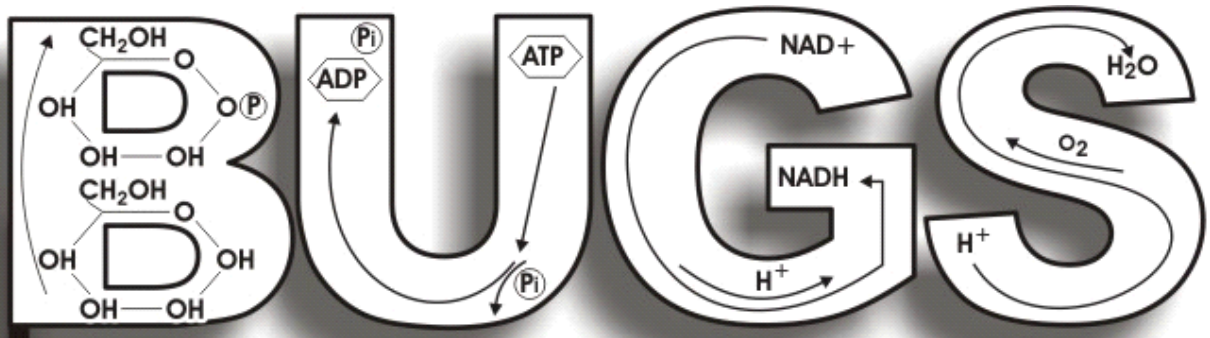
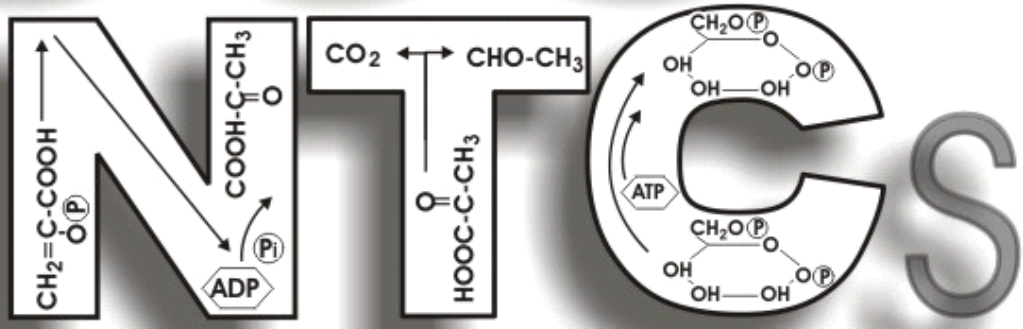




PHAR 301

SET #8 Lectures 20-21

ANNOUNCEMENTS

The BUGS office will be *closing* Thurs April 5th. Pick up your NTCs, or anything else you need from B.U.G.S. BEFORE this date!

< Biochemistry Undergraduate Society - 5th Floor McIntyre rm. 511 >
< bugs@sus.mcgill.ca - (514) 398-5247>

Tuesday, March 27th, 2007
Dr. Bowie - Lecture #20

Hypertension

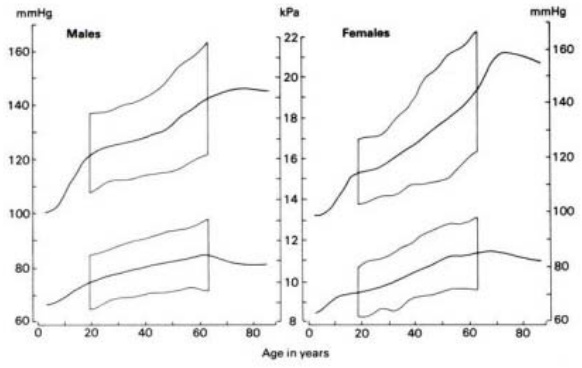
- Hypertension is a prolonged elevation of blood pressure
- It turns out we know very little about what actually causes hypertension
    - Secondary hypertension is a condition with a known cause for hypertension
- Lifestyle is the main hypothesis into what may cause hypertension in most people
    - Smoking, excessive drinking, poor diet, obesity, and lack of exercise all have negative effects with hypertension
- Most hypertensive patients are treated with drugs but it is important to know that some are treated with surgical interventions, which we will not discuss

Background Information

- Hypertension is the most common cardiovascular disease
- It is present in roughly 24% of the US population (although this is a very conservative estimate) and is more prevalent in Western and developed countries
- Its prevalence varies with age (increases with age), race (higher in African-americans), education (the higher educated are less likely to develop hypertension), diet and other factors
    - Socio-economic status is actually the biggest predicting factor in determining the prevalence of disease, lifestyle, and even intellectual deficiencies / mental illnesses
    - There was a study done in Chicago that found church-goers had a decreased prevalence of hypertension than non-churchgoers. It has to do with a better lifestyle and not "divine intervention".
- Hypertension increases with the incidence of renal failure (likely due to reduced renin-angiotensin system), coronary disease, cardiac failure, and stroke.

Diagnosing Hypertension

- to be considered having hypertension, the person must have *at rest* a repeated elevated blood pressure greater than 120/90mmHg
- hypertension is asymptomatic and therefore undetected unless specifically measured for
    - this may result in organ damage before it is detected
- mild hypertension could greatly increase stroke and heart failure risk
- blood pressure is age and gender dependant (see figure)
    - the top line represents the systolic pressure and the bottom the diastolic



(Envelopes represent the Standard Deviation of the Mean)

