Cardiac Series:
Pharmacology of Heart Failure Medications

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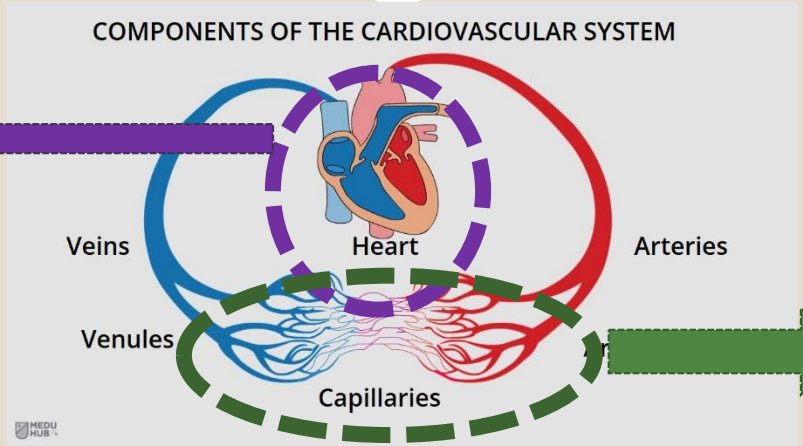
Learning Objectives

1. Organize heart failure medications based on specific heart failure target goal (e.g. preload reducer, afterload reducer, rate control, etc.)
2. Explain the importance of RAAS inhibition as it relates to the management of chronic heart failure
3. Describe the pharmacologic effects of neprilysin inhibition and specific precautions for use of these agents
4. Discuss the mechanism of action of diuretics used to treat symptomatic heart failure
5. Demonstrate understanding of how beta-blockers decrease the cardiac remodeling associated with heart failure
6. Recognize the differences in the available inotropic agents and how the distinct pharmacologic properties of each agent determines its appropriate indication for use

Background - Caveats

- Focus on HFrEF
  - Not discussing HFpEF (only symptomatic approach)
- Pharmacology, only
  - Not discussing place in therapy/evidence for use
  - Not discussing pregnancy/lactation contraindications

Pharmacologic Targets to Improve Cardiac Output



Pump/Motor

- Improve contraction
  - Improve quality of life
  - Treat cardiogenic shock
- Improve cardiac filling
- Decrease cardiac remodeling

Plumbing

- Decrease cardiac workload
  - Decrease vascular resistance
  - Decrease intravascular volume

Plumbing
(i.e. Vascular Resistance)

Components Affecting Cardiac Output

Factors Affecting Heart Rate (HR)

Factors Affecting Stroke Volume (SV)

Atrial reflex

Venous Return

Filling Time

Autonomic Innervation

Vasodilation or vasoconstriction

Preload

Contractility

Afterload

Autonomic innervation

End diastolic volume (EDV)

End systolic volume (ESV)

Heart Rate (HR)

Stroke Volume (SV) = EDV - ESV

Cardiac Output (CO) = HR x SV

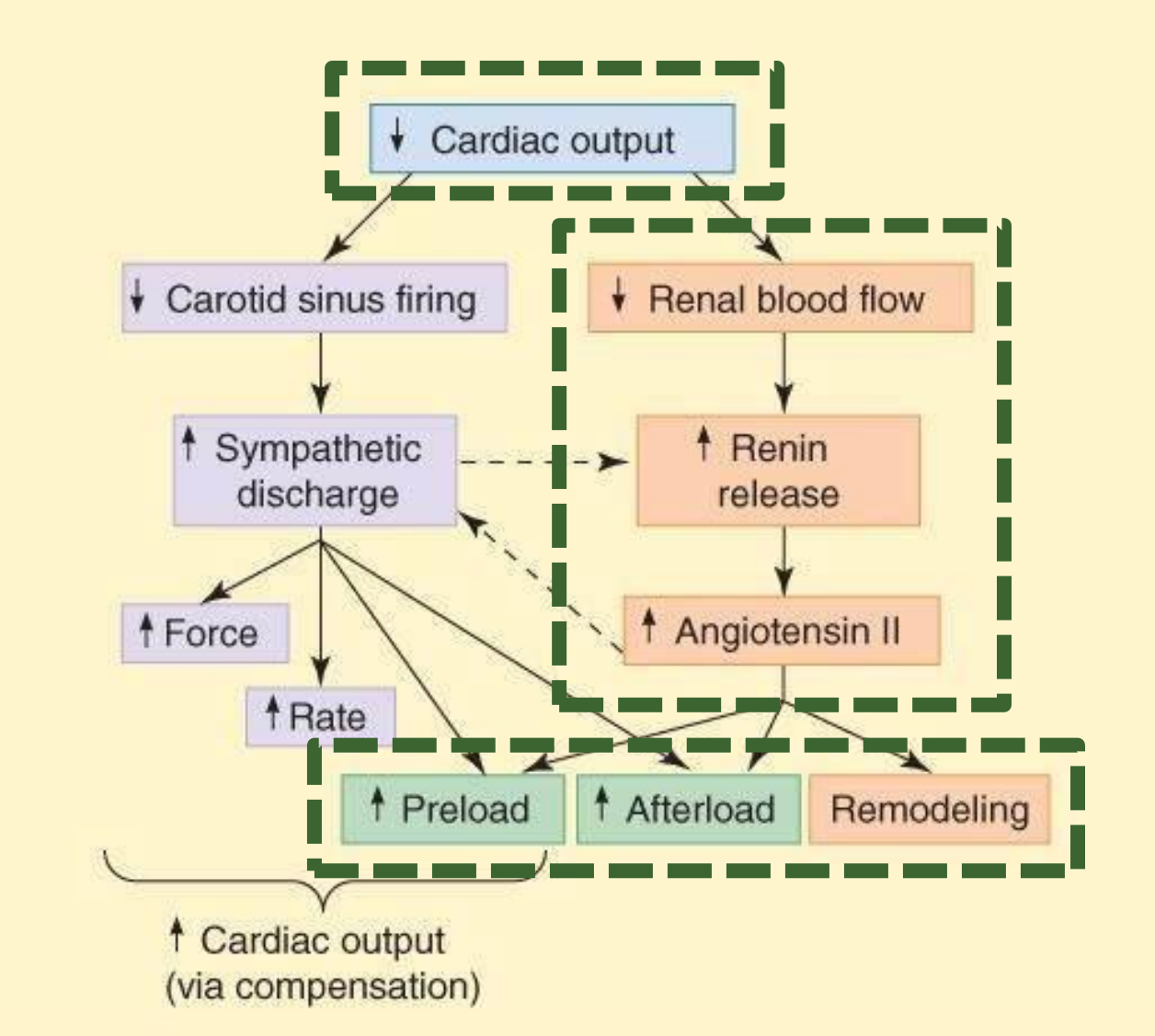
Plumbing

Pharmacologics Affecting Vascular Resistance

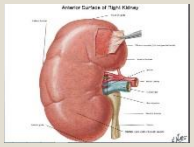
	Preload		Afterload
	Fluid Reduction	Venodilation	Arteriodilation
RAAS Inhibition • ACEi • ARB • ARA • ARNI	X	X	X
Diuretics • Thiazides (mild) • Loop • Potassium-sparing (mild)	X		
Hydralazine			X
Nitrates		X	±

