ACUTE CORONARY SYNDROME (ACS)

- ACS incudes unstable angina (UA) or acute myocardial infarction (AMI)
  - AMI is divided into:
    (1) STEMI: ST segment elevation myocardial infarction
    (2) NSTEMI: non-ST segment myocardial infarction
- NSTE-ACS (Non-ST segment elevation-ACS) includes: (1) UA and (2) NSTEMI
  - NSTEMI: depends on the presence of biomarkers (i.e., troponins) associated with necrosis
- STEMI → medical emergency requiring immediate intervention: reperfusion and revascularization using both pharmacological and nonpharmacologic interventions (PCI and CABG)
- Unstable Angina: coronary artery has enough blood flow → myocardial cells do not die
- NSTEMI: there is partial thrombotic occlusion → some myocardial cells die
- STEMI: there is total and persistent thrombotic occlusion → myocardial cell death

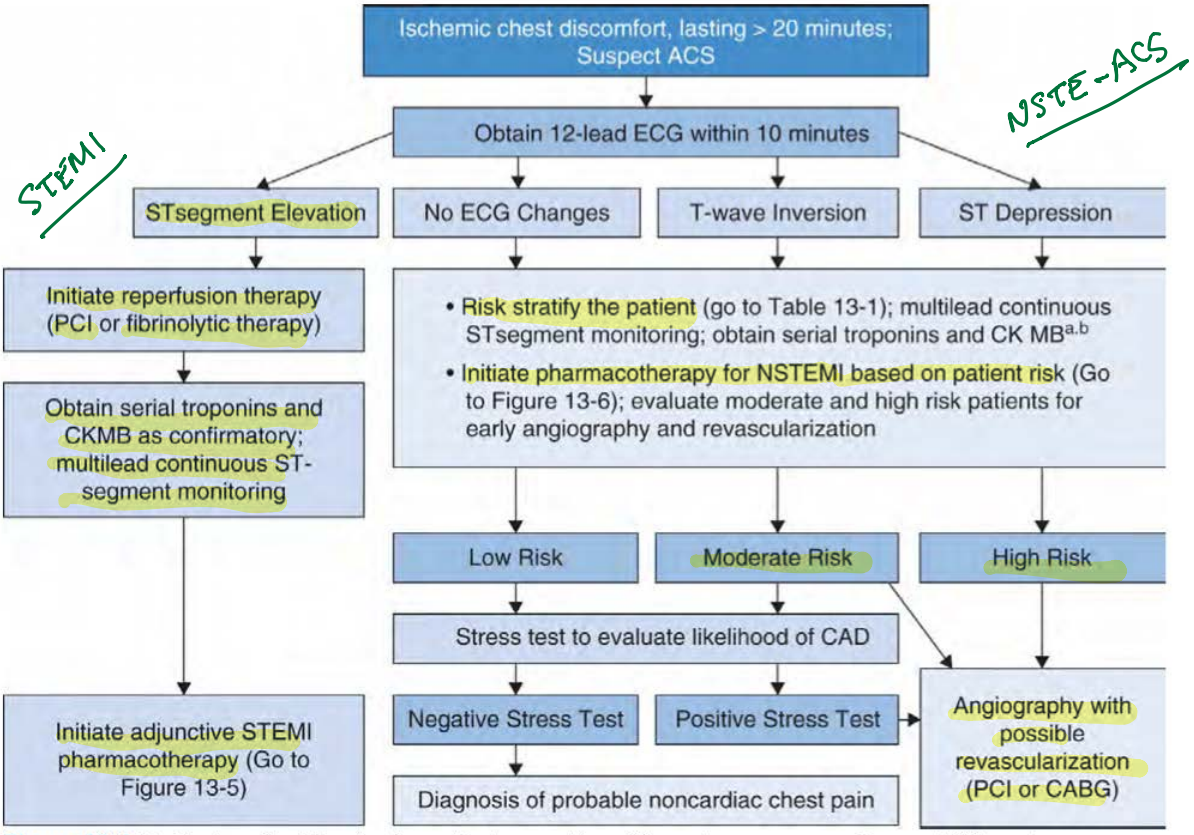


Figure 13-2 Evaluation algorithm for the patient presenting with acute coronary syndrome. ACS, acute coronary syndrome; CAD, coronary artery disease; CABG, coronary artery bypass graft; CK, creatinine; ECG, electrocardiogram; PCI, percutaneous intervention; NSTE-ACS, non-ST segment acute coronary syndrome; STEMI, ST segment myocardial infarction. **A:** Positive, above the myocardial infarction limit; **B:** Negative, below the myocardial infarction limit. (Adapted with permission from Spinler SA. Evolution of antithrombotic therapy used in acute coronary syndromes. In: Richardson M et al, eds. Pharmacotherapy Self-Assessment Program. Cardiology. 7th ed. Lenexa, KS: American College of Clinical Pharmacy; 2010:62.)

Risk Stratification

- The examination of 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 (PMHx), 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 greater amount of myocardium preserved
    - ACC/AHA guidelines: target time for reperfusion for STEMI within 30 mins of hospital presentation for fibrinolytic therapy ("door-to-needle") and within 90 mins from presentation for PCI ("door-to-balloon")
- Although primary PCI is the preferred therapy for STEMI, it has severe 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 hours/day.