Aetiology

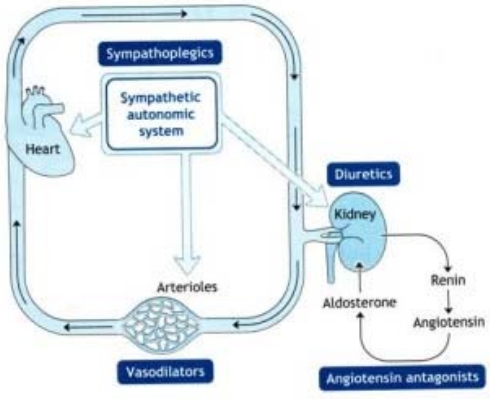
- there are two types of hypertension:
    - Essential
        - Cause is unknown though likely **multifactorial** including:
            - Hyperlipidemia (excess fat in the blood)
            - Diabetes
            - Genetics
            - Diet (high salt)
            - Stress
    - Secondary
        - 10-15% identifiable causes such as:
            - Renal artery constriction
            - Coarctation of the Aorta (narrowing)
                - Treated surgically
            - Phaeochromocytoma (tumor of the adrenal glands)
                - Increased cathecolamines that increase blood pressure
                - Treated surgically
            - Cushing's Disease (hypercorticolism)
            - Primary Aldosteronism (elevated aldosterone)
            - Hyperthyrodism
            - Oral contraceptives
- drugs we give for Essential hypertension treat the symptoms
- we are becoming more and more reliant on drugs to treat hypertension instead of promoting a lifestyle change to eliminate the prevalence of hypertension altogether

<u>Regulation of Blood Pressure</u>

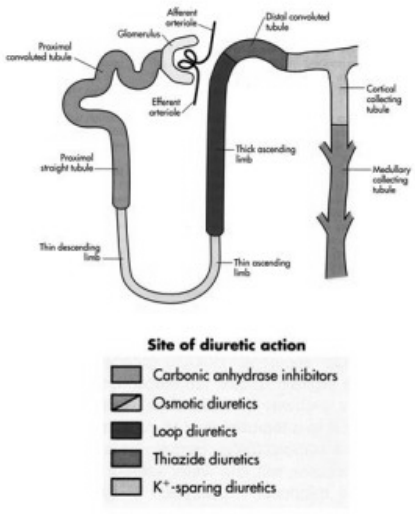
- Four Sites of regulation:
    - Resistance in Arterioles
        - These are regulated by the sympathetic nervous system
    - Capacitance of Venules
        - Difficult to target specifically
    - Pump Output by the Heart
    - Volume by the Kidney
- The subsequent drugs will target either the arterioles, the heart itself or the kidney (renin-angiotensin system)

<u>Major Drug Groups</u>

- There are four main drug groups used to treat hypertension
    - Diuretics
        - Increase urine output by working on the kidneys
    - Sympathoplegics (aka: Sympatholytics)
        - Cut the sympathetic system
    - Vasodilators
        - Open blood vessels
    - Angiotensin Antagonists
        - Cut the angiotensin system



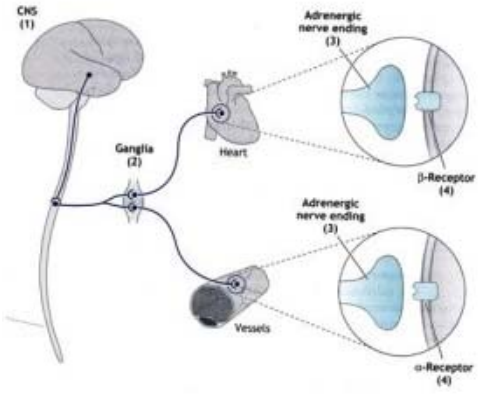
Diuretics



- decreases blood volume and affects smooth muscle tone
- work on the kidneys
- Two main classes:
    - Thiazides
        - Treats mild hypertension
    - Loop Diuretics
        - Severe hypertension
- Thiazides are usually the first drug given as a monotherapy. If it is ineffective, then instead of increasing the dosage which could produce side effects, another drug is given (synergistic polypharmacy) that works through another pathway to produce the desired effects.
- Thiazides
    - *Drug to know: **Hydrochlorothiazide**
    - Treats mild/moderate hypertension
    - Works on the *Distal Convoluted Tubule*
    - Blocks Na^+/Cl^- symporter
    - Increases Ca^{2+} reabsorbtion
    - Orally active
    - May cause Hypokalemia (K+ depletion) as a toxic effect
- Loop Diuretics
    - *Drug to know by name: **Furosemide**
    - Treats moderate/severe hypertension
    - Works on the *Thick Ascending Loop*
    - Blocks $Na^+/K^+/2Cl^-$ symporter
    - Increases Ca^{2+} excretion
    - Oral and Intravenous
    - May cause Hypokalemia (K^+ depletion) as a toxic effect

Sympathoplegics

- decreases sympathetic discharge or its effects on cardiovascular system
- works on the CNS
- targets (see figure):
    1. centrally acting agents
    2. ganglion blockers
    3. postganglionic sympathetic neuron blocker
    4. adrenoceptor blockers

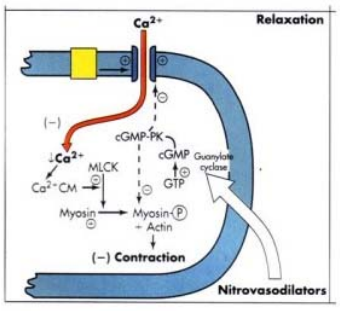


1. Centrally acting agents: α_2 selective agonists
    1. *Drug to know: **Clonidine** and Methyldopa (don't need to know)
    2. Treats mild and moderate hypertension
    3. Its mechanism of action is unknown
    4. Its toxicity is minimal; however sudden cessation of taking the drug will cause severe rebound hypertension which increases incidence of stroke

2. Ganglion blockers: nicotinic cholinoceptor antagonists
    - Trimethaphan (don't need to know)
    - Treats severe hypertension
    - Has a very rapid onset
    - Its mechanism blocks nicotinic Acetylcholine receptors (nAChR) in autonomic ganglia
    - It is highly toxic, by intolerability causing orthostatic hypotension, blurred vision and constipation
    - These drugs are not widely used since it is highly unselective, however, it is used in emergency cases (because of the rapid onset of action)
3. Postganglionic Sympathetic Neuron Blockers
    - Drug to know: **Reserpine** and Guanethidine (don't need to know)
    - Reserpine depletes nerve terminals of noradrenalin by blocking uptake
    - Guanethidine prevents neurotransmitter release
    - These drugs are rarely used as they produce intolerability toxicity causing depression, sexual dysfunction and orthostatic hypotension)
4. Adrenoceptor Blockers: α1 and β1 receptor antagonists
    - Drugs to know: **Prazosin** (α1 receptor) and **Propanolol** (β1 receptor)
    - α and β blockers treat mild hypertension as a monotherapy
    - polypharmacy of β blockers combined with either diuretics or angiotensin antagonists treats moderate to severe hypertension
    - β-receptors are found on the heart whereas α-receptors are found on blood vessels and both are blocked by antagonistic compounds to treat hypertension
    - α blockers cause mild toxicity which may cause mild tachycardia and hypotension
    - β blockers cause moderate toxicity which may cause asthma, bradycardia, and heart failure

