Anticoagulation Therapy Review

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Ascension

Financial Disclosure

- I have nothing to disclose

Objectives

- Describe the common indications for the use of warfarin
- Identify the common INR target ranges for these indications
- Discuss the factors that can influence an individual's warfarin dosing
- Discuss the dosing, monitoring, and reversal of oral anticoagulant agents
- Describe the dosing and monitoring strategies for UFH, LMWH, Factor Xa inhibitors and Direct Thrombin inhibitors

Anticoagulation

Anticoagulant is a drug that prevents the formation of abnormal blood clots

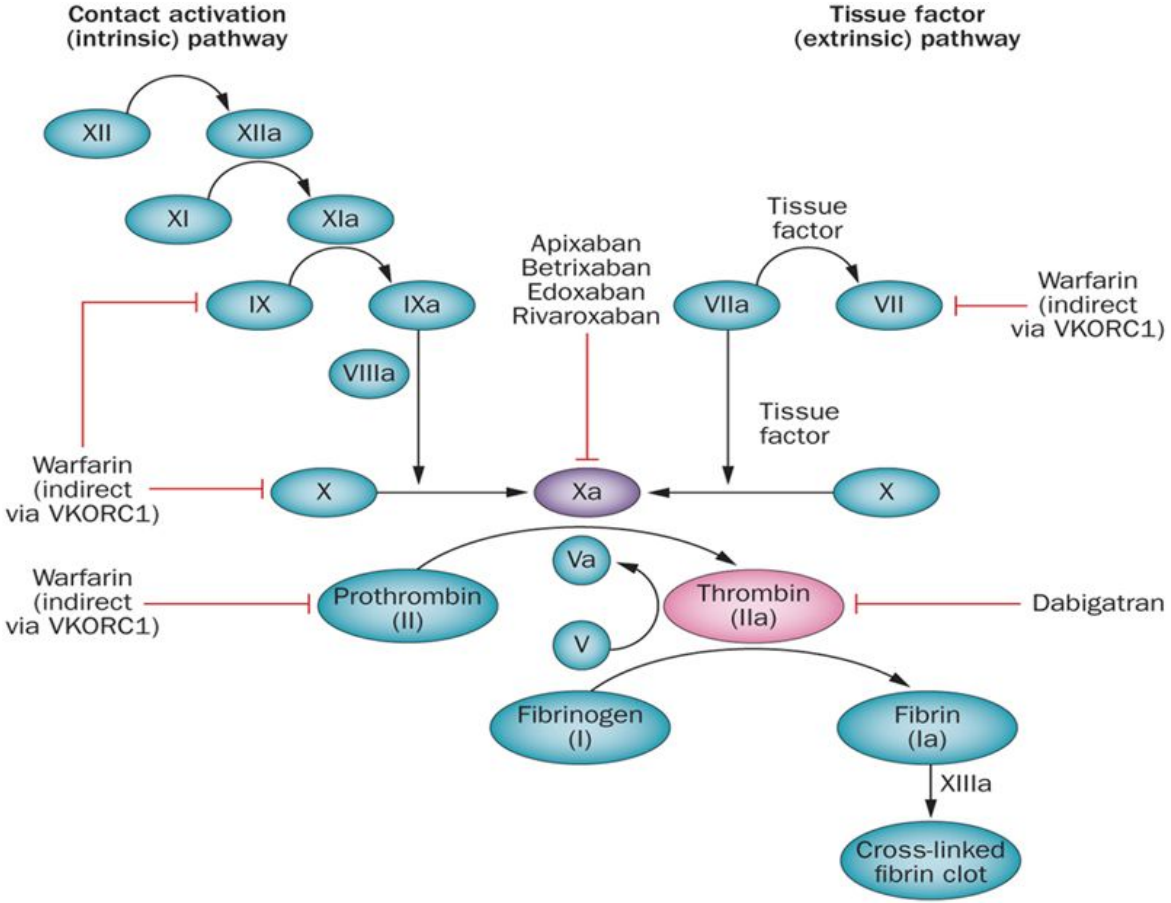
Warfarin is still the most commonly prescribed oral anticoagulant in the US

- Discovered in 1940s at the University of WI - Madison when cattle hemorrhaged and died after eating spilled Sweet Clover

Other anticoagulants

- Unfractionated heparin (UFH)
- Low molecular weight heparin (LMWH)
- Factor Xa inhibitors (oral and injectable)
- Direct thrombin inhibitors (oral and injectable)

The Coagulation Cascade



Clotting Factors

Factor Number	Function
I	Forms clot
II	IIa activates I, V, VIII, XI, XIII, protein C and platelets
VII	Activates IX, X
IX	Activates X: forms tenase complex with factor VIII
X	Activates II: forms prothrombinase complex with factor V
von Willebrand	Binds to VIII, mediates platelet adhesion

