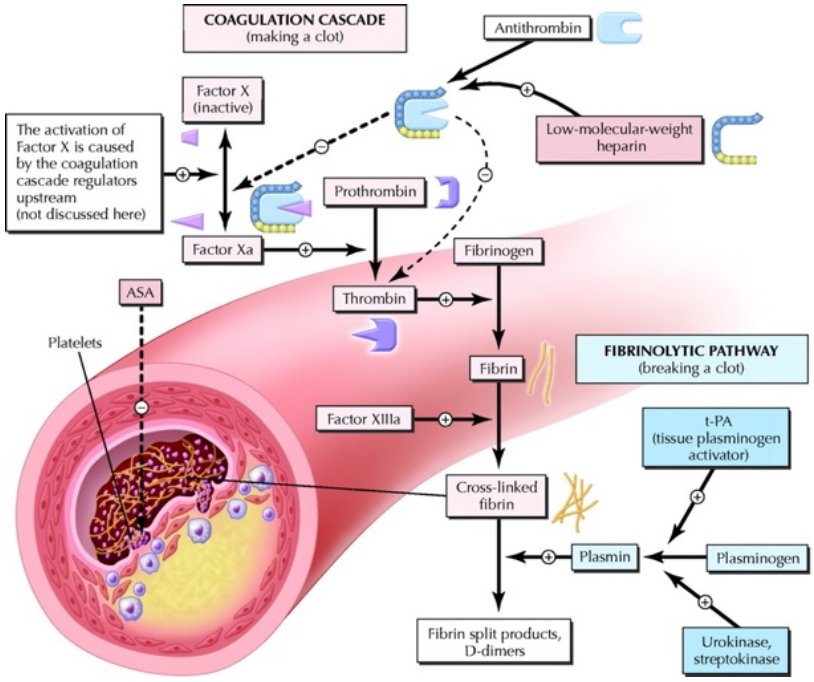
Fibrinolytics, Antiplatelets, & Anticoagulants

Fibrinolytic Agents

- Alteplase or t-PA (Activase), Reteplase or r-PA (Retavase), and Tenecteplase or TNK (TNKase).
- MOA: Fibrinolytics act either directly or indirectly to convert plasminogen to plasmin, which cleaves fibrin --> lyses thrombi.
- Indications:
  (1) Patients with STEMI who present to the hospital within 12 hours of symptom onset and are unable to undergo primary PCI (percutaneous coronary intervention) within 120 mins. from the first medical contact.
  (2) Patients with ischemic stroke who present to the hospital within 4.5 hours of symptom onset.
  (3) Patients with pulmonary embolism (PE) who present to the hospital in "high risk," i.e., patients who hemodynamically unstable, patients with refractory hypotension, shock, etc…



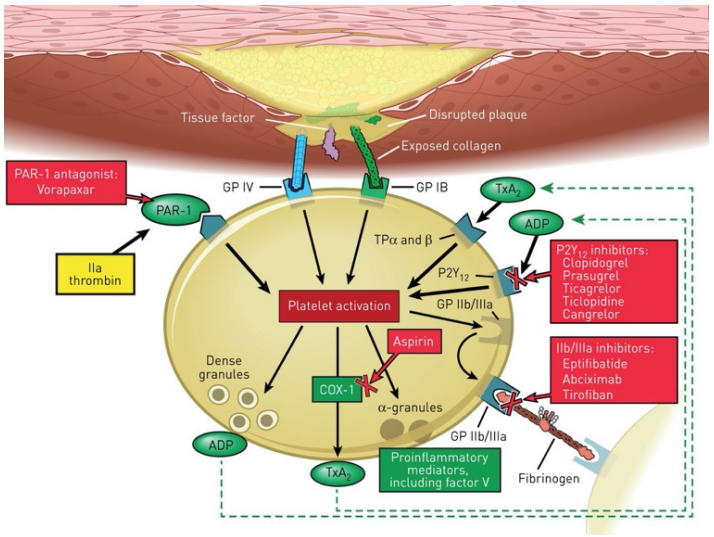
- Fibrinolytic Complications:
  (1) Bleeding (5-7% --> intracerebral hemorrhage in ischemic stroke)
  Treatment of ICH (intracerebral hemorrhage)
    a. Cryoprecipitate: 10 units to increase levels of fibrinogen and factor VIII.
    b. Platelets: 6 – 8 units for patients with PLT < 100,000.
    c. Anti-fibrinolytic agents (intravenous): aminocaproic acid and/or tranexamic acid --> MOA: inhibit conversion of plasminogen to plasmin --> stop bleeding.
  (2) Angioedema (1-8%)
  Treatment of Angioedema
    a. Methylprednisolone (Solu-Medrol) 125 mg IVP
    b. Diphenhydramine (Benadryl) 50 mg IVP
    c. Famotidine (Pepcid) 20 mg IVP
    d. Epinephrine 0.3 mg IM if needed (note: Epi may increase BP and bleeding)

