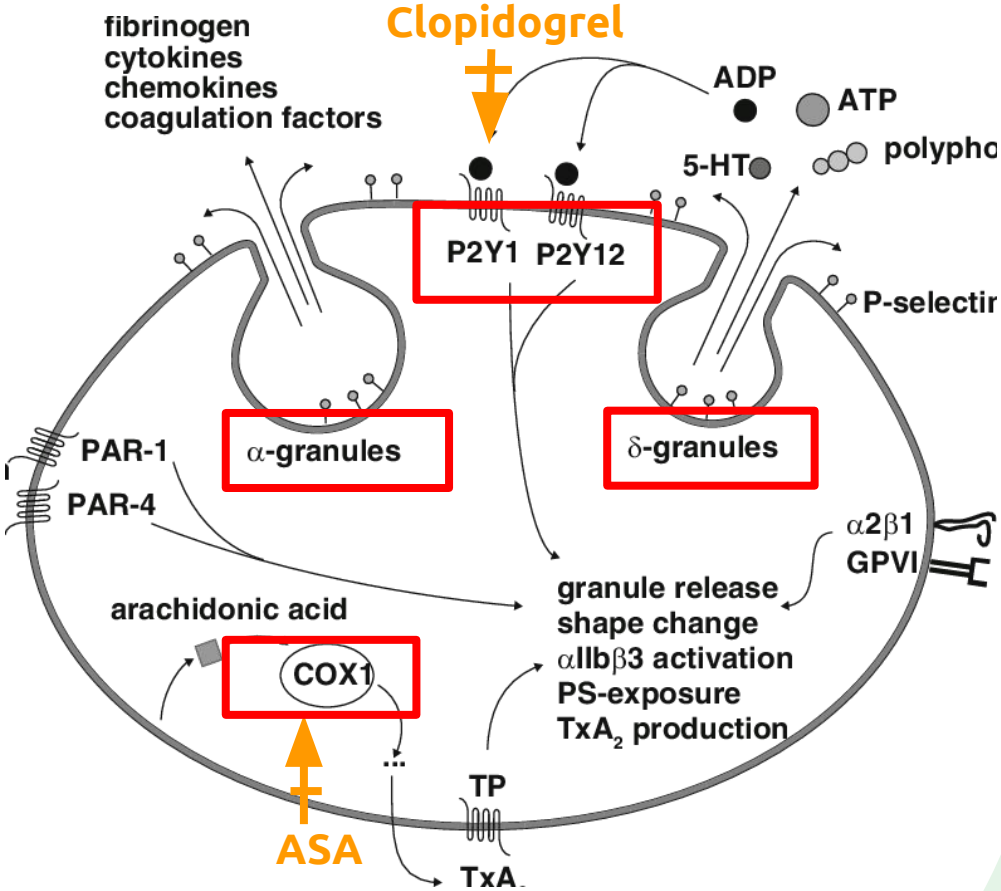
- **Bernard-Soulier disease**
- **Von Willebrand disease**



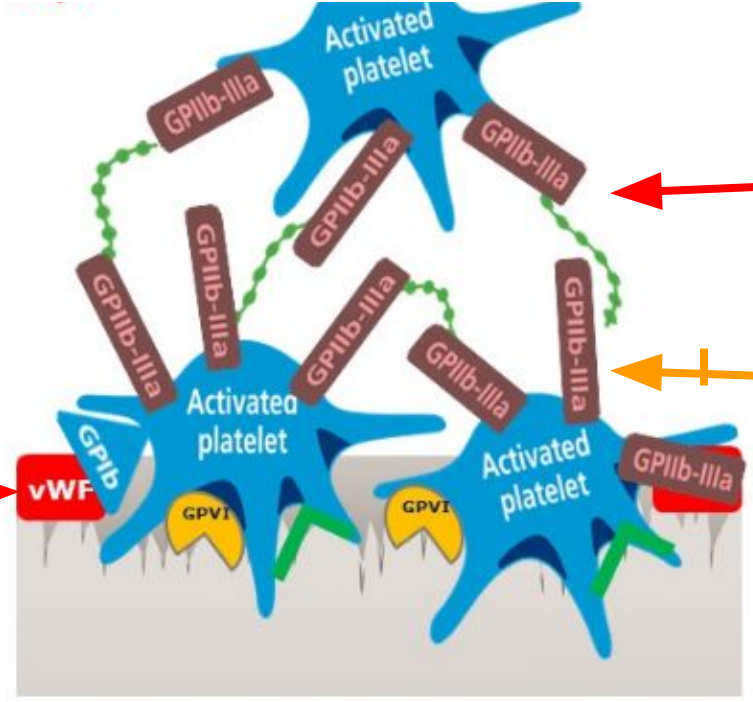
Platelet adherence

- Platelets attach to collagen via surface integrin receptors—glycoproteins (GP) Ia/IIa and GP VI
- High shear : (arterial blood flow) vWF binds to GP Ib/IX
- Low shear : (venous blood flow) collagen binds to GP Ia/IIa, GP VI
- Capillary blood flow : platelets are pushed to the periphery by red blood cells

Platelet activation



Platelet stabilization

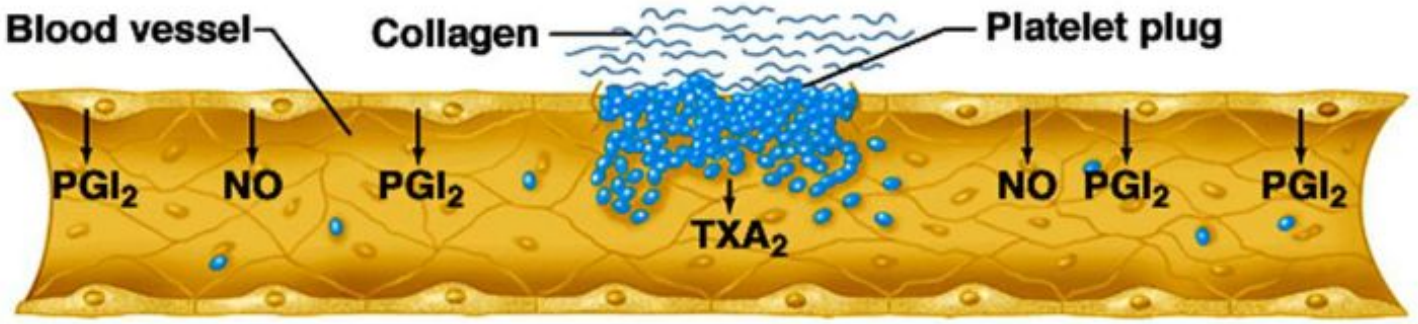


Glanzmann thrombasthenia

abciximab, eptifibatide, tirofiban

Von Willebrand disease

Platelet inhibition



Lab investigations

- **Platelet count** : 150,000 - 400,000 /µL, (PBS)
- **Platelet function tests** (PFTs)/ bleeding time test (not reccommend preop screening)
- **vWF antigen level,** vWF activity level, and FVIII activity level.

Platelet Tests
Platelet count: 140,000-450,000 cells/µL
Bleeding time: <11 min
Platelet function analysis
Collagen/epinephrine: 94-193 sec
Collagen/adenosine diphosphate: 71-118 sec
Platelet aggregation (response to aggregating agents: collagen, adenosine diphosphate, epinephrine, and ristocetin)

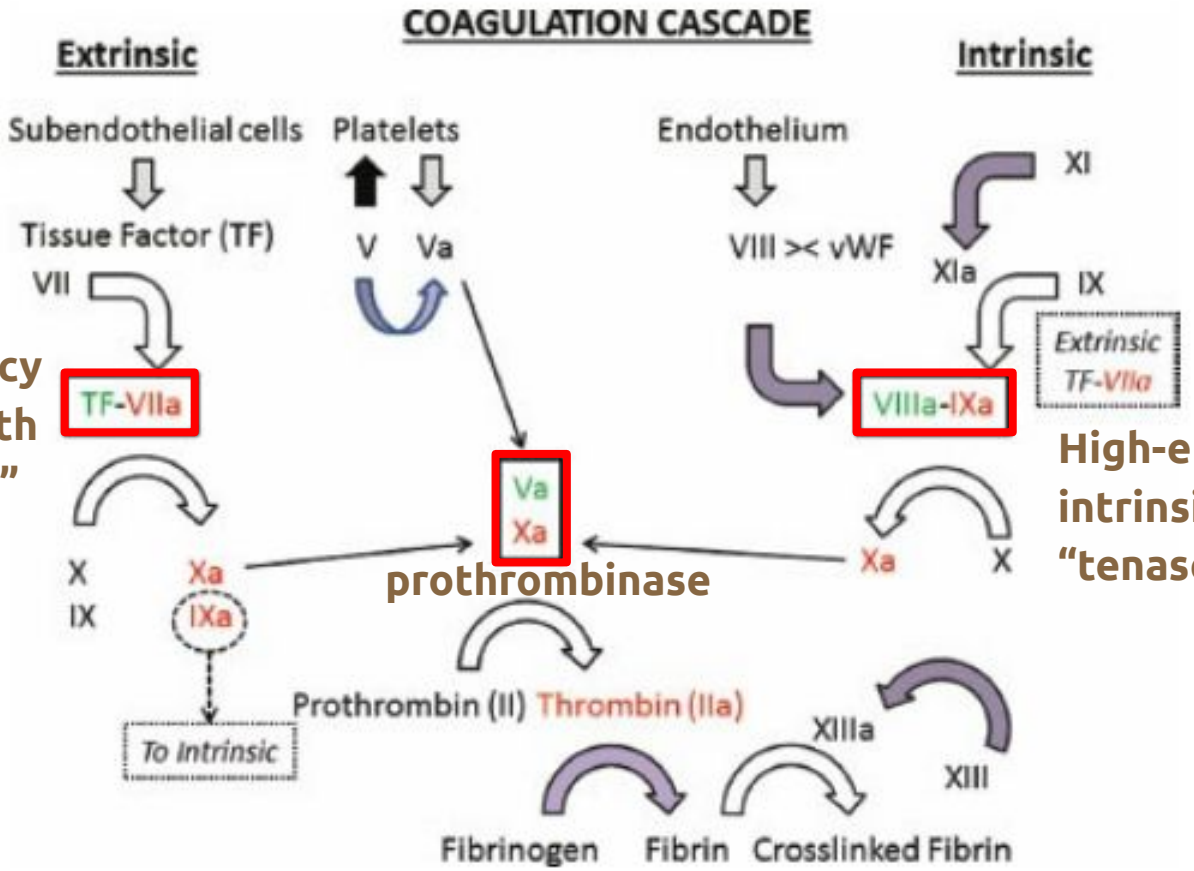
Secondary hemostasis

Coagulation cascade : Extrinsic, Intrinsic, Common pathway

Coagulation factor

FACTOR	SYNONYM
I	Fibrinogen
II	Prothrombin
III	Tissue factor, thromboplastin
IV	Calcium
V	Proaccelerin, labile factor
VI	—
VII	Proconvertin, stable factor
VIII	Antihemophilic factor
IX	Christmas factor
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin-stabilizing factor, transglutaminase