Clotting Factors

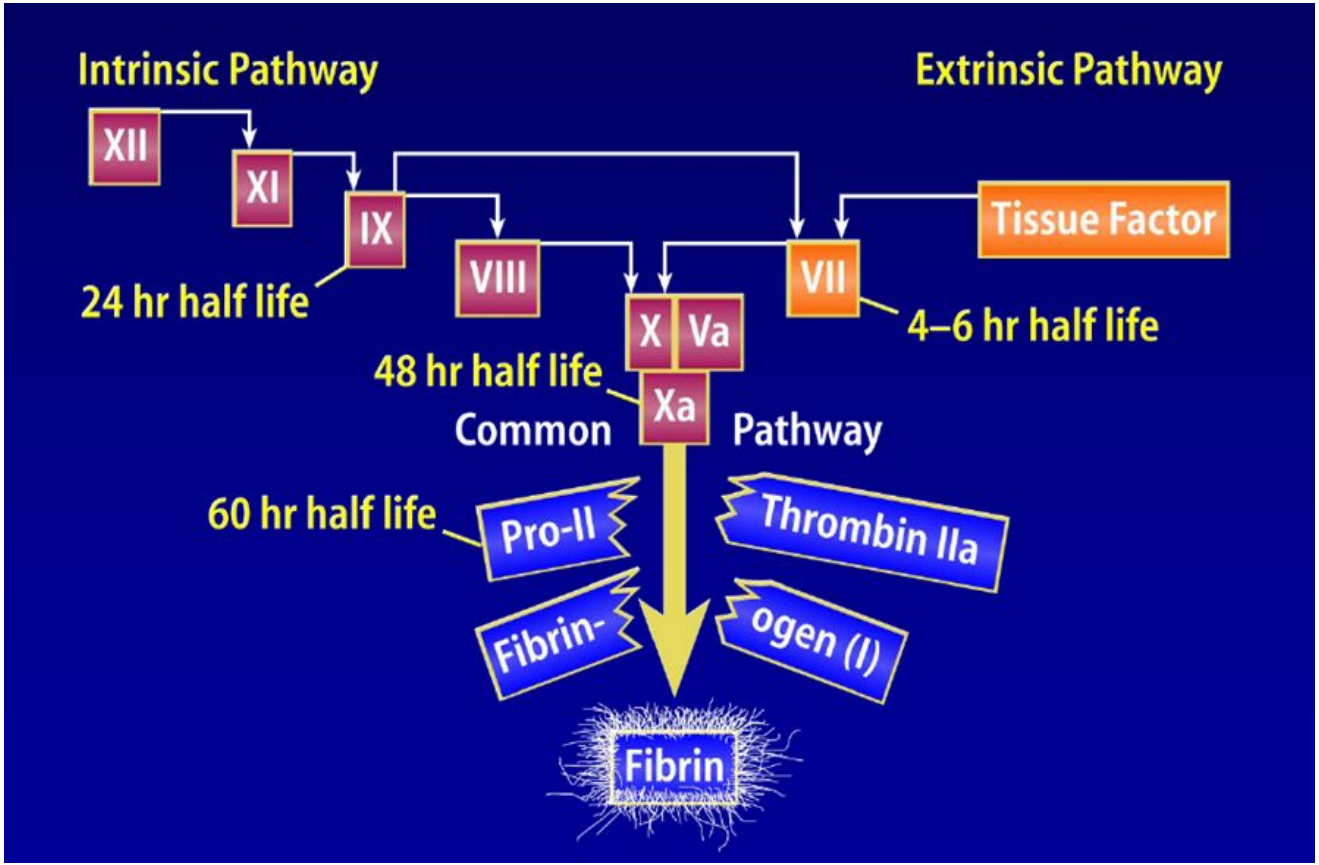
Factor Number	Function
tPA (tissue plasminogen activator)	Activates plasminogen
Plasminogen activator inhibitor-1 (PAI1)	Inactivates tPA and urokinase
Plasminogen activator inhibitor-2 (PAI2)	Inactivates tPA and urokinase

Part 1: Warfarin

Mechanism of Action

- Warfarin: Inhibits clotting by limiting hepatic synthesis of vitamin K - dependent coagulation factors - (Factors II, VII, IX, X)
- Vitamin K: Promotes liver synthesis of clotting factors (II, VII, IX, X)

Clotting Cascade with Warfarin



Common Indication & Target INR

Indication	INR Target
Prevention of systemic embolism Prophylaxis of venous thromboembolism (VTE) Treatment of VTE or PE Atrial fibrillation Cardioembolic stroke Left ventricular dysfunction Valvular disease Bioprosthetic (tissue) heart valve AMI (to prevent recurrent AMI)	2-3
Mechanical valve in aortic position (w/o other risk factors)	

Common Indication & Target INR

Indication	INR Target
Mechanical prosthetic valves (high risk) MVR (bileaflet or tilting disk) AVR or MVR (caged ball or disk) AVR or MVR with risk factors (Afib, MI, left atrial enlargement, low ejection fraction, endocardial damage)	2.5 -3.5
Prevention of VTE post TKA, THA	1.8-2.2 (per ortho surgery literature)

Warfarin Initiation

- Individualize dosing according to patient's sensitivity to the drug as indicated by the PT/INR
- Start low
  - Initiate at 5 mg daily for most patients
  - Consider lower initial dose (2.5 mg) in some patients
    - Elderly (>70)
    - Low body weight (<70 kg)
    - Elevated baseline INR (>1.3)
    - Impaired nutritional status
    - Hepatic/renal insufficiency
    - Concurrent interacting drugs
    - Clinical hyperthyroidism
    - Bleeding risk or falls risk

Warfarin Initiation

- Consider higher initial doses (7.5 - 10 mg) if:
  - Weight >85 kg
  - Clinical hypothyroidism
  - Concomitant drug therapy with enzyme inducers
  - African American patients
- Use of loading dose generally not recommended
  - Shown to increase bleeding complications
  - May cause hypercoagulable state due to rapid decrease in Protein C level
- Stabilize
  - Titrate to appropriate INR
  - Monitor INR frequently (daily, then q3-5 days)
- Adjust as needed
  - Usually results in INR of 2.0 in 4-5 days

Warfarin Initiation

- Regardless of initial dose, if acute need for anticoagulation:
  - Overlap with rapid acting anticoagulant for at least 5 days AND until INR ≥ 2 for 2 days
    - UFH
    - LMWH
    - Fondaparinux
- Follow nomogram for daily adjustments (if available)
- Remember: today's INR is the result of the last 2-3 warfarin doses
- HOLD if ~1 increase in INR in one day or >2 increase in INR over 2 days, even if not yet therapeutic

Variable Response to Warfarin

- Age (as age increases dose needs decrease)
- Gender (males tend to require more warfarin)
- Nutritional status/oral intake (poor nutrition = lower doses)
- Compliance
- Comorbid conditions (liver disease, CHF, etc.)
- Concurrent drug therapy (watch for drug interactions)
- Genetic factors

Warfarin Monitoring

- Baseline INR required
  - Must have INR drawn within 72 hours of starting warfarin therapy
  - Pharmacist will order if not ordered by provider
- Current INR required
  - Doesn't always mean daily
  - After INR stable in therapeutic range, may decrease to twice weekly INR
    - If patient is otherwise stable
    - No recent changes in interacting meds
- INR = a mathematical "correction" of the PT ratio to allow for differences in the sensitivity of reagents
  - Allows for comparison of results between labs and standardizes reporting

