Guideline Directed Medical Therapy (GDMT)  
An APRNs Approach to Heart Failure  

Carolyn M Moffa MSN, APRN,CNP,CHFN
The Age Wave

U.S. Census Bureau
65+ Population Statistics

Millions

- Elderly 65+
- Oldest Old 85+
Hospital Discharges for HF Are Increasing

1979-2009

Discharge in Thousands


Female
Male

0    100    200    300    400    500    600    700


### The Numbers

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of people diagnosed with heart failure</td>
<td>5.1 million</td>
</tr>
<tr>
<td>Annual new cases of heart failure</td>
<td>825,000</td>
</tr>
<tr>
<td>Percentage of patients who will die within 5 years of diagnosis</td>
<td>50%</td>
</tr>
<tr>
<td>Hospital days per year</td>
<td>6,500,000</td>
</tr>
<tr>
<td>Annual deaths</td>
<td>300,000</td>
</tr>
<tr>
<td>Percentage of healthcare budget</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

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(2013 ACCF/AHA Guideline for the Management of Heart Failure)
Rates of Hospital Readmission

1 in 5 Medicare patients rehospitalized in 30 days of discharge
• Half never saw outpatient doc

Costs $17.4 billion

Rehospitalizations among Patients in the Medicare Fee-for-Service Program

Stephen F. Jencks, M.D., M.P.H., Mark V. Williams, M.D., and Eric A. Coleman, M.D., M.P.H.
Definition of Heart Failure

HF is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
"The importance of blood-letting, as a medicinal agent, in comparison with other means of cure, is shown in various respects...it is the least equivocal of remedies: its good effects, when properly administered, are, in most cases, so immediate and striking as not to be mistaken...In short, blood-letting is a remedy which, when judiciously employed, is hardly possible to estimate too highly."

On the Proper Administration of Blood-Letting, for the Prevention and Cure of Disease, (London, 1840) by Henry Clutterbuck, M.D., Member of the Royal College of Physicians.*

Instruments used in Blood Letting: Scultetus, Johannes (1595-1645). Armamentarium hirurgicum...(Lugdunum Batavorum, 1693).*

Leach Bowl: Bossche, Willem van den. Historia Medica (Bruxellae,1639). (Image from: Lyons & Petrucelli. Medicine, an illustrated history. (New York, 1978).*

Anatomical points for Bloodletting: Castellani, Giovani Marie (1585-1655). Filactirion della flebotomia et arteriotomia... (Viterbo, 1619).*

* From the UCLA Biomedical Library: [www.library.ucla.edu/libraries/biomed](http://www.library.ucla.edu/libraries/biomed)
“throughout history man has suffered from a widespread illness that “ puffed their bodies into grotesque shapes, squeezed their lung, and finally brought slow but inexorable death. As the disease progresses, a water liquid filtered into every available space and expanded it like a balloon. Sometimes the liquid-quarts and gallons of it – made arms and legs swell so that they were immovable. Sometimes it waterlogged the lung cavity and thereby made it impossible for the victim to breathe unless he sat upright in bed at night”

This was the early definition of “dropsy” or HF in 1768
Systolic Heart Failure or HFrEF

- Systolic HF is defined as EF<40%
- The heart muscle progressively weakens and is unable to pump effectively to meet the body’s need for blood and O2

Diastolic Heart Failure or HFpEF

- Preserved EF
- Thickened LV wall
- Unable to relax in between contractions, which affects filling
Causes of Heart Failure

- CAD
- HTN
- Viral cardiomyopathy
- Congenital heart disease
- Rheumatic heart disease
- Valvular disorders
- Thyrotoxicosis
- Toxins: chemotherapeutic agents, alcohol, illicit drugs
- Peripartum
- Infiltrative diseases: sarcoidosis, amyloidosis
Pathophysiology of Heart Failure
Neurohormones and Heart Failure

- **Neurohormones that “worsen” HF**
  - RAAS  Renin-angiotensin-aldosterone system
  - SNS   Sympathetic nervous system
  - ET    Endothelin (proteins that constrict blood vessels and raise blood pressure)