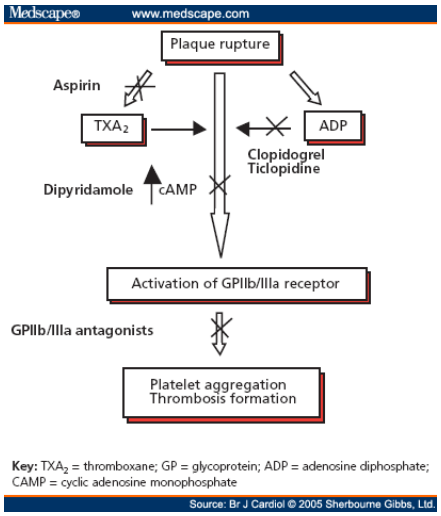
Antiplatelet Therapy

- Indications:
  (1) Antiplatelet therapy is used for management of acute ischemic stroke and for the secondary prevention of stroke.
  (2) Antiplatelet therapy is used in patients with coronary artery disease (CAD).
  (3) Dual antiplatelet therapy (DAPT) with "ASA plus $P2Y_{12}$ inhibitor" is indicated for patients with recent ACS or recent coronary artery stent placement.
  (4) "Anticoagulant plus antiplatelet" therapy is used in patients who require intensive antithrombotic therapy.

Antiplatelet Therapy (cont.)

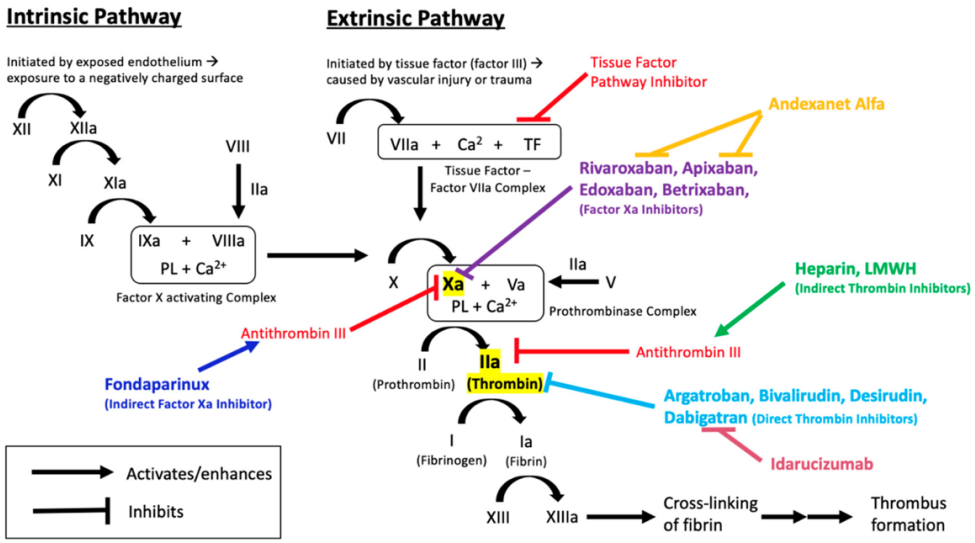
- Aspirin (ASA): inhibits COX-1 → decreases thromboxane A_2 production → inhibits platelet activation/aggregation.
- $P2Y_{12}$ receptor blockers: Clopidogrel (Plavix), Prasugrel (Effient), Ticagrelor, Cagrelor (IV) --> inhibit binding of ADP to its $P2Y_{12}$ receptors on platelets → inhibit activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other.
- GP IIb/IIIa blocker: Abciximab (Reopro) is an intravenous antiplatelet agent indicated in patients undergoing PCI (percutaneous coronary intervention) in ACS.
  Abciximab --> blocks fibrinogen from binding to GP IIa/IIIb receptors on platelets → inhibits platelet aggregation.





Anticoagulants: Unfractionated Heparin (UFH) & Low Molecular-Weight Heparin (LMWH)

- Heparin (UFH) binds to Antithrombin III and accelerates inhibition of Thrombin (IIa) and Factor Xa.
- LMWH: Enoxaparin (Lovenox) binds to Antithrombin III and selectively inhibits Factor Xa.