Renin Angiotensin Aldosterone System

Effects of Low Cardiac Output



Renin-Angiotensin-Aldosterone System



Renin

ACE

Angiotensinogen

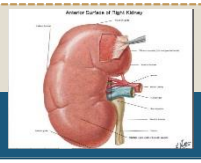
Angiotensin I

Angiotensin II

Aldosterone

Vasoconstriction

Fluid Retention



ARB = angiotensin receptor blocker

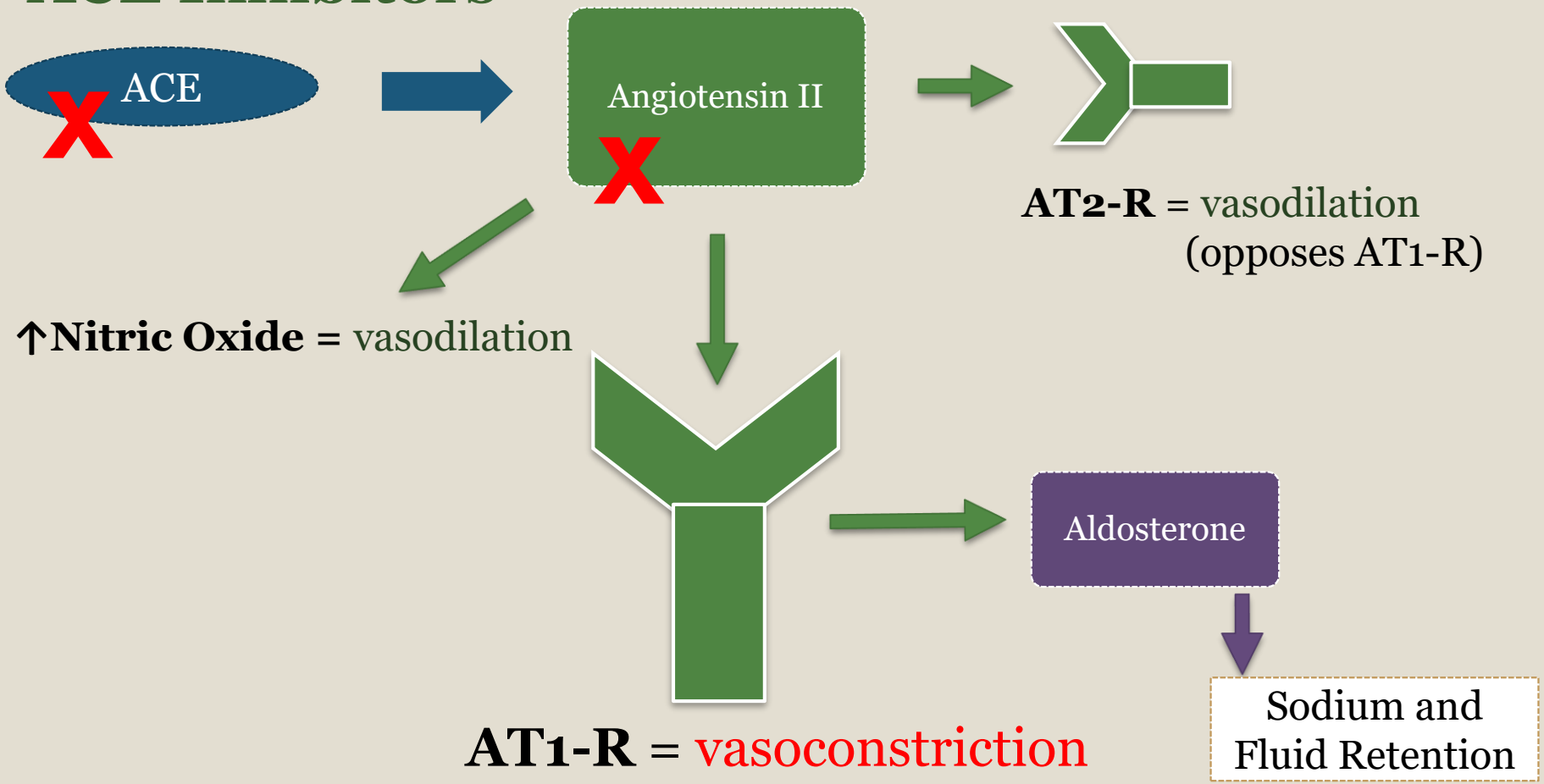
ARA = aldosterone receptor antagonist

ACEi = angiotensin-converting enzyme inhibitor

RAAS Inhibition

- Aldosterone
- Angiotensin II

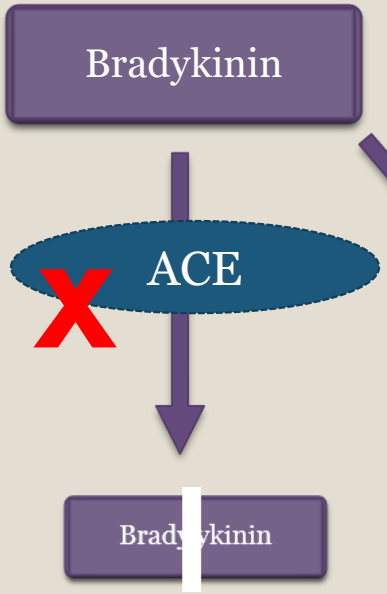
ACE Inhibitors



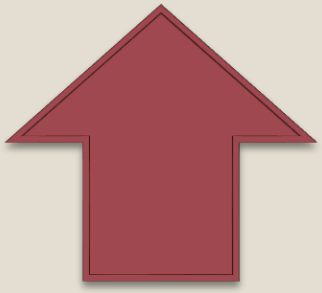
RAAS Inhibition

- Aldosterone
- Angiotensin II

ACE Inhibitors



↑Nitric Oxide = vasodilation



B2-R = endothelial dysfunction (angioedema)
↑Cytokines/Substance P = inflammation (cough)

Bhoola, et al. (1992)

RAAS Inhibition

- Aldosterone
- Angiotensin II

ACE Inhibitors

Drug	Starting Dose	Target Dose for Heart Failure
Lisinopril	2.5 to 5 mg po daily	20 to 40 mg po daily
Enalapril	2.5 mg po BID	10 to 20 mg po BID
Captopril	6.25 mg po TID	50 mg po TID

- Initiate cautiously at low doses *especially if ↓BP, hypovolemic or ↓sodium*
  - Carefully monitor SCr, K+ and BP
  - Titrate to goal or max tolerated over 1-3 months
- ADRs:
  - ↓AT1-R: hypotension
  - ↑Bradykinin: angioedema, cough
  - ↓Aldosterone: ↑K+
  - Vasodilation of glomerular efferent arteriole: ↑SCr

↓Preload
↓Afterload
↓Remodeling

J Am Coll Cardiol 2018;71:201-30.

RAAS Inhibition

- Aldosterone
- Angiotensin II

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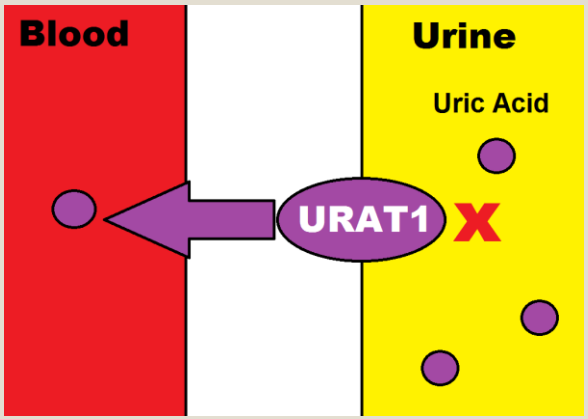
ARBs

ACE
Chymase
tPA

Angiotensin II

AT2-R = vasodilation
(opposes AT1-R)

↑**Nitric Oxide** = vasodilation



X

Aldosterone

Sodium and
Fluid Retention

AT1-R = vasoconstriction

RAAS Inhibition

- Aldosterone
- Angiotensin II

ARBs

Drug	Starting Dose	Target Dose
Losartan	25 to 50 mg po daily	150 mg po daily
Valsartan	40 mg po BID	160 mg po BID
Candesartan	4 to 8 mg po daily	32 mg po daily

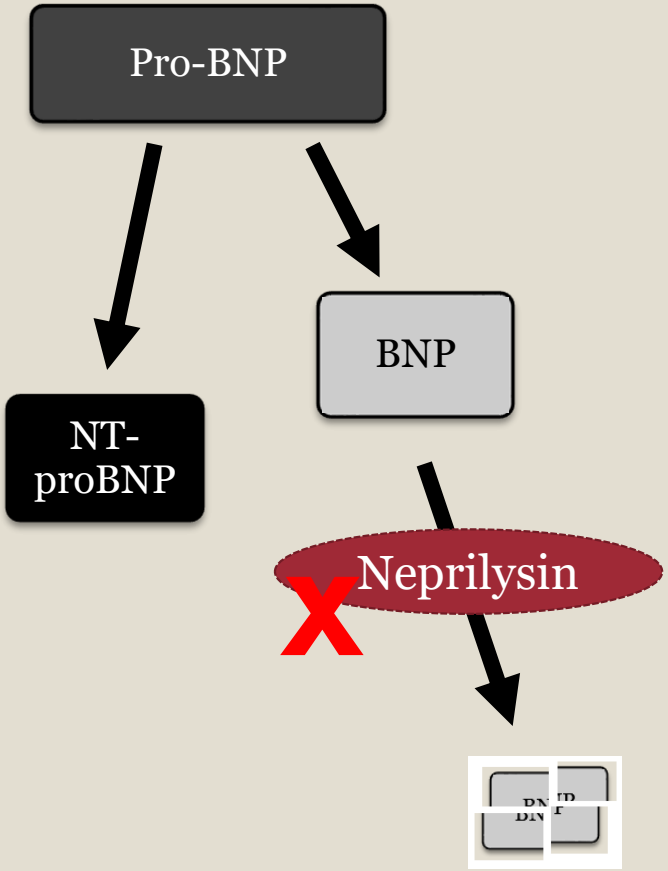
- Same precautions and titration considerations as ACEi
- Same ADRs as ACEi with the exception of bradykinin-related

