

CHF DRUGS			
Non-Inotropic drugs	Mechanism of Action	Uses/Effects	Adverse effects/Contraindications
<p>ACE Inhibitors</p> <p>Captopril, enalapril, lisinopril</p> <p>Captopril → lesser choice b/c of multiple times/day administration</p>	<ol style="list-style-type: none"> ↓ angiotensin II production <ul style="list-style-type: none"> Vasodilation ↓ Na and H₂O retention ↓ response to sympathetics ↓ tissue remodeling NET EFFECT: ↓ preload; ↓ afterload; ↓ MORTALITY (slower disease progression) ↑ circulating bradykinin <ul style="list-style-type: none"> Vasodilator: promotes NO formation, ↑ synthesis of prostacyclin Prevents vascular & cardiac growth Stimulates tPA release 	<p>Morbidity</p> <ul style="list-style-type: none"> relieves dyspnea prolong exercise tolerance ↓ need for emergency care <p>Mortality</p> <ul style="list-style-type: none"> Decreased risk of death <p><u>CHF</u></p> <ul style="list-style-type: none"> ALL pts with LV systolic dysfunction should be on ACEI (+ diuretic for fluid retention) Pts with LVSD and no symptoms – slows remodeling NOT used in acute failure (because of hypotension) – use AFTER stabilization 	<ul style="list-style-type: none"> Dry, persistent cough (bradykinin related) Severe hypotension, may be accompanied by azotemia Acute renal failure (in renal artery stenosis) Hyperkalemia – problem in DM pts Angioneurotic edema – rapid swelling in URT, LIFE THREATENING, not immune mediated, typically w/ 1st dose CONTRAINDICATED IN PREGNANCY
<p>Angiotensin (AT1) Antagonist ARBS</p>	<ul style="list-style-type: none"> Competitive blocker, unclear mechanism 	<ul style="list-style-type: none"> For pts who fail on ACEIs Approved only for HTN No documented evidence for ↑ mortality 	<ul style="list-style-type: none"> Similar to placebo in pts w/o CHF W/ CHF: hypotension with azotemia more probable
VASODILATORS			
<p>Arteriodilators (Hydralazine)</p>	<ul style="list-style-type: none"> ↓ afterload (↓ SVR) Unknown mechanism Better when combined w/ venodilators (↓ mortality) Problem with bioavailability (fast & slow acetylators → in bowel & liver, gets inactivated) 	<ul style="list-style-type: none"> Used w/ isosorbide dinitrate after failure of ACEIs 	<ul style="list-style-type: none"> Tachycardia, angina - “Coronary steal” in pts with IHD Drug-induced lupus syndrome – dose related; 5-10%; reversible
<p>Venodilators (organic nitrates)</p> <ul style="list-style-type: none"> isosorbide dinitrate nitroglycerin <p>- sodium nitroprusside</p>	<ul style="list-style-type: none"> ↓ preload ↑ exercise capacity ↓ symptoms of congestion <ul style="list-style-type: none"> rapidly hydrolyzed to NO and CN ↓ preload & ↓ afterload 	<ul style="list-style-type: none"> Useful in pts with high filling pressure Combined with hydralazine, ↓ mortality Used alone, ↓ congestion NG used acutely IV to ↓ filling pressure <ul style="list-style-type: none"> Short-term therapy in acute HF 	<ul style="list-style-type: none"> TOLERANCE, given at night to facilitate sleep <ul style="list-style-type: none"> Hypotension CN is rapidly metabolized to thiocyanate → toxicity limit

