CVS pharmacology / Final
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Drugs for heart failure

1 Give a +ve inotropic drug

HF = the heart is failing to pump blood ⟹ Forward failure = less arterial supply to organs (like : Brain, kidneys ↓) & Backward failure (congestion)

Left sided failure → Forward failure will drive the brain & kidneys to compensate (Check the pic below)

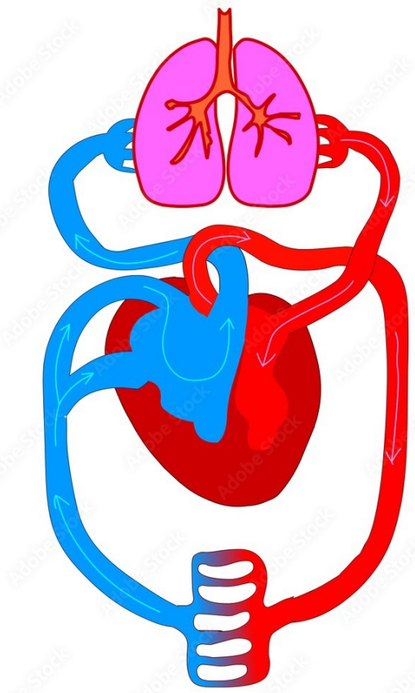
→ Backward failure will cause pulmonary edema & Dyspnea

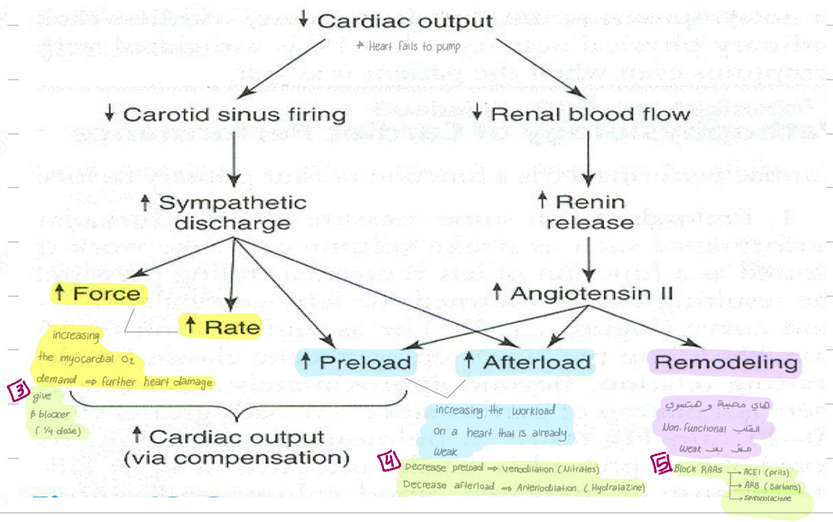
Right sided failure → Forward failure = less oxygenation

→ Backward failure = lower part edema

2 Here, we need diuretics to get rid of fluids

specifically : loop (furosamide)





So, we have many options with different mechanisms, what do we start with ?

- Start with the drug with most targets & less SE ⟹ ACEI → vasoconstriction ↓ → Afterload ↓
  → water retention ↓ → preload ↓
  → congestion ↓

⟹ CHF is a progressive disease ~. During it's course we'll need to add other drugs

But, our last drug is ⟹ +ve inotropic drugs (Dobutamine, Digoxin)

↳ Why ? ↑ mortality rate due to increasing O_2 demand

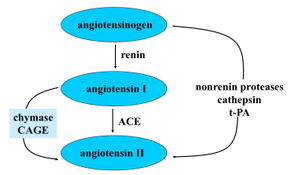
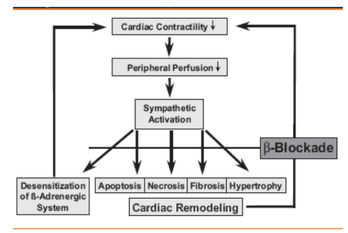
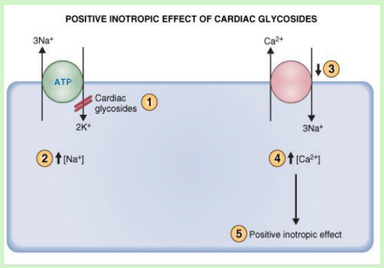
↳ Also used in Acute HF

What is our goal in treatment ?

