-Lecture 1+2: Antiarrhythmic drugs:

****NOTE: Antiarrhythmic drugs can be classified according to their predominant effects on the action potential…. SEE the next table and memorize it well, then we will talk about each class in details.**

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

****NOTE: Watch this video…. It's very helpful to understand how each class work:**
https://www.youtube.com/watch?v=9xSqezCMHnw

-Class I:

- **Class I act by blocking voltage-sensitive sodium channels.**
- **Class I drugs bind more rapidly to open or inactivated sodium channels than to channels that are fully repolarized. Therefore, these drugs show a greater degree of blockade in tissues that are frequently depolarizing (This property is called use dependence).**
- **Class I drugs are subdivided into 3 groups according to their effect on the duration of the ventricular action potential…… See the next table.**

Name of the drug+ Class subtype	Mechanism of action	Therapeutic uses	pharmacokinetics	Adverse effects
Quinidine (IA)	-Binds to open and inactivate sodium channels and prevents sodium influx, thus slowing the rapid upstroke during phase 0. -Decreases the slope of phase 4 depolarization, inhibits potassium channels, and blocks calcium channels. >>> As a result, it slows conduction velocity and increases refractoriness. -Has mild α-adrenergic blocking and anticholinergic actions.	-In atrial, AV junctional, and ventricular tachyarrhythmias.	-Complete absorption after oral intake. -Hepatic metabolism by CYP450 3A4 to form active metabolite.	-Cinchonism (Look at note 1 below the table). -Drug interactions (Inhibitor of CYP2D6 and P-glycoprotein).
Procainamide (IA)	-Similar to Quinidine but has less anticholinergic action and no α-blocking activity.	-Acute atrial and ventricular arrhythmia but it is replaced by electrical cardioversion or defibrillation and Amiodarone.	-IV intake. -Short duration of action (2-3 hours). -part of it is acetylated in the liver to NAPA, which prolongs the duration of action potential (Look at note 4). -NAPA is eliminated via the kidney.	-Hypotension.
Disopyramide (IA)	-Similar to Quinidine but has more anticholinergic activity and no α-blocking activity. -Produce negative inotropic effect. -Causes peripheral vasoconstriction. -Decrease myocardial contractility in patients with systolic heart failure.	-Ventricular arrhythmia as an alternative for Quinidine and Procainamide. -Maintain the sinus rhythm in atrial fibrillation of flutter.	-Well absorbed after oral intake. -Metabolized in the liver to a less active metabolites and several inactive metabolites. -Substrate of CYP3A4. -half of it is excreted unchanged by the kidneys.	-Most anticholinergic adverse effects.

Lidocaine (IB)	-Blocks sodium channels. -Shorten phase 3 repolarization and decrease the duration of the action potential.	-Alternative for Amiodarone in ventricular fibrillation or pulseless ventricular tachycardia. -In polymorphic VT or in combination with Amiodarone for VT storm. -little effect on atrial and AV junctional arrhythmias.	-IV intake because of extensive first-pass metabolism (no oral intake). -Dealkylated to 2 less active metabolites by CYP1A2 primarily and CYP3A4. -High extraction drug (Look at note 2).	-Has a wide therapeutic index. -No negative inotropic effect. -Low impairment of the left ventricle. -CNS effect: Nystagmus, drowsiness, slurred speech, agitation, paresthesia, confusion, and convulsions.
Mexiletine (IB)	-Similar to Lidocaine.	-Chronic treatment of ventricular arrhythmias, often in combination with Amiodarone.	-Well absorbed after oral intake. -Metabolized in the liver by CYP2D6 to inactive metabolites. -Excreted by the biliary route.	-Has narrow therapeutic index. -Caution must be used when taking the drug with inhibitors of CYP2D6. -Nausea, vomiting, and dyspepsia are common.
Flecainide (IC)	-Suppresses phase 0 upstroke in Purkinje and myocardial fibers, which causes slowing of conduction in all cardiac tissue, with minor effect on the duration of action potential and refractoriness. -Automaticity is reduced by an increase in the threshold potential.	----------	-Absorbed orally. -Metabolized by CYP2D6 to multiple metabolites. -The parent drug + metabolites are eliminated renally.	-well tolerated. -Blurred vision, dizziness, and nausea are common.
Propafenone (IC)	-Similar to Flecainide but doesn't block potassium channels.	----------	-Metabolized to active metabolites primarily via CYP2D6, and also by CYP1A2 and CYP3A4.	-Similar to Flecainide but also may cause bronchospasm so it must be avoided in patients with asthma.

			-The metabolites are excreted in the urine and feces.	-Inhibitor of P-glycoprotein.

****NOTES on class I:**

1-Symptoms of cinchonism are: blurred vision, tinnitus, headache, disorientation, psychosis.

