Heart Failure 2: Evidence Based Treatment Options

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Cardiovascular Nursing Education Association

Treatment of Heart Failure
Therapy of Heart Failure

- **Traditional**
  - Preload Reducers (diuretics, NTG)
  - Afterload Reducers (nipride, milrinone, hydralazine)
  - Inotropes (digoxin, dobutamine, milrinone)
- **Block RAAS**: ACEI, ARBs, Aldosterone blockers
- **Block SNS**: Beta Blockers
- **BNP** (B-type natriuretic peptides)
- **Biventricular Pacing**

4 groups of drugs shown to reduce mortality in HF:
Beta blockers, ACEI, ARBs, Aldosterone Blockers

Diuretics

- Diuretics should be prescribed to all patients who have evidence of or a prior history of fluid retention.
- Diuretics should be combined with an ACE inhibitor, beta blocker, and aldosterone antagonist.
- **Beneficial effects**
  - Renal Na⁺ and H₂O excretion
  - Decrease physical signs of fluid retention
  - Symptom relief (↓SOB, PND, edema)
  - Improve exercise tolerance
- **Detrimental effects**
  - Electrolyte depletion (K⁺, Mg++) → ventricular arrhythmias
  - Decreasing renal function (↑BUN, creatinine)
  - Activate RAAS: Vasoconstriction
  - Hypotension
Diuretic Therapy

- **Loop diuretics**
  - Agents of choice in HF, effective as monotherapy
  - Cause excretion of Na⁺ in ascending limb of loop of Henle
  - Rapid onset of IV form (can use continuous infusion)
  - Potent diuretic activity
    - Work in presence of renal dysfunction
    - High ceiling: increasing response with increasing dose
  - Short duration of action so need more than once a day dose
  - Side effects:
    - Hypokalemia, hypocalcemia, hypomagnesemia
    - Alkalosis
    - Deafness
    - Skin reactions (photosensitivity, rashes)
    - Worsen hyperglycemia
    - Hyperuricemia, gout
Diuretic Therapy

- **Thiazides**
  - Preferred diuretic in HTN
  - Inhibit \( Na^+ \) and \( Cl^- \) reabsorption in distal tubule
  - Less potent than loops but longer duration of action
    - Ineffective with reduced renal function
    - Low ceiling: maximum response at low dose
  - Can be added to a loop diuretic in HF
  - Side effects:
    - Hypokalemia (worse than loop diuretics) \( \rightarrow \) ventricular arrhythmias
    - Metabolic alkalosis
    - Hyperglycemia – can induce diabetes
    - Hypotension
    - Hyperuricemia, gout

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**K+ Sparing Diuretics** (also aldosterone blockers)

- Compete with aldosterone for receptor sites in the distal renal tubules.
- Decrease \( Na^+ \) reabsorption in distal tubules and collecting tubules.
- Fewer side effects than loops or thiazides
  - Hyperkalemia – especially in presence of renal disease, diabetes, ACEI or ARB therapy
Oral Diuretics Recommended for Use in the Treatment of HF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose</th>
<th>Maximum Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide (Bumex)</td>
<td>0.5 to 1.0 mg qd or bid</td>
<td>10 mg</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>20 to 40 mg qd or bid</td>
<td>600 mg</td>
</tr>
<tr>
<td>Torsemide (Demadex)</td>
<td>10 to 20 mg qd</td>
<td>200 mg</td>
</tr>
<tr>
<td><strong>Thiazide diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide (Diurol)</td>
<td>250 to 500 mg qd or bid</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>Chlorthalidone (Hygroton)</td>
<td>12.5 to 25.0 mg qd</td>
<td>100 mg</td>
</tr>
<tr>
<td>Hydrochlorothiazide (Hydrodiuril)</td>
<td>25 mg qd or bid</td>
<td>200 mg</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5 mg qd</td>
<td>5 mg</td>
</tr>
<tr>
<td>Metolazone (Zaroxolyn)</td>
<td>2.5 mg qd</td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>Potassium-sparing diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride (Midamor)</td>
<td>5 mg qd</td>
<td>20 mg</td>
</tr>
<tr>
<td>Eplerenone (Inspra)</td>
<td>25 mg qd</td>
<td>50 mg qd</td>
</tr>
<tr>
<td>Spironolactone (Aldactone)</td>
<td>12.5 to 25.0 mg qd</td>
<td>50 mg</td>
</tr>
<tr>
<td>Triamterene (Dyrenium)</td>
<td>50 to 75 mg bid</td>
<td>200 mg</td>
</tr>
</tbody>
</table>