In the News…
ARB shortages expected due to FDA recall

↓*Preload*
↓*Afterload*
↓*Remodeling*

Renin-Angiotensin-Aldosterone System

Neprilysin Inhibitor

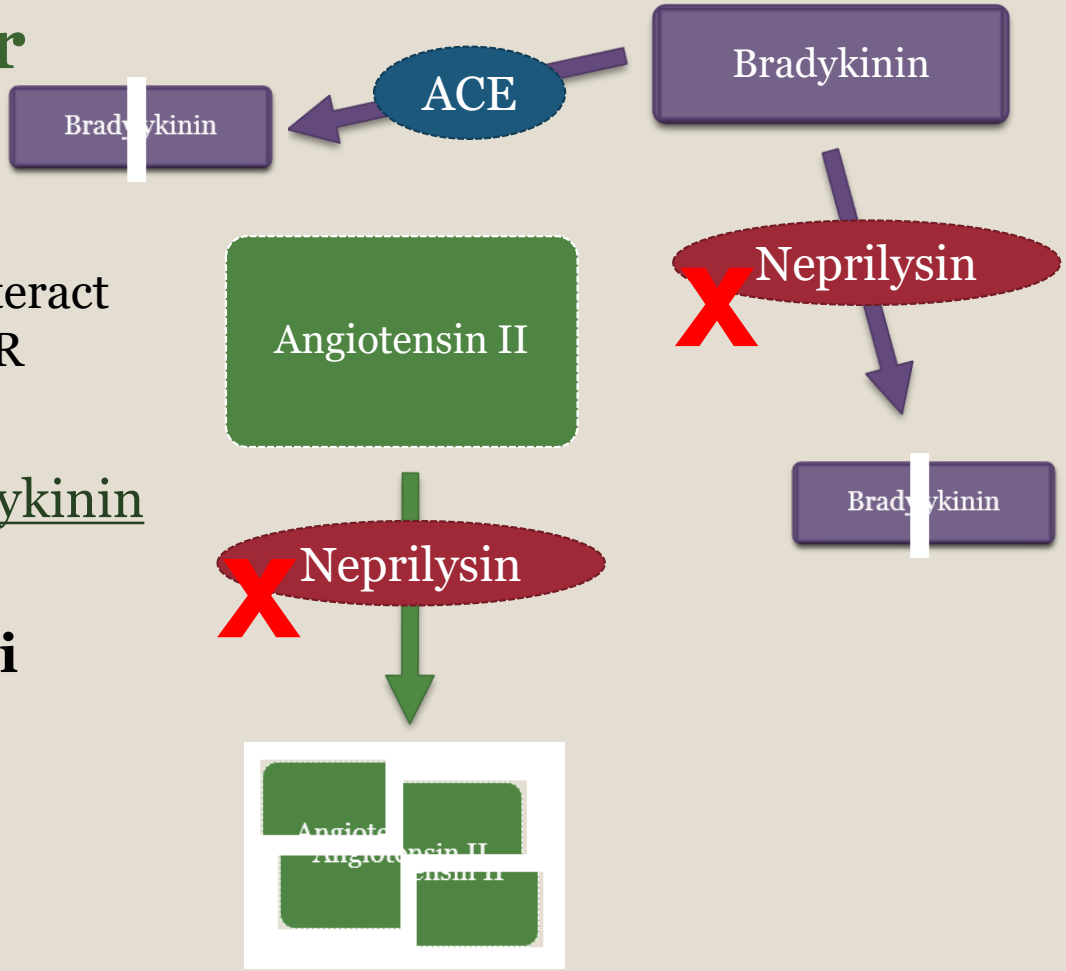


Neprilysin inhibition = ↑BNP

- BNP Effects:
  - Natriuresis/Diuresis
  - Vasodilation
- NT-proBNP marker preserved for measurement of disease progression

Renin-Angiotensin-Aldosterone System

Neprilysin Inhibitor



Neprilysin inhibition = ↑AngII

- **Requires use of ARB** to counteract effects of angiotensin II on AT1-R

Neprilysin inhibition = ↑bradykinin

- Increases risk of angioedema
- **Cannot be used with ACEi**

RAAS Inhibition + Diuretic Effect

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Angiotensin Receptor-Neprilysin Inhibitor

Drug	Starting Dose	Target Dose
Sacubitril/valsartan	24/26 mg to 49/51 mg po BID	97/103 mg po BID

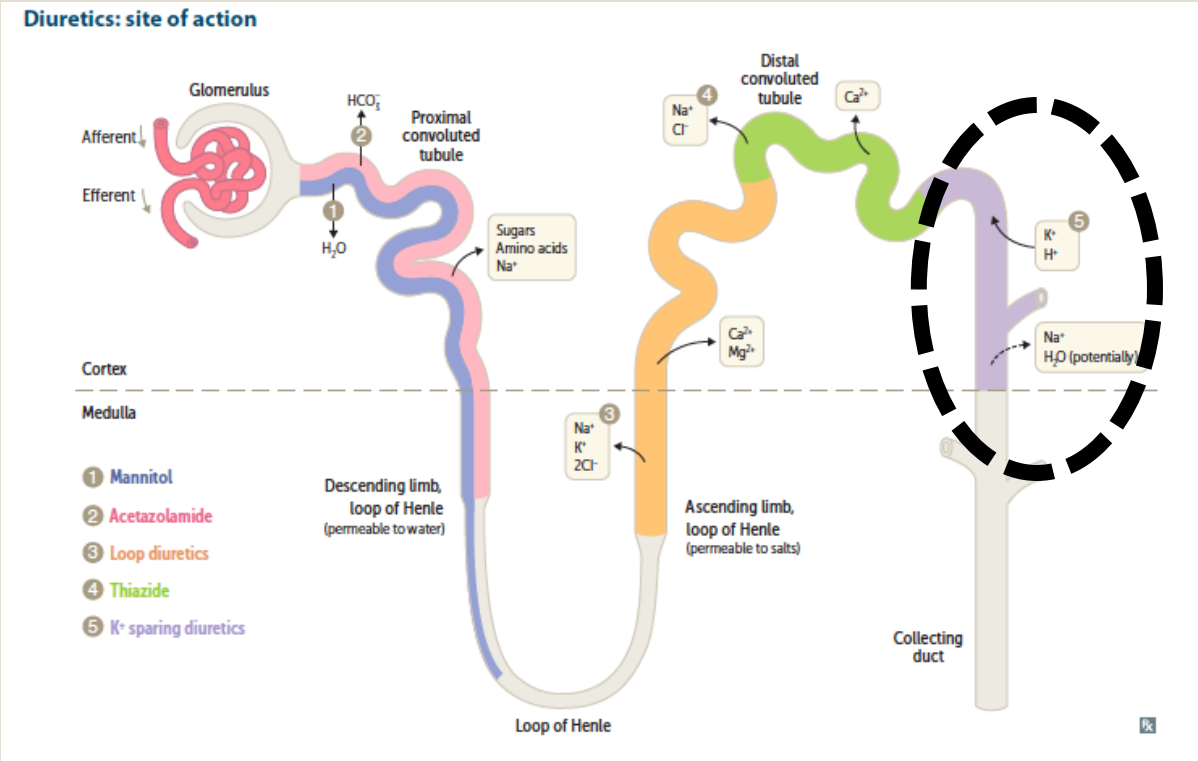
- Same as ARB precautions and ADRs (combo product)
- Contraindicated if history of angioedema
- Must allow for 36-hour wash out period following ACEi use
- ADRs:
  - ↑Bradykinin: angioedema, cough
  - ↑BNP: hypovolemia

↓*Preload*
↓*Afterload*
↓*Remodeling*

J Am Coll Cardiol 2018;71:201-30.

RAAS Inhibition + Diuretic Effect

Aldosterone Receptor Antagonists



Medications:
Spironolactone
Eplerenone

Location of Action:
Cortical Collecting Duct (Mineralocorticoid receptor)

<u>Urinary</u> Effects:
↑NaCl excretion
↓K+ excretion

Diuretics

Diuretics

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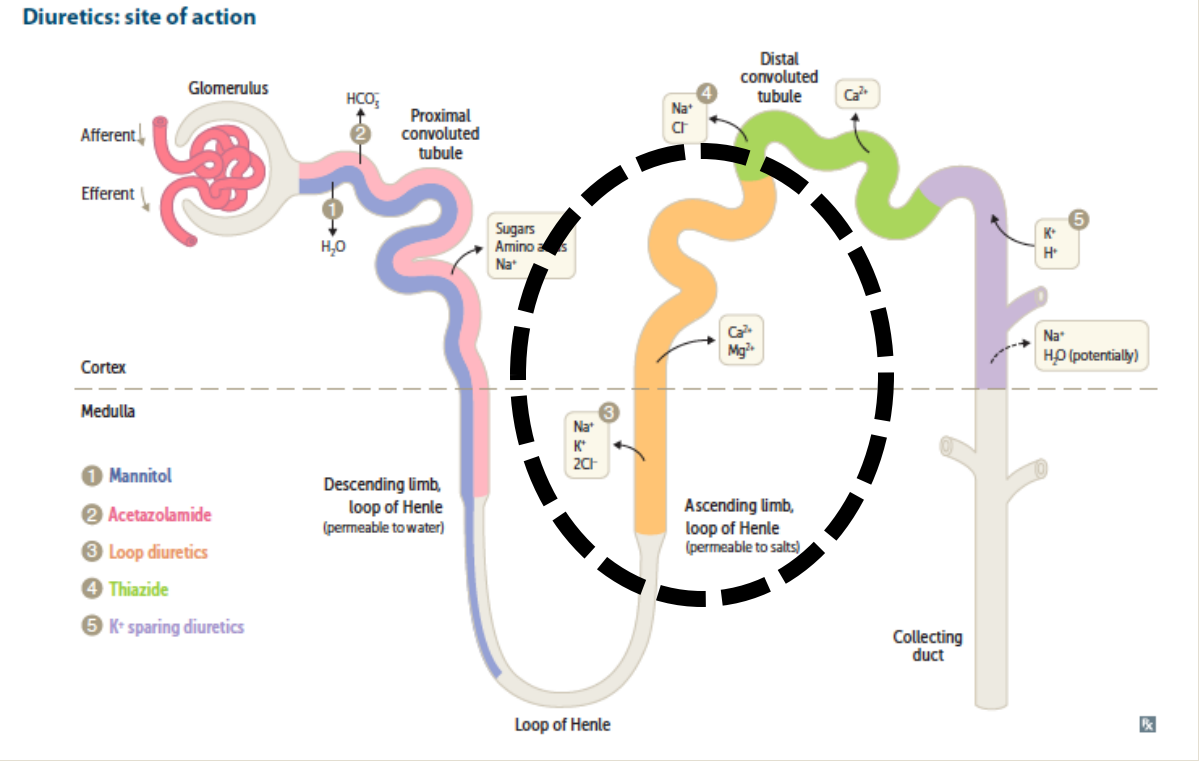
Loops