2-Lidocaine is a high extraction drug, so drugs that lower hepatic blood flow (β-blockers) may require Lidocaine dose adjustment.

3-Quinidine is the prototype class IA drug.

4-NAPA has properties and side effects of a class III drug.

5-Class IB agents rapidly associate and dissociate from sodium channels so the action of these agents are manifested when the cardiac cell is depolarized of firing rapidly. They are useful for treating ventricular arrhythmias.

6-Class IC drugs slowly dissociate from resting sodium channels and show prominent effect even at normal heart rate.

-Class II:

Name of the drug	Mechanism of action	Therapeutic uses	Pharmacokinetics
Metoprolol	-Diminish phase 4 depolarization, thus depress automaticity, prolong AV conduction, and decrease heart rate and contractility	-Treating tachyarrhythmias caused by increased sympathetic activity. -For atrial flutter and fibrillation. -For AV nodal reentrant tachycardia -Prevent life-threatening ventricular arrhythmias after a MI.	-Reduces the risk of bronchospasm. - extensively metabolized in the liver primarily by CYP2D6 and has CNS penetration.
Esmolol			-Fast onset and a very short duration of action. -used for IV intake in acute arrhythmias that occur during surgery. -Rapidly metabolized by esterases in RBCs>>> NO drug interactions.

-Class III: ⟹ **Class III agents block potassium channels, so they prolong the duration of the action potential and the effective refractory period, without altering phase 0 of depolarization or the resting membrane potential.**

Name of the drug	Mechanism of action	Therapeutic uses	pharmacokinetics	Adverse effects
Amiodarone	-Contains iodine related to thyroxine. -Has class I, II, III, and IV actions. -Has α-blocking activity. -Blocks potassium channels >>> prolongs the duration of action potential and the refractory period.	-For severe refractory supraventricular and ventricular tachyarrhythmias. -For the rhythm management of atrial fibrillation or flutter. -It's the most used antiarrhythmic drug.	-Incompletely absorbed after oral intake. -Have a long half-life and distributes in adipose tissues. -Metabolized by CYP3A4. -needs months for full clinical effect.	-Pulmonary fibrosis. -Neuropathy. -Hepatotoxicity. -Corneal deposits. -Blue-gray skin discoloration. -Hypo or hyperthyroidism.
Dronedarone (Amiodarone derivative)	-Has class I, II, III, IV actions. -Doesn't have iodine moieties.	-Maintain sinus rhythm in atrial fibrillation or flutter.	-Less lipophilic, has lower tissue accumulation, and a shorter serum half-life than Amiodarone	-better than Amiodarone. -Causes liver failure. -Contraindicated in patients with symptomatic heart failure or permanent atrial fibrillation.
Sotalol	-The levorotatory isomer (l-sotalol) has β-blocking activity, and d-sotalol has class III action. -Blocks a rapid potassium current (known as delayed rectifier)>>> prolongs repolarization and duration of action potential.	-Maintain sinus rhythm in patients with atrial fibrillation, atrial flutter, or refractory paroxysmal supraventricular tachycardia. -Treatment of ventricular arrhythmias. -For patients with left ventricular hypertrophy or atherosclerotic heart disease.	-Renally eliminated.	-adverse effects of β-blockers. -To reduce the risk of proarrhythmic effects, it's often initiated in the hospital to monitor QT interval.
Dofetilide	-Pure potassium channel blocker.	-In persistent atrial fibrillation and heart failure or in coronary artery disease.	-Half-life= 10 hours. -eliminated unchanged in the urine	-Limited to inpatient setting because of the risk of proarrhythmia.
Ibutilide	-Activates the inward sodium current	-For chemical conversion of atrial flutter.	-Undergoes extensive first-pass metabolism and is not used orally.	-Limited to inpatient setting (because of risk of QT prolongation).

-Class IV:

Class IV drugs are nondihydropyridine calcium channel blockers. There major effect is on vascular smooth muscle and the heart.

Verapamil shows greater action on the heart than on vascular smooth muscle, and Diltiazem is intermediate in its actions.

Name of the drug	Mechanism of action	Therapeutic uses	Pharmacokinetics
Verapamil	-Bind only to open depolarized voltage-sensitive channels. -Prevent repolarization until the drug dissociates from the channel. -Slow conduction in tissues that are dependent on calcium currents, such as AV and SA nodes.	-More effective against atrial than against ventricular fibrillation. -Useful in treating reentrant supraventricular tachycardia and reducing the ventricular rate in atrial flutter and fibrillation.	-Metabolized in the liver by CYP3A4. -They are inhibitors of CYP3A4, as well as substrates and inhibitors of P-glycoprotein.
Diltiazem			

