

Hemostasis/Thrombosis IV

Antithrombotic Therapy



Antithrombotic Therapy

- Mainstay of battle against thromboembolic disease
- Hot area of new drug research
- Cannot inhibit clot formation without increased risk of hemorrhage
- 2nd highest cause of iatrogenic complications
- 2nd most common cause of increased hospital stays

Antithrombotic Therapy

- Hemorrhage is consequence of overaggressive therapy
- Thrombosis is consequence of underaggressive therapy
- Always a balance between risk of thrombosis (for which you are giving the drug) vs. risk of hemorrhage

Antithrombotic Therapy

- Antiplatelet agents
 - Principally used for preventing/treating arterial thromboembolic disease
- Anticoagulants
 - Principally used for preventing/treating venous thromboembolic disease
- Thrombolytic agents
 - Used for dissolution of thrombi

Antiplatelet Therapy

- Paralyze platelet function
- Cyclooxygenase inhibitors
 - Irreversible – Aspirin
 - Competitive inhibitors – Non-steroidal antiinflammatory drugs
- Dipyridamole
- GP IIb/IIIa inhibitors
- ADP receptor inhibitors
 - Ticlopidine
 - Clopidogrel
 - Prasugrel

Aspirin

- Covalently modifies cyclooxygenase; irreversibly inhibits the enzyme
- Since platelets have no protein synthetic mechanism, cannot correct defect caused by modification of cyclooxygenase
- Blocks primary wave of platelet aggregation; NOT secondary wave
- If enough normal platelets to initiate primary aggregation, ASA poisoned platelets can be recruited into platelet plug formation

Aspirin

- At low dose (81 mg daily), inhibits thromboxane A₂ production
 - Blocks both platelet aggregation & vasoconstriction
- At higher doses (325 mg daily), blocks both thromboxane A₂ & prostacyclin (PGI₂) production
 - PGI₂ inhibits platelet aggregation & causes vasodilation

Non-steroidal Antiinflammatory Drugs

- Competitive inhibitors of cyclooxygenase (drug must be in system to be effective)
- Many block both primary & secondary waves of platelet aggregation
- As such, inhibit clot formation to a greater extent than does ASA
- Blocks ASA effects on platelets; ASA should be taken first


Dipyridamole

- ? Mechanism of action
 - Probably increases cAMP production
 - Blocks calcium release from dense granules, blocking arachidonic acid production & thereby decreasing thromboxane A₂ production
- Decreases platelet aggregation
- Enhances aspirin's effect on platelet aggregation

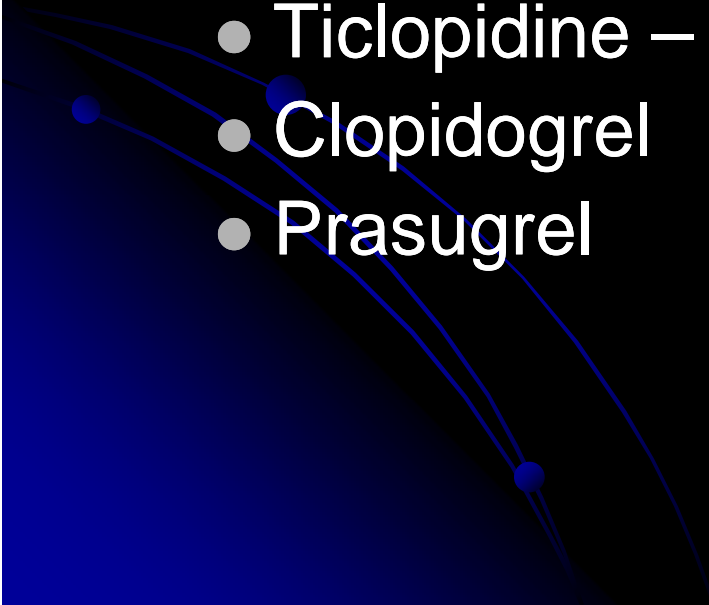
Glycoprotein IIb/IIIa Inhibitors

- All interfere with fibrinogen-induced platelet aggregation
- 3 classes:
 - Fab fragments (abciximab)
 - Peptide-based antagonists (eptifibatide)
 - Small molecule inhibitors (tirofiban)
- Extremely potent – Platelet count functionally zero
- Drug half-life:
 - Abciximab – 30 minutes
 - Eptifibatide/Tirofiban – 2-2.5 hours