- **Neurohormones that are “beneficial” in HF**
  - ANP   Atrial natriuretic peptide
  - BNP   B-type natriuretic peptide
  - CNP   C-type natriuretic peptide
Pharmacological Actions of BNP

**Hemodynamic**
- (balanced vasodilation)
- veins
- arteries
- coronary arteries

**Neurohormonal**
- ↓ aldosterone
- ↓ norepinephrine

**Renal**
- ↑ diuresis & natriuresis

Abraham WT and Schrier RW, 1994
BNP in the Diagnosis of HF

BNP elevated in
- Cor pulmonale
- Heart failure
- Systemic and pulmonary hypertension
- COPD
- Pulmonary embolism
- Hypertrophic and restrictive cardiomyopathy
Neurohormones and Heart Failure

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  - CNP   C-type natriuretic peptide
Renin-angiotensin-aldosterone system

- Decrease in renal perfusion (juxtaglomerular apparatus)
- Angiotensinogen → Angiotensin I → Angiotensin II
- Renin
- Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion, H₂O retention
- Adrenal gland: cortex
- Aldosterone secretion
- Arteriolar vasoconstriction, increase in blood pressure
- ADH secretion
- Pituitary gland: posterior lobe
- Collecting duct: H₂O absorption

Legend:
- Secretion from an organ
- Stimulatory signal
- Inhibitory signal
- Reaction
- Active transport
- Passive transport

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
## Neurohormonal Responses to Impaired Cardiac Performance

Initially Adaptive, Deleterious if Sustained

<table>
<thead>
<tr>
<th>Response</th>
<th>Short-Term Effects</th>
<th>Long-Term Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt and Water Retention</td>
<td>Augments Preload</td>
<td>Pulmonary Congestion, Anasarca</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>Maintains BP for perfusion of vital organs</td>
<td>Exacerbates pump dysfunction (excessive afterload), increases cardiac energy expenditure</td>
</tr>
<tr>
<td>Sympathetic Stimulation</td>
<td>Increases HR and ejection</td>
<td>Increases energy expenditure</td>
</tr>
</tbody>
</table>
Heart Failure Pharmacotherapies

- Angiotensin Converting Enzyme Inhibitors (ACE-I)
- Angiotensin Receptor Blockers (ARBs)
- Beta Blockers
- Diuretics
- Aldosterone Blockers
- Digoxin
- Hydralazine/Nitrates
- Angiotensin Receptor Neprilysin Inhibitors (ARNI)
  - Sacubitril/Valsartan (Entresto)
- Ivabradine (Corlanor)
- Inotropes
Current Pharmacologic Approach to Heart Failure
Angiotensin Converting Enzyme Inhibitors (ACE-I)

- **Common ACE-I**
  - Captopril
  - Lisinopril
  - Enalapril

- **Mechanism of Action**
  - Competitively inhibits the activity of ACE to prevent the formation of Angiotensin II from Angiotensin I
  - Vasodilates: reduces blood pressure
  - Delays left ventricular remodeling
  - Alleviate symptoms, decreased morbidity and mortality, reduces HF hospitalizations

- **Clinical use**
  - ACCF/AHA Guidelines
    - Class I: **ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality (Level of Evidence: A)**
    - Given to all patients with systolic dysfunction
    - Can be used in diastolic heart failure for control of BP
Renin-angiotensin-aldosterone system

ACE-I

Angiotensinogen → Angiotensin I → Angiotensin II → Renin → Decrease in renal perfusion (juxtaglomerular apparatus)

Lungs → Kidney

Surface of pulmonary and renal endothelium: ACE

Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion, H₂O retention

Adrenal gland: cortex → Aldosterone secretion

Arteriolar vasoconstriction, increase in blood pressure

ADH secretion

Pituitary gland: posterior lobe

Collecting duct: H₂O absorption

Sympathetic activity

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.