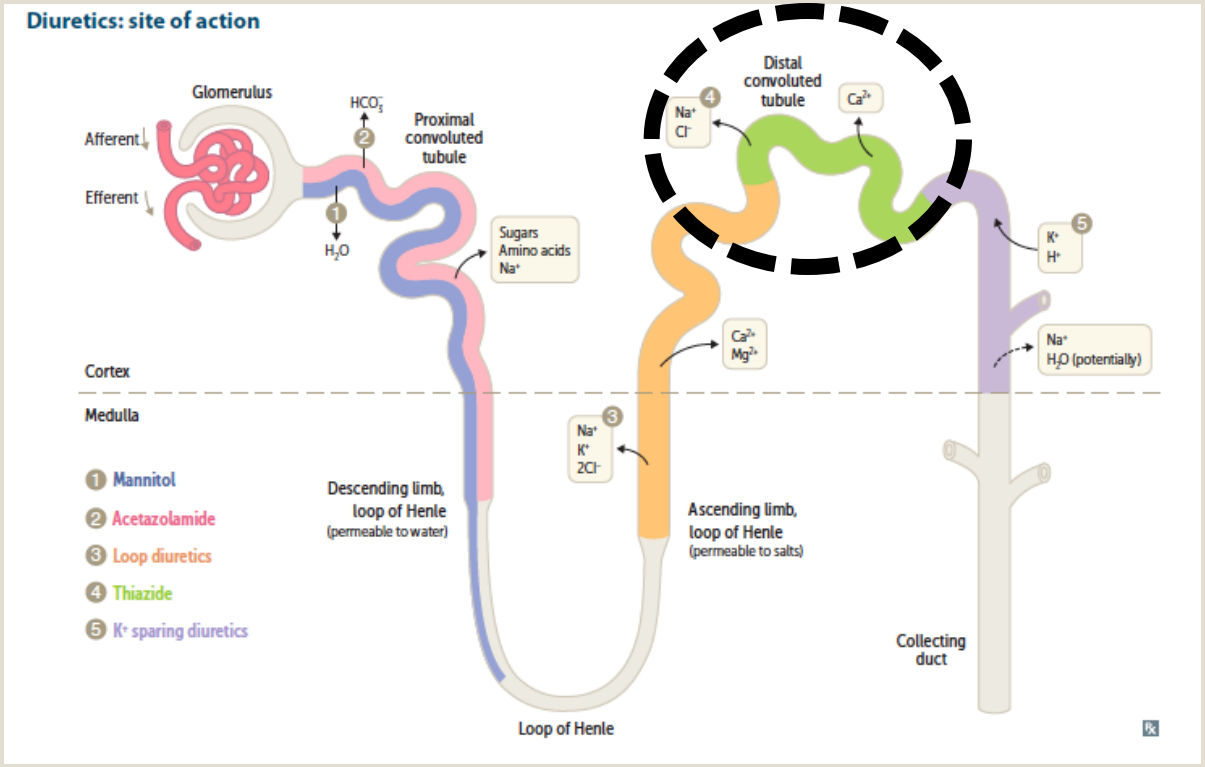
Medications:
Furosemide
Bumetanide
Torsemide
Ethacrynic Acid

Location of Action:
Ascending Loop of Henle

<u>Urinary</u> Effects:
↑NaCl excretion
↑K+ excretion

Diuretics

Thiazides



Medications:
Chlorthalidone
Hydrochlorothiazide
Metolazone

Location of Action:
Distal convoluted tubule

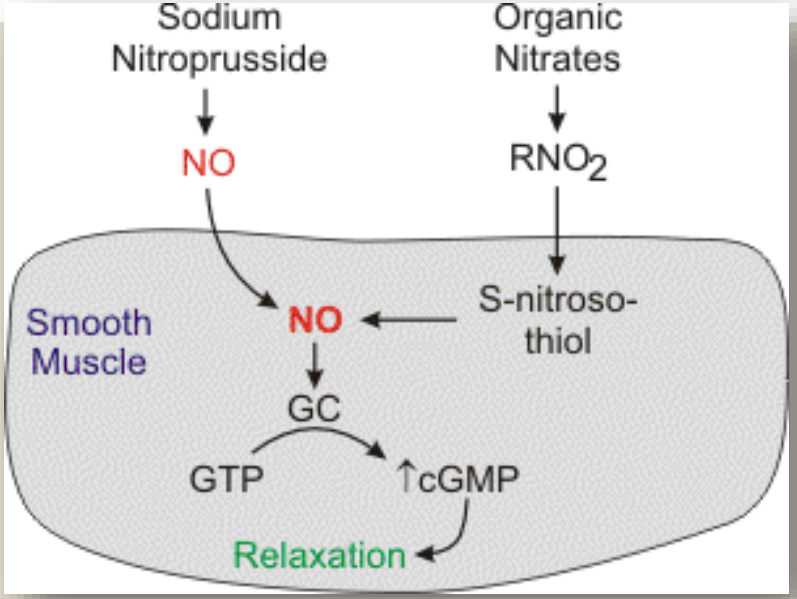
<u>Urinary</u> Effects:
↑Na excretion
↓Uric acid excretion
↓Calcium excretion

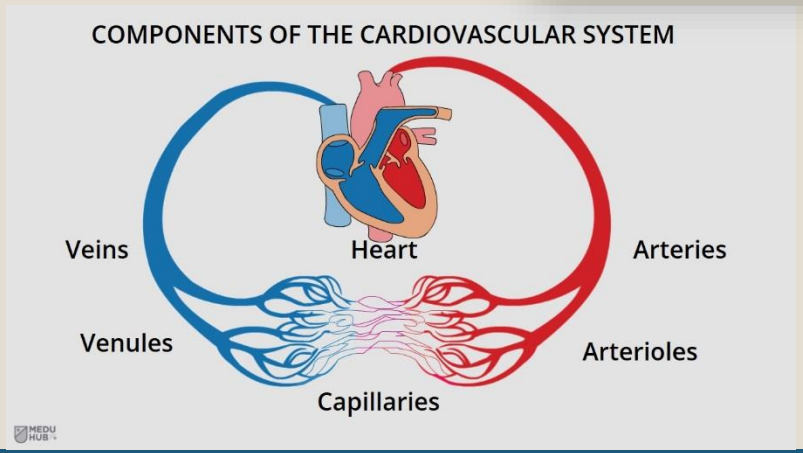
Vasodilators

Vasodilators

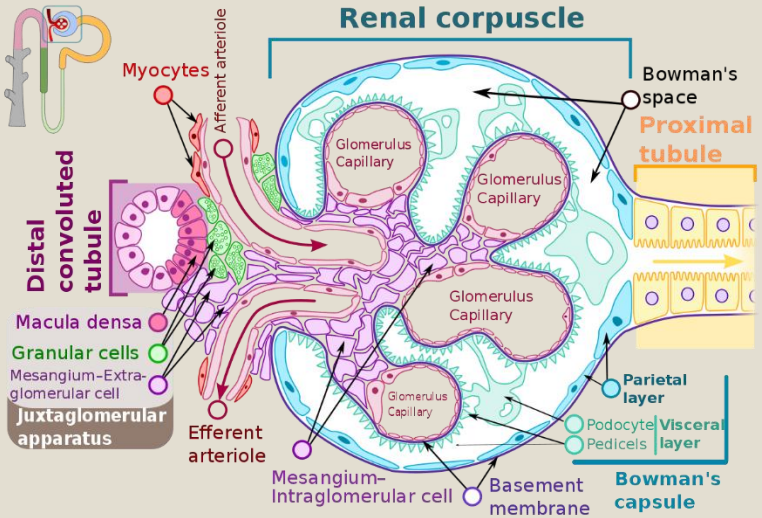
Nitrates

- Venodilator >> arteriodilator
- Coronary artery dilation
  - Reduces cardiac O2 demand
  - Reduces PRELOAD



