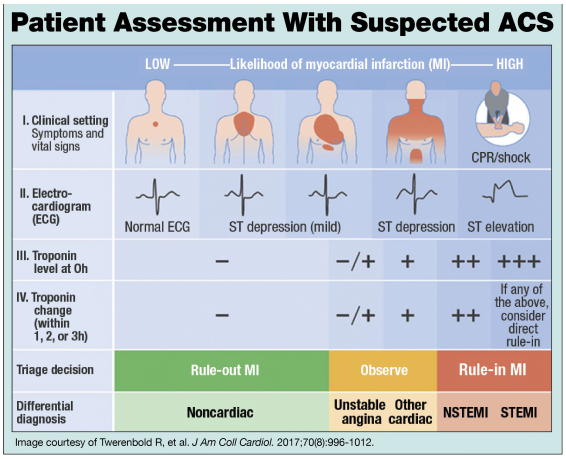
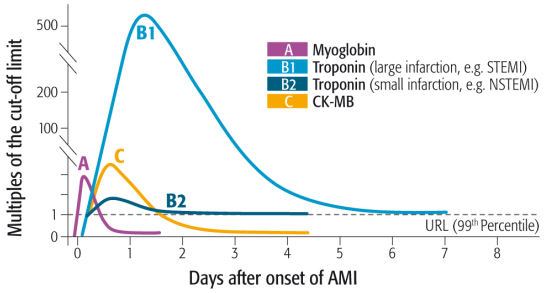
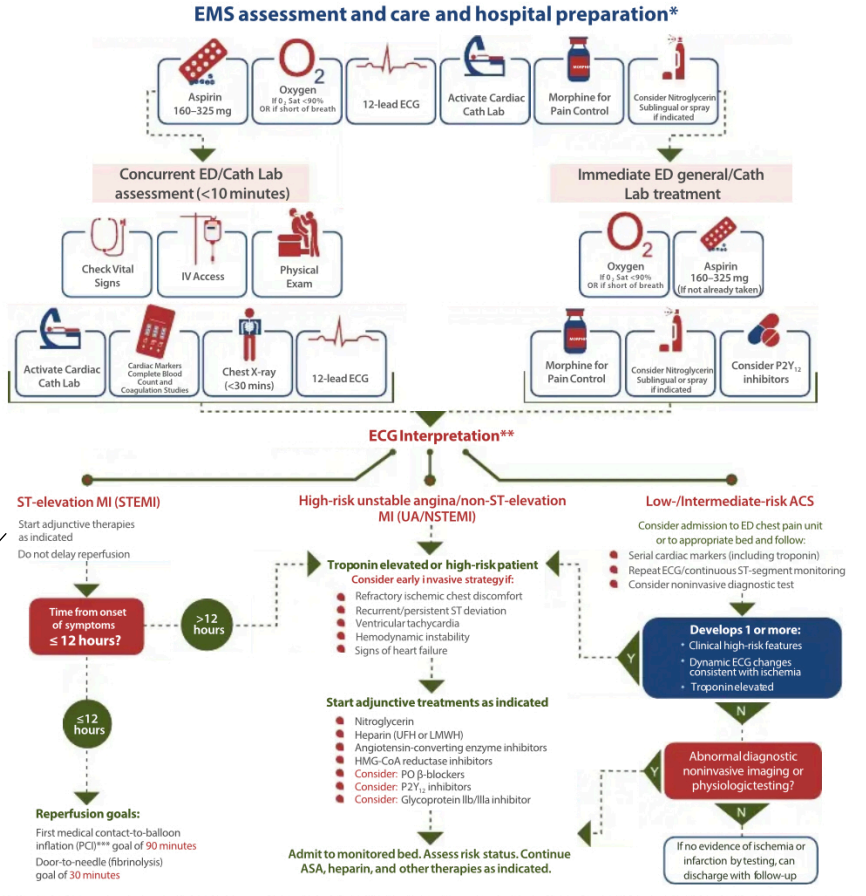
ACUTE CORONARY SYNDROME (ACS)

- ACS incudes unstable angina (UA) and acute myocardial infarction (AMI).
  AMI is divided into:
  (1) STEMI: ST segment elevation MI
  (2) NSTEMI: non-ST segment MI
- NSTE-ACS (Non-ST segment elevation-ACS) includes: (1) UA and (2) NSTEMI:
  - NSTEMI: There is partial thrombotic occlusion and the presence of biomarkers (troponins) associated with necrosis of myocardial fibers.
  - Unstable Angina (UA): There is sufficient coronary blood flow to sustain myocardial cells and prevent necrosis → absence of troponins.
- STEMI: There is total and persistent thrombotic occlusion → necrosis of myocardial fibers
  → elevated troponin
- STEMI is a medical emergency requiring immediate intervention with reperfusion and revascularization using
  (1) pharmacological and
  (2) non-pharmacologic interventions (PCI & CABG).







Adjunctive Meds
- NTG (SL/IV)
- Morphine
- Beta Blockers
- ACEi / ARB
- Anti-Platelets
- Anticoagulants
- Statins

Risk Stratification

- Assessing a patient presenting with ACS begins with stratification for the risk of death and reinfarction, taking into account the presenting signs and symptoms, past medical history (PMH), ECG, and cardiac biomarker changes (troponin, CK-MB).
- Patients with STEMI are at the highest risk of death and reinfarction and initial treatment should proceed with immediate revascularization.
    - "Time is tissue" means the sooner the thrombosed artery is opened, the lower the mortality and the greater amount of myocardium preserved.
    - ACC/AHA guidelines: target time for reperfusion for STEMI within 30 mins of hospital presentation for fibrinolytic therapy (i.e., "door-to-needle") and within 90 mins from presentation for PCI (i.e., "door-to-balloon").
- Although primary PCI is the preferred therapy for STEMI, it has logistic restraints: Treatment is delayed by patient transport, emergency dept (ED) delay, and preparation of the catheterization laboratory → skilled intervention team must be available 24/7.

Complications of ACS

- Complications of ACS: pump failure, arrhythmias, recurrent ischemia and reinfarction.
- When left ventricular damage occurs, a decrease in cardiac output and perfusion leads to activation of compensatory mechanisms:
    - Circulating catecholamines increase in an attempt to increase contractility and restore perfusion → increases myocardial oxygen demand.
    - RAAS is activated → increase in systemic vascular resistance and increase in Na/H_2O retention → increases myocardial oxygen demand.
- Beta blockers, ACEIs, ARBs, and aldosterone antagonists (i.e., spironolactone) will improve outcomes of ACS.