Legend

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Mortality Reduction with ACE-I

<table>
<thead>
<tr>
<th>Study</th>
<th>ACE-I</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>Enalapril</td>
<td>CHF</td>
</tr>
<tr>
<td>SOLVD treatment</td>
<td>Enalapril</td>
<td>CHF</td>
</tr>
<tr>
<td>AIRE</td>
<td>Ramipril</td>
<td>CHF</td>
</tr>
<tr>
<td>Vheft-II</td>
<td>Enalapril</td>
<td>CHF</td>
</tr>
<tr>
<td>TRACE</td>
<td>Trandolapril</td>
<td>CHF / LVD</td>
</tr>
<tr>
<td>SAVE</td>
<td>Captopril</td>
<td>LVD</td>
</tr>
<tr>
<td>SMILE</td>
<td>Zofenopril</td>
<td>High risk</td>
</tr>
<tr>
<td>HOPE</td>
<td>Ramipril</td>
<td>High risk</td>
</tr>
</tbody>
</table>
**Figure 4.9** Effect of enalapril on death or hospitalization due to heart failure: SOLVED treatment trial.

Current Pharmacologic Approach to Heart Failure


Angiotensin Converting Enzyme Inhibitors (ACE-I)

Adverse Effects

- Dry, irritant cough in about 15% (10% men and 20% women) attributable to accumulation of bradykinin. Not dose related and can occur with low dose.
- Angioedema also attributable to kinin potentiation. Rare but potentially fatal.
- Hyperkalemia due to potassium retention mediated by reduction of aldosterone. Rare except in renal impairment.
- First dose hypotension of renin-angiotensin system activated. Rare in essential hypertension.
- Taste disturbance. Rare
- Skin rashes. Very rare
## Target Doses of ACE-Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg tid</td>
<td>50 mg tid</td>
</tr>
<tr>
<td>Benazepril</td>
<td>10 mg qd</td>
<td>80 mg qd</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg bid</td>
<td>20 mg bid</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5 to 10 mg qd</td>
<td>40 mg qd</td>
</tr>
<tr>
<td>Imidapril</td>
<td>2.5 mg qd</td>
<td>10 mg qd</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 to 5 mg qd</td>
<td>20 to 40 mg qd</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 mg qd</td>
<td>10 mg qd</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg qd</td>
<td>4 mg qd</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg bid</td>
<td>20 mg bid</td>
</tr>
</tbody>
</table>

Reference: ACC/AHA guidelines for management of patients with chronic heart failure.
Current Pharmacologic Approach to Heart Failure

Angiotensin Receptor Blockers (ARBs)

- **Common ARBs**
  - Losartan
  - Valsartan
  - Candesartan

- **Mechanism of Action**
  - competitive angiotensin II receptor type 1 (AT₁) antagonist, reducing the end organ responses to angiotensin II
  - decrease in total peripheral resistance (afterload) and cardiac venous return (preload).
Current Pharmacologic Approach to Heart Failure

Angiotensin Receptor Blockers (ARBs)

Clinical use

- ACCF/AHA Guidelines
  - Class I: ARBs are recommended in patients with HFrEF with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality (Level of Evidence: A)
  - Class IIa: ARBs are reasonable to reduce morbidity and mortality as alternatives to ACE inhibitors as first-line therapy for patients with HFrEF, especially for patients already taking ARBs for other indications, unless contraindicated. (Level of Evidence: A)
  - Class Iib: Addition of an ARB may be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACE inhibitor and a beta blocker in whom an aldosterone antagonist is not indicated or tolerated. (Level of Evidence: A)
  - Class III: Harm: Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HFrEF. (Level of Evidence: C)
  - Given to all patients with systolic dysfunction
  - Can be used in diastolic dysfunction for control of BP
Renin-angiotensin-aldosterone system

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.

Legend:
- Secretion from an organ
- Stimulatory signal
- Inhibitory signal
- Reaction
- Active transport
- Passive transport

Angiotensin I → Angiotensin II → Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion. H₂O retention

Angiotensinogen → Angiotensin I

Decrease in renal perfusion (juxtaglomerular apparatus) → Renin

Liver → Angiotensinogen

Surface of pulmonary and renal endothelium: ACE

Kidney → Renin

Sympathetic activity

Aldosterone secretion

Adrenal gland: cortex

Arteriolar vasoconstriction. Increase in blood pressure

Pituitary gland: posterior lobe

ADH secretion

Collecting duct: H₂O absorption

Na⁺, K⁺, Cl⁻
CHARM Trial

7,601 patients with heart failure

3 Individual component randomized trials with the
ARB candesartan (4 or 8 mg/day, titrated to
target dose of 32 mg) or placebo