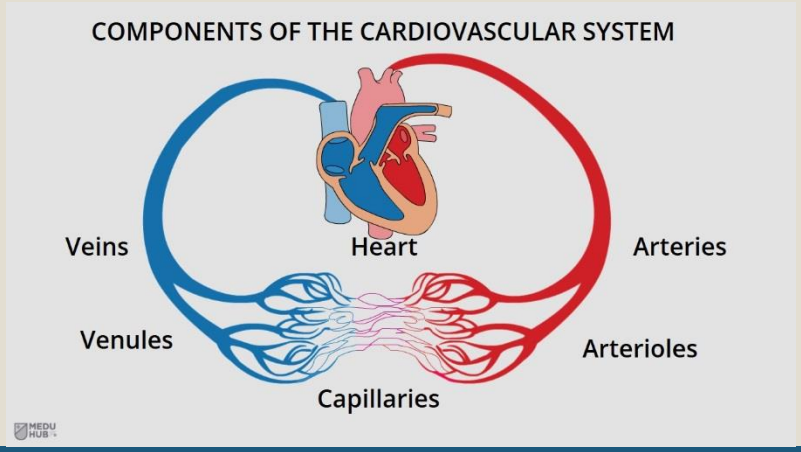


Vasodilators



Hydralazine

- Unknown Mechanism of Action
  - Alters cellular calcium metabolism
- ↓Juxtaglomerular pressure
  - ↑Renin secretion
    - ↑Sodium reabsorption



Vasodilators

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Nitrates/Hydralazine

Drug	Starting Dose	Target Dose
Hydralazine	25 mg po TID	75 mg po TID
Isosorbide dinitrate	20 mg po TID	40 mg po TID
BiDil® (isosorbide dinitrate/hydralazine)	20/37.5 mg po TID	40/75 mg po TID

- Class Considerations:
  - Good patient adherence required for TID regimens
  - ADRs:
    - **Nitrates** – headache, orthostatic hypotension, tachycardia, decreased platelet aggregation, tachyphylaxis
    - **Hydralazine** – headache, peripheral edema, nausea, anorexia, palpitations, sweating, flushing, reflex tachycardia, lupus-like syndrome, vasculitis

J Am Coll Cardiol 2018;71:201-30.

Pump/Motor
(i.e. Cardiac Function)

Components Affecting Cardiac Output

Factors Affecting Heart Rate (HR)

Factors Affecting Stroke Volume (SV)

Atrial reflex

Venous Return

Filling Time

Autonomic Innervation

Vasodilation or vasoconstriction

Preload

Contractility

Afterload

Autonomic innervation

End diastolic volume (EDV)

End systolic volume (ESV)

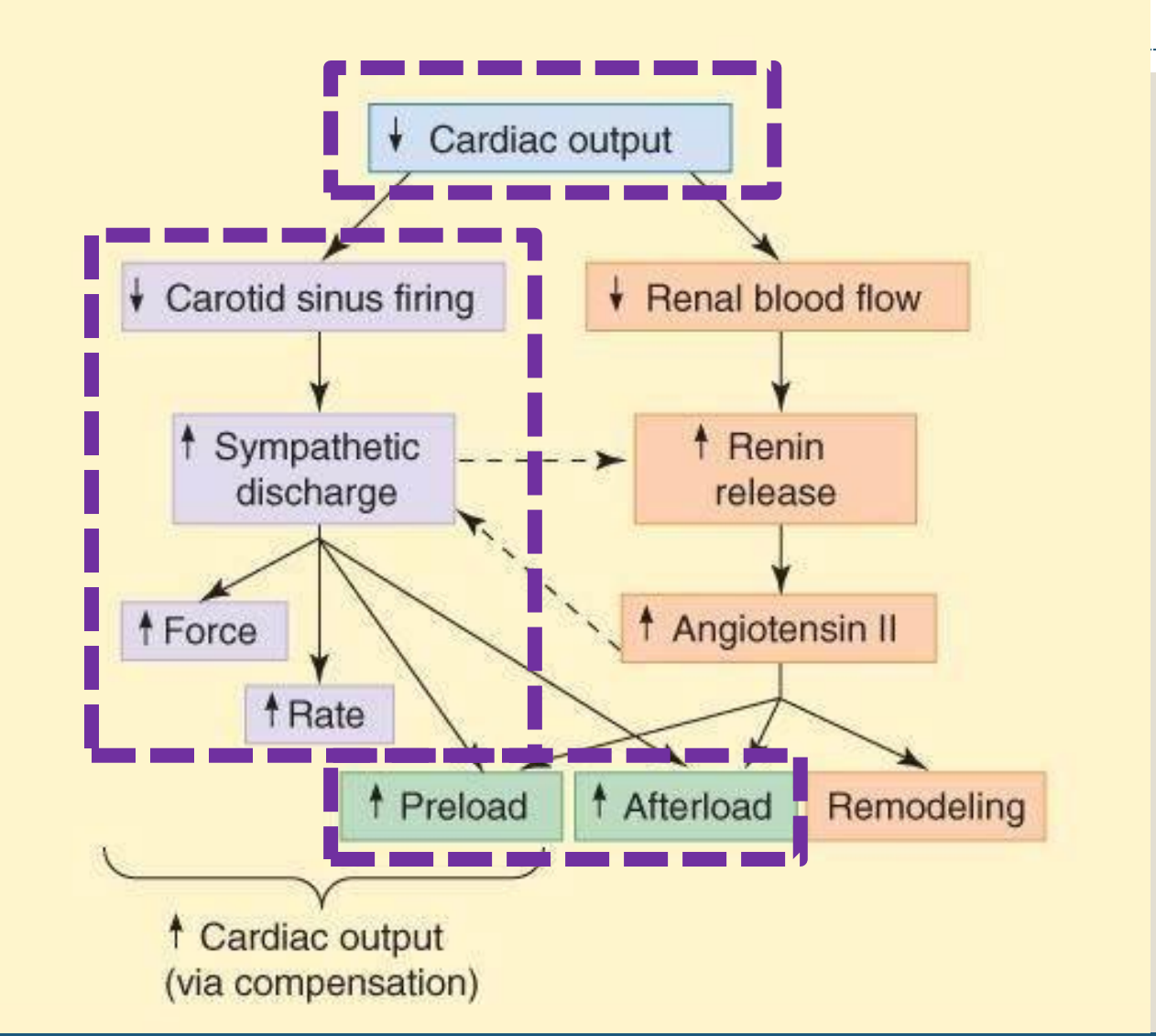
Heart Rate (HR)

