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Heart Failure

I. Definitions

A. Heart Failure (HF)

- HF Results when one or both ventricles are unable to pump sufficient blood to meet the body's needs
- There are 2 types of heart failure:

(1) normal EF, but SV & CO are low because end diastolic volume is low
(2) contractility is not impaired
(3) wall stiffness & thickness prevents full relaxation & filling of ventricle chamber

(1) HFrEF = heart failure with "reduced" ejection fraction (EF<40%)
= left ventricular systolic failure = systolic heart failure
(2) HFpEF = heart failure with "preserved" ejection fraction (EF=50-75%)
= diastolic heart failure (DHF)→ abnormal left ventricular filling and/or elevated filling pressures

B. Preload

- forces acting on the venous circulation to affect myocardial wall function
- venous constriction increases venous ~~volume~~ and thus increases preload
- elevated preload aggravates congestive failure

↑ venous return

C. Afterload

- forces acting on the arterial circulation to affect the impedance or resistance against which the left ventricle must pump during ejection
- analogous to arterial resistance or pressure

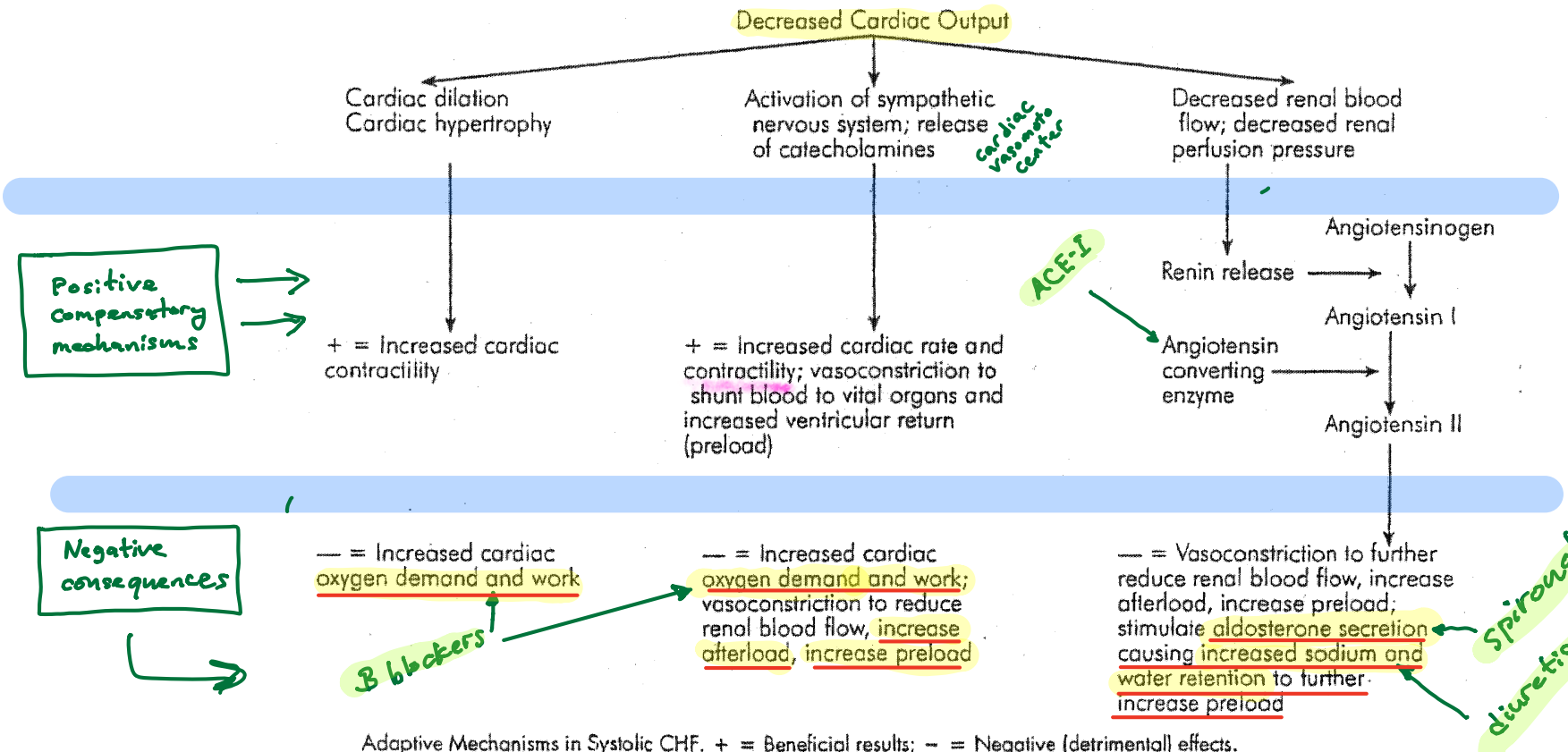
D. Contractility

- the inherent ability of the myocardium (cardiac muscle) to develop force (contract) independent of preload or afterload
- contractility is synonymous with inotropism

II. Signs and Symptoms

- The symptoms of HF are traditionally divided into those that reflect left ventricular failure and/or right ventricular failure

	Left Ventricular Failure	Right Ventricular Failure
Subjective	SOB (shortness of breath) DOE (dyspnea on exertion) Orthopnea (2-3 pillows) PND (paroxysmal nocturnal dyspnea) Weakness, fatigue	Peripheral edema Weakness, fatigue
Objective	LVH (left ventricular hypertrophy) EF (ejection fraction) < 40% Reflex tachycardia Increased BUN/Cr (d/t poor renal perfusion)	Wt gain (fluid retention) jugular vein distension Hepatomegaly / Ascites



Adaptive Mechanisms in Systolic CHF. + = Beneficial results; – = Negative (detrimental) effects.

→ inhibit RAAS system

eta-blockers

reduce effects of circulating catecholamines

blocks aldosterone

mainstay in HF to control volume

(A) Beta blockers are used in heart failure to reduce the effects of circulating catecholamines --> decrease oxygen demand and workload on the myocardium.

