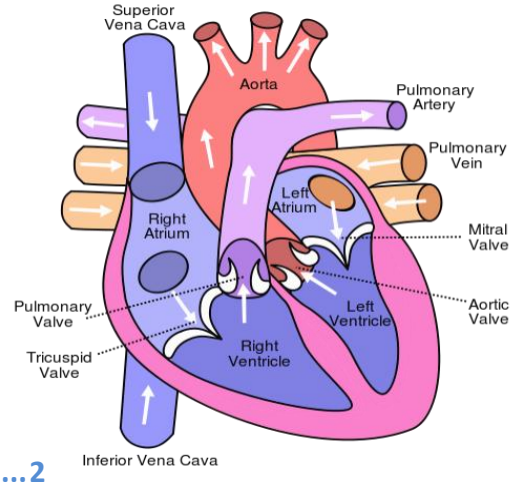
HEART/Blood Pressure/Blood Handout



Overview of Heart/BP handout

Diagnosis:	LEFT HEART FAILURE (w/ reduced EF)	ANGINA (esp. stable angina due to CAD)	HYPERTENSION	DYSRHYTHMIAs *(esp. Atrial Fib)*
Metaphor	"weak pump (heart) causes fluid backup (blood volume) in your plumbing"	**Steamboat:** "narrow pipe line (coronary vessel) not enough steam for engine (heart) to go fast" **Car:** Kinked fuel line means no gas for your engine.	"Water pressure will go down if the pipes are too wide, the pump is too slow or there's not enough water in the pipes"	"A broken mixer makes lumpy oatmeal"
Aims of Drug Therapy	**Reduce Stress on the heart by:** **Reducing Preload** Diuretics Vein dilators ARNIs ACEIs/ARBs **Reduce Afterload** Artery dilators ACEIs/ARBs **Increase strength of contraction without increasing rate** digoxin **Decrease rate without decreasing strength of contraction** ivabradine*(Corlanor®)* **Restore proper cell growth** *Weird* non-specific poorly named "beta-blockers" carvedilol	**Widen (dilate) the coronary vessels** Nitrates Ca^{++} channel blockers (CCBs) **Put upper limit on oxygen demand** Beta-blockers **Prevent clots in coronary vessels** anticoagulants ***…and reduce work of the heart:*** **Reduce Preload&** **Reduce Afterload**	**Dilate blood vessels** Alpha-blockers Indirect symp. antagonists ACE Inhibitors (or ARBs) CCBs Other direct vasodilators **Reduce blood volume** Diuretics ACE inhibitors (or ARBs) Beta-1 blockers (via kidneys) **Slow heart rate** Beta-blockers Indirect symp. antagonists	**For dysrrhythmias in general, you normalize rhythm by fixing** **1. sodium (Na^{+}) channels** Na^{+} channel blockers **2. SA node issues** Beta-blockers **3. potassium (K^{+}) issues** Class III antidysrhythmics **4. calcium (Ca^{++}) issues** Ca^{++} channel blockers ***In atrial fibrillation** you **slow heart rate** and use **strong anticoagulants** to prevent a clot from going to the lungs (pulmonary embolism) or the brain (thrombotic stroke)*

Terminology note: The abbreviation CHF usually means either Chronic HF or Congestive HF (where the lungs are congested with fluid). Fortunately in this handout, those are the same thing since I chose Chronic Congestive HF as the type for you to study! :-)

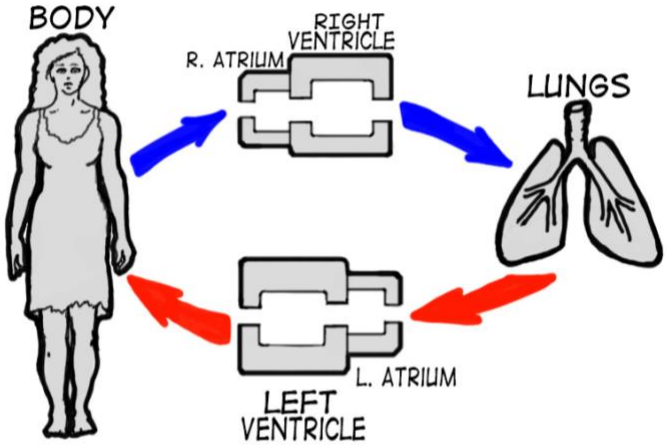
REVIEW OF THE BASICS:

See also my videos *"Heart Review" & "Basics of Heart Failure"*
The heart is a **PUMP**. (Well, the heart is really a box containing **two** side-by-side pumps.) It pumps blood around the body through a system of "pipes" called blood vessels. This system has a limited volume which can get bigger (through vasodilation of the "pipes", causing a drop in pressure) or smaller (through vasoconstriction, causing an increase in pressure).

The heart **BEATS**. An electric conduction system in the heart maintains a regular rate and rhythm. This rate can be increased (via the sympathetic system) or decreased (via the vagus nerve/parasympathetic system)

Myocardial (heart muscle) cells need **OXYGEN** and **GLUCOSE** to stay alive and use **CALCIUM** to contract**.**

REVIEW OF ANATOMY:
The body uses oxygen from blood. The deoxygenated blood (shown in blue) travels through veins back to the right side of the heart where it is pumped to the lungs to become re-oxygenated.



This oxygen-rich blood (in red) is then moved to the powerhouse of the circulatory system, the **LEFT ventricle** of the heart. During **diastole**, the heart relaxes and blood rushes into the **left ventricle**. The valve between the left ventricle and the **aorta** is closed at this time. The pressure of **arterial** blood during diastole is called the **diastolic blood pressure**.

Once the ventricle is full, the valve between the atrium and ventricle closes and the left ventricle contracts, pushing blood out into the aorta and from there out to the rest of the body. This phase is called **systole**, and the **arterial** pressure during this phase is called the **systolic pressure**. Each contraction pushes the column of blood into the circulation. The left ventricle has to pump hard enough to get blood through the ENTIRE body, all the capillaries in the fingers, toes and head, regardless of whether the person is standing up or lying down. It must do this 70-80 times a minute for (hopefully) 80 years or more without *ever* stopping even once.

By convention, we measure the heart's work as **Cardiac Output** (CO): amount of blood the heart pumps *per minute*.

Cardiac Output= Stroke Volume x Heart Rate

Stroke Volume = Amount of blood the left ventricle squeezes out with each heart beat.

Clinically speaking, we also measure something called "**ejection fraction (**aka **EF)**", which measures the **percentage of the *normal* total volume** of the ventricle that is actually pumped out with each beat.

A normal left ventricular ejection fraction (LVEF) might be 55-70%.
You might get heart failure symptoms if your LVEF falls below 50%

The **Ejection Fraction in Heart Failure determines the treatment guidelines** for that patient. We will focus on patients with **left-sided chronic heart failure due to scarring after MI** .

HEART FAILURE

Heart Failure (HF) occurs when the heart cannot maintain the cardiac output required to meet the metabolic needs of the body. In plain terms, heart failure is when the heart can't pump blood fast enough to get the body the blood it needs to thrive.

In the US, **common causes of heart failure are Myocardial Infarction** (heart attack) or chronic **hypertension** (long-term high blood pressure). Recent studies prove reduction of BP below 130/80 significantly reduces lifetime risk of HF.

Stroke Volume depends on:

Preload: How much blood rushes into the atria during diastole *(**volume** and resistance in **veins**)*

*Note: most blood volume resides in your **veins**; only 15% is in your arteries. This is why any drug that increases blood volume increases venous pressure and therefore preload.*

Afterload: The pressure the ventricle has to push against *(pressure in **arteries**)*

Remember, blood pressure measurements are only in arteries: i.e. BP of 120/80 is 120 & 80 in the arteries at different times when the heart is contracted and when it is relaxed. You will never measure blood pressure in veins with a blood pressure cuff!

Contractility: How strong the cardiac muscle can squeeze

CONSEQUENCES OF LEFT-SIDED HEART FAILURE with reduced EF (& decreased CO):

1. **Increased PRELOAD:** Because the L ventricle is weak, pressure builds upstream. Since even stretchy **VEINS** can only stretch so much, that **FLUID** in the bloodstream has to go *somewhere*, so it oozes out between the cells of the blood vessel walls and into the tissues. This leads to:

2. **Fluid backup and edema**: When fluid pools in the lungs it's called "**pulmonary edema**" and causes **shortness of breath** (S.O.B.) and "**rales**" (bubbly crackly sounds you can hear with a stethoscope).

3. **Poor Perfusion:** The reduced power of the heart means that the rest of the body is not properly **perfused,** that is, it is not getting enough oxygenated blood. When the **kidney** is not well-perfused, it and baroreceptors "think" the blood pressure is too low and sends signals to the brain that the body is in shock. This causes:

4. **Activation of the sympathetic nervous system**:

a. **Vasoconstriction of NON-ESSENTIAL ARTERIES** and arterioles through NEpi binding alpha-1 receptors. This **INCREASES AFTERLOAD**, because now it is even harder for the heart to pump the blood against all these tightly squeezed blood vessels.

(Note: Veins also constrict with alpha-1 stimulation, but the arteries are more important here. Regardless, venous constriction would increase PRELOAD. Right?)

b. **Increased heart rate.** The activated sympathetics stimulate beta-1 receptors on the heart, making the contractions stronger, which would help, sure, but they also make the heart beat **faster**. A faster rate lowers the EF; that in turn lowers SV and CO and worsens the cycle.

c. **Beta-1** receptors on the kidney stimulate the release of **renin**, which activates R-A-A-S

5. **R-A-A-S**: **Renin-angiotensin-aldosterone**: The renin enzyme, along with Angiotensin Converting Enzyme (ACE) activates angiotensin. **Angiotensin** is a **potent vasoconstrictor** with its own **angiotensin (AT1) receptors** on arteries & veins. AT1 receptors are also present on adrenal cortex and pituitary, so:

6. Angiotensin also stimulates the release of **aldosterone** and Anti-Diuretic Hormone (**ADH**): these hormones cause the **kidney retain sodium and water**. This worsens **PRELOAD** by increasing blood **VOLUME**. (You can even *see* the increased blood volume in your patient's **distended jugular veins**!)

7**. Cardiomegaly (enlarged heart)**: **Overstretching of cardiac muscle.** The heart can't pump out all the blood with each beat because it is overfilled, so it is **overstretched,** leading to **dilated cardiomegaly.** The cardiac muscle cells are stretched and can't contract efficiently because of poor actin-myosin overlap.

LEFT vs RIGHT-sided Heart Failure

Look back at that image on page 2:
Left-sided: If the left heart is weak, you get the symptoms listed above. The fluid back-up is primarily in the lungs. If your lungs are filled with fluid, you can't breathe and you die. You can actually hear how full of fluid a patient's lungs are; the sound of air bubbling through the fluid is called **rales** or **crackles**. The main symptom patients complain of is "**shortness of breath**" or SOB. *(I want to concentrate on left-sided failure in this class because I think it is easiest to think about saving a person by getting fluid out of their lungs)*

Right-sided: If the right heart is the problem, then the fluid backs up in your body and oozes out of the blood vessels into the surrounding tissue, causing **edema**. This is swelling up of tissues is sometimes so severe that you can poke a patient in their swollen leg and the place you poked will stay indented after you remove your finger, so-called **pitting edema**. You can also just see the fluid back up into the superior vena cava and jugular vein. This is called jugular vein distention. Right HF can also be caused by abnormal vasoconstriction of vessels in the lungs, so called "pulmonary hypertension".

PLEASE NOTE that if a patient has really severe left-sided heart failure the fluid will back up in the lungs, in the right heart, back to the vena cava and the body. The patient will therefore show signs and symptoms of right-sided failure even if the original problem was just in the left ventricle.

Causes of Heart Failure: **Anything that makes the heart less efficient.**

1. **Scarring after surviving a myocardial infarction (also known as MI or "heart attack"): Dead tissue in the heart wall forms a scar and the heart doesn't pump efficiently.**
2. A second type of cardiomegaly called "hypertrophic cardiomyopathy" occurs when the muscle of the heart becomes too thick and stiff.
3. Other cardiomyopathies can be genetic, metabolic, autoimmune, etc.
4. Bad heart valves
5. Compression of the heart
6. Other causes of reduced heart efficiency: chronic hypertension, fluid overload, or dysrhythmias

Severity of HF: This table is presented for your own use only

Heart Failure (HF) Classification Schemes	
New York Heart Association - NYHA (symptoms based)	ACC/AHA (disease based)
I: no symptoms	A: High risk for HF but no structural damage
	B: Damage but no symptoms
II: s.o.b. with 2 flights of stairs	C: Damage with symptoms
III: s.o.b. ½ flight of stairs, comfortable only at rest	
IV: s.o.b. all the time, confined to bed or chair all the time	D: Advanced damage; need transplant or device

In general here we will be talking specifically about ***chronic*** left-sided HFrEF, but I will also briefly mention ***acute*** decompensated left-sided HF a bit later, which is an emergency. In acute HF the lungs fill up with fluid very quickly, the patient can't breathe, and will die unless you do something fast!

Treatment of Heart Failure

(Again, for this class we are focused on left-sided chronic heart failure due to scarring after MI)
For this type of HF assume the **cause of death is pulmonary edema**.

First: reduce sodium intake. The body retains water to keep the salt concentration in the body constant. It seems counterintuitive, but the amount of water you keep in your body is far more dependent on the amount of salt you eat than the water you drink.

