Causes of Heart Failure: Multifactorial

- Hypertension
- Coronary artery disease (CAD)
- Diabetes
- Mitral valve disease
- Alcohol
# NYHA Classification of HF

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitations in physical activity by HF symptoms</td>
</tr>
<tr>
<td>II</td>
<td>Symptoms of HF with normal level of activity</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitations in physical activity because of HF symptoms</td>
</tr>
<tr>
<td>IV</td>
<td>Symptoms of HF at rest</td>
</tr>
</tbody>
</table>

**NYHA = New York Heart Association**  
**HF = Heart failure**
### ACCF/AHA Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At <strong>high risk</strong> for HF but without structural heart disease or symptoms</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but <strong>without symptoms</strong></td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with prior or current symptoms</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions</td>
</tr>
</tbody>
</table>

ACCF = American College of Cardiology Foundation  
AHA = American Heart Association
Heart Remodeling

Primary Heart Injury → Ventricular Dysfunction → Growth Factors → Pump Failure → Death

Neuroendocrine Response
1) Arteries Constrict
2) Kidneys retain water (blood volume rises)

Symptoms

*Heartfailure.org
Figure 1.
H$_2$O = water; Na = sodium; TNF$\alpha$ = tumor necrosis factor alpha.
Goals of Pharmacological Treatment of Heart Failure

- Improve symptoms
- Slow and reverse deterioration of heart function
- Prolong survival
Classes of Heart Failure Medications

- Beta blockers
- ACE-Inhibitors
- ARBs
- Hydralazine and nitrates
- Aldosterone antagonists
- Diuretics
- Digoxin
BETA BLOCKERS: 1st line (↓M/M)

How do beta blockers work?
*Piascik, University of Kentucky lecture: The Pharmacology of Adrenergic Receptors*
BETA BLOCKERS: 1st line (↓M/M)

- How do beta blockers work?
  - Slow heart rate (allow more filling of the ventricles)
  - Improve cardiac output

- Who should take them?
  - Heart failure (EF ≤ 40%) - symptomatic
  - Prior myocardial infarct (MI)

- Preferred (β1 > β2)
  - Carvedilol (has α-1 inhibition)
  - Metoprolol succinate
  - Bisoprolol
Worsens asthma

*Piascik, University of Kentucky lecture: The Pharmacology of Adrenergic Receptors*
# BETA BLOCKERS: 1st line (↓M/M)

## Dosing
- Start **LOW** and titrate to target doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>3.125mg BID</td>
<td>25mg BID</td>
</tr>
<tr>
<td>Metoprolol succ.</td>
<td>12.5mg daily</td>
<td>200mg daily</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25mg daily</td>
<td>10mg daily</td>
</tr>
</tbody>
</table>

## Side effects
- Bradycardia, dizziness, bronchospasm, fatigue

## Contraindications
- Acute cardiac failure, significant bradycardia, shock, active bronchospasm, sick sinus syndrome
Q: Mr. Mouse has a history of heart failure and has been taking metoprolol succinate 100mg po daily. He has recently been diagnosed with type II diabetes. What other medication should he be taking?
Q: Mr. Mouse has a history of heart failure and has been taking metoprolol succinate 100mg po daily. He has recently been diagnosed with type II diabetes. What other medication should he be taking?

ACE-Inhibitor
ACE-I: 1\textsuperscript{st} line (↓M/M)
Angiotensin converting enzyme inhibitors

How do ACE-I work?
Sympathetic Stimulation
Hypotension
Decreased Sodium Delivery

Kidney

Renin

Angiotensinogen

Cardiac & Vascular Hypertrophy
Systemic Vasoconstriction

Increased Blood Volume

Thirst

ADH

Renal Sodium & Fluid Retention

AI

ACE

Adrenal Cortex

Pituitary

Aldosterone

*CV pharmacology.org
*Weir, American Journal of Hypertension 2011, Nature: Diabetes and Hypertension
ACE-I: 1\textsuperscript{st} line (↓M/M)
Angiotensin converting enzyme inhibitors

- How do ACE-I work?
  - Block the enzyme that converts angiotensin I to II
  - Lower blood pressure, block harmful neurohormones

