Cardiovascular Drugs - 3

Lipids, hemostasis

PHRM 203
Allison Beale
Overview

- Anti-hyperlipidemics
  - Statins
  - Bile acid sequestrants
  - Nicotinic acid
  - Fibric acids
  - Other

- Blood thinners
  - Anticoagulants
  - Anti-platelet drugs
  - Fibrinolytic drugs

- Clotting agents
  - Anti-hemophilic drugs
  - Systemic agents
  - Topical agents
CHD RISK Equivalents

- Diabetes mellitus or metabolic syndrome
- Peripheral vascular disease
- Carotid artery disease
- Abdominal aortic aneurysm
- Calculated 10-yr risk for a coronary event that >20%

High risk have CHD or any 1 of 5 “CHD risk equivalents”

Intermediate risk
Have ≥2 of the following risk factors
- BP > 140/90 or on antihypertensives
- Smoker
- HDL <40 mg/dL
- M >45 yrs; F >55 yrs
- 1st ° relative with CHD < 55 yrs old if M and 65 yrs if F.

Low risk have < 2 of the risk factors

(ATP III was an expert panel on detection, evaluation and treatment of high blood cholesterol in adults)

PHRM 203 - Cardio 3
**Hyperlipidemia**

NCEP - ATP III guidelines, May 2001

- **Metabolic Syndrome** includes any 3 of these:
  - Abdominal obesity
    - Waist >40” (M); >35” (F)
  - High triglycerides
    - ≥ 150 mg/dL
  - Low HDL
    - <40 mg/dL (M); < 50 mg/dL (F)
  - ↑BP
    - ≥ 130/85 mmHg
  - ↑fasting glucose level
    - ≥ 110 mg/dL

- Characteristics
  - “Apple” shaped
  - Atherogenic dyslipidemia
    - ↑ TG
    - Small LDL particles
    - Low HDL
  - High BP
  - Insulin resistance
  - **Prothrombotic state**
    - ↑C-reactive protein
  - **Proinflammatory state**
    - ↑ plasminogen activator inhibitor
    - ↑ fibrinogen
Hyperlipidemia

- 5 classes of drugs & primary effect
  1. HMG-CoA reductase inhibitors (statins)
     - ↓ LDL
  2. Bile acid sequestrants
     - ↓ LDL
  3. Nicotinic acid (Niacin)
     - ↑ HDL
  4. Fibric acids
     - ↓ Triglycerides
  5. Ezetimibe (Zetia)
     - ↓ cholesterol absorption

Lipoproteins carry cholesterol in blood.

LDL & VLDL carry cholesterol to cells.

HDL carries cholesterol back to the liver

Diet can ↓ cholesterol by 15%

DASH Diet can significantly lower cholesterol in as little as two weeks

PHRM 203 - Cardio 3
• HMG-CoA reductase inhibitors (statins)

 adorned Atorvastatin (Lipitor) adorned X
  – ↓ cholesterol biosynthesis
  – ADRs for atorvastatin
    • Myopathies - serious and lead to renal failure
      – Rhabdomyolysis = breakdown of skeletal muscle releasing myoglobin → dark brown urine
      – Higher risk with fibrate (e.g., gemfibrozil or fenofibrate)
    • ↑ Liver enzymes - usually temporary
    • Grapefruit ⊗ metabolism → ↑ t_{1/2}

HMG-CoA = endoplasmic reticulum bound, rate-limiting enzyme in cholesterol biosynthesis (3-hydroxy-3-methyl-glutaryl-CoA reductase)
Hyperlipidemia

Atorvastatin (Lipitor)

- Common and well-known ADRs
  - Liver function changes and myopathies
    - Statins lower CoQ10 in a dose-responsive fashion. Muscle pain may be helped by taking CoQ10.

- Less common ADRs
  - Memory loss, inability to concentrate
  - Depression, irritability
  - Pain (headaches, joint, abdominal)
  - Peripheral neuropathies (tingling, numbness)
  - Increased blood glucose

Fun Fact: Powdered LDL from human plasma used as a nutritional source of fatty acids and lipids.
Atorvastatin (Lipitor) X

- Indications
  - Adjunct to diet to decrease the risk of MI, stroke or angina
  - Decrease triglycerides (TG)
  - Decrease total cholesterol, low density lipoproteins (LDL) and ApoB
  - Increase high density lipoproteins (HDL)

Other statins:
- Fluvastatin (Lescol)
- Lovastatin (Mevacor)
- Pravastatin (Pravacol)
- Simvastatin (Zocor)