⇒ Decrease Symptoms

⇒ Slow progression

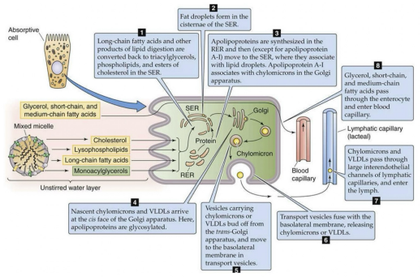
⇒ Improve Survival

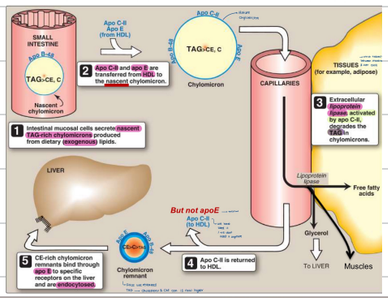
Drugs	MOA & Use	SE	Notes
ACEIs (prils)	-decrease vasoconstriction = less afterload -decrease water retention caused by aldosterone = less preload & congestion → overall = increased CO -ACEIs are considered as single agent therapy in HF pts with mild dyspnea & no signs of volume overload. -1st line therapy	-recall: dry cough, angioedema, hyperkalemia & fetal toxicity.	-pts already have dyspnea, watch for the cough
ARBs (sartans)	-used in pts with persistent symptoms despite ACEIs & β blocker		-can be combined with ACEIs (only in end stage HF) Why? To inhibit the RAAS effect after ACEI effect can be Bypassed
Spironolactone **Eplironone**	-direct aldosterone antagonist -preserved for pts with moderate to severe disease, in which ANGII stimulation can bypass ACE -dose should be no more than 25-50 mg/day -drug shows a special effect on preventing remodeling (as aldosterone is believed to be directly associated with remodeling … aldosterone has many effects, just like cortisol does)	-hyperkalemia -renal dysfunction -CNS effects, like confusion -endocrine abnormalities, like gynecomastia (only spirono) -gastric disturbances, like peptic ulcer	-can be combined with ACEIs … BUT, we need to monitor: 1. potassium levels (should be <5 mEq/L) → to prevent hyperkalemia 2. creatinine (should be <2.5 mg/dL for men < 2 mg/dL for women) → to prevent renal failure. - if monitoring isn't feasible… Don't risk! … use vasodilators instead - ACEIs, ARBs & spironolactones can't be all combined
β blockers (small dose- 1/4) **-bisoprolol** **-carvedilol** **-nebivolol**	-improve systolic functioning -reverse cardiac remodeling → due to their ability to prevent changes of the sympathetic system including decreasing the heart rate & inhibiting renin secretion. -they produce benefit on medium to long term. But, on the short term, they produce decompensation with worsening of HF & hypotension.	CI -asthma -2nd or 3rd degree heart block -symptomatic hypotension -use with caution in pts with low initial BP (sys < 90)	
Loop diuretics **-furosamide** **-bumetanide** **-thiazides (only in mild cases)**	-reducing symptoms overload, by: -decreasing extracellular volume -decreasing venous return -used in pts with pulmonary edema (causing dyspnea) or systemic edema -the dose should be individualized to decrease fluid retention without causing dehydration or renal dysfunction.	-hypokalemia	
Vasodilators **Hydralazine & nitrates (isosorbide)**	-used for Pts with persistent symptoms despite taking ACEI and β blocker. Pts who cannot be given ACEI or ARB, because of drug intolerance, hypotension or renal insufficiency. African Americans		
Digitalis **-digoxin** 	**Positive inotropic effect** Inhibiting the Na-K pump → Intracellular Na+ increases → Ca ++ efflux by passive Na+_Ca++ channel decreases → intracellular Ca++ increases → contractility of myocytes increases. **Negative chronotropic effect** By stimulation of the vagus nerve → digoxin does exactly what we need to treat a HF pt. … no good oral inotropic agents exist other than digoxin (amazing drug!) -last drug to be used in chronic HF -pts with mild to moderate HF will usually respond to ACEIs and diuretics, and do not need digoxin. -digoxin has a rapid onset of action (5-30 min)… useful in emergencies, in which the drug is given IV	-intoxication - symptoms: 1. increase in its parasympathetic effect -Anorexia, nausea (1st sign), vomiting, diarrhea -vision changes (xanthopsia :seeing yellow spots) -fatigue, headache 2.increase in intracellular positivity (easy firing) -Arrhythmias (PVC, V.tach, V.fib, A.tach)	**Narrowest therapeutic window** Dose = 0.25 mg -anything that can slightly increase the activity/ con. of digoxin is contraindicated: 1.Diuretics → they cause hypokalemia, increasing its activity 2.Macrolide and tetracycline antibiotics → they decrease the microbiome, increasing the con. of digoxin. 3.Quinidine → replaces digoxin on albumin 4.verapamil/ amiodarone → compete on renal secretion (those two are anti arrhythmic … watch out!) --> all those agents can lead to digoxin intoxication
β agonists **-Dobutamine**	-positive inotropic & chronotropic effect -the most used inotropic agent after digoxin -like digoxin, its either used in severe chronic HF or in acute HF	-although β1 selective, it can still bind to β2 causing VD and increasing the hypotension.	

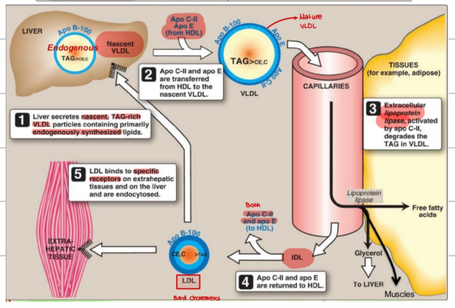
Drugs for hyperlipidemia

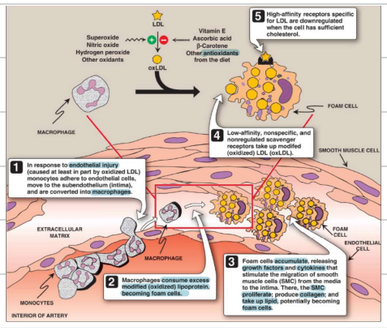
Recall lipid metabolism

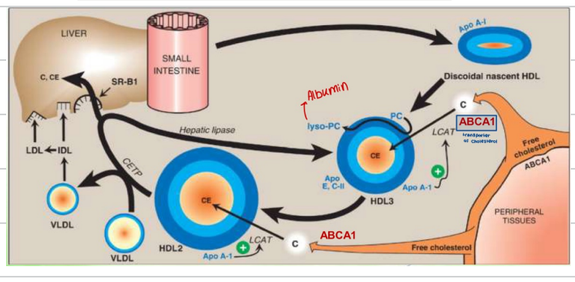
Absorption











→ Lipids (TAGs, Cholesterol)