Stroke Volume (SV) = EDV - ESV

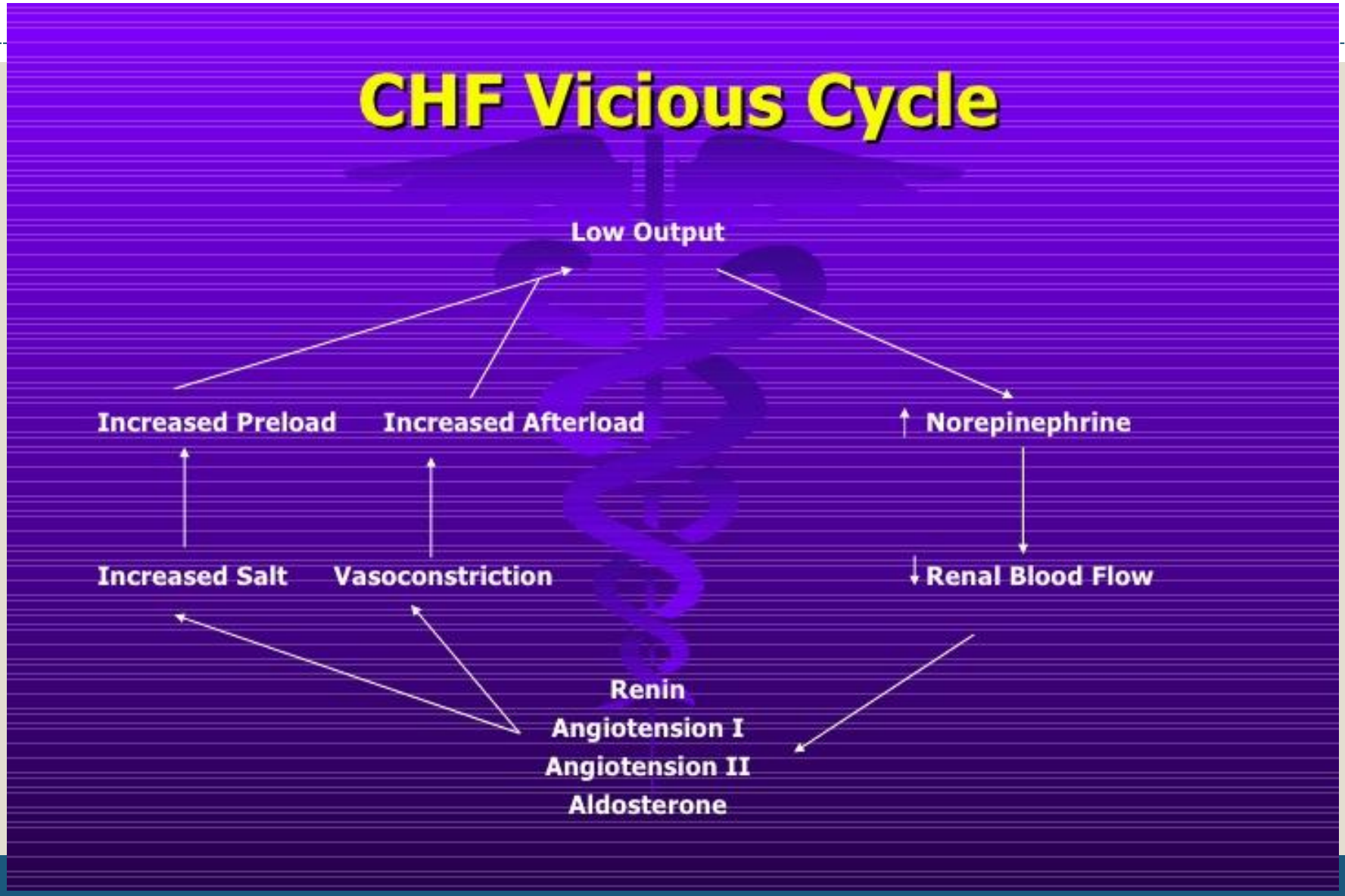
Cardiac Output (CO) = HR x SV

Pump/Motor

Background


↓ Cardiac output
↓ Carotid sinus firing
↓ Renal blood flow
↑ Sympathetic discharge
↑ Renin release
↑ Force
↑ Rate
↑ Angiotensin II
↑ Preload
↑ Afterload
Remodeling
↑ Cardiac output (via compensation)

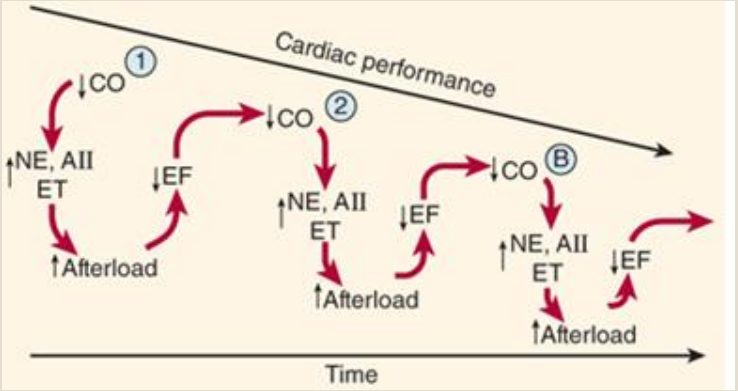
Background


CHF Vicious Cycle
Low Output
Increased Preload
Increased Afterload
Norepinephrine
Increased Salt
Vasoconstriction
Renal Blood Flow
Renin
Angiotension I
Angiotension II
Aldosterone

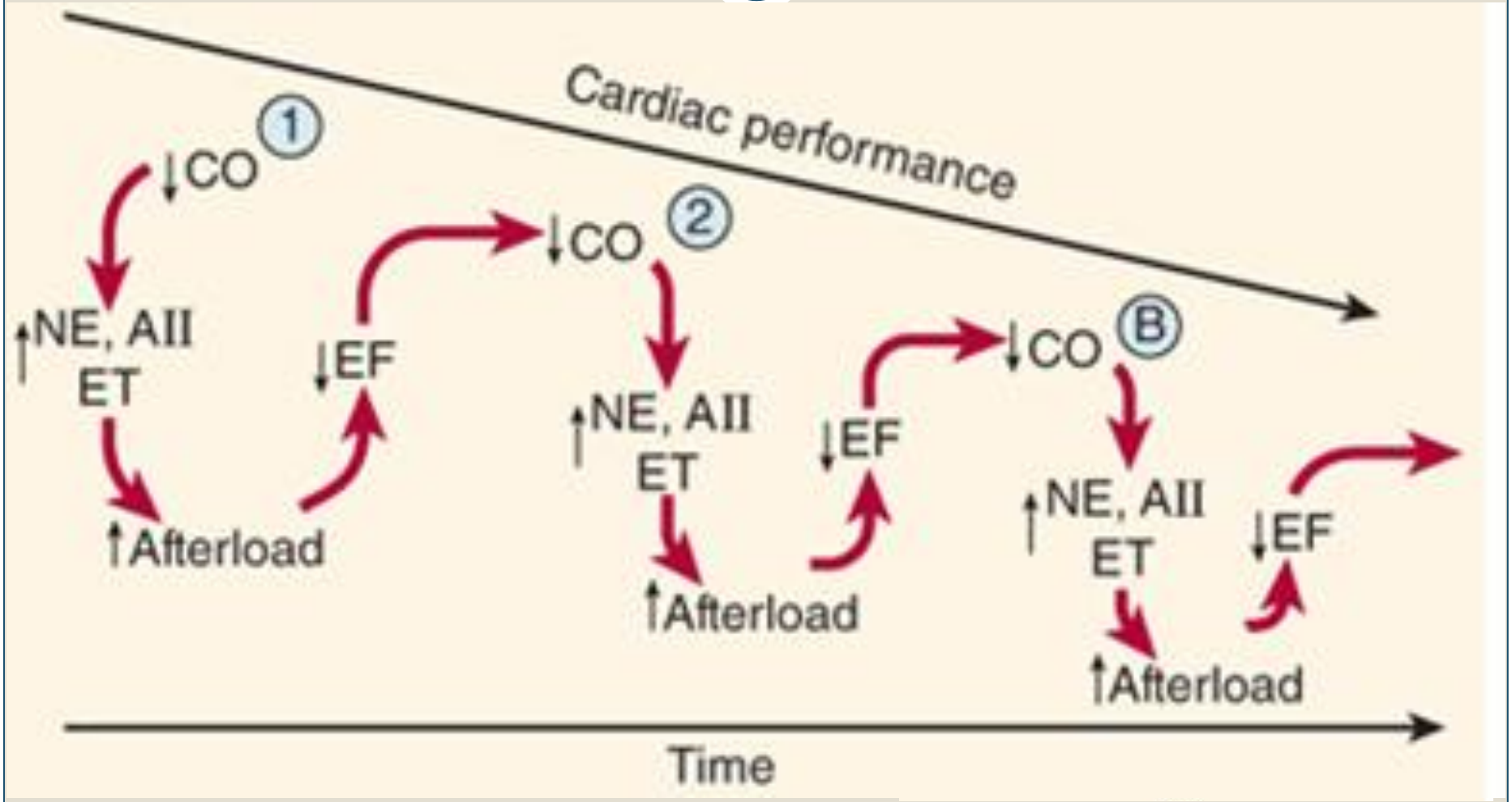
Chronic HFrEF

Beta-Blockers

- Bisoprolol, carvedilol, and metoprolol *succinate* only beta-blockers with proven mortality benefit
- Paradoxical benefit due to their negative inotropic effect
  - Not recommended to be initiated in acute decompensated HF
- Breaks the viscous cycle by decreasing effects of increased noradrenergic state



Beta-Blockers



Beta-Blockers

- Full understanding of beneficial action of beta blockers is not completely understood, suggested mechanisms include:
  - Reduce subendocardial ischemia
  - Normalize high phosphorus energetic imbalance
  - Improve myocardial work/oxygen consumption ratio
  - Improve force-frequency relation of the myocardium performance
  - Reduce renin release
  - Reduce endothelin production and release
  - Reduce sympathetic tone
  - Increase norepinephrine re-uptake
  - Increase vagal tone
  - Increase heart rate variability
  - Reduce QT-dispersion
  - Reverse of deteriorated fractal behavior of heart rate variability
  - Up-regulate beta-adrenergic receptors
  - Reduce inflammatory cytokines
  - Antagonize autoantibodies against 1-receptors
  - Antioxidant effect
  - Better response in insulin resistant patients