-Other antiarrhythmic drugs

Name of the drug	Mechanism of action	Therapeutic use	pharmacokinetics	Adverse effects
Digoxin	-Inhibits the Na+/K+-ATPase pump>>shorten the refractory period in atrial and ventricular myocardial cells while prolonging the refractory period and diminishing conduction velocity in the AV node.	-Control ventricular rate in atrial fibrillation and flutter. -Serum concentration of 1-2 ng/ml are desirable for atrial fibrillation or flutter, whereas concentration of 0.5-0.8 are targeted for systolic heart failure.	----------	-Causes ectopic ventricular beats that may result in VT and fibrillation (At toxic concentration).
Adenosine	-At high doses, it decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node.	-IV intake for abolishing acute supraventricular tachycardia.	-Short duration of action due to rapid uptake by RBCs and endothelial cells (10-15 seconds).	-Flushing. -Chest pain. -Hypotension.
Magnesium sulfate	-Slows the rate of SA node impulse formation and prolongs conduction time along the myocardial tissue.	-For fatal arrhythmia torsades de pointes and digoxin-induced arrhythmia	-IV intake (not oral).	_____

Lecture 3+4: Antihypertensives:

-Diuretics:

-The initial mechanism of action of diuretics is based upon decreasing blood volume, which ultimately leads to decreased blood pressure.

Group + Name of the drugs	Mechanism of action	Therapeutic uses	Adverse effects
Thiazide diuretics: Hydrochlorothiazide, Chlorthalidone	-Lower blood pressure initially by increasing sodium and water excretion>>>causes a decrease in extracellular volume>>>resulting in a decrease in cardiac output and renal blood flow	-Useful in combination therapy with a variety of other antihypertensive agents, including β-blockers, ACE inhibitors, ARBs, and potassium-sparing diuretic.	-Hypokalemia. -Hyperuricemia. -Hyperglycemia.
Loop diuretics: **Furosemide, Torsemide, Bumetanide, Ethacrynic acid.**	-Act by blocking sodium and chloride reabsorption in the kidney. -Cause decreased renal vascular resistance and increased renal blood flow.	-Manage symptoms of heart failure and edema.	-Hypokalemia. -Unlike Thiazides, it increases the calcium content of urine.
Potassium-sparing diuretics: **1-Amiloride and Triamterene (inhibitors of epithelial sodium transport at the late distal and collecting ducts).** **2-Spironolactone and Eplerenone (aldosterone receptor antagonists).**	-Reduce potassium loss in the urine.	-Diminish the cardiac remodeling that occurs in heart failure. -In combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.	----------

➡ **NOTE: With the exception of metolazone, thiazide diuretics are not effective in patients with inadequate kidney function (estimated glomerular filtration rate less than 30mL/min/m2). Loop diuretics may be required in these patients.**

-Other classes: **The next table will include some classes: β-blockers, ACE inhibitors, ARB, Renin inhibitors, α-Adrenergic-blocking agents, α-/β-Adrenoceptor-blocking agents, and vasodilators:**

Class + name of the drugs	Mechanism of action	Therapeutic uses	pharmacokinetics	Adverse effects
β-Blockers	-Reduce blood pressure by: 1-Decreasing cardiac output. 2-Decrease sympathetic outflow from the CNS. 3-Inhibit the release of renin.	-Hypertensive patients with concomitant heart disease, such as: 1-Supraventricular tachyarrhythmia (for example, atrial fibrillation). 2-Previous MI. 3-Angina pectoris. 4-Chronic heart failure	-Oral intake. -Propranolol undergoes extensive first-pass metabolism. -Esmolol, Metoprolol, Propranolol are available for IV intake.	-Bradycardia. -Hypotension. -CNS side effects like fatigue and insomnia -Decrease libido and cause erectile dysfunction. -Disturb lipid metabolism. -Abrupt withdrawal may cause angina, MI, death in IHD patients.
ACE inhibitors: **Enalapril, Lisinopril,** **Captopril, Fosinopril, Enalaprilat.**	-Reduce blood pressure by reducing peripheral vascular resistance without increasing cardiac output or HR. (LOOK at the notes below the table).	-Slow the progression of diabetic nephropathy and decrease albuminuria. -Decrease intraglomerular pressures. -MI. -Treatment of systolic dysfunction. -Heart failure. -Hypertension + chronic kidney disease. -Coronary artery disease.	-Oral intake. -All but Captopril and Lisinopril undergo hepatic conversion to active metabolites. -Fosinopril is the only drug that isn't eliminated by the kidney. -Enalaprilat is the only drug available IV.	-Dry mouth. -Rash. -Fever. -Altered taste. -Hypotension. -Hyperkalemia. -Dry cough. -Angioedema (because of increased levels of bradykinin). -Contraindicated in pregnant women.
ARB: **Losartan, Irbesartan.**	-Blocks the AT1 receptors>>> decreasing the activation of AT1 receptors by angiotensin II. -Similar to ACE inhibitors in producing arteriolar and venous dilation and blocking aldosterone secretion>>> lowering blood pressure and decreasing salt and water retention BUT they don't increase bradykinin levels.	-Hypertension with: 1-Diabetes. 2-Heart failure. 3-Chronic kidney disease.	----------	-Similar to ACE inhibitors BUT the risk of cough and angioedema is decreased. -Contraindicated in pregnant women. -Should not be combined with ACE inhibitors.