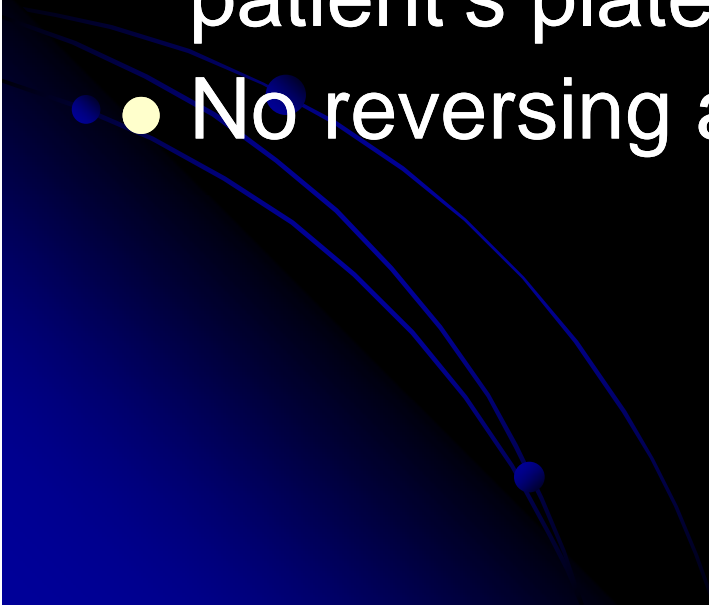
Glycoprotein IIb/IIIa Inhibitors

- Used to block immediate restenosis following cardiac intervention
 - Major cause of thrombocytopenia (2-10%)
 - Current drugs too potent for long-term use
 - Oral agents have not proven successful thus far
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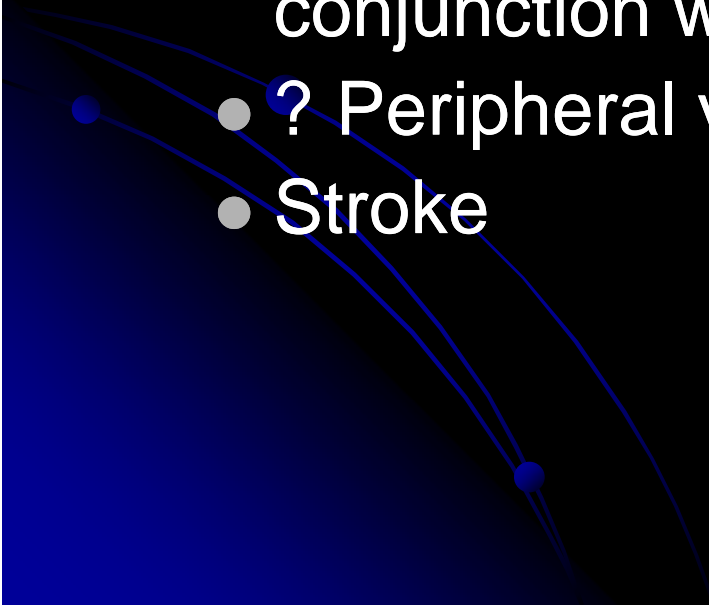
ADP Receptor Inhibitors

- Block P2Y₁₂ Receptor, inhibiting ADP-induced activation of platelets
 - 3 drugs currently approved:
 - Ticlopidine – Rarely used
 - Clopidogrel
 - Prasugrel
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ADP Receptor Inhibitors