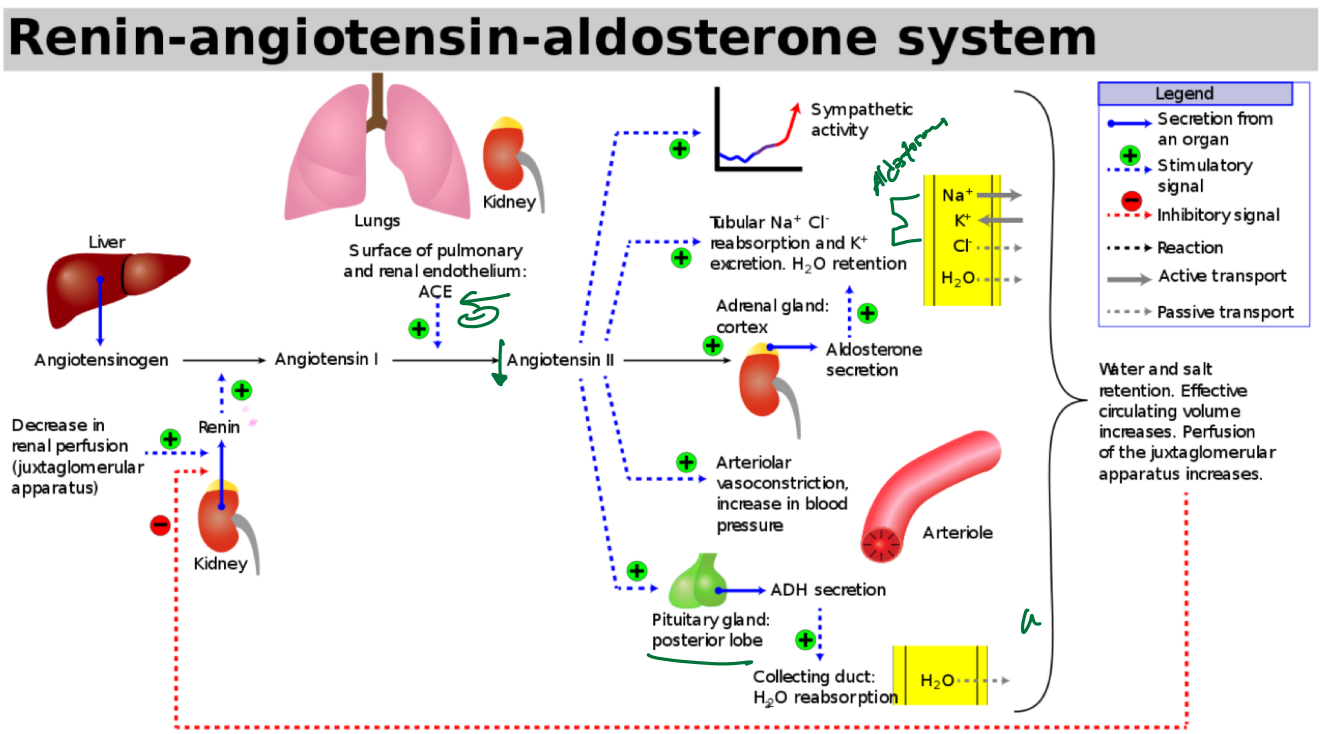
(B) ACE's and ARB's are usedin heart failure to reduce activation of RAAS --> reduce sodium/water retention and vasoconstriction.

(C) Spironolactone (Aldactone) is used in heart failure to oppose the effects of aldosterone --> decrease sodium/water retention.

(D) Diuretics are mainstay agents in heart failure to control volume expansion and treat fluid overload.

(E) All of the above are true.

Mechanisms of Action of ACE-I's and ARB's



III. Non-Pharmacological Treatment

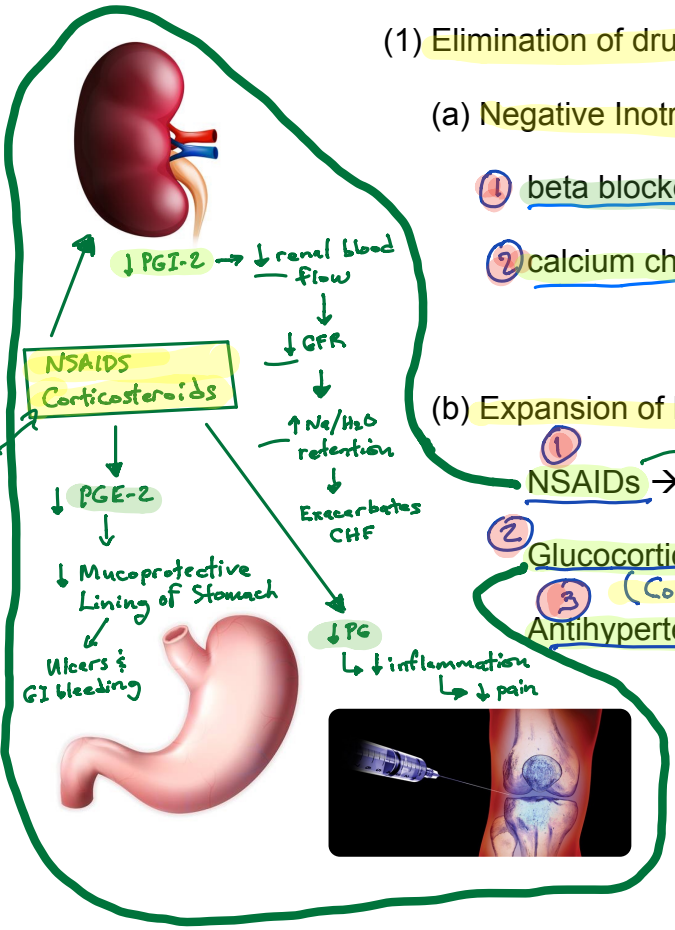
- Non-pharmacologic interventions include:

