CARDIOLOGY 2023

MEDICATIONS FOR HEART FAILURE

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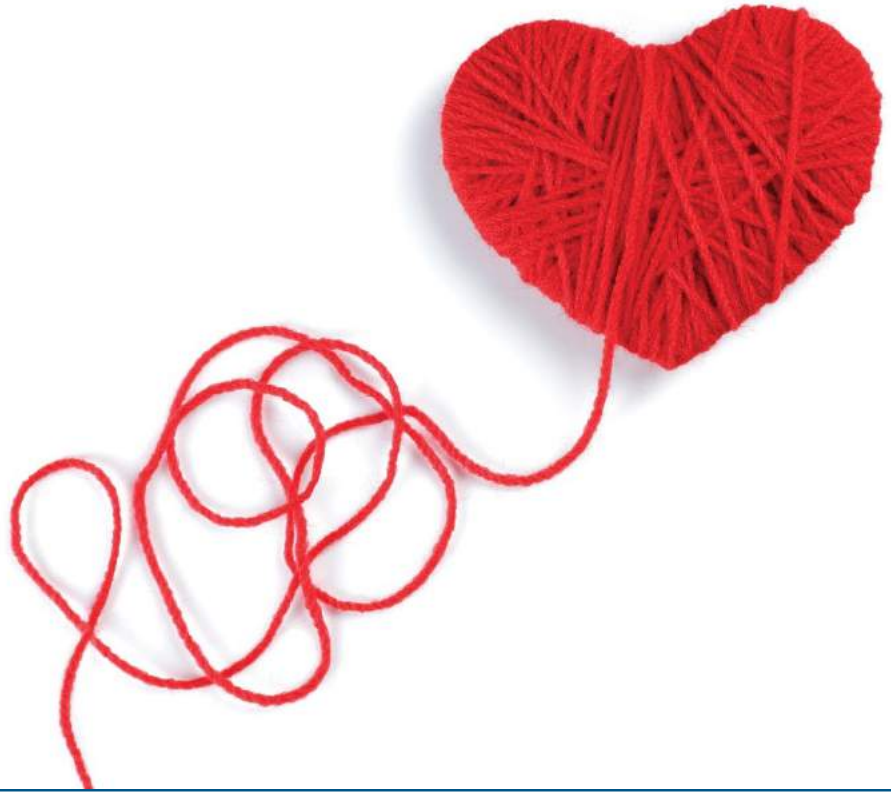
2/26/2023



Texas Children's Hospital

Baylor College of Medicine

OBJECTIVES

- Discuss pharmacologic treatment options for patients with heart failure.
- Identify possible side effects.

HEART FAILURE

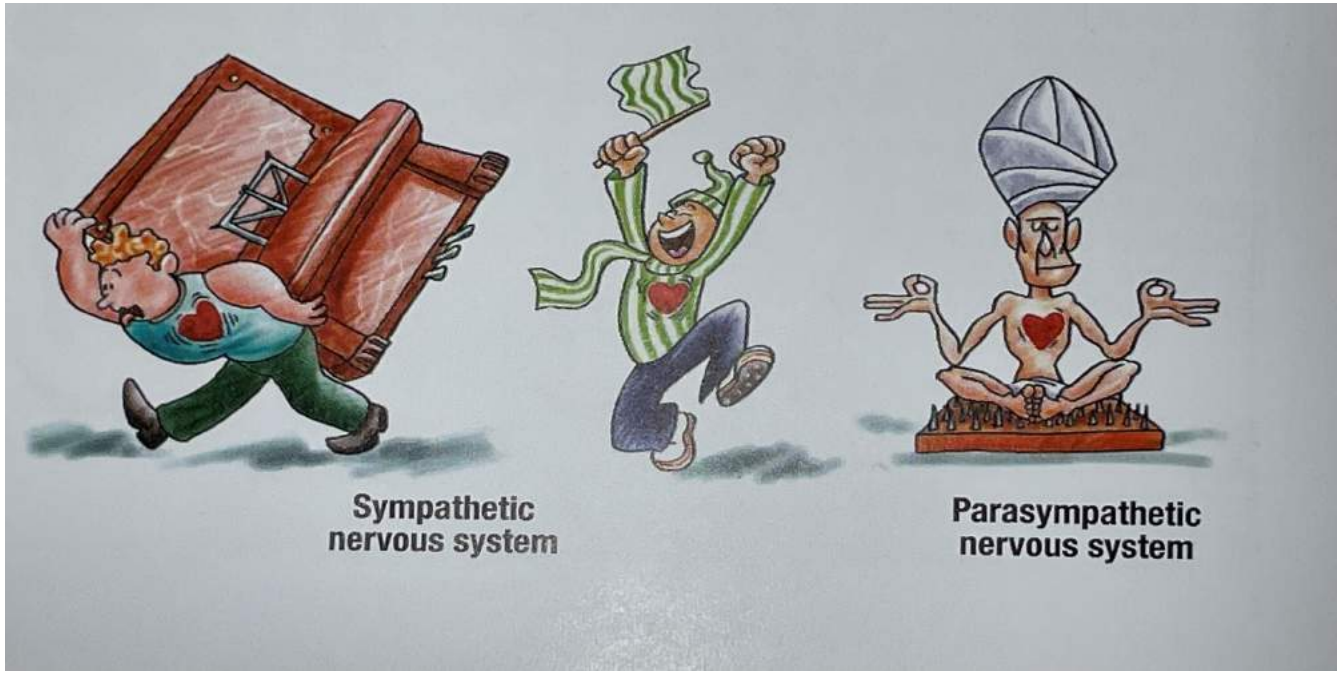
- Pathophysiologic state wherein the heart is unable to pump adequate volume of blood and oxygen at a rate appropriate to the body's metabolic demands.
- It is a cardiocirculatory disorder involving preload, afterload, contractility, and heart rate.