- Factor II, VII, IX, X, XI, XII (inactive form)
- Factor III, V, VIII (cofactor)
- All of these clotting factors are primarily produced in the liver, except for VIII, which is also released by endothelial cells
- factors II, VII, IX, X are vitamin K–dependent



low-efficiency extrinsic-pathway "tenase"

High-efficiency intrinsic-pathway "tenase"

Clinical anesthesia, 8th edition, Paul G. Barash

Extrinsic pathway

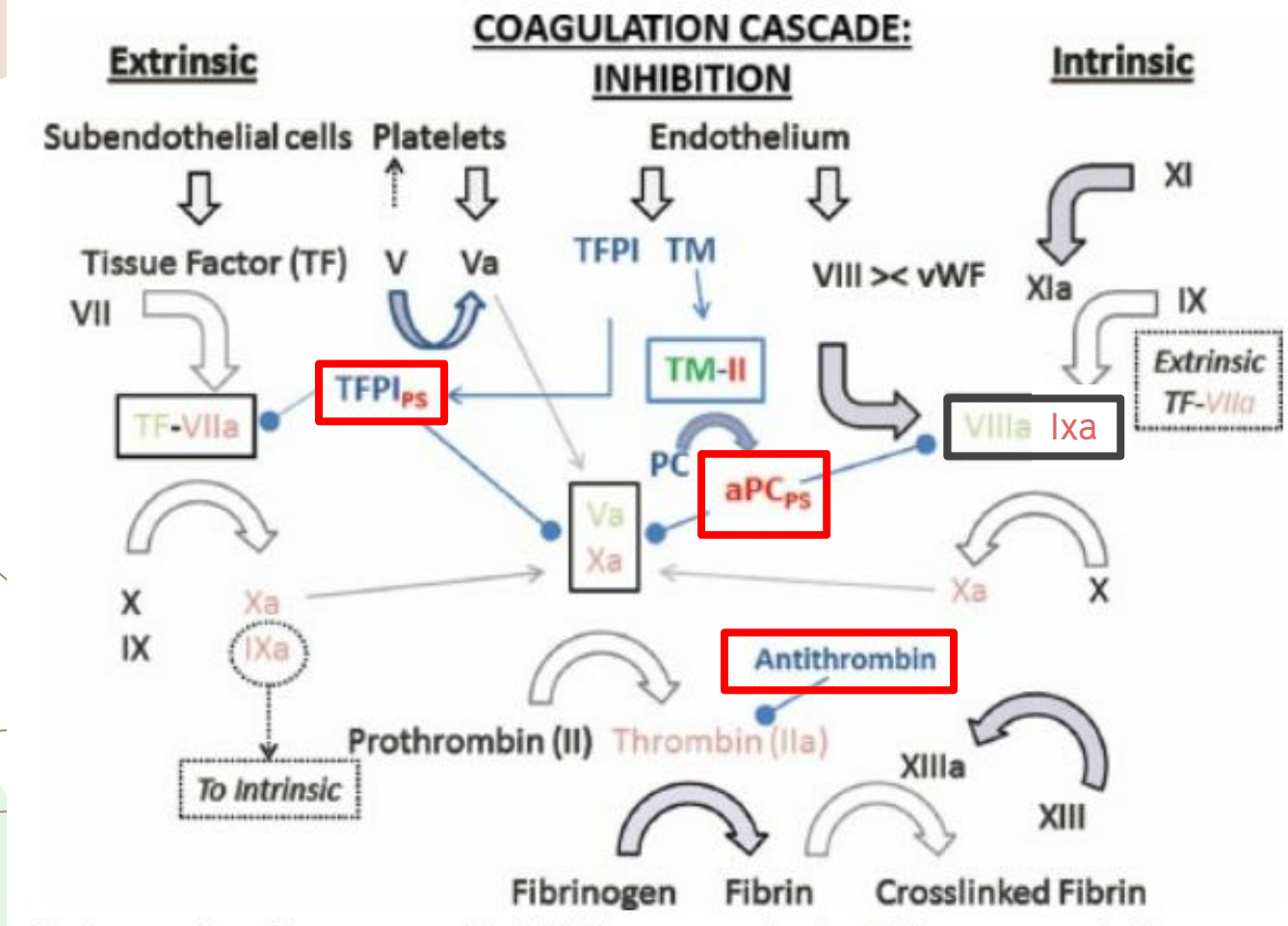
- Endothelial disruption : tissue factor (TF) binds both VII and VIIa.
- VIIa enzyme, TF cofactor, cell membrane phospholipid, and Ca2+ form the complex, a low-efficiency extrinsic-pathway **“tenase”** that activates factor X and factor IX.

Intrinsic pathway

- Cleaving factor XI to XIa.
- Factor XIa cleaves more IX to IXa.
- Thrombin also activates VIII to VIIIa. (VIII is carried and stabilized in the plasma by vWF until needed, so vWF deficiency also results in low plasma VIII levels.)
- The complex is then formed: IXa enzyme, VIIIa cofactor, phospholipid, and Ca2+. This is a high-efficiency intrinsic-pathway **“tenase,”** which provides many times more Xa.

Common pathway

- Then Xa enzyme, its cofactor Va, phospholipid, and Ca2+ assemble to form complex, a “**prothrombinase**,” which converts prothrombin (II) to thrombin (IIa)
- Thrombin cleaves fibrinogen to fibrin monomers, which then polymerize extensively.
- Fibrin polymers are cross-linked by factor XIIIa to form the stable fibrin clot.



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Regulatory inhibitors

- **TF pathway inhibitor (TFPI) :** (endothelial cell) inhibit external tenase complex by binding to the **VIIa** protease and **Xa.**
- **Protein C-ase :** enzymatic complex (enzyme, thrombin, cofactor thrombomodulin, phospholipid, and Ca2+) brakes clotting by cleaving **VIIIa and Va**. Protein C has a short half-life of 6 hours. Protein S (cofactor for protein C) ; both are vitamin K–dependent.

Regulatory inhibitors

- **Antithrombin-III (AT-III)** : serine protease inhibitor or serpin. It increase the clearance of their target proteases in all clotting pathways: **VIIa** in extrinsic tenase, **Xa** in prothrombinase, **XIa and IXa** in the intrinsic tenase pathway, and thrombin. AT-III's inhibitory function is greatly increased when bound to heparin.

Lab investigations

- **Prothrombin time (PT)** for the extrinsic (tissue) pathway evaluate the coagulation factors XII, XI, IX, VIII, X, V, II (prothrombin), and I (fibrinogen)
- **Activated partial thromboplastin time (aPTT)** for the intrinsic (contact) pathway evaluates the coagulation factors VII, X, V, II, and I (fibrinogen)

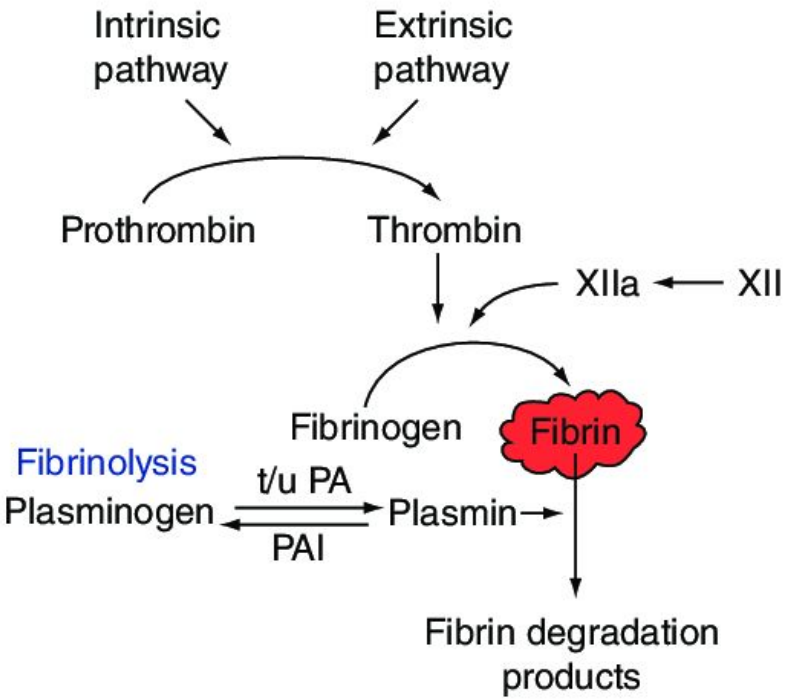
Coagulation Tests
Prothrombin time: 11.5-14.5 sec[a]
Partial thromboplastin time: 24.5-35.2 sec[a]
Thrombin time: 22.1-31.2 sec[a]
Fibrinogen: 175-433 mg/dL
Activated coagulation time: 70-180 sec

