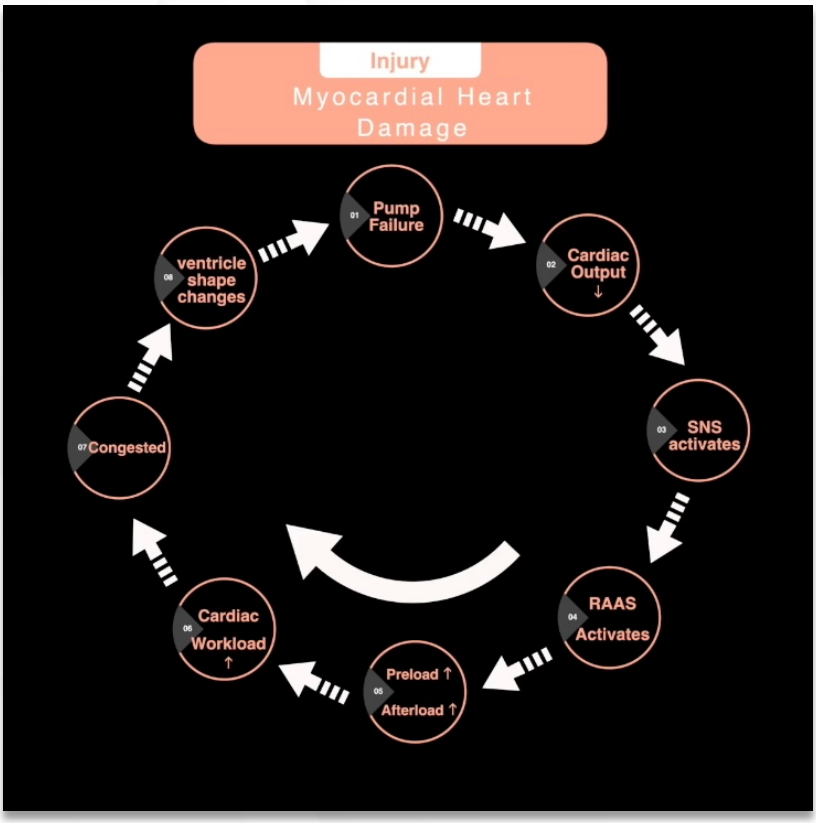
Heart Failure Medications: Stop the Cycle!

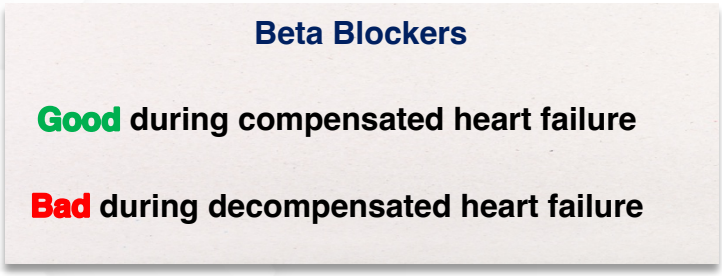
1. Medications have 2 main goals:
    a. Stop ventricular remodeling
        i. Cardiac remodeling causes permanent compromise to cardiac output and increases patient's mortality
    b. Increase cardiac output
2. The only way to stop or slow down remodeling is by interfering with the heart failure cycle at different points
    a. Requires multiple medications from several different drug classes to do this effectively

- ♥ We can give medications to **stop the SNS** effects when it's activated
- ♥ We can give medications that will **stop the effects of the RAAS**
- ♥ We can give medications to **reduce preload and afterload**
- ♥ We can give medications to **reduced cardiac workload**
- ♥ And we can give medications to **reduce congestion**