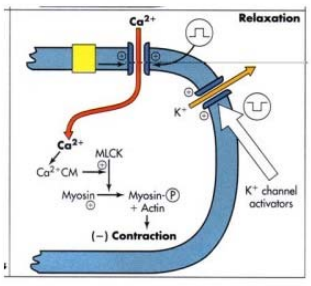
<u>Vasodilators</u>

- These cause the opening of arterioles to reduce the resistance of the flow thereby reducing blood pressure
- Three main classes:
    1. Nitrovasodilators
        - Drug to know: **Nitroprusside** and Hydralazine(don't need to know)
        - These drugs activate soluble Guanylate Cyclase which relaxes vascular smooth muscle (see figure)
        - Part of polypharmacy for severe hypertension
        - Nitroprusside is used during a hypertensive emergencies
        - Toxicity symptoms include excessive hypotension, and tachycardia



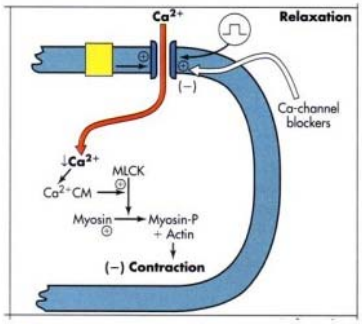
Nitrovasodilators

    2. Potassium channel openers / agonists
        - Drug to know: **Diazoxide** and Minoxidil sulfate (don't need to know)
        - Part of polypharmacy for severe hypertension
        - Diazoxide is used during a hypertensive emergencies
        - These drugs increase the probability the K+



K+ channel agonists

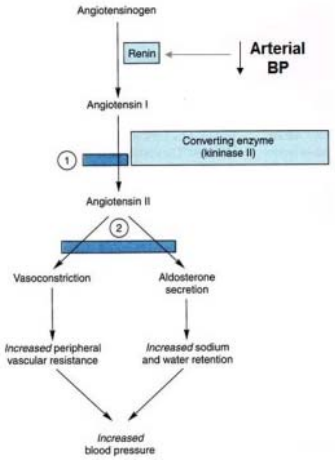
channel will open and it hyperpolarizes the cells and relaxes the smooth muscle cells much like Nitroprusside (see figure)
    - Toxicity symptoms include tachycardia, severe intensity found with use of Monoxidil
3. Calcium channel blockers / antagonists
    - There are 3main types of voltage gated Ca2+ channels
        - L-type (important for blood vessels) ← targeted for hypertension
        - N-type found in the CNS
        - T-type found in Purkinje and SA cells
    - 3 main classes of Ca blockers
        - Vasoselective
            - Dihydropyridines eg: **Nifedipine**
            - This drug is vaso-selective compared to the other drugs which also target the heart as well as the vascular system (broad action). Nifedipine has the same affinity for Ca^{2+} channel as other drugs (they would bind cardiac channels just as well) however its blocking mechanism is better suited for the physiology of the channels in vascular cells.
        - Cardiac and Vascular Acting
            - Phenylalkylamines eg: **Verapamil**
            - Benzothiazines eg: **Diltiazem**



    - Part of polypharmacy for severe hypertension
        - All three compounds work through distinct allosteric sites to reduce the probability of channels opening
    - Monotherapy for mild to moderate hypertension
    - The mechanism of their blocking is complicated but the main point to remember is that it is voltage dependant, they block more strongly at different membrane potentials. It is also frequency dependant. Heart tissue channels open more frequently and therefore will have a different degree of block. (see figure)
    - Most-side effects are due to excessive vasodilation or cardio-depression causing hypotension. Others include edema and headaches.
        - 1/5 of patients who take Nifedipine suffer some form of adverse effects. This percentage is much lower (roughly 1/20) for the other two compounds.

Angiotensin Antagonists

- when arteriole blood pressure drops this is detected by the kidney
- renin is released from the kidney
- this is an enzyme that causes the conversion of angiotensinogen to angiotensin I
- then a converting enzyme produces angiotensin II from angiotensin I
- angiotensin II does two things to increase blood pressure:
    - it causes vasoconstriction
    - it also causes aldosterone secretion which increases sodium and water retention



- to target this system there are two main classes of drugs:
    - ACE inhibitors
        - Drug to know: **Captopril**
        - These drugs inhibit converting enzyme thereby eliminating angiotensin II production
        - Used as a monotherapy to treat mild to moderate hypertension
        - Toxicity symptoms include cough and severe renal damage in fetus, therefore these aren't used in pregnant women
        - ACE inhibitors also prevents the breakdown of Bradykinin by the same converting enzyme it inhibits
            - This causes an accumulation of Bradykinin which causes a compensatory decrease in blood pressure
    - Angiotensin Receptor Inhibitors (AT_1-type)
        - Drug to know: **Losartan**
        - These are used when ACE-inhibitors cannot be used
        - They competitively block the AT_1-receptor
        - Used as a monotherapy to treat mild to moderate hypertension
        - Toxicity symptoms are the same as ACE-inhibitors however milder

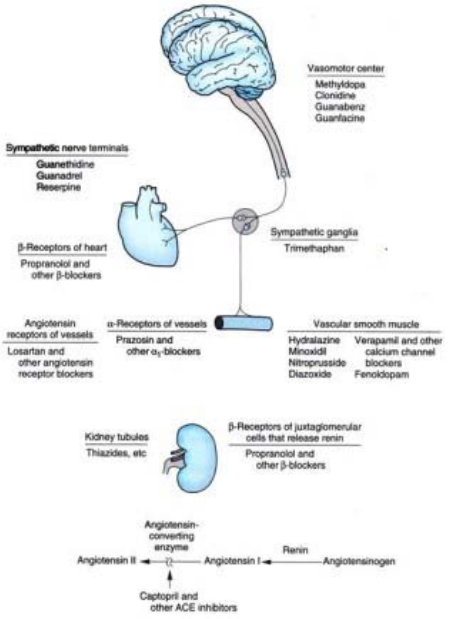
The following table is important to memorize for the exam. Dr Bowie may ask (for example) "what is the effect of plasma volume by diuretics" and we are expected to know whether it increases or decreases. MEMORIZE THIS!