Overview of Drug and Nondrug Therapy

- Overlap exists regarding the pharmacology for both STEMI and NSTE-ACS.
- ACC/AHA guidelines for STEMI, NSTEMI, and Unstable Angina (UA):

Oxygen if O_2 sat < 90%	SL and/or IV NTG	Beta Blockers
Anticoagulants	Antiplatelet Agents	IV Morphine
Statins (HMG-CoA Reductase Inhibitors)		Stool Softener

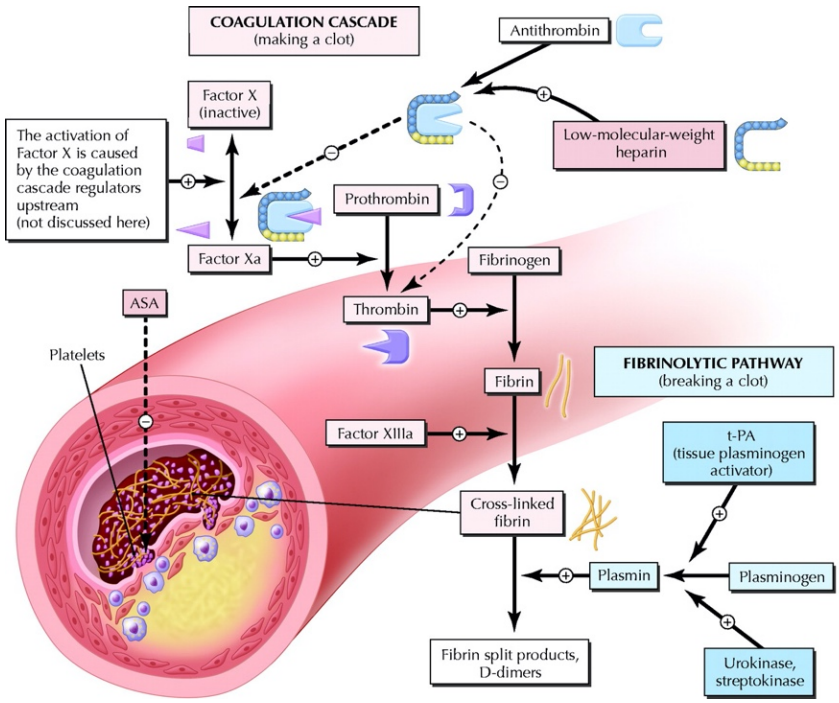
- Statins: Initiate high-intensity statin therapy regardless of baseline LDL-cholesterol levels with atorvastatin (Lipitor) 80 mg daily or rosuvastatin (Crestor) 20-40 g daily.
- Beta Blockers: Initiate within the first 24 hours, as long as no contraindications exist.

FIBRINOLYTIC AGENTS: (1) Alteplase, (2) Reteplase, and (3) Tenecteplase

(1) Alteplase or t-PA (Activase)

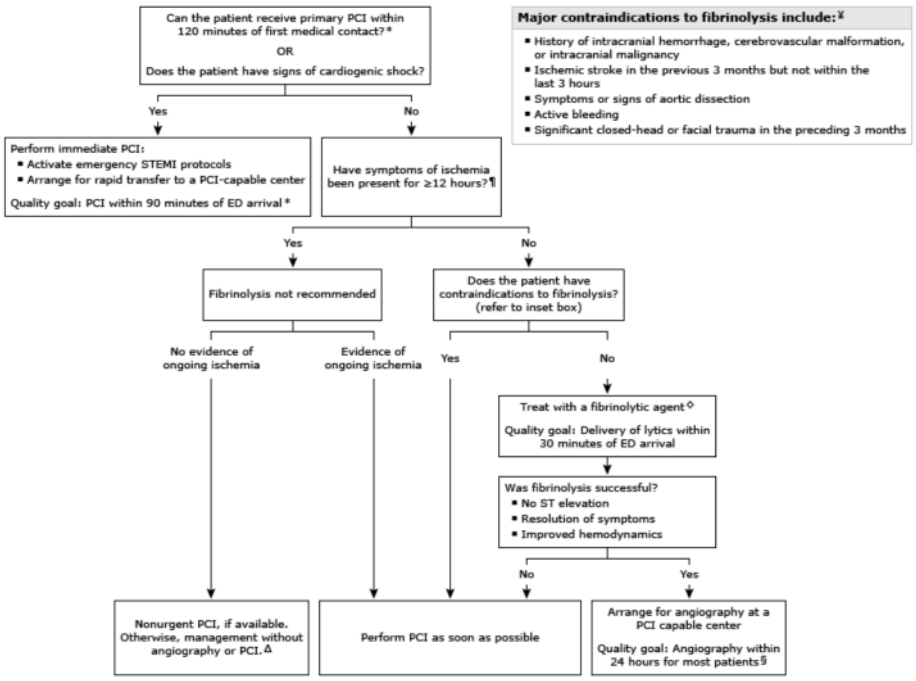
(2) Reteplase or r-PA (Retavase)

(3) Tenecteplase or (TNKase)



- MOA: Fibrinolytics act either directly or indirectly to convert plasminogen to plasmin, which cleaves fibrin → lyses thrombi.
- Fibrinolytic therapy is indicated in patients with STEMI who present to the hospital within 12 hours of symptom onset and are unable to undergo primary PCI within 2 hrs.
- Mortality from STEMI is reduced by one-third with fibrinolytic therapy and mortality reduction is greater when initiated within 0-2 hours after symptom onset. (ACC/AHA: "door-to-needle" of 30 mins).
- Once stabilized, the patient should be transferred to a facility capable of PCI in case reperfusion fails or re-occlusion occurs.

Selecting a reperfusion strategy in patients with acute STEMI



Other Indications for Fibrinolytics

(1) Patients with ischemic stroke who present to the hospital within 4.5 hours of symptom onset.

(2) Patients with pulmonary embolism (PE) who present to the hospital in "high risk" (i.e., patients who are hemodynamically unstable with refractory hypotension, shock, etc...)

FIBRINOLYTIC AGENTS: Dosage & Administration in STEMI

(1) Alteplase (Activase)
- Dose (total admin time: 1.5 hours): 15 mg IV bolus followed by 0.75 mg/kg (up to 50 mg) IV infusion over 30 mins, then 0.5 mg/kg (up to 35 mg) IV infusion over 60 mins
- Alteplase is more difficult to administer because of a short half-life.