Second step: use drugs to:
reduce afterload (reduce blood pressure - arterial),
reduce preload (reduce volume of body fluid),
strengthen heartbeat (increase EF/strength of contraction)

Drugs Used (2016 AHA/ACC/Guidelines): Heart Failure with Reduced Ejection Fraction (HFrEF)

Combinations of these drug classes are proven to decrease hospitalizations and death
Which combinations used depends on the demographics, EF and severity of HF

1. RAAS Drugs that affect the RAAS: decrease afterload and preload. (Ch. 26)
A. **ACEI**s: Angiotensin Converting Enzyme Inhibitors - Indirect acting
Ex.: **captopril** *(Capoten)*, **enalopril** *(Vasotec)*, lisinopril *(Zestril)*, benazepril *(Lotensin)*, fosinopril, moexipril, perindopril, Ramipril *(Altace)*, etc…

B. **ARB**s: Angiotensin Receptor Blockers - Direct acting
Many use ARBs if patient can't tolerate ACE Inhibitors
Ex. **losartan** *(Cozaar)*, **valsartan** *(Diovan)*, eprosartan, irbesartan, azilsartan, candesartan, etc…
C. **ARNI**s
Combination **ARB** + **neprilysin inhibitor** (like **sacubitril**)
Ex. **valsartan/sacubitril** *(Entresto)*

2. Diuretics: decrease preload. (Ch. 25)
Diuretics are drugs that increase urination to excrete sodium (salt) and water from the body. This reduces the blood volume and therefore the preload.
A. **Loop diuretics**: **furosemide** *(Lasix):* Great for removing severe fluid overload
B. **Aldosterone antagonists:** Often used for HF with preserved kidney function
i.e.. **eplerenone, spironolactone.**
C. More diuretics later.

3. *Weird* Evidence-Based "beta-blockers": mechanism not clear
Ex. carvedilol *(Coreg)*

4. Vasodilators: Hydral-nitrates: for **African-Americans** with stage III-IV NYHA HF

5. Ibravadine: see below

RAAS DRUGS:

Inhibition of **any step** in this pathways should theoretically help HF.
Beware: ALL drugs that inhibit RAAS system:
are **pregnancy category D &**
cause hyperkalemia

A direct-acting renin inhibitor (DRI) drug called aliskerin is available for BP reduction but doesn't work for HFrEF

ACEIs Angiotensin Converting Enzyme Inhibitors are *indirect* drugs that inhibit the ACE enzyme that activates **angiotensin II**. Without angiotensin, arterioles dilate, reducing afterload. ACE inhibitors also reduce water retention (through reduced aldosterone and ADH) and thus reduce preload.

Side effects to watch out for:
1st dose effect (1st dose can cause huge drop in BPand/or orthostatic hypotension
(What other drug class do we know with a 1st dose effect?)
dry cough: ACE also happens to break down a molecule called bradykinin. 1/3 patients develop **dry cough** related to bradykinin build-up in lungs
angioedema: the bradykinin build-up can also cause angioedema (giant hives)
Category D. hyperkalemia

ARBs (**Angiotensin Receptor Blockers) are *direct* acting.**
Ex. **losartan** (*Cozaar*)
No effect on bradykinin so **no dry cough**
Category D, hyperkalemia
used if patient intolerant to ACEI (ACEI has been in more clinical trials so it is tried first)

ARNIs (Angiotensin Receptor Blockers + Neprilysin Inhibitors) are combination pills:
sacubitril/valsartan *(Entresto)*

Neprilysin Inhibitors
neprilysin is an enzyme that breaks down natriuretic peptides, bradykinin, & other peptides.
(note: this is an enzyme that does not end with "-ase")
natriuretic peptides are naturally released by the body to cause urination when the heart is stretched
side effects: **angioedema:** swelling under the skin; like a big body- wide hive
happens because the neprilysin enzyme also breaks down bradykinin,
so inhibiting it causes a big buildup of bradykinin, leading to an allergic-looking reaction
Category D, hyperkalemia

Aldosterone Blockers are **potassium-sparing diuretics** are used for HFrEF & are the direct cause of hyperkalemia *(see diuretics section for the mechanism of this effect)*

"Weird beta-blockers"

Ex. **carvedilol** *(Coreg)*, metoprolol *(Lopressor)* & bisoprolol (both β-1 blockers)
Studies have proven that small, chronic doses of **only these three weird "beta-blocker" drugs** reduce progression of HF
They do decrease contractility of the heart, but they also reduce cardiac muscle cell death, reduce dysrhythmias and **increase ejection fraction.**
Three proven useful: **carvedilol**: not actually selective: it blocks α-1, β-1 & β-2
(Hint: Only I call them "weird"… but in journals they call them beta-blockers when in fact they block other stuff too and I think that's weird.)

Other Vasodilators

Dilate arteries? Reduce AFTERLOAD
Dilate veins? Reduce PRELOAD

ARTERIODILATORS: dilate only arteries/arterioles - **decrease afterload**

Ex. Hydralazine: This drug is also prescribed in combo with **isosorbide dinitrate** in (*BiDil)* which has been shown to be specifically effective in "self-identified African-American patients" with HF, possibly due to genetic differences in nitric oxide physiology.

Adverse effect of **hydralazine**: **drug-induced lupus**

A side note about *BiDil:* The hydralazine/isosorbide combination was used in a VA study called V-HeFT and shown to be useful in self-identified blacks and *not* useful in patients who identified themselves as White, Hispanic, Asian, Native, etc. After this surprising result, a trial called the A-HeFT trial specifically looked at black patients to be sure it was truly correct. And it was! (See N Engl J Med 2004; 351:2049) However, be careful about saying something like "this drug is for you because you're black" to a patient. A patient might misunderstand and think you are just being a racist jerk!

VENODILATORS: dilate only veins - **decrease <u>preload</u>**

Nitroglycerin: Nitrates dilate veins but have the added bonus of dilating *coronary* arteries, which increases blood flow (and therefore oxygen) to the heart muscle itself….
(a reason why nitroglycerin is also great for angina!)

DILATE ARTERIES AND VEINS (⇓**Pre & Afterload***):*

alpha-1 blockers: prazosin, terazosin - **1st dose effect**

RAAS drugs:

ACE Inhibitors as above by blocking angiotensin activation - **1st dose effect**

angiotensin receptor blockers (ARBs): block angiotensin receptors on blood vessel walls

ARNIs: contain the ARB losartan.

Lowering Rate OR Increasing Strength of Contraction but NOT both

Ivabradine *(Corlanor®):* reduces the heart rate without reducing strength of contraction
allows for higher EF
Approved 2015 to try after patient has used maximum amount of the weird beta-blockers;
Mechanism of action: works through "the funny channel" <- *not a joke*
reduces 2 year mortality from HF by 18%

Inotropes: Cardiac Glycosides: (Ch. 22): proven to ⇑quality of life and ⇓ hospitalizations

Digoxin, the approved cardiac glycoside drug in the US, second-line drug but used often
Its physiologic overall effect is to **increase force of contraction & control rhythm**
(indications: heart failure and atrial fibrillation).
Digoxin does not extend length of life, but **improves quality of life**

A dangerous group: -rinones: a type of Phosphodiesterase-3 inhibitors:
used only short-term when nothing else is working
mil**rinone** *(Primacor)*: inotrope, incompatible with IV furosemide *(Lasix)*
am**rinone** aka inamrinone *(Inocor)*: inotrope and vasodilator, also IV
increases mortality in acute HF

Acute Decompensated HF:

A brief note about drugs for **acute,** life-threatening, *OMG seconds count*-type **heart failure:**

1. *Fastest-acting* diuretic: **Loop** diuretics like **furosemide** *(Lasix); can cause hypokalemia*
   Furosemide is called a high ceiling diuretic because you can get a huge amout of fluid off of your patient in a short amount of time. So fast, in fact, that you usually have to put in a foley catheter and keep the patient in bed so they don't pass out from the fluid loss!
2. The opioid **morphine** is used in *acute* severe HF; it decreases preload via venous dilation and also helps make the patient a little euphoric and slightly less terrified.
3. **Oxygen** (oxygen is good)
4. Inotropes you wouldn't normally use but might use in a **last ditch** effort to save someone:
   Beta-1 Agonists: Remember dobutamine?

Speaking of inotropes, let's go back to the bane of all nursing students, digoxin:

Digoxin

Indications: **symptoms of HF**
a **dysrhythmia** called **atrial fibrillation** *(see later in handout)*

Therapeutic effects:

For heart failure:

1) **strengthens the force of contractions** (positive *inotropic* effect) but doesn't speed up heart.

2) **slows the heart** via the vagus nerve (via what neurotransmitter ? what receptor?)
NOTE: This is due to cranial nerve X stimulation because digoxin crosses the BBB

For atrial fibrillation

3) **slows conduction**: particularly between the SA and AV node

Digoxin: Pharmacokinetics

Most all is absorbed after taken PO

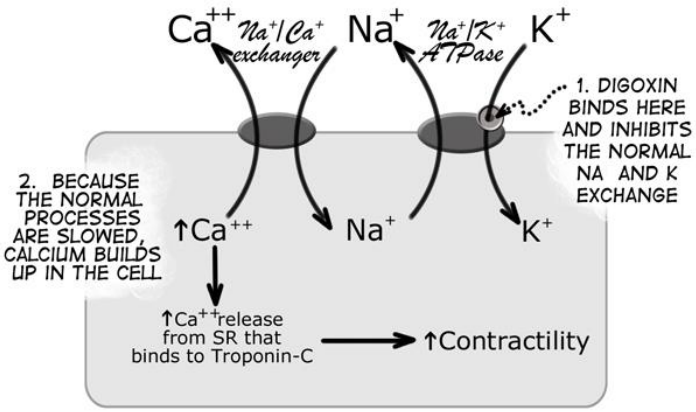
Not metabolized much: 75% is excreted by kidneys as is (must dose adjust for kidney patients)

Figuring out the dose is a pain: Have to account for kidney function, lean mass (Doesn't distribute much to fat and HF patients often edematous; when calculating dose use ideal weight, not actual weight), age and other medications

Half-life is long (almost 2 days) which means: it takes a long time to get up to a therapeutic dose *and* a long time to get it out of the system.

"**Digitalization**": process of giving high IV loading doses to achieve a therapeutic blood level fast

Therapeutic range 0.5-2.0 ng/L



Digoxin has a **very low Therapeutic Index** but is still used in many hospitals because digoxin significantly improves the quality of life for CHF patients.

(Various hospitals and doctors have *very strong* opinions about whether to use or not use digoxin.)

Digoxin: Pharmacodynamics:

Digoxin **interacts with many drugs**, and its **effectiveness is strongly related to potassium levels.**

1. **Binds to the same spot as potassium (K^+)** and inhibits the Na^+/K^+ pump causing increased Na^+ levels, which exchange with Ca^{++} levels via another pump on the cell.

2. Mechanical Effect: The **increase in intracellular Ca^{++}** increases actin and myosin binding to cause **stronger contraction** without more use of ATP and oxygen by the heart cells.

3. Autonomic Effects: via central action on cranial nerve X in the brain, digoxin stimulates the vagus nerve (to **slow the heart**). This affects the atria more than the ventricles. It also sensitizes the baroreceptors.

So, why bother learning the mechanism of digoxin? It explains a weird phenomenon where a **patient can be toxic on digoxin *even when blood levels of digoxin measure normal!***

Effect of High or Low POTASSIUM levels on digoxin levels:

Low Potassium (hypokalemia): Since digoxin competes with potassium for binding to the Na^+/K^+ ATPase, when potassium levels are *low*, digoxin can have *a stronger* effect and so **digoxin is more toxic.**

So, if you are giving a patient digoxin for HF and simultaneously giving them diuretics (*which you almost always are)*… you have to watch their potassium levels really carefully or the patients gets toxic on digoxin

High potassium (hyperkalemia): In contrast, if potassium levels get too high, the **digoxin won't work**, and the HF gets worse, and the patient dies.

High calcium or low magnesium levels in the blood can also cause digoxin toxicity, but let's not go there for now...

Common Digoxin Side Effects:

Digoxin helps increase the efficiency of contraction of cardiac muscle. But alas it also works on the smooth muscle in your intestines.

In the GI tract there is **nausea**, **diarrhea**, vomiting.

In the CNS you get dizziness, delirium, **visual disturbances** (**yellow lights, halos**).

In the heart (Common: 5-20% of patients get side effects!):

Bradycardia (slow heart rate)

Always check pulse/heart rate just prior to giving dose

So if the heart rate is low (<60bpm) don't give that next dose of digoxin!

You can also see dysrhythmias, or even cardiac arrest with digoxin toxicity

You can use **phenytoin** *(Dilantin®)* for some digoxin-related dysrhythmias

(Remember the other weird things about phenytoin?)

If **digoxin toxicity** is suspected, a test for level of digoxin (**and potassium**!) in blood an EKG can confirm the diagnosis *(See dysrhythmia section later!)*

In SEVERELY TOXIC situations you can also try:

digoxin-binding antibody (DIGIBIND):

Digibind binds up the digoxin so it can't bind that Na/K pump!
(For the same reason that albumin reduces free drug levels as we discussed in the first handout…)

a temporary **pacemaker**: the digoxin can mess up the heart rate so badly you might have to put in a temporary pacemaker until the digoxin clears the system.

