
بسم الله الرحمن الرحيم
١٤٢٥

Antithrombotics &Thrombolytics Procoagulant Drugs

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TABLE 50.1 Common Classes of Antithrombotics, Thrombolytics, and Procoagulants

Category	Subcategory	Generic Drug Names
Antiplatelet agents	Cyclooxygenase inhibitors	Aspirin, NSAIDS
	P2Y12 receptor antagonists	Ticlopidine, clopidogrel, prasugrel, cangrelor, and ticagrelor
	Platelet GPIIb/IIIa antagonists	Abciximab, eptifibatide, and tirofiban
Anticoagulants	Vitamin K antagonists	Warfarin
	Heparin	UFH, LMWH, fondaparinux
	Direct thrombin inhibitors	Argatroban, bivalirudin (IV) Desirudin (SQ) Dabigatran (PO)
	Factor Xa inhibitors	Rivaroxaban, apixaban, edoxban
Thrombolytics	Fibrin-specific agents	Alteplase, reteplase, tenecteplase
	Non-fibrin-specific agents	Streptokinase
Antifibrinolytics	Lysine analogs	Tranexamic acid, epsilon-aminocaproic acid
Factor Replacements	Recombinant Factor VIIa	
	Factor VIII-vWF	
	Prothrombin complex concentrates	3-factor PCC; 4-factor PCC, activated PCC, FEIBA
	Fibrinogen concentrates	

ANTIPLATELET AGENTS

- Antiplatelet agents inhibit thrombus formation by inhibiting platelet aggregation and/or adhesion to clot or damaged endothelium
- Depending on the drug, they can work either reversibly or irreversibly

ANTIPLATELET AGENTS

- Most common antiplatelet :
  - (1) cyclooxygenase (COX) inhibitors
  - (2) P2Y12 receptor antagonists
  - (3) platelet GPIIb/IIIa antagonists
  - several other :
    - phosphodiesterase inhibitors
    - protease-activated receptor-1 antagonists
    - adenosine reuptake inhibitors
    - thromboxane inhibitors

ANTIPLATELET AGENTS

Cyclooxygenase Inhibitors

- **Aspirin and NSAIDS**
- **Cyclooxygenase Inhibitors :** COX-1 and COX-2
- **COX-1 :**
  - the integrity of the gastric lining
  - renal blood flow
  - initiates the formation of thromboxane A2 (TxA2)
    - important for platelet aggregation
- **COX-2 :**
  - responsible for synthesizing the prostaglandin mediators in pain and inflammation

ANTIPLATELET AGENTS

Cyclooxygenase Inhibitors

Aspirin

- **Non-selective and irreversible COX inhibitor**
  - **Acetylates a serine residue on COX-1 and prevents the production of TxA2 in platelets**
- COX-2
  - Antiinflammatory and Analgesic effects
  - 170 times less sensitive than COX-1 to aspirin so only at high doses can aspirin irreversibly inhibit both COX-1 and COX-2
- Because platelets are anuclear, they are unable to synthesize new COX-1 once **aspirin has irreversibly inhibited the enzyme**
- Despite its short half-life of approximately 15 to 20 minutes, **aspirin's inhibitory effect persists through the platelet lifespan of 7 to 10 days**

ANTIPLATELET AGENTS

Cyclooxygenase Inhibitors

Aspirin

- The recovery of platelet function after aspirin depends on platelet turnover
- **Megakaryocytes generate 10% to 12% of** platelets daily, so near normal hemostasis is expected in 2 to 3 days after the last dose of aspirin with typical platelet turnover
- **High platelet turnover diseases :**
  - increased production (e.g., essential thrombocythemia)
  - increased consumption (e.g., inflammation)
  - may require more frequent than once daily aspirin dosing
- **Immediate reversal of aspirin for emergencies :**
  - **platelet transfusions**

ANTIPLATELET AGENTS
NONSTEROIDAL ANTIINFLAMMATORY DRUGS

- Most NSAIDS are nonselective
- reversible COX inhibitors
- antipyretic, analgesic
- antiplatelet aggregation effects

ANTIPLATELET AGENTS
NONSTEROIDAL ANTIINFLAMMATORY DRUGS

- Platelet function normalizes 3 days after discontinuing the use of NSAIDS
- Selective COX-2 antagonists such as celecoxib :
  - antiinflammatory, analgesic, and antipyretic activity without the gastrointestinal complications
  - **increased risks for cardiovascular complications**
  - inhibition of PGI2 without inhibition of TxA2, thus tipping the balance **toward thrombosis**
  - use COX-2 inhibitors only when necessary for pain and then with the lowest effective dose possible after weighing the risks and benefits