Cardiovascular Effects of SNS

**Alpha Receptors**
(Arteries & Veins)

- Vasoconstriction

**Beta Receptors**

- Beta₁ (Heart)
  - Heart rate
  - Contractility
  - Automaticity
  - Conduction velocity
  - Renin release (kidney)

- Beta₂ (Arteries, Veins, Lungs)
  - Vasodilation
  - Bronchodilation
Effects of Beta Blockers

Beta Receptors

Beta 1
(Heart)

Beta 2
(Arteries, Veins)
(Lungs)

All Beta Blockers:

- Heart rate
- Contractility
- Automaticity
- Conduction velocity
- Renin release (kidney)

Non-cardioselective Beta Blockers:

- Vasodilation
- Bronchodilation

Why Do We Use Beta Blockers in HF?

- Chronic SNS stimulation is cardiotoxic and contributes to the progression of HF.
- Chronic beta stimulation → downregulation of beta receptors → decreased responsiveness of beta receptors to SNS stimulation.
  - Beta blockade upregulates beta receptor density and restores inotropic and chronotropic responsiveness to improve contractility.
- Beta blockers reduce circulating levels of vasoconstrictors (norepinephrine, endothelin, renin).
- Shown to slow progression of HF, improve survival, decrease hospitalizations for HF, improve symptoms, and improve exercise capacity.
General Considerations with Beta Blockers

- Should be prescribed to all patients with stable HFrEF unless they have contraindications or are intolerant.
- Should be initiated as soon as HFrEF is diagnosed (except in ADHF).
- Beta blockers can be started before max dose of ACEI is reached.
- Should not be prescribed without diuretics in patients with a current or recent history of fluid retention.
  - Diuretics are needed to maintain sodium and fluid balance and prevent fluid retention that can occur with beta-blockers.
- Even if symptoms do not improve, long-term treatment should be maintained to reduce the risk of major clinical events.
- Abrupt withdrawal of a beta blocker can lead to clinical deterioration and should be avoided.

Recommended Beta Blockers in HF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol (Zebeta)</td>
<td>Cardioselective: β1 blocker</td>
<td>Initial: 1.25 mg qd Max: 10 mg qd</td>
</tr>
<tr>
<td>Carvedilol (Coreg)</td>
<td>Noncardioselective: β1, β2, and α blocker: vasodilator properties, antioxidant effects</td>
<td>Initial: 3.125 mg bid Max: 25 mg bid if &lt; 85 Kg or severe HF, 50 mg bid if &gt; 85 Kg Initial: 10 mg qd Max: 80 mg qd Give Coreg with food.</td>
</tr>
<tr>
<td>Carvedilol CR (extended release)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol succinate extended release (metoprolol CR/XL)</td>
<td>Cardioselective: β1 blocker</td>
<td>Initial: 12.5 mg qd in NYHA III, IV; 25 mg qd in NYHA I or II Max: 200 mg qd</td>
</tr>
</tbody>
</table>
Side Effects of Beta Blockers

