Rehabilitation Considerations for Individuals on Cardiac Medications

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Outline for today

- Key definitions
- Therapists’ role in managing medications
- Review of pharmacokinetics (PK)
- Reliable, up-to-date resources
- Pharmacology & aging
  - Effects of aging on PK
  - Frequency of ADRs in older adults
  - Beers Criteria
- Drug classes taken for common cardiovascular conditions
  - Antihypertensives
  - Drugs for angina pectoris
  - Antihyperlipidemias
  - Anticoagulants
Why should rehab therapists understand pharmacology?

- Medication use may alter clinical presentation and/or course of therapy
  - “Medications are involved in **80% of all treatments** and impact every aspect of a patient’s life.” (Patient-Centered Primary Care Collaborative; www.pcpcc.org)
- Knowledge of drug classes & mechanism of their actions is key to understanding patients’ responses to drugs
- To identify and potentially avoid or limit common **adverse drug reactions** (ADRs, ADEs, or AEs) relevant to rehab
  - *Anticipate* ADRs in patients/clients with altered pharmacokinetics and pharmacodynamics
  - We should always think - are there possible *therapy* solutions?
  - ADRs are **best** recognized by those who spend the **most** time with the patient!

What exactly is an ADR?

- “**Harmful, unintended reactions** to medicines that **occur at doses normally used for treatment** are called **adverse drug reactions (ADRs)**”  *World Health Organization*

- Typically **excludes** reactions that result from an overdose or failure of the drug to produce expected pharmacological response
  - In other words, the effects of an underdose or overdose are **not** considered ADRs.
Estimated annual incidence of ADRs in USA

- > 2 million serious ADRs
- 100,000 deaths
- Skilled nursing facility patients ADR rate – 350,000
- Ambulatory patients ADR rate – unknown

(https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm110632.htm#ADRs:%20Prevalence%20and%20Incidence)

<table>
<thead>
<tr>
<th>Incidence of ADRs in one hospital over 6 months</th>
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<tbody>
<tr>
<td>• 14.7% experienced ≥ 1 ADR</td>
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<td>• ADRs increased length of stay in ~27% of patients</td>
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<td>• Patients experiencing ADRs more likely to be:</td>
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<tr>
<td>o older</td>
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<td>o female</td>
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<tr>
<td>o have longer LOS</td>
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<tr>
<td>o be taking larger number of medications</td>
</tr>
<tr>
<td>• Most common drugs associated with ADRs:</td>
</tr>
<tr>
<td>anticoagulants, diuretics, opioids</td>
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Abstract

Adverse drug reactions (ADRs) are a major cause of hospital admissions, but recent data on the incidence and clinical manifestations of ADRs which occur following hospital admission are lacking. Patients admitted to hospital wards for various medical conditions are prescribed a wide range of medications. This study aimed to assess the incidence of ADRs in a hospital ward and to identify factors associated with ADRs. The study was conducted in a 10-bed medical ward of a tertiary care hospital. ADRs were defined as any untoward reactions associated with the use of a medication. The study included all patients admitted to the ward during a 6-month period. The primary outcome was the occurrence of ADRs. The study findings showed that 14.7% of patients experienced at least one ADR. Patients experiencing ADRs were more likely to be older, female, have longer length of stay, and be taking a larger number of medications. The most common drugs associated with ADRs were anticoagulants, diuretics, and opioids.
Potential areas of involvement for rehab therapists

- Monitor for ADRs
- Monitor for compliance with drug regimen
- Identify and differentiate rehabilitation therapy benefits versus drug therapy benefits
- Educate patient on preventative health care
- Ever-evolving scopes of practice...

Therapists’ role in managing medications

1) Take a complete drug history OR review inpatient medical chart daily
   - Include prescription, OTC, and supplements/herbal products
2) Be aware of changes in patient’s condition
3) Recognize ADRs
   - Maintain a HIGH degree of suspicion regarding ADRs and drug interactions - consider any new sign or symptom to be drug-related until proven otherwise (Beer MH, Arch Int Med, 1997; Fick DM et al., Arch Int Med, 2003)
4) Be exceptionally aware of drugs that affect mobility (especially with relationship to fall risk)
5) Communicate with physician!
**Review and think about patient’s medication list**

As a therapist, consider these questions when reviewing the medication list:

- **WHAT HAS CHANGED?**
  - New medications? Change(s) in dosage?
  - *Withdrawal* of medication patient has taken previously?
- Number of medications?
- How many medications in same class of drugs?
  - Known indications and intrinsic ADRs?
- Timing of medication with respect to therapy session?
- How would my patient’s characteristics impact pharmacokinetics?

**Key Definitions**

- **Polypharmacy...many definitions!**
  - More drugs prescribed than clinically warranted
  - All prescribed drugs are clinically warranted, but there are just too many pills to take
  - **Use of ≥ 5 drugs/day**
    - Use of ≥ 10 drugs/day is termed *excessive polypharmacy*
    - At any given time, an older patient takes 4-5 prescription drugs and 2 over-the-counter drugs

(Haider *et al.*, 2009; Beers, 1999)
Key Definitions

Why is polypharmacy a problem?

- Increased risk of ADRs
  - ~13% chance of having an ADR if taking 2 medications...
  - ~82% if taking 7 medications
  - ~100% if taking 10 medications

- Low adherence to drug therapy
- Unnecessary healthcare costs

Key Definitions

- **Pharmacodynamics**: effect of the drug on the body
  - Includes the mechanisms of action (cellular effects) by which drugs produce their physiological (systemic) effects

- **Pharmacokinetics**: effects of the body on the drug
  - Absorption: HOW do we take it?
  - Distribution: WHERE does it go?
  - Metabolism
  - Excretion
  - **Elimination**: HOW LONG does it stay in the body?
Pharmacokinetics – effects of the body on the drug

- **Absorption: HOW do we take it?**
  - Many available routes of drug administration
    - **Enteral:** oral, sublingual/buccal, rectal
    - **Parenteral:** inhalation, injection, topical, transdermal
  - Ultimately, some percentage of drug actually reaches the systemic circulation = **bioavailability**

First-pass effect with ORAL drug administration

- Drugs are taken up from capillaries in stomach & intestine and are transported by hepatic portal vein to liver cells
- Dosage of oral drug must be high enough to allow adequate amount of drug to survive metabolism by enzymes in liver cells
- Each drug has a distinct first-pass effect - can vary from ~ 0%-100%
Sublingual or buccal route

- **Path of drug...**
  - Oral mucosa ⇒ veins ⇒ superior vena cava ⇒ heart
  - **Bypasses** first-pass effect
    - *e.g.*, nitroglycerin (NTG) used to relieve anginal episodes