(1) Elimination of drugs that may induce CHF

(a) Negative Inotropic Agents

1. beta blockers (d/t neg. inotropic effects)

2. calcium channel blockers (verapamil is the most neg. inotropic and AV blocking drug; nifedipine has the least cardiac depressing property)



(b) Expansion of Plasma Volume

NSAIDs: Ibuprofen, Naproxen, ketorolac (Toradol)

1. NSAIDs → renal prostaglandin inhibition → Na and water retention

2. Glucocorticoids (prednisone) → Na and water retention
(Corticosteroids = Glucocorticoids = Anti-Inflammatory Steroids)

3. Antihypertensives: hydralazine / minoxidil (direct-acting vasodilators)
→ activation of renin-angiotensin system
→ aldosterone release
→ Na and water retention

(2) Low sodium diet: less than 2 gm sodium/day

(3) Bedrest during acute episodes

(4) Light exercise when patient is stable

IV. Pharmacologic Approaches

A. Diastolic Heart Failure (DHF)

- Treatment of DHF remains empiric since trial data are limited.
- General principles in treating DHF: (1) control systolic and diastolic hypertension, (2) control heart rate, particularly in atrial fibrillation, and (3) control pulmonary and peripheral edema with diuretics → NOTE: comorbidities worsen DHF
- Digoxin is generally not used in DHF because systolic function is intact

1st-line agents in HF

B. Systolic Heart Failure

- ACE inhibitors (ACE-I) and angiotensin receptor blockers (ARB's) are 1st line agents in systolic heart failure → associated with improved survival / quality of life
- Beta-blockers are also 1st line agents, especially in patients with atrial fibrillation and/or angina → improved survival and quality of life
- Spironolactone (aldosterone antagonist) is also associated with mortality benefit
- Diuretics are mainstay agents in heart failure patients for treating fluid overload
- Digoxin is a 2nd line agent in CHF since multiple trials failed to prove mortality benefit → primarily used in CHF patients with atrial fibrillation and/or CHF patients who have chronic low blood pressure

Digoxin does not decrease BP

AV block

Which of the following agents improve survival in systolic HF?

- ACE-I/ARBs
- Beta Blockers
- spironolactone

V. Drug Treatments

A. Diuretics

- Diuretics are indicated when Na restriction fails to control volume expansion
- The goal is symptomatic relief of CHF without causing intravascular depletion
- In patients with renal insufficiency (CrCl < 30 ml/min), the loop diuretics are preferred diuretics.
- Potassium supplementation may be required if the serum potassium is < 3.5 (30-50% of patients)