CHARM Added
- Patients with LVEF ≤40% and treated
  with an ACE-inhibitor

CHARM Alternative
- Patients with LVEF ≤40% and ACE-inhibitor intolerant

CHARM Preserved
- Patients with LVEF >40% with or without
  ACE-inhibitor

Endpoints (follow-up minimum 2 years):
- Primary – Component trials: cardiovascular mortality or CHF
  hospitalization
- Primary – Overall trial results: All-cause mortality

European Society of Cardiology 2003
CHARM Trial

- CHARM Overall:
  - Lower CV mortality
  - Trend toward lower all-cause mortality
- CHARM Added: (Candesartan and ACE-I)
  - CV mortality and HF hospitalizations decreased
- CHARM Alternative: (Candesartan without ACE-I)
  - Primary Endpoint of CV mortality or HF hospitalizations decreased
- CHARM Preserved: (EF>40%, Candesartan)
  - No statistically significant reduction in the primary endpoints
I-PRESERVE Trial
Irbesartan in Heart Failure with Preserved EF
I-PRESERVE: Objectives

- To determine whether treatment with the angiotensin receptor blocker irbesartan reduces mortality and morbidity in patients with HF-PEF
- To better define the characteristics, natural history, and underlying mechanism of heart failure in this population

I-PRESERVE: Conclusions

- In I-PRESERVE, HF-PEF patients experienced substantial mortality and cardiovascular morbidity
- Irbesartan did not reduce the primary endpoint of death and protocol-specified CV hospitalizations, nor did it significantly benefit prespecified secondary endpoints
I-PRESERVE: Primary Endpoint
Death or protocol specified CV hospitalization

HR (95% CI) = 0.95 (0.86-1.05)
Log-rank p=0.35

Cumulative Incidence of Primary Events (%)

Months from Randomization

No. at Risk
Irbesartan 2067 1929 1812 1730 1640 1569 1513 1291 1088 816 497
Placebo 2061 1921 1808 1715 1618 1539 1466 1246 1051 776 446
Current Pharmacologic Approach to Heart Failure
Angiotensin Receptor Blockers (ARBs)

- **Adverse Effects**
  - Hypotension
  - Angioedema
  - Renal impairment (caution in renal artery stenosis)
  - Hyperkalemia

- **Common Dosing**

<table>
<thead>
<tr>
<th>ARBs</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>4 to 8 mg once</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 to 50 mg once</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20 to 40 mg twice</td>
</tr>
</tbody>
</table>
β–blocker is the most important progress in Heart Failure Medical Therapy
Current Pharmacologic Approach to Heart Failure

Beta Blockers

**Common Beta Blockers**
- Carvedilol
- Bisoprolol
- Metoprolol Succinate

**Mechanism of Action**
- Inhibits the adverse effects of sympathetic system
- Delays and reverses LV remodeling
- Improves the LV function (EF)
- Decreases HF hospitalizations and mortality (25-40%)
- Improves survival

**Clinical use:**
- ACCF/AHA Guidelines
  - Class I
  - Use of 1 of the 3 beta blockers proven to reduce mortality (eg, bisoprolol, carvedilol, and sustained release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (Level of Evidence: A)
- Systolic and diastolic heart failure
- Given to all patients with systolic HF in absence of fluid overload

**Adverse effects:** Hypotension, bradycardia, worsening HF
Beta Blockers and Heart Failure

Carvedilol improves left ventricular ejection fraction

After six months of therapy in patients with heart failure, carvedilol produced a dose-related increase in left ventricular ejection fraction (LVEF) which is significant with all doses used when compared to placebo.

* p < 0.005 versus placebo.
* * p < 0.0001 versus placebo.


Graphic 65184 Version 2.0

Carvedilol

Survival benefit of carvedilol in heart failure

Kaplan-Meier analysis of survival in patients with chronic heart failure (HF) who were maintained on digoxin, diuretics, and an angiotensin converting enzyme inhibitor and then treated with carvedilol or placebo. Therapy with carvedilol was associated with a significant improvement in survival (p < 0.001).