Beta-Blockers

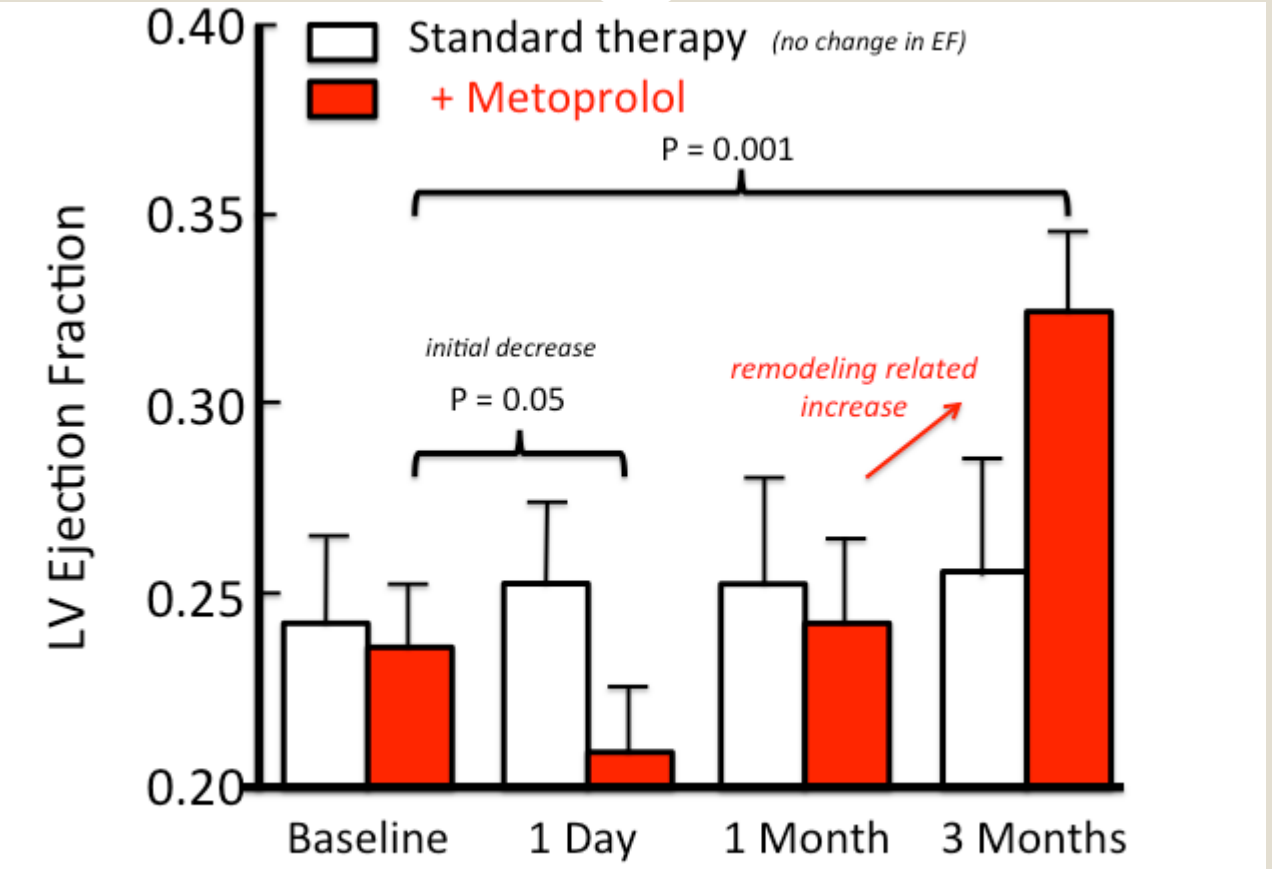
- How can beta-blockers improve myocardial energy balance in heart failure?
  - Decrease heart rate and increase diastolic flow time
  - Improve relaxation and decrease myocardial restriction
  - Increase perfusion pressure and decrease filling pressure
  - Decrease cardiac hypertrophy and remodeling
- Leads to long-term INCREASED cardiac output

Beta-Blockers

Drug	Starting Dose	Target Dose	Mean Dose Achieved in Clinical Trial
Bisoprolol	1.25mg QDay	10mg QDay	8.6mg total daily dose
Carvedilol	3.125mg BID	25mg BID 50mg BID (if ≥ 85kg)	37mg total daily dose
Metoprolol succinate	12.5-25mg QDay	200mg QDay	159mg total daily dose

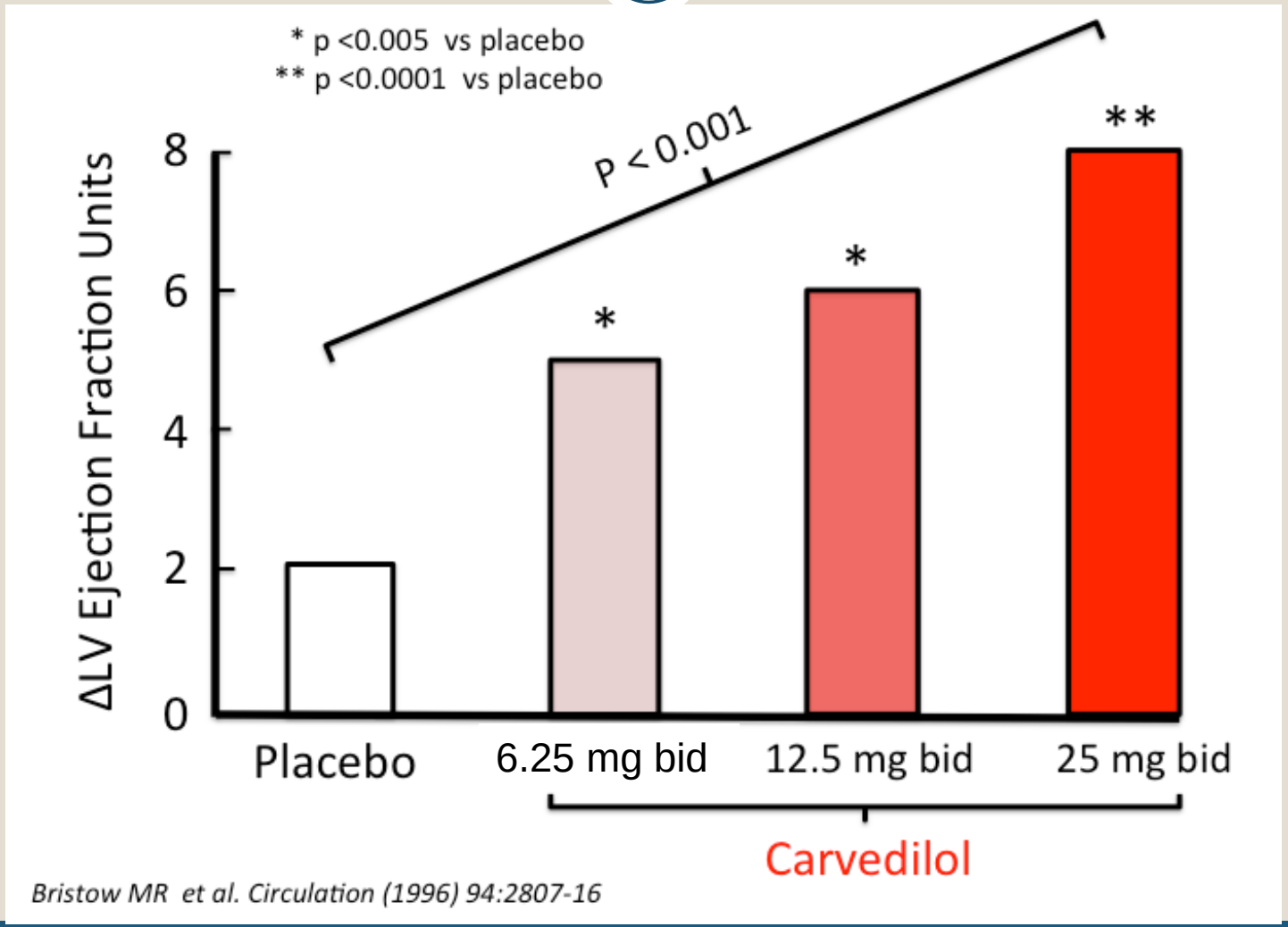
- Start low and go slow
- Recommended to titrate dose no faster than every 2 weeks and only if patient is stable
- May take months to see beneficial effects

Beta-Blockers



Hall SA et al (1995) JACC 25:1154-61

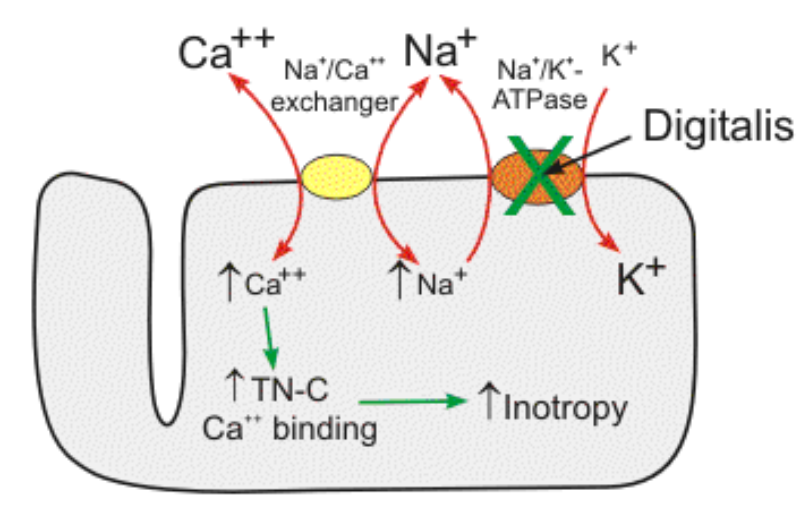
Beta-Blockers



Bristow MR et al. Circulation (1996) 94:2807-16

Digoxin

- Moderate, persistent positive inotropic effect
- Indirect MoA by inhibiting the Na/K ATPase
  - Increases intracellular calcium
- Also beneficial for atrial arrythmias through cardiac parasympathetic effects
  - Suppresses AV nodal conduction
  - Slows HR