(2) Reteplase (Retavase)
- Dose: Two vials of 10 Units IV boluses (over 2 mins) administered 30 minutes apart.
- Reteplase has similar outcomes as alteplase but easier to administer.

(3) Tenecteplase (TNKase)
- Dose: 30-50 mg IV bolus over 5 seconds
- Dosing is weight based:

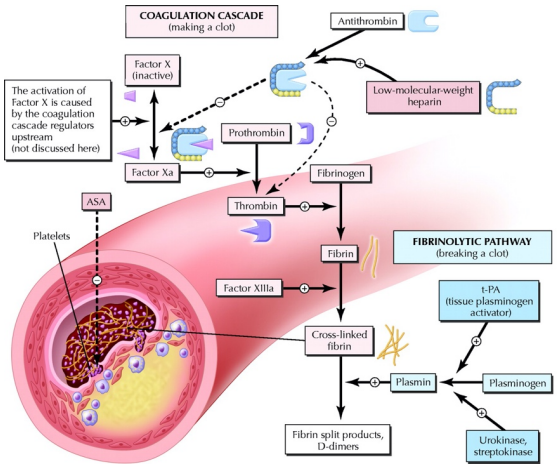
  weight < 60 kg → 30 mg IVP
  60 - 69 kg → 35 mg IVP
  70 - 79 kg → 40 mg IVP
  80-89 kg → 45 mg IVP
  weight > or = 90 kg → 50 mg

- Tenecteplase is as effective as alteplase with the following advantages:
  - Tenecteplase is associated with less non-cerebral bleeding, and
  - Tenecteplase is easier to administer in or out of the hospital as a single IV bolus.

Fibrinolytic Complications

(1) Intracerebral Hemorrhage (ICH): 0.5-1% with STEMI / 5-7% with ischemic stroke.

Treatment
- Stop fibrinolytic infusion.
- Give cryoprecipitate 10 UNITS IV to increase fibrinogen levels to 150-200 mg/dL.
- Antithrombolytic Agents:
  Aminocaproic Acid 4-5 g IV or
  Tranexamic Acid 10-15 mg/kg IV.
  - MOA: Antithrombolytics inhibit conversion of plasminogen to plasmin by inhibiting binding of plasminogen to fibrin.

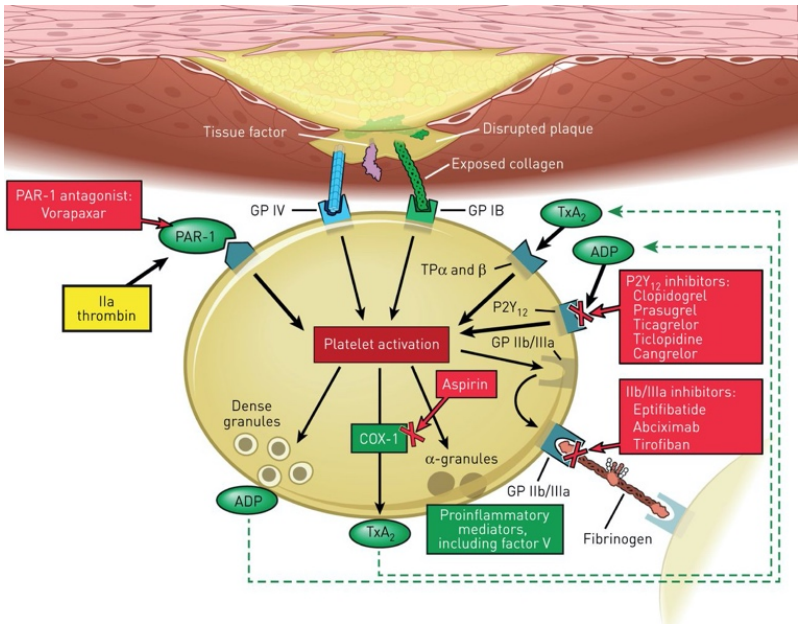


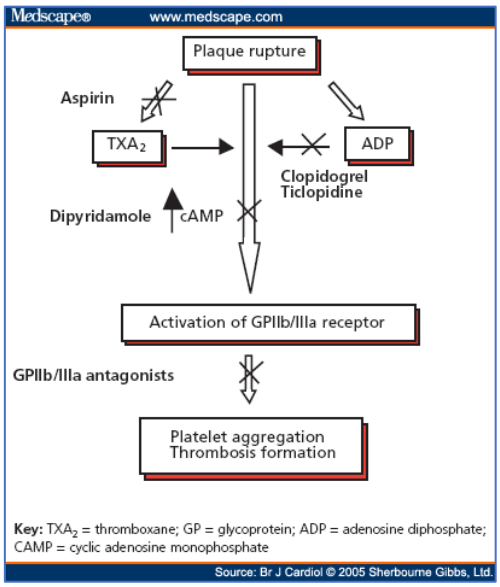
- Vit K (phytonadione) IV and PCC (prothrombin concentrate complex) IV for patients who were on warfarin therapy prior to thrombolytic treatment.
- Protamine 1 mg IV for every 100 UNITS of unfractionated heparin (UFH) in the preceding 4 hours.
- Platelets: 6-8 UNITS IV for patients with thrombocytopenia (platelet count < 100,000).

(2) Angioedema (1-8%): typically, mild and transient; w/rare severe cases requiring intubation.
Treatment: methylprednisolone (Solu-Medrol) 125 mg IVP plus diphenhydramine (Benadryl) 50 mg IVP plus famotidine (Pepcid) 20 mg IVP.
Optional: epinephrine 0.3 mg SC if needed (Note: may increase BP and bleeding risk).