- All long-acting (half life 7-8 hours, with active metabolites with half life 2-4 days); all inhibit transfused platelets as well as patient's platelets
 - No reversing agent
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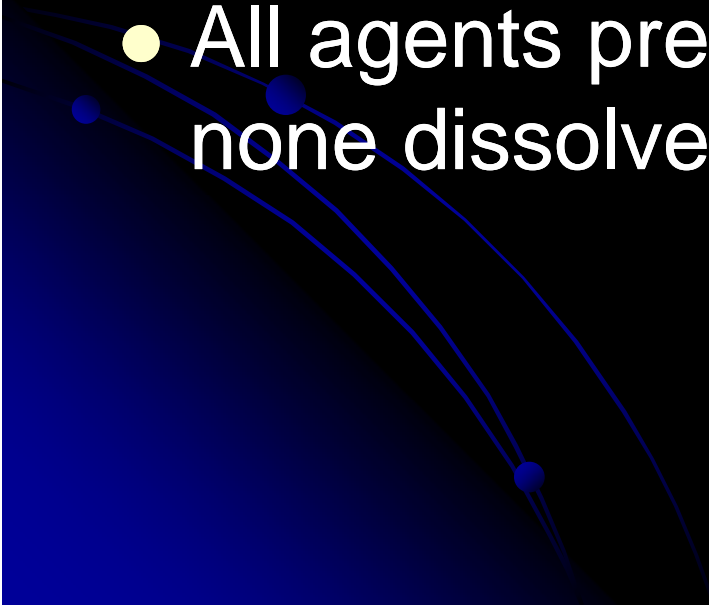
ADP Receptor Inhibitors

- Uses:
 - Unstable angina/Non-ST elevation MI
 - ST elevation MI
 - Percutaneous coronary intervention (in conjunction with aspirin)
 - ? Peripheral vascular disease
 - Stroke
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ADP Receptor Inhibitors

- Side effects:
 - Bleeding
 - Esp with surgery
 - Thrombotic thrombocytopenic purpura (esp ticlopidine)
 - Neutropenia (esp ticlopidine)

Anticoagulant Therapy

- Inhibitors of coagulation cascade
 - Useful both for prophylaxis against TE disease & treatment of TE disease
 - Lower doses required for prophylaxis
 - All agents prevent propagation of clot; none dissolve clot already formed
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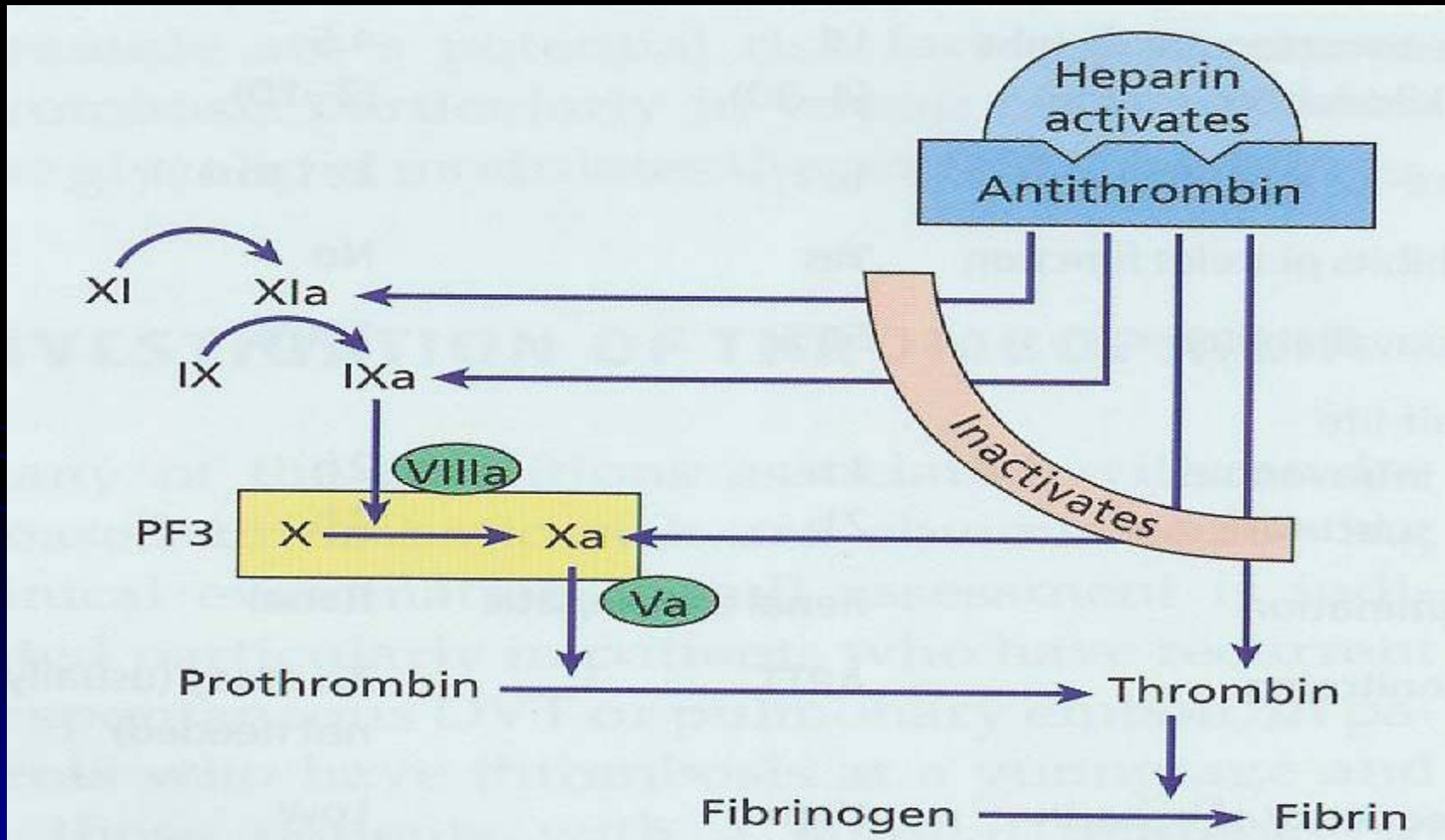
Available Anticoagulants