Blocking SNS: Beta Blockers

1. The Sympathetic Nervous System (SNS)
    a. SNS increases cardiac workload by:
        i. Increasing the heart rate
        ii. Increasing heart's oxygen consumption
    b. SNS activates the heart by sending catecholamines/hormones to activate Beta-1 cells on the heart
2. **Blocking the Sympathetic Nervous System effects on the heart will reduce cardiac workload**
    a. Beta Blockers will block beta-1 cells from being activated
    b. **Beta blockers work during exertion, not rest**
        i. At rest, the SNS is not activated, so beta blockers will NOT impact the heart rate when the patient is resting
        ii. With activity, the SNS is activated, so beta blockers will prevent beta-1 cells from being activated
3. Beta blockers slow down the heart failure cycle
    a. **Beta blockers work well in COMPENSATED heart failure**
    b. **Beta blockers are bad during decompensation** (congestion phase of heart failure cycle)
        i. During congestion, blood flow in the heart is at a standstill, and not moving forward
        ii. Beta blockers make congestion WORSE because it reduces the heart contractions and then reduces the heart's ability to pump blood volume OUT of the heart.
4. Beta blockers are primarily given when the patient is NOT actively in fluid overload



5. Beta Blockers are available in 2 different generations (2 types of beta blockers):
    a. **1st Generation Beta Blockers:**
        i. **Non-selective beta blockers**
        ii. **Block both Beta-1 receptors and Beta-2 receptors**
            - Beta-1 receptors are on the heart
            - Beta-2 receptors are in the lungs

- ♥ Activating beta-2 receptors cause blood vessels and bronchioles (in the lungs) to dilate
- ♥ Blocking bronchial dilation is not good for anyone with asthma or COPD
- ♥ **Be very cautious when giving a non-selective beta blocker to a person with asthma/COPD**

iii. **Example Brands:**
- **Carvedilol (Coreg)**
- Labetalol
- Propranolol
- Timolol

iv. Carvedilol is unique!
- Blocks both types of beta-receptors AND alpha-1 receptors
  - ♥ Alpha receptors are on the blood vessels and cause vasoconstriction when activated
  - ♥ Blocking alpha-receptors will cause vasodilation
  - ♥ So, carvedilol may cause more hypotension than other beta blockers

b. **2nd Generation Beta Blockers:**

i. **Cardio-selective**
- **Blocks <u>ONLY</u> Beta-1 receptors**

ii. Does not affect beta-2 receptors in the lungs
- Better option for patients with lung problems

iii. **Example Brands:**
- **Metoprolol**
- Bisoprolol
- Atenolol
- Nebivolol

6. Side Effects of all Beta Blockers
   a. Fatigue
   b. Bradycardia
   c. Hypotension
      i. Patients should stand up slowly to give their body enough time to pump blood back up to their head
      ii. Educate patient that if they forget to stand up slowly and feel lightheaded, they should sit back down and tuck their head until the lightheadedness passes (temporary orthostatic hypotension is normal with betablockers)
   d. Nausea (if taken on an empty stomach)
      i. Take medication with food
   e. **Diabetic Patients:**
      i. **Beta blockers can cause hypoglycemia**

ii. **Betablockers can mask episodes of hypoglycemia due to its SNS blocking effects**

7. **Patient Education:**
    a. **Stand up slowly to avoid feeling light-headed**
    b. **Take with food**

Blocking RAAS: ACE Inhibitors, ARBS, Aldosterone Antagonists

1. When cardiac output declines, blood pressure declines
2. Low cardiac output triggers the body to initiate the RAAS:
    a. What the RAAS does:
        i. **Renin Angiotensin Aldosterone System is designed to raise blood pressure to improve cardiac output**
        ii. Cascade starts with the kidneys sensing that blood pressure is too low (kidneys sense a reduction in blood flow to themselves)
            - Kidneys respond by releasing RENIN
            - Liver releases Angiotensinogen
            - RENIN and the Angiotensinogen mix to make Angiotensin I
            - Lungs release ACE (Angiotensin Converting Enzyme)
            - Angiotensin I mixes with ACE to make Angiotensin II
        iii. **Angiotensin II does TWO BIG THINGS:**
            - **Cause Vasoconstriction**
            - Trigger adrenal gland to **release Aldosterone**
                - **Aldosterone causes fluid and sodium retention** (this will increase blood volume to increase cardiac output)
                - Aldosterone also causes potassium excretion
3. **The RAAS makes heart failure worse because it causes hypertension (afterload) and fluid retention (preload)**