B. Digitalis Glycosides (Digoxin = Lanoxin)

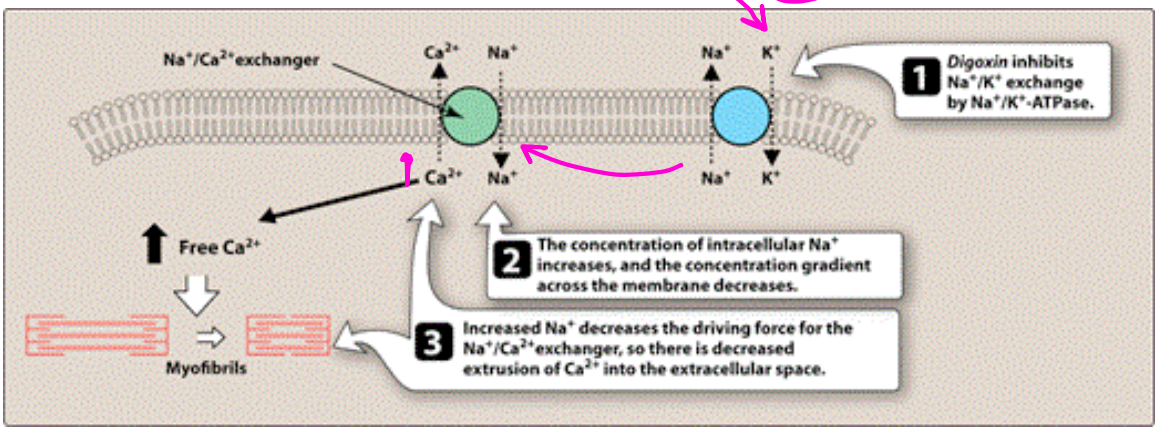
1. Mechanism of Action

→ systolic heart failure

- Digoxin improves cardiac output (CO) by increasing the force of contraction of the myocardial muscle (i.e., positive inotropic effect) in systolic heart failure

- Digoxin is most useful in CHF patients with concurrent supraventricular arrhythmias (e.g., atrial fibrillation) and/or chronic low blood pressure