- Older agents
 - Heparin (Parenteral)
 - Warfarin (Oral)
- Now, FDA approved (in addition to the above):
 - 4 low molecular weight heparins (3 available in US)
 - 1 heparinoid (not available in US)
 - 1 Factor Xa inhibitor
 - 4 direct thrombin inhibitors
- More to come

Heparin/Heparin Derivatives

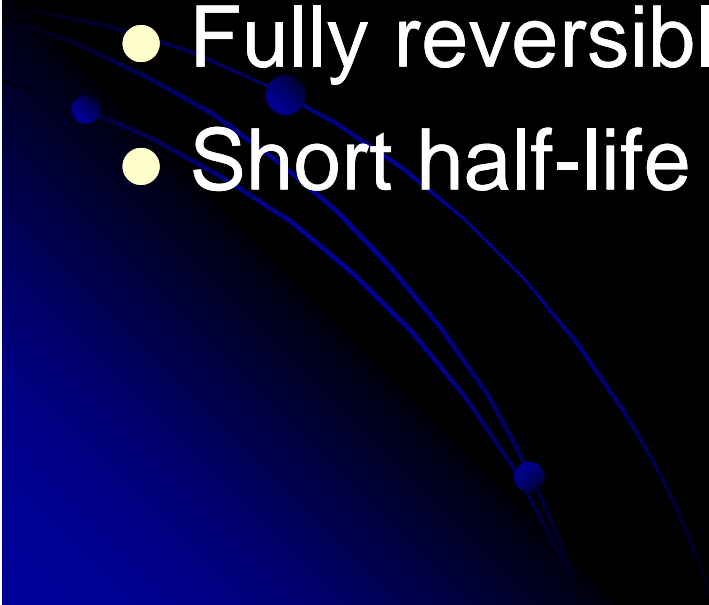
- All act to potentiate antithrombin III's inactivation of the active enzymes of the clotting cascade
- Chemical catalysts – Not consumed in reactions themselves
- All are useful in both preventing thrombosis & treating thromboembolic disease