PATHOPHYSIOLOGY OF HEART FAILURE

- The mean arterial pressure needs to be constant.
- Mean arterial pressure is regulated by baroreceptors and hormonally mediated systems.
- Chronic activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) is associated with remodeling of cardiac tissue, loss of myocytes, hypertrophy, and fibrosis.

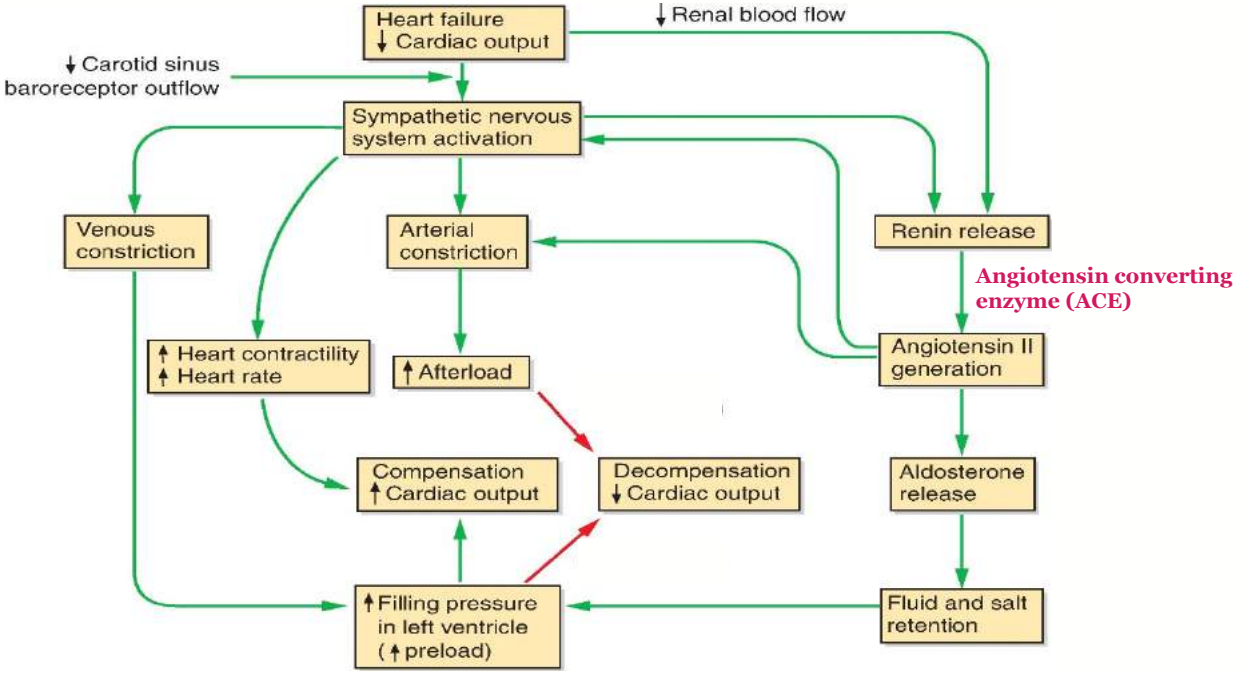
GOALS OF PHARMACOLOGIC INTERVENTIONS

- Alleviate symptoms.
- Slow disease progression.
- Improve survival.