Renin inhibitors: **Aliskiren.**	-Lowers blood pressure by inhibiting renin secretion.	-Hypertension.	-Metabolized by CYP3A4.	-Diarrhea. -cough. -Angioedema. -contraindicated in pregnancy. -should not be used with ACE inhibitors or ARB.
α-Adrenergic-blocking agents: **Prazosin, Doxazosin,** **Terazosin**	-Block α1-adrenoreceptors >>>decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle	-No longer used as initial treatment for hypertension, BUT may be used for refractory cases. -Other α1-blockers are used for the treatment of benign prostatic hyperplasia	----------	-Reflex tachycardia. -Postural hypotension
α-/β-Adrenoceptor-blocking agents: **Labetalol, Carvedilol.**	-Block α1, β1, and β2 receptors.	-Carvedilol is an antihypertensive and is also used in heart failure. -Labetalol is used in the management of gestational hypertension and hypertensive emergencies.	----------	----------
Vasodilators: **Hydralazine, Minoxidil.**	-Produce relaxation of vascular smooth muscle>>>decrease peripheral resistance>>>reduce blood pressure.	-Hydralazine is always used with a β-blocker to balance the reflex tachycardia and a diuretic to decrease sodium retention>>>this combination decreases cardiac output, plasma volume, and peripheral vascular resistance. -Hydralazine is used in controlling blood pressure in pregnancy induced hypertension.	----------	-May cause angina pectoris, MI, or cardiac failure (so we give them in combination with a β-blocker and a diuretic). -Headache. -Tachycardia. -Nausea. -Sweating. -Lupus-like syndrome. -Minoxidil causes Hypertrichosis.

**Notes:

➡ **Nebivolol is a selective blocker of β1 receptors, which also increases the production of nitric oxide, leading to vasodilation.**

➡ **Conditions that discourage the use of β-blockers include reversible bronchospastic disease such as asthma, second- and third-degree heart block, and severe peripheral vascular disease.**

➡ **ACE inhibitors lowers the blood pressure by:**

1-Blocking the ACH which cleaves angiotensin I to form angiotensin II (A potent vasoconstrictor).

2-Prevent the breakage of bradykinin (A peptide that increases the production of nitric oxide and prostacyclin …… a potent vasodilators) by ACE.

3-Decrease the secretion of aldosterone, resulting in decreased sodium and water retention.

4-Reduce both cardiac preload and afterload, thereby decreasing cardiac work.

➡ **Chronic treatment with ACE inhibitors achieves sustained blood pressure reduction, regression of left ventricular hypertrophy, and prevention of ventricular remodeling after a MI.**

➡ **Carvedilol, as well as Metoprolol succinate, and Bisoprolol have been shown to reduce morbidity and mortality associated with heart failure.**

-Calcium channel blockers (CCB):

➡ **The next table will show the classes of CCB:**

Class and name of the drugs	Cardiac/vascular effect	Treatment of
Diphenylalkylamines: Verapamil	-On both	-Treat angina. -Supraventricular tachyarrhythmia. -Prevent migraine and cluster headache.
Benzothiazepines: Diltiazem	-on both (BUT less negative inotropic effect on the heart compared to Verapamil).	----------

Dihydropyridines: **Nifedipine (the prototype), Amlodipine, Felodipine, Isradipine, Nicardipine, and Nisoldipine**	-Greater affinity on vascular calcium channels.	-Hypertension.

Now, this table will discuss the mechanism of action, therapeutic uses, pharmacokinetics, and adverse effects of CCB.

Mechanism of action	Therapeutic uses	Pharmacokinetics	Adverse effects
Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature>>> which causes vascular smooth muscle to relax, dilating mainly arterioles (Calcium channel blockers do not dilate veins).	-Hypertension with: 1-Asthma. 2-Diabetes. 3-Peripheral vascular disease. -Treatment of angina. -Diltiazem and Verapamil are used in the treatment of atrial fibrillation.	-Short half-lives (3-8 hours) after oral intake. -Amlodipine have a very long half-life and doesn't require a sustained-release formulation.	-First-degree atrioventricular block and constipation are side effects of Verapamil. -Verapamil and diltiazem should be avoided in patients with heart failure or with atrioventricular block due to their negative inotropic and dromotropic effects. -Dizziness, fatigue, headache>>> with dihydropyridines. -Peripheral edema. -Nifedipine may cause gingival hyperplasia.