Warfarin Monitoring

- Narrow therapeutic window
  - Bleeding risk if INR >4
  - Loss of efficacy if INR <1.8
  - No efficacy if INR <1.5
- Consider
  - Indication
  - Goal INR
- Monitor daily for:
  - Potential drug-drug, drug-disease interactions
  - Response to current dosing
  - Adverse drug events
    - Bleeding
    - Purple toe syndrome
    - Skin necrosis
    - GI upset

Managing High INR

Severity of Bleeding	Treatment Measures
No bleeding or minor bleeding	INR 4.5 - 9.9 - omit 1-2 doses INR >9.9 omit 1-2 doses Phytonadione 2.5 mg PO Monitor INR more frequently Resume at lower dose when INR therapeutic If only minimally above therapeutic, no dose reduction may be required
Major, non-life threatening bleeding	If ingestion within 3 hours, administer activated charcoal 50g FFP at least 2 units Phytonadione 2.5-10mg PO or IV,

Managing High INR

Severity of Bleeding	Treatment Measures
Life threatening bleeding (not CNS or spinal)	If ingestion within 3 hours, administer activated charcoal 50g Give each agent as soon as available: Phytonadione 10 mg IV PCC 25 units/kg, may repeat x 1 if life-threatening bleed persists beyond 30 min after administration
Life threatening bleeding (CNS or spinal)	If ingestion within 3 hours, administer activated charcoal 50g Give each agent as soon as available: Phytonadione 10 mg IV

Managing High INR

- Vitamin K considerations:
  - If oral vitamin K not appropriate:
    - IV vitamin K must be given slowly (≤ 1 mg/min) to avoid anaphylaxis
    - Subcutaneous absorption is delayed and unpredictable - use not recommended
    - Intramuscular absorption unpredictable and risk of hematoma - use not recommended
  - Warfarin resistance likely after Vitamin K administration
    - Increases with increasing vitamin K dose - use smallest effective dose
    - May need to use UFH or LMWH until INR therapeutic

Warfarin

Increased INR (Endogenous Factors)	Decreased INR (Endogenous Factors)
Diarrhea Hyperthyroidism Elevated temp Poor nutritional state Cancer Hepatic disorders Infectious hepatitis Vitamin K deficiency Congestive HF Stress, Illness	Edema Hypothyroidism Warfarin resistance Nephrotic syndrome Hyperlipidemia

Comorbid conditions: Liver Disease/CHF

- Liver = primary site for synthesis of clotting factors
  - May need to decrease warfarin dose if decreased clotting factor production
    Check LFTs if supratherapeutic INR with no known cause
- Exacerbation of CHF may cause increase in INR
  - During CHF exacerbation, fluid may accumulate in liver, impairing ability to produce clotting factors

Pharmacokinetics & Pharmacodynamics

Onset	36-72 hours
Peak	5-7 days
Duration of Action	2-5 days
Metabolism	Hepatic
Half-life	20-60 hours
Mean half-life	40 hours
98% protein bound (mainly to albumin)	

PK Drug Interactions

- Absorption alteration
  - Bile acid sequestrants
    - Cholestyramine
    - AVOID by spacing at least 4 hours from warfarin
- Protein binding site displacement
  - Ex) Valproic acid, Bactrim
- Enzyme induction and inhibition
  - Ex) Many antibiotics, amiodarone, anticonvulsants, antihyperlipidemics

Enzyme Induction

- Reduces anticoagulant effect of warfarin by INCREASING metabolism
  - Decreases INR
  - Higher warfarin doses needed
- Onset: gradual (few days to 1-2 weeks or longer)
  - Body needs time to make more enzyme
- Offset: gradual
  - Dependent on decay of enzyme stores

Enzyme Inducers (Decreases INR)

- Carbamazepine
- Dicloxacillin
- Griseofulvin
- Nafcillin
- Phenobarbital
- Phenytoin
- Primidone
- Rifampin

Enzyme Inducers

- Phenytoin
  - Onset: can increase INR initially, then gradually decrease INR by enzyme induction
    - Change in INR will be seen in approximately 7 days
    - Continue to check at least weekly until stable INR
  - Offset: INR quickly drops after discontinuation
    - Can be bi-modal
    - Check within 7 days after dc
    - May need further dose reduction as enzyme induction wears off

Enzyme Inhibition

- Increases anticoagulant effect of warfarin by DECREASING metabolism
  - Increases INR
  - Lower warfarin doses needed
- Inhibition effect influenced by potency of inhibition
  - Strongest effect: CYP 2C9
  - Modest, inconsistent effect: CYP1A2, CYP3A4

Enzyme Inhibition

- Onset: rapid
  - Within 24 hours, but may take 7-10 days to reach new steady-state
    - Warfarin has long half-life which is further prolonged by enzyme inhibition
- Offset: generally rapid
  - Depends mainly on elimination of inhibiting drug

Enzyme Inhibitors

- CYP 2C9 (dramatic increase in INR)
  - Amiodarone
    - Inhibits both R- and S- isomers
  - Disulfiram
  - Fluvastatin
  - Metronidazole
  - Miconazole
  - TMP/Sulfa

Enzyme Inhibitors

(modest or inconsistent increase except in predisposed patients)

CYP1A2	CYP3A4
Cimetidine Ciprofloxacin Diltiazem Erythromycin Mexiletine Norfloxacine Tacrine Fluvoxamine Levofloxacin	Triazole antifungals Clarithromycin Cyclosporine Danazole Diltiazem Erythromycin Fibrates Fluoxetine Fluvoxamine Nefazodone Omeprazole Quinidine Ritonavir Verapamil
Delayed Relatively common	

Enzyme Inhibitors

- Bactrim
  - Consider empiric weekly 20-40% dose reduction
  - Change in INR will be seen after 5-7 days
- Metronidazole
  - Consider empiric weekly 20-40% dose reduction
  - Change in INR will be seen after 5-7 days