Essential atlas of physiology(2003)

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM



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ANGIOTENSIN- CONVERTING ENZYME INHIBITORS (ACE-I)

- 1967 John Vane, British pharmacologist, and Mick Bakhle, organic chemist, demonstrated that dog lung ACE was inhibited by mixture of peptides from venom of Brazilian pit viper *Bothrops jararaca*.
- Squibb's biochemist, David Cushman, and organic chemist, Miguel A Ondetti, formulated captopril (Capoten).
- Inhibits conversion of angiotensin I to angiotensin II.
- Is associated with decreased myocyte hypertrophy, apoptosis, and fibrosis.
- Well tolerated and first line therapy.

CAPTOPRIL

- First oral ACE-I
- It was patented in 1976 and approved for medical use in 1980
- Brand name Capoten
- Metabolized via CYP2D6
- Usual dosage:
  - Neonates 0.1 mg/kg/dose every 8-12 hours
  - Infants 0.3-2.5 mg/kg/day divided every 8-12 hours
  - Children/adolescents 0.3- 6mg/kg/day every 8-24 hours

ENALAPRIL

- Developed by Arthur Patchett at Merck.
- Longer duration.
- Approved by FDA 2013.
- Brand name Epaned, Vasotec, Enacard
- Metabolized by liver to active enalaprilat.
- Usual dosage:
  - Children:
    - Oral: 0.1-0.5 mg/kg/day divided Q 12.
    - IV: 5-10µg/kg/dose every 8-24 hours.
  - Adults:
    - Oral: 2.5 mg Q 12 hours
    - IV: 0.625-1.25 mg/dose every 6 hours

LISINOPRIL

- For patients > 6 years and older
- FDA approval for use 2016
- Brand name Qbrelis
- Does not undergo metabolism.
- Usual dosage:
  - Children – 0.7-1 mg/kg/dose once a day
  - Adults- 2.5- 5 mg once a day (max 40mg)

SIDE EFFECTS

- Hypotension- dizziness, fatigue, and headache.
- Hyperkalemia
- Chronic coughs
- Rare: Rash, diminishing taste, anemia, and neutropenia

ADVERSE EFFECTS

- Angioedema
- Drug induced pancreatitis.
- Anaphylactoid reactions.
- Contraindicated in pregnancy.

*** Should avoid in patients with history of angioedema, bilateral renal artery stenosis, hypotension, or aortic stenosis.

ANGIOTENSIN RECEPTOR BLOCKERS (ARBS)

- Dupont-Merck Pharmaceuticals exploited the angiotensin II receptor in the early 1980's.
- Blocks effects of angiotensin II at the angiotensin II subtype 1 receptor.
- Useful if ACE-I intolerant.
- A reasonable alternative to ACE-I, but are not therapeutically identical.
- Can be adjunct therapy to ACE-I with close monitoring for hyperkalemia and increase in serum creatinine.
- Patients who do not tolerate ACE-I from worsening renal function, hyperkalemia, or hypotension may likely have the same response to ARBS.

LOSARTAN

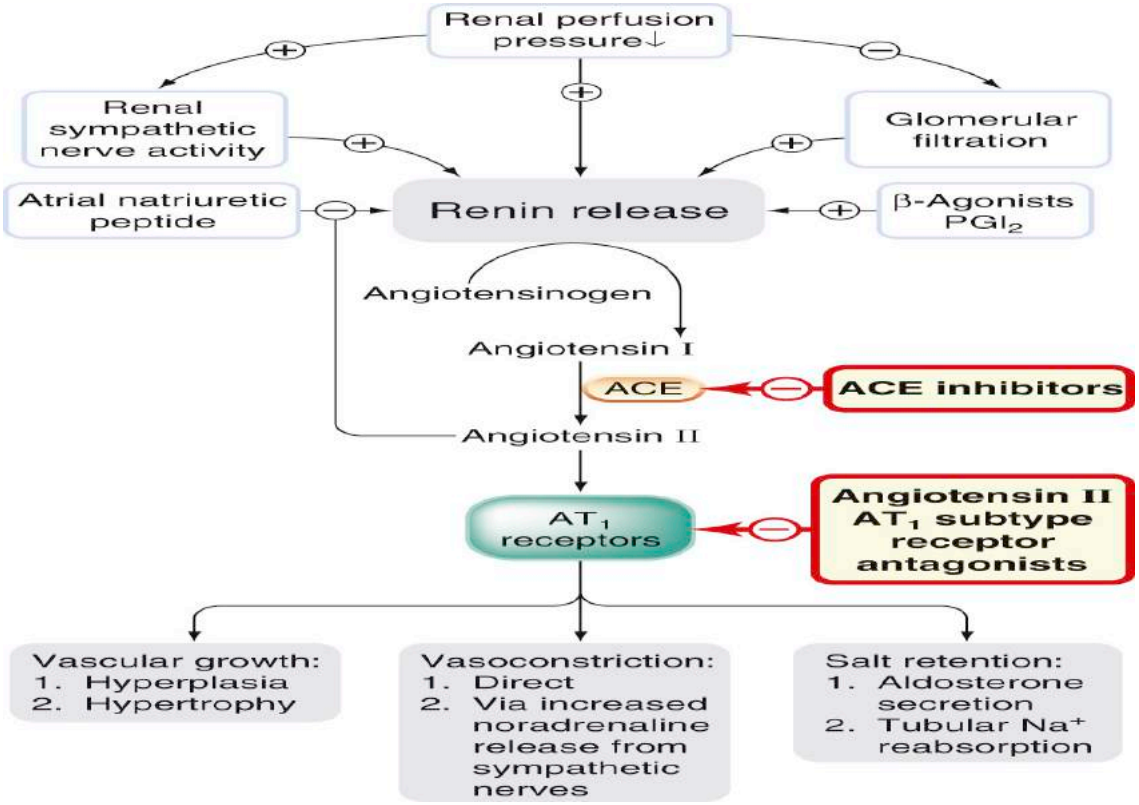
- Cozaar was launched in 1995.
- For patients 6 years and older.
- Metabolized via CYP2C9 and CYP3A4
- Usual dose:
  - Children- 0.5 mg/kg once a day; not to exceed 12.5-25 mg once daily. Up to 1.4mg/kg once daily not to exceed 150mg/day.
  - Adults- 12.5-50 mg once daily (max 150 mg)