Caduet = atorvastatin + amlodipine

Red yeast rice extract contains lovastatin
Statins

– Have been shown to:
  – ↑ endothelial function
  – ↓ C-RP levels & inflammation
  – Maintain plaque stability
  – Prevent thrombus formation
  – Improve survivorship after MI

Focus on C-Reactive Protein (C-RP):

– Plasma protein (liver)
– Adipocytes & Macs secrete factors that stimulate synthesis
– Acute Inflammatory response
– May initiate recognition & phagocytosis of damaged cells

• Sudden withdrawal of statins
  – ↑↑↑↑ C-RP
  – ↑HT & MI risk
  – ↑ Interleukin 6 levels
Bile Acid Sequestrants

- **Cholestyramine (Questran)**  
  - Mechanism: ion resin that disrupts enterohepatic circulation  
  - Other drugs in class: colesevelam (WelChol) and colestipol (Cholstid)

- **Uses**
  - Hypercholesterolemia, NOT hypertriglyceridemia  
  - ↓ Pruritus due to bile duct obstruction

- **ADRs**
  - Constipation/diarrhea  
  - Flatulence  
  - Interferes with the absorption of other drugs

PO, SID/BID  
1 hr after or 6 hr before other drugs

Cholesterol is the sole precursor of bile acids; BA are secreted into GIT & then enterohepatically cycled.

**BAS drugs**  
↑ liver cholesterol synthesis, but ↓ serum cholesterol levels
Nicotinic acid (niacin, vitamin B₃) Niacor  C

- Exact mechanism unknown
  - ≥1000mg/day (1g/day) – 250 mg to 2 g/day
  - ↓ LDL and VLDL, ↓Triglycerides (TG); ↑ HDL
- ADRs
  - Flushing
    - Vasodilator
    - Can cause severe itching and burning of skin
  - Hyperglycemia (problem for diabetics)
  - Hyperuricemia (problem for patients with gout)
  - GI distress (diarrhea, flatulence)
  - Tachyarrhythmias
  - Hepatotoxicity (especially with statins)
  - Rhabdomyolysis (especially with statins)
  - Angioedema (especially with statins)
  - Hyperpigmentation of skin
  - Toxic amblyopia, blurred vision, dry eyes

Indication
Adjunct to diet and another drug (e.g., Questran) to lower LDL-C and TGs

PO, BID/TID
Start with low dose

Tolerance to flushing develops and can be controlled with NSAIDs
Fibric acids (fibrates)

🌿 Gemfibrozil (Lopid) C

- Others: Fenofibrate (Tricor, Lofibra)
  - ⊗ synthesis of VLDL (very low density lipoprotein, a triglyceride-rich lipoprotein fraction)
  - Classified as peroxisome proliferator-activated receptor (PPAR) α agonists
    - A type of Nuclear Hormone Receptor

- ADRs
  - GI upset and pain (~20%)
  - Gallstones and liver failure
  - Myopathy (including rhabdomyolysis)
  - Unexplained non-cardiac death (!)

PO, BID
30 min before am & pm meals

Indication: Adjunct to diet to decrease TGs

↓TGs by 15-50% ↑ HDL 10-35%
No effect on LDL

Protease θ’rs stimulate liver synthesis of TGs, so Hypertriglyceridemia common in HIV-AIDs patients
Ezetimibe (Zetia) C

- ⊗ uptake of dietary & biliary cholesterol from the intestines
- Combo with simvastatin = Vytorin®
- Up-regulates LDL receptor on cell surfaces
  - ↑ LDL uptake into cells and ↓ plasma LDL
- ADRs
  - Headache
  - Diarrhea
  - Myalgia (rare)

Indication: Adjunct to diet to decrease total-C, LDL-C, ApoB and non-HDL-C

Ezetimibe is taken into intestinal epithelium where it ⊗ uptake of free cholesterol & plant sterols

The GIT epithelium glucuronidates the drug → plasma → liver → bile → GIT where bacteria recycle the glucuronide → free drug with long t₁/₂

PO, SID

PHRM 203 - Cardio 3
Hemostasis

- A balance between clotting & liquefying blood

- Clots form in response to vascular injury
Hemostasis

• Thrombus versus Embolus
  • The clot “in place” versus one that has broken free (impacting remote locations/organs/tissues)