Enzyme Inhibitors

- Amiodarone
  - Effects seen almost universally
    - Inhibits both R and S isomers
    - May result in serious or fatal bleed if not adjusted
    - INR may increase by 100% after 3-4 days
  - Onset: rapid
    - 2-4 days
    - May be delayed up to 2 weeks
  - Offset: delayed
    - 1-4 months due to amiodarone t ½ (53 days)
    - Usually no empiric reduction made
    - Check INR in 2-3 weeks

Enzyme Inhibitors

- Amiodarone, continued
  - Consider empiric weekly ~30% dose reduction
    - Adjust based on maintenance dose of amiodarone:
      - 400 mg : 40%
      - 300 mg : 35%
      - 200 mg : 30%
      - 100 mg : 25%
  - Consider INR in 7-10 days
  - Bi-modal interaction
    - May need further reduction after 2 months

PD Drug Interactions

- Cephalosporins
  - Decrease Vitamin K production = increased INR
  - Due to alteration of intestinal flora
- Thyroid hormones
  - Increase catabolism of clotting factors = increased INR
  - Monitor closely with thyroid initiation and dose adjustments

PD Drug Interactions

- Platelet inhibition
  - ASA and NSAIDs
    - Low dose ASA may increase risk for minor bleeds, but not major bleeds (benefit often outweighs risk)
    - Avoid NSAIDs - increase risk of major GI bleed
  - Clopidogrel, prasugrel, ticagrelor, ticlopidine, dipyridamole
    - Only if benefit outweighs risk
    - Higher incidence of major bleeds
- Impaired platelet function is NOT reflected in INR

PD Drug Interactions

- Acetaminophen
  - Preferred pain reliever for warfarin patients
  - Low to moderate doses (≥ 9 tabs/wk) have been associated with elevated INR
    - Daily doses > 2 grams may increase INR
    - Use lowest doses possible
    - Monitor INR with significant changes in APAP use

Herbals with Potential Increased Bleeding Risk

. Anise root . Arnica flower . Celery . Chamomile . Clover . Capsicum . Feverfew . Garlic . Ginger . Gingko	. Horse chestnut . Licorice . Meadowsweet . Onion . Parsley . Passion Flower . Poplar . Quassia . Turmeric . Willow Bark

Herbals with Potential Decreased INR

- Coenzyme Q10
- Ginseng
- Green Tea
  - Only in excessive amounts
  - Controversial (leaves vs. stems)
  - Likely need to EAT leaves
- St. John’s wort

Drug Interactions: Conclusions

- Adverse effects from most drug interactions are preventable
- Consequences: increased ER visits, hospital admits, serious or fatal bleeds, event rates, $$$$
- Patient education
  - Patient to notify provider upon start/stop/dose change of ANY prescription, OTC agent, or herbal medication
- Pharmacist/Provider responsibilities:
  - Screen medication list
  - Be familiar with interacting meds
  - Monitor frequently when required
  - Notify anticoagulation provider of therapy changes (outpatient)

Warfarin Bridge Therapy

- Patients who require temporary interruption of warfarin therapy for surgery or procedure
- For recommendations for bridge therapy needs and dosing:
  - See: Management of Antithrombotic Therapy - CHEST guidelines

Warfarin Bridge Therapy

- Stop warfarin approximately 5 days before surgery to allow time for the INR to normalize
- Resume warfarin therapy approximately 12-24 hours post-op and after hemostasis has been achieved (unless epidural is present!)
- Give the last therapeutic-dose LMWH 24 hours before surgery/procedure (aprox. ½ the total daily dose)
- Minor surgical or other invasive procedures: resume therapeutic-dose LMWH approximately 24 hours after the procedure (with hemostasis) and 4 hours after an epidural catheter removed
- No longer recommended to interrupt warfarin for dental extractions

Warfarin Bridge Therapy, cont.

- Major surgery or high bleeding risk surgery/procedure:
  - Delay **therapeutic-dose** LMWH/UFH for 48-72 hours after surgery (with hemostasis)
  - Or administer **low-dose** LMWH/UFH after surgery (with hemostasis)
  - Or completely avoid LMWH/UFH after surgery, consider the anticipated bleeding risk and postoperative hemostasis to determine the timing of resumption of anticoagulation.
- Continue LMWH concurrently with warfarin until INR is therapeutic for 2 days, but for a minimum of 5 days of concurrent therapy