AGING effects on oral drug ABSORPTION

- Slower gastric emptying
- Increase in gastric pH (less acidic)
- Decreased GI motility

**Clinical consequences**
  - Generally **slower**, but complete oral absorption
  - No significant change for **most** drugs
  - **Notable exception**: propranolol absorption is increased due to decreased first-pass effect
Pharmacokinetics – effects of the body on the drug

• **Distribution: WHERE does it go?**
  - Movement of drug out of systemic circulation and into interstitial spaces to its target site (i.e., its receptor)
  - Volume of distribution (Vd)

AGING effects on drug DISTRIBUTION

• Increase in body fat, with decrease in lean body mass
• Decrease in total body H$_2$O
• Decreased serum albumin
• Decreased cardiac output (CO)

Clinical consequences
- Longer half-lives of fat-soluble drugs
- Blood levels of H$_2$O-soluble drugs may be higher
- Decreased drug-albumin binding *may* result in more active drug in bloodstream
- Decreased CO important, if accompanied by decreased renal & hepatic blood flow
Pharmacokinetics – effects of the body on the drug

- **Metabolism:** (part of elimination) – **HOW LONG does the drug stay around?**
  - Chemical alteration of drug to make it inactive (*usually*) and more suitable for excretion from body
  - **LIVER** is primary organ for drug metabolism
    - Occurs to *lesser* extent in other organs
  - Relies on enzymes: cytochrome P450 (CYP450) enzymes
    - Opportunity for drug-drug interactions due to CYP450 enzyme system

http://www.psychresidentonline.com/CYP450druginteractions.htm
Factors affecting drug metabolism

- **AGE**: Elderly have decreased liver mass, blood flow, and CYP450 enzyme activity
  - Clinical consequences
    - May increase the intensity of the effects of some drugs
    - Can reduce clearance of some drugs by 30-40%
- **Genetics**: polymorphisms in drug-metabolizing enzymes
- **Disease**: dysfunction or decreased blood flow to liver or kidney decrease metabolism

Factors affecting drug metabolism

- **Drug and supplement interactions**
  - Evidence-to-date about the effectiveness of each supplement, as well as known interactions with drugs
    - [www.fda.gov/medwatch/safety.htm](http://www.fda.gov/medwatch/safety.htm)
- **Drug and food interactions**
  - *e.g.*, grapefruit juice, black licorice, & chocolate with many drugs
    - [http://www.fda.gov/consumers/consumerupdates/ucm096386.htm](http://www.fda.gov/consumers/consumerupdates/ucm096386.htm)
Pharmacokinetics – effects of the body on the drug

- **Excretion:** (part of elimination) – **HOW LONG does the drug stay around?**
  - Physical elimination of the drug from the body
  - **KIDNEY** is primary organ for drug excretion.
    - Generally, drugs are excreted by glomerular filtration
    - Affected by health of kidney, blood flow to kidney, pH of urine, and degree of protein binding
  - Lungs: primary role in excreting volatile drugs
  - GI: minor role

AGING effects on drug EXCRETION

- Decreased renal mass & blood flow
- Decreased GFR (estimated by plasma creatinine levels)
- Decreased tubular secretion & absorption

Clínicalsequences
- Renal excretion decreased for most drugs studied (by up to 50% at age 75)
  - Cocker-Gault equation typically used to estimate renal function & make appropriate dosage reductions
- DECREASED RENAL FUNCTION is MOST IMPORTANT pharmacokinetic factor resulting in ADRs in older adults!
Drug Elimination Rates

- *Rate* at which a drug is eliminated helps determine the dose and frequency drug is prescribed/recommended
  - At a certain point, the amount of drug administered during dosing exactly replaces the amount excreted = **steady-state**

- **Half Life** \(t_{1/2}\): amount of time required for 50% of the drug remaining in the body to be eliminated
  - \(t_{1/2} = 0.7 \times \frac{V_d}{CL}\)
  - where
    - \(V_d\) is the volume of distribution of the drug
    - \(CL\) is the clearance of the drug from the body

Why is knowledge of the half-life of a drug helpful to a rehab therapist?

1) **To determine whether symptoms/signs could be the result of the drug’s effect**

For most drugs*, it takes ~ 5 half-lives for > 95% of drug to be eliminated from the body.

2) **In patients with decreased clearance and/or increased \(V_d\), you can usually anticipate an increase in \(t_{1/2}\)**

*For drugs eliminated by 1st-order process - in which a fixed portion of drug is eliminated in a given time period
Why is knowledge of the half-life of a drug helpful to a physical therapist?

Case example: Your 45-year-old patient was taking nifedipine (Procardia), a commonly prescribed calcium channel blocker, for stable angina. He has been experiencing severe headaches & dizziness. His doctor suggested he stop taking the drug for a few days. He arrives for his therapy appointment stating that his symptoms have not changed since his last dose 2 days ago.

• Could Procardia still be the cause of his symptoms?
• It is unlikely...Why?
• \( t_{1/2} \) of Procardia is 2 hours.

• Within 10 hrs (5 X 2 = 10 hr) since the last dose, ~95% of the Procardia should be eliminated from his body.

Factors that influence dosing schedule

• The drug’s half-life (t\(_{1/2}\))
  ○ Based on animal and clinical studies as well as predicted modifications based on age, sex, kidney function, weight
• Therapeutic index (or, therapeutic window)
**Therapeutic Index**
~Indicator of a drug’s safety profile~

- **TI = (TD50)/(ED50)**
- Assessment of clinical efficacy compared to toxicity
- The closer to 1, the more toxic the drug

**Clinical relevance for drugs with LOW therapeutic indices?**

1) Patients are more likely to have ADRs at therapeutic drug concentrations
2) Plasma levels of drug are more likely to be monitored
   - warfarin (Coumadin): INR
   - digoxin (Lanoxin): plasma digoxin level

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**Where can I find reliable & up-to-date information about drugs?**

- **Concise, current, easy-to-use & free drug information:** [www.epocrates.com](http://www.epocrates.com)
  - Web-based and mobile product that enables point of care information
  - Proprietary database developed by pharmacists & physicians
  - Source of Epocrates data
    - Package inserts, FDA drug safety alerts, textbooks, specialty society recommendations, clinical guidelines, consensus documents, review articles, primary literature
  - Database updated at least 1X/wk

FAQs about Epocrates: [http://www.epocrates.com/company/content/faqs.html](http://www.epocrates.com/company/content/faqs.html)
Pharmacology

Metabolism: liver; CYP450: 1A2, 2C8, 2C19, 2C5 (primary); 2C19, 3A4 substrates

Excretion: urine 92% (minimal unchanged), bile. Half-life: 20-60h (anticoagulant effect); bio half-life highly variable based on rate of clotting factor catalysis.