• Drugs used to treat hemostatic imbalances:
  • Blood thinners
    – Inhibitors of coagulation either by interrupting the clotting cascade or platelet function
    – Promotors of fibrinolysis (the process of digesting clots)
  • Clotting agents
    – Clotting factors
    – Physical agents for clot to adhere onto

Warnings for Patients taking Anticoagulants

REPORT ANY

• Unusual bruising
• Pink or brown urine
• Red or black, tarry stools
• Coughing up blood
• Vomiting blood
• Coffee-grounds looking vomit
• Pain or swelling in a joint
• Reoccurring nose bleeds
• Bleeding from the gums
• Cuts that bleed too long
• Heavier than normal menstrual bleeding
Blood Thinners: Oral Anticoagulants

Coumarins, Warfarin (Coumadin) & dicumarol

- **Mechanism**
  - \(\ominus\) vitamin K epoxide reductase
  - \(\otimes\) the synthesis of vit K dependant clotting factors (II, VII, IX & X) in the liver (*interferes with both intrinsic and extrinsic clotting pathways by preventing production of factor X*)
  - Prothrombin Time (PT) - a lab measure of the activity of factors II, V, VII, X & fibrinogen, is used to monitor warfarin dosing
  - Periodic determination of the PT/INR (International Normalized Ratio for PT) is required and used to titrate dosage

- **Wisconsin Alumni Research Foundation + Coumarin = warfarin**

- **Kinetics**
  - Delayed onset (existing clotting factors must be cleared)
  - Orally active, 100% bioavailable, 99+% PPB, \(t_{1/2} = 2.5\) days

PO, IV
Blood Thinners: **Oral Anticoagulants**

**Warfarin (Coumadin)**

- **ADRs**
  - Hemorrhage
  - Warfarin-induced skin necrosis (WISN)
    - Fatty tissue develops petechia
    - Petechia coalesce into blisters (bullae)
    - Bullae become necrotic
    - Usually within 10d of starting warfarin
  - WISN risk factors:
    - Female - High initial dose
    - Obesity - Low Protein C or S

**Indications:**
1. Venous Thromboembolism (including deep venous thrombosis [DVT] and pulmonary embolism [PE]);
2. Thromboembolic events associated with atrial fibrillation or cardiac valve replacement;
3. ↓ risk of embolism after MI

The dose of COUMADIN must be individualized by monitoring the PT/INR. Not all factors causing warfarin dose variability are known. The maintenance dose needed to achieve a target PT/INR is influenced by:
1. Clinical factors including age, race, body weight, sex, concomitant medications, comorbidities, and
2. Genetic factors (**CYP2C9 and VKORC1 genotypes**).
Blood Thinners

Warfarin drug interactions

• Interactions that ↑ warfarin activity
  – Aspirin → impaired platelet aggregation
  – NSAIDs → compete for PPB sites and displace warfarin
  – Cimetidine, H2 antagonists → ΘP450s that metabolize warfarin
  – Vitamin K deficiency
  – Hepatic disease
  – Hypermetabolic disease (Hyperthyroidism)

• Interactions that ↓ warfarin activity
  – Pregnancy → ↑ maternal clotting factor synthesis
  – Barbiturates → ↑P450s that metabolize warfarin
  – Vit K supplements and foods high in Vit K (eg., spinach)
**Blood Thinners**

Injectable anticoagulants

- **Enoxaparin** (LMWH, Lovenox, from pig GI)
  - Indicated for DVT, Ischemia related to angina/MI
  - Boxed warning: spinal/epidural hematoma risk

- **Heparin** (UFH, from pigs or cows)
  - Indicated to prevent thrombosis and hence, embolism
  - Vials OFTEN CONFUSED WITH INSULIN
  - Partial Thromboplastin Time (PTT) monitoring every 6 hr

- **Bivalirudin** (Angiomax)
  - (synthetic form of hirudin, or leech spit, from Hirudo medicinalis)
  - Indicated, with aspirin, to prevent thrombosis during cardiac procedures and in patients who can’t use heparin – a direct thrombin inhibitor.
  - 42% of patients report back ache/pain!