Digoxin DRUG INTERACTIONS: ***many many many drug interactions!!*****!**

1. **Anything that alters potassium levels: Most diuretics**, amphotericinB, quinidine, amiodarone, black licorice
2. Anything that also decreases heart function that could precipitate acute heart failure: Normal beta-blockers, calcium channel blockers, cholinergics
3. thyroid disorders (patients with untreated hyperthyroidism need higher dose).
4. Other anti-dysrhythmic drugs (remember: all anti-dysrhythmia drugs can cause dysrhythmia!)
4. Things that increase levels of digoxin: quinidine (a antidysrhythmia drug), antibiotics (such as erythromycin and tetracycline).
5. Things that **decrease levels of digoxin:**
   By decreasing absorption: **antacids**, kaolinpectin, cholestyramine,
   Herbs and supplements: i.e. **St. John's Wort** (reduces digoxin levels 25%!)

ANGINA "The Steam Engine and its Steam Pipe Line"

Angina pectoris: Chest pain due to **ischemia** (insufficient oxygenation of the heart tissue)
The heart has its own blood supply called the **coronary vessels**.
The heart muscle itself is called the **myocardium**

Symptoms: - similar to a **MI** (**myocardial infarction** = "heart attack"):
- "crushing" chest pain goes to L arm or jaw (more often in men)
- and/or nausea, sweating, GI upset, sweating (more often in women)
- or asymptomatic *(yikes!), so called "silent angina"*

"**Stable Angina**" also called "exertional angina" or "SIHD" (Stable Ischemic Heart Disease)
Predictable pain that occurs on exercise or stress (including illness) that **goes away with rest** and causes no damage to the heart, although it can theoretically **progress to an MI**
It is due to a mismatch between the myocardial oxygen (blood) supply and demand.
Increased heart rate also reduces oxygenation, because **during systole, blood does not move through the coronary arteries**

Causes:
1. **CAD** (Coronary Artery Disease):
Arteriosclerosis- hardening of arteries prevents vasodilation
Can be due to uncontrolled hypertension
Atherosclerosis- atherosclerotic cholesterol plaques clog/block vessels
2. Coronary **vessel spasm** (also called Vasospastic/Prinzmetal's/Variant angina)
Can also caused by to cocaine use that can lead to MI
3. Microvascular angina – angina in patients with clear coronary arteries on an angiogram
More common in women

CV Risk factors: smoking, Diabetes Mellitus (DM), hypertension (HTN), obesity, age, sedentary, gender (female), family history, high cholesterol/LDL
See ArtheroSclerotic CardioVascularDisease –**ASCVD**- risk webpage or app

<u>Acute Coronary Syndromes</u>: worse than stable angina immediately dangerous
"**Unstable Angina**": Pain that that is **unpredictable, or occurs at rest**.
It can be due to spasm of the coronary vessels (vasospastic angina), but it is often due to a chunk of something (atherosclerotic plaque or clot) in a coronary vessel that blocks coronary blood flow. Very dangerous

"MI": 100% blockage of coronary vessel; if patient survives long enough to get to hospital, must treat within 90 minutes, or at worst 12 hours, to limit heart tissue destruction
Treat via **PCI** (percutaneous coronary intervention), CABG ("bypass graft"), clot dissolving agents, stents, etc.)

The pharmacologic goal in the treatment of **angina** is to **increase blood flow**, and **reduce** how hard the heart is working by **limiting heart rate** and also reducing the workload of the heart (afterload & preload).

Compare the goals of angina to our goals for cardiac muscle in CHF

In CHF we want to maximize the ***efficiency*** of the remaining, non-scarred heart

In angina: we want to *limit oxygen* ***consumption*** by cardiac muscle with poor blood supply

Mainstays of therapy for Chronic Stable Angina (SIHD):

Prevent coronary blockage by a clot: **antiplatelet anticoagulants**
Stop an attack: **nitrates,**
Prevent an attack: **beta-blockers, and Ca^{++}-Channel Blockers**
Reduce metabolic demand **in** the heart: **metabolic stress agents (ranolazine)**
Reduce metabolic demands **on** the heart: **preload/afterload reducing agents**

BLOOD THINNERS (anticoagulants): These **don't actually make your blood "thin"!**
They just prevent clots from forming or getting larger

Antiplatelet anticoagulants:

- **aspirin** - low dose **81mg** used for angina and/or to prevent MI or CVA (stroke)
  - dose of 160-325 decreases mortality of **MI** up to 1/3!
- **$P2Y_{12}$ Inhibitors**
  clopidogrel *(Plavix)*, ticagrelor (*Brilinta*), prasugrel *(Effient)*

2016 Guidelines: SIHD Patients with a **prior history of MI or PCI or stent** placement are placed on **DAPT (Dual AntiPlatelet Therapy):**
Low dose aspirin + a $P2Y_{12}$ Inhibitor

AntiPlatelet anticoagulants are NOT to be confused with more powerful oral anticoagulants used for other conditions like DVT or **atrial fibrillation** *(see later)*

- Factor Xa inhibitors: **warfarin** (*Coumadin*) – antidote Vitamin K
- Direct Thrombin inhibtors: **dabigatran** *(Pradaxa)*, rivaroxaban (*Xarelto*), apixaban *(Eliquis)* – these have no "antidote", but cause less accidental brain bleed or other life-threatening bleeds so FDA still endorses them (despite lawsuits you may see on TV!) or Parenteral blood anticoagulants
- **heparin**: IV for the unstable, hospitalized patients; SQ for outpatients
- Glycoprotein IIb/IIIa inhibitors: usu. used during PCI/CABG procedures to clear vessels: abciximab *(ReoPro)*, eptifibatide *(Integrilin)*, tirofiban *(Aggrastat)*

See anticoagulants section below.

BETA-BLOCKERS: Specifically, beta-1 blockers.

Beta-blockers act to reduce conduction, cardiac output and blood pressure. By reducing heart contractility and metabolic demand, beta-blockers keep the heart from overexerting itself. Beta-blockers have been **proven to increase survival in patients who have suffered an MI**.

SLOWING HEART RATE means:

1. The cardiac cells are **contracting less frequently**, and **using less oxygen**
2. The percent time the heart **spends in systole is less. When the heart is contracting, all the arterioles and capillaries inside the heart muscle are squeezed shut and no blood gets through**. **If the heart beats more slowly**, then there are more seconds every minute where blood can flow through heart muscle tissue. That means **more oxygen gets to the heart cells** every minute.

Using a beta-1 blocker is like putting a brick *under* the accelerator pedal in a car. You just CAN'T go faster.

Beta-blockers are said to increase exercise tolerance in angina patients. But, wait! back when we first talked about beta-blockers, we said they decreased exercise tolerance in marathon runners and other athletes…

A note about terminology. The difference between "exercise tolerance**" and "**exercise capacity**".*

*In a healthy person, beta-blockers will reduce **exercise capacity**, meaning that if a marathon runner starts taking atenolol, he will start having trouble running 26 miles because his his heart rate won't adjust as it should as he runs, which will affect his performance.*

In sharp contrast, in an old cigarette-smoking grandma angina patient who gets chest pain when she climbs three stairs, we can say a beta-blocker might increase her "exercise tolerance" because it might stop her heart from beating too fast and then becoming ischemic and painful. (Remember my in-class example of the vacuum-cleaning cat lady).

Prototype Beta-Blockers:

1. **beta-1-specific blockers: atenolol** (*Tenormin*) :
   indications: stable **angina, hypertension** and even acute MI
   contraindications: *vasospastic* angina, **bradycardia** (HR<60)

2. …and our favorite non-specific beta-1 & beta 2 -blocker: **propranolol**:

   To review **propranolol** (because it is special)
   indications**:** hypertension, angina, stable post-MI, migraine, **stage fright** & tremor, **dysrhythmias** (especially after MI), pheochromocytoma
   contraindications: **heart failure, lung problems**, **diabetics taking hypoglycemic drugs**, and also *vasospastic* angina and **bradycardia**

Black box warning: For *any* beta-1 blockers like **atenolol** (and **propranolol**):
In a patient with coronary vessel disease, when **stopping propranolol, the dose must be tapered** if the patient has been taking it for more than a month or you risk… what?

Answer: ***reflex tachycardia*** *leading to MI in angina patient*
(This makes sense, yes? Withdrawal of a drug to lower heart rate would be an increase in heart rate...)

NITRATES: for more symptomatic/severe patients
Nitroglycerin (NTG):
Acts to **dilate coronary arteries** and redistribute coronary blood flow
also dilates arteries and veins.

Indications: 1) acute or chronic angina
2) severe acute hypertension, used IV to titrate the blood pressure (ICU)

NTG also **dilates veins** in the body to reduce preload (and afterload) to reduce the workload on the heart.
Nitrates work through nitric oxide (and cGMP and other enzymes) to decrease intracellular Ca^{++} and relax smooth muscle

Pharmacokinetics: **>90% first-pass metabolism, tolerance within 24 hours**
Can take **sublingual tablet,** oral (translingual) spray: onset in 1-2 minutes
If no relief after 5 minutes consider the possibility of MI.
Definitely if no relief after three doses!

NTG also comes as slower-acting topical **creams or patches**:
use on upper arm or chest (why?)
Because of tolerance, ***tell patients to not use NTG at night!***
Oral sustained-release version available (high dose due to 1st-pass metabolism)

NTG has to be kept in **glass or special containers** in a cool dark place and *you have to use* ***special tubing*** when you give it IV

Side effects: **Headache**
Orthostatic hypotension
caused by too much vasodilation
body can't compensate if patient stands suddenly
orthostatic hypotension is generally worse with alcohol
Nitrates increase intracranial pressure; contraindicated in cerebral aneurysm

Do not mix nitrates with drugs like **sildenafil** *(Viagra)* or tadalafil *(Cialis)*
these erectile dysfunction drugs have a *synergistic effect* with nitrates that causes a **massive drop in blood pressure** leading to **reflex tachycardia.** Which is all bad.

Isosorbide dinitrate: Like NTG, used as angina prevention (remember it is also in *BiDil* for HF)
given PO, takes about 30 minutes to work, use before exercise

CALCIUM CHANNEL BLOCKERS (CCBs)
Mechanism of action: The Ca^{++}-Channel Blockers bind to receptors sitting on a particular type of Ca^{++}-channel in the walls of cells in smooth muscle and the heart. But Ca^{++} is needed for both the firing of the SA node (determines heart rate) and for cardiac (and smooth) muscle contraction.

So, all this inhibition of calcium movement by this class of drugs causes:
In the heart conduction system: **slows the AV node** (esp. verapamil) - slows heart rate
In the **coronary arteries**: dilation ⇒ **more blood supply** to the heart ⇒ less angina
In the **arteries of the body**: dilation ⇒ **lower blood pressure, reduces afterload only**
In the smooth muscle of the GI tract: less movement ⇒ ***constipation.***

Indications: **angina, dysrhythmias, hypertension**, migraines, Raynaud's (cold fingers)
Contraindications: **heart failure**
Calcium channel blockers are generally contraindicated in CHF. ***Why?***
(You'll note they weren't included as arteriolar dilators of the Heart Failure section)
Non-dihydropyridines **CCBs:** older drugs, their own receptor, better for atrial fibrillarion
verapamil (*Calan*):
Good for **supraventricular dysrhythmias** like atrial fibrillation (or even SVT)
Slows the AV node
reduces number of **angina** attacks
also used for **hypertension**
80% (high) first-pass metabolism (IV dose way smaller than po dose)

diltiazem: Does not slow the heart as much; used mostly for hypertension

Dihydropyridine **CCBs:** all have suffix "-dipine", bind a different site on Ca^{++} channels
can be used as first line treatments for angina

nifedipine *(Procardia)*: Does not affect the AV node no not so great for dysrhythmias
Studies show that ***fast-acting form of nifedipine*** *increased risk of myocardial infarction (MI) in patients with hypertension*… this is due to a **reflex tachycardia** that you see with some Ca^{++} Channel blockers in response to a rapid drop in blood pressure