Graphic 62633 Version 3.0
Beta Blockers and Heart Failure

Metoprolol XL

Bisoprolol

CIBIS-II enrolled 2647 patients with class III and IV heart failure (HF) who were receiving therapy with angiotensin converting enzyme inhibitors and diuretics. Compared to placebo, bisoprolol significantly reduced all-cause mortality (11.8 versus 17.3 percent, p


Graphic 63774 Version 1.0
Renin-angiotensin-aldosterone system

- Angiotensinogen → Angiotensin I → Angiotensin II
- Renin
- Surface of pulmonary and renal endothelium: ACE
- Decrease in renal perfusion (juxtaglomerular apparatus)
- Lungs
- Kidney
- Sympathetic activity
- Tubular Na⁺ Cl⁻ reabsorption and K⁺ excretion. H₂O retention
- Adrenal gland: cortex
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Legend:
- +: Secretion from an organ
- +: Stimulatory signal
- -: Inhibitory signal
- Reaction
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<table>
<thead>
<tr>
<th>Beta-blocker</th>
<th>Initial dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg qd</td>
<td>10 mg qd</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg bid in heart failure</td>
<td>25 mg bid (50 mg bid for weight &gt; 85 kg)</td>
</tr>
<tr>
<td></td>
<td>6.25 mg bid in post-MI</td>
<td>80 mg qd of CR preparation</td>
</tr>
<tr>
<td></td>
<td>10 mg qd of CR preparation</td>
<td></td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5 mg qd</td>
<td>200 mg qd</td>
</tr>
</tbody>
</table>

Reference: ACC/AHA guidelines for management of patients with chronic heart failure 4
Current Pharmacologic Approach to Heart Failure

Aldosterone Blockers

- **Common Aldosterone Blockers**
  - Spironolactone
  - Eplerenone

- **Mechanism of Action**
  - Antagonizes the distal convoluted tubule aldosterone receptors
  - Increases Na and H2O excretion while conserving potassium
  - Inhibits myocardial fibrosis and inflammation

- **Clinical Use**
  - NYHA Class II-IV heart failure
  - Systolic heart failure

- **ACCF/AHA Guidelines**
  - Class I
  - 1. Aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) are recommended in patients with NYHA class II–IV HF and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate >30 mL/min/1.73 m2), and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. *(Level of Evidence: A)*

  - 2. Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated. *(Level of Evidence: B)*
Current Pharmacologic Approach to Heart Failure

Aldosterone Blockers

**Adverse effects**
- Hyperkalemia (hold if K > 5.0 mEq/L)
- Renal failure (hold if Cr > 2.5 or CrCl < 30)
- Agranulocytosis
- Hepatotoxicity
- Gynecomastia (Spironolactone)

<table>
<thead>
<tr>
<th>Aldosterone antagonists</th>
<th>Maximum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>12.5 to 25.0 mg once or twice</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg once</td>
</tr>
</tbody>
</table>
Aldosterone Blockers
Current Pharmacologic Approach to Heart Failure
Hydralazine/Isosorbide

- **Mechanism of Action**
  - Directly dilates peripheral vessels (arterial and venous)

- **Clinical use**
  - Consider adding in patients already on ACE-I and B-Blocker who are still symptomatic
  - Systolic and diastolic heart failure
  - Effective in African American patients with HF

- **ACCF/AHA Guidelines**
  - Class I
    - 1. The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated. (Level of Evidence: A)
  - Class IIa
    - 1. A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated. (Level of Evidence: B)
Cardiac glycosides (cardenolides)

- Sir William Withering, 1785 (English botanist and physician)
- Purple foxglove plant (*Digitalis purpurea*)
Current Pharmacologic Approach to Heart Failure

Digoxin

**Common**
- Lanoxin

**Mechanism of Action**
- Acts on the Na-K-ATPase pump (the Sodium Pump): moves Na out of cells and K into cells
- Digoxin inhibits the Na pump
  - Increases inotropy (contractility)
  - Decreases chronotropy (heart rate)
  - Decreases conduction through the AV node
  - Decreased activation of the SNS and the RAAS