Complications of ACS

- Complications of ACS: pump failure, arrhythmias, recurrent ischemia and reinfarction
- LV (left ventricular) damage → decreased cardiac output and decreased perfusion → compensatory mechanisms become activated
    - Circulating catecholamines increase in an attempt to increase contractility and restore perfusion → increase myocardial oxygen demand
    - RAAS is enhanced → increase in systemic vascular resistance and Na/H2O retention → increase myocardial oxygen demand
- Beta blockers, ACEIs, ARBs, and aldosterone antagonists (e.g., spironolactone) will improve outcomes of ACS

Overview of Drug and Nondrug Therapy

- Overlap exists regarding the pharmacology for both STEMI and NSTE-ACS

- ACC/AHS guidelines:

Oxygen if O_2 sat < 90%	SL and/or IV NTG	Beta Blockers
Anticoagulant	Antiplatelet agents	IV morphine
Statins (HMG-CoA reductase inhibitors)		Stool softener

Fibrinolytic Agents

(1) Anteplase or t-PA (Activase)
(2) Reteplase or r-PA (Retavase)
(3) Tenecteplase or TNK (TNKase)

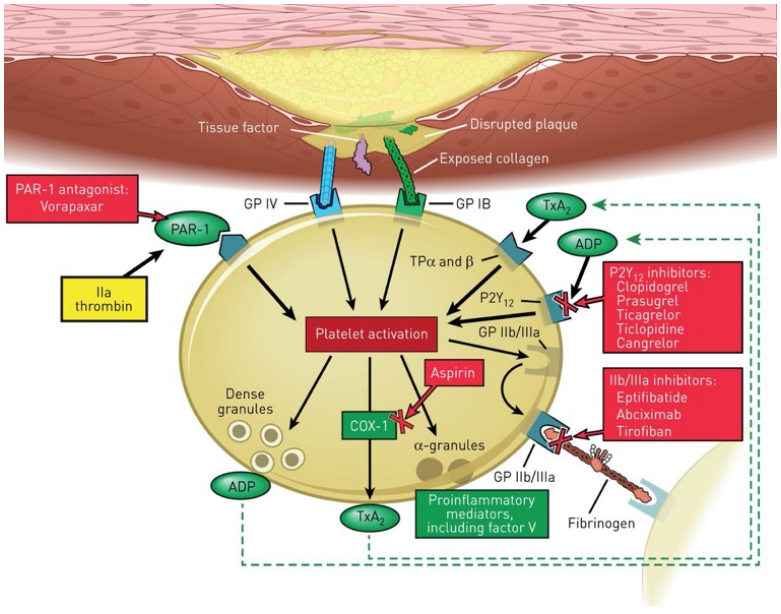
- Fibrinolytic therapy is indicated in patients with STEMI who present to the hospital within 12 hours of symptom onset and are unable to undergo primary PCI (percutaneous coronary intervention) within 120 minutes from the first medical contact
  - Mortality from STEMI is reduced by one-third with fibrinolytic therapy
  - Mortality reduction is greater when fibrinolytic therapy is initiated within 0-2 hours after symptoms have begun → ACC/AHA Guidelines recommend "door-to-needle time" of 30 mins
  - Once stabilized, the patient should be transferred to a facility capable of PCI in case reperfusion fails or re-occlusion occurs

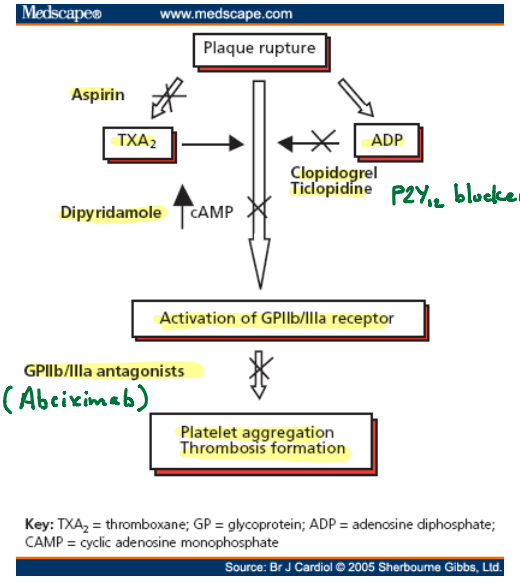
fibrinolytic therapy } ≤ 12 hrs
• best if ≤ 2 hours
• ACC/AHA recommend ↳ door-to-needle (30 mins)

- MOA: Fibrinolytics act either directly or indirectly to convert plasminogen to plasmin, which cleaves fibrin → lyses thrombi

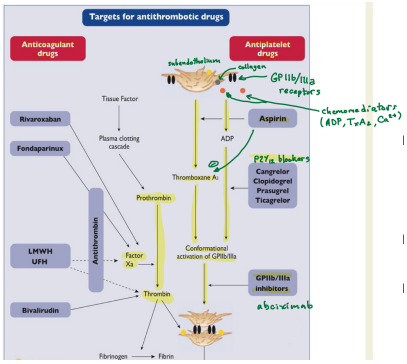
- As the clot dissolves with fibrinolytics, there is a paradoxical increase in local thrombin generation and enhanced platelet aggregation, which may lead to re-thrombosis. Antiplatelet agents: (1) Aspirin (ASA), (2) $P2Y_{12}$ receptor blockers: clopidogrel [Plavix], prasugrel [Effient], or ticagrelor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