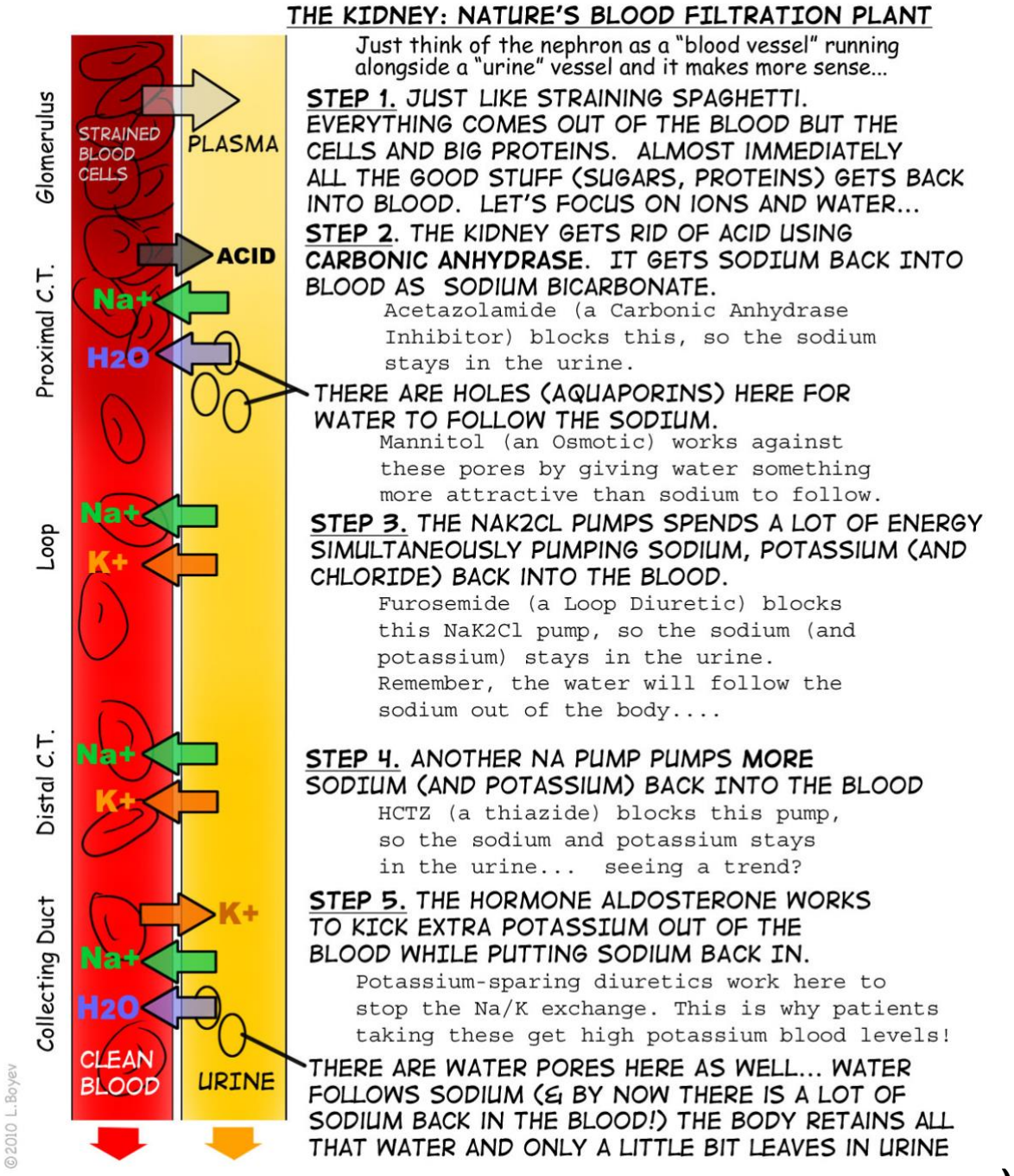
NEWER DRUGS
ranolazine *(Ranexa)***: used if contraindications to beta-blockers and CCBs**
increases chances of muscle injury caused by statins
works on sodium/calcium countertransporter in sick, ischemic heart cells
does not affect arterial pressure or heart rate, may prolong QT *(see below)*

OTHER DRUGS FOR ANGINA: In unstable, emergent angina you use all sorts of other drugs, including some we already know like:
morphine: reduces preload, reduces pain &
oxygen: …because oxygen is good, right?
... especially since the heart muscle really needs oxygen!

DIURETICS aka "Water Pills"

Na^+ = sodium, K^+ = potassium, Cl^- = Chloride, Ca^{++}=Calcium, Mg^{++}=Magnesium

Osmolarity is a term which refers to how concentrated any given solution is. Salt water with a lot of salt in it would be described as having high osmolarity. If you dilute that salt water so you can barely taste the salt, that is low osmolarity. In the body, water will always flow from low osmolarity to high osmolarity. It is almost as if Sodium (Na^+) is acting like a sponge to draw the water with it. **WATER FOLLOWS SODIUM (Na^+)**



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The kidney is responsible for excreting metabolic waste products, but is also crucial for regulating the blood volume, blood pH (acidity), electrolyte balance & blood pressure.
-It is so important that 25% of the cardiac output is to the kidneys.

Diuretic: a drug that increases the volume of urine produced and excreted

Diuretics are extremely useful to reduce blood volume a small amount (hypertension patients) or large amount (acute CHF patients) and to reduce edema.

All diuretics can cause orthostatic hypotension, some worse than others!
On a practical note, **don't forget to reduce salt intake** and that patients should take diuretics **in the morning** so they aren't up all night urinating.

MAJOR GROUPS of DIURETICS:

1) OSMOTIC DRUGS (as DIURETICS)

Big molecules that are filtered by glomerulus and can't be reabsorbed into the blood
Work by osmosis to suck water out of your blood vessels and into your urine, because water is more strongly attracted to osmotics than it is to sodium!

Mannitol: extremely large molecule that does not easily get absorbed into the GI system
Only given IV *(What would happen if you gave it orally?)*
Indications: -Acute Renal Failure, Acute Glaucoma, Brain Swelling
Can worsen HF and pulmonary edema!
Because first all the fluid will get sucked into the blood stream before it gets sucked into the nephron, and that huge increase in preload could send your patient into acute deadly heart failure!!

Other osmotics: glycerol, sugar alcohols, even glucose
Type 2 Diabetics with high glucose levels lose glucose into their urine, which draws water into the urine, causing frequent urination and susceptibility to urinary tract infections.
Remember **osmotics taken orally act like laxatives** (more on this later!)

2) **CARBONIC ANHYDRASE INHIBITORS**

The body constantly makes acid waste products. Constantly. So to stay in balance it has to constantly get rid of acid, which means getting rid of H^+ ions.
By blocking Carbonic Anhydrase, H^+ ions cannot exchange with Na^+, so Na^+ (and thus water) is not reabsorbed into the blood stream

acetazolamide (*Diamox*) is used for: emergent diuresis for acute glaucoma and altitude sickness
Use for altitude sickness may be useful if you ever practice outside of flat Illinois!
Used PO or IV, can cause hypokalemia $^+$

3) LOOP DIURETICS

Act at TAL of Loop of Henle to block that NaK2Cl pump.
Used in **moderate to severe edema**
Good for **CHF**, cirrhosis (**liver failure**), ***near* kidney failure**, or hypertensive crisis
PO or IV, can induce a huge volume loss **("high ceiling diuretic")**
IV works fast, in ~10 minutes, and lasts ~2 hours.
Examples: **furosemide** (*Lasix*), bumetanide, ethacrynic acid, torsemide

SIDE EFFECTS: **Can cause big electrolyte imbalances** Na^+, K^+, Cl^-, Ca^{++} and Mg^{++})
K^+ loss (**hypokalemia)**
Ototoxicity (especially if infused IV too fast (deafness can happen up to 6 months later))
Allergy (**furosemide- sulfa**)
Gout
Contraindicated in **anuria** (zero urine output) or **hypokalemia** *(Why?)*

THIAZIDE DIURETICS

Block NaCl reabsorption in DCT, so water stays with the salt and leaves as urine.
Some examples: hydrochlorothiazide (HCTZ, *Hydrodiuril*), chlorothiazide *(Diuril)*, indapamide *(Lozol)*,
Hydrochlorothiazide (**HCTZ**): commonly used as first-line drug in mild **hypertension**
Side Effects: **K^+ loss (hypokalemia)**
hypercalcemia
can aggravate **gout**
Sulfa allergies
Aplastic anemia/ blood count changes (usu. reversible)
Can aggravate kidney disease (can slow down the GFR (filtration rate))
Use cautiously in diabetics (it increases blood glucose and lipid levels)

"POTASSIUM- SPARING" DIURETICS

These block K^+ secretion in DCT & CCT and lead to Na^+ loss (and water) in urine
Side effects: **hyperkalemia,** remember, high K^+ levels cause the heart to slow or stop!

Drugs that work at the Na/K pump in the distal tubule:
triamterine *(Dyrenium)***: directly acts** at DCT to block that Na/K pump.
It is marketed in combination with thiazides. *Why?*
Turns urine blue. Yay?
amiloride *(Midamor)*

Aldosterone antagonists: block aldosterone receptor at that same pump
eplerenone *(Inspra)*
spironolactone *(Aldactone)*: cross-reacts with and blocks testosterone receptors
used for acne, but can cause **gynecomastia** (enlarged breasts also in men!)

ADH Antagonists: Same pump, **blocks ADH receptor.** Example: conivaptan (*Vaprisol*)

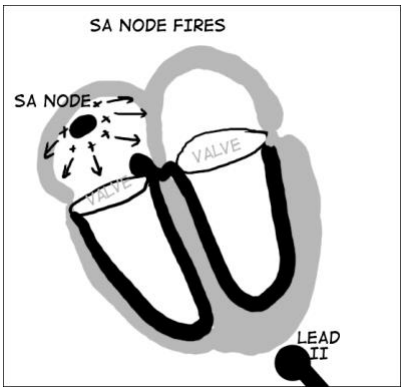
OTHER DRUG INTERACTIONS of DIURETICS:

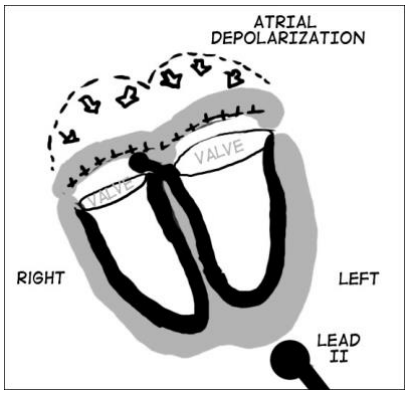
anything to do with **potassium** will interact with digoxin ***(why?)***
all diuretics worsen lithium toxicity (& actually most drugs' toxicity) ***(why?)***
all diuretics potentially increase chance of a blood clot ***(why?)***
all diuretics potentially cause orthostatic hypotension, loop diuretics are the worst ***(why?)***

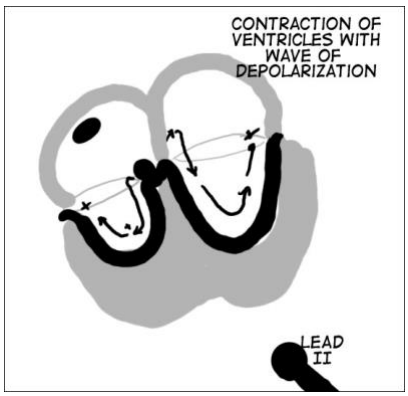
A *BRIEF* DISCUSSION OF DYSRHYTHMIA DRUGS *(This is brief?!)*

HEART EKG and Cardiac Self-Pacing – recall EKG from Bio232?
(The *BEST* book for learning EKG is **Rapid Interpretation of EKG's *[sic]* by Dale Dubin)** on reserve in the library.)

The EKG is a measurement of the wave of depolarization as it travels through the heart. The prototypical EKG tracing you see is the EKG you get when you put a negative electrode on your right shoulder and a positive lead down on your left pelvis (lead II). Whenever a wave of depolarization comes toward the positive lead down on the left the EKG tracing will go up (be positive). When the wave of depolarization moves away from the positive lead, the EKG tracing

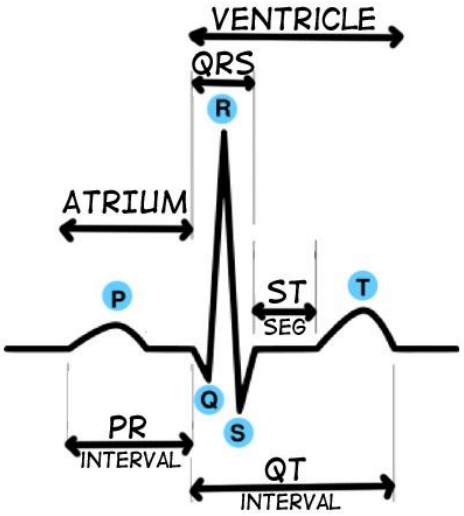






will go down (be negative).The heart itself sits a little crooked in the chest, pointed towards your lower left side. So lead II will be staring right up the middle of the heart.

The **P WAVE represents the atrium contracting**. The heart beat starts in the pacemaker cells in the right atrium within the sinoatrial **SA node**. The electrical impulse then spreads through the atrium to the **AV node** which sits at the border between the atrium and ventricle. This gets us from P to Q on the EKG tracing. (Note that the "PR" interval is really the "PQ" interval. This is because sometimes the Q wave is so small you can't see it, so by convention you just go to the beginning of that second wave when measuring PR).



Now there is a little pause because the depolarization is all gathered at the AV node. Think of the walls and valves between the atria and ventricles as being made of rubber insulation. The only place for the current to go is through the AV node, so it gathers there. This pause also ensures that the ventricles do not contract at the same time as the atria.

The QRS WAVE represents the ventricle contracting (depolarizing). Once the electrical wave of depolarization hits the AV node it shoots into the "Bundle of His" and then lightning fast through the ventricles leading to contraction.

THE T WAVE represents the ventricle recovering (repolarizing). Since repolarization is essentially a wave of *negative* charge moving *away* from Lead II, it shows up on the EKG tracing as a *positive* deflection (a negative of a negative is positive).

Of course the heart is made of four chambers, and sits crooked in the chest, and the EKG looks different depending on where you place the leads on the chest, but this is the basic idea.

Now, with digoxin, you see a lengthening of the **PR interval**, which is because you are slowing down the conduction of the electrical impulse through the atrium of the heart.

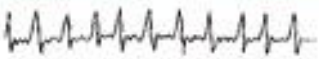
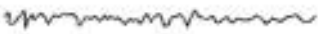
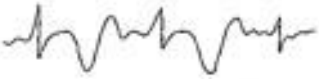
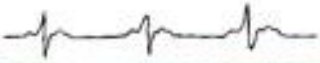
You also see some ST changes (and with toxicity some T wave changes)… but the PR lengthening is what you should concentrate on for in terms of digoxin toxicity.

Dysrhythmia refers to abnormal heart beats… not so much that the EKG wave form itself is abnormal, but the rate at which the heart beats is not regular, is too fast (**tachycardia**) or too slow (**bradycardia**).