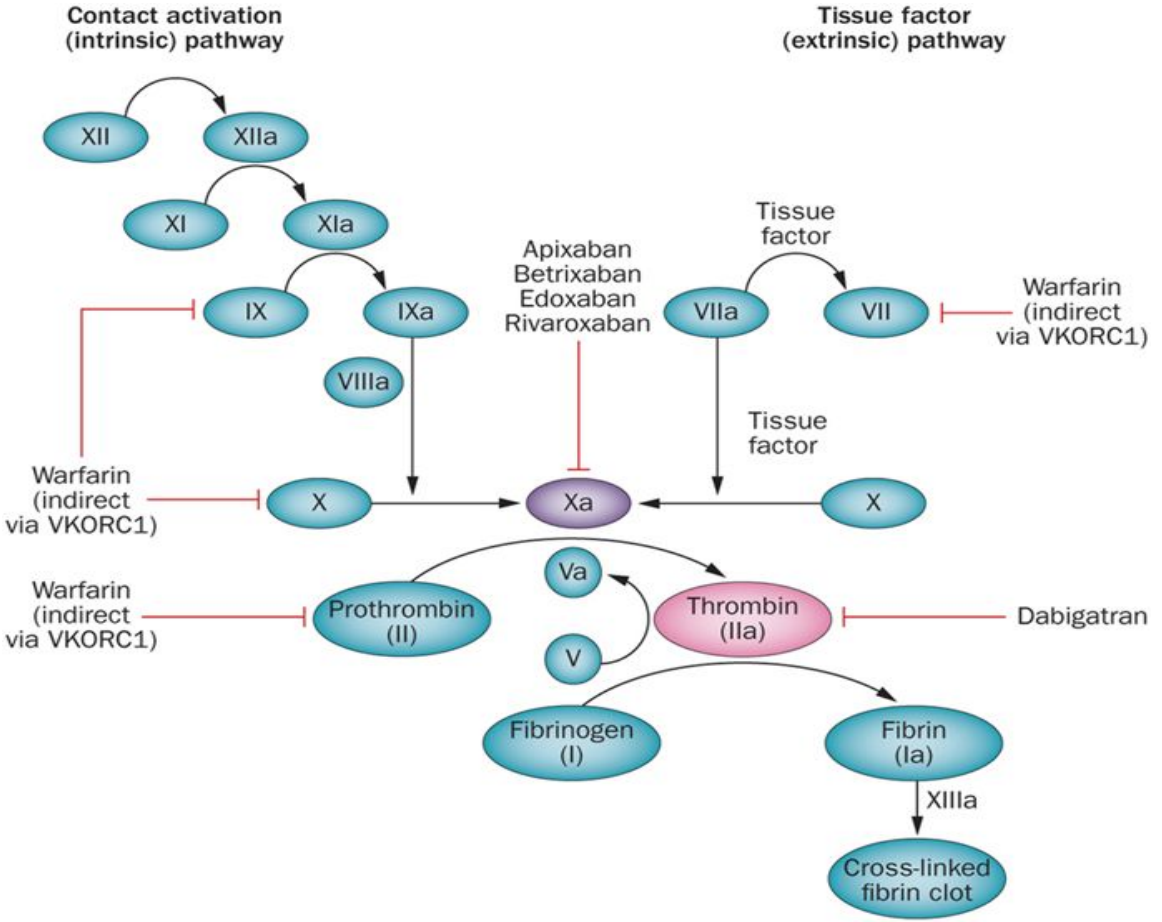
Part 2: Other Oral Anticoagulants

4 new oral anticoagulants to market since 2010

- Oral direct thrombin inhibitor
  - Dabigatran (Pradaxa) - late 2010

- Oral direct inhibitor of factor Xa
  - Rivaroxaban (Xarelto) - 2011
  - Apixaban (Eliquis) - 2012
  - Edoxaban (Savaysa) - 2015

Other oral anticoagulants



Indications

- Dabigatran (Pradaxa)
  - FDA indicated
    - Non-valvular Afib
    - DVT/PE treatment and prevention
  - Non-FDA
    - Hip/knee post-op DVT prevention of recurrence
- Rivaroxaban (Xarelto) and Apixaban (Eliquis)
  - FDA indicated
    - Non-valvular Afib
    - DVT or PE treatment or prevention of recurrence
    - DVT or PE prophylaxis after hip or knee replacement
  - Non-FDA
    - ACS
    - VTE prevention in acutely-ill medical patients

Indications, cont.

- Edoxaban (Savaysa)
  - FDA indicated
    - Non-valvular Afib
    - Treatment or prevention of DVT or PE
  - Non-FDA
    - Hip/knee post-op DVT prevention

Precautions/Contraindications (all 4)

- Precautions
  - Abrupt discontinuation
  - Causes bleeding: significant, can be fatal
  - No specific reversal agent exists for Xa inhibitors
  - Combined use with other anticoagulants or P-glycoprotein inducers
    - And strong CYP3A4 inducers (rivaroxaban and apixaban)
  - Epidural and spinal catheters (rivaroxaban)
- Contraindications
  - Active major bleed
  - Hypersensitivity
  - Use with prosthetic heart valves

Dabigatran (Pradaxa)

- Dosing and Administration
  - 150 mg PO BID with or w/o food
  - Capsules must be dispensed and stored in original container
  - Do not crush, chew, or empty capsule
  - Renal
    - CrCl>50: No adjustment
      - CrCL 30-49 may need adjustment if taking dronedarone or ketoconazole
    - CrCl 15-20: 75 mg BID
    - CrCl <15 or dialysis - no recommendations available
- Cost
  - $6.24/day ($3.12 each)
    - Warfarin ~$0.05/day

Dabigatran

- Kinetics
  - Time to peak ~1-2 hr
  - Half-life: 12-17 hr (prolonged in renal impairment)
  - Metabolism: hydrolyzed, not metabolized by CYP450
  - Dialyzable
- Monitor
  - Signs and symptoms of bleeding
  - No current reliable means to monitor for effect or toxicity
  - ECT (ecarin clotting time) may be useful in future

Rivaroxaban (Xarelto)

Dosing and Administration

- DVT/PE prevention in hip/knee surgery
  - 10mg daily x 35 days hip, 12 days knee, avoid if CrCl <30
  - Initial dose 6-10 hours post-op
- Non-valvular Afib
  - 20mg daily, 15mg if CrCl 15-30
  - Avoid if CrCl ,15
- DVT/PE
  - 15mg BID x 21 days (treatment)
  - 20 mg daily (secondary prevention)
- ACS
  - 2.4-5mg BID
- VTE prevention: acute illness
  - 10mg daily

Rivaroxaban

- Kinetics
  - Time to peak 2-4 hours
  - Half-life: 5-9 hours
  - Metabolism: CYP3A4/5, CYP2J2, hydrolysis
  - NOT dialyzable
- Monitor
  - Signs and symptoms of bleeding
  - LFTs
  - Renal function
  - No reliable monitor for therapeutic or toxic effect
  - Xa levels can determine presence
- Surgery
  - Discontinue at least 24 hours prior to surgery or invasive procedure

Apixaban (Eliquis)

- Dosing and administration
  - Stroke prevention in Afib
    - 5mg po BID
      - Reduce dose to 2.5mg po BID If any 2 of the following:
        - Age >80 yo
        - Body weight <60 kg
        - SCR >1.5 mg/dL
        - Or if also taking strong inhibitor of CYP3A4 and P-gp
  - DVT/PE prophylaxis hip/knee
    - 2.5mg po BID beginning 12-24 hours post-op
      - For 10-14 days knee
      - For 32-28 days hip
  - DVT Treatment
    - 10 mg BID x 7 days
  - DVT secondary prevention
    - 2.5 mg daily x 6 months

Apixaban

- Kinetics
  - Time to peak: 3-4 hours
  - Half-life: 12 hours
  - Metabolism: CYP3A4 (major), and other CYP enzymes
  - Not dialyzable
- Monitor
  - Signs and symptoms of bleeding
  - LFTs
  - Renal function
  - No reliable monitor for therapeutic or toxic effect
    - Xa levels can determine presence