			duration of drug use
Diuretics	<ul style="list-style-type: none"> REVIEW RENAL 	<ul style="list-style-type: none"> Loops for acute HF Most CHF pts require loops chronically to maintain euvolemia Seldom use alone → may cause adverse neurohormonal activation (renin system) due to ↓ volume 	<ul style="list-style-type: none"> RESISTANCE occurs, if so, add metolazone (thiazide-like) Diuretic-induced hypokalemia (important when on cardiac glycosides)
<p>β-blockers</p> <ul style="list-style-type: none"> Approved β blockers: <ul style="list-style-type: none"> BISOPROLOL CARVEDILOL (non-selective; also has α1 blocking effects) approved for class II/III HF Sustained release METOPROLOL (metoprolol succinate) 	<ul style="list-style-type: none"> Mechanism unclear; could be: High sympathetic tone in CHF causes β-receptor down regulation, β blockers may counteract this effect by inducing receptor spread OR B-blockade may directly prevent remodeling caused by catecholamines 	<ul style="list-style-type: none"> For stable CHF, useful in slowing the remodeling of the heart = ↓mortality in Class 2/3, 4 is unclear...may worsen 	<ul style="list-style-type: none"> CONTRAINDICATED IN ACUTE CHF (b/c sympathetics are highly active & β blockers would dangerously lower CO) Symptomatic hypotension common initially Fluid retention Bronchospasm (asthmatics) <u>HF may worsen initially</u>
Aldosterone antagonists (Spironolactone)	<ul style="list-style-type: none"> a diuretic but enhanced Na & H₂O excretion is minimal INHIBITS ALDOSTERONE EFFECTS ON COLLECTING DUCTS - ↓ Na⁺/K⁺ exchange → promotes hyperkalemia, usually slight (can be pronounced when coupled with an ACEI) 	<ul style="list-style-type: none"> Improves mortality & morbidity with severe CHF Approved for Stage 4 CHF 	
Positive Inotropic drugs – all ↑contractility of the myocardium			
Cardiac glycosides <ul style="list-style-type: none"> Digoxin: <<40-90% intestinal absorption, 20- 	<ul style="list-style-type: none"> generally well absorbed (<i>Eubacteria lentum</i> in 10% rapidly metabolize to inactive) 	<ul style="list-style-type: none"> digitoxin: may be useful in kidney failure pts Mechanical Effects: 	<ul style="list-style-type: none"> K⁺ and Digitalis – hyperkalemia → ↓affinity for ATPase to digitalis AND hypokalemia ↑

<p>40% plasma protein binding, 1.7 d elimination half-time, small enterohepatic circ., 0.5-2.0 ng/mL therapeutic conc.</p> <ul style="list-style-type: none"> - Digitoxin: 90-100% intestinal absorption, >90% plasma protein binding, 7 d elimination half-time, large enterohepatic circ., 14-26 ng/mL therapeutic conc. - Factors influencing toxicity <ul style="list-style-type: none"> o Acute MI o AV nodal disease o Renal failure ($\downarrow K^+$) o CCBs (up to 100%, \downarrow renal clearance) and erythromycin, tetracycline (40-100%) \uparrow digoxin levels 	<p>state) \rightarrow variability in dosing</p> <ul style="list-style-type: none"> • inhibits cell membrane Na/K ATP-ase (relatively selective for cardiac enzyme) \rightarrow increased Ca^{2+} inside the cell \rightarrow more Ca^{2+} inside sarcoplasmic reticulum \rightarrow increase contractility • binds preferentially & stabilizes the phosphorylated form of the enzyme 	<ul style="list-style-type: none"> - \uparrowintensity of actin-myosin interaction \rightarrow \uparrowmyocardial contractile force, \uparrowvelocity of contraction, \downarrowduration of systole (small effect) <p>Electrical effects:</p> <ul style="list-style-type: none"> - both direct & indirect (vagal) - myocardial impulse conduction \rightarrow slowing sinus rate (vagal on SA node); AV node (blocks) indirectly \uparrowin ERP, \downarrowconduction velocity; direct same as indirect - \uparrow myocardial automaticity \rightarrow \uparrowrate of phase 4, may also be caused by delay after depolarizations - indirect is predominant <p>EKG:</p> <ol style="list-style-type: none"> 1. ST segment depression 2. inversion of T wave 3. prolongs PR interval (up to 0.25 s) (\downarrow conduction velocity at AV node) 4. shortens QT interval (due to accelerated ventricular repolarization) <p>NO EFFECT ON SURVIVAL</p> <ul style="list-style-type: none"> - Improves clinical status - Give w/ diuretic, ACEI, β blocker (watch sinus, AV function) - Indicated with CHF with a-fib <p>Also can use with a-fib, a-flutter, paroxysmal tachycardia</p>	<p>affinity</p> <ul style="list-style-type: none"> • Dysrhythmias • Extracardiac effects <ul style="list-style-type: none"> - GI: anorexia, diarrhea, abd. Discomfort, nausea/vomiting (mediated via excitation of chemoreceptor trigger zone); salivation - CNS: headache, fatigue, malaise, drowsiness; neuralgic pain (lower 1/3 of face) early and severe; mental symptoms - Vision: blurred, white (halos on dark objects), color vision (chromotopsia, yellow & green) - Vascular: initial \uparrowin smooth muscle tone due to \uparrowintracellular Ca^{2+} (<i>generally, net effect of cardiac glycosides is a \downarrow in vascular tone via \downarrow sympathetic activity</i>) • TOXICITY: treat by stopping glycosides, minimizing aggravating circumstances, avoid catecholamines & β blockers, treating arrhythmias, avoid cardioversion • SEVERE TOXICITY: extracellular hyperkalemia, give Fab fragments: Ab to digoxin/digitoxin \rightarrow very rapid, effective, expensive
<p>Phosphodiesterase inhibitors</p> <ul style="list-style-type: none"> - Amrinone 	<ul style="list-style-type: none"> • Inotropic, vasodilatory, short-term parenteral use • Inhibition of cAMP 	<ul style="list-style-type: none"> • Acute HF, IV only, requires large 	<ul style="list-style-type: none"> • GI (nausea, vomiting)