Normal rhythm is usually called **sinus rhythm,** since it is stimulated by the SA node. :-)

In common parlance, many healthcare workers say "arrhythmia" instead of "dysrhythmia".
Sorry, shamefully, I slip and do it too sometimes. ;-)

TABLE 23:1 Commonly Occurring Arrhythmias and Their ECG Patterns

ARRHYTHMIA	CHARACTERISTIC RATE (BEATS/MINUTE)	ECG
Tachycardia (atrial or ventricular)	150–250	
Atrial flutter	200–350	
Atrial fibrillation	Greater than 350	
Ventricular fibrillation	Uncoordinated contractions	
Premature contraction of the atria	Variable	
Premature contractions of the ventricles	Variable	
Bradycardia	Less than 60	

Although we usually want to fix an dysrhythmia to make it normal, in treating **atrial fibrillation** (see below), **treating the rate can be more important than the rhythm** provided the patient is properly **anticoagulated**.

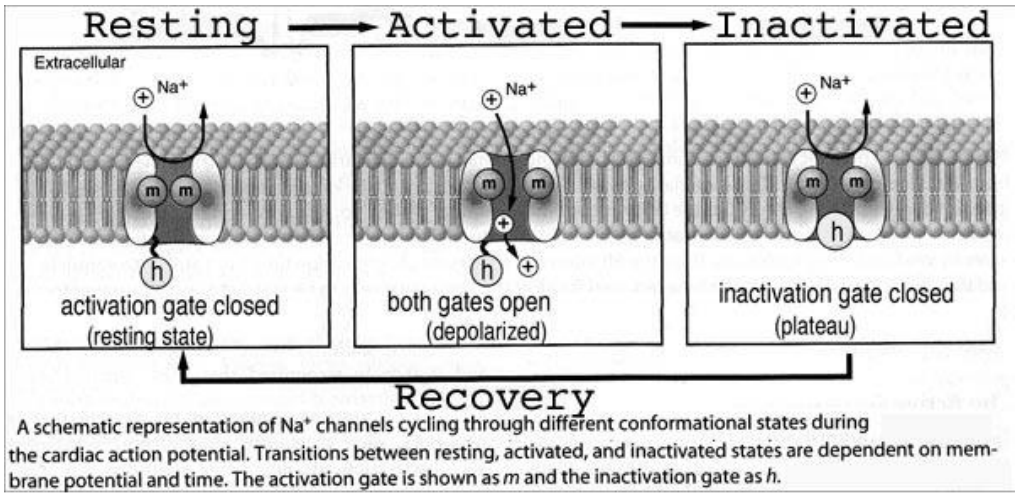
In contrast, ventricular fibrillation (V. fib.), in which the heart flops around shuddering like an fish on dry land, is uniformly fatal in minutes if not converted back to something more useful to the

body. In contrast with what you see in movies, CPR alone won't fix Vfib. You have to use a defibrillator to reboot the electrical system of the heart.

In order to understand **how** the **drugs** used to treat dysrhythmias work you first have to know a little about how heart muscle cells conduct electricity:

Review from Bio232: If this makes you nervous, just remember the action potential dice game. Remember the EKG waveform on the page before last? That is a combination of **all** the individual waves of all the heart cells; it is a snapshot taken from afar. The movement of ions determines the charge across the membrane. When one side is more positive than the other you have hyperpolarization. When the Na_+ channels open, the Na_+ rushes in and the difference in charge across the membrane goes away (depolarization). Then after a brief plateau phase the sodium pumps get to work and the membrane becomes hyperpolarized again.

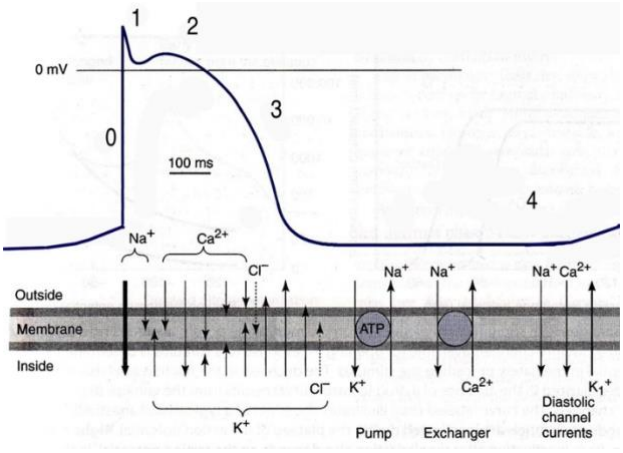
The Na+ channels actually look like this:



A schematic representation of Na^+ channels cycling through different conformational states during the cardiac action potential. Transitions between resting, activated, and inactivated states are dependent on membrane potential and time. The activation gate is shown as *m* and the inactivation gate as *h*.

The time it takes to "recover" is called the **refractory period**.

If we were to take a voltmeter and measure the **voltage across just one cardiac cell** during contraction we would see this, the so-called "Cardiac Action Potential. It is shown in the next picture:



Phase 0: Excitability. When the cell is hyperpolarized (negatively charged), it can fire.
Phase 1-3: **Refractory Period**. During this phase the special Na_+ inactivation channels are all closed, so the cell can't fire again. The cell has to wait for the voltage to get low enough for some of the channels to open again. Most Potassium **(K_+)** movement happens here.
Phase 2: Plateau Phase: **Calcium** works with the actin and myosin to make the muscle contract.
Phase 4: This is the phase in which the cell waits to fire again, or in the case of the SA node (or an abnormal focus) triggers itself to fire again via **slow inward Ca_{++} and Na_+ currents** and a slow outward potassium current. **The rate at which this climbs to the "trigger level" is slowed by the vagus nerve and sped up by activating the beta-adrenergic receptors.**

Other important terms:
Ectopic focus or foci (plural): Areas other than the SA node that abnormally fire on their own

Various Heart Conduction-Related terms you should know:

SA node: the normal place where the heart beat is triggered; it sits in Right Atrium
AV node: the spot between the atrium and ventricle where the conduction slows down in order for the atrium to have enough time to squeeze all its blood into the ventricle.
the AV node also acts as a gatekeeper… if the SA node or an **ectopic focus** starts firing way too fast, the AV node only lets every few beats through so the ventricle can maintain normal rhythm, so called "block".
Purkinje Fibers: They speed up ventricular depolarization so the entire heart can contract simultaneously. They also have their own ability to self-pace, so can be a source of dysrhythmias

Dysrhythmias are classified by
location: atrial (supraventricular) or ventricular
type: flutter, fibrillation, or block

"Atrial" or "supraventricular" dysrhythmias: starts **in the atrium** (atria – plural)
Ex: **Atrial Fibrillation: disorganized electrical signals from** ectopic foci in the atrium cause the atria to contract fast and irregularly (all wiggly).
The patient's pulse will be "irregularly irregular".

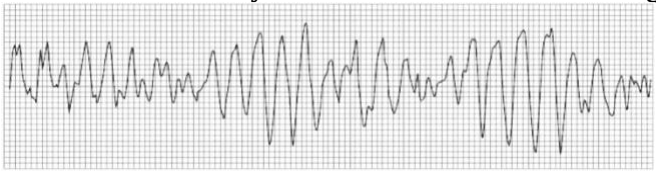
Supraventricular Tachycardia (SVT): usu. >150 bpm, up to ~250bpm
episodes of rapid heart rate due to the SA node firing *way* too fast
treated with **adenosine** or "vagal maneuvers" (such as bearing down or coughing)
SUPRA- means above the ventricle, or in the atrium and AV node

PVC: If the heart beats in response to an ectopic focus in the ventricle, that is called a premature ventricular contraction (PVC). A few are not a problem; too many can trigger VFib

Ventricular Tachycardia: The heart is beating with normal-looking EKG waves but way too fast.

Ventricular Fibrillation (VFib): The ventricles are contracting in a completely uncoordinated fashion. As mentioned above, this will kill the patient unless you can fix it within a few minutes.
ACLS protocol 2016 uses defibrillator shocks + **epinephrine** + **amiodarone**

Torsades de Pointes (TdP): A distinctively patterned dysrhythmia (pictured below) usually caused by **drug toxicity** (including **drugs for dysrhythmia** and **phenothiazines**!) or birth defects.
Seen most commonly with Class IA, IC, and III drugs.



-Causes palpitations, dizziness, syncope or sudden death.
-**Treated with magnesium sulfate** and other drugs.

Long QT Syndrome: A condition in which the QT interval is too long. This can predispose the patient to episodes of erratic heartbeats that can cause sudden death, fainting or seizures (all bad). It can be due to an inherited problem, **certain medications** or conditions, **or electrolyte disturbances like hypokalemia,** low calcium or low magnesium levels.

QT Prolongation: **A number of drugs can cause prolongation of the QT wave** (remember, the QT interval is the ventricle depolarizing and then repolarizing), and can cause a potentially fatal dysrhythmia. **Avoid drugs that cause QT prolongation in patients that have Long QT Syndrome** to prevent death.

SOME of the drugs we've seen (or will see soon) that cause QT prolongation include: *Do NOT memorize this list for me!*
Antidysrhythmics: like Sotalol, Quinidine, Amiodarone, Ibutilide, Disopyramide, Procainamide, Flecainide, Dofetilide,
Antibiotics, antiviral or antimalarial drugs like erythromycin or amantadine
Antidepressants: like SSNRI Venlafaxine, SSRIs Paroxetine, Fluoxetine, Sertraline, TCAs: Amitriptyline, Nortriptyline,
Anti-fungal drugs like ketoconazole or itraconazole
Antihistamines like Diphenhydramine
Anti-hypertensives like Nicardipine, HCTZ
Anti-mania: Lithium
Anti-nausea/antiemetic like ondansetron
Anti-psychotic Thioridazine, Risperidone, Haloperidol
Appetite suppressant/amphetamines: Phentermine, Sibutramine, methylphenidate, amphetamine
Bladder Antispasmodic: α1-blockers
Bronchodilator/decongestant Albuterol, Salmeterol, Metaproterenol, Ephedrine, Pseudoephedrine
GI H2-receptor antagonist like famotidine
Inotropic agent/vasoconstrictor: Dopamine, Isoproterenol, Dobutamine, Epinephrine, Norepinephrine, Phenylephrine
Local anesthetic: Cocaine
Opiate agonists like methadone
Metabolic Stress Drugs for Angina like ranazoline
And also Anesthetics, Cancer drugs, Antiseizure drugs, Antiviral drugs, cholinesterase inhibitors (-stigmines), Diuretics and many more.

(don't memorize this list for now!)

In the future: You'll see questions (and real life patients!) where the patient complains of dizziness and they are on one of the MANY drugs that can get QT prolongation and you are supposed to be able to spot that the dizziness may be a problem caused by dysrrhythmia!

CARDIAC DYSRHYTHMIA DRUGS (Ch 23)

Dysrhythmia means "bad rhythm" & **dysrhythmia** theoretically means "no rhythm" but the two terms are used interchangeably by most people

You can treat dysrhythmias with electric pulses, or by ablating (burning) the ectopic foci, or with anti-dysrhythmia drugs.

Drugs to treat **dysrhythmias** fall into 4 major classes:

Class I: Mostly Na+ channel blockers (phase 0)
- IA. blocks Na channels a medium amount
- IB. blocks channels a little
- IC. blocks Na channels a lot

Class II: Beta-blockers (Phase 4)

Class III: Drugs that prolong the refractory period (phase 1-3) mostly through action on K+

Class IV: Calcium Channel Blockers (phase 2)

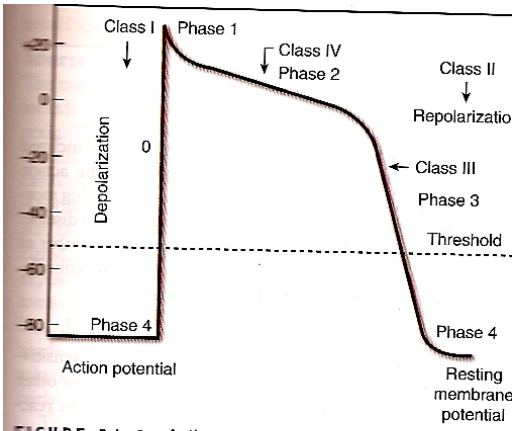


FIGURE 31.9 Action potential and antiarrhythmic drugs. The change in the charge of the myocardial cell that occurs when sodium (Na+) and calcium (Ca++) flow into the cell and potassium (K+) flows out is called the action potential. Different antiarrhythmic drugs act at different phases of polarization and repolarization. Class I drugs (quinidine) act during depolarization, class II drugs (propranolol) act during the resting period of repolarization, class III drugs (amiodarone) act during rapid repolarization, and class IV drugs (verapamil) act during early repolarization.

The Vaughan-Williams system (above) is classified by *where* in the cardiac action potential the drugs act, and which ion channels are affected.

In general, these drugs decrease automaticity by suppressing ectopic foci, slowing conduction and stopping re-entry of electrical impulses in diseased or injured heart tissue

Pearl of Wisdom: All anti-dysrhythmia agents can also *cause* dysrhythmias in toxic doses!

Examples of Drugs for Dysrhythmias in the Four Major Classes.

CLASS I: Sodium Channel blockers

Not surprisingly, these drugs are, or are related to Local Anesthetics… which block Na^+ channels!