Fibrinolysis

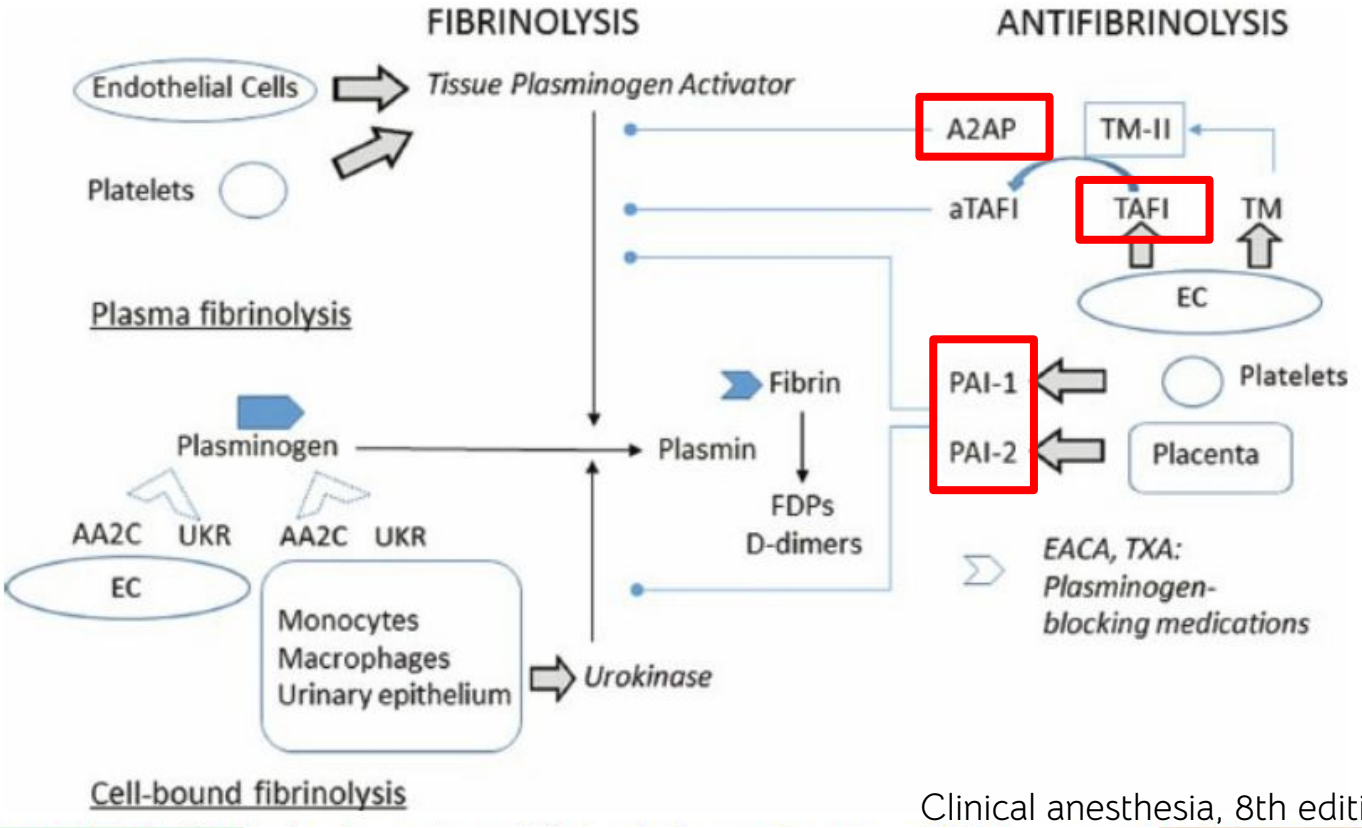
Clot lysis

Fibrinolysis

- Fibrin clots must be broken down after their job is done.
- Plasminogen is activated to plasmin, which breaks down fibrin polymers.
- The major activator of plasminogen in the blood is tissue plasminogen activator (tPA), secreted from endothelial cells and platelets.



Inhibition of Fibrinolysis



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Inhibition of Fibrinolysis

- **Plasminogen activation inhibitor-1 (PAI-1)** is a serpin which binds to **tPA and urokinase** and accelerates their clearance from plasma. Activated platelets release **PAI-1 from α-granules**. **PAI-2** is secreted **by the placenta** and is prominent in pregnancy.

- **α2-Antiplasmin** binds to plasmin and blocks its action, although this also slows the metabolism of plasmin

Inhibition of Fibrinolysis

- **Thrombin-activated fibrinolysis inhibitor (TAFI)** is secreted from endothelial cells and is activated by the thrombin–thrombomodulin complex. TAFI cleaves fibrin and fibrin polymers in a fashion that inhibits the action of tPA, and TAFI also inhibits the action of plasmin on fibrin.

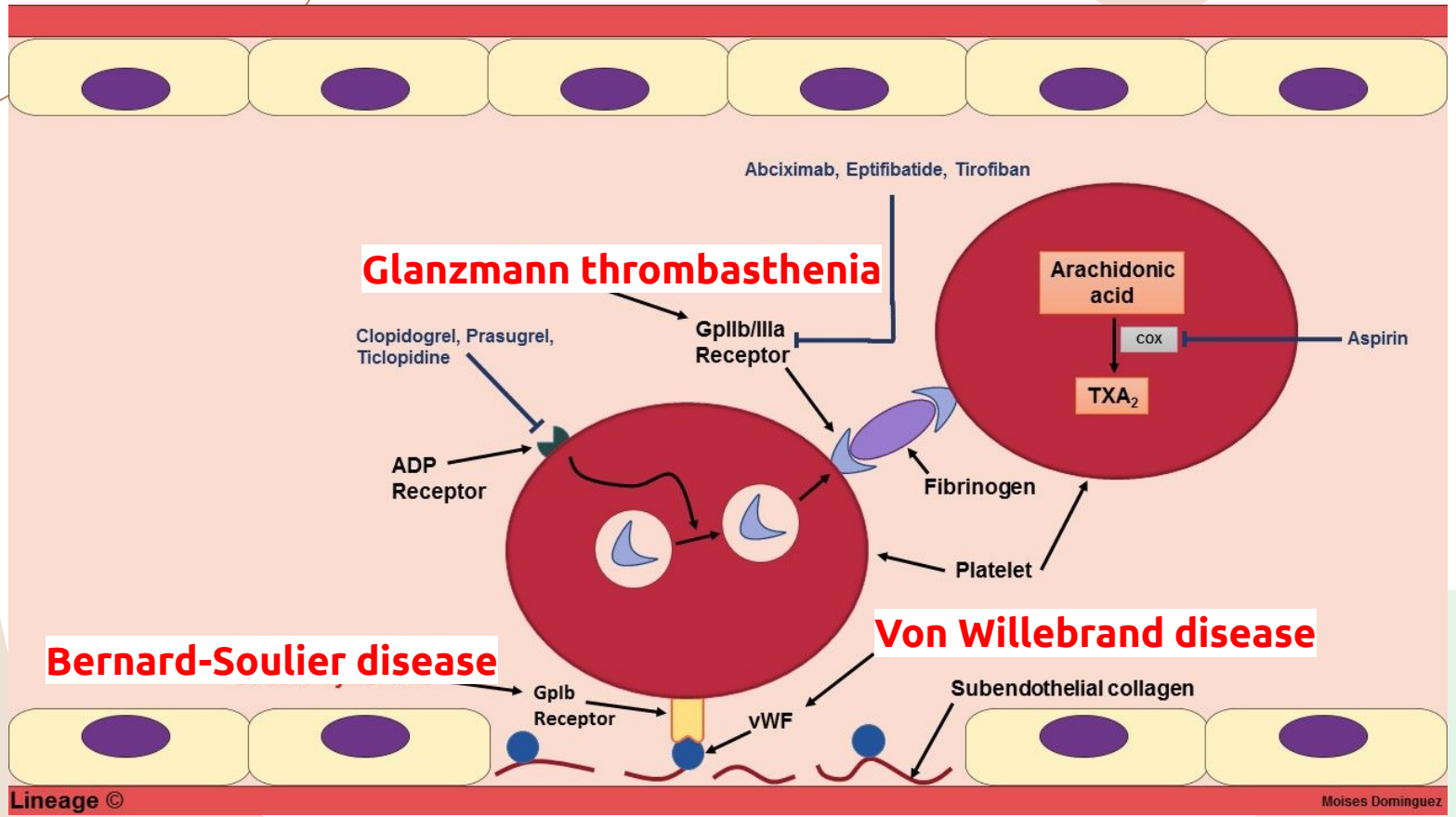
02

Hemostasis disorders

- Primary hemostasis disorders
- Secondary hemostasis disorders

Primary hemostasis disorders

Von Willebrand disease, Bernard–Soulier syndrome, Glanzmann thrombasthenia


Abciximab, Eptifibatide, Tirofiban
Glanzmann thrombasthenia
Arachidonic acid
COX
Aspirin
TXA2
Clopidogrel, Prasugrel, Ticlopidine
GpIIb/IIIa Receptor
ADP Receptor
Fibrinogen
Platelet
Bernard-Soulier disease
Von Willebrand disease
GpIb Receptor
vWF
Subendothelial collagen
Lineage ©
Moises Dominguez

Primary hemostasis disorders

Von Willebrand disease

- most common hereditary bleeding disorder, (prevalences 1%, symptomaic 0.01%)
- Different genetic mutations affect various domains of **vWF**, causing different quantitative and functional deficiencies. 3 types of vWD.
- vWF : platelet plug and subsequent platelet activation, circulates as a complex with FVIII

Primary hemostasis disorders

Von Willebrand disease

Table 22.1 Classification of von Willebrand Disease

Type	Characteristic	Frequency	Inheritance	Diagnosis	Treatment
1	Not enough vWF	70-80%	AD	vWF:Ag, vWF:RCo, FVIII	1. DDAVP 2. FVIII/vWF concentrate
2	Qualitative defect of vWF	15-20%	AD		
A	↓ binding of vWF to platelets, ↓ large multimers	Common		vWF:RCo << vWF:Ag (↓ large multimers)	
B	↑ binding of vWF to platelets, ↓ large multimers			RIPA (much less ristocetin required for aggregation)	FVIII/vWF concentrate (DDAVP contraindicated)
M	↓ vWF function despite normal large multimers	Rare		↓ vWF:RCo compared with vWF:Ag	1. FVIII/vWF concentrate 2. DDAVP
N	↓ binding of VWF to FVIII	Rare			1. FVIII/vWF concentrate? 2. DDAVP?
3	Absent vWF	Very rare	AR	vWF:Ag	1. FVIII/vWF concentrate/rFVIII 2. Platelet concentrate