fibrinolysis → paradoxical increase in thrombin → antiplatelets

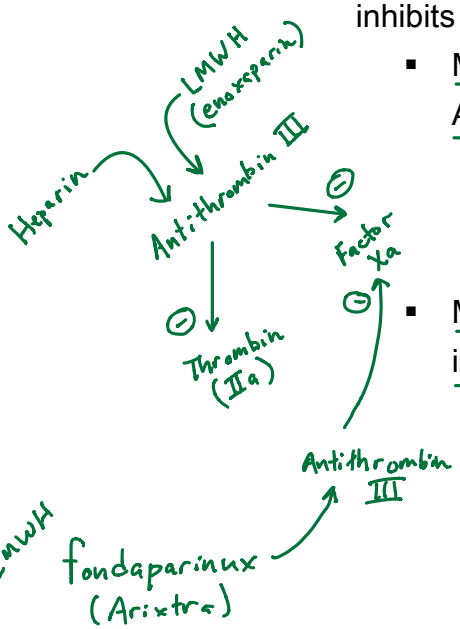


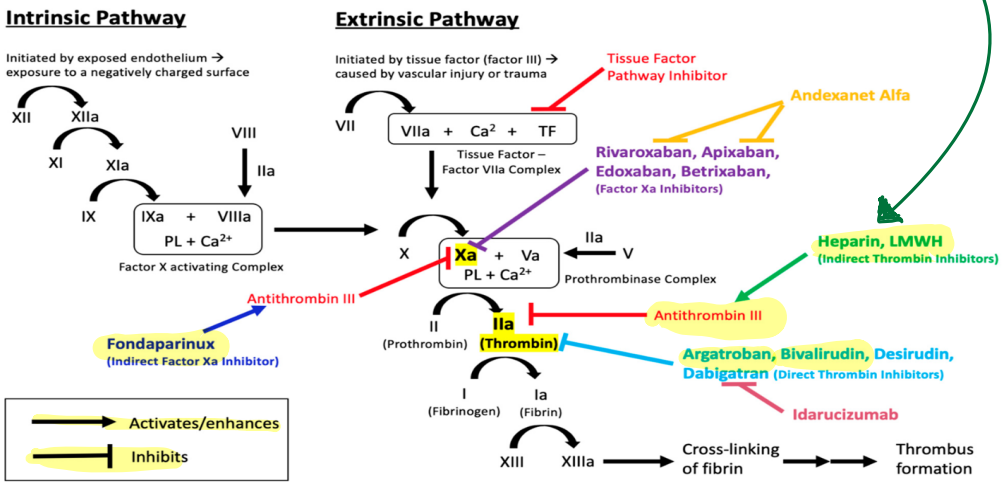


- Aspirin (ASA): 162-325 mg of chewable aspirin then 81 mg PO daily indefinitely
- $P2Y_{12}$ receptor blockers: Clopidogrel, Prasugrel, Ticagrelor, Cagrelor (IV)
  - MOA: $P2Y_{12}$ receptor blockers → inhibit binding of ADP to its $P2Y_{12}$ receptors on platelets and, thereby inhibits the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other
  - Patients < or = 75 years: Clopidogrel 300 mg PO loading dose, then 75 mg PO daily for up to 1 year
  - Patients > 75 years: No loading dose (i.e., Clopidogrel 75 mg daily)
  - Prasugrel (Effient) is more effective than clopidogrel → useful for PCI; however, associated with more bleeding risk

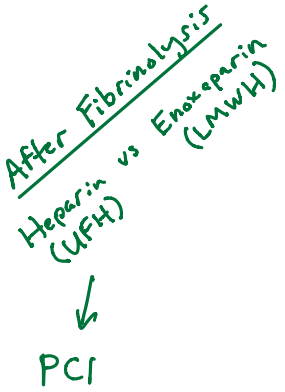


- Heparin: (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH] inhibits thrombin)
  - MOA: UFH → binds to Antithrombin III and accelerates interaction of Antithrombin III with both Thrombin (IIa) and Factor Xa by 1000-fold
    - Note: Antithrombin III, Protein C, and protein S are endogenous inhibitors of coagulation factors
    - Note: Factor Xa converts Prothrombin (II) to Thrombin (IIa)
  - MOA: LMWH → binds to Antithrombin III selectively accelerates interaction of Antithrombin III with Xa, with less inhibition of thrombin (IIa) → inactivation of Factor Xa



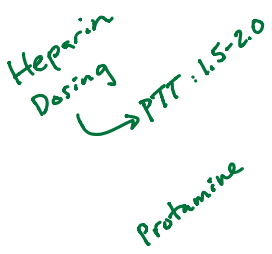


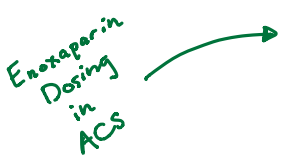
- For patients who will likely receive PCI after fibrinolytic therapy, UFH is preferred over enoxaparin (Lovenox) since it leaves open the option to proceed with rescue PCI if there is evidence of failed reperfusion.
  - For patients who will not receive PCI after fibrinolysis, enoxaparin (Lovenox) is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