Class 1a: prolong QT, **can cause Torsades de Pointes (TdP),** not much effect on SA node

Quinidine:
- -related to the anti-malaria drug quinine
- -**slows ventricular heart rate**, good for select types of **atrial fibrillation** and ventricular tachycardia
- -lots of side effects including anticholinergic GI effects *(which would be?)*
- - common cause of drug-induced **lupus erythematosis** with prolonged use rash, arthritis. Reversible if quinidine is stopped
- -toxicity to CNS called "**cinchonism"** (**ringing in the ears,** dizziness, hallucinations)
- -interacts with *many* other drugs: antacids, cimetidine, barbiturates, antibiotics, verapamil, e
- - low TI; monitor levels
- **EKG helpful for monitoring dose (prolongs QT interval)**

Procainamide - generally used for *ventricular* dysrhythmias
- -similar to the local anesthetic procaine
- -slows conduction, also prolongs QRS on EKG

-Black Box warning**: agranulocytosis** (blood disorder lowered WBCs):
check CBCs weekly for 3 months
-also causes drug-induced **lupus erythematosis** with prolonged use
-**EKG helpful for monitoring dose (prolongs QT interval)**

Disopyramide- similar effects as two above
-has more anti-cholinergic (anti-vagus) effects, so can speed up heart rate.

Class 1b:

Lidocaine: -Yep, this is also a local anesthetic drug (blocks Na^+ channels, right?)!
-used for ***ventricular*** **dysrhythmias**
-**Only used I.V.** (~97% first-pass metabolism)
(review question: what happens in a liver failure patient?)
-overdose: CNS effects (seizures, coma, etc)
-When used IV you have to have the patient on a continuous EKG monitor

Phenytoin (*Dilantin*) – The seizure drug?! No way! Yes way!
Off-label use in treating digoxin-induced dysrhythmia.

Class 1c:

Flecanide -Good for paroxysmal atrial and ventricular tachycardias, only available PO
-Black Box warning: CAST trial showed drug dangerous if pre-existing MI and ventricular ectopic foci so not used prophylactically anymore. Only used in life-threatening cases. Do not use for atrial fibrillation Can cause TdP

CLASS II: Beta Blockers

Very good to prevent repeat infarction or sudden cardiac death in patients recovering from a heart attack. Slows heart rate and conduction

propranolol -A non-specific **(β-1 & β-2**) blocker
- Slows Heart Rate (SA node) and conduction through AV node
-**reduce automaticity** (reduce chance of new dysrhythmic focus from forming!)
-Several dysrrhythmia indications, including:
preventing sudden death from post-MI dysrhythmias,
SVT, V-tach, digoxin-toxicity, others
-okay to use at same time as class I or IV drugs
-**Contraindications:**
asthmatics, COPD, lung-disease
depression
diabetics (blocks symptoms of hypoglycemia)
heart failure (do not use with digoxin)
-metabolized by liver
remember, also used for many other indications (including HTN and angina!)
black box warning for ALL beta-blockers: if used for several weeks, **must taper dose** when stopping the drug or will trigger **reflex tachycardia** and an MI

esmolol A selective beta-1 blocker used IV; metabolized in the bloodstream, can use w/ digoxin
acebutolol also approved for use as an antidysrhythmic drug.
sotalol (*Betapace*)- is a weird nonspecific (β-1 & β-2) blocker
- acts mostly as class III drug *(say what?).* Can cause TdP

Class III: Drugs that block K+ current (Prolong the Action Potential/ phase 3)

*These work mostly by blocking **the outward K+ current** in phase 3.*

amiodarone **-V. Fib**, good for preventing recurrent Ventricular Tachycardia, and for treating atrial fibrillation (off label)

not only blocks Action potentials (K channels) but also weakly blocks Na & Ca channels and Beta-receptors (...so it has weak I, II and IV effects)

2 month half-life so you give a loading dose when starting the drug

excreted by liver into the bile (and then recycled... so takes forever to excrete!)

contraindicated: **thyroid patients** (contains iodine)

weirdo side effects:

Spots on cornea & skin: 10% photosensitive with blue-grey skin splotches

Liver toxicity

Pulmonary fibrosis (lung scarring) ~10% get it and ~10% of those die!

Pregnancy category D

Interacts/increases serum levels of digoxin, warfarin

Toxicity increases with low Potassium, low Magnesium

Monitor with EKGs

ibutilide, dofetilide –newer "pure" Class III drugs that only act at phase 3 with shorter half-lives, used for some atrial dysrhythmias.

sotalol (*Betapace*) Class II and III as above

Class IV: Calcium Channel Blockers

Blocking calcium movement lengthens phase 4 and so slows heart rate and reduces contractility. CCBs act by blocking the movement of calcium through channels on artery wall muscle cells and in cardiac muscle cells. ***Do NOT use in heart failure***

The *most* calcium-dependent tissue in the heart is the AV node, so Class IV drugs are great for dysrhythmias involving the AV node.

Mostly the **non-dihydropyridine CCBs** are used for dysrhythmias

verapamil *(Calan)* -Decreases heart rate at SA node, slows conduction at AV node

-Good for atrial fibrillation / flutter or SVT

-Also good for **hypertension**, migraines and **angina**

-Side effect: ***constipation***, hypotension

-increases digoxin levels

⇑s **AV node suppression by beta-blockers** (slows heart rate)

diltiazem *(Cardizem)* -approved for IV use in some dysrhythmias (but this drug is better for hypertension)

OTHER DYSRHYTHMIA DRUGS

that don't fit into one of the four classes above:

Adenosine-Used IV for **Paroxysmal SVT (SupraVentricularTachycardia)**

-metabolized in blood so fast you must give it IV FAST PUSH

Digoxin -used for **atrial fibrillation** and flutter, **and heart failure**!

Epinephrine - used for **V. fib**, pulseless V Tach

Postscript RE **BRADYCARDIA (Slow heart rate):**
ACLS guidelines and various causes of **bradycardia**:

The first choice is **atropine**.
If atropine fails, then **dopamine** or **epinephrine** can be tried or external pacing (pacemaker) would be used.

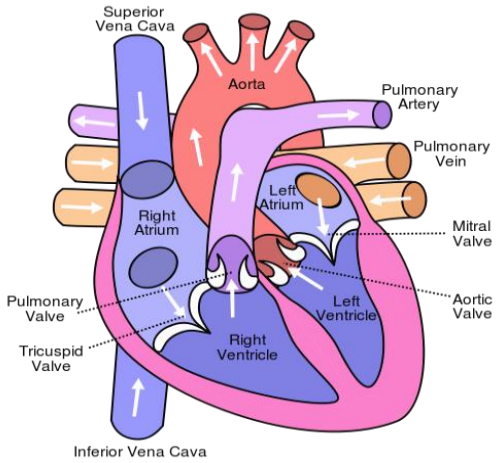
ATRIAL FIBRILLATION (AFib)

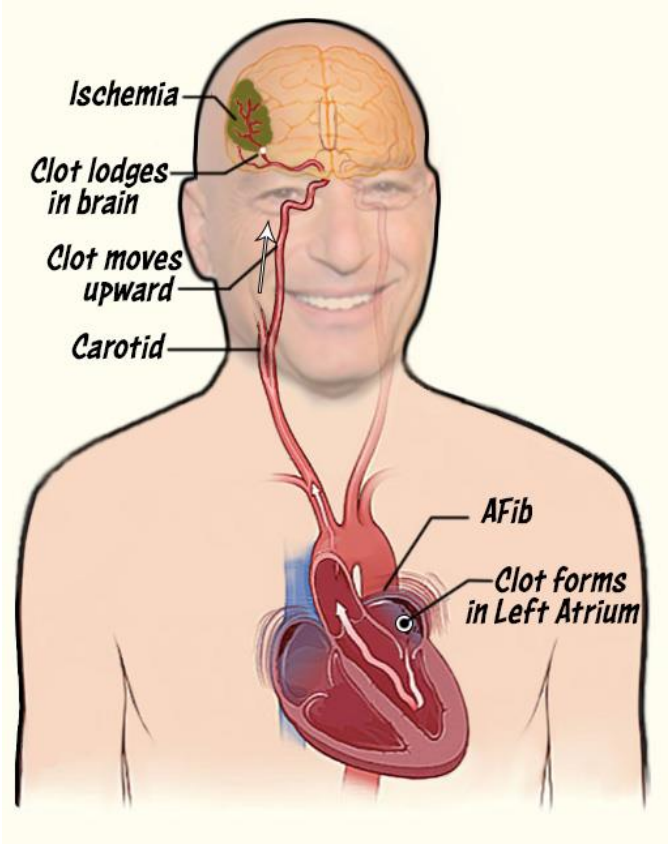
Atrial fibrillation causes the atria to contract in a disorganized way. This causes areas of turbulence and stagnation of blood flow within the atria. That leads to blood clots.

A blood clot in the right atrium can lead to **pulmonary embolism (PE)**

A blood clot in the left atrium can lead to stroke (CVA), specifically **thromboembolic stroke** (a stroke caused by a blood clot breaking off somewhere else and lodging in the brain).

Take a look again at the diagram below to be 100% sure you understand the connection between the site of the clot and whether this risks a PE versus a CVA. This image of Howie Mandel ⇒ shows what happens when the clot is on the left side.





Risk factors and causes of atrial fibrillation include:

> **High blood pressure, angina, MI,** abnormal valves, congenital abnormalities, **hyperthyroidism,** medications (including caffeine, tobacco and alcohol), lung and viral diseases, severe infection, and other serious illnesses.

Symptoms of AFib: Symptoms include: dizziness, shortness of breath (SOB), thumping or a feeling of palpitations. Depending on the severity of AFib a patient can even develop symptoms of pulmonary edema or MI! But let's not worry about that right now. Let's concentrate on the possibility of PE or CVA.

Goals of treating AFib:

1. Anticoagulation: (see also end of handout: anticoagulants)
as long as atrial fibrillation is occurring there is risk of stroke or pulmonary embolism.

- Factor Xa inhibitors: **warfarin** (*Coumadin*) – **antidote is Vitamin K**
- Direct Thrombin inhibtors: **dabigatran** *(Pradaxa),* rivaroxaban (*Xarelto*), apixaban *(Eliquis)*
    - these direct thromibin inhibitors have no "antidote", but cause less accidental brain bleed or other life-threatening bleeds so FDA still endorses them (despite lawsuits you may see on TV!) See FDA announcement Oct 16, 2015 at fda.gov

2. Heart rate control: with **beta-blockers** or
calcium channel blockers (non-dihydropyridines only)
Surprisingly, numerous studies have shown that in order to prolong life, it is **more important to slow the rate of the heart than to normalize the EKG**. Isn't that unexpected? I think it is.

3. Normalize the rhythm itself (depending on the underlying cause)
with drugs: disopyramide, **quinidine**, flecanide, propafenone, **amiodarone**, dofetilide, dronedarone, sotalol
invasive procedures: electrical cardioversion or cryotherapy

HYPERTENSION DRUGS

(aka lots of drugs you already learned no low anxiety here, folks!)

Hypertension is defined as an arterial blood pressure **>140/90** for age <60
2014 Guidelines: 150/90 if over 60 years old
(Usually measured over three visits – to reduce **white coat syndrome**)
"Normal" is considered <120/80
>90% of hypertension is "**essential hypertension**" (unknown cause)

- Normal: < 120 mm Hg Systolic BP (SBP) and < 80 mm Hg Diastolic BP (DBP)
- Elevated: 120-129 mm Hg SBP and < 80 mm Hg DBP
- Stage 1 Hypertension: 130-139 mm Hg SBP or 80-89 mm Hg DBP and
- Stage 2 Hypertension: ≥ 140 mm Hg SBP or ≥ 90 mm Hg DBP

The top number is **systolic pressure** (the pressure while the ventricle contracts)
The bottom is **diastolic pressure** (the pressure while the ventricle relaxes)

Note! If you measure a patient's BP right after they run up the stairs or exert themselves their BP will be high. So try to always take BP on a patient who is calm and sitting comfortably.

Long-term hypertension leads to **hardened or narrow arteries**, which leads to ischemia and organ failure, particularly in organs that depend on lots of tiny blood vessels like the eyes or kidneys. Also, you can develop weak spots in your arteries called **aneurysms** which can burst and kill you. Hypertension is a proven contributor to **heart disease** (**MI, CHF**) and **stroke** as well.

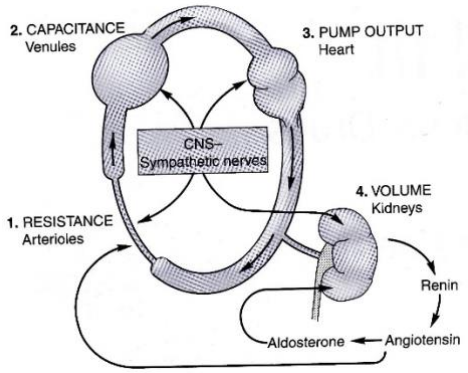
Blood pressure is determined by the amount of blood and resistance inside blood vessels.
The math:
Average arterial **blood pressure = cardiac output x peripheral resistance (BP=COxPR)**
And we know **cardiac output = stroke volume x heart rate (CO=SVxHR)**

Things that increase blood pressure

Increased heart rate
Vasoconstriction *(afterload)*
Increased cardiac output *(contractility)*
Increased blood volume *(preload)*

Things that decrease blood pressure (fill in):

The body monitors its own arterial blood pressure via **baroreceptors** in the **carotids** and in the **aorta.** This signals the brain, which sends signals to the sympathetic nerves as well as the RAAS.



Unfortunately with age the kidney can lose the ability to accurately judge its own blood flow so it will improperly cause renin to be released, causing an endless feedback loop that makes the blood pressure get out of control. And the brain will forget what the BP is supposed to be. :(
So how do we choose a drug for HTN?