ANTITHROMBIN III – Mechanism of Action

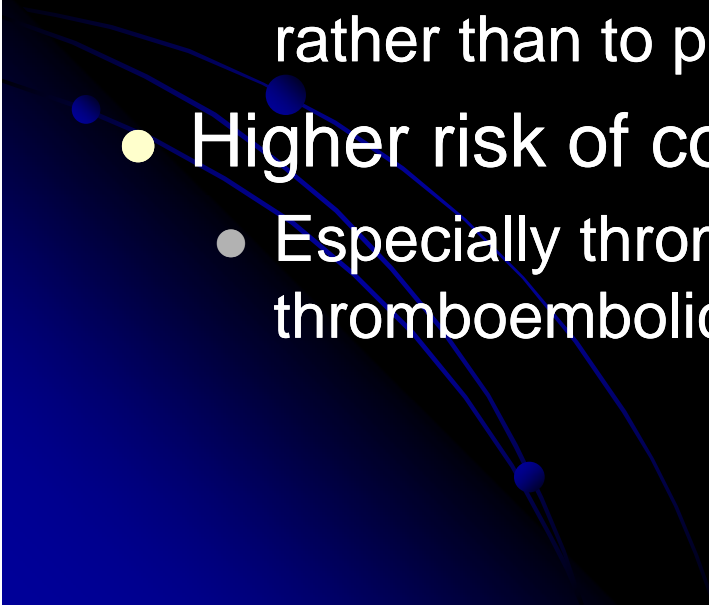


Unfractionated Heparin

Advantages

- Long track record
 - Dirt cheap
 - Clearly effective for treatment & in some prophylaxis settings
 - Fully reversible with protamine
 - Short half-life
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Unfractionated Heparin Disadvantages

- Short half life – Requires continuous infusion
 - Variable bioavailability
 - Monitoring required for treatment of thromboembolic disease
 - To ensure attainment of therapeutic anticoagulation, rather than to prevent bleeding
 - Higher risk of complications
 - Especially thrombocytopenia with paradoxical thromboembolic disease
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Low Molecular Weight Heparins Advantages

- Higher bioavailability; makes dosing without monitoring a reality (except in renal disease, morbid obesity, cachexia, pregnancy)
- Longer half-life; therefore can be given subcutaneously 1-2x/day
- Much lower (but not 0) risk of *de novo* thrombocytopenia
- At least as effective for treatment; more effective for high risk prophylaxis than heparin

Low Molecular Weight Heparins

Disadvantages

- More expensive than heparin
- Longer acting, and only partially reversible with protamine
- Renally excreted, making dosing problematic in renal disease
- Cross-reactive with HIT causing antibodies
- Much more effective for prophylaxis if given pre-op
- All carry black box warning vs. use with regional anesthesia

Low Molecular Weight Heparins (US)

- Enoxaparin (Lovenox®) – Approved for VTE prophylaxis, VTE treatment, acute coronary syndrome)
- Dalteparin (Fragmin®) – Same as enoxaparin RE: approvals, except for VTE treatment
- Tinzaparin (Innohep®) – Approved for treatment of VTE
- Ardeparin (Normiflo®) – Not being marketed in US
- All behave similarly, but dosing of each is different

FACTOR Xa INHIBITOR

- Fondaparinux (Arixtra®) – Semisynthetic sulfated pentasaccharide; active moiety of heparin
- Only inhibits factor Xa
- Bioavailability virtually 100%; can be given QD
- No thrombocytopenia seen in trials (does not bind to platelet factor IV)
- Data clearly shows it to be superior to LMWH when given postoperatively, & probably superior to LMWH given preoperatively

FONDAPARINUX

- Offers possibility of post-op prophylaxis against DVT with same or better efficacy as preop administration of LMWH
- Small but real incidence of wound hematomas (nil if given > 6 hrs post-op); bleeding risk otherwise similar to LMWH
- Avoids problems with administration of drug during regional anesthesia, since can be given after the epidural catheter is pulled
- Approved for treatment of VTE (7.5 mg QD)