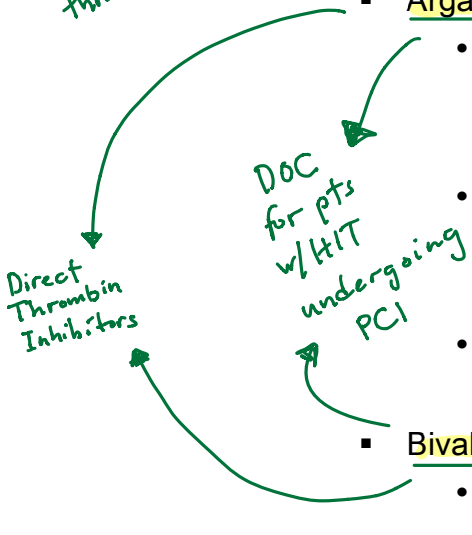


- UFH in ACS: 60 UNITS/kg IV bolus (max: 4000 UNITS) followed by 12 U/kg/hr (max: 1000 U/hr) infusion for 48 hours after fibrinolysis, adjusted to maintain activated partial thromboplastin time (aPTT) at 1.5-2 times the control value.
  - Protamine sulfate is an antidote when severe bleeding occurs with heparin (MOA: binds to and inactivates heparin)
    - Dose: Protamine 1 mg for every 100 UNITS of heparin
- LMWH: (1) enoxaparin [Lovenox]) and (2) Dalteparin (Fragmin) are alternatives to UFH used in prevention & treatment of ACS, DVT, PE

  Enoxaparin Dosing (ACS)
  - Patients < 75 years: 30 mg IV bolus, then 1 mg/kg SC Q12H
  - Patients > or = 75 years: 0.75 mg/kg SC Q12H (No IV bolus)
  - Regardless of age, if CrCl < 30 ml/min, the dose is 1 mg/kg SC Q24H
- Fondaparinux (Arixtra) → MOA: selectively inhibits factor Xa
  - Fondaparinux is associated with less bleeding than enoxaparin and is associated with less risk of heparin-induced thrombocytopenia (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 → increase risk of thromboembolism with thrombocytopenia
  - Fondaperinux is contraindicated in patients with CrCl < 30 ml/min
- Argatroban (Acova) → MOA: intravenous direct thrombin (IIa) inhibitor
  - 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 HIT undergoing PCI → bolus: 350 mcg/kg then 25 mcg/kg/min infusion
  - May be used in patients with renal dysfunction since it's metabolized in the liver
- Bivalirudin (Angiomax) → MOA: intravenous direct thrombin inhibitor
  - Bivalirudin is an alternative to heparin in patients undergoing PCI at risk of developing HIT
  - Dosing: 0.75 mg/kg IV bolus then 1.75 mg/kg/hr infusion







Summary: Targets for Antithrombotic Drugs

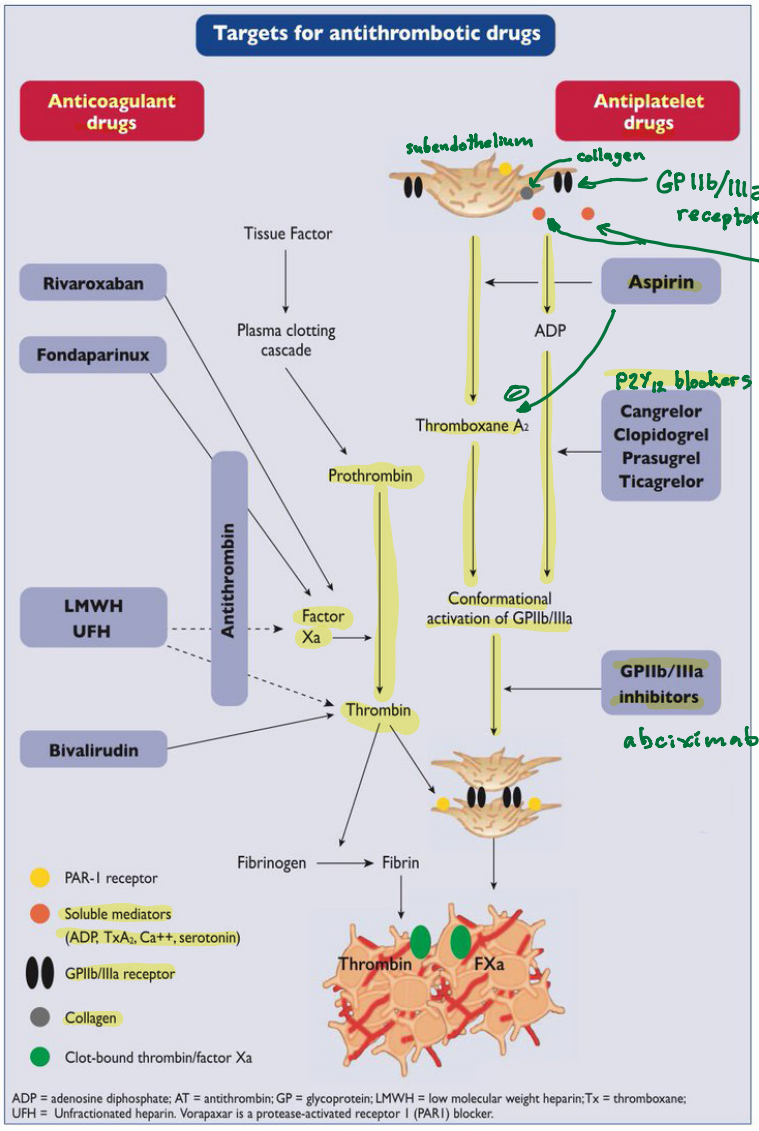


Figure 4 Antithrombotic drugs for non-ST-elevation acute coronary syndromes. The figure depicts the targets of available antithrombotic drugs that can be used to inhibit blood coagulation and platelet aggregation during and after thrombus formation.