Secondary hemostasis disorders

Hereditary, Acquired

Disorders of Secondary hemostasis

01

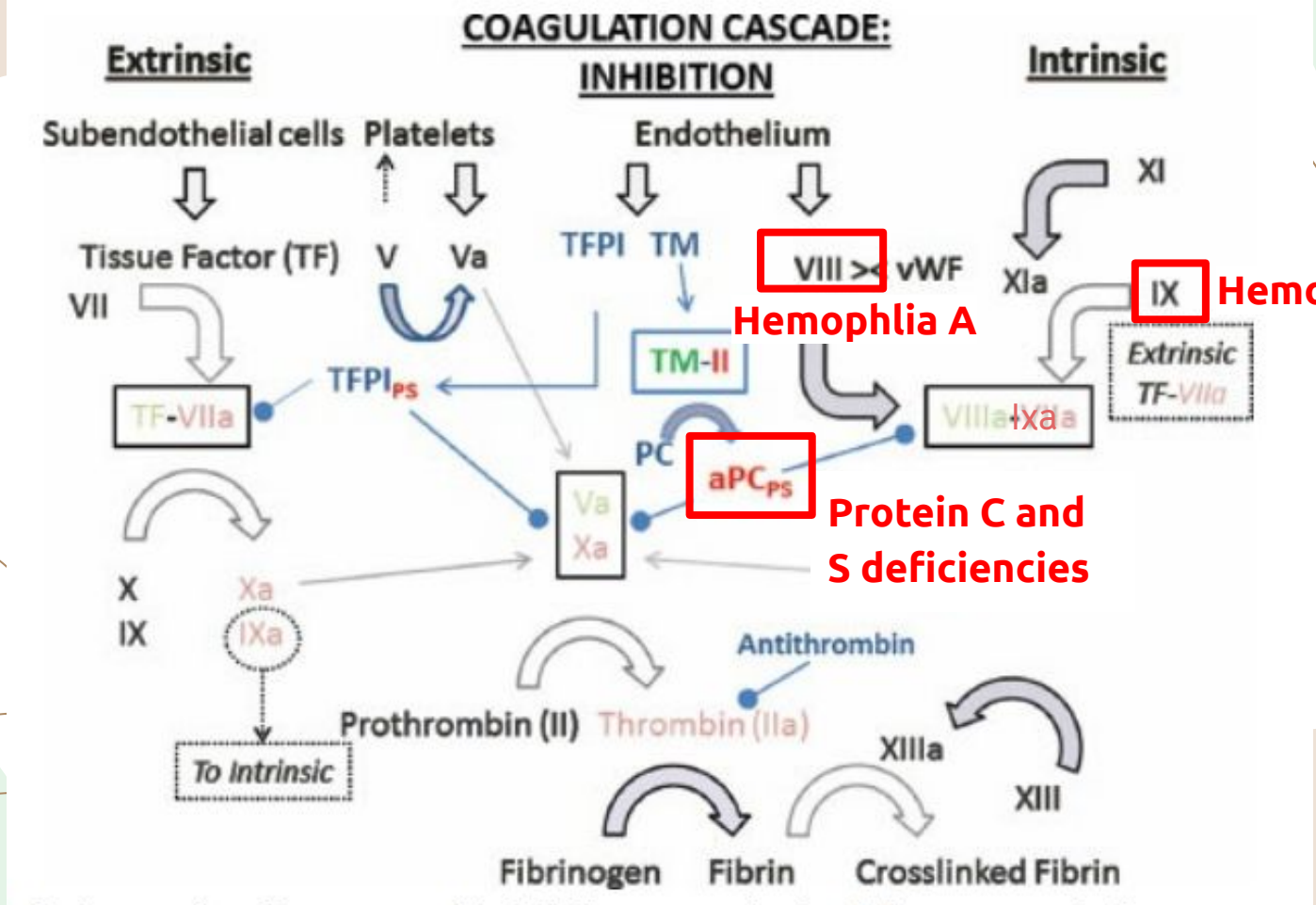
Hereditary

- Hemophilia A
- Hemophilia B
- Protein C and Protein S deficiency

02

Acquired

- Acquired hemophilia
- Vit K deficiency
- Liver disease
- DIC



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Secondary hemostasis disorders

Hemophilia A (Factor VIII deficiency)

- X link recessive, 1 in 5,000 males worldwide
- Normal plasma concentrations of FVIII range 100- 200 ng/mL.
- Mild disease (50%) maintain factor levels 5-40% of normal
- Moderate disease (10%) with only 1- 5% of residual FVIII activity.
- Severe disease (40%) have less than 1% of normal factor activity.
- Carrier females generally maintain about 50% of FVIII activity with no clinical signs of bleeding.

Secondary hemostasis disorders

Hemophilia A (Factor VIII deficiency)

- Prolonged aPTT and low factor activity levels. PT and bleeding times will be normal, distinguish from vWD by normal vWF Ag
- FVIII concentrate 1U, 2% activity(Shorter hL 12 hours)
- FFP or cryoprecipitate (factor VIII, vWF, fibrinogen, and factor XIII) may be necessary.
- Adjuvant therapies : DDAVP, Antifibrinolytics (tranexamic acid)

Secondary hemostasis disorders

Hemophilia B (Factor IX deficiency)

- affecting roughly 1 in 25,000 males
- FIX concentrates, 1U, 1% activity, longer half-life 18 hours
- FFP may be necessary
- Prothrombin complex concentrates (PCCs) contain factor IX and can be used for bleeding control in hemophilia B
- Dose targeted to achieve : at least 50% of normal factor activity levels for minor surgery and 80-100% for major surgery.

Secondary hemostasis disorders

Protein C and S deficiencies (Hypercoagulable state)

- Increased risk of venous thromboembolism (AD).
- Protein C inactivates factor V to curb the clotting cascade, and depends on protein S as a cofactor for appropriate function
- Warfarin is indicated for long-term management

Disorders of Secondary hemostasis

01

Hereditary

- Hemophilia A
- Hemophilia B
- Protein C and Protein S deficiency

02

Acquired

- Vit K deficiency
- Liver disease
- DIC

Secondary hemostasis disorders

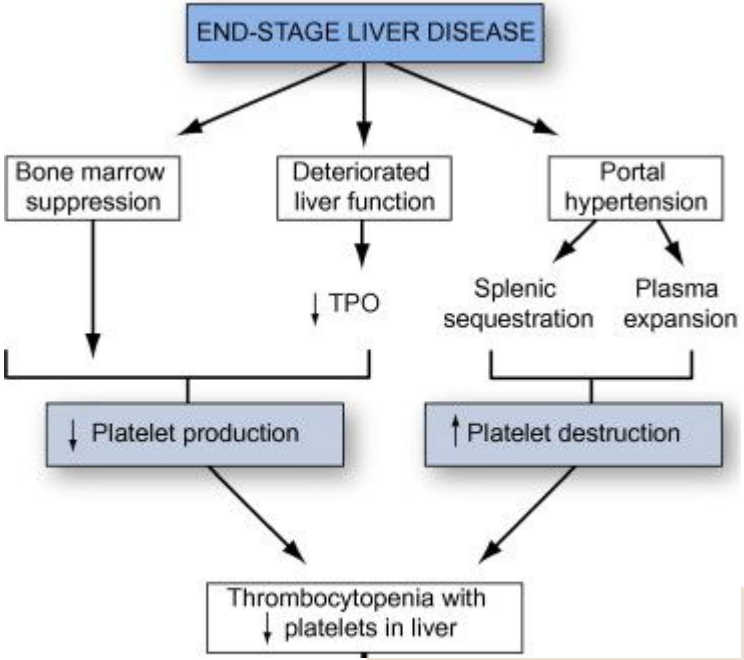
Vit K deficiency

- vit K is required for the carboxylation of **factors II, VII, IX, and X and proteins C and S** for binding phospholipid membrane.
- Phylloquinone (K1) from foods such as leafy greens
- Menaquinone (K2) from intestinal bacteria
- Lab : Prolonged PT and aPTT
- Treated with vitamin K replacement, which can be administered parenterally (High dose 5-10mg, improve 6-8hr), orally (24hr full effect), or subcutaneously.

Secondary hemostasis disorders

Liver disease

- Bleeding diathesis : thrombocytopenia, portal hypertension, procoagulant imbalance, endothelial dysfunction.
- Decreased production of thrombopoietin in the liver
- Deficiencies of factors II, V, VII, IX, X, and XI that will prolong the PT and aPTT, Increased FVIII activity.



Secondary hemostasis disorders

Liver disease

- PT and aPTT : Not reflect bleeding/thrombotic risk
- No longer recommended to prophylactically transfuse plasma in minor procedures without signs of bleeding.

Clinical and Lab Criteria	Points*		
	1	*2*	*3*
Encephalopathy	None	Mild	Severe
Ascites	None	Mild	Severe
Bilirubin(mg/dl)	<2	2-3	>3
Albumin(g/dl)	>3.5	2.8-3.5	<2.8
International Normalized Ratio(INR)	<1.7	1.7-2.3	>2.3

*Child-Pugh classification is obtained by adding score for each Parameter
Class A = 5 to 6 points(least severe liver disease)
Class B = 7 to 9 points (Moderately severe liver disease)
Class c = 10 to 15 points most severe liver disease

Secondary hemostasis disorders

Disseminated Intravascular Coagulation (DIC)

Disorder	Average Incidence of DIC	Comments
Sepsis	30–50%	Highest with gram-negative bacilli
Trauma and burns	Rare	Associated with the degree of tissue injury
Malignancy	Up to 20%	Highest with adenocarcinoma or leukemia and lymphoma
Vascular disease	Rare	Higher with giant hemangiomas
Obstetric complication	Up to 50%	Including preeclampsia, placental abruption, or amniotic fluid embolism
Hemolysis	Rare	Higher with intravascular hemolysis
Severe organ dysfunction	Rare	Including pancreatitis, hepatitis, and end-stage renal failure

Secondary hemostasis disorders

Disseminated Intravascular Coagulation (DIC)

- Excessive consumption of circulating coagulation factors, platelets, and fibrinogen
- Uncontrolled intravascular thrombin generation and fibrin deposition in small blood vessels DIC
    - Decreased levels of anticoagulants; AT-III, protein C, TFPI.
    - Increase levels of PAI-1
- leads to end-organ dysfunction and multiorgan failure.

Secondary hemostasis disorders

Disseminated Intravascular Coagulation (DIC)

The ISTH scoring system (sensitivity91%, specificity is 97%)

Parameter	Result	Score
Platelet count	>100K <100K <50K	0 1 2
D-dimer	<1mcg/ml 1.0-5.0 mcg/ml > 5.0 mcg/ml	0 2 3
PTT	<3sec >3sec >6sec	0 1 2
Fibrinogen	>100 mg/dl <100 mg/dl	0 1
Score ≥ 5 is indicative of overt DIC with increasing scores correlating with higher mortality.		