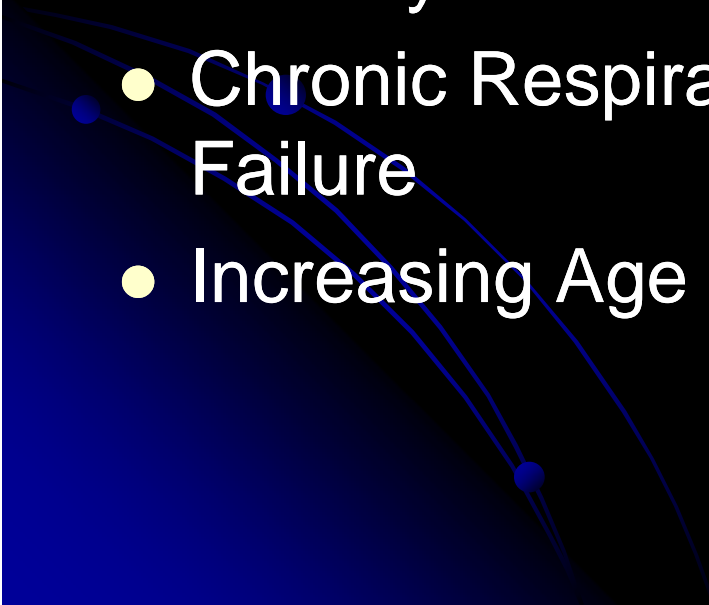
Prophylaxis vs TE Disease

- Requires smaller dose than does treatment
- Less risk of bleeding with prophylaxis doses
- Stratified by risk of developing thromboembolic disease
- In surgery patients, pre-op therapy generally more effective than post-op therapy (with one exception)

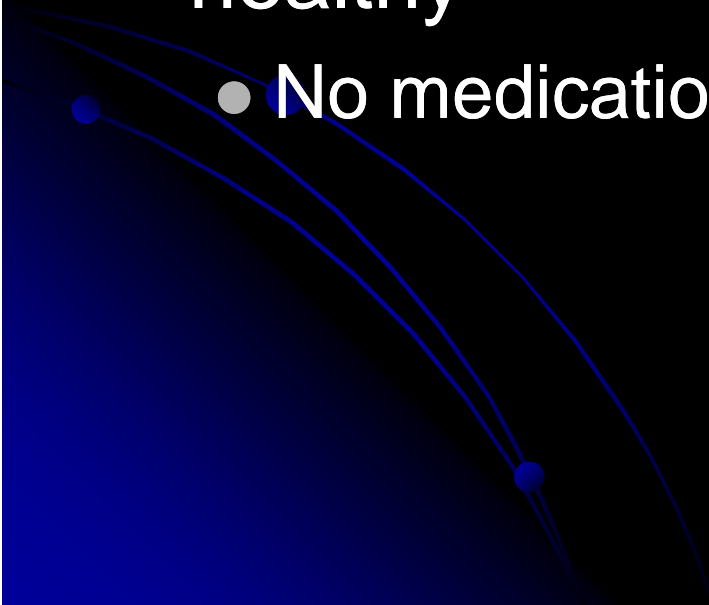
Primary Risk Factors for VTE

- Major Surgery
 - Leg > Pelvic > Abdominal or Thoracic
- Acute MI
- Major Trauma
- Paralytic Stroke
- Cancer
- Spinal Cord Injury
- Pelvic Fracture

Secondary Risk Factors for VTE

- Congestive Heart Failure
 - Previous VTE
 - Immobilization
 - Obesity
 - Chronic Respiratory Failure
 - Increasing Age
 - Hematological Disorders
 - Central Venous Catheter
 - Varicose Veins
 - Pregnancy
 - Estrogen Therapy
 - Hospitalization
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Prophylaxis vs TE Disease