Overview of Drug and Nondrug Therapy in ACS: STEMI (cont.)

- Statins → Initiate high intensity statin therapy regardless of baseline LDL-cholesterol levels → atorvastatin (Lipitor) 80 mg PO daily or rosuvastatin (Crestor) 20-40 mg PO daily.

- Beta Blockers → initiate oral beta blockers within the first 24 hours, as long as no contraindications are present.

- Absolute contraindications for fibrinolytic use in STEMI include:
  - Prior intracranial hemorrhage (ICH)
  - Known structural cerebral vascular lesion
  - Known malignant intracranial neoplasm
  - Ischemic stroke within 3 months
  - Suspected aortic dissection
  - Active bleeding or bleeding diathesis (excluding menses)
  - Significant closed head trauma or facial trauma within 3 months
  - Intracranial or intraspinal surgery within 2 months
  - Severe uncontrolled hypertension (unresponsive to emergency therapy)
  - For streptokinase, prior treatment within the previous 6 months (due to antigenic/hypersensitivity reactions with repeated doses)

- Relative contraindications for fibrinolytic use in STEMI include:
  - History of chronic, severe, poorly controlled hypertension (SBP > 180)
  - Significant hypertension on presentation (SBP > 180 or DBP > 110)
  - Traumatic or prolonged (>10 mins) CPR or major surgery less than 3 weeks previously
  - Ischemic Stroke more than 3 months previously
  - Dementia or other intracranial pathology
  - Recent (2-4 weeks) internal bleeding
  - Noncompressible vascular puncture
  - Pregnancy
  - Active peptic ulcer
  - Current use of an anticoagulant (e.g., warfarin) that has produced an elevated INR > 1.7 or PT

- 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, and then 0.5 mg/kg (up to 35 mg) IV infusion over 60 mins
  - Alteplase is more difficult to administer because of short half-life

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

- 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

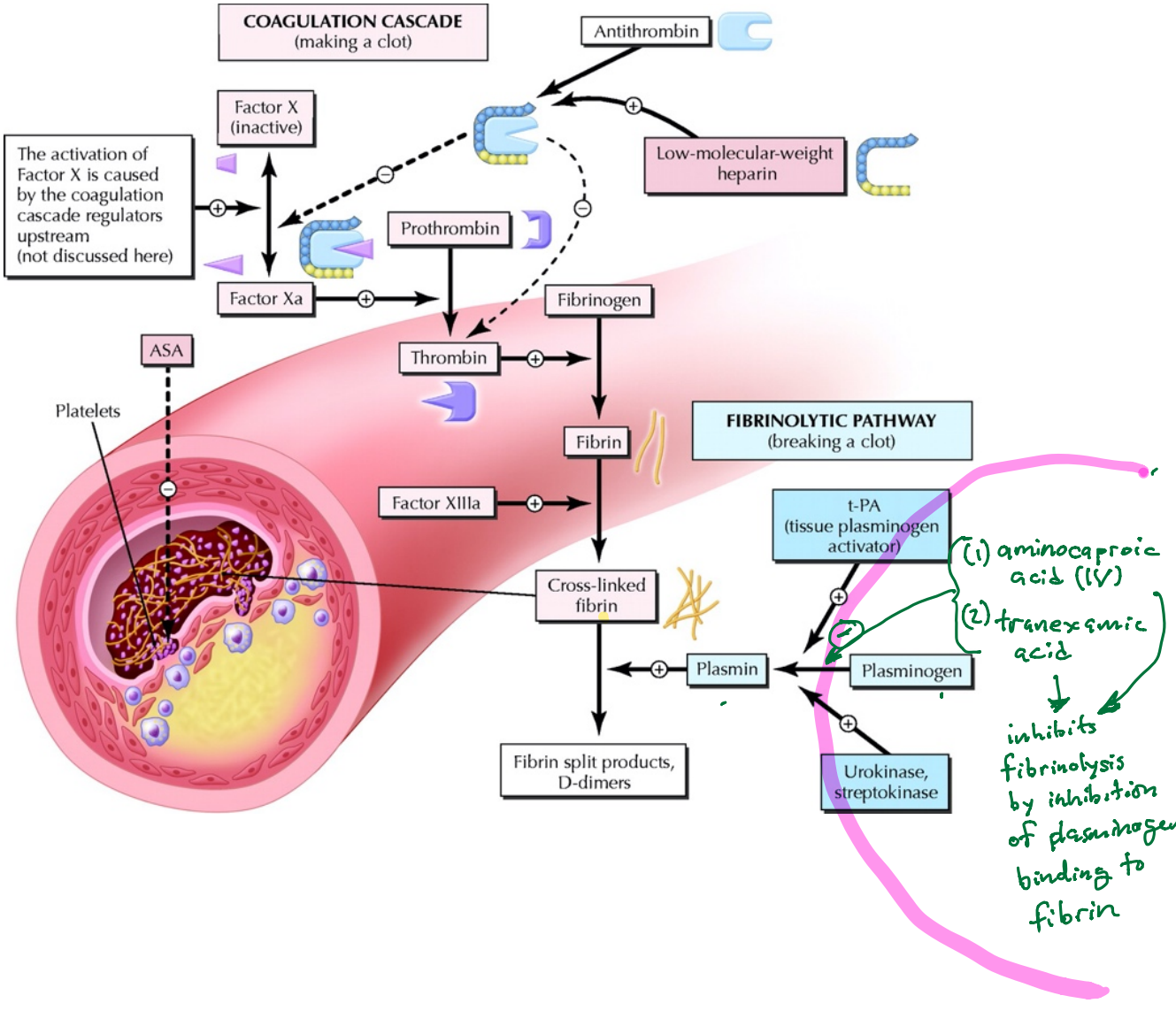
    70 – 79 kg → 40 mg IVP 80-89 kg → 45 mg IVP