<p>- Milrinone</p>	<p>phosphodiesterase → ↑cAMP → ↑ CO, ↓ SVR, ↓ PCWP → NET result: IMPROVED HEMODYNAMICS</p> <ul style="list-style-type: none"> • Like amrinone • Half life is 30-60 min 	<p>initial dose for + inotropic effect</p> <ul style="list-style-type: none"> • DOC for short-term! • Parenteral administration 	<ul style="list-style-type: none"> • Thrombocytopenia • Abnormal liver function • Short-term: fewer than amrinone • Long-term: ↑ mortality; arrhythmias
<p>Adrenergic agonists</p> <ul style="list-style-type: none"> • Dobutamine • Dopamine 	<ul style="list-style-type: none"> • β1, β2 agonist • ↑ CO; ↓ ventricular filling pressure • β1, DA1 agonist 	<ul style="list-style-type: none"> • Short-term support of CO in advanced HF • Short-term only → useful in ↑ splanchnic & renal blood flow (pts with hypotension) 	<ul style="list-style-type: none"> • TOLERANCE prevents long-term use • Tachycardia w/ possible ↑ in myocardial O₂ consumption (angina) • Tachycardia (WORSE than dobutamine) • @ higher doses → ↑ SVR (α agonist effects) → limits CO and worsens congestion

AntiAnginal and Antihyperlipidemia

Name	Mechanism of Action	Therapeutic Uses and Specificity	Toxicity and Side Effects	Other
<p>Organic Nitrates (nitroglycerin, others)</p> <p>Mainstay of treatment of all 3 types of angina!</p>	<p>Mainly relaxation of large veins ↓ venous return → ↓ preload → ↓ O₂ demand (major effect-<i>important in angina of effort</i>) - smaller ↓ in afterload</p> <p>NTG donates NO → Stimulates g. cyclase to generate cGMP → dephosph myosin light chain → sm mm relaxation</p>	<ul style="list-style-type: none"> • Angina • Congestive Heart Failure · ↑ Cardiac output • After MI · ↓ work of heart · ↓ platelet aggregation • Raynaud's disease <p>Specific agents <u>NTG</u> sublingual = short onset, short-acting <u>Amyl nitrite</u> inhalational (poppers, snappers) most rapid onset <u>Isosorbide dinitrate</u> slower, less potent than NTG</p>	<ul style="list-style-type: none"> • HA, dizziness (Monday dx) • Orthostatic hypotension • Tolerance Requires 8-hr drug-free/day (take last dose at 8 PM then don't take another until 8 AM) 	<p>Sildenafil is absolutely contraindicated with nitrates</p> <p><u>Drug Interactions</u> Combo of <u>sildenafil and nitrates</u> dramatically enhances vascular effects (vasodilation), including severe hypotension</p>