Apixaban

- Surgery
  - Discontinue at least **48 hours** prior to elective or invasive procedures with a **moderate-high risk** of clinically significant bleeding
  - Discontinue at least **24 hours** prior to elective or invasive procedures with a **low risk** of bleeding or where the bleeding would be in a non-critical location and easily controlled

Conversion to/from Warfarin

- From warfarin
  - Discontinue warfarin
  - Start apixaban or dabigatran when INR <2
  - Start rivaroxaban when INR < 3
  - Start edoxaban when INR <2.5
- Converting patients to warfarin
  - Rivaroxaban or Apixaban
    - Discontinue rivaroxaban or apixaban and start both parental anticoagulation and warfarin at time of next scheduled dose of riva/apix
    - Discontinue parenteral anticoagulation when INR is within therapeutic range
  - Edoxaban
    - Reduce edoxaban dose by 50%, start warfarin
    - Stop edoxaban when INR stable and ≥ 2
    - OR
    - Stop edoxaban and start both parental anticoagulation and warfarin at time of next scheduled dose of edoxaban

Conversion to/from Warfarin

- Converting patients to warfarin
  - Dabigatran
    - Depends on renal function

Apixaban/Rivaroxaban

- Drug interactions: Substrate of CYP3A4 and P-gp
  - CYP3A4 and P-gp **inducers** decrease levels and therefore decrease efficacy (increase risk for clotting)
    - AVOID use of: rifampin, carbamazepine, phenytoin, St. John's wort
  - CYP3A4 and P-gp **inhibitors** increase levels (increase risk of bleeding)
    - AVOID use of: ketoconazole, itraconazole, clarithromycin, ritonavir, lopinavir, indinavir, and conivaptan
    - If used, decrease apixaban dose to 2.5mg BID
      - If patient is already at reduced dose due to other risk factors **avoid** co-administration
  - Avoid use with other anticoagulants, including warfarin, due to increased bleeding risk

Summary

	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Target	IIa,VII, IX, X	IIa	Xa	Xa
Bioavailability	99%	7%	60-80%	80%
T (max)	4 hr	2 hr	2.5-4 hr	3 hr
Half-life	50+ hr	12-17 hr	5-9 hr	12 hr
Renal elimination	Minimal	80% renal	60% Renal 33% Biliary	25% Renal 75% Biliary
Metabolism	CYP 2C9, 3A4	Conjugation	CYP3A4, 2J2	CYP3A4
Dosing	Daily	Daily, BID	Daily	BID
Antidote	Vitamin K; FFP; PCC; r-VIIa	Praxbind; dialysis, FFP, PRBC	Supportive; PRBC, Kcentra, FFP	Supportive, PRBC, Kcentra, FFP

General Management of Bleeding

- **Discontinue anticoagulant**
- Control of bleeding site and supportive care
  - If bleeding complications occur, surgical intervention, fluid replacement, FFP, or PRBC can be used
    - Note: this **will not reverse** the effects of anticoagulants, but will replace clotting factors
- Remove drug from circulation
  - Activated charcoal if the drug has been given within the last 2 hours
  - Vigorous diuresis should be maintained to increase clearance
  - HD may remove approx. 60% of dabigatran at 2 hours
- Lab testing: CBC, Platelet count, LFT, aPTT, INR, TT

Reversal

Dabigatran

Praxbind (Idarucizumab) available

If no significant bleeding
- Maintain adequate diuresis
- HD: 2-3 hours will remove 60% of drug

If significant bleeding
- PRBC: utilize first
- Consider dialysis
- FFP: if prolonge

Life threatening bleeding
- Praxbind (Idarucizumab)
- Factor VIIa: efficacy has not been established but may be considered

Reversal

Rivaroxaban, Apixaban, Edoxaban

Andexxa (Andexanet Alfa)

Andexanet alfa Dose Based on Apixaban or Rivaroxaban Dose			
Factor Xa Inhibitor	Factor Xa Inhibitor Last Dose	Timing of Factor Xa Inhibitor Last Dose Before Andexanet alfa Initiation	
		<8 Hours or Unknown	≥8 Hours
Apixaban	≤5 mg	Low dose	Low dose
	>5 mg or unknown	High dose	
Rivaroxaban	≤10 mg	Low dose	
	>10 mg or unknown	High dose	

Low dose: 400 mg IV bolus administered at a rate of ~30 mg/minute, followed within 2 minutes by an IV infusion of 4 mg/minute for up to 120 minutes.
High dose: 800 mg IV bolus administered at a rate of ~30 mg/minute, followed within 2 minutes by an IV infusion of 8 mg/minute for up to 120 minutes.

Management of Life-threatening Bleeding

Apixaban, rivaroxaban, edoxaban

Prothrombin Complex Concentrate - 4 factor PCC (Kcentra)

- First US PCC with significant amounts of factors II, VII, IX, and X

Coagulation Factor IX complex (Profilnine) can be used as a last-line effort to replace clotting factors lost due to rivaroxaban, edoxaban, or apixaban (not dabigatran)

- Contains very little factor VII

Recombinant factor VIIa (Novoseven) can be used as a last-line effort to replace factors inhibited by rivaroxaban, edoxaban, apixaban, and dabigatran

Management of Life-threatening Bleeding

Dabigatran

Praxbind (idarucizumab) indication
- Management of life-threatening bleed due to dabigatran
- Reversal of dabigatran for emergent surgery