- Who should take them?
  - Heart failure (EF ≤ 40\%) - \textit{symptomatic OR asymptomatic}
  - High risk for HF:
    - CAD
    - Peripheral vascular disease
    - Prior stroke
    - Diabetes (with another risk factor or who also smoke)
ACE-I: 1st line (↓M/M)

- Dosing
  - Start **LOW** and titrate to target doses

- Preferred: ACE-I over ARBs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25mg TID</td>
<td>50mg TID</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5mg BID</td>
<td>10-20mg BID</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5-5mg daily</td>
<td>20-40mg daily</td>
</tr>
</tbody>
</table>

*Captopril: can be given sublingually*
ACE-I: 1st line (↓M/M)

- Side effects
  - Hypotension, dizziness, renal insufficiency, angioedema, hyperK+, dry cough
  - LABS: Scr, K+

- Contraindications
  - Acute renal failure, hyperK+, pregnancy, bilateral renal stenosis, angioedema (caused by ACE-I)
**CLINICAL QUESTION**

- Mrs. Mouse comes to clinic complaining of an irritating dry cough since starting her lisinopril several months ago and refuses to keep taking it. What other medication can she take?
Mrs. Mouse comes to clinic complaining of an irritating dry cough since starting her lisinopril several months ago and refuses to keep taking it. What other medication can she take?

**ARBs**
(Angiotensin Receptor Blockers)
*Weir, American Journal of Hypertension 2011, Nature: Diabetes and Hypertension
ARBs: 1st line (↓M/M) Angiotensin receptor blockers

- **How do ARBs work?**
  - Block angiotensin II at the AT1 receptor

- **Who should take them?**
  - Fail ACE-Inhibitors due to cough
  - ACE-I and ARB combo – generally NO

- **Disadvantages: less clinical studies, $$**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>12.5-25mg daily</td>
<td>150mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40mg BID</td>
<td>160mg BID</td>
</tr>
</tbody>
</table>
Mr. Duck is an African American with severe heart failure who still has symptoms (edema, SOB) while on a beta blocker, ACE-I, and high dose furosemide. What medication combination might help Mr. Duck?
Mr. Duck is an African American with severe heart failure who still has symptoms (edema, SOB) while on a beta blocker, ACE-I, and high dose furosemide. What medication combination might help Mr. Duck?

Hydralazine and Nitrates
Hydralazine/nitrates: 1st line* (↓M/M) Vasodilators

- **How do they work?**
  - Nitrates (isosorbide dinitrate): releases nitric oxide, dilates arteries and veins
  - Hydralazine: dilates arteries, prevents nitrate tolerance

- **Who should take them?**
  - African Americans with NYHA III-IV (AHeFT) already on ACE-I and beta blocker

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>10-25mg 3-4 x/day</td>
<td>225-300mg/day</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>20mg 3-4x/day</td>
<td>240mg/day (max)</td>
</tr>
</tbody>
</table>
Hydralazine/nitrates: 1\textsuperscript{st} line* (↓M/M) 
Vasodilators

- **Side effects:**
  - Headache, dizziness, hypotension, drug-induced lupus syndrome (hydralazine)

- **Contraindications:**
  - Concurrent use of phosphodiesterase-5 inhibitors (ie Viagra)
Mrs. Duck has severe heart failure (LVEF<20%) and still has symptoms (edema, dyspnea) while on a beta blocker, ACE-I, and high dose furosemide. What additional medication might help Mrs. Duck?
Mrs. Duck has severe heart failure (LVEF<20%) and still has symptoms (edema, dyspnea) while on a beta blocker, ACE-I, and high dose furosemide. What additional medication might help Mrs. Duck?

**Aldosterone Antagonists**
Aldosterone Antagonists: 1st line (↓M/M)

- How do they work?
  - Potassium sparing diuretic that blocks aldosterone

- Indications:
  - LVEF ≤ 30% & NYHA II (some symptoms)
  - LVEF < 35% & NYHA III- IV (moderate to severe)
  - LVEF ≤ 40% & Post-MI, on therapeutic ACE-I, and symptomatic HF or diabetes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>12.5-25mg daily</td>
<td>50mg daily</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25-50mg daily</td>
<td>100mg daily</td>
</tr>
</tbody>
</table>
Aldosterone Antagonists: 1\textsuperscript{st} line (↓M/M)

- Monitoring:
  - Labs: electrolytes (K+) and renal function

- Side effects:
  - HyperK+
  - Hirsutism, gynecomastia (switch to eplerenone)