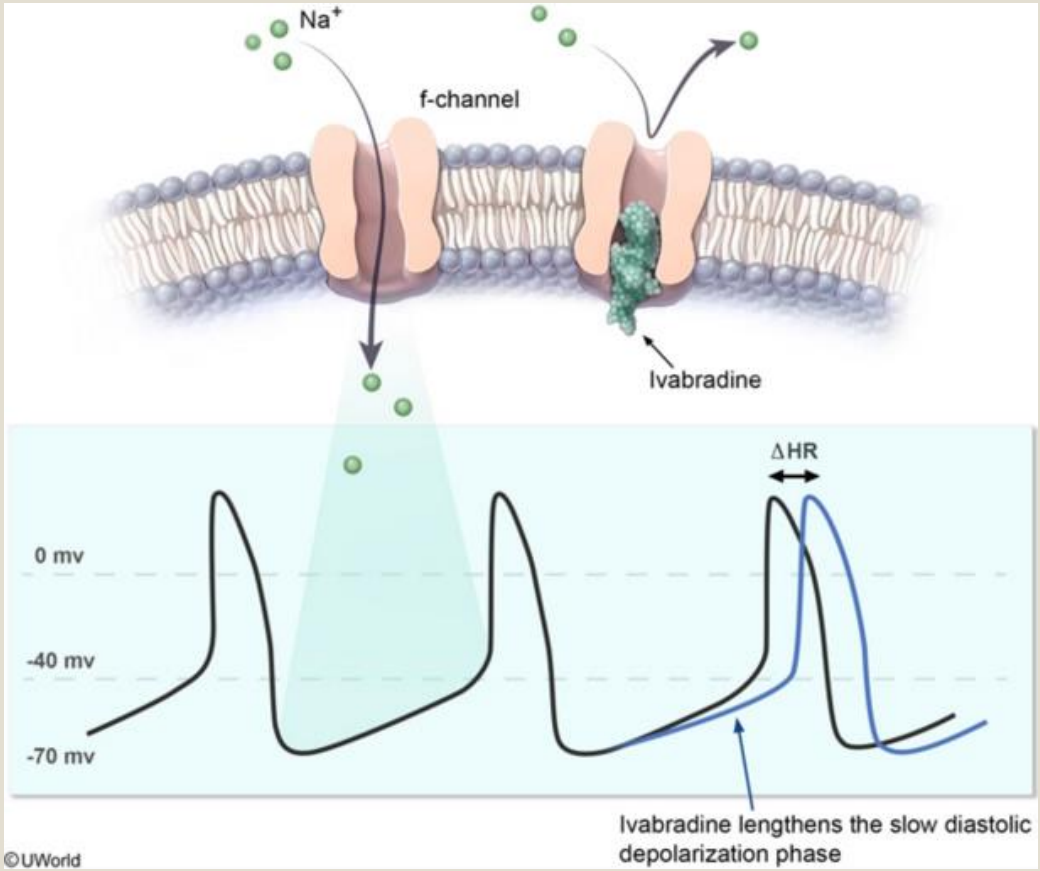


Digoxin

- Shown to reduce hospitalizations but not mortality
- Requires careful therapeutic monitoring and pharmacokinetic considerations
  - Reference range: 0.5-0.9 ng/mL
  - Levels > 1.2 ng/mL associated with increased mortality
- Generally only recommended for patients with HF and afib or symptomatic HF patients already on GDMT

Ivabradine

- Directly inhibits the funny channel (sodium channel) within the SA node
  - Prolongs the slow depolarization phase
- Reduces HR with minimal to no effect on BP



Ivabradine

- Recommended for patients with stable HFrEF and resting HR ≥ 70 bpm who are receiving maximally tolerated beta-blockers or who have contraindications to beta-blocker use
- Starting dose 5mg BID
  - Increase to 7.5mg BID if HR ≥ 60 bpm after 2 weeks
- Associated with an increase risk of afib and is relatively contraindicated in patients with afib

Acute Decompensated Heart Failure

Dobutamine

- Primarily a beta-1 and beta-2 agonist
  - Small alpha-1 agonist effect
- Beta-1 stimulation leads to positive inotropic effects
  - Generally does not produce a significant increase in HR
- Modest peripheral beta-2 receptor-mediated vasodilation tends to offset minor alpha-1 receptor-mediated vasoconstriction
  - Net vascular effect is usually vasodilation (i.e. afterload reduction)

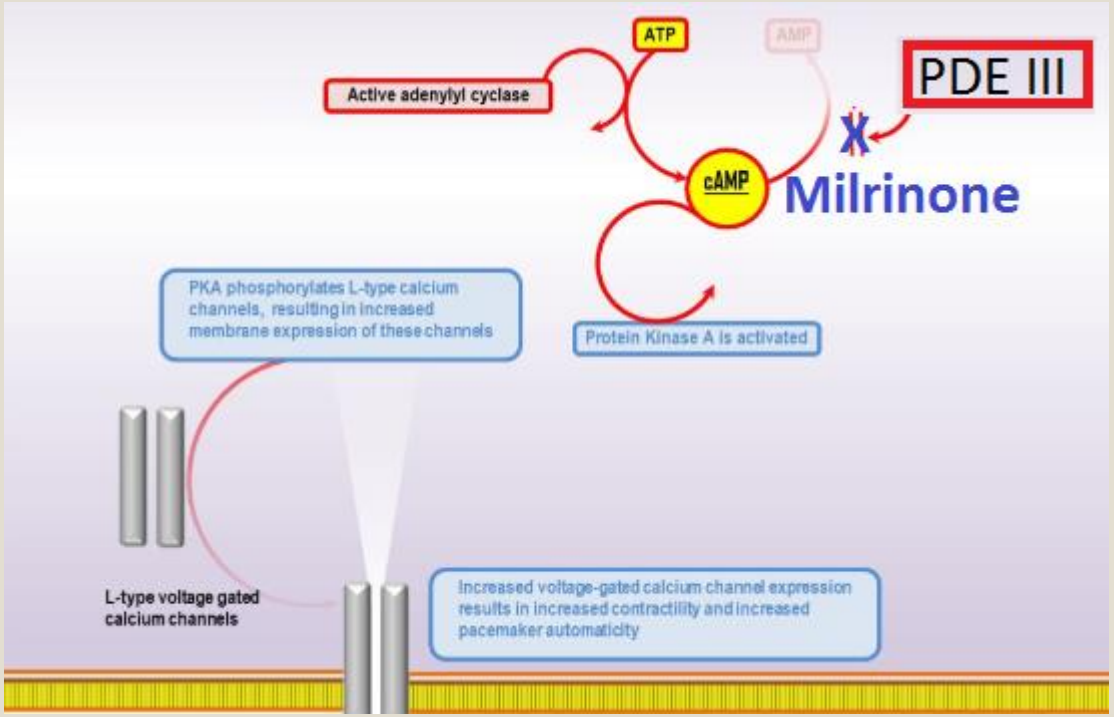
Dobutamine

- Initial dose is 1-2 mcg/kg/min, titrated 1-2mcg/kg/min every 10-20 minutes based upon clinical and hemodynamic response
  - Max dose 20mcg/kg/min
- May see attenuation of hemodynamic effects with prolonged administration
  - Generally only recommended for short-term, acute decompensated heart failure or as “bridge” therapy
- Adverse effects
  - Arrythmias
  - Angina (increased myocardial oxygen consumption)

Milrinone

PDE-III inhibitor

- Prevents degradation of cAMP
- Leads to increased calcium channel expression
  - Cardiac and peripheral
- Increases cardiac contractility and causes arterial and venous dilator
  - Inodilator



Milrinone

- Increases stroke volume and cardiac output with minimal change in heart rate
- Also lowers PCWP through venodilatory effects
  - Useful in patients with a low CI and elevated LV filling pressure
- Venodilating effects may predominate
  - Leading to decreased BP and reflex tachycardia

Milrinone

- Given as a continuous IV infusion 0.1-0.3 mcg/kg/min
  - Max dose 0.75 mcg/kg/min
- Renally eliminated (83%)
  - t-½ and risk of hypotension increased in patients with renal dysfunction
  - May require dose-adjustment
- Adverse effects
  - Hypotension
  - Arrhythmia
  - Thrombocytopenia (rare)

Dopamine

- Produces dose-dependent hemodynamic effects due to its relatively affinity for different receptors

Dose	Predominate Receptor	Predominate Effect
2-5 mcg/kg/min	Dopamine	Possible increased renal blood flow and urine output
5-10 mcg/kg/min	Beta-1	Increased contractility and HR
10-20 mcg/kg/min	Alpha-1	Increased vasoconstriction

- Generally avoided in HF due to availability of other treatment options and high risk of arrhythmias

Pharmacologics Affecting Contractility

	Effect on HR	Effect on Contractility	Effect on BP
Beta Blockers	↓	↓ Short-term ↑ Long-term	↓
Digoxin	↓	↑	↔
Ivabradine	↓	↔	↔
Dobutamine	↔	↑	↑
Dopamine	↑	↑	↑
Milrinone	↔ Possible reflex tachycardia	↑	↑ or ↓

↔ = minimal or no anticipated effect

Conclusion

- Heart failure is an increasingly common disease state which requires early pharmacologic intervention to reduce the progressive nature of the disease
- Understanding pathophysiological changes that occur in heart failure is helpful for guiding treatment options
- Improvement in overall outcomes can be achieved by utilizing goal-directed medication therapy tailored to specific patient factors

Questions?

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