Anticoagulants: Unfractionated Heparin (UFH)

Unfractionated Heparin (UFH) in Acute Coronary Syndrome: 60 UNITS/kg IV bolus (max: 5000 UNITS), followed by 12 UNITS/kg/hour (max: 1000 UNITS/hour) infusion, titrated to maintain activated partial thromboplastin time (aPTT) at 1.5-2 times the control value.

Heparin-adjusted nomogram for stroke

Initial dosing for continuous intravenous heparin infusion			
Weight (kg)		**Initial infusion (U/hour)**	
<50		500	
50 to 59		600	
60 to 69		700	
70 to 79		800	
80 to 89		900	
90 to 99		1000	
100 to 109		1100	
110 to 119		1200	
>119		1400	
Heparin adjustment based upon aPTT drawn six hours after initiation of therapy			
aPTT (seconds)	**Stop infusion**	**Rate change**	**Repeat aPTT**
<40	No	Increase by 250 U/hour	6 hours
40 to 49	No	Increase by 150 U/hour	6 hours
50 to 59	No	Increase by 100 U/hour	6 hours
60 to 90	No	No change	Next morning
91 to 100	No	Decrease by 100 U/hour	6 hours
101 to 120	No	Decrease by 150 U/hour	6 hours
>120	No	Decrease by 250 U/hour	6 hours

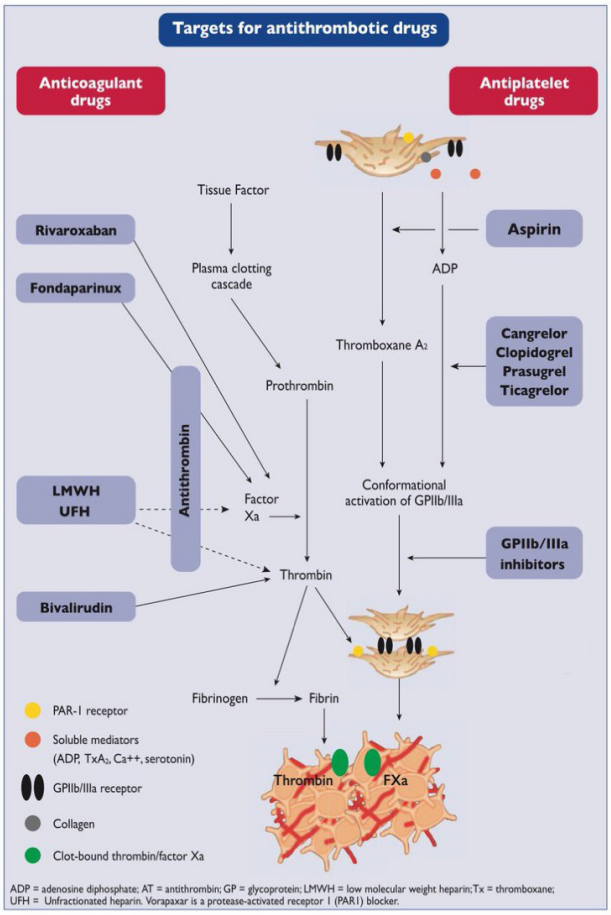
No bolus is administered in patients with acute stroke.

LMWH: Enoxaparin (Lovenox)

- Anticoagulant Dose: 1 mg/kg SC Q12H OR 1 mg/kg SC Q24H (CrCl < 30 mll/min)
- DVT Prophylaxis Dose: 40 mg SC Q24H OR 30 mg SC Q24H (CrCl < 30 ml/min)
- Note: Heparin (UFH) DVT Prophylaxis Dose: 5000 UNITS SC Q12H is recommended in patients with renal failure.