Table 15-1 Physiological Responses to Antihypertensive Drugs

Drug Class	Plasma Volume	CO	Heart Rate	TPR	Plasma Renin Activity	Sympathetic Nervous System Activity
Diuretics	↓	↓	⇆ ↑	↓	↑	⇆ ↑
β-blockers	⇆	↓	↓	↑ ⇆	↓	⇆ ↓
Centrally acting sympatholytics	↑ ⇆	↓	↓	↓	↓ ⇆	↓
Peripherally acting sympatholytics	⇆ ↑	⇆ ↓	⇆ ↓	↓	⇆	↑
Calcium-channel blockers	⇆	⇆	⇆ ↑	↓	↑ ⇆	⇆ ↑
Orally active vasodilators	↑	⇆ ↑	↑	↓	↑	↑
ACE inhibitors	⇆	↑ ⇆	⇆	↓	↑	

↑ Increase; ↓ decrease; ⇆ no change.

The following figures are simply for exam purposes. They summarize the lecture and show what we must know. We should be able to which types and which specific drugs affect which specific organs.



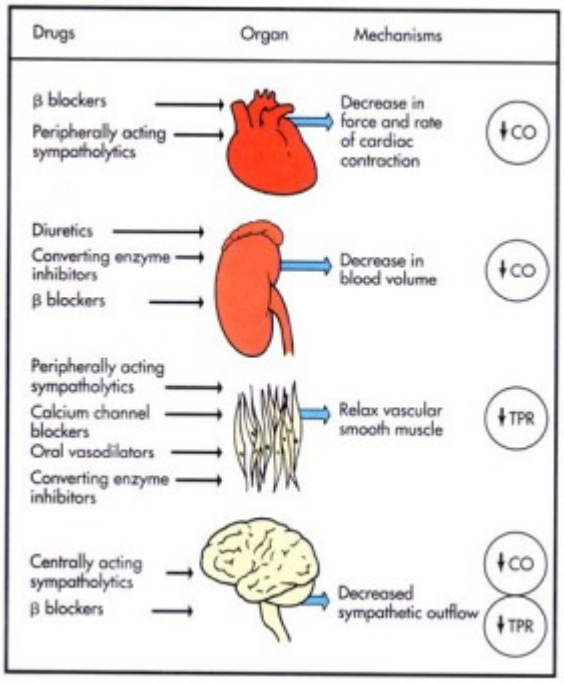
Major Drug Groups:

Diuretics
Thiazides
Loop Diuretics

Sympathoplegics
Centrally Acting Agents
Ganglion Blockers
Postganglionic Sympathetic Neuron Blocker
Adrenoceptor Blockers (α and β)

Vasodilators
Nitrovasodilators
K^+ channel openers/agonists
Ca^{2+} Channel Blockers

Angiotensin Antagonists
ACE inhibitors
Competitive block of AT1-receptor



- Patients with Essential hypertension are initially given monotherapy
  - usually β-blocker, calcium channel blocker or ACE inhibitors
- Therapy is increased to polypharmacy if monotherapy doesn't not decrease the hypertension
  - Drugs are chosen from different groups to maximize the efficacy and minimize toxicity (eg: diuretic + sympathoplegic + vasodilator)
- Emergency of Malignant hypertension is associated with risk of imminent strokes
  - Patients are hospitalized and treated with parenteral vasodilator, β-blocker and a loop diuretic

Tuesday, March 29th, 2007
Dr. Bowie - Lecture #21

Myocardial Ischemia

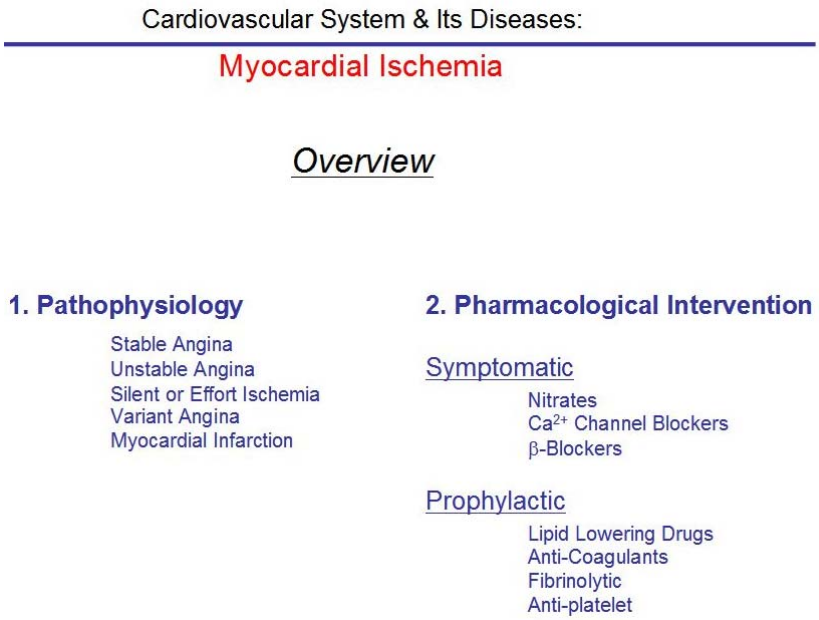
Note: Myocardial Ischemia will be abbreviated to MI throughout the NTC

Key point to remember as we go through these lectures is that we will focus on **treatment** of a condition rather than the condition itself.