Intestinal lumen —Diffusion→ enterocytes —lipoprotein (Chylomycron)→ lymph (lacteals) —At thoracic duct end→ Blood —on the way: lipoprotein lipases take TAGs (TAG rich Chylomicron → Cholesterol rich)→ Liver

liver

→ Cholesterol Synthesis [Rate limiting enzyme = HMG-co reductase

→ production of VLDL → into the blood —TAGs by lipoprotein lipase→ LDL (Bad Cholesterol)

Why? increased LDL + vessel injury → inflammation → Macrophages with Scavenger receptor

phagocytize LDL → Foam cells → Accumulation in vessel wall → Atherosclerosis

↳ Why would LDL increase? High F.A & Cholesterol intake OR Genetic defect in lipid metabolism

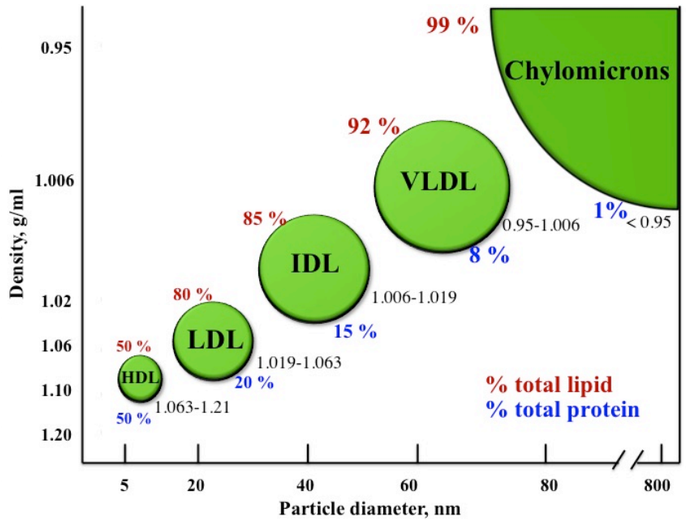
↳ This doesn't only cause Atherosclerosis ... It's also associated with HF.

→ production of HDL (Good Cholesterol)

Why? it's responsible of transporting cholesterol from tissues to liver

Where do hepatocytes get F.A from? → De novo Synthesis

↳ From Adipocytes by Hormone Sensitive Lipase



Antihyperlipidemic drugs

- Antihyperlipidimic drugs must be taken indefinitely, when terminated plasma levels return to pretreatments levels.

- Antihyperlipidimic drugs target the problem with complimentary strategies, including:

  1. decrease production of the lipoproteins carriers of cholesterol and triglyceride.

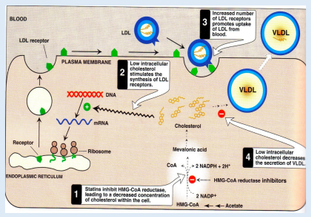
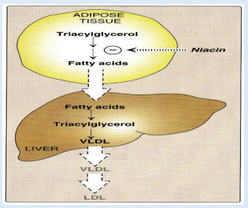
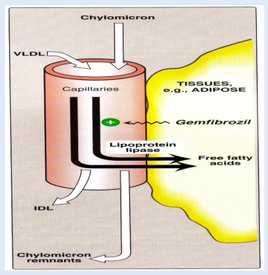
  2. others increase the degradation of lipoproteins.

  3. decrease cholesterol absorption or directly increase cholesterol removal from the body.

- These agents may used as a singly or in combination.

Hyperlipoproteinemia		Labs description
Type I	Familial hyperchylomicronemia	Elevated Chylomicrons and VLDL
Type IIa	Familial hypercholesterolemia	Elevated LDL only
Type IIb	Combined hyperlipidemia	Elevated LDL and VLDL and Triglycerides
Type III	Familial Dysbetalipoproteinemia	Increased IDL
Type IV	Familial Hyperlipemia	Increased VLDL
Type V	Endogenous Hypertriglyceridemia	Increased VLDL and Chylomicrons