ANTIPLATELETS: (1) Aspirin, (2) $P2Y_{12}$ Receptor Blockers, and (3) GP IIb/IIIa Blockers

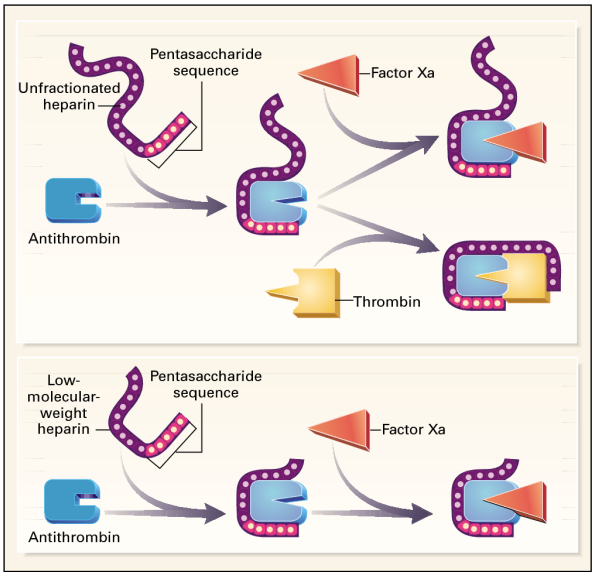
- As the clot dissolves with fibrinolytics, there is a paradoxical increase in local thrombin generation and enhanced platelet aggregation, which may lead to re-thrombosis.
- **Antiplatelet agents**: (1) Aspirin (ASA), (2) $P2Y_{12}$ receptor blockers: clopidogrel (Plavix), prasugrel (Effient), or ticagrelor (Brilinta), and
  (3) GP IIb/IIIa blocker: Abciximab [Reopro] → Intravenous GP IIb/IIIa blocker is indicated in patients undergoing PCI.



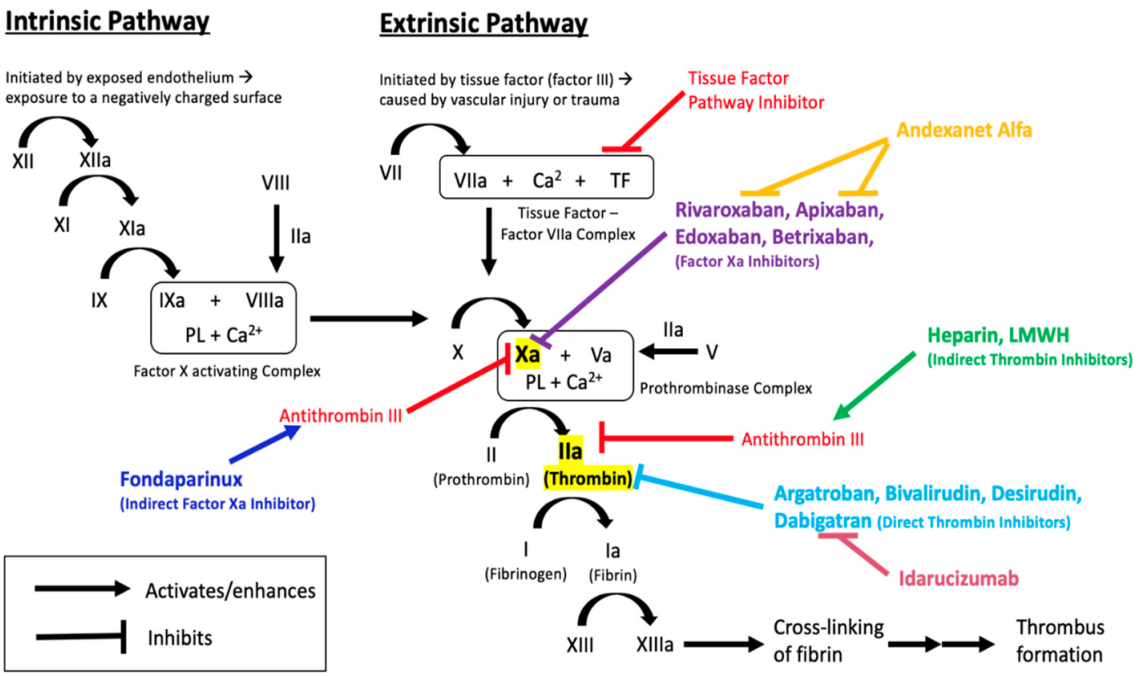


- Aspirin (ASA): 162-325 mg of chewable aspirin, then 81 mg PO daily indefinitely
  - MOA: blocks thromboxane A_2 (TxA_2) → inhibits platelet activation/aggregation
- $P2Y_{12}$ receptor blockers: Clopidogrel, Prasugrel, Ticagrelor, Cagrelor (IV)
  - MOA: $P2Y_{12}$ receptor blockers → block ADP from binding to $P2Y_{12}$ receptors on platelets → inhibit activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other.
  - Patients ≤ 75 years: Clopidogrel 300 mg PO loading dose, then 75 mg PO daily for up to 1 year.
  - Patients > 75 years: Clopidogrel 75 mg PO daily (w/out 300 mg loading dose)
  - Prasugrel (Effient) is more effective than clopidogrel → useful for PCI; however, it's associated with greater bleeding risk.

ANTICOAGULANTS: Heparin (UFH) and Low Molecular-Weight Heparin (LMWH)



- Heparin (UFH) and Low Molecular-Weight Heparin (LMWH) accelerate the activity of Antithrombin → prevents formation of fibrin clot.
- MOA: UFH → binds to Antithrombin III and accelerates interaction of Antithrombin III with both Thrombin (IIa) and Factor Xa by 1000-fold.
  - Note: Antithrombin III, Protein C, and protein S are endogenous inhibitors of coagulation factors.
  - Note: Factor Xa converts Prothrombin (II) to Thrombin (IIa, with "a" denoting "activated').
- MOA: LMWH (e.g., enoxaparin) → selectively binds to and accelerates the activity of Antithrombin III with Factor Xa, with less inhibition of Thrombin (IIa) → prevents formation of fibrin clot.