As mentioned in previous classes, if one does not take evasive treatment for hypertension, it can lead to Myocardial Ischemia.

A drug like a beta blocker or a calcium channel blocker is useful for hypertension and myocardial ischemia and often heart failure despite the contradictory seeming nature. We must try and understand how certain drugs can work to treat these different conditions.

Side note: Pharmaceutical companies these days often market drugs to patients who use these drugs as opposed to clinicians (ex. advertisements on television).



Pathophysiology: there are a number of different ways MI manifests itself (listed on the slide to the right); usually there are a variety of anginas (chest pain) which sometimes indicates that one is on the path to getting a heart attack. There may however, be a continuum of anginas. Myocardial infarction is the block of the blood vessels that supply the heart (what you commonly call a heart attack). During a heart attack, cardiac muscle cells die when there is no oxygen around. Once this happens, you are on your way to heart failure and arrhythmias. Once you get that dead cardiac tissue, then the extinction of the cardiac action potential does not occur as well and this can lead to ventricular fibrillations and subsequently death.

Two classes of compounds are used to treat the symptoms of MI (1. Symptomatic and 2. Prophylatic). There are a variety of factors that predispose an individual to MI however, and pharmaceutical companies tend to market these in a prophylactic (preventative) manner. Be aware that these compounds have questionable opinions by various clinicians and cardiologists.

The following slide is an important slide to remember, Bowie stressed that he will not ask for particular names but he will mention names of drugs and we will have to know what they are for.

Major Drug Groups

Symptomatic

Nitrates
Ca^{2+} Channel Blockers
β-Blockers

Prophylactic

Lipid Lowering Drugs

1. Statins Inhibit cholesterol synthesis
2. Resins Block cholesterol reabsorption
3. Niacin Decreased VLDL secretion
4. Fibrates Lipoprotein lipase synthesis

Anti-Coagulants

1. Warfarin Vitamin K antagonist
2. Heparin Factor Xa & AT III

Fibrinolytic

1. Streptokinase Plasmin activation
2. Tissue Plasminogen Activators Endogenous

Anti-platelet

1. Aspirin / Ibuporfen TXA_2 inhibition
2. Ticlopidine / Clopidogrel Adenosine-R block

Side notes:

Warfarin - was originally a rat poison (rats die of internal bleeding); beneficial in heart disease because it's an anti coagulant.

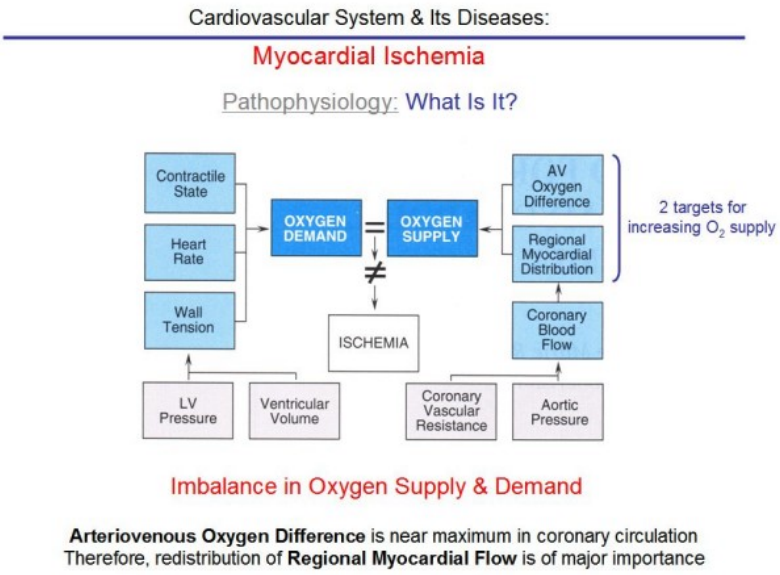
Vioxx scandal: Merck had an anti-arthritic compound that caused heart attacks.

What is MI?

Pathophysiology - Imbalance in Oxygen Supply and Demand. In terms of oxygen demand we know that the contractile state of heart is important, heart rate is important, wall tension (if volume in ventricles increases, then the tension changes which pushes out more blood - requires more energy and oxygen when blood pressure is higher), and volume.

We can change oxygen supply pharmacologically:

- **Arteriovenous oxygen difference** (the difference in O_2 concentrations in arteries and veins) cannot be improved pharmacologically but we can have redistribution of the regional myocardial flow.



MI Symptoms

Angina Pectoris: Chest pain, primary symptom associated with ischaemic heart disease. Caused by transient episodes of MI, pain is due to accumulation of metabolites in muscle tissue (e.g. lactic acid). Doesn't really matter though what the pain is caused by, because that isn't the problem – the main

problem is that your blood vessels are not serving the heart. Affects 6.4 million Americans and manifests in different forms:

Stable Angina (typical-smokers, fatty diet, etc.): atherosclerotic block of coronary artery
Unstable Angina: rupture of atherosclerotic plaque, can be a result of hypertension
Silent/Effort Ischemia: often induced by some kind of stress, e.g. exercise, can be tested for in a clinic, often heart attacks develop during testing and defibrillators are present to prevent deaths (eek!)
Variant Angina: focal/diffuse coronary vasospasm-independent of plugging up of artery, random spasm
Myocardial Infarction: "full blown" heart attack, death of tissue occurs