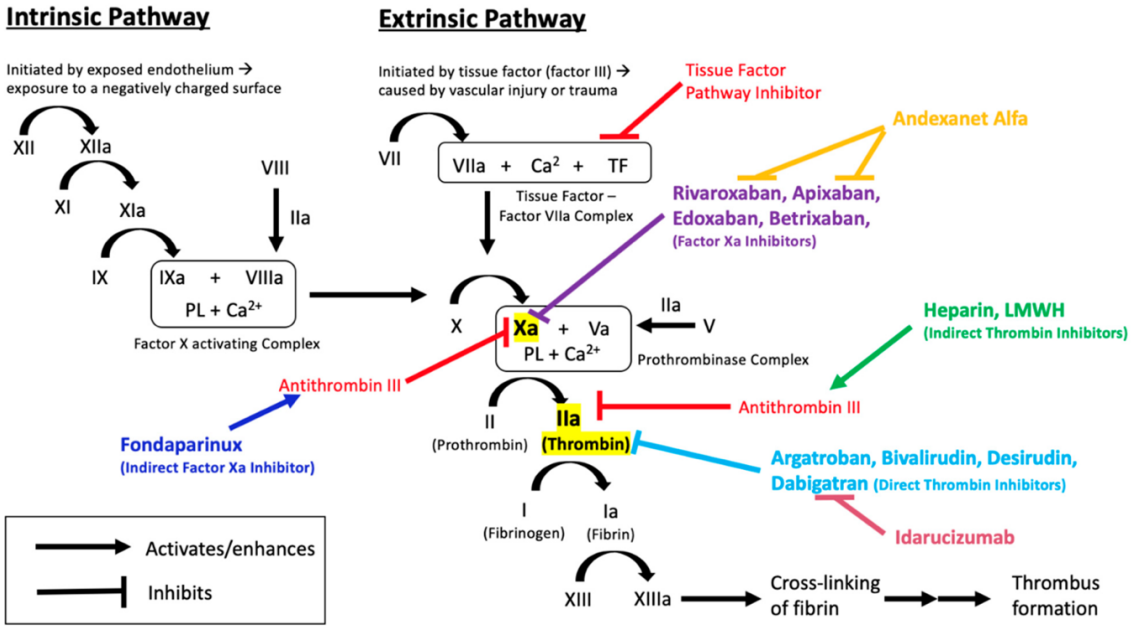
Oral Anticoagulants: Warfarin (Coumandin)

- MOA: inhibits vitamin K-dependent clotting factors: II (prothrombin), VII, IX, & X
- Unlike heparin, the anticoagulant effects of warfarin are delayed for 3-5 days, which is the time required to deplete the pool of vitamin K dependent clotting factors.
- Adverse Effect: Bleeding
  Reversal Agent: Vitamin K (phytonadione)
  5-10 mg IV/SC/PO – onset (IV) is approx. 2 hours and peak is 12-14 hours, since time is needed for degradation of already inhibited clotting factors.
  - If INR > 10 with severe bleeding FFP / KCentra (Prothrombin Complex Concentrate: Factors II, VII, IX, X).



Warfarin (cont.)

- Adverse Effect: Warfarin-induced skin necrosis
  - Warfarin inhibits Vit K dependent anticoagulant proteins C and S, which have shorter half-lives than the Vit K dependent clotting factors. Therefore, for the first 2-5 days after initiating warfarin, patients are "procoagulant" and must be bridged with heparin for at least 5 days (i.e., 48 hours after achieving a therapeutic INR).
- Food Interactions with vitamin K-containing products: green vegetables, spinach, kale → reduce warfarin effectiveness.
- Drug-Drug Interactions: (1) Inhibitors of the CP-450 hepatic enzymes (e.g. fluconazole) → increase warfarin levels, and (2) Inducers of CP-450 enzymes Inducers → decrease warfarin levels.
  - Warfarin is highly bound to plasma proteins (albumin) and competes with other plasma protein-bound drugs (e.g., ASA, NSAIDs, sulfonylureas, etc…)
- Pregnancy: warfarin is a teratogen and is contraindicated in pregnancy.
  - LMWH (i.e., enoxaparin) is the anticoagulant of choice during pregnancy.



Oral Anticoagulants: Direct-Acting Oral Anticoagulants (DOACs)

- Compared to warfarin (Coumadin), DOACs have fewer drug-drug interactions and do not require lab monitoring of PT/INR.

(1) Dabigatran (Pradaxa) → binds to and inhibits thrombin directly ("Direct Thrombin Inhibitor").

- Indications: (1) Prevention and treatment of DVT/PE and (2) Prevention of stroke in non-valvular atrial fibrillation.
- SEs: bleeding (like all anticoagulants), dyspepsia, abdominal pain, esophagitis.
- Reversal Agent: idarucizumab (Praxbind) / Note: hemodialysis removes dabigatran.

(2) Rivaroxaban (Xarelto) and Apixaban (Eliquis) → selectively inhibit Factor Xa.