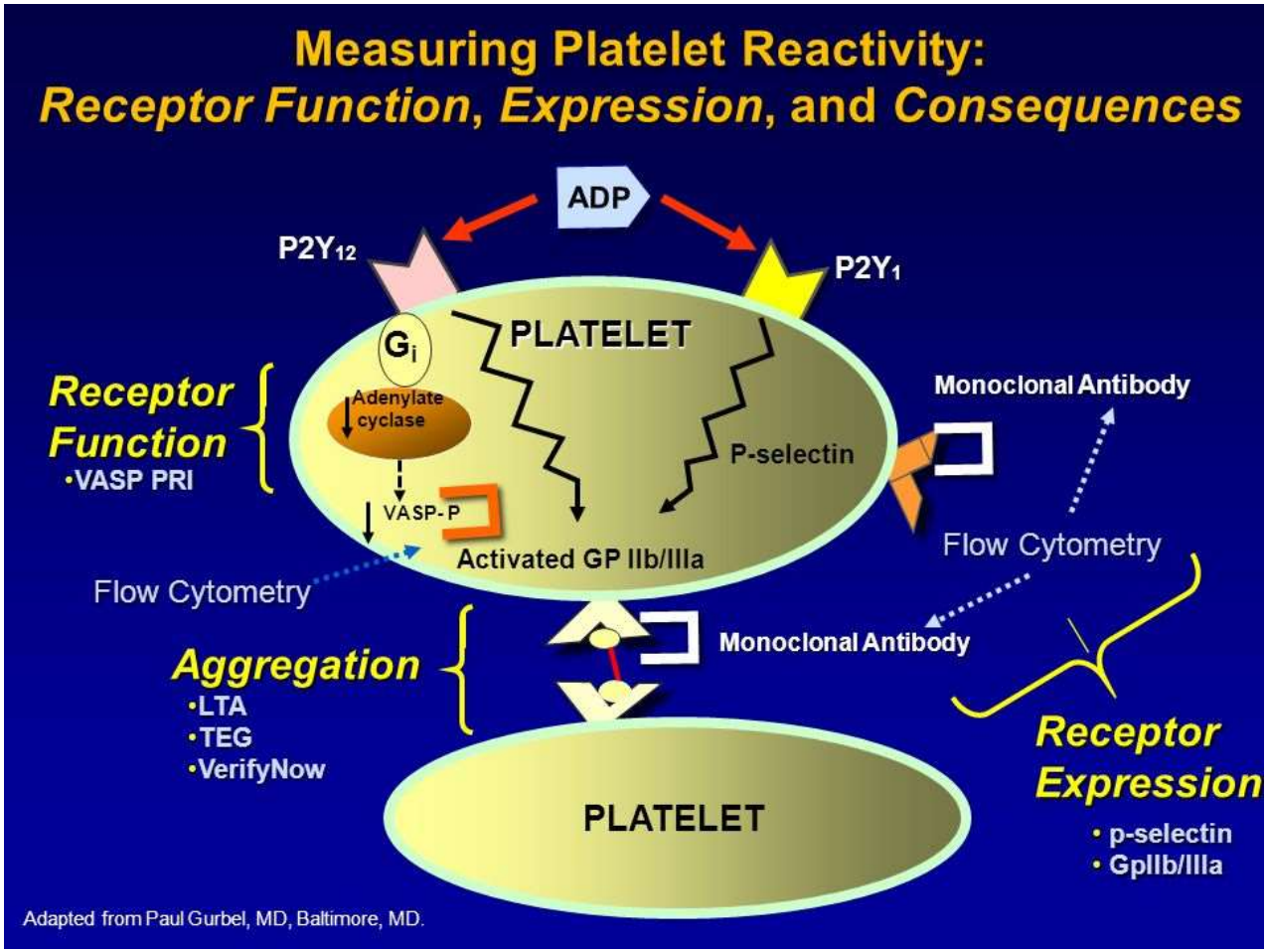
ANTIPLATELET AGENTS

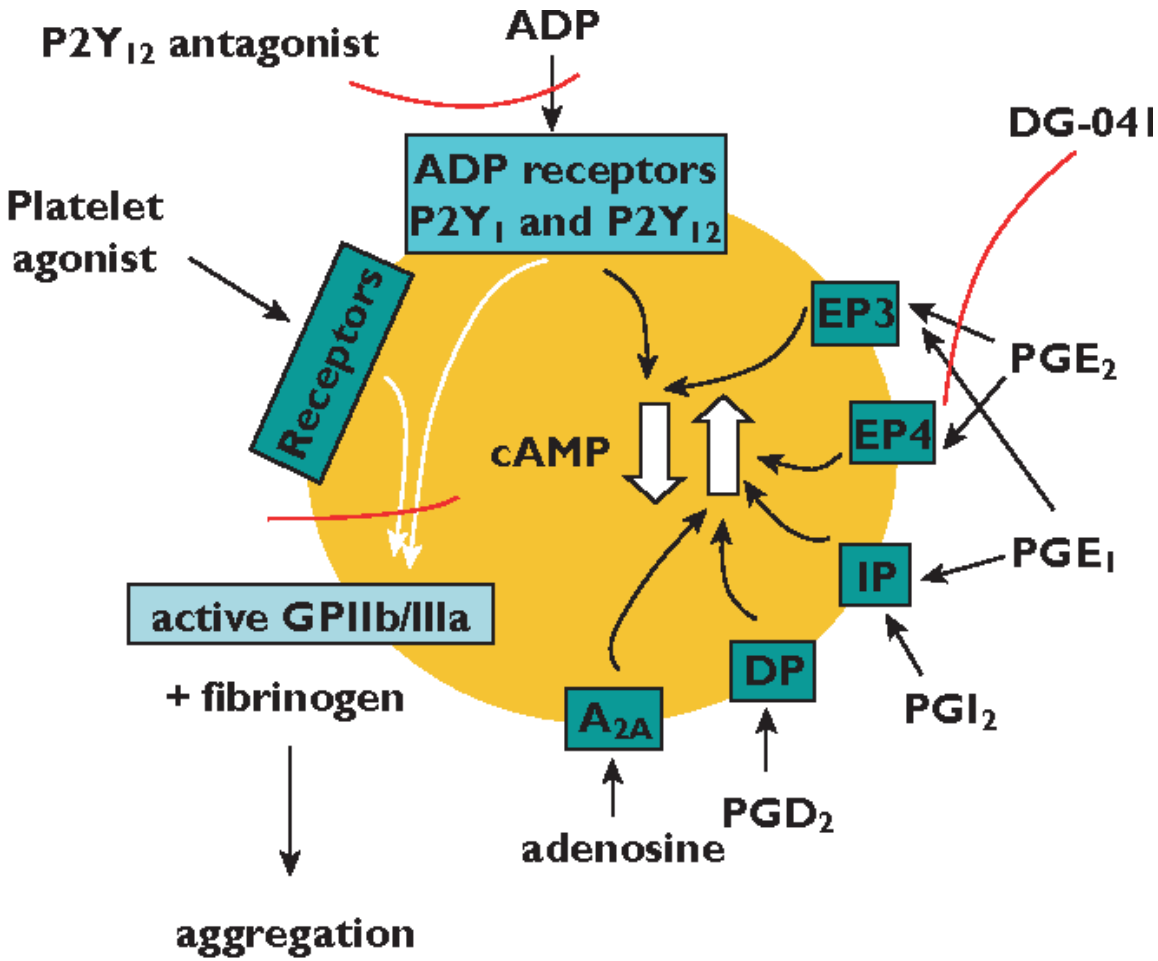
P2Y12 RECEPTOR ANTAGONISTS

- These drugs : ticlopidine, clopidogrel, prasugrel, cangrelor, and ticagrelor
- **inhibiting the P2Y12 receptor :**
  - inhibits platelet adhesion and aggregation
  - **preventing the expression of GPIIb/IIIa on the surface of activated platelets**
- **Ticlopidine, clopidogrel, and prasugrel**
  - Thienopyridines
  - **pro-drugs requiring hepatic metabolism to generate the active metabolite** that then **irreversibly inactivates the ADP-binding site of the P2Y12 receptor**
- **Ticagrelor and cangrelor : reversible inhibitors**

ANTIPLATELET AGENTS

P2Y12 RECEPTOR ANTAGONISTS



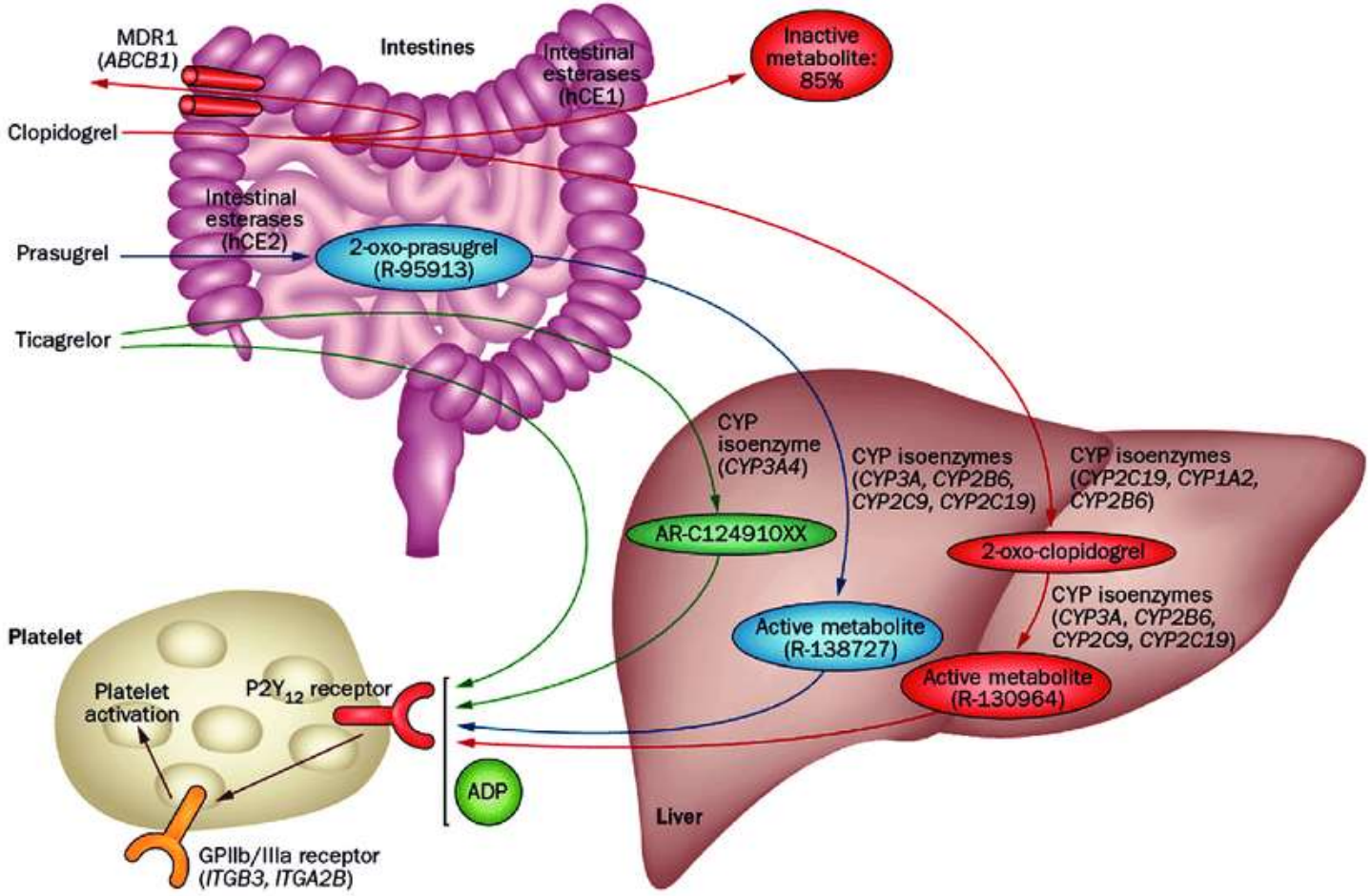

P2Y12 antagonist
ADP
DG-041
ADP receptors
P2Y1 and P2Y12
Platelet
agonist
Receptors
EP3
PGE2
cAMP
EP4
IP
PGE1
active GPIIb/IIIa
+ fibrinogen
DP
A2A
PGI2
PGD2
adenosine
aggregation

ANTIPLATELET AGENTS
P2Y12 RECEPTOR ANTAGONISTS

- **Clopidogrel (Plavix)**
- Platelet functions normalize
  - 7 days after discontinuing clopidogrel
  - 14 to 21 days after discontinuing ticlopidine
- **Genetic polymorphism :** CYP2C19 ,ABCB1 gene
- Decreased CYP2C19 and ABCB1 activity :
  - increased risk of major cardiovascular events

ANTIPLATELET AGENTS

P2Y12 RECEPTOR ANTAGONISTS



ANTIPLATELET AGENTS

P2Y12 RECEPTOR ANTAGONISTS

Ticagrelor

- Ticagrelor binds to the P2Y12 receptor
  - conformational change of the receptor
- needs to undergo metabolism to an active metabolite
- both the parent drug and the active metabolite have anti-platelet effects
- ~~Genetic polymorphisms~~
- shorter acting than clopidogrel
  - ticagrelor must be dosed twice daily
  - may be of benefit prior to surgery