<p>B-Blockers</p> <ul style="list-style-type: none"> •Non-Selective •Propranolol •Nadolol- long acting •Timolol- also for glaucoma <p>•Beta1 Selective</p> <ul style="list-style-type: none"> •Metoprolol •Atenolol-long acting 	<p>↓ heart rate (<i>major effect</i>); and also ↓ contractility (<i>lesser effect</i>) → ↓ cardiac work → ↓ O₂ demand</p> <p>- ↓ peripheral resistance (<i>block renin release</i>) → O₂ demand via ↓ afterload</p> <p>•no effect on O₂ supply</p>	<ul style="list-style-type: none"> •monotherapy for mild-moderate angina of effort (**not for Prinzmetal- can make vasospasm worse!) •combination therapy (angina of effort) •after MI 	<ul style="list-style-type: none"> •bradyarrhythmias (<i>due to increased AV node delay</i>) •congestive heart failure •extracardiac effects- (<i>asthma, COPD, Diabetics</i>) 	
<p>Ca Channel Blockers</p> <p>Predominately Vascular dihydropyridines ("pines") - <i>Work mostly in Prinzmetal Angina</i></p> <p>Predominately Cardiac verapamil and diltiazem <i>Work mostly in Angina of Effort!</i></p>	<p>block Ca entry through L-type channels → relaxation of arteriolar smooth muscle → ↓ afterload → ↓ O₂ demand</p> <p>Also ↑ supply due to dilation of coronaries</p> <ul style="list-style-type: none"> •In addition to their vascular effects, verapamil and diltiazem <ul style="list-style-type: none"> • SA and AV node function • Cardiac contractility •Both effects lead to less cardiac work (useful in angina of effort) 	<p>↓ Excitability of vascular smooth muscle (<i>↓ propensity of art to spasm-useful in Prinzmetal's</i>)</p> <p>↓ Tone of vascular smooth muscle → ↓ afterload (<i>helpful in angina of effort</i>)</p> <p><u>Verapamil + diltiazem</u></p> <p>↓ SA and AV node function and ↓ Cardiac contractility → ↓ cardiac work (<i>useful in angina of effort</i>)</p> <p>Monotherapy</p> <ol style="list-style-type: none"> 1) Pts w/sinus bradycardia, AV dysfxn – use a "pine" 2) Pts w/ atrial fib/flutter-use verapamil 3) Pts resistant/tolerant to nitrates or b-blockers 4) Prinzmetal angina 	<p>Verapamil-constipation due to blockade of L-type Ca channel in gut smooth muscle</p> <p>"Pines"- vasodilation effects → edema, HA, dizziness, flushing</p>	<p>"pines"-NO direct effects on the heart (SA or AV node); Causes: signif vasodilation + hypotension → reflex tachycardia</p> <p>Verapamil and diltiazem more direct effects on the heart (slow SA+AV node+ ↓ contract)</p> <p>See no reflex tachy</p> <p>DRUG INTERACTIONS:</p> <p>digoxin- <i>due to AV node block, alpha adrenergic blockers – increased vasodilation, nitrates-increased vasodilation</i>)</p>

Aspirin	-effects due to inhibition of platelet aggregation	↓ mortality in patients with unstable angina, reducing incidence of MI and death ↓ incidence of MI in chronic stable angina		
Abciximab	-glycoprotein iib/iiia receptor antagonist -inhibits platelet aggregation	unstable angina when angioplasty or atherectomy planned within 24 hours)		
Drugs that don't work in angina	A- Blockers -no benefit; may cause ↑freq anginal attks ACEI -not efficacious ARB -not efficacious Hydralazine - <i>coronary steal syndrome</i> , due to shunting of blood away from ischemic areas			
<u>Antihyperlipidemia</u>				
Lovastatin (Mevacor) and many other " <i>statin</i> " drugs	<ul style="list-style-type: none"> •Inhibition of HMG-CoA reductase -- essential step in cholesterol synthesis. These drugs are structural analogs of the HMG-CoA intermediate. •Leads to Increased synthesis of LDL receptors (liver attempts to get more cholesterol from plasma) 	<p>-Elevated cholesterol of all types. -<i>Particularly effective at lowering levels of LDL.</i></p> <p>-If the primary prob. is too much cholesterol, "statins" are good choices.</p> <ul style="list-style-type: none"> •↓cholesterol → ↑LDL receptors in the liver → ↓LDL cholesterol (often see a small decrease in triglycerides and a small increase in HDL cholesterol) 	<ul style="list-style-type: none"> •Numerous, but incidence is low and severity is relatively lesser than with other lipid lowering drugs 1)Hepatic damage (1-2%)-most common (<i>Elevate serum levels of hepatic enzymes and can cause hepatitis</i>) 2)Peripheral neuropathies-reversible on discontinuation of the drugs 3)Lovastatin and simvastatin <u>cross blood-brain-barrier</u> and may cause sleep disturbances 	<ul style="list-style-type: none"> •Contraindicated in hepatic disease •Contraindicated in pregnancy (<i>Fetus needs cholesterol for formation of cell walls</i>) •Watch being too aggressive with therapy (<i>Abrupt drop in circulating cholesterol and/or direct cellular impairment of cholesterol metabolism may impair ability to maintain cell wall structure</i>) <p><u>DRUG INTERACTIONS:</u></p>