Subclass: Anticoagulants

Mechanism of Action

Inhibits vitamin K-dependent coagulation factor synthesis (II, VII, IX, X, proteins C and S)

Adverse Reactions

Serious Reactions

- hemorrhage
- skin/tissue necrosis
- gingivitis
- peripheral edema
- purpura blebs syndrome
- hyperreactivity rts
- anaphylacts
- cholestatic jaundice
- nephritis
- vasculitis
- systemic arterial vasculitis
- anemia
- syncope
- cerebrovascular

Common Reactions

- bleeding
- ecchymosis
- alopecia
- furrowed papillae
- nosebleed
- diarrhea
- abdominal distension/inflammation
- fatigue/weakness
- fever
- edema
- dyspnea
- dysuria
- testicular pain
- pruritus
- pruritus
warfarin (Coumadin)

- **Most common ADR is bleeding!**
  - Nosebleeds, rectal bleeding, bruising, tarry stools, joint or muscle aches
- **Patients should have plasma INR checked regularly**
  - **Therapeutic levels for patients on warfarin:** 2.0-3.0 (3.5)
  - Greater risk of hemarthrosis during exercise with INR ≥ 3.0 or 3.5
    - Guidelines for when to defer physical therapy are hard to find!
    - No evidence-based guidelines for physical activity in the patient/client with elevated INR are currently available
    - Excellent review: Tuzson A, *Acute Care Perspectives*, 2009

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warfarin (Coumadin)

- **Changes in Vit K intake change the anticoagulant effects of warfarin**
  - Increase in dietary Vitamin K decreases anticoagulation effect
  - Decrease in dietary Vitamin K increases risk of bleeding

- **MANY drug and supplement interactions with warfarin!**
  - www.mayoclinic.com/health/warfarin-side-effects/HB00101

digoxin (Lanoxin)

- Increases heart contractility
  - Used in treatment of systolic heart failure, atrial fibrillation/flutter

- Signs/symptoms of “dig toxicity”
  - Fatigue, bradycardia, palpitations, syncope, confusion, agitation, nausea/vomiting, SOB, dizziness, vision disturbances
    - Increased risk in patients with decreased kidney function
  - If signs/symptoms, report to PCP immediately!

Digitalis purpurea (foxglove)

Pharmacology and aging

- In the USA, the population of older adults will more than double between 2000 and 2030, growing from ~35 million to >70 million.
- For the next 20 years, ~10,000 people each day will reach 65 years of age.*
- Though older adults make up ~13% of the population, they consume ~33% of prescription medications.
- There is a positive association between increasing age & increased incidence of ADRs


U.S. Census Bureau, “65+ in the United States: 2005”
Common themes in older adults
Decline, Disease, Diversity

- **Polypharmacy** - many reasons why...
- **Altered pharmacokinetics**
- **Altered pharmacodynamics**
  - Increased sensitivity to warfarin, benzodiazepines, opiates, NSAIDs

**Beers Criteria**
“Potentially inappropriate medications” in older adults

- List of medications ("PIMs") generally considered inappropriate to give to elderly secondary to ADRs due to physiological changes accompanying aging
  - **PIMs: risks tend to outweigh the potential benefits**

Fick DM et al., *Arch Int Med*, 2003
**Beers Criteria**

- Most frequently consulted source for information about safety of prescribing medications to older adults
  - Used in: research; training of HCPs; inform quality measures (CMS uses to evaluate nursing home adherence to medication-related regulations)
- Do **not prevent or ban** the use of certain drugs for older adults
  - Emphasize that certain drugs should be avoided because they are ineffective, benefit/risk profile is poor, or that a safer (sometimes nonpharmacological) alternative is available
  - Do not substitute for professional judgment for treating an individual patient

Resnick and Pacala, *JAGS*, 2012

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**2012 Beers Criteria**

- Includes **53 drugs or drug classes**,
- Divided into 3 categories
  - PIMs and drugs classes to avoid in older adults
  - PIMs and drugs classes to avoid in older adults with certain diseases and syndromes that the drugs listed can exacerbate
  - Medications to be used with caution in older adults

2012 Beers Criteria
2 documents intended for the public

Common cardiovascular conditions

- Hypertension (HTN)
- Angina
- Hyperlipidemia
- Anticoagulants
**Blood Pressure for adults:**
**Normal range/Abnormalities**

- **Normal:** < 120/< 80 mm Hg*
- **Prehypertension:** 120-139/80-89 mm Hg
- **Hypertension**
  - Stage 1: 140-159/90-99 mm Hg
  - Stage 2: 160-179/100-109 mm Hg
  - Stage 3: 180-209/110-119 mm Hg
  - Stage 4: >210/>120 mm Hg

*Unusually low readings should be evaluated for clinical significance

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**Factors affecting blood pressure**

- Emotional state
- Age
- Weight
- Exercise
- Fitness level
- Arm position
  - AHA states that cuff should be at level of right atrium (for BP measured at brachial artery)
Anti-hypertensive medications

- Specific cause for HTN is only established in <15% of patients
- **Essential HTN means there is no identified cause**
- All anti-hypertensive drugs act by *interfering* with normal mechanisms of BP control
- **Multiple** sites of BP control
  - Brain
  - Heart
  - Sympathetic ganglia
  - Vascular smooth muscle
  - Kidneys

(Tanus et al., *Pharmacology for the Physical Therapist*, Fig 7-3)

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Treatment of HTN: **Lifestyle changes + drug therapy**

- **Optimal** improvement in HTN occurs when patients make lifestyle changes along with antihypertensive drug therapy.
- **Initial** approach in a newly diagnosed patient
  1) Education regarding risks associated with HTN
  2) In patients *willing* to make lifestyle changes, a 3-month trial of lifestyle modifications is recommended *prior* to determining whether drug therapy is required
  3) Drug therapy
What ARE the recommended lifestyle changes?