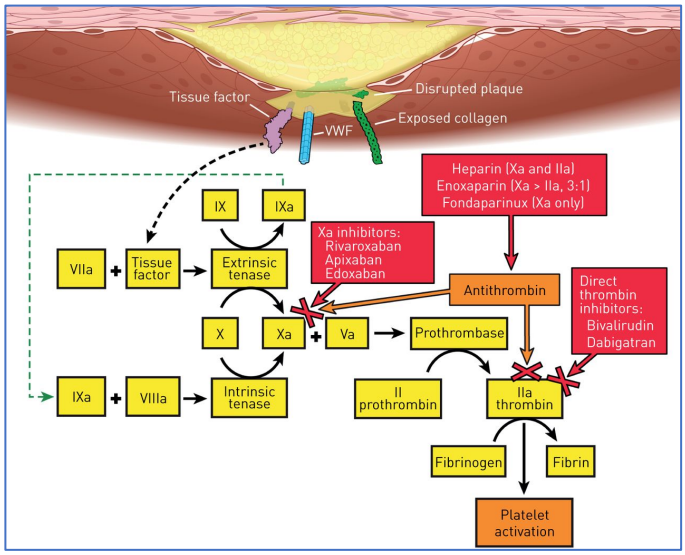


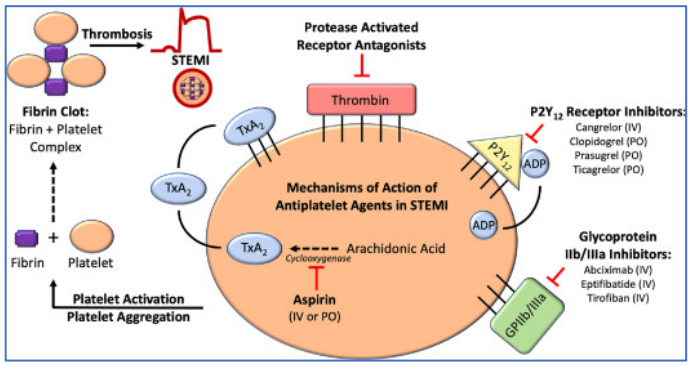
- For patients who will likely receive PCI after fibrinolytic therapy, UFH is preferred over enoxaparin (Lovenox), since it leaves open the option to proceed with rescue PCI if there is evidence of failed reperfusion. For patients who will not receive PCI after fibrinolysis, enoxaparin (Lovenox) is preferred over UFH.

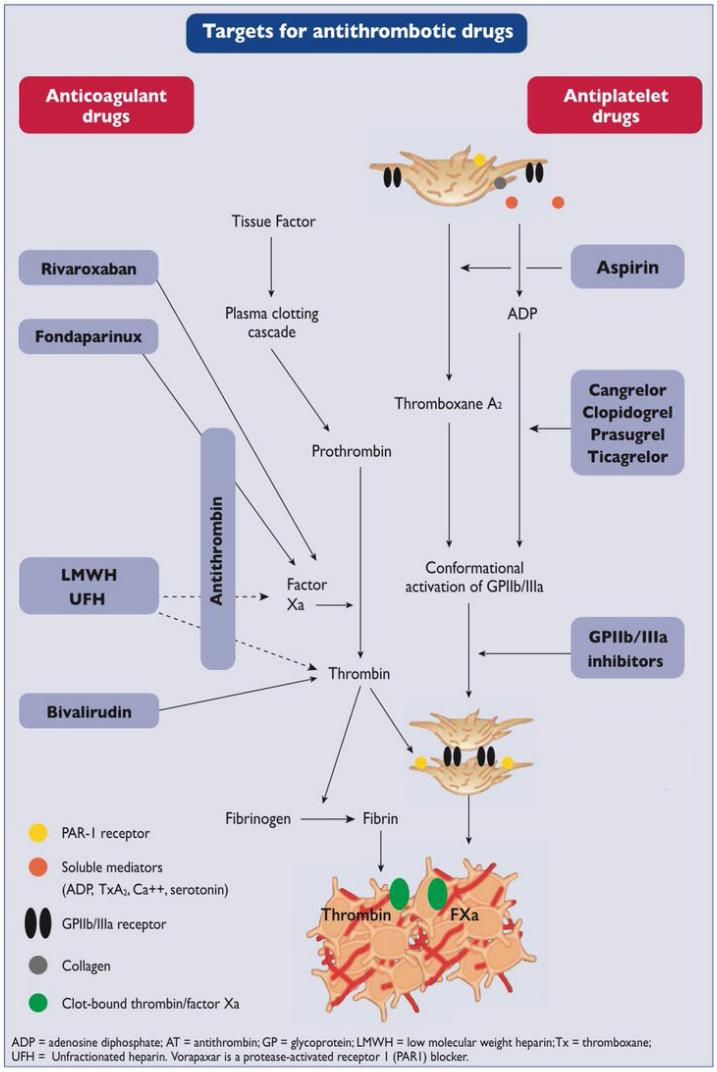
ANTICOAGULANTS: Heparin (UFH) and LMWH (cont.)

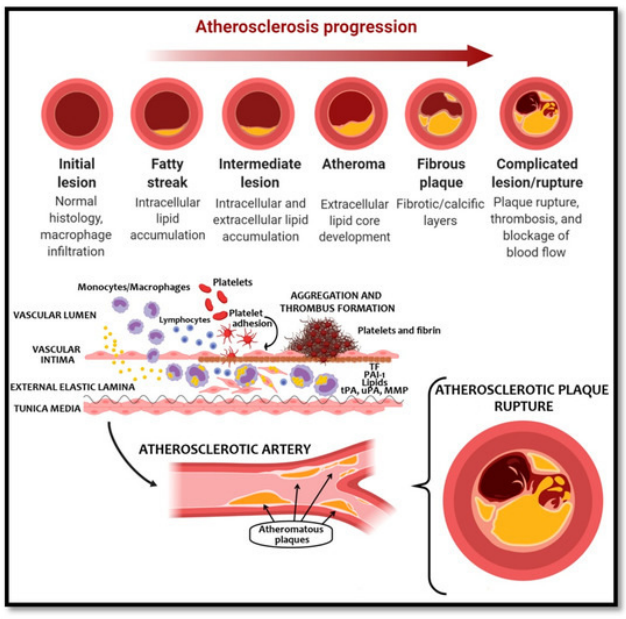
- Heparin (UFH) Dosing in ACS: 60 UNITS/kg IV bolus (max: 4000 UNITS) followed by 12 UNITS/kg/hour (max: 1000 UNITS/hour) infusion for 48 hours after fibrinolysis, adjusted to maintain activated partial thromboplastin time (aPTT) at 1.5-2 times the control (i.e., baseline) value.
    - Protamine is an antidote for severe bleeding with heparin (UFH) and LMWH.
        - MOA: Protamine binds to and inactivates heparin and enoxaparin.
        - Protamine dose: 1 mg for every 100 UNITS of UFH in preceding 4 hours, and 1 mg for every 1 mg of enoxaparin in preceding 8 hours.
- LMWH: (1) Enoxaparin (Lovenox) and (2) Fondaparinux (Arixtra) are alternatives to UFH used in prevention and treatment of ACS, DVT, PE.
    - Enoxaparin (Lovenox) Dosing in ACS (STEMI)
        - Patients < 75 years: 30 mg IV bolus plus 1 mg/kg SC Q12H.
        - Patients ≥ 75 years: 0.75 mg/kg SC Q12H (without an IV bolus).
        - In NSTEMI: Enoxaparin 1 mg/kg SC Q12H (Q24H, if CrCl < 30 ml/min).
    - Fondaparinux (Arixtra) → MOA: selectively inhibits Factor Xa.
        - Fondaparinux is associated with less bleeding than enoxaparin and is associated with less risk of HIT than LMWH and UFH.
            - HIT (heparin-induced thrombocytopenia) is an immune-mediated reaction that occurs when negatively charged heparin binds to positively charged platelet factor 4 (PF4) → antibodies bind and activate platelets → increases risk of thromboembolism with thrombocytopenia.
            - Fondaparinux is contraindicated in patients with CrCl < 30 ml/min.
    - Argatroban (Acova) → MOA: intravenous direct Thrombin (IIa) inhibitor.
        - Argatroban is indicated for prophylaxis or treatment of thrombosis in patients with HIT → Dosing: Initial 2 mcg/kg/min IV continuous infusion over 1-3 hours until steady state aPTT is 1.5-3.0 times baseline.
        - PCI: Argatroban is also indicated as an anticoagulant of choice in patients with a past medical history of HIT undergoing PCI → bolus: 350 mcg/kg then 25 mcg/kg/min infusion.
        - Argatroban may be used in patients with renal dysfunction since it's metabolized in the liver.