Anti hyperlipidemia

Drugs	MOA	SE	Notes
Statins **-Lovastatin** **-Pravastatin** **-Simvastatin (40 mg)** **-Fluvastatin** **-Cerivastatin** **-Atrovastatin (20 mg)** **-Rosuvastatin (10 mg)** 	-HMG CoA reductase inhibitors → no cholesterol synthesis in the liver. -liver response: 1. increase in LDL receptors on hepatocytes → Receptors can bind and internalize circulating LDL → reduction in plasma cholesterol (LDL). 2. increases HDL synthesis from the liver → HDL brings the liver cholesterol from foam cells → reduces atheroma production. THERE IS NO DRUG AS STATIN IN TREATING HYPERLIPIDEMIA. —used before sleeping	**Myopathy** -<u>How?</u> By inhibiting Q enzyme in the electron transport chain in skeletal muscles → less ATP production = weak muscles. -nearly 20% of women, less in men. -SE increases with large doses. **Rhabdomyolysis** Progression of myopathy leads to muscle death Its very very very rare **Kidney failure** A result of rhabdomyolysis due to myoglobin accumulation. -elevate liver enzymes (AST& ALT) Not significant but you need to evaluate liver fun. -contraindicated in pregnant, breast feeding women & in children and teenagers.	-the guidelines suggest using the *highest possible dose* of statins for *maximal efficacy*. -all statins have the same efficacy, but they differ with <u>*potency*</u>. -meaning that, the drug with highest potency can give you the maximal efficacy with smaller dose. -why is that so important? MYOPATHY We need to increase the dose and have the maximal efficacy with minimal myopathy → so, we use the most potent drugs (in blue) -for statins to reach their site of action, they need a transporter (SLOP1P). This receptor is highly polymorphic, and its one of the reasons why some people will have myopathy rather than others. -If we test this transporter activity, we can predict myopathy possibility. -Drug interactions: Verapamil & amiodarone increase the risk of myopathy.
Niacin (vitamin B3) 	-inhibits hormone sensitive lipase in adipose tissues → reduces circulating free fatty acids + reduces VLDL. -increases HDL in an unknown mechanism → decreases cholesterol. أو على الأقل هيك كانوا مفكرين -for 10 years (2009-2020), Niacin was prescribed for type IIb and IV pts. As an add on drug with statins. Later on, it was discovered that this drug had no effect.	**Flushing, itching, burning, GI irritation, nausea, vomiting, peptic ulcer activation** By increasing arachidonic acid → increase inflammatory PG → increase permeability of blood vessels. **Hyperglycemia** By inhibiting insulin release from pancreas **Hyperuricemia** CI in gout pts. -elevation of liver enzymes.	
Fibrates **-Fenofibrate** **-Benzafibrate** **-Gemfebrozil** 	-Bind PPAR (peroxisome proliferator activated receptors) → increase expression of lipoprotein lipase → lower serum level of <u>TAGs (mostly VLDL)</u> -increase HDL	-gastrointestinal disturbances -lithiasis -what does it mean? Formation of gallstones & obstruction of bile duct -how does it happen? Fibrates inhibit α hydroxylase enzyme (which is responsible of bile acid production) → bile with less bile acid = very lipidic & viscous bile → high risk of gallstones. -myositis (inflammation of voluntary muscles)	

Drug combinations

- Background of drugs kinetics & dynamics

  Statins → lova , Simva , atorva ⇒ Metabolized by CYP3A4
  → Fluva , Rosuva ⇒ Metabolized by CYP2C9
  → prava ⇒ Metabolized by Sulfation (CYP450 independent)

  Fibrates → Gemfibrazol ⇒ inhibits CYP450 (finfibrate doesn't)

- Why do we need to combine ?

  - Remember , our typical Jordanian pt. (IIb) has → Elevated LDL (we need Statins)
    → Elevated VLDL (we need fibrates)

- When combining , keep in mind :

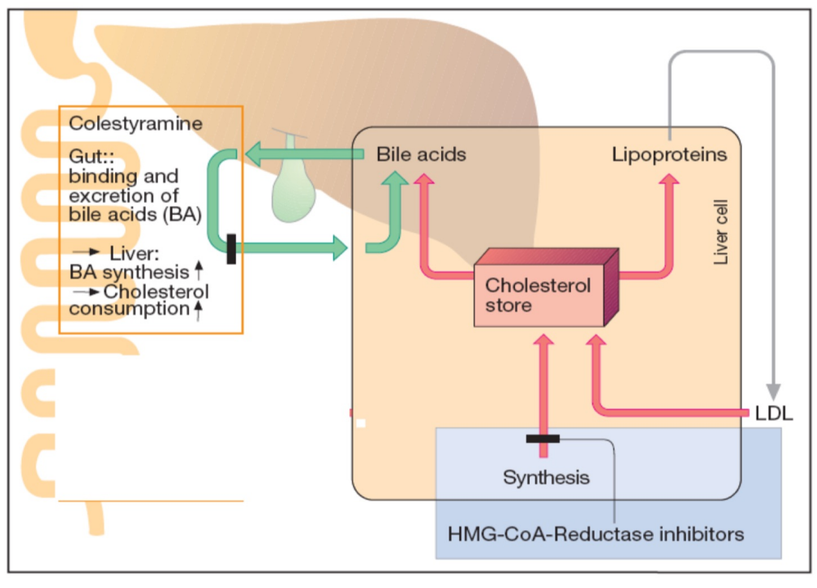
  1. Both drugs have Side effects on muscles ... given together may lead us to Rhabdomyolysis ⇒ Solution : Give Statin at night , fibrate in the morning
  2. Drug interactions → Gemfibrazol can only be given with pravastatin (CYP450 independent)
     → Finfibrates can be given with all Statins