(1) Sodium reduction (<2 g/day)

(2) Dietary Approaches to Stop Hypertension (DASH) diet
   - 3 servings of fruit & vegetables/day, whole grain, low sodium, low-fat proteins
   - Weight loss/maintenance: BMI < 30 kg/m²

(3) Moderate intensity aerobic exercise: 3-5 days/week for 30-50 minutes

(4) Limited alcohol consumption
   - < 7 drinks/week for men; < 5 drinks/week for women

(5) Smoking cessation

Made 9 recommendations, varying from Grade A (Strong) to Grade E (Expert Opinion)

In general population aged ≥ 60 years, initiate pharmacologic treatment to lower BP at SBP ≤150 mm Hg or DBP ≤90 mm Hg and treat to a goal SBP <150 mm Hg and DBP <90 mm Hg. (Strong Recommendation – Grade A)

In general nonblack population, including those with diabetes, initial anti-HTN sive treatment should include thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)

In population aged ≥18 years with CKD, initial (or add-on) anti-HTNsive treatment should include ACEI or ARB to improve kidney outcomes. Applies to all CKD patients with HTN regardless of race or diabetes status. (Moderate Recommendation – Grade B)
Hypertension guideline management algorithm

5 major anti-hypertensive drug classes

1) Diuretics
2) ACE inhibitors (and angiotensin receptor blockers)
3) Beta-adrenergic blockers
4) Vasodilators (includes some CCBs)
5) Calcium channel blockers (CCBs)
Diuretics

- Drugs that interfere with water and/or salt reabsorption into the vascular system

**ALL diuretics result in increased urine volume – this is NOT an ADR!**

*Different diuretic classes act on different parts of the nephron*

Classes of diuretics

- **Strongest**
  - Loop and thiazide: inhibit salt & water reabsorption as much as 25%
    - loop diuretic: furosemide (Lasix)
    - thiazide diuretic: hydrochlorothiazide (HCT; Microzide)

- **Weak**
  - Carbonic anhydrase inhibitors: act in PCT to prevent water reabsorption
    - acetazolamide (Diamox)

- **Potassium-sparing**
  - Prevent excessive K⁺ secretion by inhibiting action of aldosterone
    - spironolactone (Aldactone)
Clinical uses for diuretics

- HTN
- Congestive heart failure (CHF)
- Edema

Rehabilitation Relevance: DIURETICS

**ADRs affecting rehab**

1. Orthostatic hypotension & reflex tachycardia
2. Hypokalemia (if not a K⁺-sparing diuretic)
3. Hyperkalemia (if a K⁺-sparing diuretic)
4. Ototoxicity (loop diuretics)
5. Hyperglycemia (thiazides)

**Solutions/considerations**

1. Instruct patients to perform transfers slowly to avoid fainting or lightheadedness
   - Incorporate cool-down in aerobic exercise
2 & 3. Recognize signs/symptoms of altered potassium levels (muscle weakness, cramps, heart arrhythmias)
   - For patient on K⁺-sparing diuretics, risk of hyperkalemia is higher if patient has renal impairment or is consuming high K⁺ diet
4. Stay alert for patient complaints of hearing (or tinnitus) or balance changes ⇒ report to primary HCP immediately
5. Diabetic patients should bring glucose monitor to PT sessions
Renin-angiotensin-aldosterone system

- Regulates BP by changing arterial vasoconstriction and plasma volume
- When this system is activated, BP increases
- **Drugs to treat HTN are aimed at disrupting specific steps**
- *All have Black Box Warnings: should not be taken during pregnancy*

Angiotensin-converting enzyme (ACE) inhibitors

- **Pharmaceutics:** the “-prils”
  - benazepril (Lotensin)
  - captopril (Capoten)
  - enalapril (Vasotec)
  - lisinopril (Zestril)
  - quinapril (Accupril)
- **Fairly low incidence of serious ADRs**
- **Common ADRs**
  - Hypotension, dizziness
  - Hyperkalemia (increased risk if patient is on K⁺-sparing diuretic)
  - Chronic cough in ~30% of patients
Angiotensin-receptor (AT1) antagonists

- Often referred to as angiotensin receptor blockers, or ARBS
- Pharmaceutics: the “-artans”
  - candesartan (Atacand)
  - eprosartan (Teveten)
  - irbesartan (Avapro)
  - losartan (Cozaar)
- As effective as ACE inhibitors
- Common ADRs
  - Hypotension, dizziness
  - URI symptoms
  - Back pain/musculoskeletal pain

Beta blockers - the “-lols”

- Antagonists at beta adrenergic receptors
  - atenolol (Tenormin)
  - metoprolol (Lopressor)
  - sotalol (Betapace)
  - propranolol (Inderal)
  - Most beta blockers are selective antagonists at beta, receptors on cardiac cells
    - Exception is propranolol: nonselective antagonist that binds to beta, & beta, receptors
    - Consequences:

- Effects of beta blockers
  - Decrease contractility
  - Decrease resting and exercise HR and BP
  - Increase exercise capacity in patients with angina
  - Decrease or no effect on exercise capacity in patients without angina

Be aware of many clinical uses for beta blockers

- HTN
- Arrhythmias
- Heart failure
- Angina
- Acute post-MI
- Glaucoma
- Migraines
- Generalized anxiety disorder
- Hyperthyroidism
- Certain types of tremors

Exercise prescription for patients taking beta blockers

- Metabolic load for aerobic training (60-80% VO$_2$max) may be achieved at conventional relative HR recommendation for training (70%-85% HRmax), but...

- Perceived exertion rating is a more appropriate measure of exercise intensity

- Best to use RPE 11-13 (on Borg scale of 6-20) or 3-5 (on modified 0-10 scale)
  - Corresponds to “fairly light” to “somewhat hard”

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<th>%VO$_2$max</th>
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<tr>
<td>50</td>
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<td>83</td>
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<td>100</td>
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(McArdle, Katch, & Katch. *Exercise Physiology*, 4th Ed., 2001)
Rehabilitation Relevance
Beta Blockers

**ADRs affecting rehab**
1) Fatigue, weakness
2) Dizziness
3) Bronchoconstriction
4) Blunted early manifestations of hypoglycemia
5) Sleep disturbances
6) Depression
7) Sexual dysfunction

**Solutions/considerations**
1, 2, 3) Allow increased time to complete aerobic tasks to prevent/limit dyspnea and account for depressed cardiac output
- Use RPE for aerobic intensity prescription (RPE ~11-13/20 or 3-5/10)
4) Diabetic patients should check blood glucose levels prior to and after exercise
5) Review sleep hygiene
6 & 7) Encourage patients to discuss fatigue, depression, sexual dysfunction with prescribing provider
- Strong data supporting morbidity and mortality benefits of this class of drugs

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**Mechanism of action**

**Examples**

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Reduction of Ca²⁺ influx (L-type CCBs)</td>
<td>verapamil, diltiazam, nifedipine</td>
</tr>
<tr>
<td>Antagonists at alpha, adrenergic receptors on vasculature, inhibiting binding of norepinephrine, primarily vasodilating arterial vasculature</td>
<td>doxazosin (Cardura), prazosin (Minipress)</td>
</tr>
<tr>
<td>Release of nitric oxide from drug or endothelium</td>
<td>nitroprusside, hydralazine</td>
</tr>
<tr>
<td>Hyperpolarization of vascular smooth muscle by opening K⁺ channels</td>
<td>minoxidil sulfate, diazoxide</td>
</tr>
<tr>
<td>Activation of dopamine-1 receptors</td>
<td>fenoldopam</td>
</tr>
</tbody>
</table>

(From Panas et al., *Pharmacology for the Physical Therapist*, modified from Table 7-1)
Considerations for exercise prescription with patients/clients on vasodilators

- Typically do not affect HR response to exercise, so exercise intensity using target % of age-predicted maximal HR can be used
  - When patients are taking vasodilators, heart does not have to work as hard to pump out blood because TPR is decreased, causing an increased SV and CO rather than affecting HR directly.