Digoxin MOA



2. Digoxin Side Effects (most prevalent when serum digoxin > or = 2 mcg/l or if serum K < 3.0 mEq/l)

(a) Cardiac: bradycardia (HR < 50) → d/t AV block
(b) GI → anorexia, nausea/vomiting (N/V)
(c) Visual disturbances → altered color perception, haloes
(d) Fatigue/weakness
(e) Hyperkalemia
(f) Gynecomastia (with long-term use)

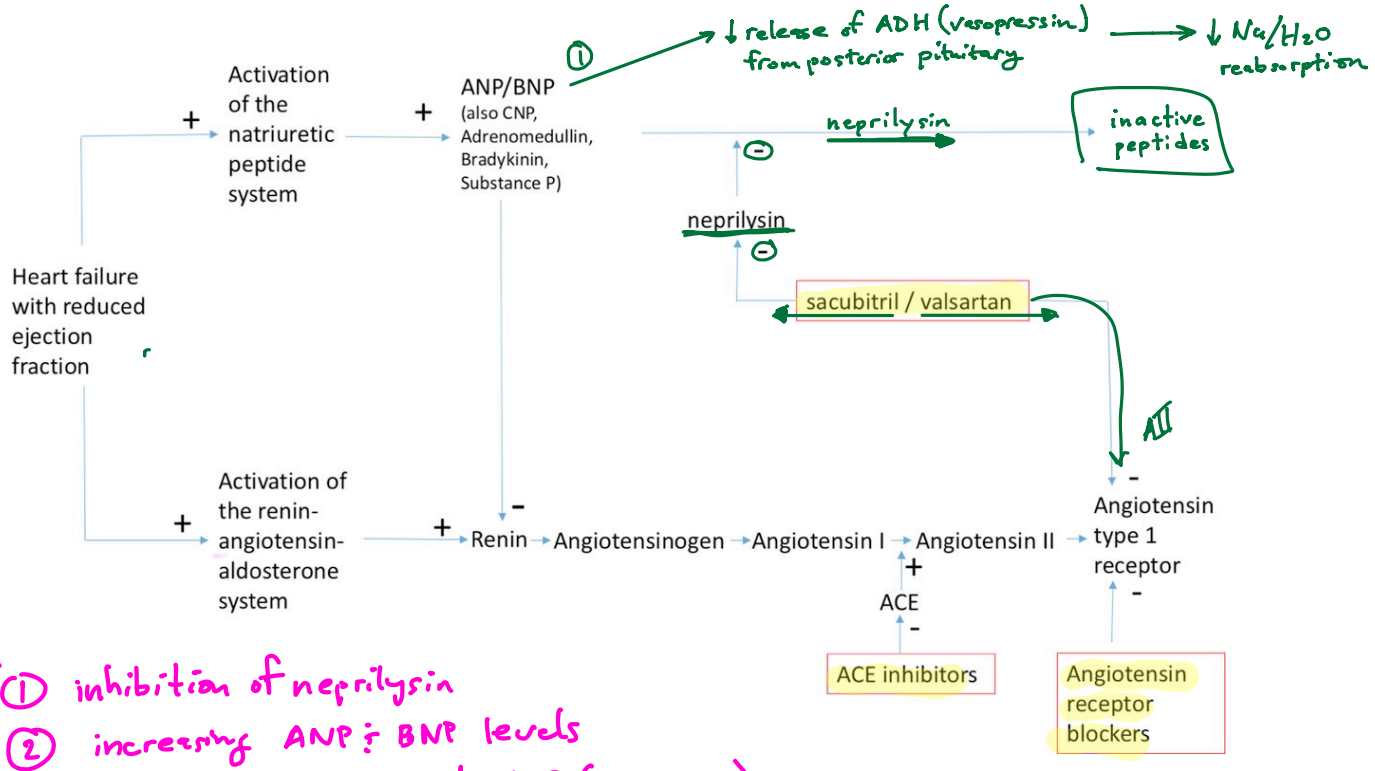
digoxin therapeutic levels: 0.5 - 2 ng/ml
HF: 0.5-0.9
Atrial Fib 0.5-2.0