ANTIPLATELET AGENTS

P2Y12 RECEPTOR ANTAGONISTS

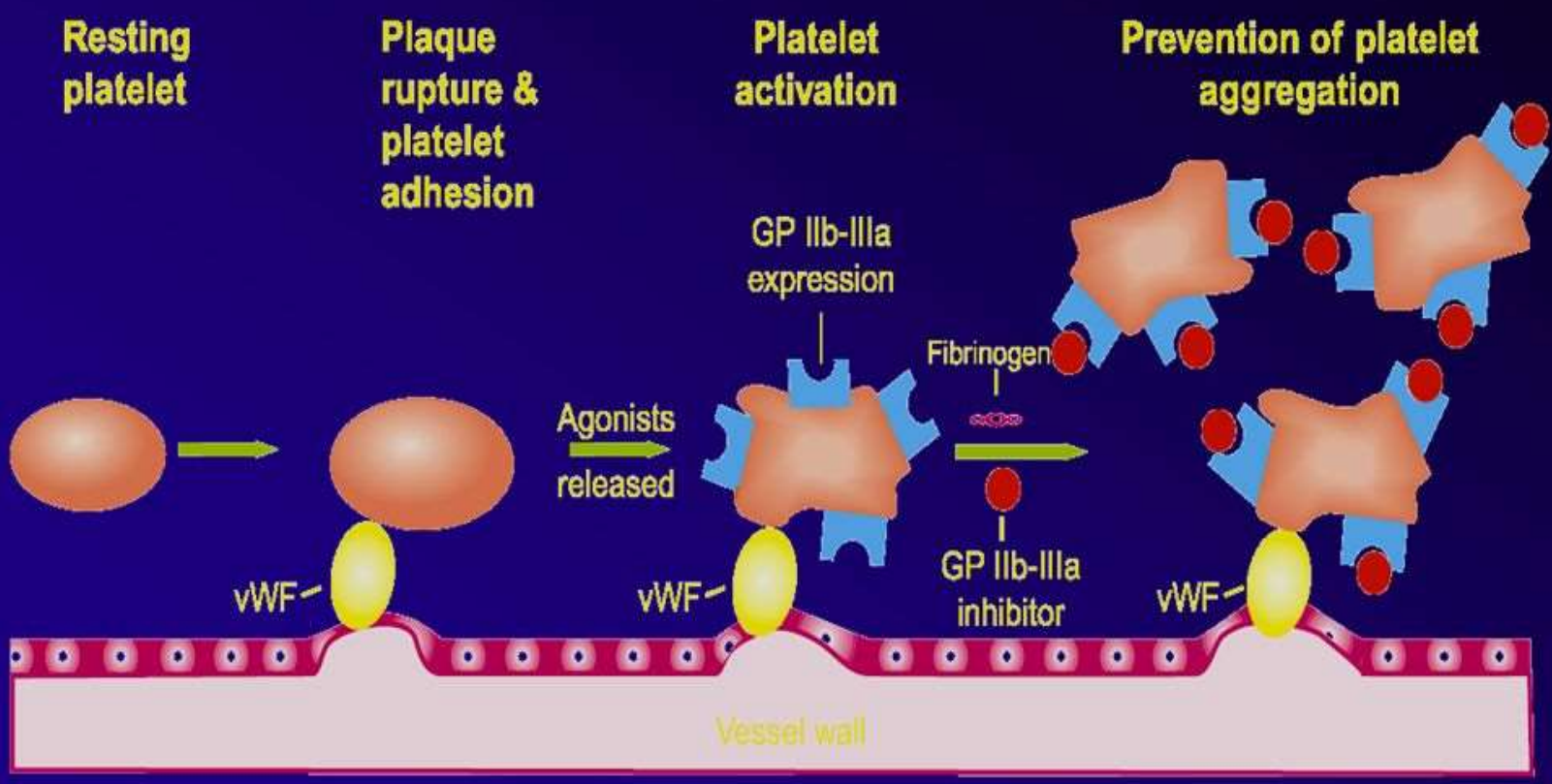
Cangrelor

- Only one available for **intravenous administration**
- changes the conformation of the P2Y12 receptor, resulting in inhibition of ADP-induced platelet aggregation
- **Fastest onset of action (seconds)**
  - platelet function normalizes within 60 minutes after drug discontinuation
  - This rapid onset may allow for bridging therapy in patients with drug-eluting stents who require surgery

ANTIPLATELET AGENTS
GLYCOPROTEIN IIB/IIIA INHIBITORS

- Glycoprotein IIb/IIIa inhibitors (GPI) :
  - **(abciximab, eptifibatide, and tirofiban)**
  - prevent platelet aggregation by decreasing the binding of fibrinogen and vWF to glycoprotein IIb/IIIa receptors on the surface of activated platelets
- **Intravenously in order to:**
  - **(1)stop ongoing arterial thrombosis**
  - **(2) eliminate excessive platelet reactivity in diseased vessels so that occlusive thrombi and restenosis do not occur**

Mechanism of action: GP IIb-IIIa inhibitors



White HD. *Am J Cardiol.* 1997; 80(4A):2B-10B.

ANTIPLATELET AGENTS
GLYCOPROTEIN IIB/IIIA INHIBITORS

- Their use was highly touted in the past with balloon angioplasty where acute closure was a feared complication
- GPI have become less popular in routine PCI :
  - associated bleeding risk
  - use is only recommended in a subset of patients with high risk angiographic features
  - those not loaded adequately with dual antiplatelet agents
- **abciximab** has a short plasma half-life (10 minutes)
  - its effects on platelet function can be seen for much longer, even after the infusion has been stopped
  - One rare, but serious side effect to be aware of, **abciximab** : **thrombocytopenia** immediately after drug administration

ANTICOAGULANTS

- Vitamin K Antagonists
- Unfractionated Heparin
- Low Molecular Weight Heparin and Fondaparinux
- Direct Thrombin Inhibitors
- Direct Oral Anticoagulants

ANTICOAGULANTS

Vitamin K Antagonists

Warfarin

- Warfarin, the most frequently used oral VKA
- **inhibits the vitamin K-dependent carboxylation of coagulation factors II, VII, IX, and X and proteins C and S**
- highly effective in reducing the risk of venous and arterial thromboemboli
- **still the anticoagulant of choice for patients with valvular atrial fibrillation and mechanical heart valves** despite the popularity and increased utilization of DOACs for nonvalvular atrial fibrillation

ANTICOAGULANTS

Vitamin K Antagonists

Warfarin

- **long half-life (40 hours)**
- **the complete anticoagulant effect can take 3 to 4 days :** the long half-lives of the preexisting coagulation factors :
  - Prothrombin (factor II) has the longest half-life (~60 hours)
  - Factor VII and protein C have the shortest halflives (3-6 hours)
- Because of this long initiation period
  - **patients at high risk for thromboembolism must be bridged with another anticoagulant (usually UFH or LMWH) until the target INR is achieved**

ANTICOAGULANTS

Vitamin K Antagonists

Warfarin

- **Early reductions in the anticoagulant protein C** : imbalance toward a **hypercoagulable state** if warfarin is started alone, resulting in **thrombosis or warfarin-induced skin necrosis**
- Warfarin is monitored using the INR
  - therapeutic range :
    - **INR of 2.0 to 3.0**
    - **patients with mechanical heart valves,where higher values are necessary (INR 2.5-3.5)**

ANTICOAGULANTS

Vitamin K Antagonists

Warfarin

- **The INR :**
  - not calibrated to evaluate non-warfarin deficiencies such as liver disease and should not be used to evaluate therapeutic effects of other anticoagulants
- **very narrow therapeutic window**
  - can be easily affected by drug-drug interactions and patient variability
- The need for frequent laboratory monitoring makes warfarin a difficult drug for patients to maintain compliance and the reported time in therapeutic range is only about 65% ± 20% in patients with atrial fibrillation