- Adequate cool down period is NECESSARY to prevent (symptomatic) hypotensive episodes!

Calcium channel blockers (CCBs)

- CCBs are antagonists at L-type calcium channels on cardiac & vascular smooth muscle cells
- CCBs block voltage-gated Ca\(^{2+}\) channels, decreasing intracellular Ca\(^{2+}\) and reducing muscle contraction

\[
\begin{align*}
\text{CO} &= \text{HR} \times \text{SV} \\
\text{BP} &= \text{CO} \times \text{TPR}
\end{align*}
\]

- When CCBs bind to L-type Ca\(^{2+}\) channels on:
  1) Smooth muscle cells in blood vessels, result is vasodilation of peripheral and coronary blood vessels = decreased TPR and increased blood flow to heart
  2) Cardiac cells: decreased cardiac contractility
Clinical uses for calcium channel blockers

- HTN
- Arrhythmias
- Angina
- Migraines

Calcium channel blockers (CCBs)

- 2 main classes of CCBs
  - Dihydropyridines
  - Non-dihydropyridines
- Agents differ in selectivity for cardiac versus vascular L-type calcium channels
- Dihydropyridines are relatively selective for L-type calcium channels in blood vessels
- Pharmaceutics: the “-dipines”
  - amlodipine (Norvasc)
  - felodipine
  - nifedipine (Procardia)
- Primarily used to treat HTN because these agents effectively decrease TPR
Calcium channel blockers (CCBs)

- **Non-dihydropyridine CCBs**
  - verapamil (Calan)
  - diltiazem (Cardizem)

- **Verapamil**
  - Relatively selective for heart
  - **Important in treating angina** (decreases myocardial $O_2$ demand) and arrhythmias

- **Diltiazem**
  - Intermediate between verapamil and dihydropyridines in selectivity for vascular calcium channels
  - **Used to treat HTN**

Rehabilitation Relevance
Calcium channel blockers (CCBs)

**ADRs affecting rehab**
1) Orthostatic hypotension, dizziness
2) Bradycardia
3) Weakness or muscle cramps
4) Peripheral edema
5) Headache

**PT solutions/considerations**
1 & 2) Transfer slowly, incorporate appropriate cool-down period after aerobic exercise
- Allow increased time to complete aerobic tasks to account for depressed cardiac output
- Measure BP and HR prior to, during, and after aerobic activities
- Use RPE to monitor exercise intensity (~11-13/20 or 3-5/10)
3-5) Have patients discuss with PCP
Stepwise approach to HTN treatment

Examples...

**Stage 1 HTN (140-159/90-99 mmHg)**
- 1st step: lifestyle modification + diuretic...no success?, then...
- 2nd step:
  o lifestyle modification + ACE inhibitor, or
  o lifestyle modification + beta blocker, or
  o lifestyle modification + dihydropyridine CCB

**No success with Stage 1 treatment, or Stage 2 HTN (≥160/100 mm Hg)**
- lifestyle modification + ACE inhibitor + dihydropyridine CCB
- lifestyle modification + beta blocker + dihydropyridine CCB
- lifestyle modification + beta blocker + thiazide diuretic

Sometimes, a 2nd antihypertensive medication is used to minimize the compensatory responses that occur with the BP-lowering effect caused by the 1st antihypertensive drug.

(Panus et al., Pharmacology for the Physical Therapist, Figure 7-12)
Case study

• Brief history
  o Patient is a 56-year-old male who is employed in a manufacturing facility. His job requires constant standing and lifting heavy boxes (often overhead) throughout the day. His right shoulder has been persistently painful for the past ~2 years, but the pain has increased over the last few weeks such that he is unable to lift anything over his head. Outside of work, the patient has a sedentary lifestyle, except walking 10 min/day to the train station. He has occasionally sought medical care for complaints of right shoulder pain. He has a 5-year history of essential HTN that is stable on current drugs. He has no other co-morbidities.

• Current medical status & drug therapy
  o One week ago, the patient had elective arthroscopic right shoulder girdle repair. He is referred to OP PT. His BMI is 27 kg/m². Resting vitals: BP 130/82 mm Hg; HR 66 bpm. Current drugs: hydrochlorothiazide and propanolol (in a single formulation: Inderide). The patient is also taking an opiate analgesic to reduce postsurgical pain.

Case study

• Rehabilitation setting
  o Patient arrives for PT evaluation/treatment after his work. PROM in gravity-reduced position and in pain-free range was examined for right UE. AROM is significantly limited by both pain & surgeon’s guidelines. Patient expresses extreme urgency in regaining right arm function in order to return to work.

  o The PT has worked closely with the referring surgeon on other patients following similar arthroscopic procedures. They have established a general treatment guideline. This initially involves having patients in a therapool up to neck level to allow buoyancy of shoulder facilitate pain-free movement. The 35°C temperature promotes muscle relaxation and decreases guarding.

  o Patient entered pool up to his neck and under guidance of the PT, began right UE movements. After 15 min in the water, patient complained of SOB, and started up pool stairs with assistance of the PT. At the top of the stairs, patient felt lightheaded and was assisted to a chair; he fainted, losing consciousness for several seconds. Vitals were taken in seated position as quickly as possible: BP 90/50 mm Hg; HR 84 bpm. The patient was coherent and returned to standing after several minutes.
Case study

**Identified problems**
1. Difficulty breathing:

2. Hypotension/fainting:

**Clinical options**

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**Coronary artery disease (CAD)**

- **Definition**: atherosclerosis in epicardial coronary arteries
- **Etiology**
  - Atherosclerotic plaques progressively narrow coronary artery lumen and impair myocardial blood flow.
  - Reduction in coronary artery flow may be symptomatic or asymptomatic, may occur with exertion or at rest, and may culminate in MI, depending on obstruction severity and rapidity of development.
Atherosclerosis - “hardening of the arteries”

- Atherosclerosis represents an attempt at healing in response to some initial endothelial injury
- Localized plaques protrude into arterial lumen, compromising blood flow
- Most frequent cause of cardiac dysfunction (MI, arrhythmia)

What events cause initial damage to endothelial lining of blood vessels?