**Clinical Use**
- Used to improve symptoms in patients with EF <40% who have s&s of HF on standard therapy (ACE-I and BB)
- Give smallest dose to maintain Dig level <1.0 (0.5-0.9 preferred)
- Consider its use in atrial fib to control ventricular rate
Current Pharmacologic Approach to Heart Failure

Digoxin

ACCF/AHA Guidelines
- Class IIa
- 1. Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (Level of Evidence: B)
Digoxin Study

- **Digoxin Trial-The Digitalis Investigation Group**
  - 37 weeks
  - Multicenter, randomized, double-blind study
  - 6800 adults
  - Digoxin vs Placebo

- **Results**
  - Significant reduction in hospitalizations for heart failure or all-cause
  - Digoxin had no effect on mortality
Digoxin

- **Adverse Effects**
  - Dizziness, headache, confusion, diarrhea, nausea/vomiting, visual changes
  - Potential serious adverse effects include
    - AV block, arrhythmias, thrombocytopenia, delirium, hallucinations
Current Pharmacologic Approach to Heart Failure

Angiotensin Receptor Neprilysin Inhibitor (ARNI)

- **Common ARNI:**
  - Entresto (Sacubitril/Valsartan)

- **Effect**
  - enhances the protective neurohormonal systems of the heart (NP system) while simultaneously suppressing the harmful system (the RAAS)
  - Reduces the strain of the failing heart

- **Clinical Use**
  - Systolic dysfunction, NYHA Class II-IV
  - Reduce the risk of cardiovascular death and hospitalization

- **Adverse effects**
  - Hypotension
  - Angioedema
  - Worsening renal function
Current Pharmacologic Approach to Heart Failure

Angiotensin Receptor Neprilysin Inhibitor (ARNI)

- **Dosing: Sacubitril/Valsartan**

- **24/26mg:**
  - recommended if not previously treated with an ACE-I or ARB (or is on a very low dose)
  - Recommended in patients with severe renal impairment
  - Recommended in patients with moderate hepatic impairment

- **49/51mg**

- **97/103mg**

- **Note:** Take patient off ACE-I x3 days prior to starting Sacubitril/Valsartan
In HF patients, some systems become stimulated, causing harmful effects, while others have beneficial effects.  

**TREATMENTS THAT INHIBIT OVERACTIVE RAAS**
- ACEis
- ARBs
- ENTRESTO

**TREATMENTS THAT INHIBIT NEPRILYSIN**
- Only ENTRESTO

Neprilysin breaks down compensatory endogenous peptides, including vasoactive peptides, which have beneficial effects.  

**ENTRESTO**
- The first and only ARB and neprilysin inhibitor combination

**OVERACTIVE RAAS**
- Harmful effects:
  - Vasoconstriction
  - Fibrosis
  - Sodium retention
  - Hypertrophy

**VASOACTIVE PEPTIDES**
- Beneficial effects:
  - Vasodilation
  - Natriuresis
  - Renin suppression
  - Aldosterone suppression
  - Anti-fibrosis

ENTRESTO not only inhibits the overactive RAAS, but also inhibits the breakdown of vasoactive peptides, such as natriuretic peptides.

**RAAS** = renin-angiotensin-aldosterone system.
The PARADIGM-HF trial stopped early due to compelling efficacy\(^1\)

ENTRESTO was superior in reducing the relative risk of the combined end point of CV death or first HF hospitalization, and treatment effect reflected a reduction in both\(^2\)


Current Pharmacologic Approach to Heart Failure
Ivabradine (Corlanor)

■ Mechanism of Action
  ▪ A hyperpolarization-activated cyclic nucleotide-gated channel blocker!!
    ▪ channel responsible for the cardiac pacemaker If current, which regulates heart rate. In clinical electrophysiology studies, the cardiac effects were most pronounced in the sinoatrial (SA) node,
    ▪ Influences the activity of the heart’s natural pacemaker
    ▪ Prevents the SA node from cycling
    ▪ Slows the HR and decreases MVO2 consumption