Warfarin

ANTICOAGULANTS

Vitamin K Antagonists

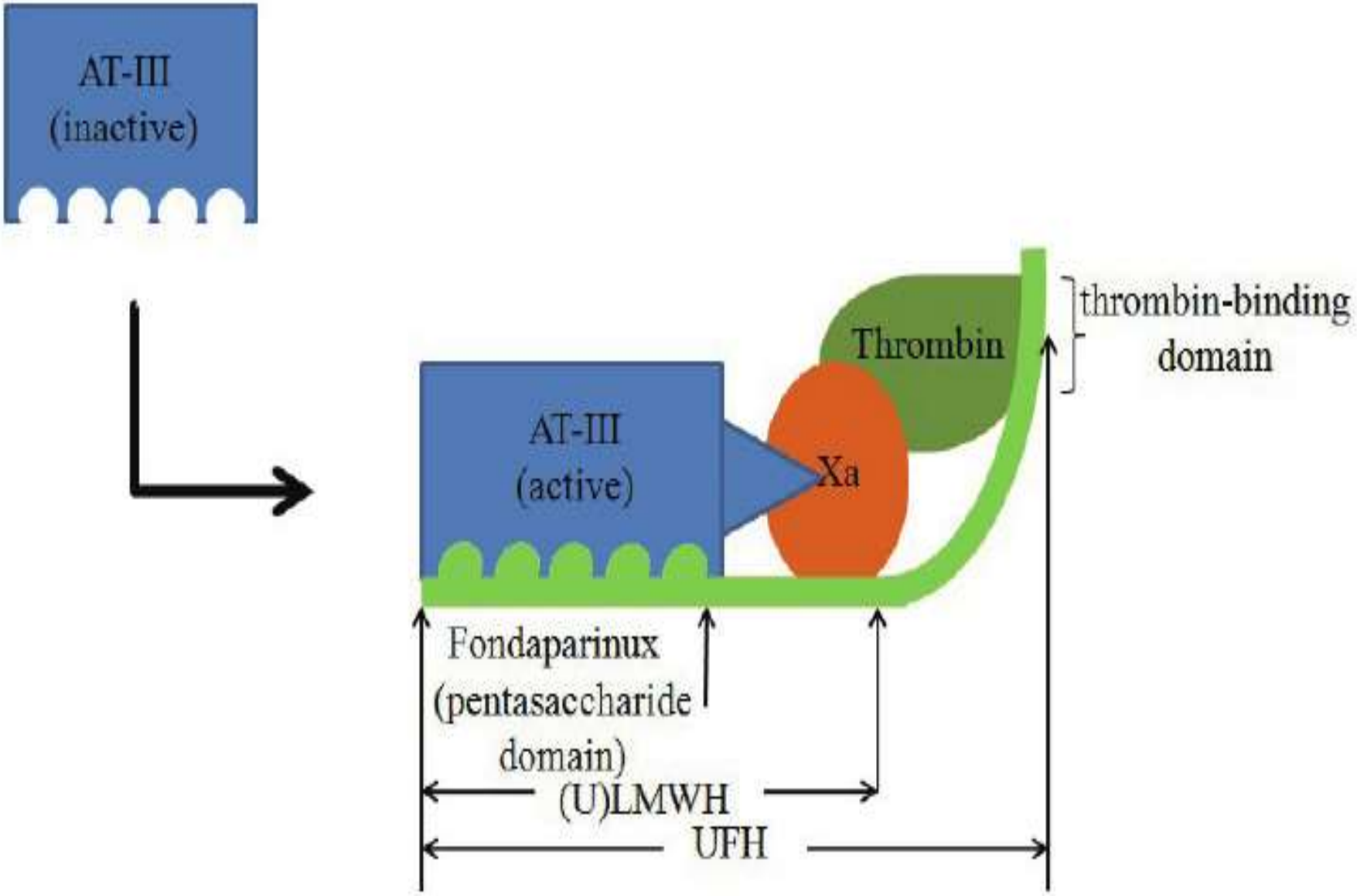
Warfarin

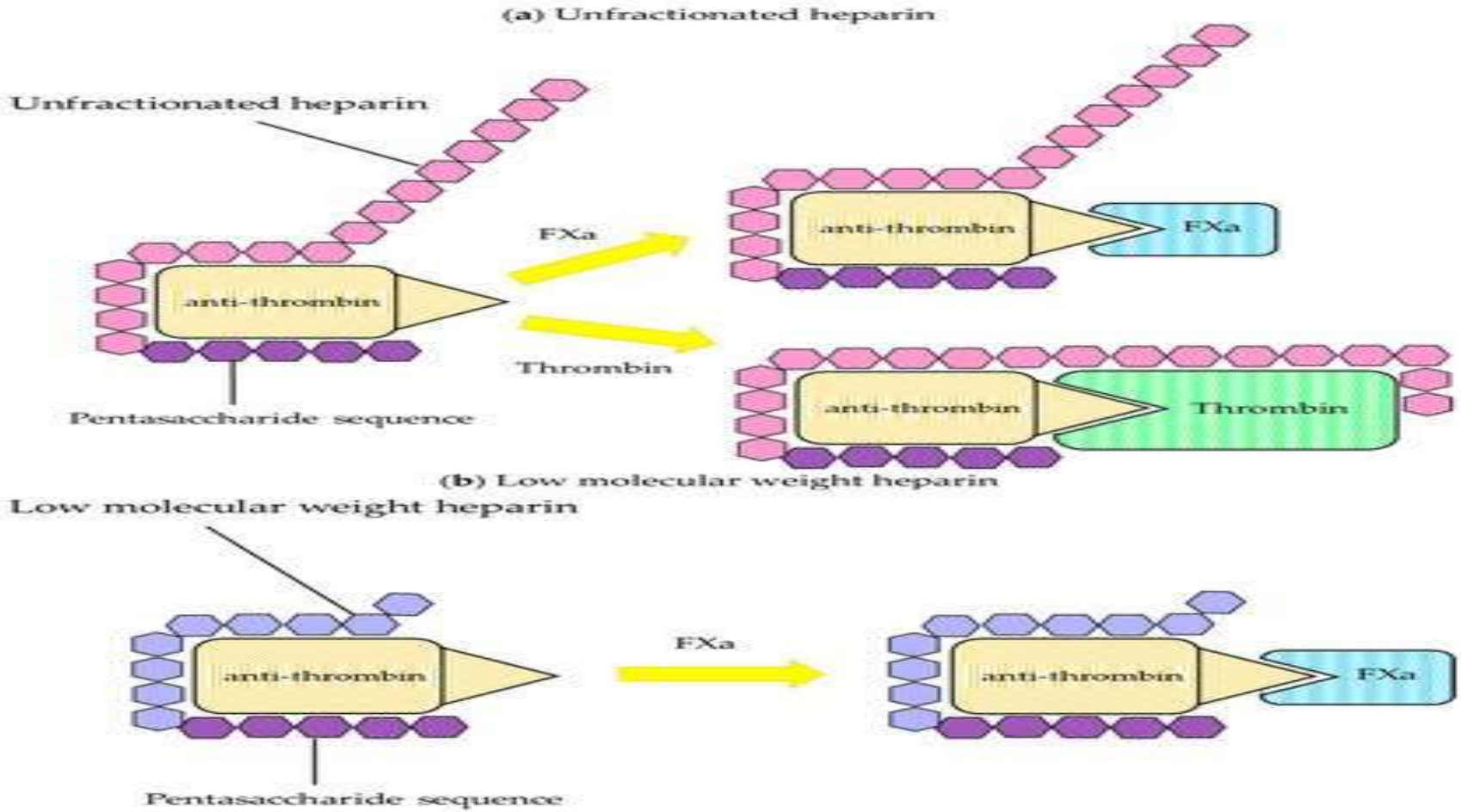
- **Warfarin's pharmacology can be affected :**
  - genetic variations in the metabolism of the drug (CYP2C9)
  - in the production of a vitamin K epoxide reductase enzyme (VKORC1), which reduces vitamin K after it has been oxidized
- Current recommendations pharmacogenetics testing :
  - patients who consistently have INRs outside the therapeutic range
  - who have an adverse event while on therapy