digoxin toxicity > 2.4
- Digibind → binds & inactivates dig (digoxin immune Fab)

C. Entresto (sacubitril/valsartan) ARNI = angiotensin receptor neprilysin inhibitor

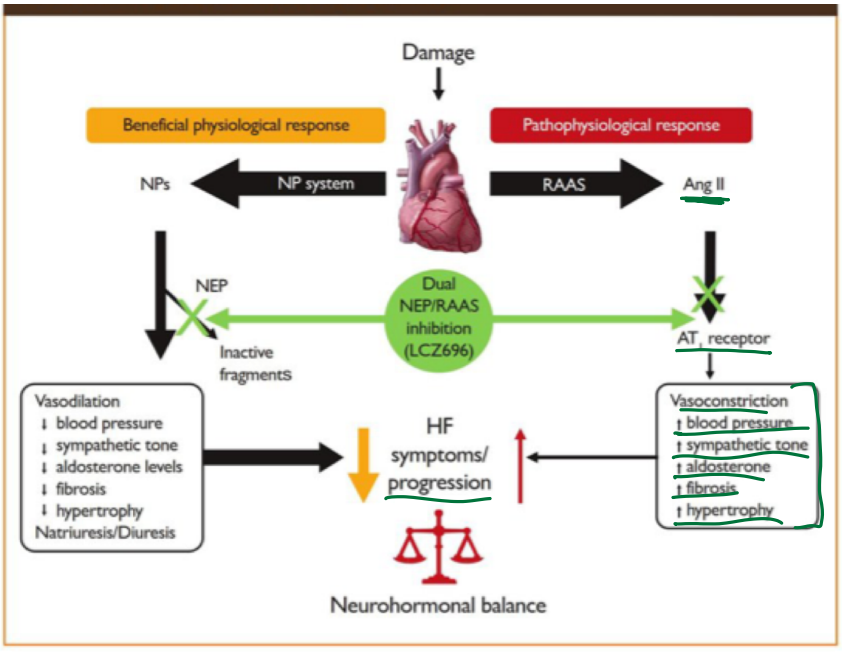
- Entresto is used to replace an ACE-I or ARB in HFrEF
- Entersto in clinical trial (Paradigm-HF) proved to be more effective than enalapril in reducing hospitalizations and mortality in patients with systolic HF (HFrEF)
- Rx cost: Entresto ($375/month) vs Enalpril ($0.96/month)
- MOA: sacubitril → inhibits neprilysin → increases ANP (atrial natriuretic peptide) / BNP (B-type natriuretic peptide) → decreases RAAS and vasopressin (ADH)

cost diminishes its widespread use



MOA of Secubitril:
1. inhibition of neprilysin
2. increasing ANP & BNP levels
3. decreasing RAAS and ADP (vasopressin)