■ Clinical Use
  ▪ Reduce the risk of hospitalizations (no effect on mortality)
  ▪ EF <35%, in NSR, HR >70bpm, on maximally tolerated dose of BB

■ Adverse effects
  ▪ Bradycardia, HTN, atrial fibrillation, luminous visual phenomena
SHIFT Trial
The Systolic Heart Failure Treatment with the \( I_f \) Inhibitor Ivabradine Trial

- Enrolled 6558 patients
- NYHA Class II-IV heart failure
- EF \(<35%\)
- Resting HR \(>70 \text{ bpm}\)
- On maximally tolerated doses of Beta Blockers

**Results:**
- Statistically significant decrease in hospitalizations due to worsening HF
- No statistically significant benefit on cardiovascular death
Current Pharmacologic Approach to Heart Failure
Ivabradine (Corlanor)

- **Ivabradine dosing**
- Starting dose **5mg BID**
- In two weeks can increase to **7.5mg BID** (based on heart rate)
- In patients with conduction defects, or in whom bradycardia may lead to hemodynamic compromise, start at **2.5mg BID**
**Current Pharmacologic Approach to Heart Failure**

**Diuretics in HF**

- Mainstay in HF treatment
- Directly reduces excess levels of extracellular fluid
- Symptom relief from congestion
- Loop diuretics preferred due to increase in sodium excretion up to 20-25%, enhances free water clearance, and is effective until renal function severely impaired
- Intravenous use-review of several small studies noted better safety profile with continuous infusions vs high bolus doses.
Diuretics are the Tools of the Devil
Diuretics: Double-Edged Sword

Natriuresis

Diuresis

Volume depletion
Decreased renal perfusion
RAAS and SNS activation
  – Increased fluid and sodium retention
  – Decreased renal function
Reflex vasoconstriction
  – Increased SVR
  – Decreased cardiac output
Electrolyte excretion of K, Na, Mg
Nephron sites of action of diuretics
### Diuretic Dosing Chart

**Table 14. Oral Diuretics Recommended for Use in the Treatment of Chronic HF**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Total Daily Dose</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.5 to 1.0 mg once or twice</td>
<td>10 mg</td>
<td>4 to 6 h</td>
</tr>
<tr>
<td>Furosemide</td>
<td>20 to 40 mg once or twice</td>
<td>600 mg</td>
<td>6 to 8 h</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10 to 20 mg once</td>
<td>200 mg</td>
<td>12 to 16 h</td>
</tr>
<tr>
<td><strong>Thiazide diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>250 to 500 mg once or twice</td>
<td>1,000 mg</td>
<td>6 to 12 h</td>
</tr>
<tr>
<td>Chlorothalidone</td>
<td>12.5 to 25.0 mg once</td>
<td>100 mg</td>
<td>24 to 72 h</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25 mg once or twice</td>
<td>200 mg</td>
<td>6 to 12 h</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5 mg once</td>
<td>5 mg</td>
<td>36 h</td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5 mg once</td>
<td>20 mg</td>
<td>12 to 24 h</td>
</tr>
<tr>
<td><strong>Potassium-sparing diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>5 mg once</td>
<td>20 mg</td>
<td>24 h</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5 to 25.0 mg once</td>
<td>50 mg†</td>
<td>1 to 3 h</td>
</tr>
<tr>
<td>Triamterene</td>
<td>50 to 75 mg twice</td>
<td>200 mg</td>
<td>7 to 9 h</td>
</tr>
<tr>
<td><strong>Sequential nephron blockade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5 to 10.0 mg once plus loop diuretic</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25 to 100 mg once or twice plus loop diuretic</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Chlorothiazide (IV)</td>
<td>500 to 1,000 mg once plus loop diuretic</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Eplerenone, although also a diuretic, is primarily used in chronic HF.
†Higher doses may occasionally be used with close monitoring.