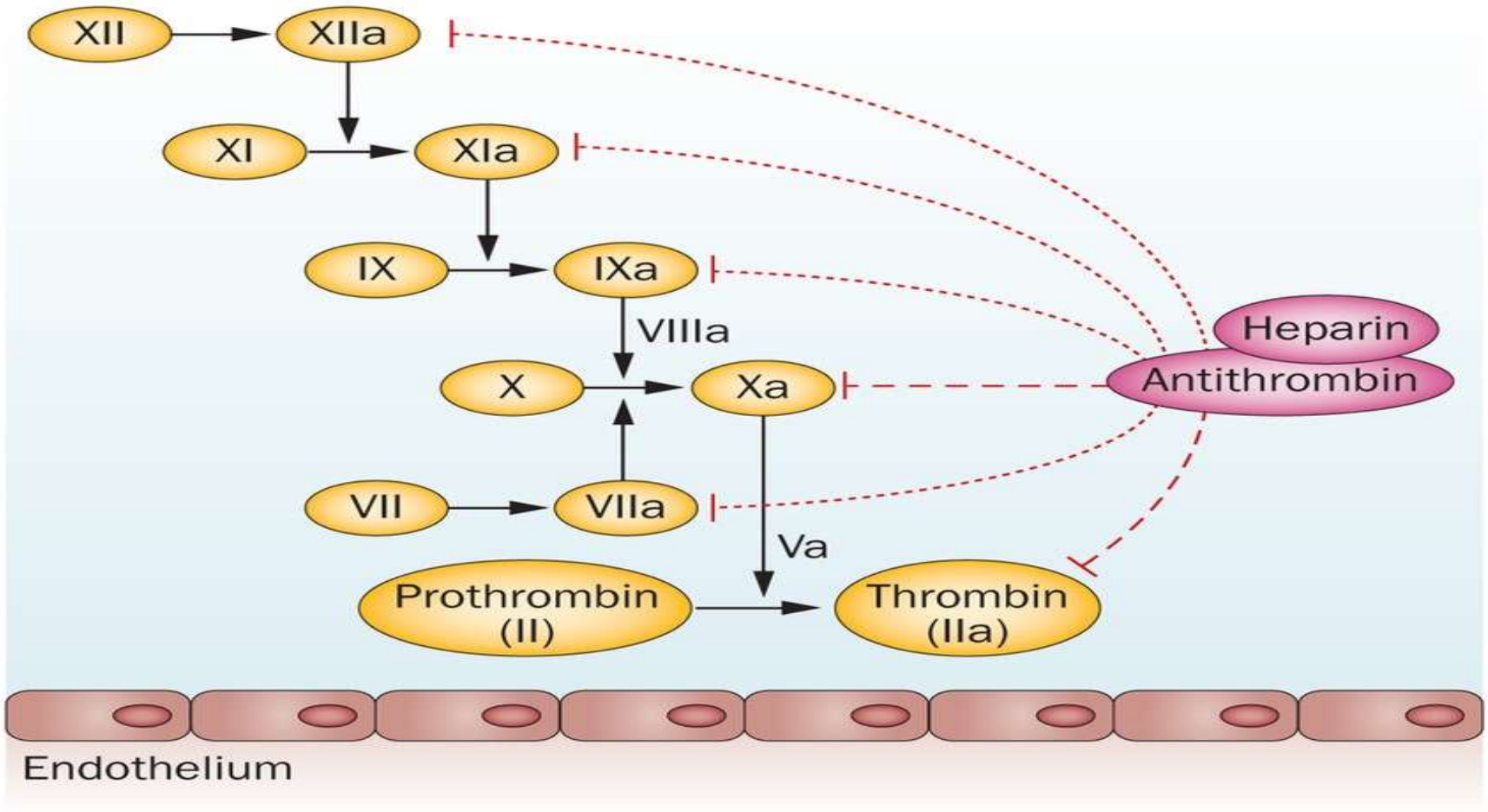
ANTICOAGULANTS

Unfractionated Heparin

- **UFH : isolated from porcine or bovine intestines**
- mixture of different length polysaccharides with a high molecular weight (mean molecular weight around 15,000 daltons or 35-45 polysaccharide units)
- **UFH binds to AT and indirectly inhibits thrombin (factor IIa) and factor Xa**
- **Benefits of heparin :**
  - **short half-life and full reversibility with protamine**
- **Heparin does not have any fibrinolytic activity**
- **Full-dose heparin for cardiac surgery :**
  - **intravenous bolus of 300 to 400 U/kg**
  - **ACT safe for initiation of CPB : greater than 400 to 480**


AT-III
(inactive)
AT-III
(active)
Xa
Thrombin
thrombin-binding
domain
Fondaparinux
(pentasaccharide
domain)
(U)LMWH
UFH


(a) Unfractionated heparin
Unfractionated heparin
anti-thrombin
Pentasaccharide sequence
FXa
Thrombin
anti-thrombin
FXa
anti-thrombin
Thrombin
(b) Low molecular weight heparin
Low molecular weight heparin
anti-thrombin
Pentasaccharide sequence
FXa
anti-thrombin
FXa


XII
XIIa
XI
XIa
IX
IXa
VIIIa
X
Xa
VII
VIIa
Va
Prothrombin
(II)
Thrombin
(IIa)
Heparin
Antithrombin
Endothelium

Unfractionated Heparin
Resistant to UFH

- **Hereditary deficiency of AT**
- **Acquired deficiency of AT from prolonged heparin administration**
- **During CPB : 21%**
- **Treatment : Fresh frozen plasma (FFP) transfusions or AT concentrate**
  - which will replenish AT levels and restore heparin response
- **Other causes of heparin resistance :**
  - **increased heparin clearance**
  - **increased levels of heparin-binding proteins**
  - **elevations of fibrinogen and factor VIII levels**

ANTICOAGULANTS

Low Molecular Weight Heparin and Fondaparinux

LMWH

- **LMWH :** produced by **cleaving UFH** into shorter fragments (mean molecular weight approximately 4000 daltons,approximately 15 saccharide units)
- **Fondaparinux** : **synthetic pentasaccharide** (mean molecular weight 1700 daltons) of the AT binding region of heparin
  - **Act more specifically via AT to inhibit factor Xa**

ANTICOAGULANTS

Low Molecular Weight Heparin and Fondaparinux

LMWH

- **LMWH and fondaparinux :**
  - **do not affect the aPTT assay**
  - **coagulation testing : usually not needed**
- **Anti-factor Xa activity levels** may be necessary in patients who may have unpredictable drug levels (e.g., renal failure, pregnancy, and body weight less than 50 kg or more than 80 kg)

ANTICOAGULANTS

Low Molecular Weight Heparin and Fondaparinux

LMWH

- **LMWH : longer half-life than heparin**
  - administered **subcutaneously** either once or twice daily
- **LMWH : excreted by the kidney**
  - half-life is prolonged in patients with renal failure
- 25% to 50% of LMWH molecules contain 18 or more saccharide units and can **inhibit factor Xa and thrombin**
- the remaining 50% to 75% of LMWH molecules contain <18 saccharide units and **only inhibit factor Xa**
- **Protamine requires more than 14 saccharide units in the heparin molecule for interaction**
- **Protamine** : **partially effective in reversing LMWH**
  - It does not completely abolish the anti-Xa activity
  - may neutralize the higher molecular weight fractions of LMWH
- **Fondaparinux** : longer half-life (17-21 hours) , daily

ANTICOAGULANTS

Fondaparinux

LMWH

- **Fondaparinux :** only 5 saccharide units, protamine is not effective for reversing fondaparinux
- **Because antigen formation by the PF4/heparin complex requires a polysaccharide chain of at least 8 to 10 saccharides**
- **HIT : unlikely to occur**
- **Only eight cases of HIT**

ANTICOAGULANTS

Direct Thrombin Inhibitors

- **DTIs bind directly to thrombin**
  - **do not require a cofactor such as antithrombin to exert their effect**
- **All DTIs inhibit thrombin in its free (soluble) and fibrin-bound (insoluble) states**
  - unlike heparin, which only has effect on free thrombin
- **Other advantages over heparin include:**
  - **lack of binding to other plasma proteins**
    - **more predictable anticoagulant effect**
  - **no concern for developing an immune-mediated thrombocytopenia**

ANTICOAGULANTS

Direct Thrombin Inhibitors

- **Hirudin :** naturally occurring anticoagulant found in leeches
- **Argatroban and Bivalirudin :** synthetic agents
- **Reversibly** binds to the active site on thrombin
- **Argatroban :** FDA approved for the prophylaxis and treatment of thrombosis and for PCI anticoagulation in patients with HIT
- **Clinical effects** : aPTT or ACT in the operating room

- **Dosing goals :** maintain an aPTT 1.5 to 3 times baseline
- Because argatroban prolongs thrombin-dependent coagulation, the PT and INR will be prolonged as well, which can complicate transition to warfarin therapy for long-term anticoagulation

ANTICOAGULANTS

Direct Thrombin Inhibitors

Bivalirudin

- **Bivalirudin :**
  - **20-amino acid synthetic analogue of hirudin**
  - **reversible DTI**
  - **metabolized by proteolytic cleavage and hepatic metabolism**
- **Shortest halflife among the intravenous DTIs**
- **Drug of choice for patients with both renal and hepatic dysfunction**
  - **Dose adjustments : necessary**
  - have better efficacy in preventing primary outcomes with lower bleeding rates when compared with UFH for percutaneous transluminal coronary angioplasty for unstable or postinfarction angina,and for use as an alternative to heparin in patients with HIT undergoing PCI

ANTICOAGULANTS

Direct Thrombin Inhibitors

Desirudin

- Only DTI available for subcutaneous administration
- Cost-effective alternative to argatroban for patients with suspected HIT
- More predictable pharmacokinetics, and dosage adjustments and aPTT monitoring may be unnecessary in patients with a creatinine clearance greater than 30 mL/min

ANTICOAGULANTS

Direct Oral Anticoagulants

- more predictable pharmacokinetics and pharmacodynamics and fewer drug-drug interactions, allowing them to be dosed without daily laboratory monitoring
- **The drawback has been the lack of specific antidotes** for anticoagulation reversal, but this is slowly changing with the introduction of idarucizumab
-
-

ANTICOAGULANTS
Direct Oral Anticoagulants

- Most DOACs :
  - prevention of venous thromboembolism after hip or knee replacement surgery,treatment
  - secondary prevention of venous thromboembolism
  - prevention of stroke in nonvalvular atrialfibrillation
- use in :
  - secondary prevention of coronary events after acute coronary syndrome
  - prevention of thrombosis in elective PCI
  - prevention of thrombus formation on mechanical heart valves

ANTICOAGULANTS
Direct Oral Anticoagulants

- DOACs have a shorter half-life than warfarin
- Demonstrated noninferior efficacy to warfarin
- Dabigatran (Pradaxa), an oral DTI, was the first new antithrombotic agent approved for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation since warfarin
- When given at a dose of 150 mg twice daily, dabigatran was shown to reduce the risk of stroke while having a similar bleeding risk as warfarin at an INR of 2.0 to 3.0

ANTICOAGULANTS

Direct Oral Anticoagulants

Dabigatran

- **Dabigatran** : predominantly eliminated by the kidneys, so the dose should be reduced in patients with a creatinine clearance less than 30 mL/min
- **Monitoring of dabigatran therapy :**
  - difficult because the perfect laboratory test does not exist
- The aPTT does not become linear until dabigatran concentrations are quite high (>200 ng/mL)
- The TT is very sensitive to dabigatran, so while it is useful to detect any presence of the drug,it cannot be used to quantify the amount of drug present
- dilute TT or ecarin clotting time are both linear at clinically relevant dabigatran concentrations and are the tests of choice if monitoring is necessary