			<ul style="list-style-type: none"> •**Watch for myalgia, myopathy (<1%) and rhabdomyolysis (rare).- (unusual toxicity, and it is a frequent favorite to test on board examinations) <ul style="list-style-type: none"> -•Monitor creatine phosphokinase (CPK; CK) 	<ul style="list-style-type: none"> •Monitor more carefully when combining with niacin (2%) or fibrate drugs (5%), which can also cause myopathy). •Avoid combining with erythromycin (dec. metabolism of statins, with inc. myopathy)
Niacin	<ul style="list-style-type: none"> •Inhibits VLDL secretion → ↓VLDL, ↓LDL and ↑HDL. (↑HDL levels occur because rate of catabolism of HDL is decreased) 	<ul style="list-style-type: none"> •Any lipoprotein disorder, particularly <u>mixed hyperlipidemia with elevated triglycerides</u> •Have to take gram quantities (<i>NOT acting as a vitamin</i>) 	<ul style="list-style-type: none"> •<u>Itching, flushing and unpleasant sensation of being warm.</u> •<u>Prostaglandin mediated.</u> •<u>Give aspirin</u> (blunts, but does not remove, this effect). •G.I. distress (may activate ulcers) •Elevates transaminase levels and may (rarely) cause hepatitis •Glucose intolerance – aggravates diabetes •Inhibits urate secretion. Hyperuricemia in 20% of pts. 	
Fibrate Derivatives gemfibrozil (Lopid) & fenofibrate	<ul style="list-style-type: none"> •↑activity of lipoprotein lipase (<i>cleaves free fatty acids from triglycerides more readily, which promotes delivery of triglycerides to adipose tissue</i>) •↓VLDL formation in the liver → ↓triglyc; <u>modest reduction in LDL</u> (may increase in some patients); <u>more impressive rise in HDL</u> 	<ul style="list-style-type: none"> •Reduction of triglycerides when VLDL is very high, or when IDL is elevated •<u>Follow VLDL.</u> If it is elevated, gemfibrozil is a candidate drug. <i>If LDL is elevated but VLDL is not elevated, do not use this drug.</i> 	<ul style="list-style-type: none"> •Blood cell defic, skin rash and other hypersensitive rx •g.i. problems •liver enzyme abnorm(<i>usu transient</i>) •lithiasis (↑biliary chol. excr) 	<ul style="list-style-type: none"> Do NOT use in pts with gall bladder problems <u>DRUG INTERACTION</u> •myositis -- myopathy and rhabdomyolysis are reported when combined with HMG-CoA reductase inhibitors
Cholestyramine (Questran)	<ul style="list-style-type: none"> •Enhanced excretion of bile acids → ↑conversion 	<ul style="list-style-type: none"> •Hypercholesterolemia, espec ↑ LDL cholest 	<ul style="list-style-type: none"> •Constipation and a feeling of bloating (<i>easily controlled</i>) 	

Colestipol (Colestid)	of cholest to bile acids in liver. •Loss of cholesterol triggers up regulation of LDL recept in the liver →↓ LDL	<i>(Follow LDL. If it is elevated, these drugs are potentially useful)</i>	<i>with a high fiber diet but pt. compliance is not good)</i>	
Omega-3-Fatty Acids Fish Oils	Data support multiple mechanisms for cardio protection •Antiatherogenic by reducing triglyceride and VLDL synthesis in the liver			