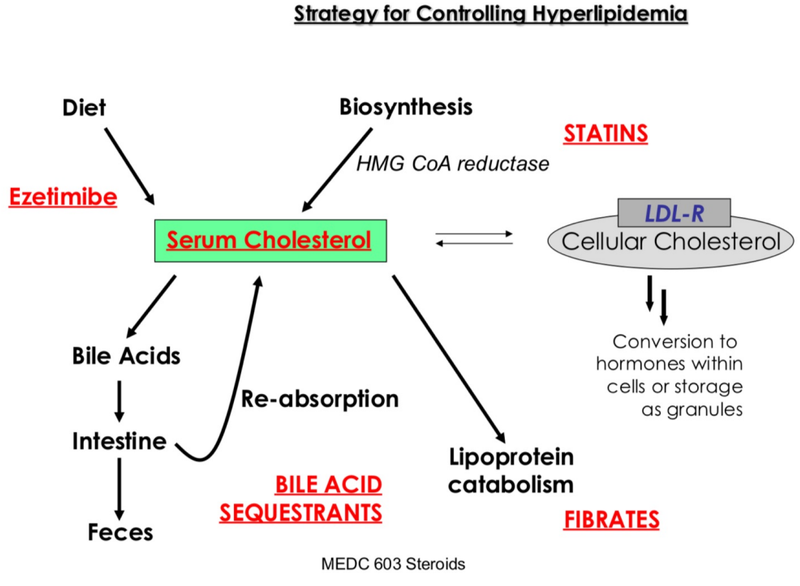
     ] in any combination , Don't forget واحد الصبح , واحد المسا

✡ Note : grapefruit juice also inhibits CYP450

Anti hyperlipidemia

Drug	MOA	Use	SE
Bile acid binding resins **-cholestyramine** **-colestipol**	- they bind bile acid in the intestine → forming insoluble complexes that will be excreted in feces → lowering bile acid will trigger the liver to use cholesterol in the synthesis of new bile acid → reduction in cholesterol concentrations (thus, LDL). - drug is taken <u>with food</u>, to insure secretion of bile acid into gut lumen.	- significant <u>LDL & cholesterol</u> lowering effect, although less efficient than statins. -so, usually used as add on drugs with statins in pts with low response to statins. - drugs of choice to treat type IIa hyperlipidemia (familial hypercholeserolemia) in combination with diet or niacin.	-**GI disturbances (**since the drug functions there**)** **-**constipation/ nausea **Lipid dependent absorption** - at high doses, they impair the absorption of fat soluble vitamins (A, D, E, K) -interact with the absorption of many drugs Ex. Tetracycline, Digoxin, Warfarin, Aspirin. → those drugs should be taken 1-6 hrs after
Cholesterol absorption inhibitors **-Ezitimibe**	- selectively inhibit intestinal absorption of dietary and biliary cholesterol in the small intestine → resulting in an increase in the clearance of cholesterol from the blood.	-alone, they have a minimal effect in <u>lowering LDL</u>. -with statins, they have a great synergistic effect HOW? Statins inhibit cholesterol synthesis in the liver → body responses with increasing cholesterol absorption. Ezetimibe inhibits the body response to statins, providing better effect.	-headache -diarrhea

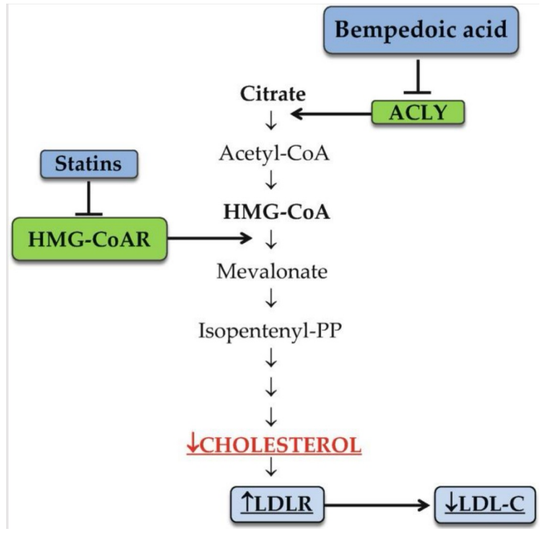
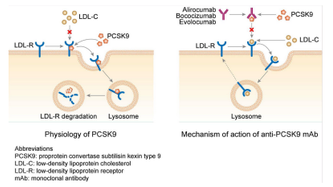
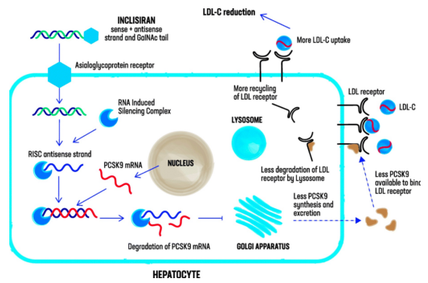
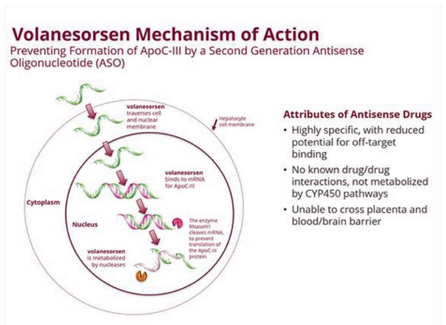
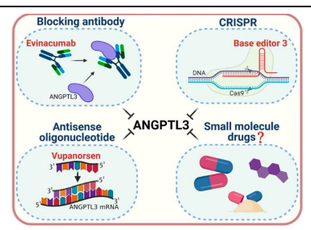




TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
HMG-CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

Figure 21.14
Characteristics of hyperlipidemic drug families. HDL = high-density lipoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl–coenzyme A; LDL = low-density lipoprotein.