    weight > or = 90 kg → 50 mg

  - Tenecteplase is as effective as alteplase with the following advantages:

    (1) less non-cerebral bleeding

    (2) easier to administer in and out of the hospital as a single IV bolus dose



INITIAL TREATMENT ALGORITHM FOR STEMI

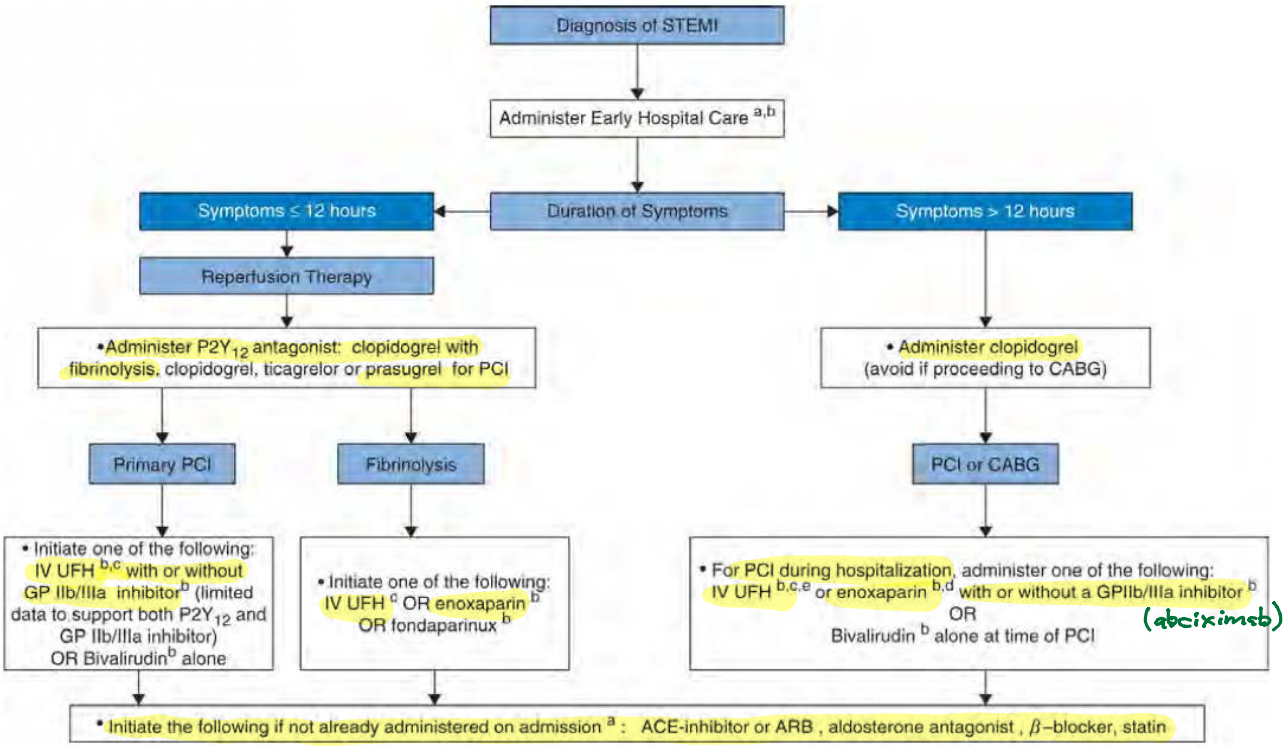


Figure 13-5 Initial treatment algorithm for STEMI. a: Early hospital care consists of oxygen for oxygen saturation <90%, SL nitroglycerin, IV nitroglycerin, IV morphine, β-blocker, ACE inhibitor or ARB, aldosterone antagonist, stool softener, and statin. b: Refer to Table 13-2 for indications, dosing, and contraindications. c: For at least 48 hours. d: For the duration of the hospitalization, up to 8 days. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; GP IIb/IIIa, glycoprotein IIB/IIIA; NTG, nitroglycerin; O_2, oxygen; PCI, percutaneous coronary intervention; SL, sublingual; STEMI, ST segment elevation myocardial infarction; UFH, unfractionated heparin. (Source: Kushner FG et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published corrections appear in J Am Coll Cardiol. 2010;55:612 (dosage error in article text); J Am Coll Cardiol. 2009;54:2464]. J Am Coll Cardiol. 2009;54:2205; Anderson JL et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine [published correction appears in J Am Coll Cardiol. 2008;51:974]. J Am Coll Cardiol. 2007;50:e1; O'Gara PT et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362–e425.)