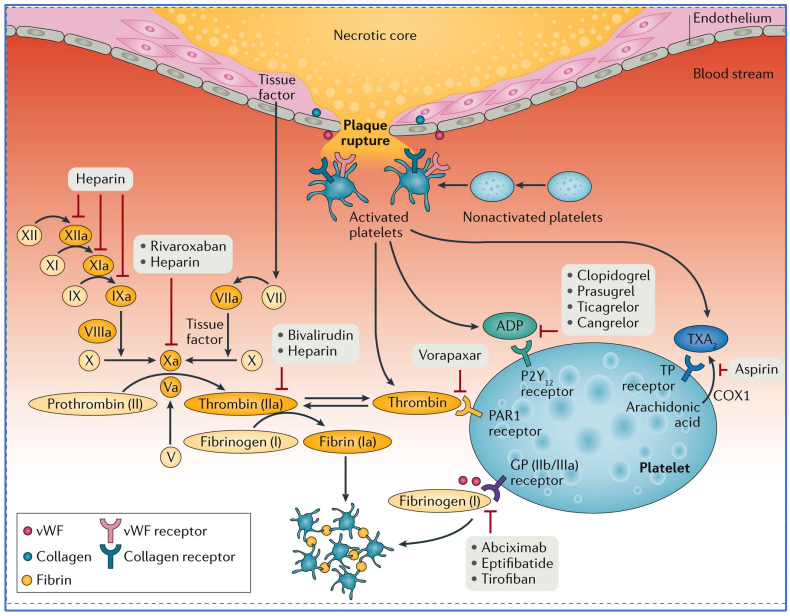
Graphic Illustrations: Targets for Antithrombotic Drugs



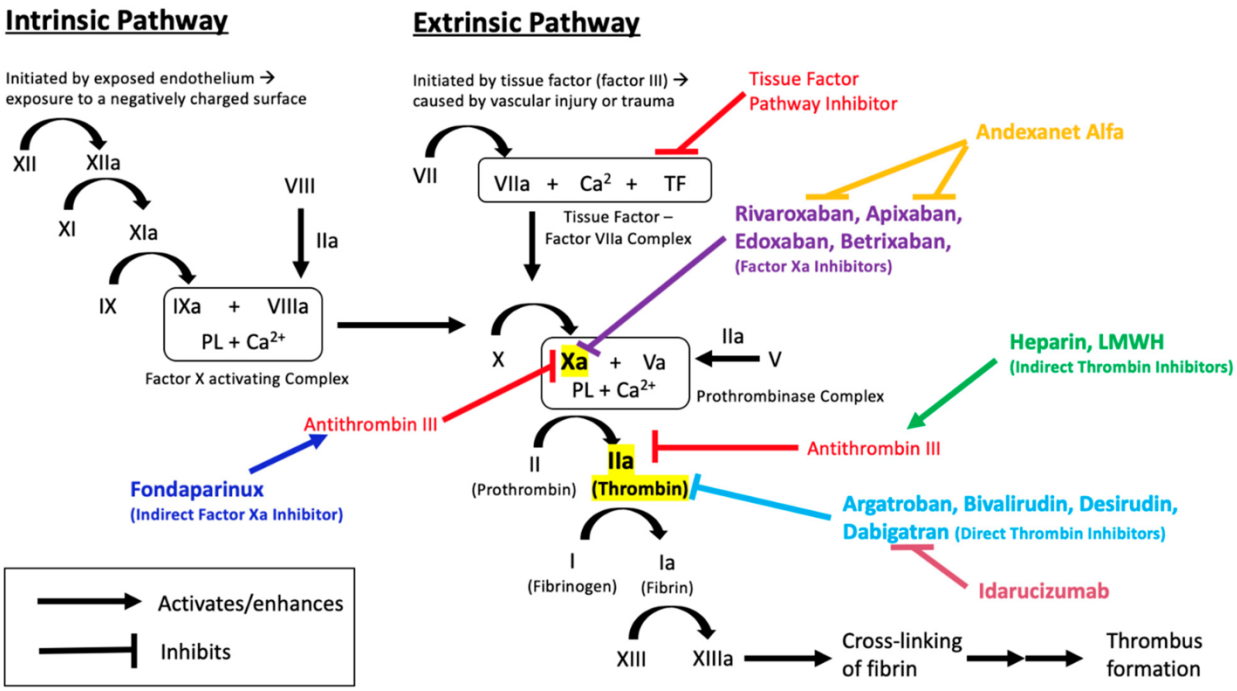








COAGULATION PATHWAYS



Direct-Acting Oral Anticoagulants (DOACs): Dabigatran, Rivaroxaban, and Apixaban

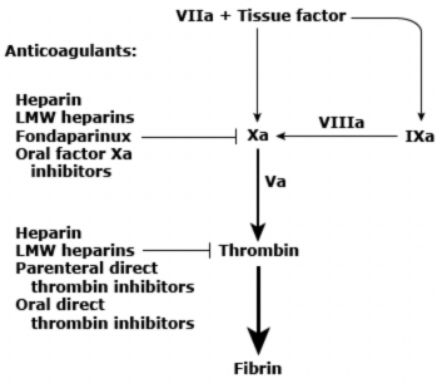
- General Statement: Compared to warfarin (Coumadin), DOACs have fewer drug-drug interactions and no requirement for lab monitoring of PT/INR.

(1) Dabigatran (Pradaxa) → MOA: binds to and inhibits Thrombin (Factor IIa) directly.