Mechanism
- Binds to dabigatran and metabolites, neutralizing anticoagulation

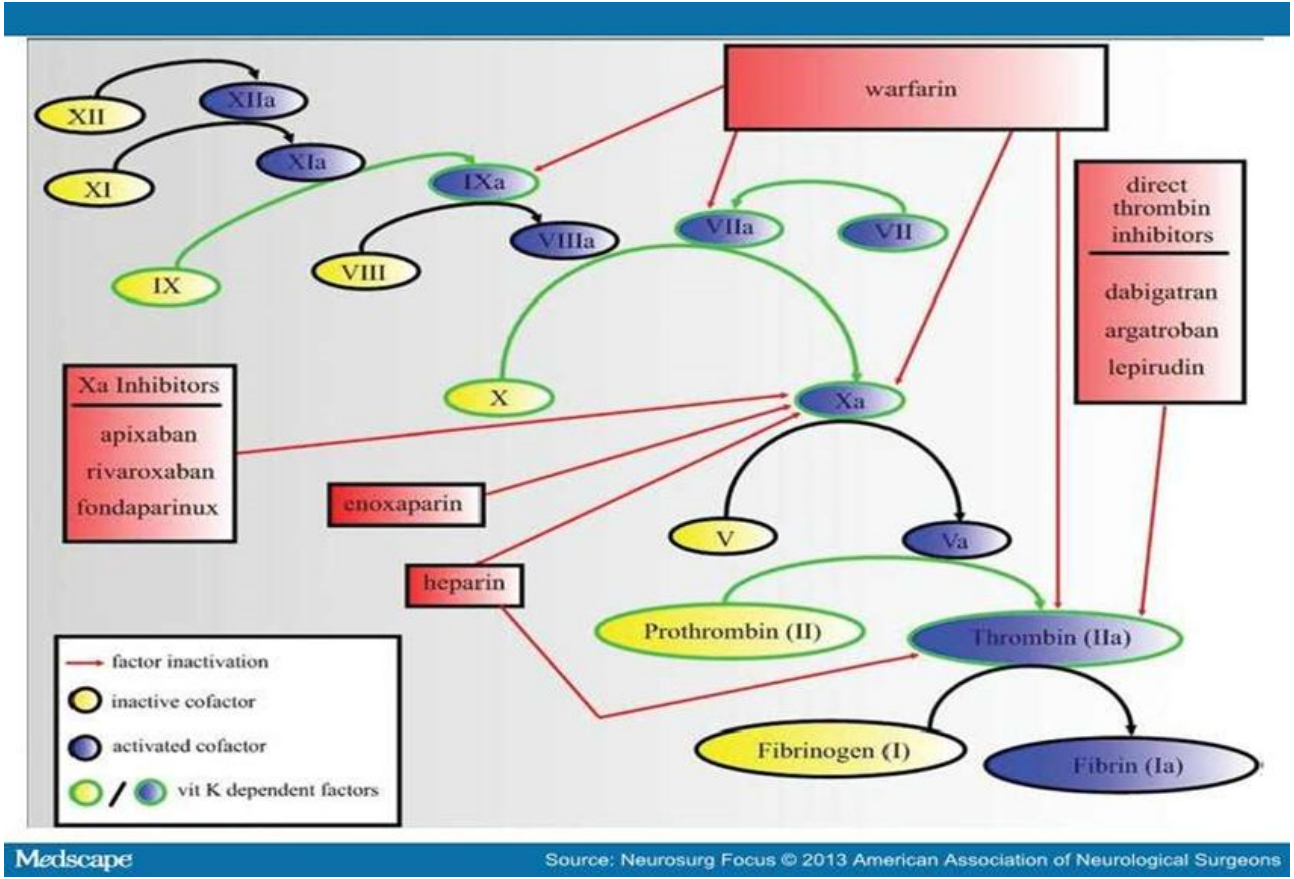
Dosing
- 5 g, administered as two consecutive infusions or bolus injections of 2.5 g each

Part 3: Injectable Anticoagulants

Injectable Anticoagulants

- Heparin (UFH)
- Low-molecular weight heparin (LMWH)
- Factor Xa Inhibitor
- Direct Thrombin Inhibitors

Clotting cascade effects



Mechanism of Action

- Forms a complex with antithrombin
  - Inhibits coagulation factors
    - XIIa
    - XIa
    - IXa
    - Xa
    - IIa (thrombin)

Common Indications

- Treatment or prevention of systemic embolism in the inpatient setting
  - Massive PE
  - Cardiovascular disease
  - Following
    - Angioplasty
    - CABG
    - Thrombolysis
    - Peripheral vascular surgery
  - Bridge therapy of oral anticoagulation during invasive procedures

Monitoring

- Signs & symptoms of thromboembolism
- Signs & symptoms of bleeding
- Platelet count
- Hematocrit
- Activated partial thrombin time (aPTT)

Pros & Cons

- Pros
  - IV UFH has a short half-life
  - Lowest acquisition cost of all parenteral anticoagulants
- Cons
  - Routine monitoring needed
  - Greater incidence of heparin induced thrombocytopenia (HIT)
  - Mainly inpatient use
    - Costs associated with hospitalization and IV therapy

Low-Molecular Weight Heparin: Mechanism of Action

- Primary MOA
  - Inhibits Factor Xa
    - Factor Xa transforms prothrombin to thrombin
- Secondary MOA
  - Inhibits Factor IIa (thrombin)
    - Thrombin needed for the formation of fibrin

Common indications

- Treatment of VTE
  - Pregnancy
    - Duration: Throughout pregnancy
  - Cancer patients
    - Duration: at least 3-6 months
- Prevention of VTE
  - Total knee or hip replacement
    - Duration: at least 7-10 days (or warfarin alone)
  - High-risk pregnancy
    - Duration: throughout pregnancy
  - Extended THR of hip fracture surgery
    - Duration: until warfarin therapeutic, total anticoagulation of 28-35 days

Common indications

- Prevention of systemic embolism
  - Pregnant patients
    - Duration: throughout pregnancy
  - Management of oral anticoagulation during invasive procedures
- Acute STEMI
- Ischemia prevention
  - MI
  - Angina

VTE Treatment Dosing

- Enoxaparin (Lovenox)
  - 1 mg/kg q12h

OR

  - 2 mg/kg q24h

VTE Prevention Dosing

- Enoxaparin (Lovenox)
  - Immobility or post-abdominal surgery
    - 40 mg daily
  - Post orthopedic surgery or trauma dosing
    - 30 mg q12h

Dosing in Special Populations

- Elderly
  - STEMI, recommended enoxaparin dose for age >75 = 0.75 mg/kg q12h
  - Elderly patients <45 kg or decreased renal function should be watched closely
- Obese
  - Vd not linear with total body weight
  - Few randomized trials include patients >150 kg
  - Consider monitoring Xa levels if available and if patient >150 kg
  - Dose by total body weight (no capping)
  - Increase prophylactic dose for patients with BSA > 40