3 Medications that Stop the RAAS Activation:

ACE-Inhibitors
Inhibits the ACE enzyme from being released from the lungs

Angiotensin II Receptor Blockers (ARBs)
Blocks Angiotensin II

Aldosterone Blockers/Inhibitors
Inhibits Aldosterone from being released from the adrenal glands

ACE-Inhibitors

1. **ACE-I are the GOLD STANDARD therapy for heart failure**
    a. Patients should take at the beginning of their heart failure diagnosis
    b. Start during New York Heart Association Class I
2. Side Effects:
    a. Cough
        i. Cough is not dangerous
        ii. **Cough can be life disrupting**
        iii. Discontinue ACE-I if intolerable
    b. **Angioedema**
        i. **Sudden swelling around the eyes and lips**
        ii. **Rare**
        iii. **This is LIFE THREATENING allergy**
        iv. Discontinue and call 9-1-1
3. Contraindications:
    a. Renal failure
        i. ACE-I is GOOD for *chronic kidney disease*
            - ACE-I slightly improves blood flow to kidneys
        ii. ACE-I is BAD for kidney failure
            - **Discontinue if creatinine level is > 3**
    b. Hyperkalemia
        i. ACE-I blocks aldosterone
            - This causes potassium retention
        ii. **Discontinue if potassium level > 5**
    c. Hypotension
        i. ACE-I decreases blood pressure
        ii. **Discontinue if systolic blood pressure is low or < 90**
4. **Avoid NSAIDS**
    a. NSAIDS combined with ACE-I increases side effects and reduces effectiveness
    b. NSAIDS are medications like ibuprofen and naproxen
5. **Example Brands of ACE Inhibitors:**
    a. **Lisinopril**
    b. **Ramipril**
    c. **Enalapril**

Angiotensin II Receptor Blockers (ARBS)

1. ARBS can be given to patients who cannot tolerate ACE inhibitors
    a. ARBs do not affect the lungs
        i. No coughing side effect
        ii. Much less risk for angioedema
2. **Never ever take both an ACE Inhibitor and an ARB together**
3. Contraindications:
    a. Discontinue if creatinine is > 3
    b. Discontinue if potassium levels are > 5
    c. Discontinue if systolic blood pressure is low or < 90
4. Avoid NSAIDS
5. **Example Brands of ARBS:**
    a. **Losartan**
    b. **Irbesartan**
    c. **Olmesartan**
    d. **Valsartan (Diovan)**

Aldosterone Inhibitors/Antagonists/Blockers

1. Aldosterone inhibitors are also called:
    a. Aldosterone Antagonists
    b. Aldosterone Blockers
2. **Aldosterone Inhibitors block aldosterone**
    a. **Potassium-sparing diuretic effect**
        i. **Causes kidneys to rid of fluid and sodium, but hold onto potassium**
3. Contraindication:
    a. **Discontinue if potassium level is > 5**
        i. **Avoid potassium supplements**
    b. **Discontinue if creatinine is > 3**
4. Aldosterone Inhibitors are not the first line of defense for heart failure and are usually given when a person enters the NYHA Class II
    a. Aldosterone Inhibitor medications can be given in conjunction with an ACE Inhibitor or an ARB
5. **Example Brand:**
    a. **Spironolactone**

Reducing Preload and Afterload

1. **Preload: the volume of blood returning to the heart**
    a. In heart failure:
        i. Preload is the incoming congestion entering the heart
        ii. Goal: reduce congestion. Methods:
            - Reduce blood volume return to the heart
            - **Dilate vena cavas**
                - ♥ **Venous vasodilator medications**
2. **Afterload: the resistance the heart must pump against to get blood out of the heart**
    a. In heart failure:
        i. Afterload is the congestion after the exit of the heart
        ii. The resistance the heart must pump against
        iii. Goal: reduce resistance. Methods:
            - Reduce blood volume exiting the heart
            - **Dilate aorta and peripheral arteries**
                - ♥ **Arterial vasodilators medications**