*LMWH = low molecular wt. heparin
UFH = unfractionated heparin*
Differences between LMWH & UFH

• LMWH
  – 3000 Daltons
    • Hence Low Molecular Weight Heparin
  – SID
    • 3-5 hours to onset
  – Smaller risk of
    • Osteoporosis with long term use
    • Thrombocytopenia
  – Not easily reversed with protamine sulfate

• UFH
  – 20000 Daltons
    • A mixture, hence Unfractionated Heparin
  – Continuous infusion
    • IV- immediate onset
    • SC – onset within 1hr.
  – High risk of
    • Osteoporosis
    • Thrombocytopenia
  – Effects reversed with protamine sulfate
Blood Thinners

Heparin – deep SC/IV 🎧 ⚒ C

• Mechanism
  – ↑ *activity of antithrombin III* (activates ATIII which inactivates thrombin and Factors IX, X, XI & XII)

• Kinetics
  – Animal source: pig GI, cow lung
  – Orally inactive, $t_{1/2} = 1.5$ hr, hepatic metabolism

• ADRs
  – Heparin-induced *thrombocytopenia* (WBCs wipeout platelets)
    • White Clot Syndrome – aggregation of platelets caused by heparin
  – Avoid IM injections due to hemorrhage in muscle
  – Osteoporosis after long term use (>6 mos)
  – Heparin rebound = Hemorrhage
  – Drug-induced *alopecia* in up to 50% of patients

*Suppresses aldosterone leading to hyperkalemia in 5-10% of patients*
Alternative to Heparin

 importância

 Dabigatran (Pradaxa)

 - Indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation

  - *Direct thrombin inhibitor*
  - Used as an alternative to heparin in HIT patients
  - ½ the dose in kidney patients
  - Elderly may be more sensitive

 - Capsules are very moisture sensitive

 - ADRs
  - Dyspepsia, abdominal pain or discomfort, GERD

PO

Fall 2008

PHRM 203 - Cardio 3
Platelet Aggregation

- Thrombin
- TXA$_2$
- ADP
- Epinephrine
- Collagen
- Arachidonic acid
- Shear stress
- Fibrinogen
- Serotonin
- Von Willebrand factor
- Platelet activating factor
- ADH/vasopressin

Collagen stimulates the platelet to:
1. Secrete vesicles
   - Thrombin, VWF, growth factors, ADP
2. Activate phospholipase A
   - To synthesize TXA$_2$
3. Change shape
4. Become “sticky”

$PGD_2$, $PGI_2$, $PGE_2$, all ⊗ aggregation
Antiplatelet drugs
Cyclooxygenase Θ-ers

Aspirin

• Mechanism
  – Non-selective Θ cyclooxygenase (COX) →
    • ↓ production of prostaglandins, prostacyclins and thromboxanes
    • By modifying the activity of COX2, ↑ production of lipoxins (anti-inflammatory autacoids).

• Indications
  Headache, fever, rheumatoid arthritis, Θ platelet aggregation, transient ischemic attacks, unstable angina (men), pericarditis, coronary artery disease, acute myocardial infarction, stroke and MI prophylaxis

• ADRs
  – GI ulcers, Reye’s syndrome, tinnitus

PO
See Autocoids
Antiplatelet drugs
Adenosine diphosphate (ADP) receptor \( \Theta \) ’ers

🎉 **Clopidogrel (Plavix) 🎉 B**

- **Mechanism**
  - \( \otimes \) ADP receptors on platelets \( \rightarrow \otimes \) platelet aggregation by inhibiting activation of the glycoprotein IIb/IIIa pathway

- **Kinetics**
  - Clopidogrel is a prodrug, hepatic activation by CYP2C19 (avoid giving with omeprazole, a CYP2C19 inhibitor)

- **Indications**
  - CAD, peripheral vascular disease, and cerebrovascular disease.

- **ADRs**
  - Most common complaint: back pain

PO, SID

Lab test to screen CYP2C19 function available

Poor metabolizers have ↓↓↓ response due to lack of active metabolite!
Antiplatelet drugs

cAMP Phosphodiesterase Θ’ers

%! Cilostazol (Pletal) ♦ C

• Mechanism
  – Selective Θ 3-PDE → ⊗ platelet aggregation and arterial dilation

• Kinetics
  – PO, 95-98% PPB, hepatic metabolism (CYP2C19 & CYP3A4), renal excretion

• Indications
  – Intermittent claudication

• ADRs
  – Drug interactions: CYP inhibitors or inducers, including itraconazole, erythromycin, ketoconazole, diltiazem and omeprazole. Grapefruit juice, but not other citrus.
  – Headache, diarrhea, palpitations, ↑ infections, back pain, rhinitis…

PO, BID
30 min before or 2 hr after meals

Boxed warning: 3-PDE inhibitors increase the risk of death in congestive HF patients
Antiplatelet drugs
Glycoprotein IIB/IIIA \( \Theta \)’ers

Eptifibatide (Integrilin) \( \% \)B

– **Mechanism**
  - \( \Theta \) glycoprotein IIB/IIIA receptors \( \rightarrow \otimes \) platelet aggregation by preventing the binding of adhesive ligands (fibrinogen, von Willebrand factor, etc.)