C. Entresto (sacubitril/valsartan)



Schematic representation of the mechanism of action of sacubitril/valsartan

PRELOAD & AFTERLOAD REDUCING AGENTS

Comparative Pharmacology of Unloading Agents

Drug	Dose	Comments
Predominantly After-Load Reduction (Arterial Dilators)		↓ systemic vascular resistance; ↑ cardiac output
Direct Vasodilators (Oral)		
Hydralazine	*Initial*: 12.5–25 mg *Maintenance*: 25–100 mg Q 6–8 hr	Concurrent diuretics to block Na^+ retention; less reflex tachycardia than when treating hypertension
Minoxidil	*Initial*: 2.5–5 mg *Maintenance*: 5–20 mg Q 8–12 hr	Concurrent diuretics to block Na^+ retention; less reflex tachycardia than when treating hypertension
Calcium Channel Blockers (Oral)[b]		
Nifedipine	10–40 mg Q 6–8 hr 40–120 mg SR QD	Nifedipine most vasodilating
Verapamil	40–60 mg Q 6–8 hr 120–240 SR Q 12 hr	Concern over negative inotropic effect (V>D>N)
Diltiazem	30–90 mg Q 6–8 hr 60–180 SR Q 12 hr	May ↑ digoxin levels (V>D>N)
Predominantly Pre-Load Reduction (Venous Dilators)		↓ pulmonary capillary wedge pressure and left ventricular filling pressure
Nitrates		
IV (NTG)[c]	5 μg/min; titrate to effect. (*max* = 200 μg/min)	
Sustained-release (NTG)	6.5–9 mg Q 8-12 hr PO	6–8 hr duration
Ointment (NTG)	½"–2" Q 4–8 hr PO	3–6 hr duration
Transdermal (NTG)	5–40 mg/day (remove at night)	Concern over tolerance with SR and transdermal

Agents[a] (*Continued*)

Drug	Dose	Comments
Predominantly Pre-Load Reduction (Venous Dilators) (*Continued*)		
Isosorbide		
Sublingual	5–20 mg Q 3–6 hr	Short acting (1–3 hr)
Tablets PO	10–80 mg Q 4–6 hr	4–6 hr duration
SR[d]	20–120 mg Q 6–8 hr	6–8 hr duration
Mixed After-Load and Pre-Load Reduction		
Nitroprusside	*Initial*: 5–20 μg/min Titrate to effect (*max*: 300–800 μg/min)	Parenteral only
Prazosin	1–5 mg Q 6–8 hr	↓ effect with chronic use due to Na^+ retention
ACE Inhibitors		Mild diuretic properties also. Well documented long-term efficacy, but delayed onset
ARBS		
Captopril	*Initial*: 6.25–12.5 mg *Maintenance*: 12.5–75 mg Q 8 hr	
Enalapril	*Initial*: 2.5–5 mg QD *Maintenance*: 10–40 mg Q 12–24 hr	Enalapril slower than captopril since must be converted to enalaprilat
Lisinopril	*Initial*: 2.5–5 mg QD *Maintenance*: 5–40 mg	Lisinopril has longest t½

[a] See Chapter 7: Essential Hypertension and Chapter 11: Angina Pectoris for side effects and listing of additional calcium blockers and ACE inhibitors; on balance the benefits of afterload reduction exceed those of preload reduction.
[b] Least desirable class of drugs due to negative inotropic effects.
[c] May bind to plastic IV bags and many plastic tubing sets.
[d] SR = Sustained-Release.

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