Newer lipid lowering drugs (used as add on drugs with statins & fibrates)

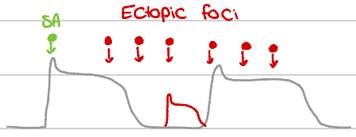
Drug	MOA	SE	Notes
Bempedoic acid **Notice: drug is mainly lowering LDL & cholesterol** **Key: increasing LDLR**	**ATP citrate lyase (ACLY) <u>selective</u> inhibitor →** reduction of cholesterol synthesis in the liver → increased LDLR expression → decrease in plasma cholesterol + increased expression of HDL → extract cholesterol from foam cells. (same mechanism of statins, BUT lower efficacy) <u>What is ACLY?</u> An enzyme that catalyzes the ATP dependent conversion *citrate* and CoA into oxaloacetate and *acetyl CoA.* Which is an early step of cholesterol synthesis in the liver, and comes upstream to HMG CoA synthesis. <u>How is it selective?</u> it is administered as a prodrug → activated by very long chain acyl CoA synthetase 1, which is an enzyme mainly expressed in the liver. This process minimizes the exposure of the active drug to non-hepatic tissues (such as skeletal muscles).	**Kidney effect** Increase of blood urea, nitrogen, creatinine and <u>uric acid.</u> → <u>CI In gout pts + can cause gout</u> **Anemia** Decreases hemoglobin Doesn't cause hyperglycemia or diabetes	
Inhibitors of PCSK9 <u>What is PCSK9?</u> Proprotein convertase subtilisin/ kexin type 9 An enzyme predominantly produced in the liver, and degrades the LDL receptor on hepatocytes, leading to subsequent increase in the plasma LDL-C levels. →Thus, the inhibition of the protein leads to increase in the LDLR. **Notice: drug is mainly lowering LDL & cholesterol** **Key: increasing LDLR**	**Monoclonal Ab (Evolocumab, Alirocumab)**	Flu like symptoms that resolves within a week	
	Inclisarin -it is a synthetic small interfering RNA **(siRNA)** <u>What does that mean?</u> A sequence of dsRNA that is complementary to the PCSK9 sequence. When bound to *RNA induced silencing complex* (RISC), it leads to degradation of its complementary sequence (in this case it's PCSK9 mRNA). Drug is given IV 3 times a year. So, don't worry about compliance.	Injection site reaction.	
Volanesoren **Notice: drug is mainly lowering TGs** **Key: decreasing ApoC III**	ApoC III inhibitor <u>What is ApoC III?</u> An enzyme present in VLDL & chylomicrons. It inhibits lipoprotein lipase → inhibiting lipolysis and raising the blood TGs level. →by inhibiting ApoC III, we increase lipolysis & decrease blood levels of TGs. -loss of function mutations in ApoC III gene is associated with 40% lower plasma TG levels and 40% less risk of CVD. <u>How does the drug work?</u> It is an antisense oligonucleotide (ASO) targeting ApoC III mRNA … ASO has the same MOA of siRNA except that they are single stranded (complementary to the target _ ApoC III)	Thrombocytopenia Injection site reaction	-volanesorsen has been tested in pts with elevated plasma TGs and pts with familial chylomicronemia syndrome (FCS) , an autosomal recessive disease of chylomicron metabolism. -in 2019, it was approved by EU for the treatment of adults with FCS. 
ANGPTL3 inhibitors <u>What is ANGPTL3?</u> Again, a lipoprotein lipase & endothelial lipase inhibitor that regulates plasma TG and HDL-C respectively. --> Inhibiting ANGPTL3 preserves the function of LPL and EL with a subsequent decline in TG, LDL-C and HDL-C.	Evinacumab -monoclonal Ab neutralizing ANGPTL3 serum levels	Flu like symptoms (11%)	
	Vupanorsen -antisense oligonucleotide inhibiting production in hepatocytes.		

Drugs for arrhythmia

Anti - arrhythmic drugs

Background

Arrhythmias have 2 main mechanisms
- Re-entry circuits (Abnormal electrical loops that repeatedly excite myocytes)
  - the loop depends on
    - a critical speed of conduction ⇒ Tx : Drug that Slows down the conduction
    - for a myocyte to fire in response to the loop it needs not to be in the Refractory period ⇒ Tx : Drug that prolongs the RP
- Ectopic foci (Abnormal focus firing independently)

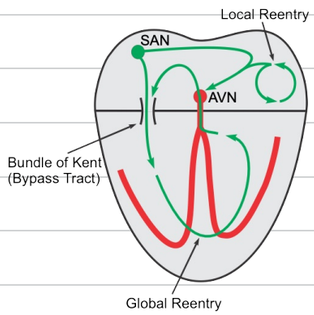


- Notice that: the ectopic foci can generate an AP, thus arrhythmia, ONLY When it fires during phase 4 ⇒ Tx : Drug that prolongs RP
  [When myocytes are not in the refractory period]

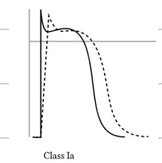
Also, Ectopic foci rely on quick depolarization to trigger abnormal beats. ⇒ Tx : Drug that Slows down the conduction.