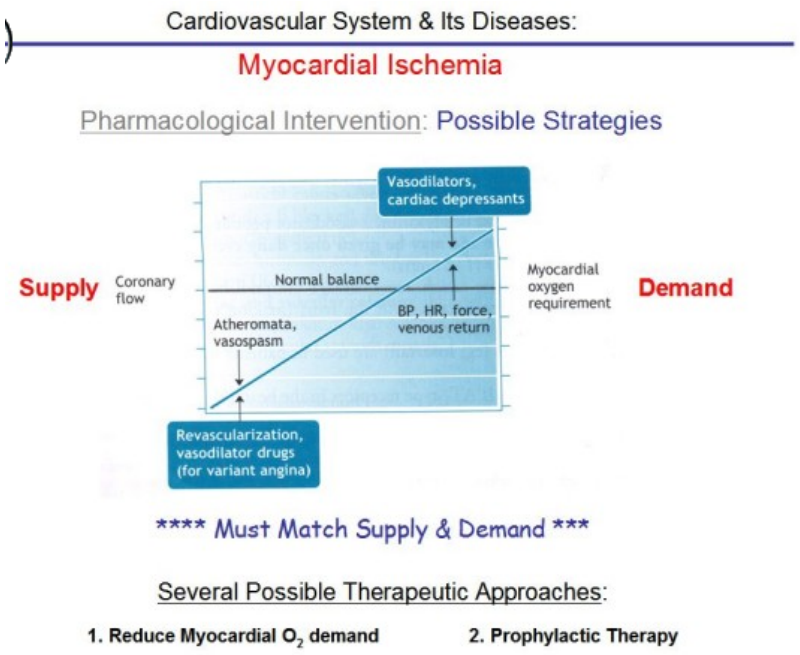
MI Aetiology
Atherosclerosis: Deposition of fatty substances, especially cholesterol or fatty acids in arteries. Risk Factors include hypertension, hyperlipidemia (high triglycerides), obesity, carbon monoxide in smoke and sedentary life style. Avoid these and you could avoid a heart attack for your whole life. Quality of life for many of these patients drops dramatically.
Coronary Artery Spasm: Cause unknown, may occur in patients with or without atherosclerosis. Risk factors include smoking and stress. Very difficult to study this type of heart attack.

MI Arteriosclerosis and Plaques
Blood Vessel Damage (the chances of this increase with hypertension) → Plaque formation due to inflammation→**TWO** different types of plaque (endothelium-smooth muscle interface or ruptured lesion in endothelium). These can lead to narrowing of the blood vessel lumen.

Possible Pharmacological Intervention Strategies

If oxygen requirement increases, we are more likely to develop angina→ must balance this with coronary flow. Ideally this whole thing must be balanced so flow meets demand.

If we get an increased force of heart rate and venous return, this increases oxygen requirement of heart. The drugs that counteract this are vasodilators and cardiac depressants (e.g. beta blockers). Must push this back down. Some drugs cause new blood vessels to form from the existing blood vessels.



Three main compounds for **symptomatic** treatment:
1. Nitrates
2. Calcium channel blockers
3. Beta blockers.

They all reduce blood pressure, venous return and force/rate of heart. They most importantly, reduce oxygen demand and or/improve coronary flow.

Two main classes of **prophylactic** treatment:

1. Lipid lowering drugs
2. Drugs affecting coagulation, fibrinolysis and platelet aggregation

These are targeted towards reducing plaque formation to slow the development of ischemia.

Nitrates

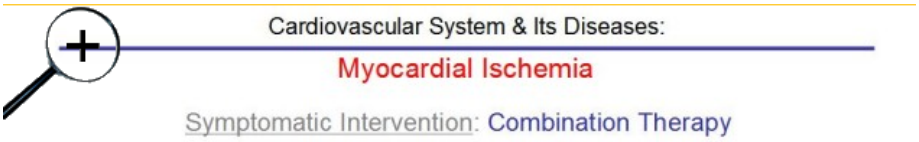
- Most famous: Nitroglycerin (synthesized in 1846), originally used as an explosive. Elevates Nitric Oxide (NO) levels-causes relaxation of blood vessels, reduces blood pressure. Beneficial in terms of oxygen demand on the heart. Isosorbide Nitrate is yet another.
- Indications are Effort and Variant Angina as well as Acute Coronary Syndrome.
- Mechanism is to reduce venous return, cardiac size and diastolic myocardial oxygen consumption.
- Side effects include orthostatic hypotension (ex. if you are sitting down and then all of a sudden stand up, there is a whole reflex in which the sympathetic nervous system tells the heart and blood vessels to rectify the fact that all this blood is rushing to your feet; if you don't have this reflex, you can faint), tachycardia, headache (often disappear).

Calcium Channel Blockers

- Three main compounds: Verapamil, Nifedipine and Diltiazem.
- Indications are Effort and Variant angina, both prophylactic.
- Mechanism is peripheral vasodilation and reduction of cardiac work.
- Toxicity however is orthostatic hypotension once again, AV blockade (action potential blockage because signaling between atria and ventricles blocked - can induce arrhythmias!!) and edema.

Beta Blockers

- Propanolol is the main one
- used mostly in Effort Angina (very important!) and Acute Coronary Syndrome (also very important!) and with no benefit in Variant Angina.
- Mechanism is to reduce oxygen demand on heart by reducing blood pressure and cardiac work.
- Side effects include orthostatic hypotension, tachycardia and headache (often disappear).



Variable	Nitrates Alone	β Blockers or Calcium Blockers Alone	*Combined Nitrate and* β Blocker or Calcium Blocker
Heart rate	*Reflex increase*	**Decrease**	**Decrease** or no effect
Arterial pressure	**Decrease**	**Decrease**	**Decrease**
End-diastolic pressure and fiber tension	**Decrease**	*Increase*	**Decrease**
Contractility	*Reflex increase*	**Decrease**	No effect or **decrease**
Ejection time	Reflex **decrease**	*Increase*	No effect

[1]Undesirable effects (effects that increase myocardial oxygen requirement) are shown in *italics*; beneficial effects are shown in **bold.**

****** Important table ******

Words in bold are the beneficial effects of the drug, italics are the non beneficial effects. However, in combination, negative effect is cancelled out by another drug. We counteract negative aspects of drug with another compound that works in the opposite direction – therefore, we obtain solely the **benefits** of the compound.