- Mechanical, chemical, and inflammatory mediators can trigger dysfunction to the endothelium
  - HTN
  - Smoking
  - Elevated blood levels of homocysteine
  - Inflammatory stimuli
  - Hyperlipidemia (increased cholesterol, LDLs, triglycerides)
Presentation of CAD

Angina is the most common and typical indicator of CAD
- Stable angina
- Unstable angina
- Prinzmetal angina
- Myocardial infarction (MI)

Classic clinical presentation of angina

- Substernal symptoms
  - Heaviness, pressure, tightness, burning, squeezing, choking
  - Radiation to (L) neck, arms, back or epigastrium

Anginal equivalent: symptom(s) of myocardial ischemia that do not include chest pain
- Shortness of breath, diaphoresis, extreme fatigue, pain at site other than the chest
Medical treatment of acute anginal episode

Sublingual or buccal nitroglycerin (acts by releasing nitric oxide, which vasodilates arteries and veins)
- Have patient lie down before taking NTG.
- Dose should act in 1-2 min to relieve pain.
- If no relief after 2-3 doses or within 20 min, may indicate an evolving MI: seek immediate medical attention!

NTG should burn under tongue. If it does not, it is not active!

Medical prophylaxis of anginal episodes

Several agents used to decrease frequency of angina attacks

(1) Long-acting nitrates
- Oral sustained-release preparations (e.g., isosorbide dinitrate): 4-8 hr duration of action
- Transdermal patches: 8-10 hr duration of action

(2) Beta-blockers
- Propranolol, metoprolol (β₁-selective)

(3) CCBs
- Diltiazem, verapamil, nifedipine

(4) Platelet-inhibiting agents or anticoagulants
- aspirin, Coumadin
Medical prophylaxis of anginal episodes

- Be sure that patients with angina bring nitroglycerin to each therapy session. (If a therapy session can raise BP, it can induce angina...)
- It is not appropriate to exercise to angina level...because angina is a symptom indicating that heart muscle is being starved of oxygen!
- Administration of drugs such as long-acting nitrates before aerobic activity or painful treatments may help prevent exertional angina.

Rehabilitation Relevance
Drugs for angina management

<table>
<thead>
<tr>
<th>ADRs affecting rehab</th>
<th>Solutions/considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Orthostatic hypotension</td>
<td>1) Transfer slowly; incorporate appropriate cool-down period after aerobic exercise</td>
</tr>
<tr>
<td>2) Bronchoconstriction (with beta blockers)</td>
<td>2) Dyspnea may limit aerobic capacity</td>
</tr>
<tr>
<td>3) Decreased HR &amp; contractility (with beta blockers)</td>
<td>3) Cardiac output may be decreased, which can limit aerobic activities</td>
</tr>
<tr>
<td>4) Nitrates can cause reflex tachycardia</td>
<td>4) Use RPE when determining aerobic intensity</td>
</tr>
</tbody>
</table>
Cholesterol and plasma lipoproteins

- Lipoproteins are the main form of lipid transport in the plasma.
- 4 different lipoproteins travel in plasma:
  - Chylomicrons
  - Very low density lipoproteins (VLDL)
  - Low-density lipoproteins (LDL)
  - High-density lipoproteins (HDL)
- VLDLs, LDLs, and HDLs are made in the liver.
- Cholesterol is carried by VLDLs, LDLs, and HDLs.

Cells in various organs - including smooth muscle cells of arterial walls - contain receptors for LDLs to bind to.
- These cells engulf LDLs and use the cholesterol.
- Most LDL particles are removed by the liver.

Excessive cholesterol is released from cells and travels in plasma as HDLs.

HDLs are then removed by the liver.
**LDLs – It’s **GOOD** to have LOW plasma concentration**

- If plasma [LDL] is high, can exceed liver’s ability to remove LDLs from blood.
- Endothelial cells lining blood vessels engulf the LDLs and these become oxidized.
- **Oxidized LDLs contribute to endothelial cell wall injury and progression of atherosclerosis.**

**To decrease blood [LDL]**

1. Lower cholesterol in diet
2. Lower saturated fat in diet (saturated fat raises cholesterol levels)
3. Lower *trans* fat in diet
   - *Trans* fats increase [LDL] and [triglyceride], and decrease [HDL]
4. *(Increase antioxidant intake: Vitamins C and E; beta-carotene)*
5. Lipid-modifying drugs

**HDLs – It’s **GOOD** to have HIGH plasma concentration**

- Cholesterol in HDL is not taken up by endothelial lining of blood vessels, because arterial walls have no HDL receptors.
- HDLs remove cholesterol from peripheral tissues (including arterial walls) and take it to the liver for bile synthesis.

**To increase blood [HDL]**

1. **Exercise** - most effective means of raising HDL concentration
2. Genetics
3. Moderate alcohol intake
4. Lipid-modifying drugs
**Lipid Profile:** *Distribution* of cholesterol is a more powerful predictor of heart disease than total cholesterol level.

<table>
<thead>
<tr>
<th>Fasting Blood Level</th>
<th>Optimal, Healthy Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>&lt; 200 mg/dl</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>&lt; 100 mg/dl</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>≥ 60 mg/dl</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 100 mg/dl</td>
</tr>
</tbody>
</table>

Recommendations from American Heart Association, 2014

**Rehabilitation focus**

- **Optimal** improvement in blood lipid profiles occur when patients make lifestyle changes along with antihyperlipidemic drug therapy.
- Several lipid-lowering drugs can cause myalgia, arthralgia, and muscle weakness
  - PTs are likely HCPs to help differentiate these ADRs from the anticipated muscle pain/fatigue due to exercise.
5 classes of lipid-modifying drugs

1) HMG-CoA reductase inhibitors (the “statins”)
2) Resins
3) Ezetimibe (Zetia®)
4) Niacin
5) Fibrates

<table>
<thead>
<tr>
<th>Drug</th>
<th>LDL cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglycride</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atorvastatin (Lipitor)</td>
<td>-25% to -40%</td>
<td>+5% to +10%</td>
<td>↓↓</td>
</tr>
<tr>
<td>fluvastatin (Lescol)</td>
<td>-20% to -30%</td>
<td>+5% to +10%</td>
<td>↓</td>
</tr>
<tr>
<td>lovastatin (Mevacor)</td>
<td>-25% to -40%</td>
<td>+5% to +10%</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Resins</strong> (e.g., cholestyramine - Questran)</td>
<td>-15% to -25%</td>
<td>+5%</td>
<td>± or ↑</td>
</tr>
<tr>
<td>ezetimibe (Zetia)</td>
<td>-13% to -19%</td>
<td>+3%</td>
<td>±</td>
</tr>
<tr>
<td><strong>Niacin</strong></td>
<td>-15% to -40%</td>
<td>+25% to +35%</td>
<td>↓↓</td>
</tr>
<tr>
<td><strong>Fibrates</strong> (e.g., fenfibrate - Tricor)</td>
<td>-10% to -15%</td>
<td>+15% to +20%</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