2014 JNC8 Hypertension Guidelines suggest:
Lifestyle Changes:
Stop smoking, reduce alcohol consumption
Reduce salt ro <2400 mg/day
DASH diet/MyPlate etc
Moderate activity
No diabetes:
Under 60 years: Goal 140/90
Over 60 years Goal 150/90
African American: Thiazide or CCB as first line
Non-black: Thiazide, CCB, ACEI or ARB as first line

Diabetes present:
Same as above but goal 140/90 all ages
Be cautious with thiazides

If chronic kidney disease (CKD) is present
Regardless of race, **add ACEI or ARB**

Unfortunately, not all patients respond to the above drug classes. Luckily:

There are many STRATEGIES TO TREAT HYPERTENSION:

REMEMBER: **ALL drugs that lower BP can potentially cause orthostatic hypotension**!

To reduce volume overload:
DIURETICS (see prior handout): Remember about monitoring for electrolyte imbalances!
Osmotics*: the sponges. Not for CHF! For anuria/oliguria*
Mannitol (IV): good for brain swelling
Glycerin (oral)

Carbonic Anhydrase Inhibitors: *works a few days only for HTN or HF*
Acetazolamide – *works longer-term for glaucoma &* ***altitude sickness***

Loop Diuretics- *hypoK (& also digoxin toxicity!), hypo Mg, hypoCa, ototoxicity, gout*
furosemide- *sulfa allergy*
bumetanide
Can use in patients in kidney failure but not anuria (zero urine output)

Thiazides – a *first line drug for mild hypertension*

bad for diabetics, hypoK (digoxin toxicity), sulfa allergies, gout

hydrochlorothiazide (HCTZ)

Potassium Sparing Diuretics-*hyperK*

eplerenone, **spironolactone** (aldosterone antagonists)

triamterine, amiloride (act on the DCT Na/K pumps)

conivaptan (ADH antagonist)

To reduce sympathetic stimulation from the brain:

CENTRAL-ACTING SYMPATHETIC DRUGS

Alpha-TWO agonist: On the adrenergic synapse, recall that there was a mechanism for re-uptake of norepinephrine. There is *also* a special receptor there (unfortunately called the alpha-2 receptor) which actually inhibits the release of more NE!

So an AGONIST of the alpha-2 receptor actually INHIBITS stimulation of the sympathetic nervous system by the brain. Confusing!

These are drugs that act at the medulla oblongata to suppress sympathetic activity, so vessels dilate and the heart slows down. Right? Examples: alpha-methyldopa, clonidine

Side effects: dry mouth, **bradycardia.**

Clonidine can be **po or a weekly patch.**

doesn't affect kidney flow so can use in kidney patients

WARNING: **If you stop clonidine suddenly: get hypertensive crisis and/or HF!**

To block sympathetic receptors in the heart and kidney:

BETA-BLOCKERS: **atenolol**, **metoprolol**, **propranolol**

Beta-blockers reduce heart rate and contractility but ALSO

reduce the release of **renin** from kidneys, leads to vasodilation and drop in blood pressure.

Beta-blockers ALSO act to reset the baroreceptors so the body will accept a lower blood pressure as "normal"

Side effects: Depression, impotence, lung (beta-2) effects, etc etc etc etc

Long-term beta-blocker patients **should have their drug tapered** if they stop using it (in case you forgot)

To dilate blood vessels

ALPHA-BLOCKERS: block vasoconstriction, vessels relax

prazosin

Side effects: ***"first dose effect"*** and orthostatic hypotension

CALCIUM CHANNEL BLOCKERS: block Ca movement (& contraction) smooth muscle

Blood vessels relax (dilate) and blood pressure drops

verapamil & diltiazem:

These two affect the heart more than other Ca^{++} channel blockers.

Remember verapamil is good for dysrhythmias!

nifedipine , amlodipine and other calcium channel blockers:

Don't depress the myocardium in the short term and more commonly used

For just hypertension

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

captopril *(Capoten),* **enalopril** *(Vasotec)*

Side effect: **weird dry cough, *first dose effect***

"first dose effect "of hypotension

Because of effect on aldosterone can get hyperkalemia

Preg Cat D in 2nd/3rd trimester (RAAS drugs kill fetus)

ANGIOTENSIN RECEPTOR BLOCKERS
Example: **losartan** *(Cozaar); also Category D, right?*

DIRECT RENIN INHIBITORs
Ex. aliskerin *(Tekturna)*

ANGIOTENSIN RECEPTOR BLOCKERS NEPRILYSIN INHIBITORS ARNIs
sacubitril/valsartan *(Entresto)*
see p7

DIRECT-ACTING VASODILATORS
Since these act to directly dilate blood vessels they cause a big drop in blood pressure to which the body responds by increasing the heart rate (**reflex tachycardia**).
You can give these along with something like a beta-blocker to prevent the reflex tach.

hydralazine – side effect of **lupus, +isosorbide** in *BiDil*

minoxidil (*Rogaine*)- side effect of hair growth

sildenafil (*Viagra, Revatio*) – mostly used for Erectile dysfunction, but also pulmonary hypertension causes major vessel dilation
Don't combine with nitrates!

sodium nitroprusside – if used emergently and given IV, causes big drop in blood pressure.

ANTICOAGULANTS, THROMBOLYTICS

Glossary of Terms:

Anticoagulants = **drugs that prevent blood clots formation. They do NOT break down existing clots.**

Antiplatelet agent = a drug that interferes with the activation or aggregation of platelets like ASA

Clotting factor = one of many enzymes, usually named by a roman numeral (like II, V, or VIII), each getting activated by the previous one in a "cascade" that leads to a clot being formed.

Deep Vein Thrombosis (DVT) = a blood clot in a major vein, usually in the leg, often due to inactivity

Embolus: a clot or undissolved matter that is carried along in the blood until it lodges somewhere and occludes (blocks) the vessel; it can be a clot, air, fat, talc, powder, etc.

Platelet = a small cell fragment in the blood stream important in forming clots

Pulmonary Embolism (PE) = a clot or solid object that travels through the veins and becomes lodged in the lungs, blocking blood flow and oxygen exchange. Frequently due to a clot such as a DVT, but can also be from other causes.

Thromboembolism = an abnormal clot which completely blocks a blood vessel, rather than sealing an injury, and thus causes the tissue around that blood vessel to die.

Thrombolytic agent = a drug that breaks down a clot that has already formed

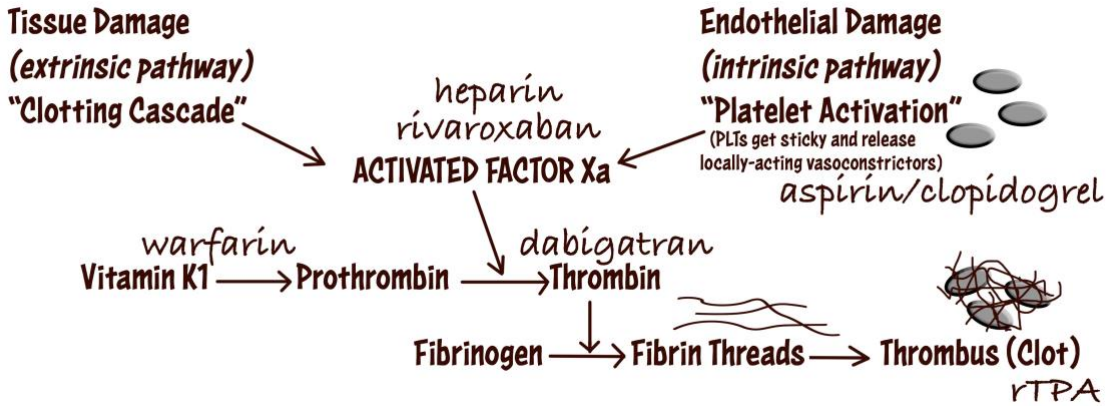
Thrombus = a blood clot

Vitamin K1 = a vitamin crucial to formation of many clotting factors, discovered by a German (coagulation in German starts with a "K". Don't confuse this with potassium: "K^{+}")

SITUATIONS THAT CAN LEAD TO BLOOD CLOTS:

Turbulence: Irregular heart beat, bad valves, prosthetic valves
Stagnation: Bed-ridden/ Immobility/ paralysis during surgery
Trauma: Tissue Injury or Injury to Blood Vessels
Disease: Infection, cancer
Genetics: Defects in natural anticoagulant proteins such as Protein C or protein S

To *make* a clot: clotting occurs on cell surfaces, and there are three *basic* steps:



To *break up* a clot the body has all sorts of things to break up fibrin and thrombin like:

Plasmin: breaks up fibrin

Antithrombin (**AT**, also called Antithrombin III or ATIII):
Inactivates Factor X (does this *really* well if heparin is also around)

Protein C, protein S: inhibit various clotting factors
if C or S is genetically absent, patients die young from clots (stroke, MI)

Tissue Plasminogen Activator (tPA) tPA binds fibrin, fibrin activates plasminogen to plasmin, plasmin breaks down fibrin.

ANTICOAGULANTS

	HEPARIN	**WARFARIN *(Coumadin)***
Mechanism of Action	Helps Antithrombin III to **inhibit Factor Xa.** Also inhibits *free* thrombin	**Antagonizes Vitamin K1** and thus the production of several clotting factors, Blocks action of prothrombin
Indications	Prevent or prevent the worsening of a **DVT or PE**, short-term for high-risk (major long GI or cardiac surgery, DIC (Deseminated Intravascular Coagulation), **dialysis**	Deep Vein Thrombosis DVT Used prophylactically in patients with hi risk for thrombus: Rheumatic heart disease **Atrial fibrillation** **Prosthetic valve**
Contraindications	**Bleeding** situations or possibilities (CNS, eye, spinal surgery, hemophilia, etc), if you can't monitor PTT, active bleeding (except DIC)	**Bleeding** disorders (hemophilia), CNS surgery (brain, eye, spinal tap), bacterial endocarditis, unsupervised demented patient
Side effects	**Bleeding**	**Bleeding**
Safe for Pregnancy?	Yes, sort of, Category C	**No! Category X** **Fetal Warfarin Syndrome** Crosses placenta & interferes with bone formation of fetus
Pharmacokinetics	**IV, SQ**. Never IM Metabolized in LIVER	**PO** Metabolized in LIVER 99% bound to protein Half-life =37 hours **Takes 3-4 days** to get maximum effect!
How to monitor	a**PTT** time (Partial Thromboplastin Time) until is 1.5-2x control value	**INR** value… to 2-3 for most patients to get effect (Above 4 is too high)
Antidote	**Protamine sulfate** (Forms a salt with heparin and neutralizes it)	**Vitamin K** (Patients need to know about effects of dietary Vitamin K on their clotting risk)
Drug Interactions	**Bleeding risk increases** with: ***Aspirin, NSAIDS***, penicillin **Bleeding risk decreases** with: Digoxin, tetracycline, antihistamines, nicotine	**MANY MANY** drug interactions. Anything that: -induces P450: barbiturates -inhibits platelets: **aspirin** -displaces it from protein: sulfinpyrazone (a gout drug) -decreases absorption of po warfarin cholestyramine (a GI drug) ...and many more

Low Molecular Weight Heparin (LMWH) is not as effective as standard heparin but has higher bioavailability and doesn't need as intensive monitoring. It's only given SQ. Special procedure for injection can prevent hematoma

All anticoagulants require monitoring of the blood, either by PTT (heparin), INR (warfarin) or regular blood and platelet counts.

Note: Patients are sometimes put on heparin in the hospital **at the same time** they are started on warfarin. Once their warfarin blood levels are therapeutic, the i.v. heparin can be stopped and the patient can be discharged home.

ANTIPLATELET ANTICOAGULANT DRUGS

	ASPIRIN *(review)*	**CLOPIDOGREL *(Plavix)***
Mechanism of Action	**Inhibits platelet aggregation** by inhibiting the COX enzymes (involved in inflammation & causes platelets to change shape and aggregate) **Irreversible**	Block the ADP receptor on platelets. Thus, **blocking platelet aggregation.** Also **irreversible.**
Indications	**Reduces risk of MI and mortality** in patients with **angina**. Reduces risk of stroke. Additive with warfarin in high-risk cases (prosthetic heart valve) mild **pain** **fever** **inflammation**	Reduces risk of artherosclerotic events like MI, stroke and other vascular death **angina** **acute MI** in combination with ASA **allergy/sensitivity to Aspirin** Cardiac Stent placement Peripheral arterial disease, recent MI, stroke
Contraindications	Hemophilia, **Bleeding**, **Kids** (esp **w/**chicken pox or **flu- Reye Syndrome**)	**Bleeding** Severe liver disease
Side effects	**GI ulcer:** at pain/fever doses **Bleeding** ***Salicylism****:* Tinnitus, nausea, vertigo (reversible) Very high doses: respiratory depression, liver damage, cardio toxicity	**GI distress** **Bleeding** Rarely severe neutropenia (your white cells disappear. This is bad)
Other concerns	**Bleeding**	**Bleeding**
Safe for Pregnancy?	Category C	Category B
Pharmacokinetics	PO Metabolized in LIVER Half-life=15 minutes But **effect on platelets is irreversible**	PO **Black Box Warning: Will not work well in patients with poor CYP2C19 function.** Metabolized in LIVER to its active form by CYP2C19
How to monitor	CBC	CBC
Drug Interactions	Increased bleeding risk **(esp. GI**) with alcohol, corticosteroids. Decreases effect of spironolactone and tetracycline	Increased bleeding risk with other anticoagulants. Interferes with some P450 enzymes in liver.