HF indicates heart failure; IV, intravenous; and N/A, not applicable.
# Medication Benefits in Systolic Heart Failure

<table>
<thead>
<tr>
<th>Medication</th>
<th>Improves Survival</th>
<th>Reduces Hospitalizations</th>
<th>Improves Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Diuretics</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Isosorbide dinitrate and hydralazine</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Digoxin</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>
Case Study

- **63 year old African American female**
  - Hospitalized x8 days with SOB/weight gain/edema/fatigue
  - Newly diagnosed cardiomyopathy (EF15%)
    - What’s the etiology???
  - LHC reveals angiographically normal coronaries
  - Echo: No valvular abnormalities; severe systolic dysfunction, EF 15%, normal pulmonary pressures
  - No h/o afib (tachycardia induced)
  - No h/o drugs/ETOH
  - No recent travel or illness/infection (myocarditis)
  - EKG normal voltage (amyloidosis)
  - No recent stressful events (Takotsubo)
  - Not post-partum 😊
Case Study

- Diuresed 25lbs!!
- Discharged home...to follow-up in 7 days
  - VS: BP 137/86, HR 75, Wgt 255 lbs (unchanged from discharge)
  - PE: appears euvoletic (no JVD, no LE edema, lungs clear)
  - Labs normal
  - Medications (on discharge)
    - Lisinopril 5mg po daily
    - Furosemide 40mg po BID
    - Spironolactone 12.5mg po daily
Case Study

- **What is the plan today?**
  - Continue the same meds? Increase dosages of current meds? Add additional med?
  - How about adding a Beta Blocker:
    - Coreg
    - Metoprolol XL
    - Bisoprolol

- **Why add a Beta Blocker?**
  - Guideline Directed Medical Therapy!! (GDMT)
  - Decrease SNS stimulation and decrease BP
  - Decrease morbidity/mortality
  - Decrease hospitalizations
  - Reverse remodelling of the LV
Case Study

- **Patient returns in 1 week for follow-up**
  - Taking Carvedilol 3.125mg BID, and compliant with her other meds
  - However.....weight is up 6 lbs; c/o SOB, ankle swelling, fatigue

- **What should the ARNP do??**
  - Stop the Carvedilol?
  - Increase the Furosemide?
  - Anything else?

- **Plan:**
  - Cont low dose Carvedilol (but DO NOT uptitrate in setting of volume excess)
  - Increase Furosemide to 80mg BID or add HCTZ 25mg daily
  - Consider Hydralazine/Isosorbide (AA and still HTN)
Case Study

- Need to check BMP while titrating meds!!
- Don’t forget about education:
  - Low NA diet restrictions
  - Fluid restrictions
  - Weight loss
  - Exercise
  - S&S of worsening HF….and who to call for onset of symptoms
Case Study

■ One week follow-up eval:
  ▪ Feels symptomatically improved!
  ▪ Weight is down 8 lbs
  ▪ SOB, edema, fatigue have all improved
  ▪ BMP normal: Cr 0.9; K 4.0
  ▪ BP 128/66, HR 72

■ Can we adjust anything at this time?
  ▪ Consider cutting back on the diuretic
  ▪ Begin uptitration of Beta Blocker +/- ACE-I (usually done at 2 week intervals to allow patient to adjust)
  ▪ If BP too low, preferentially keep the BB and ACE-I and decrease/or d/c the Hydralazine and Isosorbide
2 months after hospital discharge:
- Patient feels great!!
- Continue to evaluate medical therapy regimen and look for opportunities to optimize
- Current meds:
  - Carvedilol 25mg BID
  - Lisinopril 5mg daily
  - Spironolactone 12.5mg daily
  - Hydralazine 10mg TID/Imdur 30mg daily
- Might consider increasing the Spironolactone (ONLY IF K+ and Cr ALLOW)
  - Aldosterone Blockers
    - Reduce Na retention
    - Decreases myocardial hypertrophy and fibrosis
Case Study

- OK....this patient’s fixed.....now what?
  - Usual regimen is to continue to uptitrate medical therapy for a period of 3-4 months
  - After fully optimized...as BP/HR/BMP allow, repeat Echo to evaluate for improvement in EF
  - If EF remains <35%: refer to EP for ICD implant for Sudden Cardiac Death (SCD) prophylaxis
  - If EF >35%: stop all meds and send patient on her merry way??? (NEVER!!)
    - Continue all current meds as tolerated
    - In some cases, gradual discontinuation of some meds may be achieved, but needs to be evaluated on an individual basis.