Secondary hemostasis disorders

Disseminated Intravascular Coagulation (DIC)

- Treatment of the causative and control progressive thrombosis and hemorrhage.
- No evidence for improved outcomes with transfusion of plasma or platelets unless thrombocytopenia is
    - severe (platelet counts<10,000 to 20,000/μL)
    - moderate (<50,000/μL), with signs of bleeding
    - preparation for invasive procedures

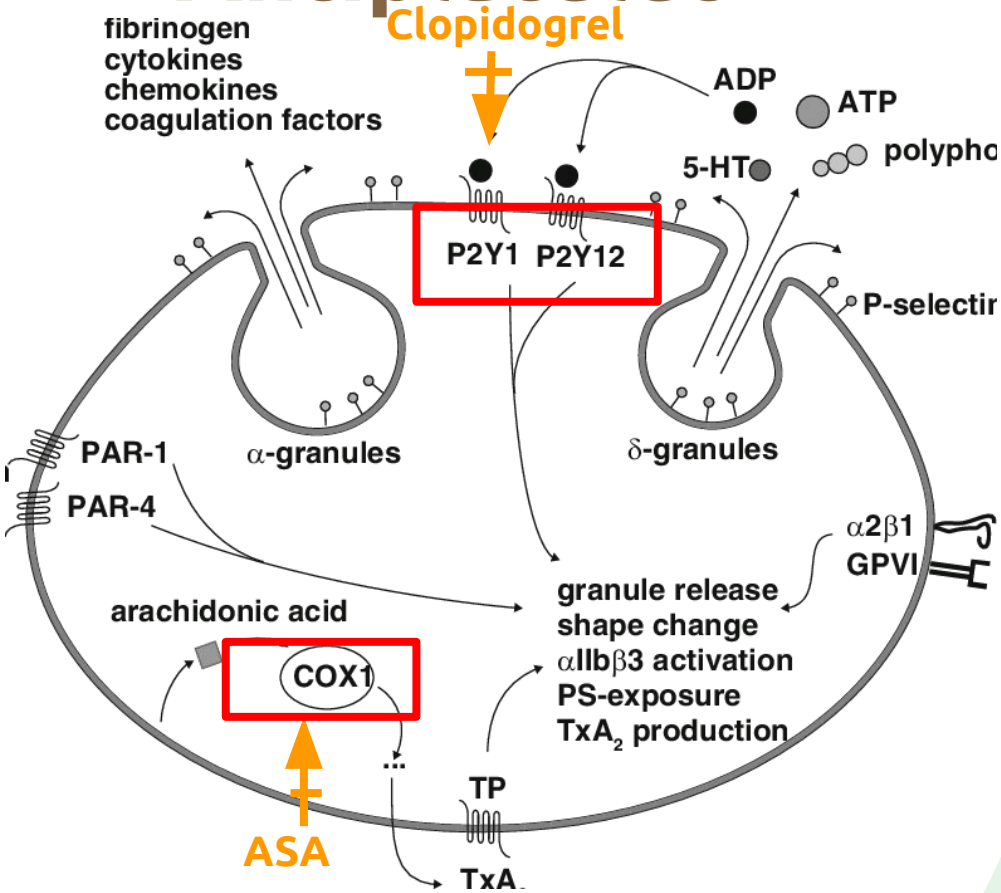
03 Anticoagulation & Pharmacological

- Antiplatelets
- Anticoagulants
- Procoagulants

Antiplatelet

COX inhibitors, P2Y12 receptor antagonist, GPIIb/IIIa antagonist

Antiplatelet



COX Inhibitors

- COX-1 : maintains the integrity of the gastric lining, renal blood flow and initiates the formation of TxA2 (platelet aggregation)
- COX-2 : synthesizing the prostaglandin mediators in pain and inflammation
- **Aspirin** (Noncompetitive, irreversibly inhibit both COX-1,COX-2)
    - anti-inflammatory and analgesic effects
    - hL 15-20min but works 7-10 days (expected lifetime of anucleated platelets)
    - Recovery of platelet function : platelet turnover 2-3d
    - Immediate reversal : plt transfusion

COX Inhibitors

- **NSAIDs**
  - Nonselective reversible COX inhibitors : Mostly of NSAIDs ex. naprosyn and ibuprofen
  - Selective COX-2 antagonists : celecoxib (risks cardiovascular complications)

P2Y12 receptor antagonists

- Inhibiting the P2Y12 receptor, which prevent the expression of GP IIb/IIIa (platelet adhesion and aggregation)

- **Clopidogrel** : noncompetitive and irreversible antagonist

  • inactive prodrug that requires oxidation to its active metabolite.

  • Platelet functions normalize 7 days after discontinuing

P2Y12 receptor antagonists

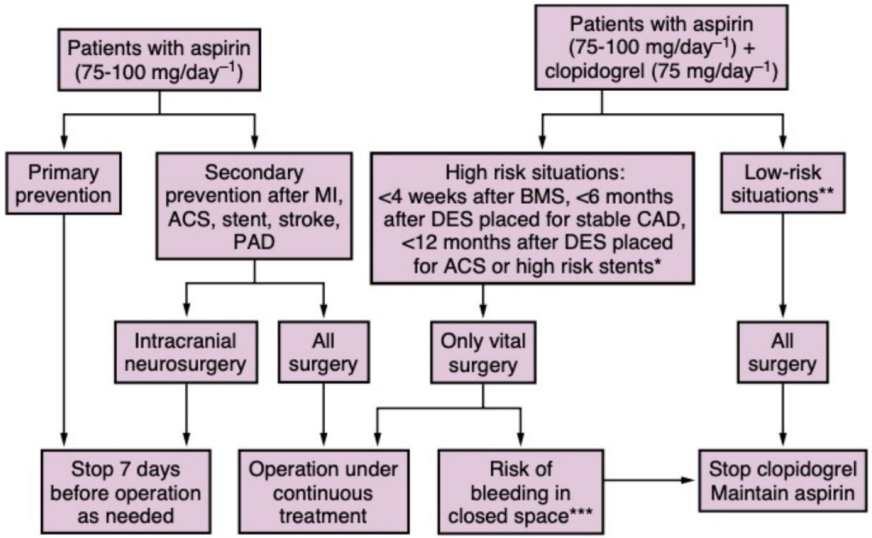
- **Prasugrel** : irreversible P2Y12 ADP inhibitor
    - primary prevention of acute coronary syndrome
- **Ticagrelor :** reversible inhibitor (active drug, shorter duration)
    - AHA : treatment acute coronary syndrome.

- Both ticagrelor and prasugrel are associated with higher bleeding risk than clopidogrel and should not be used with aspirin doses over 100 mg/day.

GP IIb/IIIa receptor antagonist

- Inhibit the cross-linkage of fibrinogen
- Primarily used for management of acute coronary syndrome.
- **Abciximab** (noncompetitive irreversible inhibitor)
    - Platelet aggregation normalizes 24- 48 hours after discontinuing (protein binding)
- **Eptifibatide** and **Tirofiban** (competitive, reversible)
    - Platelet aggregation normalizes 8 hours after discontinuing
- All of these drugs cause thrombocytopenia

Discontinue Antiplatelet



MI, Myocardial infarction; *ACS,* acute coronary syndrome; *PAD,* peripheral arterial disease; *PCI,* percutaneous coronary intervention; *BMS,* bare metal stent; *DES,* drug-eluting stent.

*High-risk stents: long (>36 mm), proximal, overlapping, or multiple stents, stents in chronic total occlusions, or in small vessels or bifurcated lesions.

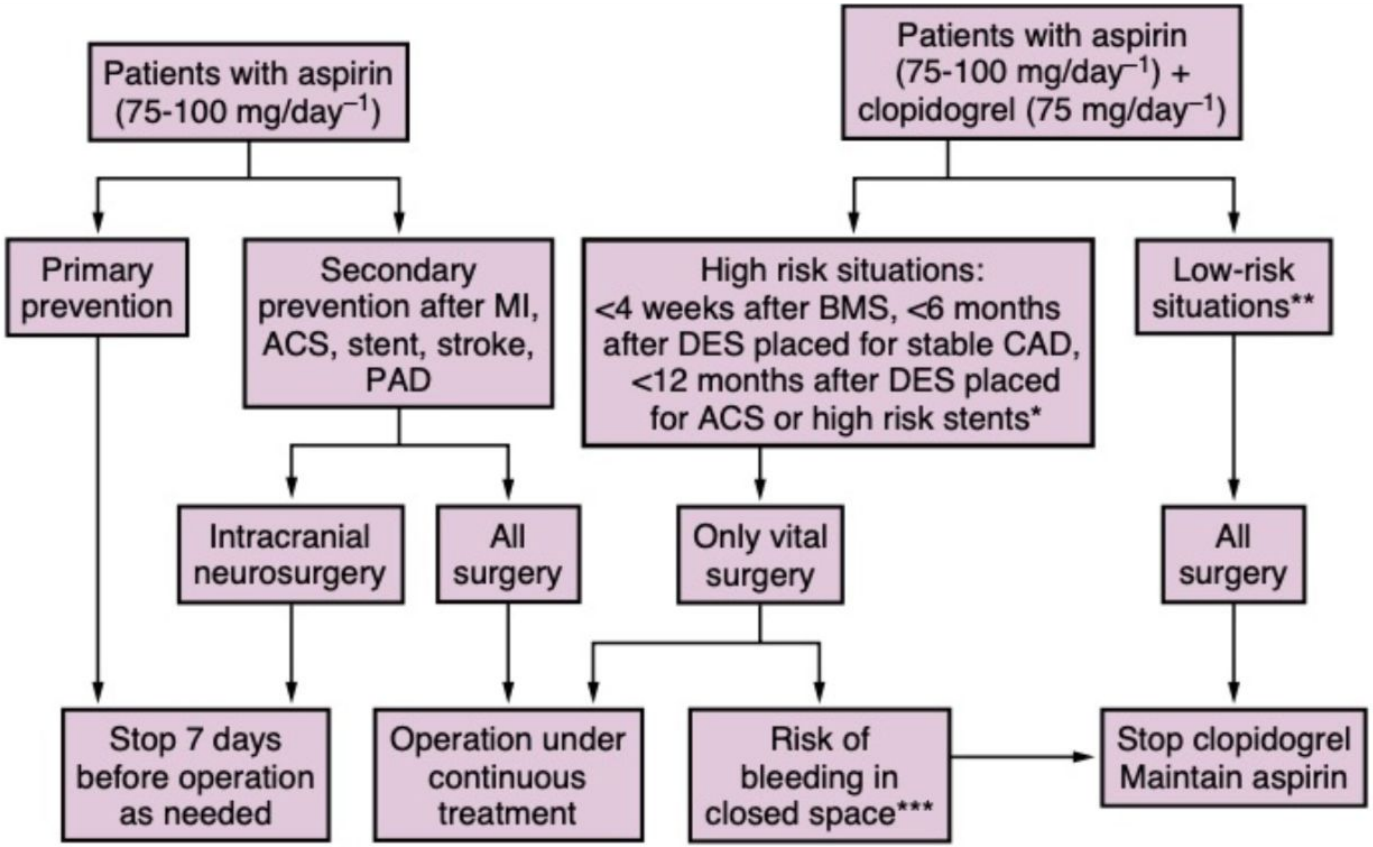
**Examples of low-risk situations: >1 month after BMS, stroke, uncomplicated MI, PCI without stenting.

***Risk of bleeding in closed space: intracranial neurosurgery, intra-medullary canal surgery, posterior eye chamber ophthalmic surgery. In these situations, the risk/benefit ratio of upholding vs. withdrawing aspirin must be evaluated for each case individually; in case of aspirin upholding, early postoperative re-institution is important.