Other mechanisms :

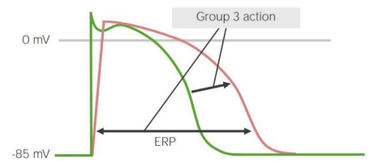
- WPW → tract that bypasses the AV Septum



Refractory period prolongation methods



Blocking Na^+ Channels
→ targeting phase 0



Blocking K^+ Channels
→ targeting phase 3

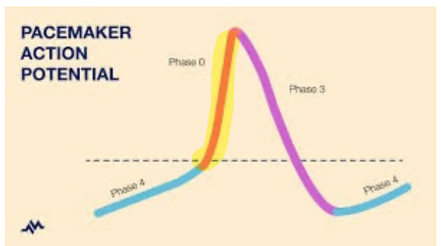
Approach to choosing the Suitable drug

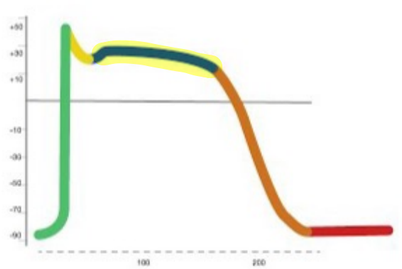
Determine the origin of arrhythmia
- Supraventricular → Start With drugs that target the Conduction via AV node (β-blockers, CCB), No need to risk With Class I / III drugs because an atrial arrhythmia isn't of high risk if we can regulate the ventricles
- WPW → Never inhibit the AV. Otherwise, you will have zero delay of Conduction
- Ventricular → Start With Class I, III drugs that target the circuit / Ectopic foci

Class	Drugs	MOA	Use	SE & CI
Class II	All β blockers except Satolol	- the main effect is reduction in AV node conduction … preventing the atrial tachyarrhythmia to affect the ventricles. - reduction in ectopic atrial/ ventricular automaticity -note : how do β blockers slow down the conduction in AV node ? By inhibiting L-Ca^{++} Channels ⟶ depolarization (phase 0) last more time	- mainly used as a prophylactic drug for pts at risk of arr.	-sinus bradycardia -AV block -mask symptoms of hypoglycemia -contraindicated in asthma -don't forget about withdrawal symptoms
	IId / Digoxin	-activates muscarinic M2 receptor (parasympathetic activation) → slows the electrical conduction in the AV node -M2 receptor is a GPCR: α subunit of the activated G protein decreases Ca influx → decreased excitability (-ve chronotropic effect) γβ subunit activate K+ channels, causing hyperpolarization → slow down AV conduction (-ve dromotropic effect)	-sinus tachycardia -supraventricular tachyarrhythmia	-pro arrhythmic
	IIe / Adenosine	-A1 receptor activators -A1 receptors are GPCR … (same as digoxin, but more significant)	**Emergencies** Acute termination of AV nodal tachycardia and cAMP mediated v. tachycardia. -the drug is given as an alternative to cardioversion shock –given as bolus (single concentrated IV shot) It works within seconds and finishes within seconds.	**-sinus bradycardia** **-sinus arrest or AV block** -nausea, vomiting, diarrhea

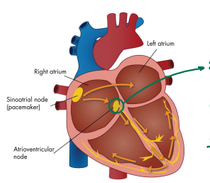
Class	Drugs	MOA	Use
Class IV / CCB	Verapamil Diltiazem (affect cardiac channels)	-decreased excitability of SA/ AV nodes	-Same as β blockers, used as prophylactic drugs.