INITIAL TREATMENT ALGORITHM FOR NSTE-ACS

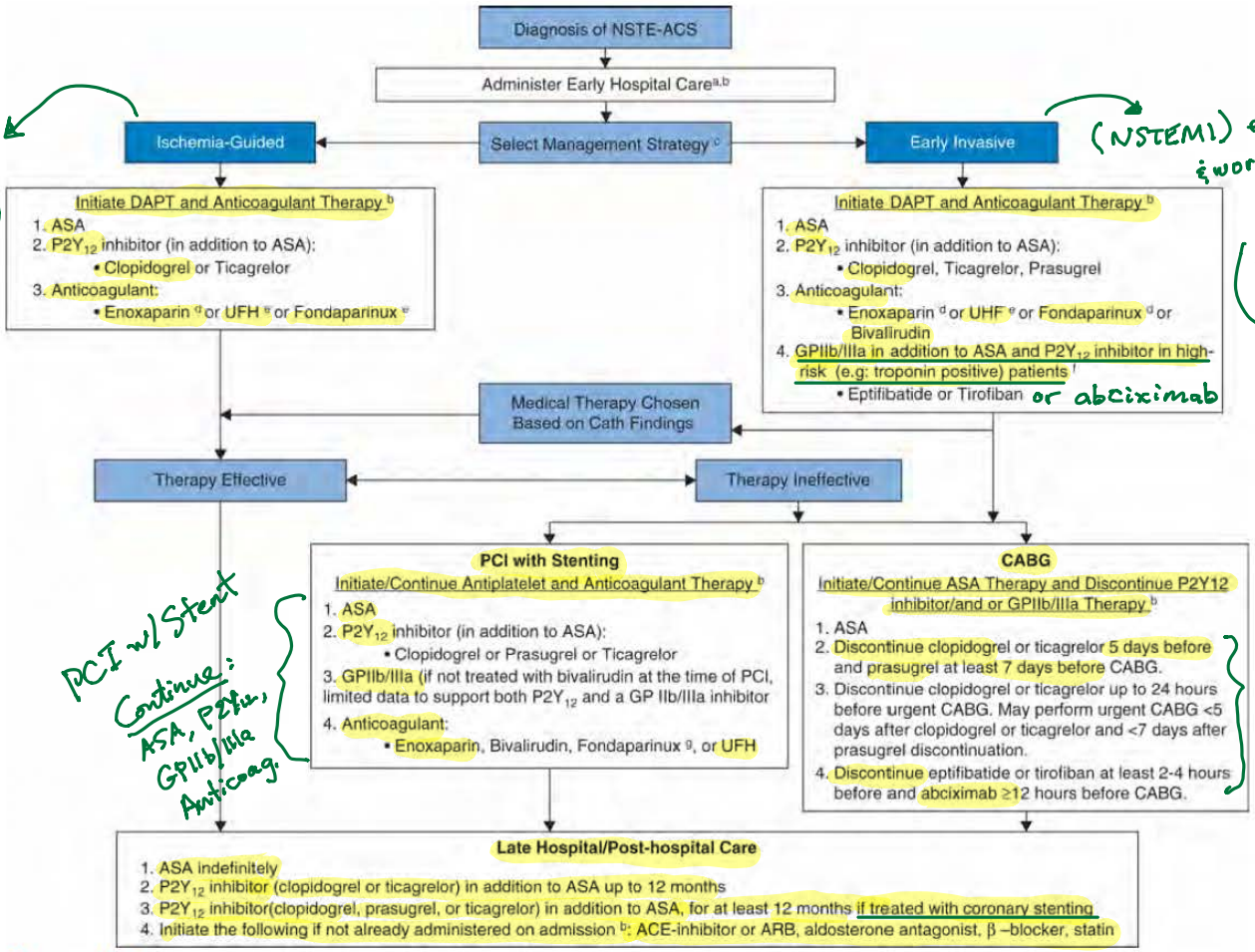
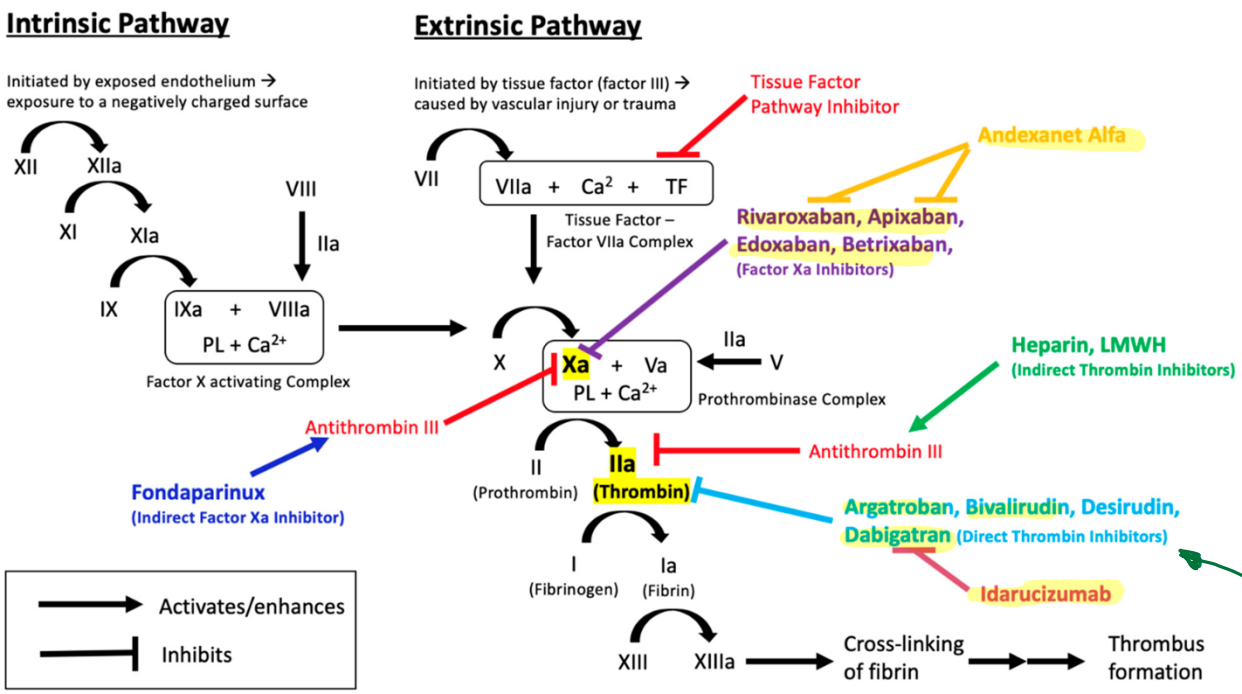