Dosing - Renal Insufficiency

Enoxaparin

CrCl <30

- Treatment of DVT/PE = 1mg/kg daily
- Prevention of DVT/PE = 30 mg daily

Enoxaparin Rounding

- Round all doses of enoxaparin ordered on a mg/kg basis
- Doses ≤ 100 mg should be rounded to the nearest 10 mg
- Doses ≥ 100 mg should be rounded to the nearest 15 mg
- Doses in the middle should be rounded UP

Monitoring

- Signs and symptoms of thromboembolism or bleeding
- Platelet count
  - Baseline and q 2-3 days (debatable)
- Peak anti-factor Xa levels (4hr after SQ injection, after 3 or more doses) IF:
  - Extremes in body weight (<40 kg or >150 kg)
  - Renal or hepatic insufficiency (severe)
  - Pregnancy
  - Prolonged therapy (>7-10 days)
  - Peds
- Target anti-factor Xa level = 0.5 -1 unit/mL

Pros & Cons

Pros

Generally no routine monitoring
Lower incidence of HIT
SQ injections
- Patients can self administer
- Transfers well to outpatient management

Cons

Dose adjustments needed in:
- Obese
- Renal insufficiency (CrCl <30 mL/min)
- Higher acquisition cost than UFH

Fondaparinux (Arixtra)

- Inhibits only factor Xa
  - Binds to antithrombin III (ATIII)
    - To neutralize factor Xa
  - Inhibition of Xa disrupts coagulation cascade
    - Inhibits thrombin formation and thrombus development

Fondaparinux: Indications

- FDA-labeled
  - Post-op DVT prophylaxis
  - DVT/PE treatment in combination with warfarin
- Off-label uses:
  - Acute STEMI
  - Angioplasty
  - NSTEMI
  - Superficial vein thrombosis lower limb
- Does not bind with HIT antibodies - useful in patients with history of HIT

Fondaparinux Dosing

- Acute STEMI
  - 2.5 mg IV, then 2.5 mg SQ once daily for up to 8 days
- DVT or PE **treatment** (with warfarin)
  - <50 kg = 5 mg
  - 50-100 kg = 7.5 mg
  - >100 kg = 10 mg
  - SQ once daily for 5-9 days (until INR therapeutic)
- NSTEMI
  - 2.5 mg SQ once daily up to 8 days
- Post-op DVT **prevention**
  - 2.5 mg SQ once daily for 5-10 days
    - Hip fracture up to 24 days
  - 1st dose 6-8 hours post-op

Fondaparinux: Dose Adjustments

- CrCl 50-80 mL/min
  - 25% dose reduction
- CrCl 30-50 mL/min
  - 40% dose reduction
- CrCl <30 mL/min
  - Contraindicated
- Age >75
  - Total drug clearance reduced by 25%

Fondaparinux: Monitoring

- Signs & symptoms of thromboembolism or bleeding
- CBC
- Anti-factor Xa levels in some patients:
  - Significant renal impairment
  - Bleeding or abnormal coagulation
  - Pregnancy
  - Extremes in body weight
  - Pediatrics
- BP
- Hepatic and Renal function

Fondaparinux: Pros & Cons

Pros

SQ injections
- Patients can self-administer
- Transfers well to outpatient management

No cross-reactivity with HIT antibodies

Cons

Dose adjustment needed for CrCl <80 mL/min
Contraindicated if CrCl <30 mL/min
Higher acquisition cost than UFH

Direct Thrombin Inhibitors

Bivalent

Hirudin
Bivalirudin
Lepirudin (Refludan)
Withdrawn from market in 2012
Desirudin

Univalent

Argatroban
Melagatran
Dabigatran

Bivalirudin

- Use in place of argatroban for HIT or to anticoagulate patients with a history of HIT
- MOA
  - Highly specific and reversible direct inhibitor of thrombin
- FDA-labeled indications
  - HIT
  - PCI (for high bleed risk)
  - Unstable angina
- Off-label
  - ACS
  - DVT prophylaxis
  - CV surgery if HIT

Bivalirudin: Dosing

PCI

0.75 mg/kg IV bolus
1.75 mg/kg/hr IV during procedure and up to 4 hours after
- May add 0.2 mg/kg/hr x 20 hours post procedure

HIT

No bolus
0.15 mg/kg/hr IV infusion (normal renal function)
- CrCl 30-60: 0.08 mg/kg/hr
- CrCl <30: 0.05 mg/kg/hr
- Dialysis: 0.02 mg/kg/hr

Adjust dose to 1.5 - 2.5 x baseline aPTT

Bivalirudin: Monitoring

- Activated clotting time (ACT) 5 min after initial bolus during PCI
- aPTT to goal of 1.5 - 2.5 x baseline in HIT
- CBC
- Renal function prior to start
  - Dose adjustment needed
- Signs & symptoms of thromboembolism or bleeding

Argatroban

- MOA
  - Selectively and reversibly binds to thrombin
- FDA-labeled indications
  - Prevention or treatment of thrombosis in patients with or at risk of HIT
  - Patients with or at risk of HIT undergoing PCI
- Off-label uses
  - Cerebral thrombosis
  - CV surgery
  - DIC
  - HD catheter occlusion
  - AMI
  - Unstable angina

Argatroban: Dosing

HIT - thrombotic disorder, treatment, and prevention

2 mcg/kg/min continuous IV
Adjust until aPTT = 1.5 - 3x baseline (not to exceed 100 sec)
MAX of 10 mcg/kg/min

MI

100 mcg/kg IV bolus, then 1-3 mcg/kg/min continuous IV for 6-72 hours
Maintain aPTT 50-85 sec
Give with alteplase and aspirin

Dose adjustment:

Renal, geriatric: none
Hepatic: decrease initial dose

Pros & Cons

Pros

Safe alternative in patients with HIT
Argatroban - no renal adjustment
Bivalirudin - no hepatic adjustment

Cons

Need dose adjustment for hepatic impairment (argatroban)
Need dose reduction for renal impairment (bivalirudin)
Given as inpatient
IV

Anticoagulation Therapy Review

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