Remember ⁂ Here is where Ca^{++} channels are functioning :-

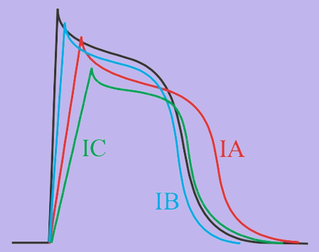




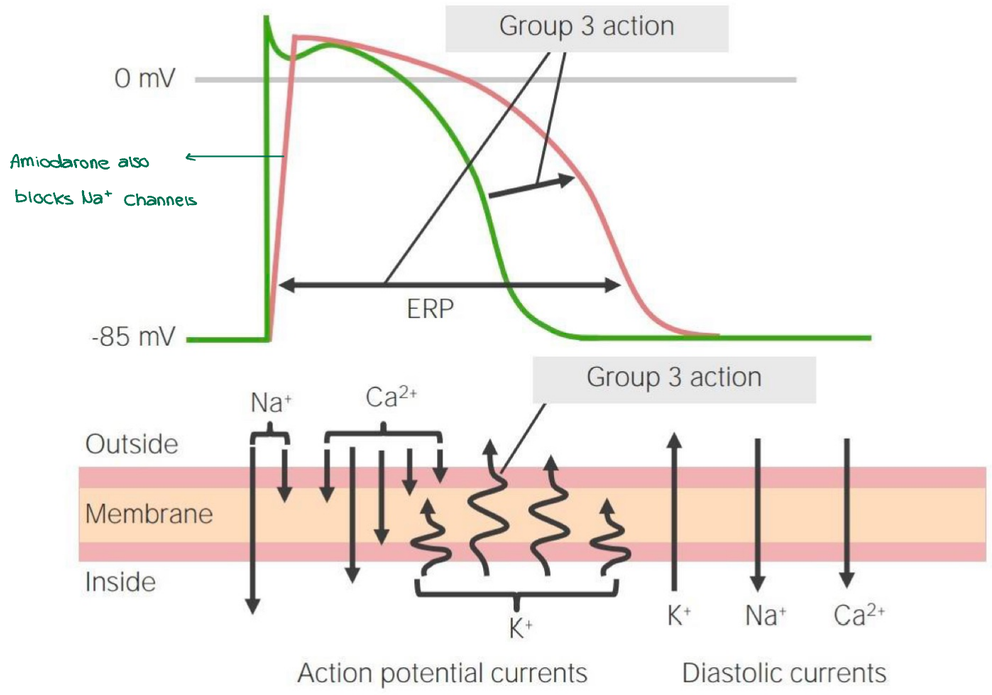
CCB affect both , but more significantly ⟹ So, here is our target



Slowing down the transmission of arrhythmic pulses from Atria to ventricles ⟹ keeping ventricles under control

Class	Drugs	MOA	Use	SE & CI
Class I / Na+ channel blockers Divided according to: 1.the degree of blocking (slope of phase 0) 2.the prolongation of AP (thus, QT interval)  Ventricular Action Potential Class IA: *e.g., quinidine* · Moderate Na^+-channel blockade · ↑ ERP Class IB: *e.g., lodocaine* · Weak Na^+-channel blockade · ↓ ERP Class IC: *e.g., flecainide* · Strong Na^+-channel blockade · → ERP RK 22	Ia -Quinidine -procainamide -Didopyramide	**Degree of blocking** Moderately block the open state of Na channels Effect → moderate decrease in slope (reduction in conduction velocity) **Effect on AP duration** Prolongs the APD and ERP → prolonged QT	-V. tachycardia -A. fib	**CI** -prolonged QT of any reason (drug, congenital…) -with digoxin → it increases the plasma con. of digoxin leading to digitalis toxicity. **Quinidine SE** - QT prolongation → risk of Tosades de pointes - GIT SE: diarrhea, nausea, vomiting - Cinchonism → headache, dizziness, tinnitus **Procainamide SE** - QT prolongation → Torsades de pointes - Lupus like syndrome (rash & arthralgia) - Nausea, vomiting - Fever, hepatitis, pleuritis, pericarditis - Hypotension (bc it unselectively blocks α receptors)
	Ib -Lidocaine	**Degree of blocking** Weakly block inactivated state of Na channels Effect → weak decrease in the slope (reduction in conduction velocity) **Effect on AP duration** Shortens the APD and ERP → no prolonged QT (this isn't problematic bc the drug acts preferentially on ischemic rather than healthy tissues)	-V. tachyarrhythmia (v. tach/ v.fib) -dentists use it for anesthesia -In pts with **Angina, MI, CHF** (where cells' permeability is already abnormal) … Lidocaine is the best choice, because it doesn't have an aggressive effect at the same time, it's capable of bringing the rhythm back to normal.	**CNS side effects** Slurred speech, drowsiness, muscle twitching, seizures
	Ic -Propafenone -Flecainide	**Degree of blocking** Strongly block thr inactivated state of Na channels Effect → marked decrease in the slope (reduction in conduction velocity) **Effect on AP duration** No effect	-supraventricular tachyarrhythmias (a. tach/ a.fl/ a.fib) -ventricular tachyarrhythmias resistant to other treatment	**Flecainide SE** -ventricular tachycardia if pt. has IHD or old MI (contraindicated/ use lidocaine instead) -vision problems -headache, dizziness -teratogenic **Propafenone SE** - ventricular tachycardia if pt. has IHD or old MI (contraindicated/ use lidocaine instead) -slowed sinus rate -chest pain, shortness of breath -dizziness -nausea, vomiting, constipation/ diarrhea
	Id	Includes drug acting on recently reported late Na currents		

Class	Drugs	MOA	Use	SE
Class III / K+ channel blockers	**Non- selective** -Amiodarone -Ambasilide **Selective** -Sotalol -Dofetilide -Ibutilide	-block K+ channels → prolonged repolarization → increased ERP and APD and QT prolongation Don't mix up between -K+ channel activator → hyperpolarization -K+ channel inhibitors → increase APD **Note: amiodarone has a long t1/2**	**Sotalol** Drug of choice for pediatric arrhythmias + arrhythmias of increased sympathetic effect. **Amiodarone** Drug of choice in many ventricular arrhythmias BUT, not those that come with QT prolongation	-QT prolongation → Torsades de pointes -Heart block -bradycardia **Amiodarone SE (iodine is an irritant)** -thyroid abnormalities (hypo/ hyper) -photosensitivity -peripheral neuropathy -pulmonary fibrosis -liver damage -cardiac depression -corneal microdeposits



Good luck