- Parenteral (IV) Thrombin (IIa) inhibitors include Argatroban and Bivalirudin.
- Indications: Prevention of stroke in non-valvular atrial fibrillation and VTE.
- Adverse Effects: Bleeding (like all anticoagulants).
  - GI: dyspepsia, abdominal pain, esophagitis, GI bleeding.
- Reversal Agent: Idarucizumab (Praxbind) / hemodialysis removes dabigatran.

(2) Rivaroxaban (Xarelto) and Apixaban (Eliquis)

- MOA: Selectively inhibits Factor Xa.
- Parenteral Xa inhibitor: Fondaparinux (Arixtra).
- Rivaroxaban Indications: (1) Prevention and treatment of VTE and PE, and (2) Prevention of stroke in non-valvular atrial fibrillation.
- Adverse Effects: Bleeding, GI (gastroenteritis, N/V).
- Reversal Agent: Andexanet alfa.



Direct-Acting Oral Anticoagulants (cont.)

- Standard Dosing of DOACs

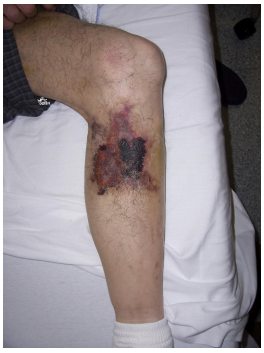
Anticoagulant	Nonvalvular AF - stroke prophylaxis*	VTE treatment¶	VTE primary prophylaxisΔ
Dabigatran (Pradaxa)	150 mg twice daily	Parenteral anticoagulation for 5 to 10 days; then dabigatran 150 mg twice daily	110 mg for the first day, then 220 mg once daily
Apixaban (Eliquis)	5 mg twice daily	10 mg twice daily for one week, then 5 mg twice daily	2.5 mg twice daily
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

- Advantages & Disadvantages of Oral Anticoagulants: Warfarin vs 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

Warfarin (Coumadin)

- MOA: Inhibits vitamin K-dependent clotting factors: II (Prothrombin), VII, IX, & X.
- Unlike heparin, the anticoagulant effects of warfarin are delayed for 5 days, which is the time required to deplete the pool of vitamin K dependent clotting factors w/long half-lives.
- Reversal Agent: Vitamin K (phytonadione) → 5-10 mg IV/SC/PO .
  (Note: reversal after administration of Vit K takes approx. 24 hours, time needed for degradation of already inhibited clotting factors).
  - If INR > 10 with severe bleeding FFP / PCC (Prothrombin Complex Concentrate) called KCentra^{R} → IV formulation includes Factors II, VII, IX, X.
- Adverse Effect: Bleedings
  - 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, and kale → reduce warfarin effectiveness.
- Drug-Drug Interactions: (1) Inhibitors of the CP-450 hepatic enzymes → increase warfarin levels, and (2) Inducers of CP-450 enzymes Inducers → decrease warfarin levels.
  - Note: Warfarin is also 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.
- Warfarin Dosing: Nomogram for Initiating Warfarin

	Standard dosing for patients who are *not* expected to be sensitive to warfarin[b]	**Reduced dosing for patients expected to be more sensitive to warfarin[c]**
Initial dose	5 mg daily for 3 days[d]	2.5 mg daily for 3 days
Check INR the morning of day 4		
<1.5	7.5 to 10 mg daily for 2 to 3 days	5 to 7.5 mg daily for 2 to 3 days
1.5 to 1.9	5 mg daily for 2 to 3 days	2.5 mg daily for 2 to 3 days
2 to 3	2.5 mg daily for 2 to 3 days	1.25 mg daily for 2 to 3 days
3.1 to 4	1.25 mg daily for 2 to 3 days	0.5 mg daily for 2 to 3 days
>4	Hold until INR <3	Hold until INR <3

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 drip (i.e., 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 → Although an INR of 2-3 may be seen in approx. 3 days, this does not represent therapeutic anticoagulation since clotting factors with longer half-lives must also be depleted. So, warfarin requires bridging with UFH (Heparin Infusion) or enoxaparin for approx. 5 days for a complete therapeutic response and thromboembolic protection.

Renal Considerations

- Warfarin and UFH are recommended in patients with renal failure and patients on hemodialysis since warfarin and UFH are hepatically eliminated.
- Note: In patients with severe or ESKD (end-stage kidney disease) with CrCl of 15-29 ml/min not requiring hemodialysis, it's considered appropriate by most experts to use either warfarin or apixaban (Eliquis) 2.5 mg PO BID for non-valvular atrial fibrillation.
    - Apixaban is dosed 5 mg PO BID unless patient has 2 of the following: Cr ≥ 1.5 mg/dL, Age ≥ 80, or body wt. ≤ 60 kg. (Official Labeling / FDA)

Detailed Timeline for Pharmacologic and Nonpharmacologic Interventions in ACS

(UpToDate 2023)

Initial Assessment

- Consider the diagnosis in patient with chest discomfort, SOB, and other suggestive symptoms of ACS.
- Obtain 12-lead ECG within 10 mins of arrival; repeat every 10-15 mins if initial ECG is nondiagnostic as clinical suspicion remains high. Note: Initial ECG often is not diagnostic.
    - STEMI
    - NSTEMI or UA (unstable angina)

Overview of approach to patients with suspected acute myocardial infarction in the emergency department

Initial Interventions

- Assess and stabilize airway, breathing, and circulation.
- Attach cardiac and oxygen saturation monitors.
- Provide supplemental oxygen as needed to maintain O_2-saturation > 90%.
- Establish IV access.
- Give chewable aspirin 325 mg PO (or aspirin suppository if PO is not feasible).
- Obtain blood for cardiac biomarkers (troponin preferred), electrolytes, CBC (HGB/HCT/platelet), coagulation studies for patients taking anticoagulants (PT / INR / PTT). Assess any coagulopathies.
- Give 3 tabs of SL NTG Q5min for 3 doses if patient has persistent chest discomfort/pain, HTN, and signs of heart failure. Note: make sure patient is not on phosphodiesterase inhibitors (PDE-inhibitors) for erectile dysfunction: Sildenafil (Viagra), Tadalafil (Cialis).
- Add NTG IV drip (40 mcg/min) for hypertension or persistent symptoms of chest discomfort/pain or heart failure. Note: avoid NTG in patients on PDE-inhibitors for erectile dysfunction.
- Give beta blocker (e.g., metoprolol tartrate 25 mg PO) if no signs of heart failure and no signs of hemodynamic compromise, bradycardia, or severe reactive airway disease. If hypertensive, may initiate beta blocker IV: metoprolol tartrate 5 mg IV Q5min x 3 doses as tolerated. (Conversion: 5 mg of IV metoprolol tartrate = 12.5 mg of PO metoprolol tartrate)
- Morphine sulfate (2-4 mg slow IVP Q5-15mins) is indicated for chest discomfort refractory to nitrates and other anti-ischemic therapies.
- Atorvastatin 80 mg as early as possible and preferably before PCI in patients not on a statin. (Note: if patient is on a low- to mod-intensity statin, switch to atorvastatin 80 mg)

Acute Management of STEMI

Select reperfusion strategy.