(Panis et al., Pharmacology for the Physical Therapist, 2009)
Statins

- **Majority** of circulating cholesterol comes from endogenous production by the liver
- **Statins:** inhibit the liver’s production of cholesterol (and increase the liver’s synthesis of LDL receptors)
- **Effects of statins**
  - More favorable plasma lipid profile ($\downarrow$LDLs & $\uparrow$HDLs)
  - Reduces risk of MI, CVA, & mortality in patients with CAD
  - Also evidence for: improved endothelial function, modulation of inflammation, maintenance of plaque stability, prevention of thrombus formation

Statins

- ~33 million US adults are currently taking statins
- **Pharmaceutics** (7 currently on the market)
  - atorvastatin (Lipitor)*
  - fluvastatin (Lescol)
  - lovastatin (Mevacor, Altoprev)
  - pitavastatin (Livalo)
  - pravastatin (Pravachol)
  - rosuvastatin (Crestor)*
  - simvastatin (Zocor)*

*new guidelines show these have the best evidence for preventing MI and CVA
Who should take statins?

- **Previous guidelines** recommended that individuals take a statin **based on plasma LDL level**; also recommended that people should aim for LDL levels at 70 mg/dL, even if this required a statin plus other medications (even though this has not been proven to prevent MI or CVA)

Who should take statins?

2013 recommendations

American College of Cardiology and American Heart Association recommend a statin for anyone with:

1) CVD (including angina), a previous MI or CVA, or other related condition

2) Very high LDL (> 190 mg/dL)

3) Diabetes and between 40-75 years of age

4) Greater than 7.5% chance of having MI or CVA or developing other form of CVD in the next 10 yr
Calculator used to determine 10-yr probability of developing atherosclerotic CVD (MI, CVA, TIA, angina, CAD, PAD)

http://www.cvriskcalculator.com/

Why were these recommendations controversial?

- Would increase number of individuals eligible for statin therapy by ~13 million people - mostly older adults and those without CVD
- No controversy over first 3 groups that statins are recommended for because significant amount of research shows that benefits outweigh risks
- Controversy centers around category 4 - those individuals who do not yet have visible CVD
If the guidelines are followed...

- Of 115 million adults 40-75 years old, 49% would be taking statins (up from 37.5% under previous guidelines)

- Of adults 60-75 years old, 87% of men and 54% of women would be taking statins

**Common Reactions**
- URI/sx
- headache
- arthralgia/arthritis
- diarrhea
- extremity pain
- UTI
- dyspepsia
- nausea
- musculoskeletal pain
- muscle spasms
- myalgia
- insomnia
- pharyngolaryngeal pain
- diabetes mellitus
- abdominal pain
- constipation
- flatulence
- asthma
- urticaria
- CK elevated
- ALT, AST elevated
- coenzyme Q10 levels decre.
- cognitive impairment

**Statin ADRs**

**Adverse Reactions**

- myopathy, incl. immune-mediated
- tendon rupture
- rhabdomyolysis
- acute renal failure
- hepatotoxicity
- pancreatitis
- hypersensitivity rxn
- anaphylaxis
- photosensitivity
- toxic epidermal necrolysis
- erythema multiforme
- Stevens-Johnson syndrome
- thrombocytopenia
- leukopenia
- hemolytic anemia
- diabetes mellitus
### Statins

- Medical opinion has been that statins are **underutilized**
  - ~25% of adults who start statins stop taking them by 6 months
  - 60% stop by 2 years
- Primary reason for stopping is **fear of** statin-induced myopathy

**Statin-induced myopathy**

**can include:**

- **Myalgia**: muscle weakness, soreness, cramping (at rest or with exertion) **without** elevation in plasma CK
- **Myositis**: elevated plasma CK with **or** without muscle symptoms
- **Rhabdomyolysis**: muscle symptoms with plasma CK level ≥10 times upper limit of normal (patient may notice dark, red/brown colored urine)

*This term encompasses many signs/symptoms with no agreed upon definition*

---

### FDA’s advice on statin risks (Jan 2014)

*The value of statins in preventing heart disease has been clearly established. Their benefit is indisputable, but they need to be taken with care and knowledge of their side effects."

1. Routine monitoring of liver enzymes in blood is **no longer needed** because it does not predict the rare occurrences of serious liver injury.
2. Cognitive impairment (memory loss, forgetfulness, confusion) has been reported by some statin users.
3. People on statins may have increased blood glucose levels and develop Type 2 diabetes.
4. Some medications interact with lovastatin and can increase the risk of muscle damage.
How common ARE statin ADRs?

- Systematic review of randomized placebo controlled studies (14 primary-prevention studies with 46,262 subjects and 15 secondary-prevention studies with 37,618 subjects)
  - Majority of ADRs were as common in placebo arm as in the statin arm, with exception of: asymptomatic liver enzyme elevations and an increase in diabetes in the primary-prevention population (absolute increase of 0.5%, which is the same as the reduction in number of deaths)
  - Author quote – “For every 1 primary-prevention patient in whom we cause diabetes, we save 1 life, prevent 2 heart attacks, and half a stroke.”

Finegold et al., European J of Preventive Cardiology, 2014

Statins

- Physical therapists need to differentiate between muscle pain/fatigue associated with exercise or therapy interventions from that potentially associated with ADRs of statins

- To do this, we need to know:
  - What are the risk factors for statin toxicity? (next slides)
  - What are findings suggestive of statin toxicity? (next slides)

- Contact referring HCP ASAP, if you suspect statin-induced myopathy
Risk factors for statin-induced myopathy

**Endogenous**
- > 65 years old
- Female
- Low BMI
- Diabetes
- Renal and/or hepatic dysfunction
- Metabolic muscle diseases
- Family/personal history of muscle symptoms or elevated plasma CK

**Exogenous**
- Excessive alcohol consumption
- Concurrent use of medications/supplements that increase plasma statin concentration
- Heavy exercise

(Fernandez et al., Cleveland Clinic J of Med., 2011)

Findings suggestive of statin-induced myopathy

- Most often occurs **within first 6 weeks of statin initiation**, when statin dosage is increased, and/or when another medication affects statin metabolism
  - Muscle symptoms usually resolve within 2 weeks of starting statin
- Burning, cramps, or pain in **large symmetrical muscles during exercise** that was not present before statin use
- **More common in LEs** (especially calf muscles) than UEs
- Muscle complaints associated with dyspnea and fatigue
- Physically active patients more likely to suffer muscle symptoms than sedentary patients

(Fernandez et al., Cleveland Clinic J of Med., 2011)
Statins: food and supplement concerns