- Parenteral Xa inhibitor: Fondaparinux (Arixtra)
- Indications: (1) Prevention and treatment of DVT/PE and (2) Prevention of stroke in non-valvular atrial fibrillation.
- SEs: bleeding, nausea/vomiting, gastroenteritis.
- Reversal Agent: Andexanet alfa

Standard Doses of DOACs

Anticoagulant	Nonvalvular AF - stroke prophylaxis *	VTE treatment ¶	VTE primary prophylaxis Δ
Dabigatran (Pradaxa)	150 mg twice daily	Parenteral anticoagulation for 5 to 10 days; then dabigatran 150 mg twice daily	110 mg for the first day, then 220 mg once daily
Apixaban (Eliquis)	5 mg twice daily	10 mg twice daily for one week, then 5 mg twice daily	2.5 mg twice daily
Betrixaban (Bevyxxa)			160 mg on the first day, followed by 80 mg once daily, with food
Edoxaban (Savaysa, Lixiana)	60 mg once daily	Parenteral anticoagulation for 5 to 10 days; then edoxaban 60 mg once daily	
Rivaroxaban (Xarelto)	20 mg once daily with the evening meal	15 mg twice daily with food for three weeks; then 20 mg once daily with food	10 mg once daily, with or without food

Oral Anticoagulants: Warfarin versus DOACs

	Warfarin	Direct oral anticoagulants*
Dosing	Once-daily dosing may be more convenient	May require more frequent dosing
Dietary restrictions	Need to ensure relatively constant level of vitamin K intake	None. Rivaroxaban should be taken with food when used for atrial fibrillation thromboprophylaxis. Betrixaban should be taken with food when used for VTE prophylaxis.
Monitoring therapy	PT/INR monitoring is required, which entails regular visits to a facility for most patients (point-of-care devices may be an option for some)	Not required; however, noncompliance will not be as readily apparent
Drug interactions	Many	Rivaroxaban interacts with CYP-3A4 and P-glycoprotein inhibitors; other factor Xa inhibitors interact with P-glycoprotein; dabigatran may be affected by P-glycoprotein inducers or inhibitors
Time in therapeutic range	Approximately 65% based on clinical trials	Expected to be superior to warfarin, although therapeutic ranges have not been established
Reversal agent(s)	Several available (eg, vitamin K, FFP, PCC)	For dabigatran: idarucizumab; for direct factor Xa inhibitors: andexanet alfa. Activated charcoal may be used to remove unabsorbed drug if the last ingestion was recent. Hemodialysis may be used to remove dabigatran from the circulation.
Monitoring drug activity after reversal	PT/INR can be used	TT can be used for dabigatran; anti-factor Xa activity can be used for apixaban
Effect of comorbid conditions		Renal function affects pharmacokinetics; dosing unclear in those with obesity

DOSING CONSIDERATIONS

Enoxaparin (Lovenox) Dosing

Anticoagulant Dosing

Enoxaparin 1 mg/kg SC Q12H → CrCl ≥ 30 ml/min

Enoxaparin 1 mg/kg SC Q24H → CrCl: 15-30 ml/min

- If CrCl < 15 ml/min → use UFH (Heparin Infusion)

DVT Prophylaxis (DVT PPX)

Enoxaparin 40 mg SC Q24H → CrCl ≥ 30 ml/min

Enoxaparin 30 mg SC Q24H → CrCl: 15-30 ml/min

- If CrCl < 15 ml/min → use UFH: Heparin 5000 UNITS SC Q12H

Onset of Action

- UFH, Enoxaparin, DOAC's → provide immediate anticoagulant effects
- Warfarin → requires 3-5 days to achieve anticoagulant effect, with therapeutic INR (INR=2-3); therefore, Warfarin requires bridging with UFH (Heparin Infusion) or Enoxaparin.

Renal Considerations

- UFH is recommended in patients with renal failure and patients on hemodialysis, since UFH are hepatically eliminated.
- In patients with ESKD (end-stage kidney disease) on hemodialysis, warfarin or apixaban may be used for anticoagulation.
- Apixaban (Eliquis) Dosing Guidelines in Non-Valvular Atrial Fibrillation:
  - Apixaban (standard dose): 5 mg PO BID
  - If sCr ≥ 1.5 mg/dL and either ≥ 80 years of age or body wt ≤ 60 kg, reduce apixaban dose to 2.5 mg PO BID.
  - In patients with ESKD on hemodialysis, some experts recommend reducing dose of apixaban to 2.5 mg PO BID since safety and efficacy remain untested and cannot be assured.
  - Patients with ESKD should be closely monitored for apixaban accumulation and bleeding.

Graphic Illustrations: Targets for Antithrombotic Drugs