ANTICOAGULANTS

Direct Oral Anticoagulants

Direct Xa inhibitors

- **Direct Xa inhibitors :**
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)
  - Edoxaban (Savaysa)
- fewer strokes and embolic events, fewer intracranial hemorrhages, and lower all-cause mortality compared with warfarin
- The anti-factor Xa assays :
  - monitoring the effects of the direct Xa inhibitors
  - but assays must be individually calibrated for each drug

THROMBOLYTICS

- break up or dissolve blood clots
- Indication :
  - acute myocardial infarctions
  - Strokes
  - massive pulmonary embolus
  - arterial thromboembolism
  - venous thrombosis
- Thrombolytics may be given through an intravenous line systemically or directly to the site of the blockage
- Most thrombolytic agents are serine proteases that work by converting plasminogen to plasmin
- Plasmin then lyses the clot by breaking down fibrinogen and fibrin

THROMBOLYTICS

- Fibrinolytic agents :
  - (1) fibrin-specific agents
    - alteplase (tPA)
    - Reteplase
    - Tenecteplase
    - produce less plasminogen conversion in the absence of fibrin and result in less fibrinogen depletion
  - (2) non–fibrin-specific agents
    - (e.g., streptokinase) catalyze systemic fibrinolysis
    - Streptokinase, produced by betahemolytic streptococci
    - highly antigenic ,immunologic sensitization and allergic reactions, particularly with repeat administration even several years after previous exposure

THROMBOLYTICS

- t-Pas
  - Thrombolytics
  - anticoagulants
  - fibrinolysis generates increased amounts of circulating fibrin degradation products, which inhibit platelet aggregation
- Surgery or puncture of noncompressible vessels is contraindicated within a 10-day period after the use of thrombolytic drugs

THROMBOLYTICS

- the use of thrombolytics in acute pulmonary embolus, ST-elevation myocardial infarction (STEMI), and ischemic stroke
- Thrombolytics :in the setting of hemodynamic instability due to acute pulmonary embolus
- Primary PCI is the preferred treatment for patients with acute STEMI if it can be performed by an experienced operator within 2 hours from presentation to the emergency department, but fibrinolytic therapy remains an important modality in hospitals with limited primary PCI
- primary goal is to restore blood flow to ischemic regions in order to reduce stroke-related disability and mortality

THROMBOLYTICS

- **Alteplase** : treatment of acute ischemic stroke if treatment can be initiated within 4.5 hours of symptom onset
- Mechanical thrombectomy should still be considered even if thrombolysis has been administered for ischemic stroke

THROMBOLYTICS

TABLE 50.2 Absolute and Relative Contraindications for Thrombolytics

Absolute Contraindications	Relative Contraindications
Vascular lesions	Ischemic stroke >3 months prior
Severe, uncontrolled hypertension (SBP > 185 or DBP > 110)	Active peptic ulcer
Recent cranial surgery or trauma	Current use of anticoagulant drugs
Brain tumor	Pregnancy
Ischemic stroke <3 months prior	Prolonged/traumatic CPR <3 weeks prior
Active bleeding	Major surgery <3 weeks prior

PROCOAGULANT DRUGS

- Antifibrinolytics
- Factor Replacements

PROCOAGULANT DRUGS

Antifibrinolytics

EPSILON AMINO-CAPROIC ACID(EACA)

- Analogue of lysine

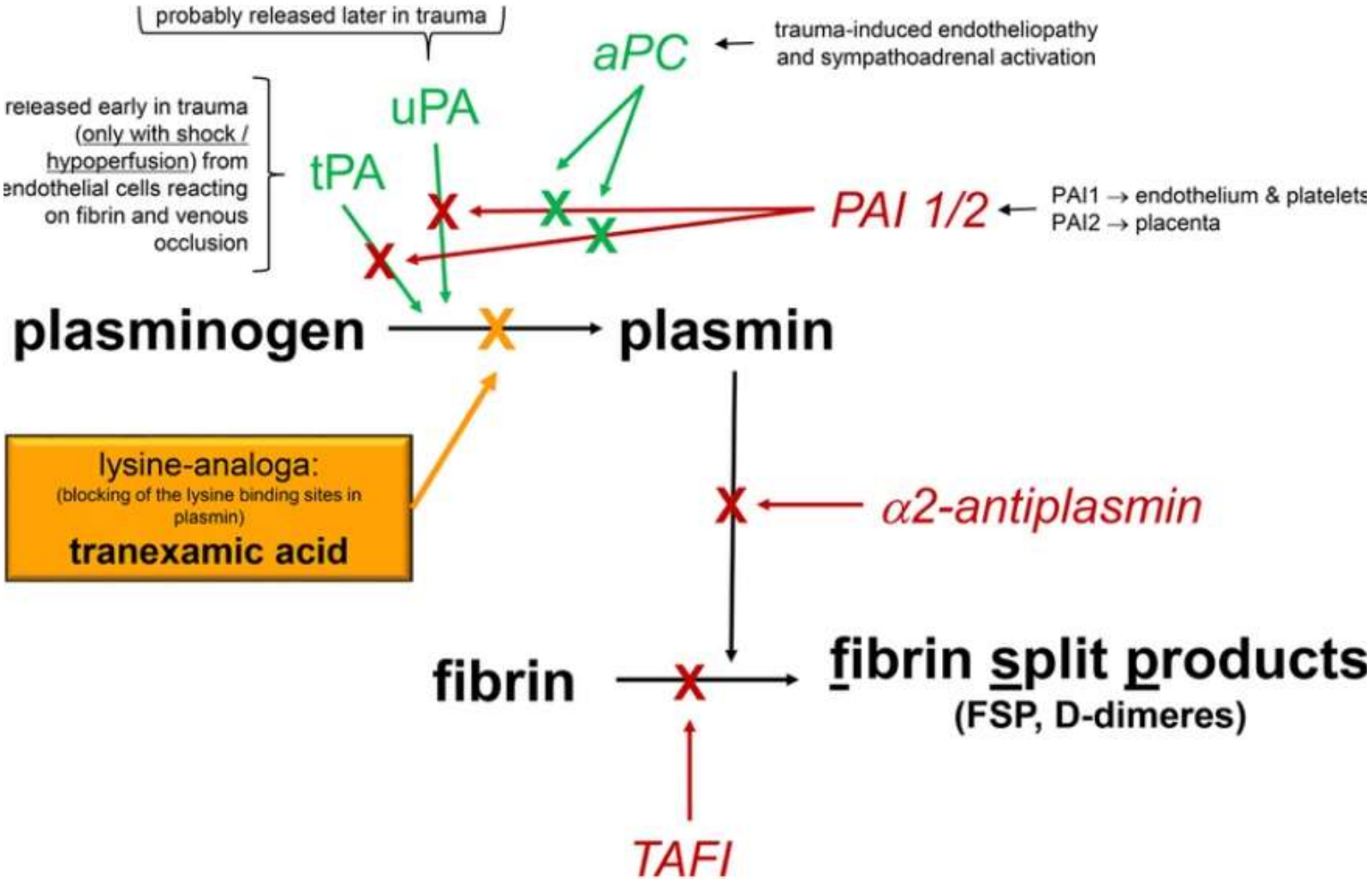
- Binds to lysine binding sites of plasminogen & plasmin so that it cannot bind to fibrin & lyse the clot