- Many drugs & foods are metabolized by same CYP450 enzymes that metabolize the statin (e.g., grapefruit juice)
  - Result: ↑ risk of ADRs (hepatotoxicity & myopathy)
- **Supplement concern:** red yeast rice is a yeast grown on rice
  - Sold as “natural” cholesterol-lowering agent
  - Red yeast rice IS lovastatin!
- **Take home message:** statins should be taken as prescribed; grapefruit products & red yeast rice should **not** be taken concurrently

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Anticoagulants

- Used primarily to prevent clot formation in the venous system
- Work by preventing or disrupting the synthesis and/or function of clotting factors
- Do not dissolve the thrombus (clot)
Anticoagulants – 5 main classes

1) Unfractionated heparin (UFH): not orally active; typically given via subcutaneous (SQ) or intravenous (IV) injection
2) Low molecular weight heparins (LMWHs): not orally active; given SQ
   - enoxaparin (Lovenox)
   - dalteparin (Fragmin)
3) warfarin (Coumadin): orally active
4) fondaparinux (Arixtra): not orally active; given SQ; inhibits thrombin formation
5) Novel oral anticoagulants (NOACs): orally active; direct thrombin inhibitor* and direct factor Xa inhibitors
   - dabigatran (Pradaxa)*
   - rivaroxaban (Xarelto)
   - apixaban (Eliquis)
   - edoxaban (Savaysa)

Deep Vein Thrombosis (DVT)

1) Is the patient/client at risk for DVT?

2) Does the patient/client demonstrate signs/symptoms of DVT?
Role of Physical Therapists in the Management of Individuals at Risk for or Diagnosed With Venous Thromboembolism: Evidence-Based Clinical Practice Guideline

Ellen Hillegass, Michael Puthoff, Ethel M. Frese, Mary Thigpen, Dennis C. Sobush, Beth Auten; for the Guideline Development Group

The American Physical Therapy Association (APTA), in conjunction with the Cardiovascular & Pulmonary and Acute Care sections of APTA, have developed this clinical practice guideline to assist physical therapists in their decision-making process when treating patients at risk for venous thromboembolism (VTE) or diagnosed with a lower extremity deep vein thrombosis (LE-DVT). No matter the practice setting, physical therapists work with patients who are at risk for or have a history of VTE. This document will guide physical therapist practice in the prevention of, screening for, and treatment of patients at risk for or diagnosed with LE-DVT. Through a systematic review of published studies and a structured appraisal process, key action statements were written to guide the physical therapist. The evidence supporting each action was rated, and the strength of statement was determined. Clinical practice algorithms, based on the key action statements, were developed that can assist with clinical decision making. Physical therapists, along with other members of the healthcare team, should work to implement these key action statements to decrease the incidence of VTE, improve the diagnosis and acute management of LE-DVT, and reduce the long-term complications of LE-DVT.

(Hillegass et al., Physical Therapy, 96 (2); February 2016)
5 classes of lipid-modifying drugs

1) HMG-CoA reductase inhibitors (the “statins”)
2) Resins
3) Ezetimibe (Zetia®)
4) Niacin
5) Fibrates
Resins

- Resins bind to bile acids in the intestine to prevent re-absorption
  - Bile acids are excreted in feces
  - Plasma cholesterol is then converted to bile acids
  - Compensatory increase in liver’s LDL receptors (which remove LDLs from blood)

- **Result**
  - *Modest ↓ LDLs; little effect on HDLs or triglycerides*

- **Pharmaceutics**
  - cholestyramine (Questran)
  - colestipol (Colestid)
  - colesevelam (Welchol)
- Available as powder or tablets

- **Other clinical uses**
  - Reduce severe itching that occurs with liver failure
  - Decrease diarrhea associated with Crohn’s disease and *C. difficile*

- **ADRs & drug interactions**
  - Bloating
  - Constipation
  - Impairs absorption of some vitamins and drugs
  - Other drugs should be taken > 1 hr or 4-6 hr after resins
ezetimibe (Zetia)

- *Lipid-modifying* drug that inhibits absorption of dietary cholesterol and cholesterol that is excreted in the bile
  - Compensatory increase in liver’s LDL receptors (which remove LDLs from blood)

- **Result**
  - Mildly reduces plasma LDL concentration (monotherapy); more effective when combined with a statin

---

ezetimibe (Zetia)

- **Pharmaceutics**
  - ezetimibe (Zetia)
  - ezetimibe + simvastatin (Vytorin®)

- **ADRs**
  - Ezetimibe alone fairly well tolerated, though diarrhea is common
  - Combination product with simvastatin has similar ADR profile to statins
Niacin (Vitamin B3)

- Water-soluble vitamin B3 (nicotinic acid) plays large role in metabolism, DNA repair, and production of steroid hormones

- In pharmacological doses, B3 has effects on lipids:
  - Reduces liver’s production & secretion of VLDLs & LDLs
  - Increases HDL concentration
  - Decreases circulating fibrinogen

- Result
  - Improved lipid profile (↓LDLs & triglycerides; ↑HDLs)

Niacin (Vitamin B3)

- Dosage
  - Typical multivitamin contains 20 mg of niacin (100% of daily value recommendation)
  - Pharmacological dosages taken for hyperlipidemia: 1,500 to 3,000 mg
  - Niaspan®: extended release form

- Common ADRs
  - Cutaneous flushing - tolerance usually develops within days to weeks
  - Nausea/vomiting (dose-dependent)
  - Pruritus
  - Minor insulin resistance
  - Abnormal liver function tests (LFTs)

- Serious ADRs
  - Hepatotoxicity
**Fibrates**

- *Lipid-modifying* drugs that bind to receptors (PPAR-α) that regulate transcription of genes involved in lipid metabolism
  - Increase activity of lipoprotein lipase
  - Inhibit triglyceride synthesis in liver
  - Increase breakdown of triglycerides from plasma

- **Result**
  - *Modest* ↓ triglycerides and ↑ in HDLs

---

**Fibrates**

- **Pharmaceutics**
  - gemfibrozil (Lopid)
  - fenofibrate (Lipofen, Tricor)

- Used as *monotherapy* to treat hypertriglyceridemia

- Often used with other antihyperlipidemic drugs to treat patients with increased LDL and VLDL plasma concentration

- **ADRs & drug interactions**
  - Most common ADR is nausea
  - Increased risk of gallstones
  - Elevated LFTs
  - If used in combination with statins, fibrates significantly increase risk of myopathy
Questions???

Thank you for your interest!
Feel free to contact me any time:

Erin E. Jobst: jobste@pacificu.edu

References & Resources
(in addition to those listed throughout course)

- Epocrates: http://www.epocrates.com/
- FDA MedWatch: http://www.fda.gov/medwatch/