- Low Risk – Minor procedure, otherwise healthy
 - No medications; rapid mobilization
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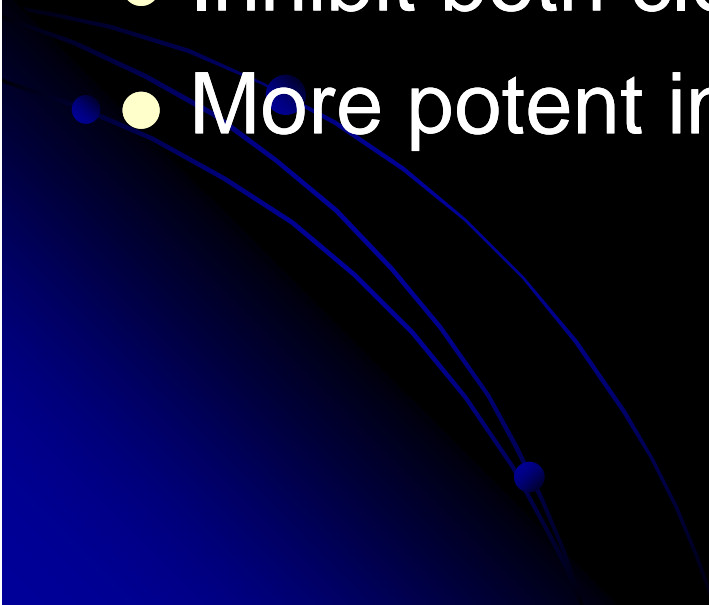
VTE Prophylaxis Moderate Risk

- Moderate Risk – Abdominal surgery, thoracic surgery, Medical patient
 - Multiple medical regimens effective, including:
 - Heparin 5000 units SQ Q 8-12h
 - Enoxaparin 40 mg SQ QD
 - Dalteparin 5000 units SQ QD

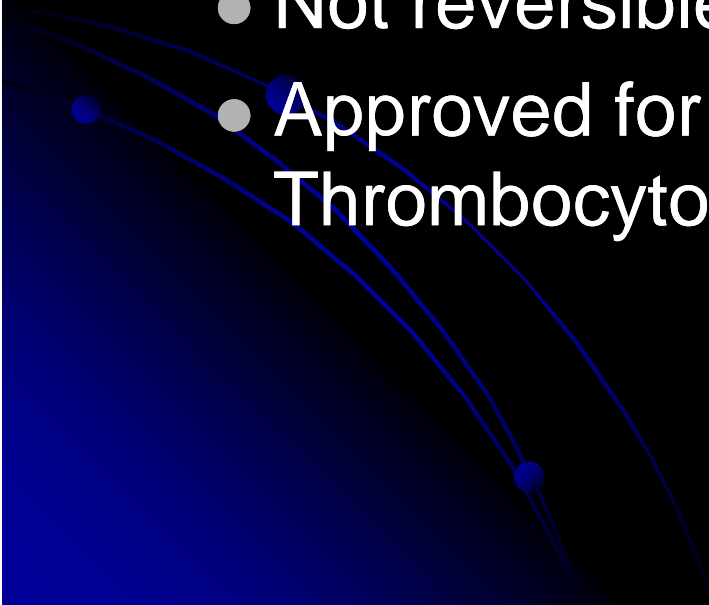
VTE Prophylaxis High Risk

- High Risk – Paraplegic, hemiplegic, pelvic surgery, leg surgery
 - Moderate risk therapy ineffective; more clearly needed
 - Enoxaparin 30 mg SQ Q 12h
 - Fondaparinux 2.5 mg SQ QD

Direct Thrombin Inhibitors

- Block active site of thrombin
 - Inhibit both clot-bound and free thrombin
 - More potent inhibitors than heparin
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Direct Thrombin Inhibitors