Other anticoagulant or otherwise helpful drugs:
Ticlopidine (Ticlid) PO: like Plavix. Also cilostazol *(Pletal)* PO, used for intermittant claudication
Dipyridamole (Persantine): helps warfarin in prosthetic heart valve patients
Glycoprotein IIb/IIa-receptor antagonists: abciximab *(Reopro)- a receptor binding antibody*
-eptifibatide *(Integrilin)* & tirofiban: used IV in acute cases.
Direct thrombin inhibitors: argatroban, lepirudin

Intermittant claudication: pain of muscle brought on by exercise because the blood supply to that muscle is bad. Like angina, but in a skeletal muscle. Can be legs, or jaw, anywhere

pentoxyfilline (*Trental*): a methylxanthene. Methylxanthenes are drugs like caffeine found in tea, coffee, chocolate and elsewhere. They can raise heart rate (to the point of dysrhythmia), cause vasodilation and some are good for asthma. One form called pentoxyfilline (*Trental*) decreases blood viscosity, improves blood flow and is used for intermittent claudication. It seems to make red blood cells more bendy and flexible so they can squeeze through narrowed vessels.

THROMBIN INHIBITORS AND FACTOR Xa INHIBITORS

	DABIGATRAN *(Pradaxa)*	**RIVAROXABAN *(Xarelto)***
Mechanism of Action	**Binds all thrombin** and so **prevents formation of fibrin.** Less likely to cause serious bleeding than warfarin	Binds activated Factor X (Xa) to **prevent formation of thrombin** Less likely to cause serious bleeding than warfarin
Indications	**Atrial fibrillation** Knee or hip replacement.	Nonvalvular **Atrial Fibrillation** Knee or hip replacement **DVT or PE** after hip or knee replacement
Contraindications	**Black Box Warning: Don't stop the drug or your chance of a clot goes up.** (Duh?) & **can cause hematoma in spinal tap** Bleeding	**Black Box Warning: Don't stop the drug or your chance of a clot goes up.** (Duh?) & **can cause hematoma in spinal tap** Bleeding Severe liver disease
Side effects	Stomach pain (take with food) **Bleeding**	**Bleeding**
Other concerns	**Bleeding**	**Bleeding**
Safe for Pregnancy?	Category C	Category C
Pharmacokinetics	PO Not metabolized so be careful with renal patients	PO Highly protein bound
How to monitor	Generally no need	Generally no need
"Antidote"	**idarucizumab *(Praxbind)***	-
Drug Interactions	Levels increased with drugs that inhibit p-glycoprotein Chance of bleeding *much* worse if another anticoagulant used in combination	CYP3A4 Levels increased with drugs that inhibit p-glycoprotein Chance of bleeding *much* worse if another anticoagulant used in combination

Approved 2017: betrixaban *(Bevyxxa):* approved to prevent venous clots in acutely ill patients in hospital at risk because of restricted mobility without increased risk of bleeding.

THROMBOLYTIC DRUGS

These are drugs used to ***break up a clot*** that has already formed.

Tissue Plasminogen Activator (tPA): the artificially-made version of this is:

Alteplase *(Activase)* aka rTPA

Mechanism of Action: Artificial recombinant human tPA

Activates plasminogen to plasmin, which breaks down fibrin

Indication: Acute Myocardial Infarction (to clear the blocked coronary arteries)

Acute stroke (blocked blood vessel in brain)

Acute Pulmonary Embolism

Works best if used soon after start of problem (MI: 6 h, Stroke: 3h)

Contraindication: Acute bleeding

-So for stroke, a head scan has to prove there is no bleeding before you can use!

-Pregnancy or delivery in last 10 days increases risk of bleeding

Side effect: bleeding

Pharmacokinetics: IV, half-life 8 minutes Metabolized by liver

Others like Altepase/rTPA:

-Reteplase (Retavase): like Altepase, not used for PE, cheaper

-Streptokinase: made from beta-hemolytic streptococcal bacteria which leads to weird pharmacokinetics: half-life 12 minutes unless the patients has had a strep infection before, then it is up to 2h.

-Urokinase: like streptokinase, except it is made from cultured human kidney cells and is really expensive

DRUGS that STOP BLEEDING or help FORM CLOTS:

Other terms (in addition to those highlighted above):

Hemophilia: an inherited disorder of blood coagulation

Hemostasis: the arrest of bleeding

(not to be confused with homeostasis: the state of equilibrium in the body and the processes by which that equilibrium is maintained…)

aminocaproic acid (*Amicar*)

Mechanism: blocks plasminogen activator and plasmin

Indication: emergency situations with systemic bleeding disorders (severe trauma, some cancers, abruptio placentae, others)

IV or PO

antihemophilic factors *(many trade names)*

Mechanism: replaces missing clotting factors in hemophilia patients (usu. Factor VIII)

Topical hemostatic agents

Used in dental, neurosurgical, oral procedures, for bloody noses (epistaxis) or oozing bleeding

Consist of various films or gels or collagen sheets (i.e. Gelfoam, Avitene, Surgicel,

Topical thrombin can also be used in this way

Other situations: nose bleeds: vasoconstrictors (pressure & pressure dressings, cautery)

LIPID-LOWERING DRUGS

Numerous studies show high cholesterol, familial hypercholesterolemia, diabetes, smoking, lack of exercise, obesity and hypertension increase risk of heart disease.
Lowering LDL-cholesterol, total cholesterol and TG can reduce risk of MI in these patients by 10%-30% (depending on the study; however, most studies also include exercise, weight loss and dietary changes, so…?)

Dietary Guidelines for Americans, 2015-2020:
Acceptable Macronutrient Distribution Range for fats is 20-35% of calories from fat
(Note: people trying to lose weight do better with 20-25% fat, not zero!)

2013 ACC/AHA Guidelines determined that it wasn't helpful to try to reach a "goal" LDL level, but rather the intensity of treatment should be tailored to the patients' risk factors
10-year risk for AtheroSclerotic CardioVascular Disease (ASCVD) can be calculated with a number of free web pages or apps.

Quick Nutrition Review:
Dietary fats come in three forms:
Triglycerides (glycerol + 3 fatty acids) (TGs): most fats in the diet come like this
Phospholipids (glycerol + 2 fatty acids): i.e. lecithin
Sterols: i.e. cholesterol and cholesterol esters
Fatty acids come in 4 forms:
Saturated fatty acids: replacement with polyunsaturated fats seems to reduce risk
trans fatty acids artificially manufactured by "hydrogenation", increase risk
Unsaturated and possibly decrease risk for heart disease
Omega-3 fatty acids: supplements are not helpful. Maybe dietary ones are?
Cholesterol in the body comes from your liver (75%) and your food (25%)

Digestion of fats:
As fat enters the intestine, bile is secreted from the gallbladder. Bile emulsifies the fat
Fat globules at the intestinal brush border are broken into glycerol and fatty acids
Inside the intestinal cell, the fatty acids are repackaged into triglycerides and along with protein are made into chylomicrons which have a shell of phospholipids so they can dissolve in blood.
Triglycerides are carried in the bloodstream by chylomicrons and VLDL (see below)
Remember that fat-soluble vitamins (ADE & K) require fat for absorption as well.

Serum Lipids are transported in blood as lipoproteins:

- Chylomicrons
- Very-Low Density Lipoproteins (VLDLs)
- Low Density Lipoproteins (LDLs) : <100mg/dL desirable
  "bad cholesterol": *these are NOT cholesterol!* They are proteins (So annoying!)
  Are just VLDLs that dropped off some Triglyceride
  LDLs carry cholesterol to the cells of the body
- High Density Lipoproteins (HDLs) >40mg/dL desirable
  "good cholesterol": *ALSO NOT cholesterol!* They are proteins
  HDLs scavenge extra cholesterol from the body and return it to the liver

Note: **Lipoproteins like LDL & HDL** are made in the body, they are **NOT in your food**

Cholesterol: is required for cell membranes, myelin sheath, steroid molecules and bile
Getting rid of bile lowers the level of cholesterol in the blood
Liver makes all the cholesterol you need, so dietary cholesterol is extra
"Normal levels": <200mg/dL total blood cholesterol
<100 LDL, >40 HDL and <150 TG
These numbers are simply *guidelines* for patients with risk factors…
Total Cholesterol = LDL +HDL +TG/5.

Atherosclerosis is exacerbated by high blood levels of LDL. Each 10% reduction in cholesterol reduces incidence of heart disease 20-30%. High triglyceride levels are also correlated with other risk factors for heart disease.

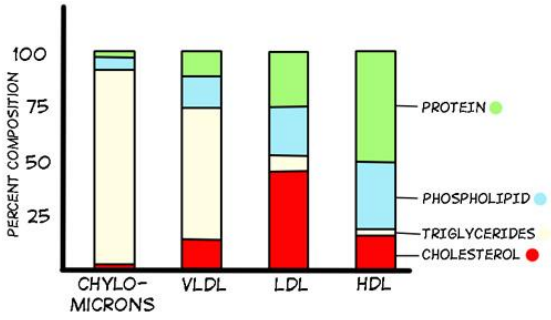
Treatment
First step to reduce LDL: diet modification, especially reducing saturated and *trans* fats and increase exercise
Then: drugs: all reduce cholesterol and most reduce triglyceride levels as well.

Also be aware that there are at least six genetic variants of hyperlipidemia ("familial hypercholesterolemia") that may lead to high lipid levels.
The selection of drugs for these patients depends on which variant the patient has.

HMG-CoA reductase Inhibitors ("Statins")

lovastatin (*Mevacor*, *Altoprev*) - first generation ⇓ LDL 30%
simvastatin (*Zocor*) ⇓ LDL 45%
also marketed: simvastatin+ezetembe (*Vytorin*), simvastatin+niacin (*Simcor*)
atorvastatin (*Lipitor*) ⇓ LDL 60%
rosuvastatin *(Crestor):* better than atorvastatin and almost NO P450 metabolism
pravastatin (*Pravachol*), pitacastatin (*Livalo*),

Mechanism of action: The statins are all analogs of HMG, the precursor to cholesterol. They block the action of HMG-CoA reductase and reduce the intracellular supply of cholesterol. This in turn increases the number of LDL receptors on the cells' surfaces and the LDL receptors gobble up circulating LDL.
How cool is this: Most statins undergo first-pass metabolism, so they mostly only act on the liver, which is perfect!



Warnings: **Myopathy** (muscle damage aka rhabdomyolysis) – leads to kidney failure.
Check **creatinine kinase** (CK) for this, warn patients about muscle pain
Dose-related, so other drugs that raise statin levels should be taken cautiously
Liver dysfunction - check "LFT"s at start of treatment and if liver injury symptoms occur (jaundice, pain, fatigue…)
Increased **blood glucose**
Confusion
Contraindications: several antibiotics (e.g. erythromycin), some antifungals (e.g. itraconazole), some HIV drugs

Other dangerous interactions with:CYP3A4 inhibitors, gemfibrozil, niacin, verapamil, amiodarone, large amounts of grapefruit juice, etc
Increased chance of muscle injury with: fibrates, niacin, ranolazine, gout medications
Pregnancy Category X
Most studies on patients age 40-75, usually recommended only if **ASCVD** risk >10%

Note: **Chinese red yeast rice** contains lovastatin as well as other compounds that may lower LDL and TG. The red yeast rice supplement *Cholestin™* was proven useful in controlled studies, but that trade name has been applied to a different formulation that no longer contains the statin, and is no longer monitored by USP. ONLY buy a supplements monitored by the USP!

Omega-2 fatty acids (docosahexaenoic acid (DHA)/ eicopentaenoic acid (EPA))
Omega-3s normally found in: cold water fish like: anchovies, bluefish, carp, catfish, halibut, herring, lake trout, mackerel, pompano, salmon, striped sea bass, tuna (albacore), and whitefish, nuts (especially walnuts) vegetable oils (flaxseed, canola oil, soybeans, olive oil, canola oil), fish sources contain DHA/EPA, plant sources contain alpha-linolenic acid (ALA)
Recent evidence >77,000 patients suggests
Omega-3 SUPPLEMENTS DO NOT reduce cardiovascular risk
March 2018: JAMA Cardiol. 2018;3(3):225-234. *(So get them from your diet!)*

American Heart Association recommends 2 servings of fish per week. No Recommended Daily Allowance

Other drugs that reduce lipids include:
FIBRATES such as: fenofibrate *(Fibricor) or* gemfibrozil *(Lopid)*
that work by increasing fatty acid breakdown in cells
They also can cause myopathy, gallstones, and kidney or liver disease
They also increase warfarin levels.

NIACIN: the vitamin! In very high doses it reduces LDL and increases HDL
However, like all vitamins taken in high dose, there are bad side effects, including flushing of & gout

BILE ACID BINDING RESINS like:
colestipol (*Colestid*), colesevelam (*Welchol*), cholestyramine (*Questran*)
Mechanism of action: Resins bind bile in the intestines and carry the bile out of the body with defecation. Since bile is 70% cholesterol, the liver is forced to take more cholesterol (thus LDLs) from the bloodstream to replenish the bile.
These resins are all giant molecules that aren't absorbed into the bloodstream. They are only taken orally, stay in the gut and are pooped out.
Fun fact: the fiber in oatmeal binds bile the same way, and that is why oatmeal lowers cholesterol!

CHOLESTEROL ABSORPTION INHIBITORS like ezetimibe (*Zetia*)
Mechanism of action:
ezetimibe binds fats and prevents absorption of biliary and dietary cholesterol
Decrease LDL
Often used in combination with statins (synergistic effect)

OATMEAL: contains soluble fiber that adsorbs cholesterol so you **poop it out.**
Other soluble fibers work in a similar way.