-Centrally acting adrenergic drugs:

Name of the drug	Mechanism of action	Therapeutic uses	pharmacokinetics	Adverse effects
Clonidine	**-Acts as α2 agonist >>>inhibits sympathetic vasomotor centers, decreases sympathetic outflow to the periphery>>>this leads to reduced total peripheral resistance and decreased blood pressure**	**-treatment of hypertension that has not responded adequately to treatment with two or more drugs** **-Treatment of hypertension complicated by renal diseases.**	**-Oral intake.** **-Eliminated by the kidney.** **-Available in a transdermal patch.**	**-Sedation.** **-Dry mouth.** **-Constipation.**

Methyldopa	**-α2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS.**	**-Management of hypertension in pregnancy.**	**----------**	**-Sedation.** **-Drowsiness.**

-Hypertensive emergency: is a rare but life-threatening situation characterized by severe elevations in blood pressure (systolic greater than 180 mm Hg or diastolic greater than 120 mm Hg) with evidence of impending or progressive target organ damage (for example, stroke, MI).

****A variety of medications are used, including:**

1-Calcium channel blockers (nicardipine and clevidipine).

2-Nitric oxide vasodilators (nitroprusside and nitroglycerin).

3-Adrenergic receptor antagonists (phentolamine, esmolol, and labetalol).

4-The vasodilator hydralazine.

5- The Dopamine agonist fenoldopam

-Hypertensive urgency: A severe elevation in blood pressure without evidence of target organ damage.

-Resistant hypertension: Blood pressure that remains elevated (above goal) despite administration of an optimal three-drug regimen that includes a diuretic.

****Causes:**

1-Poor compliance.

2-Excessive ethanol intake.

3-concomitant conditions: Diabetes, obesity, Sleep apnea.

4-Concomitant medications: NSAIDs, sympathomimetics.

*****NOTE: Initiating therapy with two antihypertensive drugs should be considered in patients with blood pressures that are more than 20/10 mm Hg above the goal.**

****NOTE: Watch this video…. It's very helpful to understand how each class work:**

https://www.youtube.com/watch?v=V2sEay-E-Ro

-Lecture 5: Drugs for hyperlipidemia:

****NOTE: The next table shows the drugs for hyperlipidemia:**

Class + name of the drugs	Mechanism of action	Therapeutic uses	Pharmacokinetics	Adverse effects
HMG CoA reductase inhibitors (statins): **Lovastatin, Simvastatin, Pitavastatin, Rosuvastatin, Atorvastatin, Pravastatin, Fluvastatin.**	-Inhibits HMG CoA reductase>>> depletion of intracellular supply of cholesterol>>> the cell increases the number of cell surface LDL receptors that bind LDL>>> plasma cholesterol is decreased. **Plasma cholesterol is reduced, by both decreased cholesterol synthesis and increased LDL catabolism.	-Lowers plasma cholesterol levels in all types of hyperlipidemia (BUT patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs.	-Lovastatin and Simvastatin are lactones that are hydrolyzed to the active drug. The remaining are taken in their active form. -Metabolized in the liver. -Excreted primarily by bile and feces, but some by urine.	-Their dominant effect is on the liver: 1-Elevated liver enzymes. 2-Hepatic insufficiency. -Myopathy and rhabdomyolysis. -May increase the effect of Warfarin. -Contraindicated in pregnancy and lactation.
Niacin (Nicotinic acid).	-Inhibits lipolysis in adipose tissue>>> reduce production of free fatty acids. **Reduce liver TGs levels>>> decrease hepatic VLDL production>>> reduces LDL-C plasma concentrations.	-Treatment of familial hyperlipidemias (because it lowers plasma levels of cholesterol and TGs). -Treatment of other severe hypercholesterolemias.	-Oral intake. -Converted to nicotinamide, which is incorporated into the cofactor NAD+. -Niacin and its metabolites are excreted in the urine.	-Intense cutaneous flush (taking Aspirin before taking Niacin decreases the flush). -Pruritus. -Nausea and abdominal pain. -Hyperuricemia and gout. -Impaired glucose tolerance. -Hepatotoxicity (IT MUST be avoided in hepatic disease).