Reducing Preload with Venous Vasodilators

1. **ACE-Inhibitors and ARBS dilate venous vessels**
2. **Isosorbide Dinitrate dilates venous vessels**
    a. Discontinue if systolic blood pressure < 90
    b. AVOID standing up quickly
    c. **Requires tapering**
    d. **No effect on the heart rate**
    e. Effective in Black patients
        i. Great alternative medication for patients who don't respond well to ACE-Inhibitors or ARBS
    f. **Side Effects:**
        i. **Headaches** (treat with pain relievers)
        ii. Dizziness
    g. **Do not mix with isosorbide with Phosphodiesterase-5 Inhibitors** (erectile dysfunction medications)
        i. Phosphodiesterase-5 Inhibitors significantly lower blood pressure
        ii. Combining these two medications causes fatal drop in blood pressure
    h. Relieves pulmonary congestion

Reducing Afterload with Arterial Vasodilators

1. **ACE-Inhibitors and ARBS dilate arterial vessels**
2. **Hydralazine dilates arterial vessels**
    a. Discontinue if systolic blood pressure < 90
    b. AVOID standing up quickly (hydralazine can cause orthostatic hypotension)
    c. **Requires tapering**
    d. **No effect on the heart rate**
    e. Effective in Black patients
        i. Great alternative medication for patients who don't respond well to ACE-Inhibitors or ARBS
    f. Hydralazine is safe during in pregnancy
    g. **Must be taken three times a day**
        i. **Medication compliance can be difficult for some patients**

Reducing Cardiac Workload: Digoxin, Dobutamine, Milrinone

1. Inotropic Medications:
    a. **Positive inotropes: medications that *increase the strength* of the heart muscle contraction**
        i. **Increases the ejection fraction (temporarily)**
        ii. **Useful in patients with heart failure with a reduced ejection fraction (HFrEF)**
    b. Negative inotropes: medications that decrease the strength of the heart muscle contraction
2. Positive Inotropic Medications are used for HFrEF in NYHA class III

Positive Inotropic Medications:

Cardiac Glycosides
Digoxin

Beta-Receptor Agonists
Dobutamine

Phosphodiesterase-3 Inhibitors
Milrinone

Digoxin

1. Pathophysiology:
    a. Digoxin indirectly traps calcium inside myocardial cells (cardiac *muscle* cells)
    b. Calcium is what causes/maintains the cell contraction
2. **Digoxin Effects:**
    a. **Digoxin causes stronger cardiac contractions**
    b. **Digoxin reduces heart rate**
    c. **ECG changes:**
        i. **Slurred ST segment in every lead**
3. **Digoxin Toxicity is very dangerous**
    a. Digoxin requires close monitoring for signs and symptoms of digoxin toxicity
    b. Digoxin toxicity can cause fatal heart rhythms
    c. **Therapeutic levels 0.5-0.8 ng/mL**
        i. **Digoxin toxicity can occur <u>even if the digoxin blood levels are normal</u>**
        ii. **Trust the symptoms more than the blood levels**
    d. **Symptoms of digoxin toxicity:**
        i. **Confusion**
        ii. **Loss of appetite**
        iii. **Nausea and vomiting**
        iv. **Vision problems**
            - **Seeing green or yellow halos around bright lights**
    e. **Causes of toxicity:**
        i. Accidental overdose
            - **Digoxin blood levels > 2.0 is toxic!**
            - Keep digoxin level on lower end to avoid approaching toxic levels
        ii. **Hypokalemia**
            - *Pathophysiology:*
                - ♥ *Digoxin binds to the SAME receptor sites as potassium. So, with hypokalemia, there are MORE receptor sites available for digoxin to bind to. This causes digoxin to be really POTENT.*
                - ♥ *Opposite is true: hyperkalemia makes digoxin less potent since there are less receptor sites available for digoxin to bind to. This causes the therapeutic effects of digoxin to decrease.*
        iii. **Medication Interactions**
            - **Amiodarone**
            - **Diltiazem**
            - **Diuretics that reduce potassium levels**
            - Antacids