- Contraindications: K+>5, Scr>2.5 (or GFR<30)
Summary of 1st line medications that ↓M/M

BAAHₙ

- Beta-blockers (BB)
- ACE-I and ARBs
- Aldosterone antagonist (AA)
- Hydralazine/nitrates (for African Americans)
Medications to improve symptoms

- Symptoms:
  - Shortness of breath
  - Edema
  - Fatigue
**Diuretics (aka 'water pills')**

- **How do they work?**
  - Act at different sections of the kidneys to remove sodium and water, thereby reducing volume overload

- **Types:**
  - **Loop (1st line)**, thiazides, potassium-sparing

- **Dosing:**
  - Furosemide 80mg **PO** = furosemide 40mg **IV**
  - **IV equivalencies:**
    - Furosemide 40mg = Torsemide 20mg = Bumetanide 1mg
Diuretics (aka 'water pills')

- Monitoring:
  - Electrolytes (K, Na, Mg), renal function, daily weight

- Side effects:
  - ↓ K, Mg, & Ca, hyperuricemia, dizziness, hypotension, tinnitus

- Precautions:
  - Sulfa allergy, gout

- Loop diuretics are cornerstone for acute HF
  - In diuretic resistance, add thiazide (30 min prior) to augment diuretic effect
**TRIVIA QUESTION**

- What heart failure medication DOES NOT improve morbidity/mortality and comes from the foxglove plant (seen below)?
**TRIVIA QUESTION**

- What heart failure medication DOES NOT improve morbidity/mortality and comes from the foxglove plant (seen below)?

**DIGOXIN**
**Digoxin: Reduces hospitalizations**

- **How does it work?**
  - Cardiac glycoside: inhibits Na+/K+ ATPase pump to increase intracellular sodium concentration, eventually increasing systolic calcium
  - Improves pump filling and improves HF symptoms; first line for HF with atrial fibrillation

- **Who should take it?**
  - LVEF ≤ 40%, on standard HF therapy, & w/ persistent symptoms

- **Target level:** 0.5 – 0.8 mcg/mL

- **Does not improve morbidity/mortality**
**Digoxin: Reduces hospitalizations**

- **Monitoring:**
  - Electrolytes (K, Mg, Ca), renal function

- **Side effects:**
  - Nausea, vomiting, bradycardia, visual disturbances, diarrhea, arrhythmias

- **Toxicity:**
  - Symptomatic control
  - Digibind: antidote made of sheep antibodies
  - Cholestyramine or activated charcoal (2nd line)
Acute vs Chronic Heart Failure

- **Chronic:**
  - Fatigue, fluid retention, dyspnea, exercise intolerance

- **Acute:**
  - Rapid accumulation of fluid within the lungs, pulmonary edema, shortness of breath
Acute Decompensated HF (ADHF)

- **Stabilize**, then rapid correction of hemodynamic and intravascular volume abnormalities

- **MEDICATIONS:**
  - IV diuretics and vasodilator therapy (nitroglycerin or nitroprusside)
  - Inotropes (dobutamine, milrinone) for advanced HF, decreased LVEF, diminished peripheral perfusion or end-organ function
Medications to Avoid or Use with Caution

- **Anti-arrhythmics** (quinidine, sotalol, ibutilide)
  - Pro-arrhythmic or cardio-depressant

- **Calcium channel blockers** (non-dihydropyridines, i.e. verapamil, diltiazem)
  - Worsening heart failure

- **NSAIDs** (ibuprofen, naproxen, diclofenac)
  - Na+ retention & increases toxicity of diuretics/ACE-I

- **Thiazolidinediones (TZDs)** (pioglitazone, rosiglitazone)
  - Worsening heart failure
SUMMARY

- **Beta blockers**
- **ACE-Inhibitors & ARBs**
- **Aldosterone antagonists**
- **Hydralazine and nitrates**

- **Diuretics**
  - Symptoms

- **Digoxin**
  - Symptoms and hospital reduction
References

- Heart Failure Society of America (HFSA): Comprehensive Heart Failure Practice Guidelines 2010.
- American College of Cardiology Foundation/American Heart Association (ACC/AHA) 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults based on the 2009 Focused Update.
- Micromedex, eFacts and Comparisons, Up-to-Date- Nov 2011