Risk assessment

1. Perioperative cardiovascular event
2. Risk of surgery (minor procedure, major procedure, or cardiac procedure)
3. Timing and type of stent placement undergone recent PCI

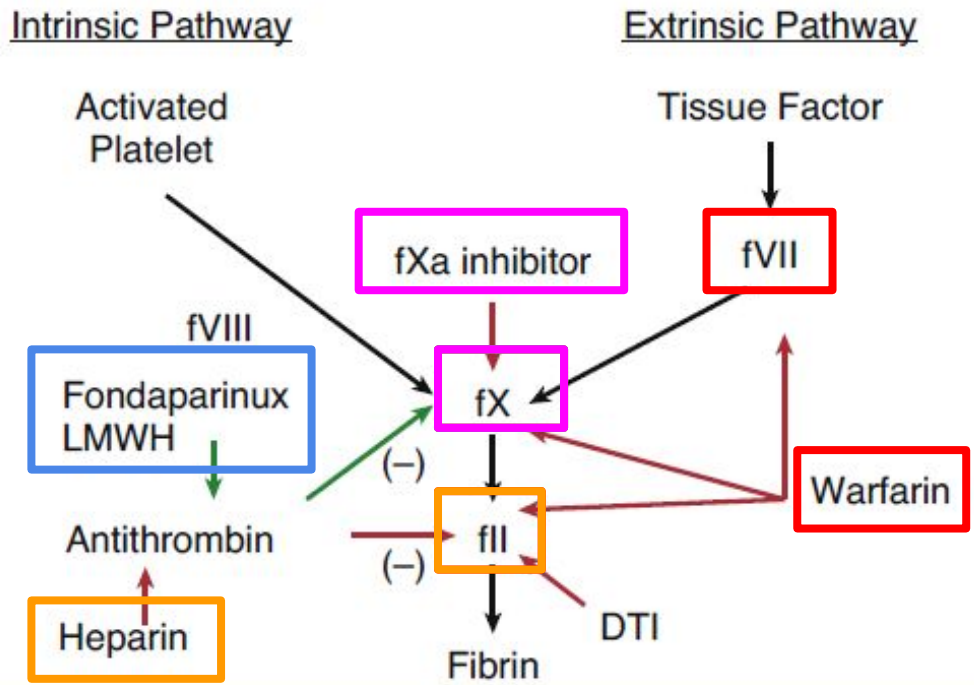
Discontinue Antiplatelet



Anticoagulants

VKA, UFH, LMWH, NOAC

Anticoagulants



Vitamin K Antagonists

Warfarin

- disrupts carboxylation FII, VII, IX, X, proteins C and S
- Hypercoagulable disorders, venous thromboembolism, and stroke prophylaxis in patients with atrial fibrillation
- long half-life (40 hours), complete effects take 48-72 hours
- therapeutic range INR 2-3. Except mechanical heart valves, target INR 2.5 - 3.5
- contraindicated in pregnancy due to embryopathy.
- Reversal : Vitamin K, FFP, PCC

Unfractionated Heparin

UFH

- Inhibits thrombin and factor Xa by binding to ATIII
- ACS, PE, and during cardiopulmonary bypass or vascular surgery.
- Short half-life, Monitored with the aPTT or ACT
- Insufficiency or Deficiency of AT : FFP transfusions, which will replenish AT levels
- can stimulate the production of antibodies against the heparin platelet factor 4 (PF4) complex.
- Reversal : 1mg protamine to 100 units of heparin

Unfractionated Heparin

UFH

- **HIT** : mortality rate of 20-30%. These antibodies can activate platelets to induce thromboembolic event and cause HIT.

    • Plt <100,000 cells or <50% baseline 5-10 days after initiation.

    • HIT Ab testing : (ELISA) is sensitive but not as specific as the serotonin release assay (gold standard)

- Types : HIT1 (mild thrombocytopenia) ,HIT2 (immune-mediated response) carries a significant risk of hypercoagulability.

Unfractionated Heparin

UFH

- **HIT**

  • Treatment : therapeutic anticoagulation and discontinuation of all heparin. Parenteral DTIs (bivalirudin and argatroban)

  • Platelet transfusions should also be held unless the patient is severely thrombocytopenic (<20,000 cells/μL) with signs of bleeding

Low-Molecular-Weight Heparin

- fractionated form of heparin, more specific inhibition of FXa
- longer half-life, DVT prophylaxis and treatment
- **Fondaparinux,** a synthetic pentasaccharide, renal elimination, no antidote
- **Enoxaparin, dalteparin, and reviparin**
- factor Xa levels. (may be helpful in renal failure, pregnant women, obese patients, and neonates)
- LMWH is contraindicated in HIT.

New Oral Anticoagulants

- More predictable pK/pD, fewer interactions with foods, drugs
- **Dabigatran** (Competitive, Direct factor Xa inhibitors)

  • prevention of ischemic stroke in patients with nonvalvular atrial fibrillation and the treatment of VTE

  • Reversal : Idarucizumab

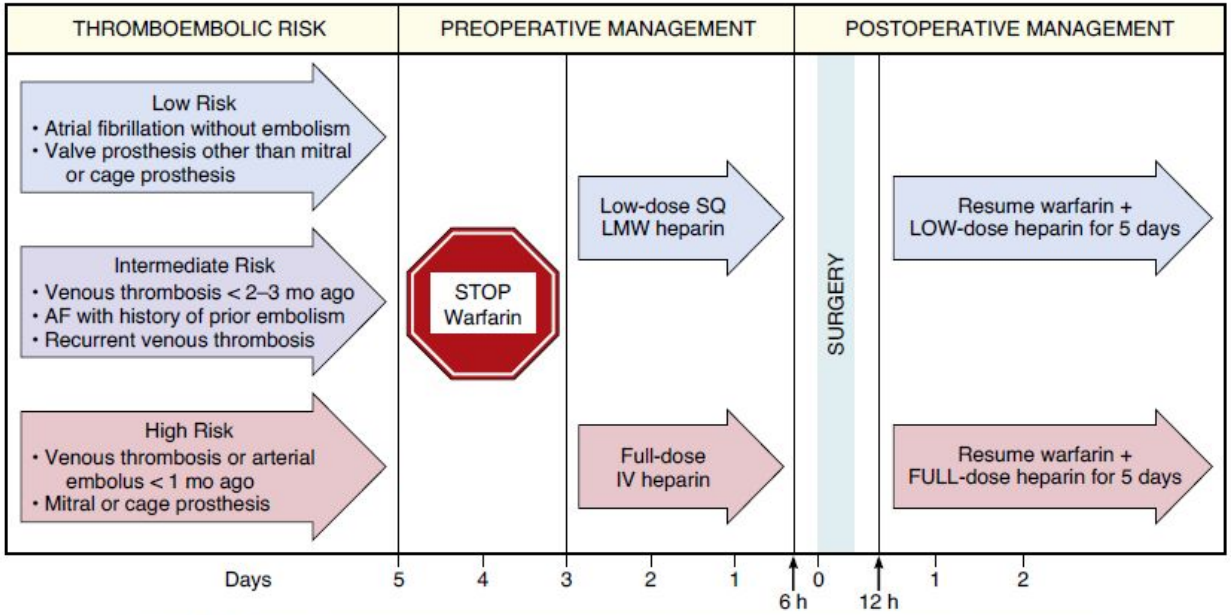
- **Rivaroxaban** (Xarelto) and **Apixaban** (Eliquis) (directed against the active site of factor Xa)

  • use in DVT/PE prophylaxis, stroke prophylaxis in patients with atrial fibrillation, and VTE treatment.

Anticoagulants

Anticoagulants	Drug Name	Monitoring	Reversal Agents
Vitamin K antagonists	Warfarin	PT, INR	PCC, FFP, vitamin K
Heparins	Unfractionated heparin (UFH)	aPTT	Protamine
	Low-molecular-weight heparin (LMWH)	None required, but anti–factor Xa assay can monitor levels	Partially reversed by protamine
Pentasaccharide	Fondaparinux	None required, but anti–factor Xa assay can monitor levels	None
Direct thrombin inhibitors	Hirudin, argatroban, bivalirudin	aPTT or ACT	None
	Dabigatran	None required	Idarucizumab, dialysis may remove drug
Factor Xa inhibitors	Rivaroxaban, apixaban	None required	None

Discontinue Anticoagulant



Low risk : Stop 5 day, restart 12-24 hrs

High risk : Bridging heparin or LMWH

Basic of anesthesia, 7th edition, Manuel C. Pardo, Jr., Ronald D.Miller

Discontinue Anticoagulant

TABLE 50.3 Perioperative Thromboembolism Risk Stratification

Risk	Indication
High	Mechanical heart valve
	Rheumatic valvular heart disease
	CHADS score ≥ 5
	VTE within 3 months or h/o VTE when VKAs are discontinued
Moderate	CHADS score of 3 or 4
	VTE between 3 and 12 months or h/o recurrence
	Active cancer
Low	CHADS score 0-2
	VTE > 12 months prior and no other risk factors

CHADS, Congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke; *VKA*, vitamin K antagonists; *VTE*, venous thromboembolism.

UFH : stop 4- 6 hours, resumed without a bolus dose 12 hours (should delayed 48-72 hrs in high postoperative risk bleeding)

LMWH : stop 24 hours, resumed 24 hrs (should delayed 48-72 hrs in high postoperative risk bleeding)

Discontinue Anticoagulant

TABLE 31.11 Expert Consensus Recommendations on Preoperative Direct Oral Anticoagulant Discontinuation (Recommended Time Interval from Last Preoperative Dose)

Direct Thrombin Inhibitor (i.e., Dabigatran)	Direct Factor Xa Inhibitor (i.e., Rivaroxaban, Edoxaban, Apixaban)
LOW BLEEDING RISK PROCEDURES (ACC RECOMMENDATIONS)*	
eGFR ≥ 80 mL/min: ≥ 24 h eGFR 50–79 mL/min: ≥ 36 h eGFR 30–49 mL/min: ≥ 48 h eGFR 15–29 mL/min: ≥ 72 h eGFR < 15 mL/min: No data	eGFR ≥ 30 mL/min: ≥ 24 h eGFR 15–29 mL/min: ≥ 36 h eGFR < 15 mL/min: No data (consider ≥ 48 h)
UNCERTAIN, INTERMEDIATE, OR HIGH BLEEDING RISK PROCEDURES (ACC RECOMMENDATIONS)*	
eGFR ≥ 80 mL/min: ≥ 48 h eGFR 50–79 mL/min: ≥ 72 h eGFR 30–49 mL/min: ≥ 96 h eGFR 15–29 mL/min: ≥ 120 h eGFR < 15 mL/min: No data	eGFR ≥ 30 mL/min: ≥ 48 h eGFR < 30 mL/min: No data (consider ≥ 72 h)
PLANNED NEURAXIAL ANESTHESIA (ASRA RECOMMENDATIONS)†	
Uniform approach: 120 h Approach based on eGFR ▪ eGFR ≥ 80 mL/min: ≥ 72 h ▪ eGFR 50–79 mL/min: ≥ 96 h ▪ eGFR 30–49 mL/min: ≥ 120 h ▪ eGFR < 30 mL/min: Not recommended	72 h