Fibrates: **Fenofibrate, Gemfibrozil.**	-Activates the peroxisome proliferator-activated receptors (PPARs)>>> which bind to peroxisome proliferator response elements>>> which decreases TGs concentrations through increased expression of lipoprotein lipase and decreased apo CII concentration.	-Treatment of hypertriglyceridemias. -Treatment of type III hyperlipidemia (dysbetalipoproteinemia) in which IDL accumulates	-Oral intake. -Distribute widely bound to albumin -Fenofibrate is converted to Fenofibric acid. -Eliminated in the urine as glucuronide conjugates.	-GI disturbances. -Gallstones. -Myositis. -Myopathy and rhabdomyolysis in patients taking Gemfibrozil and statins. -Increase the effects of Warfarin.
Bile acid-binding resins: **Colesevelam, Colestipol, Cholestyramine.**	-Binds to negatively charged bile acids and bile salts in the small intestine>>> the resin/bile complex is excreted in the feces, which lowers the bile acid concentration>>> hepatocytes increase the conversion of cholesterol to bile acid>>> intracellular cholesterol concentration decreases>>> activates the hepatic uptake of cholesterol containing LDL >>> a fall in plasma LDL.	-Treating type IIA (LDL) and type IIB (LDL+VLDL) hyperlipidemias (often in combination with diet or niacin). -Cholestyramine can relieve pruritus caused by accumulation of bile acids. -Colesevelam is indicated for type 2 diabetes.	-Insoluble in water. -Have large molecular weight -Oral intake. -Not absorbed nor metabolized by the intestine. -Excreted in feces	-GI disturbances (Colesevelam has the least effect). -Impair the absorption of the fat-soluble vitamins. -Interfere with the absorption of many drugs (ex: Digoxin, Warfarin)>>> so, other drugs must be taken 1 to 2 hours before or 4 to 6 hours after resins. -May rise TGs levels, so it's contraindicated in patients with significant hypertriglyceridemia.
Cholesterol absorption inhibitor: **Ezetimibe.**	-Inhibits absorption of dietary and biliary cholesterol in the small intestine>>> decrease the delivery of intestinal cholesterol to the liver>>> reduction of hepatic cholesterol stores and increase in clearance of cholesterol from the blood.	----------	-Metabolized in the small intestine and liver via glucuronide conjugation. -Biliary and renal excretion.	-Patients with moderate to severe hepatic insufficiency shouldn't be treated with Ezetimibe.

	-Its primary target of action is the cholesterol transport protein Nieman Pick C1 like 1 protein.			
Omega-3 fatty acids	-Inhibits VLDL and TGs synthesis in the liver.	-4 g of marine-derived omega-3 PUFA daily decreases serum TGs concentration by 25%-30%. -Icosapent ethyl doesn't increase LDL-C as other fish oil supplements. -Omega-3 PUFAs can be considered as an adjunct to other lipid-lowering therapies for individuals with significantly elevated triglycerides (≥500 mg/dL).	----------	-GI effects. -Fishy aftertaste. -Bleeding risk in patients taking anticoagulants.

****Notes:**

⟹ **Potency for LDL-C lower (From the most potent to the least):**

1-Pitavastatin, Rosuvastatin, and Atorvastatin.

2-Simvastatin and Pravastatin.

3-Lovastatin and Fluvastatin.

⟹ **Simvastatin is metabolized by cytochrome P450 3A4, and inhibitors of this enzyme may increase the risk of rhabdomyolysis.**

⟹ **Niacin can reduce LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C. It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 grams/day.**

⟹ **The use of Gemfibrozil is contraindicated with Simvastatin.**

⟹ **The omega-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in marine sources such as tuna, halibut, and salmon.**

-Combination drug therapy:

⟹ **It is often necessary to use two antihyperlipidemic drugs to achieve treatment goals in plasma lipid levels. For example, the combination of an HMG CoA reductase inhibitor with a bile acid–binding agent has been shown to be very useful in lowering LDL-C levels.**

⟹ **many experts recommend maximizing statin dosages and adding niacin or fibrates only in those with persistently elevated triglycerides (greater than 500 mg/dL) or those with low HDL cholesterol levels (less than 40 mg/dL).**

⟹ **Treatment with HMG CoA reductase inhibitors (statins) is the primary treatment option for hypercholesterolemia.**

⟹ **If indicated, niacin and fibric acid derivatives are the most efficacious in lowering triglycerides.**

⟹ **Triglyceride reduction is a secondary benefit of the statins, with the primary benefit being reduction of LDL-C.**

****NOTE: Watch this video…. It's very helpful:**

https://www.youtube.com/watch?v=Of1Aewx-zRM

-Lecture 6: Anti-anginal drugs:

⟹Treatment strategies: 4 types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina:

1-β-blockers.

2-Calcium channel blockers.

3-Organic nitrates.

4-Sodium channel–blocking drug.