- PCI: PCI is preferred in patients with cardiogenic shock, heart failure, late presentation, or contraindication to fibrinolysis. Note: In patients with symptoms of > 12 hours, fibrinolysis is not indication; but, emergent PCI may be considered.
- Fibrinolysis: Treat patient with fibrinolytic therapy if PCI is not available within 120 mins of first medical contact, symptoms < 12 hours, and no contraindications.

Give oral antiplatelet therapy (in addition to aspirin) to all patients.

- Patients treated with fibrinolytic therapy: Clopidogrel (Plavix) 300 mg PO LD (loading dose) if age ≤ 75. Give clopidogrel 75 mg PO loading dose if patient age > 75 years-old.
- Patients treated with no reperfusion therapy: Ticagrelor (Brilinta) 180 mg PO LD.
- Patients treated with primary PCI: Ticagrelor (Brilinta) 180 mg LD; or Prasugrel (Effient) 60 mg LD, if no contraindications (i.e., prior strokes or TIA) or relative contraindications (i.e., age ≥ 75, weight < 60 kg).
    - Patients at high risk of bleeding or those for whom prasugrel or ticagrelor cannot be used, give clopidogrel 600 mg PO LD.

Give anticoagulant therapy to all patients

- Patients treated with PCI: (1) UFH for patients treated with ticagrelor or prasugrel, or (2) bivalirudin (Angiomax) for patients treated with clopidogrel.
    - UFH: 50-70 UNITS/kg up to a max of 5000 UNITS IV bolus.
    - Bivalirudin: 0.75 g/kg IV bolus, followed by 1.75 mg/kg/hour.
- Patients treated with fibrinolysis: (1) enoxaparin (Lovenox) for patients not at high risk of bleeding or (2) fondaparinux (Arixtra) for those at high bleeding risk.
  Note: Patients whom PCI is possible or likely after fibrinolysis, UFH is preferred.
    - Enoxaparin (Lovenox)
        - Patients < 75 years-old: Enoxaparin 30 mg IV bolus, followed by 1 mg/kg SC Q12H, with max dose of 100 mg for first two SC doses. Note: the 1st SC dose given with the IV bolus.
            - In renal impairment (CrCl < 30 ml/min), enoxaparin 30 mg IV bolus, followed by 1 mg/kg SC Q24H.
        - Patients ≥ 75 years-old: Enoxaparin 0.75 mg/kg SC Q12H, with a max dose of 75 mg for first two SC doses. Note: No enoxaparin IV bolus given.
            - In renal impairment (CrCl < 30 ml/min), enoxaparin 1 mg/kg SC Q24H.
    - UFH (Heparin): UFH 60-1000 UNITS/kg IV bolus (max: 4000 UNITS), followed by 12 UNITS/kg/hour infusion (max: 1000 UNITS/hour) adjusted to achieve a goal an aPTT of approx. 50-70 seconds (1.5-2.0 times control).
    - Fondaparinux: 2.5 mg IV, followed by 2.5 mg SC Q24H. Note: Avoid if CrCl < 30 ml/min.
- Patients not receiving reperfusion therapy with fibrinolysis or PCI
    - Enoxaparin or UHF, with same dosing as patients treated with fibrinolysis.

Acute Management of Unstable Angina or NSTEMI

Give antiplatelet therapy (in addition to aspirin) to all patients.

- Patients not treated with an invasive approach
  - Ticagrelor (Brilinta) 180 mg PO LD.
- Patients managed with an invasive approach (i.e., diagnostic coronary angiography)
  - Ticagrelor (Brilinta) 180 mg PO LD at presentation.
    - Prasugrel (Effient) 60 mg PO LD may be used as an alternative if given after diagnostic coronary angiography.
  - Patients who are ≥ 75 years-old, who weigh < 60 kg, or with past stroke or TIA, ticagrelor 180 mg PO or clopidogrel 300 mg PO are preferred over prasugrel.
  - Patients treated with an invasive approach who received bivalirudin (Angiomax), we do not recommend routinely giving a GP IIb/IIIa inhibitor.
  - Patients treated with an invasive approach who received UFH and who are troponin-positive, we suggest adding a GP IIb/IIIa inhibitor, e.g., abciximab (ReoPro), given after diagnostic angiography.
  - Patients undergoing an invasive approach who are at very high risk of recurrent ischemic discomfort, dynamic ECG changes, or hemodynamic instability, we consider adding a GP IIb/IIIa inhibitor prior to and after diagnostic angiography.

Give anticoagulant therapy in all patients.

- Patients undergoing urgent catheterization (within 4 hours) or those managed with early invasive strategy (angiography within 4-48 hours), use either UFH or bivalirudin.
  - UFH: 60-70 UNITS/kg IV bolus (max: 5000 UNITS), following by 12 UNITS/kg/hour IV infusion to achieve a goal aPTT of approx. 50-70 seconds (1.5-2 times control).
- Patients receiving a noninvasive approach: use either enoxaparin (Lovenox) or fondaprinux (Arixtra).

  Note: Enoxaparin is an alternative to UFH for patients not undergoing an early invasive approach.
  - Enoxaparin (Lovenox) dosing: 1 mg/kg SC Q12H (if CrCl < 30 ml/min, 1 mg/kg SC Q24H).
  - Fondaparinux (Arixtra) dosing: 2.5 mg SC Q24H (if CrCl < 30 ml/min, avoid use).

Other Important Considerations

Cocaine-related ACS: give benzodiazepines.

- Give benzodiazepines as needed to alleviate symptoms and standard therapies; but do NOT give beta blockers.
  - Lorazepam (Ativan) 2-4 mg IV Q15mins as needed to alleviate symptoms.

Stop NSAID therapy if possible.

Correct any electrolyte abnormalities, especially hypokalemia and hypomagnesemia, which often occur together.