Discontinue Drug before surgery

TABLE 50.5 Common Anticoagulants Along with the Required Laboratory Monitoring and Possible Reversal Agents for Emergencies

Antithrombotic Agent	Drug Name	Stop Before Procedure	Monitoring	Reversal Agents
Antiplatelet agents	ASA P2Y12 receptor antagonists GPIIb/IIIa antagonists	7 days 7-14 days 24-72 h	None	Platelet transfusion
Vitamin K antagonists	Warfarin	2-5 days	PT, INR	PCC, FFP, vitamin K
Heparins	Unfractionated heparin (UFH)(IV)	6 h	aPTT	Protamine
	Low-molecular weight heparin (LMWH)	12-24 h	None required, but fXa levels can monitor levels	Partially reversed by protamine
Pentasaccharide	Fondaparinux	3 days (prophylactic dosing)	None required, but fXa levels can monitor levels	None
Direct thrombin inhibitors	Argatroban, Bivalirudin	4-6 h 3 h	aPTT or ACT	None
	Dabigatran	2-4 days (longer if renal impairment)	None required, thrombin time can monitor levels	Idarucizumab
FXa inhibitors	Rivaroxaban, Apixaban, Edoxaban	2-3 days 2-3 days 2-3 days	None required, but fXa levels can monitor levels	Andexanet alfa for rivaroxaban and apixaban

Discontinue Drug before surgery

TABLE 7. European Society of Anaesthesiology's Recommended Time Intervals Before and After Neuraxial Puncture or Catheter Removal*

	Time Before Puncture/Catheter Manipulation or Removal	Time After Puncture/Catheter Manipulation or Removal	Laboratory Tests
UFHs (for prophylaxis, ≤15,000 IU/d)	4–6 h	1 h	Platelets during treatment for >5 d
UFHs (for treatment)	IV 4–6 h	1 h	aPTT, ACT, platelets
	SC 8–12 h	1 h	
LMWHs (for prophylaxis)	12 h	4 h	Platelets during treatment for >5 d
LMWHs (for treatment)	24 h	4 h	Platelets during treatment for >5 d
Fondaparinux (for prophylaxis, 2.5 mg/d)	36–42 h	6–12 h	(Anti–factor Xa, standardized for specific agent)
Rivaroxaban (for prophylaxis, 10 mg daily)	22–26 h	4–6 h	(Anti–factor Xa, standardized for specific agent)
Apixaban (for prophylaxis, 2.5 mg BID)	26–30 h	4–6 h	(Anti–factor Xa, standardized for specific agent)
Dabigatran (for prophylaxis, 150–220 mg)	Contraindicated according to the manufacturer	6 h	TT
Coumarins	INR ≤1.4	After catheter removal	INR
Hirudins (desirudin)	8–10 h	2–4 h	aPTT, ECT
Argatroban	4 h	2 h	aPTT, ECT, ACT
Acetylsalicylic acid	None	None	
Clopidogrel	7 d	After catheter removal	
Ticlopidine	10 d	After catheter removal	
Prasugrel	7–10 d	6 h after catheter removal	
Ticagrelor	5 d	6 h after catheter removal	
Cilostazol	42 h	5 h after catheter removal	
NSAIDs	None	None	

Procoagulants

Antifibrinolytic drug, rFVII, PCC

Antifibrinolytic drugs

- **EACA** and **TXA**, Lysine analogues
    - competitively inhibit the binding site on plasminogen,
    - moderately decrease perioperative blood loss in cardiac surgery, liver transplantation, obstetrics, orthopedics, spine fusion, TURP, trauma.
    - Contraindication : Intracranial hemorrhage, Color vision defect, Thromboembolism disorder, >3hrs
- **Aprotinin**, serine protease inhibitor

Recombinant Factor VIIa

- Increases the generation of thrombin (factor II)
- In extrinsic system, rFVIIa binds to TF at the site of vessel injury. Burst for procoagulant activity
- FDA approved for use in hemophilia patients.
- hL 2- 2.5 hours
- off-label uses of rFVIIa : intracranial hemorrhage, cardiac surgery, trauma, traumatic brain injury, and liver transplantation.
- **Adverse effects** : arterial and venous thromboembolism
- **Contraindications** : DIC and high thromboembolism risk

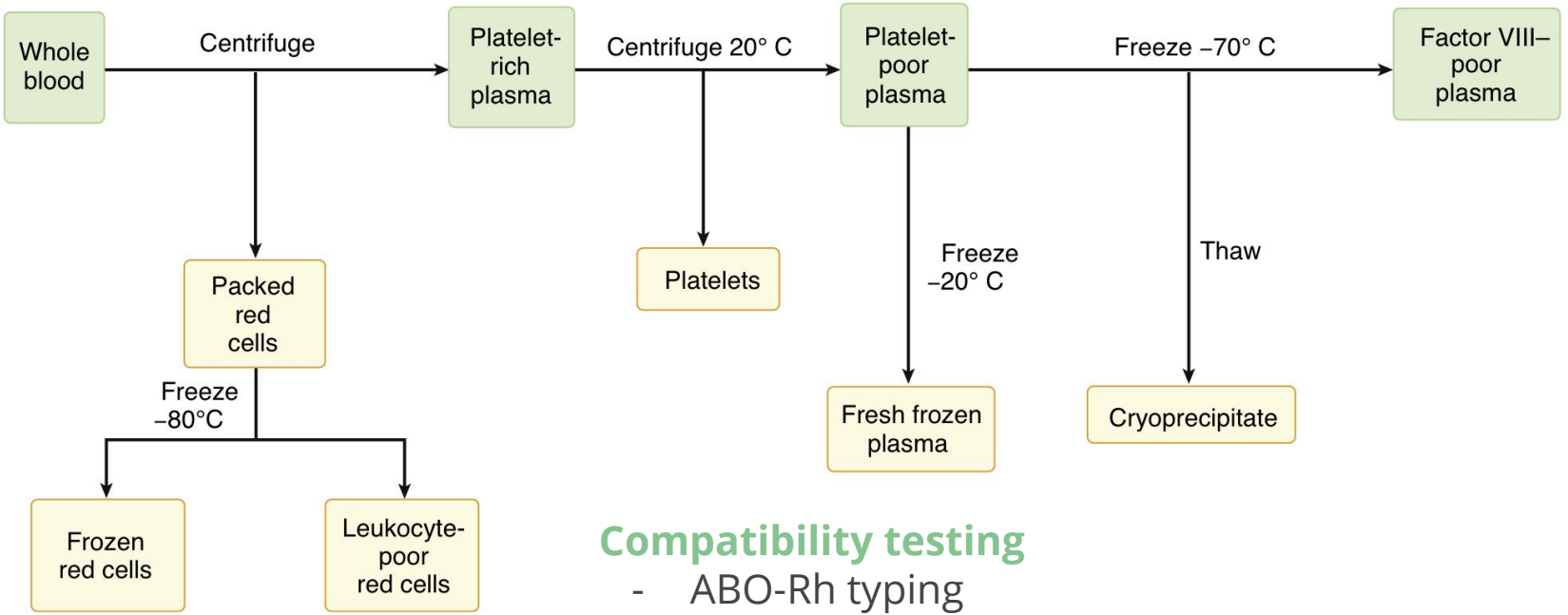
Prothrombin Complex Concentrate

- factors II, VII, IX, and X as well as one or more types of anticoagulants (protein C or S).
- Hemophilia B, drug of choice for emergent reversal of VKAs in place of rFVIIa or FFP, massive transfusion, Reversal DOAC
- Contraindication : pregnancy, thromboembolism disorders

04 Blood component therapy

- PRC
- Plt conc
- FFP
- Cryoprecipitate

Blood transfusions

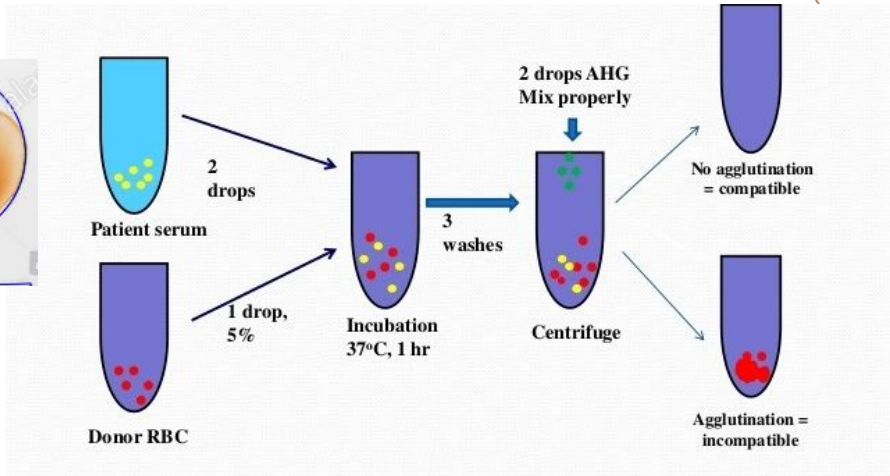


Compatibility testing

- ABO-Rh typing
- Cross matching
- Ab screening

Blood transfusions

Blood Group	Antigens	Antibodies	Can give blood (RBC) to	Can receive blood (RBC) from
AB	A and B	None	AB	AB, A, B, O
A	A	B	A and AB	A and O
B	B	A	B and AB	B and O
O	None	A and B	AB, A, B, O	O



BOX 49.1 Infectious Disease Testing for Blood Transfusions

1. Discontinue serum alanine aminotransferase testing
2. Hepatitis C antibody testing
3. Antibody to hepatitis B core antigen
4. Human immunodeficiency virus (HIV) type 1
5. HIV-2
6. HIV Ag (p24 antigen)
7. Human T-cell lymphotropic virus (HTLV) types 1 and 2
8. Serologic test for syphilis

Blood transfusions

TABLE 49.1 Percentage Risk of Transfusion-Transmitted Infection With a Unit of Screened Blood in the United States

Infection	Risk	Window Period (Days)
Human immunodeficiency virus-1 and -2	1:1,476,000	5-6
Human T-lymphotropic virus (HTLV-II)	1:2,993,000	51
Cytomegalovirus (CMV)	Infrequent with leukocyte-reduced components	
Hepatitis C virus (HCV)	1:1,149,000	3-4
Hepatitis B virus (HBV)	1: 280,000	24
Hepatitis A virus (HAV00)	1:1,000,000	
Bacteria red blood cells	1:1,000 with septic reaction in 1:500,000	
Pheresis platelets (with early aerobic culture)		
Parasites: Babesia and malaria	<1:4,000,000	7-14
West Nile virus (WNV)	1/1,100,000	?
Acute hemolytic transfusion reactions	1:38,000-1:70,000	

High risk : drug use, recent tattoos, MSM

CMV :

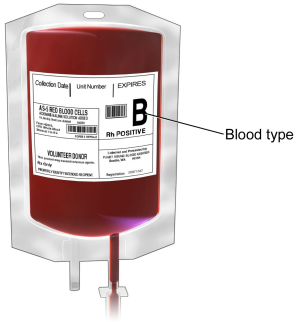
- premature neonates, allograft recipients, post splenectomy, Immunocompromised, pregnancy
- leukocyte-reduced blood, frozen deglycerolized RBCs, and screening for CMV antibody negative donors
- Plasma components (FFP, cryoprecipitate, leukoreduced) from seropositive donors are considered to be CMV safe.