****The next table shows these drugs:**

Class + name of the drugs	Mechanism of action	Therapeutic uses	Pharmacokinetics	Adverse effects
β-blockers.	-Decrease the oxygen demands of the myocardium during exertion and at rest by blocking β1 receptors, resulting in decreased: 1-Heart rate. 2-Contractilitly. 3-Cardiac output. 4-Blood pressure.	-Used to increase exercise duration tolerance in patients with effort-induced angina. -Recommended as initial antianginal therapy unless contraindicated (See the notes below the table. -Reduce the risk of death and MI in patients who have had a prior MI.	----------	----------
Calcium channel blockers: **1-Dihydropyridine CCB (Amlodipine and Nifedipine).** **2-Non-dihydropyridine CCB: (Verapamil and Diltiazem).**	-Inhibits the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds (SO they are vasodilators). -They reduce the myocardial oxygen consumption by decreasing vascular resistance, thereby decreasing afterload.	-Amlodipine is useful in the treatment of variant angina caused by spontaneous coronary spasm. -Verapamil slows AV conduction >>> decreases heart rate, contractility, blood pressure, and oxygen demands. -Diltiazem slows AV conduction, decreases the rate of firing of the sinus node pacemaker, is a coronary vasodilator, and can relieve coronary artery spasm (USEFUL in patients with variant angina).	-Amlodipine and Nifedipine are taken orally.	-Verapamil is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities. -Should be avoided in patients with heart failure (because of its negative inotropic effects).

Organic nitrates: **Nitroglycerin,** **Isosorbide mononitrate.**	-Relax vascular smooth muscle by their intracellular conversion to nitrate ions>>> then to nitric oxide>>> which activates guanylate cyclase and increases the cell's cGMP>>> which leads to dephosphorylation of the myosin light chain -Nitroglycerin cause dilation of the large veins>>> reduces preload>>> reduces the work of the heart.	-For angina precipitated by exercise or emotional stress, sublingual form of Nitroglycerin is the drug of choice.	-The onset of action varies from 1 minute for Nitroglycerin to 30 minutes for Isosorbide mononitrate. -Sublingual or transdermal intake of Nitroglycerin (to avoid the first-pass metabolism in the liver). -Isosorbide dinitrate is taken orally and undergoes denitration to 2 mononitrates.	-Headache. -Postural hypotension. -Facial flushing. -Tachycardia.
Sodium channel blocker: Ranolazine.	-Inhibits the late phase of the sodium current>>> improve the oxygen supply and demand equation.	-For angina. -For arrhythmia. -For chronic angina. -In patients who have failed other antianginal therapies.	-Metabolized in the liver mainly by CYP3A family and also by CYP2D6. -Substrate for P-glycoprotein.	-Prolongs the QT interval -Headache. -Constipation. -Edema.

****Notes:**

⟹ **Agents with intrinsic sympathomimetic activity (ISA) such as Pindolol should be avoided in patients with angina and those who have had a MI.**

⟹ **β-Blockers should be avoided in patients with severe bradycardia; however, they can be used in patients with diabetes, peripheral vascular disease, and chronic obstructive pulmonary disease, as long as they are monitored closely.**

⟹ **Verapamil mainly affects the myocardium, whereas Amlodipine exerts a greater effect on smooth muscle in the peripheral vasculature. Diltiazem is intermediate in its actions.**

⟹ **Verapamil has greater negative inotropic effects than amlodipine, but it is a weaker vasodilator**

⟹ **Phosphodiesterase type 5 inhibitors such as Sildenafil potentiates the action of the nitrates. So, to preclude the dangerous hypotension that may occur, this combination is contraindicated.**

⟹ **Tolerance can be overcome by providing a daily Nitrate-free interval" to restore sensitivity to the drug. This interval of 10 to 12 hours is usually taken at night because demand on the heart is decreased at that time (However, variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. Therefore, the Nitrate-free interval in these patients should occur in the late afternoon).**

-Lecture 7: Drugs for heart failure:

****Note: The next table shows the drugs for heart failure:**

Class + name of the drugs	Mechanism of action	Therapeutic uses	pharmacokinetics	Adverse effects
ACE inhibitors: **Fosinopril, Captopril….**	-Decrease preload and afterload>>> increased cardiac output. -Blunt the usual angiotensin II-mediated increase in epinephrine and aldosterone seen in HF.	-In patients with asymptomatic and symptomatic HFrEF (heart failure with reduced ejection fraction). -For all stages of left ventricular failure.	-Absorbed after oral intake. -Food may decrease the absorption of Captopril (MUST be taken on empty stomach). -Renal elimination except for Fosinopril. -Half-lives varies from 2-12 hours.	-Postural hypotension. -Renal insufficiency. -Hyperkalemia. -Dry cough. -Angioedema. -Contraindicated in pregnancy.
ARB: **Losartan, Valsartan**	-Decrease preload and afterload	-As a substitute for ACE inhibitors in those patients with severe cough or angioedema.	-Oral intake. -Dosed once-daily except Valsartan which is taken twice a day. -Have large volumes of distribution except for Candesartan. -Losartan undergoes extensive first-pass hepatic metabolism. -Eliminated in urine and feces.	-Similar to ACE inhibitors but has lower incidence of cough and angioedema. -Contraindicated in pregnancy.
Aldosterone antagonists: **Spironolactone, Eplerenone.**	-Spironolactone prevents salt retention, myocardial hypertrophy, and hyperkalemia. -Eplerenone is a competitive antagonist of aldosterone at mineralocorticoid receptors.	-For severe stages of HFrEF or HFrEF with recent MI.	----------	-Eplerenone has a lower incidence of endocrine-related side effects due to its reduced affinity for glucocorticoid, androgen, and progesterone receptors.