VALSARTAN

- Diovan was developed by Novartis and approved for use in 1996.
- Generic valsartan was approved in 2019.
- For patients 6 years and older.
- Metabolized minimally by liver to inactive metabolite
- Usual dose:
  - Children- 1.3 mg/kg/dose once a day (max 2.7 mg/kg/dose)
  - Adults- 40 mg twice daily (max 160 mg twice daily)

SIDE EFFECTS

- Hypotension
- Dizziness
- Headache
- Diarrhea
- Increase in serum creatinine



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ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR

- Natriuretic peptides production is stimulated by myocyte stretch.
- Natriuretic peptides directly protect against excess salt and water retention.
- Neprilysin, an enzyme, was isolated in 1970.
- Inhibition of neprilysin increases atrial natriuretic peptides, blocks activation of aldosterone, and improve diuresis and natriuresis.
- Inhibition of neprilysin also activate RAAS.
- Adding ARB helps blocks RAAS.

ENTRESTO (SACUBITRIL/VALSARTAN)

- Approval for use 2015
- Treatment of symptomatic heart failure with systemic left ventricular dysfunction > 1 year of age.
- Dosage: Dose titration every 2 weeks
- For < 40 kg: 1.6 mg/kg BID, 2.3 mg/kg BID, to 3.1 mg/kg BID (suspension 4mg/ml)
- For 40 to < 50 kg 24/26 mg BID, 49/51 BID, 72/78 mg BID
- For >/= 50 kg 49/51 mg BID, 72/78 mg BID, 97/103 mg BID
- Side effects: Hypotension, renal impairment, hyperkalemia, angioedema

SPIRONOLACTONE

- Mineralocorticoid/aldosterone receptor antagonist
- Approval for use in 1960.
- Brand name Aldactone.
- Well absorbed (73%).
- Metabolism: Hepatic to active and inactive metabolites.
- Potassium-sparing diuretic effect in the distal tubules of the kidney.
- Usual dose: 1 mg/kg/day in divided doses every 6-24 hours. Max 3.3-6 mg/kg/day divided every 6- 24 hours (Not to exceed 100 mg/day).
- Side effects: Diarrhea, Nausea, vomiting, and gynecomastia.

NOT BLUEBONNET

DIGOXIN

- 1785 William Withering, physician and botanist in Birmingham, England wrote a book describing using extract of foxgloves for treatment of dropsy.
- Main use was diuretic effects for patients with swelling of the abdomen, legs, or difficulty in breathing.

DIGOXIN

- Approved for use by FDA in 1954
- Inhibition of Na - K- ATPase:
  - Increase force and velocity of myocardial contraction.
  - Slowing of the heart rate.
  - Decreased conduction velocity through the AV node.
  - Decrease in degree of activation of sympathetic nervous system and RAAS.
- Significant toxicity, especially with renal dysfunction.
- Usual dose: 5-15 mcg/kg/day divided every 12 hours (Oral); 4-12 mcg/kg/day divided every 12 hours
- Serum levels of 0.5-0.9 ng/ml are typically targeted for optimal benefit.

SIDE EFFECTS

- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Headaches
- Dizziness

ADVERSE EFFECTS

- Cardiac arrhythmia
- Digoxin toxicity

THANK YOU…

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