Figure 13-6 Initial treatment algorithm for NSTE-ACS. a: Early hospital care consists of oxygen for oxygen saturation <90%, SL nitroglycerin, IV nitroglycerin, IV morphine, β-blocker, ACE inhibitor or ARB, aldosterone antagonist, stool softener, and statin. b: Refer to Table 13-2 for indications, dosing, and contraindications. c: An early invasive strategy would be considered if one or more of the following occurs: recurrent angina or ischemia at rest, presence of elevated cardiac biomarkers, new or presumably new ST segment depression, signs or symptoms of HF or new worsening mitral regurgitation, hemodynamic instability, sustained ventricular tachycardia, PCI within 6 months, prior CABG, considered high risk per TIMI or GRACE risk score, LVEF < 40%. An ischemia-guided conservative strategy would be considered if the patient is classified as low-moderate risk per the TIMI or GRACE risk score or if the patient or clinician prefers this approach in the absence of high-risk features. d: For the duration of the hospitalization, up to 8 days. e: For at least 48 hours. f: Factors favoring administration of a GP IIb/IIIa in addition to a ASA and a $P2Y^{12}$ inhibitor are delay to angiography, high-risk features, and early recurrent ischemia. g: In patients who have been treated with fondaparinux (as upfront therapy) who are undergoing PCI, an additional anticoagulant with anti-IIa activity should be administered at the time of PCI due to the risk of catheter thrombosis. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, aspirin; CABG, coronary artery bypass graft; Cath, catheterization; DAPT, dual antiplatelet therapy; GP IIb/IIIa, glycoprotein IIb/IIIa; HF, heart failure; GRACE, Global Registry of Acute Coronary Events; IV, intravenous; NSTE-ACS, non–ST segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SL, sublingual; TIMI, Thrombolysis in Myocardial Infarction; UFH, unfractionated heparin. (Adapted with permission from Amsterdam et al. AHA/ACC 2014 guidelines for the management of patients with unstable angina/non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines developed in collaboration with the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons endorsed by the American Association of Thoracic Surgeons. J Am Coll Cardiol. 2014;64:e1–e228.)

COAGULATION PATHWAYS



Direct-Acting Oral Anticoagulants (DOACs)

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

A. Dabigatran (Pradaxa) → MOA: binds to and inhibits thrombin (IIa) directly
   - Parenteral thrombin (IIa) inhibitors: Argatroban, Bivalirudin
   - Indications: Prevention of stroke in non-valvular atrial fibrillation
   - Adverse Effects: bleeding (like all anticoagulants)
     - GI: dyspepsia, abdominal pain, esophagitis, GI bleeding
   - Reversal Agent: idarucizumab (Praxbind) / hemodialysis removes dabigatran

B. Rivaroxaban (Xarelto) and Apixaban (Eliquis)
   - MOA: selectively inhibits Factor Xa
   - Parenteral Xa inhibitor: Fondaparinux (Arixtra)
   - Rivaroxaban Indication: (1) Prevention and treatment of DVT & PE, and (2) prevention of stroke in non-valvular atrial fibrillation
   - Apixaban Indication: stroke prevention in non-valvular atrial fibrillation
   - Adverse Effects: bleeding
   - Reversal Agent: Andexanet alfa

Standard dosing of direct oral anticoagulants

Anticoagulant	Nonvalvular AF - stroke prophylaxis*	VTE treatment¶	VTE primary prophylaxis△
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

Advantages and disadvantages of oral anticoagulants (warfarin versus direct oral anticoagulants*)

	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

K-Centra (IV) { Prothrombin Complex Concentrate → factors: II, VII, IX, X

Renal Impairment

CrCl < 30 (rivaroxaban)
CrCl < 15 (apixaban)

Warfarin (Coumadin)

- 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
    - Functional levels of factors X and II (prothrombin) have half-lives of 24 and 72 hours, respectively
- 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 / KCentra (Prothrombin Complex Concentrate) → Factors II, VII, IX, X
- Adverse Effects: bleeding
    - 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 after initiating warfarin, patients are "procoagulant" and must be bridged with heparin for at least 5 days, even if the INR is within therapeutic range and 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 → 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).