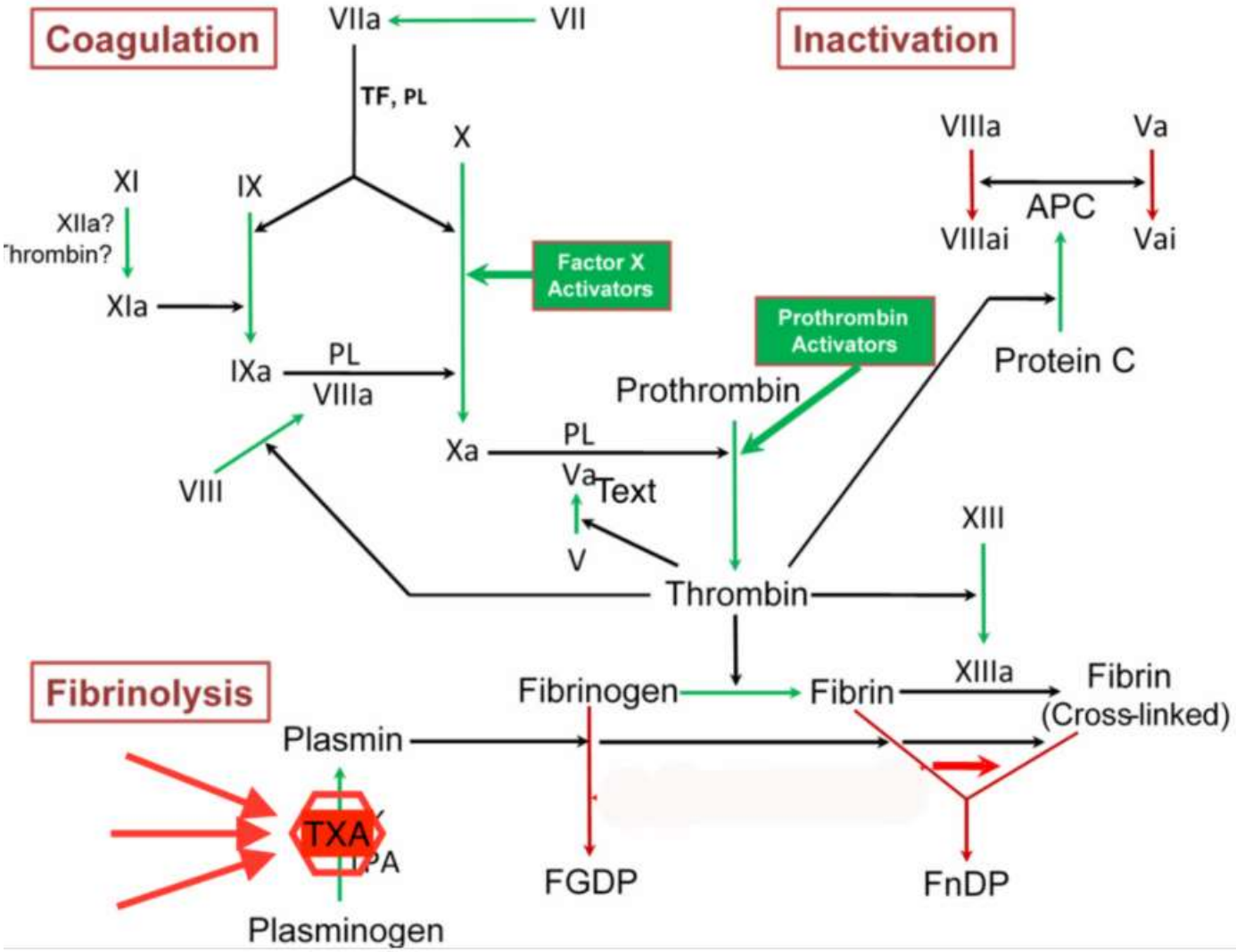
PROCOAGULANT DRUGS

Antifibrinolytics

- **Two types of antifibrinolytics :**
  - **Lysine analogs : epsilon-aminocaproic acid (EACA) a**
  - **SERPIN : aprotinin**
  - The lysine analogs act by competitively inhibiting the binding site on plasminogen, leading to inhibition of plasminogen activation as well as preventing plasminogen binding of fibrin, therefore impairing fibrinolysis
  - TXA , EACA : both agents appear to have similar efficacy

- **Use of TXA : cardiac surgery, orthopedic surgery, neurosurgery,hepatic surgery, and obstetric and gynecology surgery**
- **Dose-response relationship of high-dose TXA and seizures in patients undergoing cardiac surgery**
  - mechanism is TXA binding to GABA receptors, subsequently blocking GABAA-mediated inhibition in the central nervous system


probably released later in trauma
aPC
trauma-induced endotheliopathy and sympathoadrenal activation
released early in trauma (only with shock / hypoperfusion) from endothelial cells reacting on fibrin and venous occlusion
uPA
tPA
PAI 1/2
PAI1 → endothelium & platelets
PAI2 → placenta
plasminogen
plasmin
lysine-analoga:
(blocking of the lysine binding sites in plasmin)
tranexamic acid
α2-antiplasmin
fibrin
fibrin split products
(FSP, D-dimeres)
TAFI


Coagulation
VIIa
VII
TF, PL
X
XI
IX
XIIa?
Thrombin?
XIa
Factor X Activators
IXa
PL
VIIIa
VIII
Xa
PL
Va
Text
V
Prothrombin
Prothrombin Activators
Thrombin
Inactivation
VIIIa
Va
APC
VIIIai
Vai
Protein C
XIII
XIIIa
Fibrin (Cross-linked)
Fibrinolysis
Fibrinogen
Fibrin
Plasmin
TXA
tPA
Plasminogen
FGDP
FnDP

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	Non-fibrin-specific agents	Streptokinase
Antifibrinolytics	Lysine analogs	Tranexamic acid, epsilon-aminocaproic acid
Factor Replacements	Recombinant Factor VIIa	
	Factor VIII-vWF	
	Prothrombin complex concentrates	3-factor PCC; 4-factor PCC, activated PCC, FEIBA
	Fibrinogen concentrates	

PROCOAGULANT DRUGS

Factor Replacements

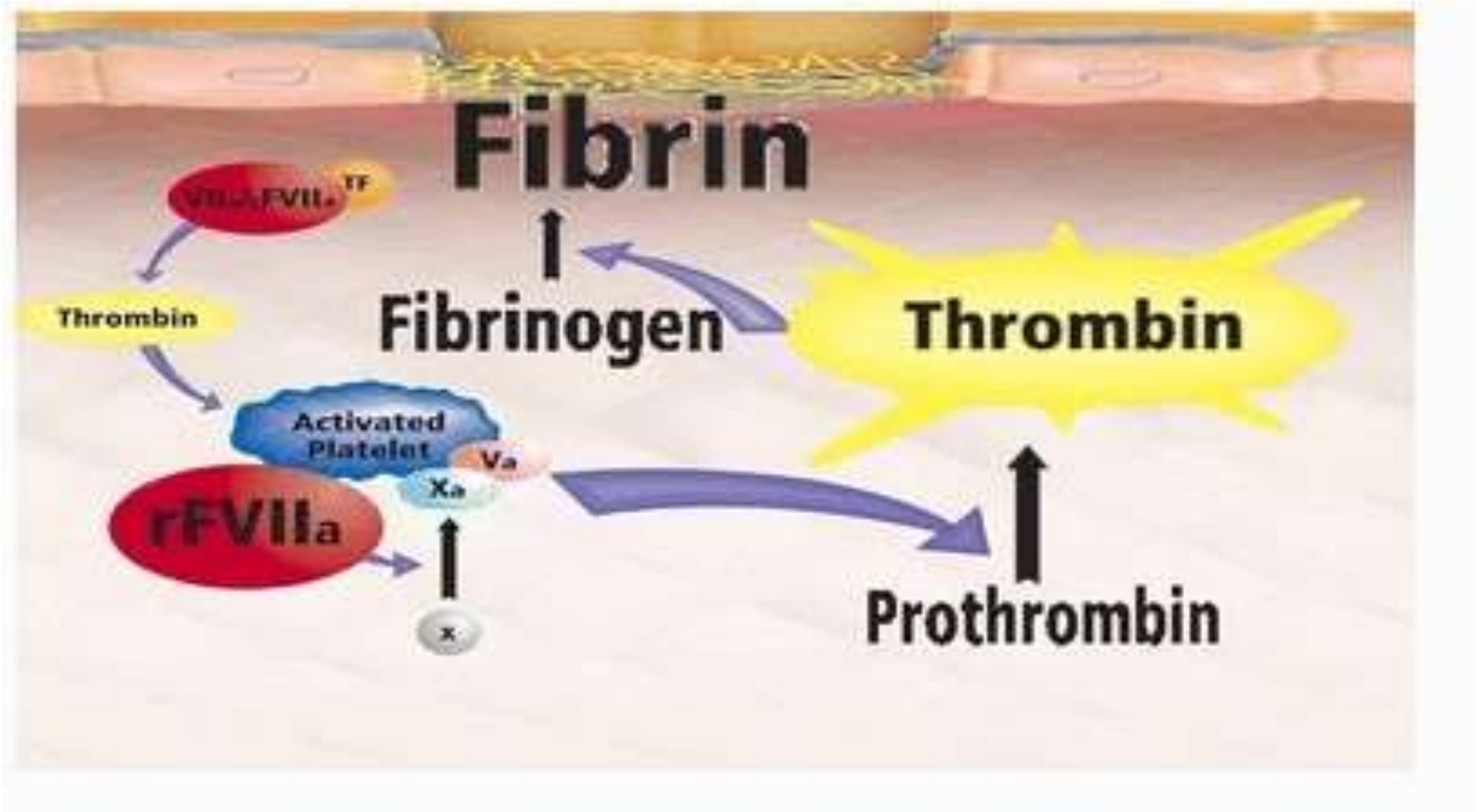
Recombinant Factor VIIa (rFVIIa)

- Increases the generation of thrombin via the intrinsic and extrinsic pathways to enhance hemostasis
- The drug was originally FDA approved for use in hemophilia patients
- It binds to tissue factor at the site of vessel injury and to the surface of the activated platelet, leading to activation of factor X
- Both mechanisms result in a “burst” of thrombin and fibrin generation, which leads to clot formation
- The halflife of rFVIIa is only 2 to 2.5 hours
  - May require repeating until the bleeding is controlled

PROCOAGULANT DRUGS

Factor Replacements

Recombinant Factor VIIa (rFVIIa)



PROCOAGULANT DRUGS

Factor Replacements

Recombinant Factor VIIa (rFVIIa)

- Successful use of rFVIIa in hemophilia patients with inhibitors generated a great deal of interest in the drug's ability to enhance hemostasis in hemorrhaging patients without a preexistent coagulation disorder
- **Use of rFVIIa :**
  - **intracranial hemorrhage**
  - **Trauma**
  - **traumatic brain injury**
  - **undergoing cardiac surgery**
  - **liver transplantation**
- While treatment with rFVIIa reduced the progression of the hematoma following intracranial hemorrhage and reduced the risk of acute respiratory distress syndrome in trauma patients, mortality or functional outcomes were not improved in any patient subset