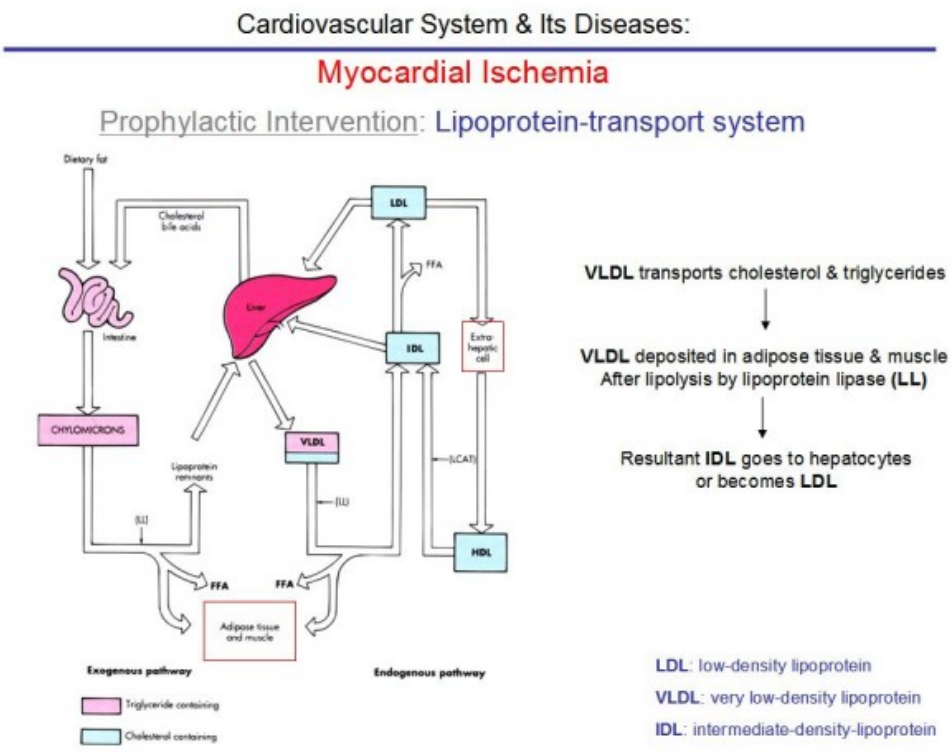
Atherosclerosis: Deposition of fatty substances especially cholesterol or fatty acids in arteries. Prophylactic interventions include dietary changes, cessation of smoking, control of blood pressure and diabetes, exercise and drugs to reduce plasma cholesterol.

- Exercise is VERY IMPORTANT, even in young people. It is a fantastic way to counteract the potential to have a heart attack. It induces collaterals forming in blood vessels outside AND INSIDE the heart. Sometimes, people don't want to change their lifestyle and depend solely on the drug to control plasma cholesterol levels however this is not the most positive way to prevent MI.

Overview of Lipid Lowering Drugs

Therapeutic overview - GOAL: prevent MI and other atherosclerotic disorders.

How do we affect cholesterol levels? Our body makes cholesterol - it is an essential part of normal functioning. Our liver can make up to one gram of cholesterol but depending on how much intake we have, it can vary. There's a balance that's trying to be met by the liver, it's a dynamic process that's balanced between dietary intake and de novo synthesis in the liver. Some cholesterol is excreted by bile salts, some is reabsorbed and ends up in the blood stream. There's a critical rate limiting step in the synthesis of cholesterol: **HMG-CoA reductase**. Critical to synthesize cholesterol, this enzyme comes out of TCA cycle to do so. Knowing that one can target this enzyme, drug companies discovered that one can reduce de novo synthesis of cholesterol.



- When biochemists started to study the metabolism/distribution of lipids throughout the body, some ends up as LDL - not beneficial. Lipoprotein lipase is an enzyme whose release into the blood will result in the take up of LDL by the liver which is beneficial. Increase lipoprotein lipase, we lower amount of cholesterol/fats in blood stream which is good (prevents formation of a plaque).

We should know the key areas where pharmaceutical companies intend to target:

Cardiovascular System & Its Diseases:

Myocardial Ischemia

Prophylactic Intervention: Strategy For Lipid Lowering Drugs

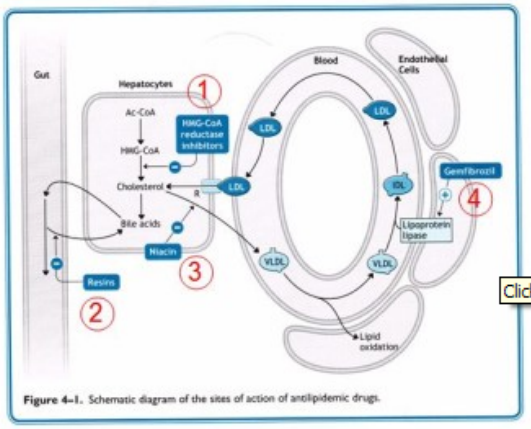


Figure 4–1. Schematic diagram of the sites of action of antilipidemic drugs.

Click on Picture to view Full screen

1. Inhibition of Cholesterol Synthesis
(HMG-CoA Reductase Inhibitors, e.g. Statins)

2. Prevention of Cholesterol Reabsorption
(e.g. Resins)

3. Reduction of VLDL Secretion
(e.g. Niacin)

4. Increased Synthesis of Lipoprotein Lipase
(e.g. Fibrates)

This is a key slide in this lecture; know these four pharmacological target sites to lower cholesterol.

1. Inhibition of Cholesterol Synthesis: HMG-CoA Reductase by Statins
2. Prevention of Cholesterol Reabsorption: bypassing the pathway of reabsorption by resins can result in anal leakage (very uncomfortable) - not the best compounds to be taken!
3. Reduction of VLDL Secretion e.g. Niacin
4. Increased Synthesis of Lipoprotein Lipase by Fibrates

Inhibition of Cholesterol Synthesis

- Done by Statins (e.g. **lovastatin**, atorvastatin)
- works by inhibiting HMG-CoA reductase that blocks the de novo synthesis of cholesterol. Must be coupled with restriction on diet.
- Unfortunately may damage skeletal muscle and liver - people have died. Also contraindicated in pregnancy because interferes with myelination of infants.

Preventing Cholesterol Reabsorption

- Resins e.g. **cholestyramine**, colestipol
- non-absorbable macromolecules that bind cholesterol, preventing reabsorption from gut.
- Unfortunately has an unpleasant gritty taste, results in GI tract discomfort (anal leakage) and interferes with vitamin/drug absorption.