– **Kinetics**
  - \( T \frac{1}{2} \) is 30 min - 2 hrs

– **Indications**
  - Heart surgery (angioplasty) & acute coronary syndrome

– **ADRs**
  - Drug interactions: thrombolytics or other platelet receptor inhibitors
  - Headache, diarrhea, palpitations, hemorrhage, allergic rxs, thrombocytopenia, back pain, chest pain.

**Fun Fact:** Derived from the venom of the southeastern pygmy rattlesnake (Sistrurus miliarus barbouri)

**Others:**
- Abciximab (ReoPro), a monoclonal antibody
- Tirofiban (Aggrastat), a non-peptide synthetic

**IV only**
Fibrinolytic Drugs

Alteplase (Activase) C

- Recombinant tissue plasminogen activator (t-PA)
  - Indications
    - Acute MI (ASAP)
    - Lysis of objectively Dx’d thrombi in lungs (or deep veins)
    - Acute ischemic stroke (within 3 hours of event)
  - Mechanism
    - Enzymes that convert plasminogen to plasmin, which is an enzyme that breaks down clots (thrombolytic)
  - ADRs
    - Hemorrhage, hypotension, arrhythmias (secondary to clot lysis), cholesterol emboli (may be fatal), allergic reactions.
    - Drug interactions: additive with anticoagulants (heparin, warfarin), platelet function modifiers (NSAIDs, dipyridamole), other thrombolytics.

IV only

Others:
- Anistreplase (Eminase) – Metabolized to streptokinase - plasminogen activator complex
- Streptokinase A type of t-PA from Streptococci bacteria
Clotting agents

• Conditions requiring drugs to control bleeding
  – Hemophilia
  – Liver disease
  – Child birth
  – Bone marrow disorders
  – Repeat coronary artery bypass graft surgery
  – Surface injuries with extensive damage
Fibrinolytic Bleeding Associated With

- Surgery
  - Heart
  - Prostate
  - Kidney
- Blood disorders
  - Amegakaryocytic thrombocytopenia with aplastic anemia
- Abruptio placenta
- Hepatic cirrhosis

- Cancer
  - Prostate
  - Lung
  - Stomach
  - Cervix
- Urinary fibrinolysis
  - Following surgery or polycystic or neoplastic genitourinary diseases

*May use anti-fibrinolytic agent such as aminocaproic acid*
# Systemic Hemostatic agents

Adapted from: Focus on Nursing Pharmacology, 4th Ed., AM Karch. Lippincott, Williams & Wilkins 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fibrinolysis inhibitor Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminocaproic acid (Amicar)</td>
<td>Hyperfibrinolytic states or subarachnoid hemorrhage, also management of amegakaryocytic thrombocytopenia, and <em>hereditary</em> angioneurotic edema</td>
<td>Allergy, Disseminated Intravascular Coagulopathy (DIC), CHD/arrhythmias, renal or liver dysfunction</td>
</tr>
<tr>
<td></td>
<td><strong>PO, IV infusion for ~8 hr</strong></td>
<td></td>
</tr>
<tr>
<td>Aprotinin (Trasylol)</td>
<td>Repeat coronary artery bypass graft surgery <em>it inhibits both fibrinolysis and the intrinsic clotting pathway by inhibiting plasma proteases</em></td>
<td>As above <em>(NOTE: Aprotinin lost FDA approval and was withdrawn May 08, but may still be obtained &amp; used.)</em></td>
</tr>
</tbody>
</table>

PHRM 203 - Cardio 3
# Antihemophilic agents

Adapted from: *Focus on Nursing Pharmacology, 4th Ed.*, AM Karch. Lippincott, Williams & Wilkins 2008

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Adverse effects/Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihemophilic factor (Bioclate)</td>
<td>Hemophilia A</td>
<td>Allergic reactions, should not be used during pregnancy or lactation</td>
</tr>
<tr>
<td>Coagulation factor VIIa (NovoSeven)</td>
<td>Hemophilia A or B</td>
<td>As above</td>
</tr>
</tbody>
</table>
| Factor IX complex (BeneFIX)                       | Hemophilia B or Factor VII and VIII deficiencies | • As above, don’t use if liver disease or signs of intra-vascular coagulation seen  
• Derived from pooled human plasma                   |