- Cholestyramine
- Albuterol
- Nifedipine
- Omeprazole
- Flecainid
- Verapamil
- Many antibiotics
- Many, many more medications

iv. **Food interactions**
- **Grapefruit juice**
- Fiber
- Black licorice

f. **Treatment for digoxin toxicity:**
i. **Immediately discontinue digoxin**
ii. **Fix hypokalemia and discontinue ALL medications that reduce potassium levels**
iii. **Give Digibind: medication that reduces toxicity**
iv. **Closely monitor heart rhythm**
- **Treat any dysrhythmias**

Dobutamine

1. **Beta-Receptor Agonists: make the beta-1 receptors on the heart work harder**
   a. **Increases cardiac contractility**
   b. More effective than digoxin
   c. Increases blood pressure
2. **Dobutamine is an end-stage heart failure medication**
3. **Side effects:**
   a. **Hypertension**
   b. Tachycardia
4. **Administered as an IV drip infusion through a central line**

Milrinone

1. Phosphodiesterase-3 Inhibitors:
    a. Stimulates and increases cardiac contractility
    b. Dilates arterial and venous blood vessels
2. Used when Digoxin AND Dobutamine are no longer effective
3. Side effects:
    a. Tachydysrhythmias
    b. Hypotension
    c. Headaches
4. For short term use through a central line

Reducing Congestion: Diuretics

1. Diuretics reduce blood volume, which reduces fluid congestion (fluid overload)
    a. Pathophysiology:
        i. Diuretics tell the kidneys to excrete water and sodium into the urine
2. Types of Diuretics:
    a. **Loop diuretics:**
        i. **#1 choice for heart failure patients to reduce fluid volume overload**
        ii. Works at the ascending loop of Henle:
            - Normally water and sodium are reabsorbed by blood vessels here
            - Loop diuretics prevent some sodium and potassium from being reabsorbed
                - ♥ Since sodium holds onto water, water is excreted too
            - **So, sodium, potassium, and water are excreted into the urine**
        iii. **Loop diuretics work best in conjunction with a sodium restricted diet**
        iv. **Brands include:**
            - **Furosemide**
            - **Torsemide**
            - **Bumetanide**

b. **Thiazide Diuretics:**
    i. Can be added to loop diuretics to enhance diuresis
    ii. Work in the distal tubule:
        - Excretes a little sodium, but not as much as loop diuretics
    iii. Brands include:
        - Hydrochlorothiazide
        - Metolazone
        - Chlorthalidone
c. **Potassium Sparing Diuretics (Aldosterone Inhibitors):**
    i. **Brand:**
        - **Spironolactone**

3. Side Effects:
    a. Diuretic tolerance:
        i. **Overtime patients build a tolerance to diuretics** and need regular dose adjustments or add a second type of diuretic
    b. Kidney Failure
        i. Diuretics require close renal function monitoring
        ii. Diuretics act directly on the kidneys (adding stress to kidneys)
        iii. **Monitor BUN and Creatinine levels closely**
    c. **Hypokalemia**
        i. **Monitor in loop diuretics and thiazide diuretics**
        ii. Hypokalemia can cause other heart problems
        iii. Prescription potassium supplements can be added
    d. **Hyperkalemia**
        i. **Potassium sparing diuretics can cause potassium retention**
    e. Hypotension
        i. Optimal dosing includes titrating to avoid symptomatic hypotension
    f. **Hearing Loss**
        i. **A small study showed furosemide has been associated with hearing loss when given intraveneously**
4. Daily weights:
    a. Measures diuretic effectiveness
    b. Daily weights measure fluid volume loss
    c. Daily weights help physicians know how much diuretic the patient needs to be prescribed

Helping our BNP Messengers: Entresto

1. How BNP messengers work:
    a. BNP messengers tell the brain to tell the kidneys to diurese fluid to reduce fluid volume overload
    b. Neprilysin (enzymes) eventually deactivate BNP (to avoid over diuresis)
2. **Entresto:**
    a. **A combination of 2 drugs: Valsartan (an ARB) and Sacubitril**
    b. **Sacubitril is a neprilysin inhibitor**
        i. Sacubitril prevents neprilysin from breaking BNP messengers down
        ii. BNP can last longer and continue getting rid of that extra fluid