PRC

- **Anemia** : Criteria for transfusion : Hb<8 g/dL , ICU Hb 7-10g/dL
- **Acute blood loss** : 1,500-2,000 ml or 30% blood volume

Guideline Sponsoring Society	Asymptomatic ICU Patients	ACS	Neurologic Injury	Other
American Society of Anesthesiologists (ASA), *Anesthesiology 2015*				Restrictive goal: 6–10 g/dL
British Committee for Standards in Haemotology (BCSH), *BJH 2013*	>7 g/dL	8–9 g/dL	TBI: 7–9 g/dL Ischemia: >9 g/dL	Early sepsis: >9 g/dL Late sepsis: 7–9 g/dL
European Society of Anaesthesiology (ESA), *Eur J Anaesthesia 2013*			TBI: 7–9 g/dL	7–9 g/dL for active bleeding
AABB (Former American Association of Blood Banks), *JAMA 2016*	>7 g/dL	>8 g/dL	No supportive evidence	Postoperative: >8 g/dL
Society of Cardiovascular Anesthesiologists and Society of Thoracic Surgeons (SCA/STS), *Ann Thor Surg 2011*	>6–7 g/dL			Higher goal >7 g/dL for at-risk patients
Society of Critical Care Medicine (SCCM), *CCM 2009*	>7 g/dL	>8 g/dL	No supportive evidence	

PRC

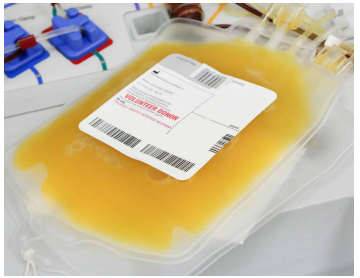


Labeled Blood Bag

- Shelf life : 42 days, 2-6℃
- **Emergency transfusion**
- Type-specific, Partial crossmatched blood
- Type-specific, Uncrossmatched blood
- Type O Rh-negative (Universal donor), Uncrossmatched blood
- **Whole blood, PRC, LPRC** (febrile non hemolytic transfusion reaction, organ transplant)
- Hb should rise 1 g/dL (3% Hct) for each unit of packed RBCs
- Citrate toxicity (Large volume transfusion, Hypocalcemia), Hyperkalemia

Plt conc

Stable patients without evidence of bleeding or coagulopathy	<10,000/μL
Prophylaxis for central venous catheterization	<20,000/μL
Prophylaxis for invasive procedures such as lumbar puncture, neuraxial anesthesia, endoscopy with biopsy, liver biopsy, or major nonneuraxial surgery	<50,000/μL
Stable patients with clinical evidence of bleeding or coagulopathy including DIC	<50,000/μL
Patients undergoing massive transfusion	<75,000–100,000/μL
Patients having surgery at critical sites such as the eye or central nervous system	<80,000–100,000/μL
Microvascular bleeding attributed to platelet dysfunction such as uremia, liver disease, postcardiopulmonary bypass	Clinician judgment



-Plt conc, SDP, Pooled leukocyte poor Plt conc

- Shelf life : 5 days, 20-24℃

- factor : splenomegaly,fever, sepsis, and active bleeding,

- Contraindication : ITP, TTP/HUS, HIT

- 5,000–10,000/ μL(RDP) or 10,000–60,000/μL (SDP)

FFP

- Correction of inherited factor deficiencies when there is no specific factor concentrate (e.g., factor V) and when the PT or aPTT is >1.5 times the mean control or INR >2.0.
- Replacement of multifactor deficiencies with clinical bleeding after transfusion of more than one blood volume (>70 mL/kg) when PT, INR, or aPTT cannot be obtained immediately.
- Correction of acquired multifactor deficiencies with clinical evidence of bleeding or in anticipation of major surgery or an invasive procedure with PT or aPTT >1.5 times the control, or INR >2.0.
  - Liver dysfunction with clinical signs of bleeding.
  - DIC with clinical signs of bleeding.
  - Reversal of vitamin K antagonists (warfarin) *when PCCs are not available.*
  - Heparin resistance secondary to AT deficiency when AT concentrate is not available.
  - Treatment of thrombotic microangiopathies (thrombotic thrombocytopenic purpura, HELLP syndrome, or hemolytic uremic syndrome).
- Treatment of hereditary angioedema when C1-esterase inhibitor is not available.

- All coagulation factors, except platelets
- Shelf life : 1 years, freezer
- 10-15 ml/kg/dose (obtain at least 30% factor activity)

Cryoprecipitate

- Containing fibrinogen, fibronectin, vWF, FVIII, and FXIII.
- Shelf life : 1 year, freezer
- **Indications**

  • Fibrinogen conc < 80–100mg/dl with excessive bleeding

  • Adjunct in massively transfusion, congenital fibrinogen deficiency, dysfibrinogenemia, Factor XIII deficiency, hemophilia A, or von Willebrand disease (when other blood component not available)

05

Blood transfusion reactions

- Febrile
- TACO
- TRALI
- Allergic
- Hemolysis

Blood transfusion reactions

Transfusion Reaction	Incidence (per 10^5 Transfusions)	Etiology	Therapy	Prevention
Febrile	All components: 70-6800	Storage-generated proinflammatory cytokines Patient antileukocyte antibodies bind to donor leukocytes	Stop transfusing Give antipyretics Supportive care	Prestorage leukoreduction
TACO	All components: 16.8-8000 Practice-dependent	Circulatory overload Patients with cardiac or renal disease, infants, and the critically ill are at increased risk	Stop transfusing Give diuretics Oxygen	Identify patients at high risk Transfuse slowly
TRALI	Erythrocytes: 10-20 Platelets/plasma: 50-100	Passive transfusion of donor antibodies Storage-generated toxic lipids	Supportive care	Remove high-risk donors from the donor pool
Allergic	All components: 3000 mild, 2 anaphylactic	Mild reactions: Transfusion of soluble antigens in donor plasma Anaphylaxis: IgA deficiency or other recipient protein deficiency	Stop transfusing ASA monitors Large-bore IV access Epinephrine Antihistamines Supportive care	Pretransfusion antihistamine use remains common practice despite limited evidence
Hemolytic	Erythrocytes: 1.1-9.0	Donor antibodies bind to patient erythrocytes Patient antibodies bind to donor erythrocytes	Stop transfusing Repeat matching Supportive care Treat DIC	Standard operating procedures

TACO vs TRALI

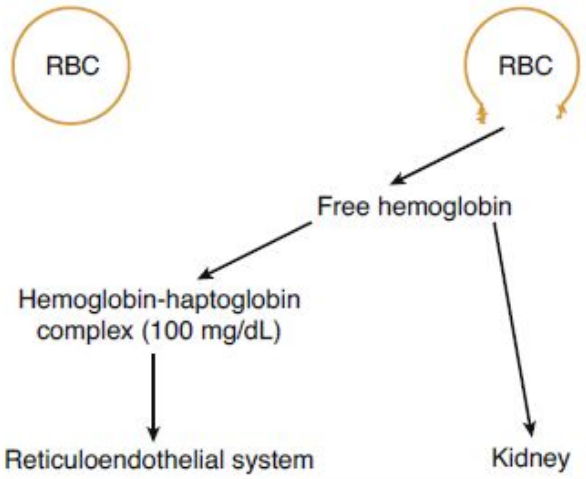
TRANSFUSION ASSOCIATED CIRCULATORY OVERLOAD

TABLE 49.17 Comparison of definitions of TACO and TRALI per CDC Guidelines.

TACO	TRALI
New onset or exacerbation of 3 or more of the following within 6 h of cessation of transfusion: ■ Acute respiratory distress (dyspnea, cough, orthopnea) ■ Elevated brain natriuretic peptide (BNP) ■ Elevated central venous pressure (CVP) ■ Evidence of left heart failure ■ Evidence of positive fluid balance ■ Radiographic evidence of pulmonary edema	No evidence of acute lung injury prior to transfusion AND ALI onset during or within 6 h of cessation of transfusion AND Hypoxemia defined by any of these methods ■ PaO2/FiO2 less than or equal to 300 mm Hg ■ Oxygen saturation less than 90% on room air ■ Other clinical evidence AND Radiographic evidence of bilateral infiltrates without evidence of left atrial hypertension (i.e., circulatory overload)

TRANSFUSION RELATED ACUTE LUNG INJURY

Hemolytic transfusion reactions



BOX 49.6 Steps in the Treatment of a Hemolytic Transfusion Reaction

1. Stop the transfusion.
2. Maintain the urine output at a minimum of 75-100 mL/h by the following methods:
   a. Administer fluids intravenously and possibly mannitol
   b. Administer furosemide if intravenous fluids and mannitol are ineffective
3. Alkalinize the urine
4. Assay urine and plasma hemoglobin concentrations.
5. Determine platelet count, prothrombin time, partial thromboplastin time, and serum fibrinogen level.
6. Return unused blood to blood bank for repeat crossmatch.
7. Send patient's blood and urine sample to blood bank for examination.
8. Prevent hypotension to ensure adequate renal blood flow.

Take home message

- **Common Hemostasis disorder**
    - Abnormal pathway, Lab investigations, Management.
- **Pharmacological**
    - Mechanism of action, Lab monitoring, Reversal agent.
    - Discontinue before surgery.
- **Blood transfusion**
    - Component, Indication, Transfusion Reaction.

References

- **Basic of anesthesia**, 7th edition, Manuel C. Pardo, Jr., Ronald D.Miller
- **Clinical anesthesia**, 8th edition, Paul G. Barash
- **Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy**, American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition), volume 43, number3, April 2018
- **A Compendium of Transfusion Practice Guidelines** Edition 4.0 January 2021, AMERICAN RED CROSS

THANK YOU