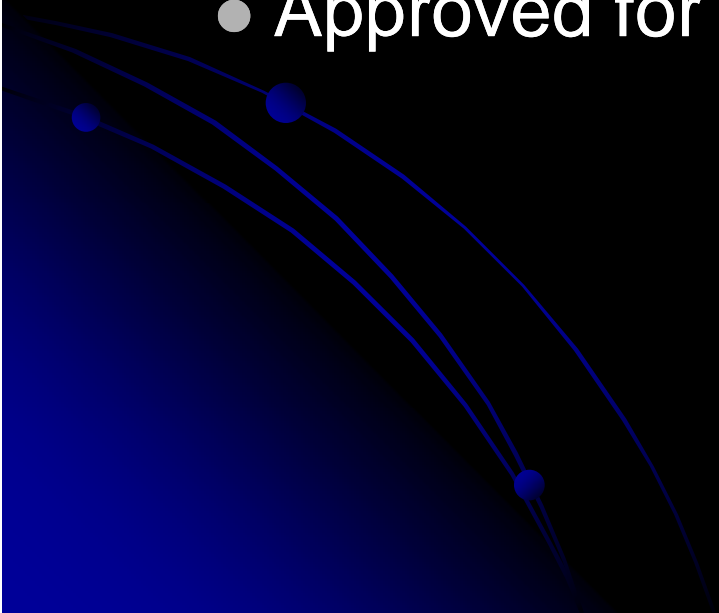
- Lepirudin (Refludan®)
 - Hirudin derivative
 - Half life 30-40 minutes
 - Problematic in renal disease
 - Not reversible
 - Approved for Heparin-Induced Thrombocytopenia and Thrombosis
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Direct Thrombin Inhibitors

- Argatroban®
 - Small molecule active site blocker of thrombin
 - Half life 30-40 minutes
 - Problematic in liver disease
 - Not reversible
 - Approved for Heparin-Induced Thrombocytopenia and Thrombosis & for Acute Coronary Syndromes

Direct Thrombin Inhibitors

- Bivalirudin (Angiomax®)
 - Hirudin derivative
 - Short-acting
 - Not reversible
 - Approved for unstable angina/angioplasty



Direct Thrombin Inhibitors

- Desirudin
 - Hirudin derivative (minus 1 sulfate group)
 - Half-life 6-7 hours
 - Approved for DVT prophylaxis in HIT
 - Not yet available

COUMADIN (warfarin)

Mechanism of Action

- Inhibits Vitamin K dependent carboxylase activity
- Prevents reduction of Vitamin K
- Humans secrete proteins lacking γ -carboxyglutamic acid, which are inactive
- DOES NOT AFFECT PROTEINS ALREADY SYNTHESIZED
- Monitor using prothrombin time
- Multiple interactions with other drugs
- Antidote-Vitamin K

Thrombolytic Therapy

- Lyses clot already formed
- Does not discriminate between therapeutic & pathologic thrombosis; therefore
- Markedly increased risk of hemorrhage compared with other antithrombotic therapies
- Only therapy documented to prevent tissue death in acute arterial thrombosis

THROMBOLYTIC THERAPY

- Streptokinase
 - Purified from bacteria (Streptococcus)
 - Binds to plasminogen, & complex activates a second plasminogen molecule to plasmin
 - High incidence of allergic reactions
- Urokinase
 - Purified from urine initially
 - Recombinant form now available
 - Activates plasminogen directly
- Tissue plasminogen activator
 - Made by endothelial cells
 - Increased affinity for fibrin-bound plasminogen → relative fibrin specificity
 - Recombinant form available
 - Activates plasminogen directly

THROMBOLYTIC THERAPY

Actions

- Used in myocardial infarction
 - Lyses coronary thrombi
 - Improves/preserves LV function
 - Decreases mortality
 - High rate of reocclusion-esp with TPA
- Lyses hemostatic plugs everywhere
 - Increased incidence of bleeding - esp CNS
 - Lowers plasma fibrinogen
- ? which drug is superior

Future Agents (Not yet approved)

- Rivaroxaban – Oral Xa inhibitor; in final stages @ FDA now (approved in Europe & Canada)
- Dabigatran – Oral thrombin inhibitor - @ FDA (approved in Europe & Canada)
- Apixaban – Oral factor Xa inhibitor; in final FDA stages now
- Idraparinux – Hyperglycosylated fondaparinux; $\frac{1}{2}$ life 1 week; for extended prophylaxis
- ? Other direct thrombin inhibitors for uses other than HIT
- ? Orally active heparin/LMWH derivatives