β-blockers: **Carvedilol, Bisoprolol, Metoprolol succinate.**	-Decrease HR and inhibit release of renin in the kidneys -prevent the deleterious effects of norepinephrine on the cardiac muscle fibers.	-Reduce mortality and morbidity associated with HFrEF.	----------	----------
Diuretics	-Decrease plasma volume>>> decrease preload>>>decrease cardiac workload and oxygen demand. -May decrease afterload>>> decreasing blood pressure.	-Relieve pulmonary congestion and peripheral edema. -Reduce symptoms of volume overload, including orthopnea and paroxysmal nocturnal dyspnea,	----------	----------
Vaso- and venodilators: **Nitrates (Hydralazine,** **Isosorbide dinitrate.**	-Dilates the blood vessels>>>increase venous capacitance >>>decrease arteriolar resistance>>> decrease preload.	-Nitrates reduce preload for patients with chronic HF.	----------	-Headache. -Hypotension. -Tachycardia.

****Notes:**

⟹ **Loop diuretics are the most commonly used diuretics in HF.**

⟹ **If the patient is intolerant of ACE inhibitors or β-blockers, or if additional vasodilator response is required, a combination of Hydralazine and Isosorbide dinitrate may be used.**

****NOW, we'll talk about the last group of drugs in CVS ☺ >>> The Inotropic drugs:**

⟹ **Although these drugs act by different mechanisms, the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle…. See the next table to know the drugs of this class:**

Subclass +name of the drugs	Mechanism of action	Therapeutic uses	pharmacokinetics	Adverse effects
Digitalis glycosides: Digoxin	-Regulation of cytosolic calcium concentration by: inhibiting Na+/K+-ATPase enzyme>>>less ability for the myocyte to pump Na+ out of the cell>>> higher cellular Na+ is exchanged for extracellular Ca2+ >>> increases the free Ca2+. -Increased contractility of the cardiac muscle -Neurohormonal inhibition.	-For severe HFrEF after initiation of ACE inhibitor, β-blocker, and diuretic therapy. -Digoxin is not indicated in patients with diastolic or right sided HF unless the patient has concomitant atrial fibrillation or flutter.	-Available in oral and injectable formulations. -Has large volume of distribution. -The dose is based on lean body weight. -Half-life =30-40 hours. -Eliminated by the kidney. -Substrate of P-glycoprotein.	-Has narrow therapeutic index. -Anorexia. -Nausea and vomiting. -Blurred vision. -Yellowish vision (Xanthopsia).
β-Adrenergic agonists: **Dobutamine and Dopamine.**	-Increase intracellular cAMP>>> activates protein kinase>>>phosphorylates slow calcium channels>>> increases entry of calcium ions into the myocardial cells>>> enhances contraction.	-Improve cardiac performance by causing positive inotropic effects and vasodilation.	----------	----------
Phosphodiesterase inhibitors: **Milrinone.**	-Same as β-Adrenergic agonists.	-See the notes below the table.	----------	----------

****Notes:**

⟹ **Digoxin toxicity is one of the most common adverse drug reactions leading to hospitalization.**

⟹ **Dobutamine is the most commonly used inotropic agent other than Digoxin.**

⟹ **short-term use of intravenous Milrinone is not associated with increased mortality in patients without a history of coronary artery disease, and some symptomatic benefit may be obtained in patients with refractory HF.**

****Order of therapy: Experts have classified HF into four stages, from least severe to most severe:**

1-In patients with overt HF, loop diuretics are often introduced first for relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema.

2-ACE inhibitors or ARBs (if ACE inhibitors are not tolerated) are added after the optimization of diuretic therapy.

3-Historically, β-blockers were added after optimization of ACE inhibitor or ARB therapy; however, most patients newly diagnosed with HFrEF are initiated on both low doses of an ACE inhibitor and β-blocker after initial stabilization.

4-Digoxin, aldosterone antagonists, and fixed-dose Hydralazine and Isosorbide dinitrate are initiated in patients who continue to have HF symptoms despite optimal doses of an ACE inhibitor and β-blocker.

It's the end ☺. GOOD LUCK