PROCOAGULANT DRUGS

Factor Replacements

Prothrombin Complex Concentrate PCCs

- **Containing varying amounts of vitamin K-dependent coagulation factors**
- Three-factor PCCs differ from 4-factor PCCs in that they do not contain significant amounts of factor VII
- Most of the factors are preserved in the **inactive state**, with the aim of decreasing thrombogenic risk
- **FEIBA is a 4-factor PCC that contains activated factor VII**
- Also contain coagulation inhibitors such as **heparin, AT,protein C, and protein S** to mitigate the thrombotic risk by providing more balanced replacement of procoagulant factors and anticoagulant proteins

PROCOAGULANT DRUGS

Factor Replacements

Prothrombin Complex Concentrate PCCs

- **PCCs : derived from human plasma**
- treated with at least one viral reduction process, reducing the risk of transfusion-transmitted infection and the lower administration volume decreases the risk of transfusion-associated circulatory overload (TACO)
- While PCCs appear to be safe and have low risk of thrombosis
- there is accumulating evidence that the level of factor II and its balance with the coagulation inhibitors may be the important key

PROCOAGULANT DRUGS

Factor Replacements

Fibrinogen Concentrate

- **Produced from pooled human plasma**
- Correct hypofibrinogenemia with the goals of reducing coagulopathy, bleeding, and transfusion requirements
- **Offers benefits over FFP and cryoprecipitate :**
  - **in terms of standardized fibrinogen content**
  - **Low infusion volume**
  - **faster time to administration due to rapid reconstitution**
- **Cryoprecipitate and FFP**
  - **Cheaper**
  - **they also provide additional procoagulant factors that could be beneficial during massive bleeding**

Perioperative Management of Anticoagulation

- **Balancing the risk of surgical bleeding against the risk of developing postoperative thromboembolism**

- **Patients should be evaluated with enough time prior to elective surgery to perform these necessary risk assessments and make management decisions regarding discontinuation and reinstitution of anticoagulation or antiplatelet therapy**

Perioperative Management of Anticoagulation

VITAMIN K ANTAGONISTS

- **Stop VKAs 5 days prior to surgery** for those who are at **low risk for perioperative VTE**
- VKAs restarted 12 to 24 hours postoperatively if there is adequate hemostasis
- **Patients at high risk of VTE , bridging anticoagulation with UFH or LMWH after discontinuation of VKAs should occur**
- **The difficulty arises in defining a plan for patients who are at moderate risk**
- **No definitive evidence exists**
- **The approach chosen should be based on individual patient and surgical risk factors**

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

Perioperative Management of Anticoagulation

HEPARINS

- therapy with UFH, the infusion should be stopped 4 to 6 hours prior to surgery
- and resumed without a bolus dose no sooner than 12 hours postoperatively
- **In surgeries with high postoperative bleeding risk : resumption of UFH should be delayed 48 to 72 hours until adequate hemostasis has been achieved**
- **Therapy with LMWH :**
  - The last dose of LMWH 24 hours prior to surgery
  - low bleeding risk surgery : resumed 24 hours postoperatively
  - high bleeding risk surgery : delayed until 48 to 72 hours

Perioperative Management of Anticoagulation

ASPIRIN

- **Risk assessment :**
  - (1) the patient's risk of a perioperative cardiovascular Event
  - (2) whether the surgery is a minor procedure,major procedure, or cardiac procedure
  - (3) the timing and type of stent placement for those patients who have undergone recent PCI

Perioperative Management of Anticoagulation

ASPIRIN

- **Low-dose aspirin (acetylsalicylic acid,ASA) :**
  - **Reduce the risk of stroke and myocardial infarction**
- The decision to discontinue low-dose aspirin must weigh the risks of bleeding versus the benefits of cardiovascular risk reduction
- perioperative aspirin :
  - small increase in the risk for major bleeding
  - continuation of perioperative aspirin may confer a significant reduction in myocardial infarction and other major cardiovascular events

Perioperative Management of Anticoagulation

ASPIRIN

- continue aspirin for patients who are at moderate to high risk for cardiovascular events requiring noncardiac surgery
- stop aspirin use 7 to 10 days prior to surgery for patients at low risk for cardiovascular events
- minor procedures (e.g., minor dental, dermatologic procedures, or cataract surgery) and are **on aspirin for the secondary prevention of cardiovascular disease should continue taking it in the perioperative period**

Perioperative Management of Anticoagulation

ASPIRIN

- Patients with coronary stents presenting for surgery : concerns for in-stent thrombosis that can occur with stopping antiplatelet therapy
- Surgery should be delayed :
  - for at least 6 weeks after baremetal stent placement
  - for at least 6 months after drugeluting stent placement
- **If surgery is required before this time has passed, dual anti-platelet therapy should be continued unless the risk of bleeding is thought to outweigh the risk of stent thrombosis**

Perioperative Management of Anticoagulation

ASPIRIN

- aspirin provides benefit that outweighs the bleeding risk and should be continued unless the patient is undergoing intracranial procedures,transurethral prostatectomy, intraocular procedures, or surgeries with extremely high bleeding risk
- **For patients with a very high risk of stent thrombosis :**
  - **bridging therapy with intravenous reversible glycoprotein inhibitors or a reversible intravenous P2Y12 inhibitor have been suggested**
  - **concomitant parenteral anticoagulation therapy is not recommended**

TABLE 50.4 UCSF Guidelines for the Use of Antithrombotic Agents in the Setting of Neuraxial Procedures

Anticoagulant	Minimum Time Between the Last Dose and When Neuraxial Catheter can Occur	Minimum Time After Catheter Placement to Drug Start	Minimum Time Between Last Dose of Drug and Catheter Removal	Minimum Time Between Neuraxial Catheter Removal and When Next Dose can be Given
NSAIDs/ASA	No restrictions for catheter placement or removal			
Heparin SQ BID	No restrictions for catheter placement or removal			
Heparin SQ TID	4 h	2 h	4 h	2 h
Lovenox qD	12 h	6 h	12 h	4 h
Warfarin	5 days and INR < 1.5	Contraindicated while catheter in place		2 h
Clopidogrel	7 days	Contraindicated while catheter in place		2 h
Ticlodipine	14 days	Contraindicated while catheter in place		2 h
Dabigatran	5 days	Contraindicated while catheter in place		6 h
Rivaroxaban	3 days	Contraindicated while catheter in place		6 h
Apixaban	3 days	Contraindicated while catheter in place		6 h
Abciximab	48 h	Contraindicated while catheter in place		2 h
Eptifibatide	8 h	Contraindicated while catheter in place		2 h
Alteplase*	10 days	Contraindicated while catheter in place		10 days

Emergent Reversal of Anticoagulants
VITAMIN K ANTAGONISTS

- **VKA-associated major bleeding**
  - Some of these patients will require warfarin reversal for bleeding
  - patients will require warfarin reversal prior to emergency surgery
- Four-factor PCCs as opposed to three-factor PCCs are now the drug of choice for emergent reversal of oral VKA in place of FFP or rFVIIa
- **PCCs only provide a transient correction** due to the short half-life of these factors relative to the long halflife of warfarin
- **Concomitant administration of vitamin K**
  - **required to restore carboxylation of the vitamin K dependent factors (VKDFs) by the liver** and provide a more sustained correction after the factors in the PCC infusion have been metabolized
  - Intravenous administration of vitamin K gives a more rapid response than subcutaneous or oral administration

Emergent Reversal of Anticoagulants
VITAMIN K ANTAGONISTS

- **The dose required** depends on the clinical situation and the need to be able to re-establish anticoagulation after surgery
  - **lower doses (3 mg) may allow for warfarin reversal during the acute event,while avoiding warfarin resistance if rapid re-establishment of a therapeutic INR is required**
  - **Rapid reversal of VKA with FFP is difficult and often unrealistic**
- **Time to thaw ABO-compatible units is a concern**
  - **the large volume** required to raise the VKDF by 50% is often untenable, especially in a patient population prone to pulmonary, renal, and cardiac disease
- **Concerns for transmission of viral diseases,transfusionrelated complications such as volume overload, TACO,and lung injury (transfusion-related acute lung injury)**

Emergent Reversal of Anticoagulants

DIRECT THROMBIN INHIBITORS

- No direct reversal agents for intravenous DTIs
- their half-lives : relatively short, so time and supportive medical care are often sufficient to manage their anticoagulant effect in acute clinical situations
- **Specific antidote for Dabigatran : Idarucizumab**
  - humanized antibody fragment that binds to dabigatran with an affinity 350 times greater than thrombin
- **Andexanet alfa :**
  - Recombinant derivative of factor Xa
  - Reverse the factor Xa inhibitors
    - by acting as a decoy

Idarucizumab

Emergent Reversal of Anticoagulants
EMERGING AGENTS

- **Ciraparantag (PER977) :**
  - **Small, synthetic, water-soluble, cationic molecule, binds and neutralizes UFH, LMWH, fondaparinux, dabigatran,and factor Xa inhibitors through hydrogen bonding and charge-charge interactions**
  - **Phase I trials have been completed in healthy volunteers**

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