Reduction of VLDL Secretion

- Niacin (nicotinic acid, vitamin B3)
- mechanism of action not well understood but decrease secretion of VLDL particles from liver (this compound is often given when there is some type of intolerance to statins and fibrates).

- Side effects include flush with itching (but patients tend to like this because they feel as if it is working!), on rare occasions glucose intolerance.

Increased synthesis of lipoprotein lipase

- Fibrates (**gemfibrozil**, fenofibrate)
- activates peroxisome proliferation-activated receptor alpha which increases lipoprotein lipase synthesis.
- Side effects can include nausea, skin rash and occasional increased risk of gallstones.

not expected to know specific side effects

PLAQUES

Three main ways to affect plaque formation:
1. Anticoagulation by Heparin or Coumarins - make sure plaque doesn't grow
2. Fibrinolysis by Streptokinase - eats away at plaque
3. Platelet Aggregation Inhibition by Aspirin

Interference of plaque formation - inhibit platelet function, inhibit blood coagulation, stimulate lysis of pre-formed thrombus.

Inhibition of blood coagulation

- **Warfarin** (rat poison) and **Heparin** are the main drugs
- inhibit some enzymes that coagulate -block reactivation of Vitamin K epoxide and binds coagulation factors II, VII, IX and X (Warfarin) and bind coagulation factor Xa and antithrombin III (Heparin) – **main point**: as an effect, you don't get as efficient coagulation.
- Indications are for prevention and treatment of venous clotting especially in deep vein thrombosis.
- Side effects are that they are teratogenic and bleeding (increased risk of stroke) can occur with both.

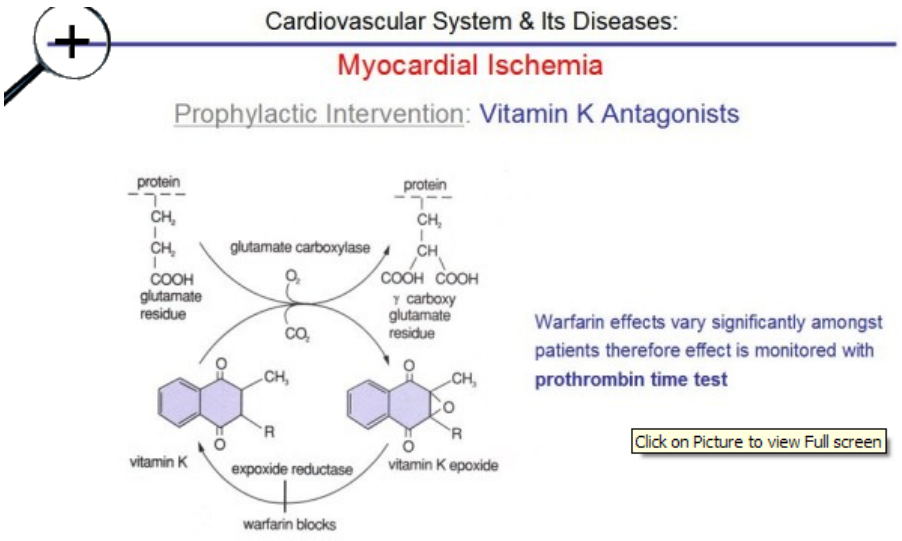


FIGURE 23-8 The role of vitamin K in the conversion of glutamate residues in certain plasma proteins to γ-carboxyglutamate *(GLA)* residues in the liver. Warfarin and other coumarin derivatives block the reduction of vitamin K epoxide formed in this reaction to its active form.

Similar structural elements with Vitamin K and its antagonists. Looking at Warfarin:

- Know this slide, but not in great detail. Just know enzymes involved and Warfarin's general effect

Heparin

Know that it's available in high molecular weight and low molecular weight form (HMW and LMW respectively). HMW Heparin binds coagulation factor Xa and antithrombin III-anticlotting process

must be monitored in a hospital, like Warfarin. LMW Heparin inhibit factor Xa but less effect of antithrombin III; in this case, there is a predictable response and therefore no monitoring is needed.

Fibrinolytic Drugs

- **Streptokinase -** activates endogenous plasminogen to **plasmin,** which is an enzyme that breaks down fibrin, dissolving blood clots. It is made from bacteria and activates the enzyme that produces plasmin - cost effective. **Tissue Plasminogen Activators** (tPA) used in brain surgery to prevent clotting, incredibly expensive. Activates plasminogen bound to fibrin.
- Indications are for pulmonary embolism and MI.
- Side effects include allergic response (streptokinase) and bleeding (both)

Anti-platelet drugs

- When platelets are activated by collagen wall, release of thromboxane A2 and secretion of ADP occur. Thromboxane A2 is a potent aggregating agent and vasoconstrictor. Thromboxane A2 and ADP stimulates appearance of fibrinogen binding sites on platelet membrane.
- There are two main types of drug: Asprin (binds irreversibly) and Ibuprofen (competitive). They inhibit platelet cyclooxygenase, blocking the synthesis of thromboxane A2.
- Indications are for transient ischemic attacks and MI.
- Side effects include bleeding and GI ulceration (aspirin).

Adenosine receptor blockers

- Drugs are Ticlopidine and Clopidogrel. Alternative to Aspirin (allergic response avoided) and inhibits platelet response to secret ADP at adenosine receptors.
- Used with transient ischemic attacks and MI.
- Side effects include bleeding and skin rashes.

Summary – commit to memory!!!

Major Drug Groups

Symptomatic

Nitrates
Ca^{2+} Channel Blockers
β-Blockers

Prophylactic

Lipid Lowering Drugs
1. Statins Inhibit cholesterol synthesis
2. Resins Block cholesterol reabsorption
3. Niacin Decreased VLDL secretion
4. Fibrates Lipoprotein lipase synthesis

Anti-Coagulants
1. Warfarin Vitamin K antagonist
2. Heparin Factor Xa & AT III

Fibrinolytic
1. Streptokinase Plasmin activation
2. Tissue Plasminogen Activators Endogenous

Anti-platelet
1. Aspirin / Ibuporfen TXA_2 inhibition
2. Ticlopidine / Clopidogrel Adenosine-R block