- **Cardiac**
  - Bradycardia, AV block
  - Heart Failure
  - Hypotension
- **Pulmonary**
  - Bronchoconstriction
  - Pulmonary edema
- **Peripheral Vascular**
  - Vasoconstriction
- **Metabolic**
  - Mask signs of hypoglycemia
  - Augment hypoglycemic actions of insulin (facilitates hypoglycemia)
  - Increase serum triglycerides
- **Other**
  - Fatigue, sleep disturbances
  - Depression
  - Sexual dysfunction
  - Weight gain

Fluid retention and worsening HF; fatigue; bradycardia or heart block; and hypotension are most common side effects

Drugs to Block the RAAS

- **Renal blood flow**
  - (Beta Blockers)
  - Renin release
  - (Renin Blockers)

- Angiotensinogen → Angiotensin I → Angiotensin II
  - (ACE Inhibitors)
  - (ARBs)
  - (Aldosterone Blockers)

- Vasoconstriction → Aldosterone release → Na⁺ & H₂O retention
- ↑ BP & Organ perfusion
ACEI & ARB Mechanism of Action

Angiotensin I
(converting enzyme)

\[ \text{Angiotensin II} \]

\[ \text{ACEI} \]

\[ \text{ARBs} \]

↓ Vasoconstriction

↓ Aldosterone release

\[ \text{Aldosterone Blockers} \]

↓ Na\(^+\) & H\(_2\)O retention

↓ preload

Venous dilation = ↓ preload
Arterial dilation = ↓ afterload

ACE INHIBITORS

- Block conversion of Angiotensin I to Angiotensin II
  - ↓ Preload
  - ↓ Afterload
  - ↑ Levels of Bradykinin – additive vasodilation, responsible for ACEI cough
  - ↑ Prostaglandin Production – additive vasodilation
  - ↓ Ventricular Remodeling – relieve pressure/volume overload

**Do not use if:**
Previous angioedema
Pregnant or plan to become pregnant

**Use with caution:**
Systolic blood pressure <80 mmHg
Serum creatinine >3 mg/dL
Bilateral renal artery stenosis
Hyperkalemia >5.0 mEq/L
ACEI Recommendations

- ACE inhibitors should be used in all patients with HFrEF to reduce morbidity and mortality (unless contraindicated).
  - ACE inhibitors reduce the risk of death and reduce hospitalization in HFrEF.
  - The benefits of ACE inhibition were seen in patients with all stages of HF, with or without CAD.
- ACE inhibitors are used together with a beta blocker unless contraindications.
- There are no differences among ACEI in their effects on symptoms or survival.

General Considerations with ACEI / ARBs

- Initiate therapy at low doses and increase gradually (every 2 weeks) until target dose reached, if tolerated.
- Assess BP (including posturals), renal function and K⁺ in 1-2 weeks after therapy started and periodically thereafter.
- Should attempt to reach target doses if tolerated. If not, use best tolerated dose.
- Abrupt withdrawal of an ACE inhibitor can lead to clinical deterioration and should be avoided.
- Up to 20% of patients will get the ACEI cough.
- ARBs are used in patients who are ACEI intolerant and are equally recommended for most indications as ACEI.
### Recommended ACEI and ARBs in HF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin Converting Enzyme Inhibitors (ACEI)</strong></td>
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</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg tid</td>
<td>50 mg tid</td>
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<tr>
<td>Enalapril</td>
<td>2.5 mg bid</td>
<td>10 – 20 mg bid</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5 to 10 mg qd</td>
<td>40 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>Perindopril</td>
<td>2 mg qd</td>
<td>8 to 16 mg qd</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg bid</td>
<td>20 mg bid</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 to 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><strong>Angiotensin Receptor Blockers (ARB)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 to 8 mg qd</td>
<td>32 mg qd</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 to 50 mg qd</td>
<td>50 – 100 mg qd</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20 to 40 mg bid</td>
<td>160 mg bid</td>
</tr>
</tbody>
</table>

### Effects of Aldosterone in Heart Failure

- Contributes to the pathophysiology of heart failure:
  - Promotes retention of Na⁺
  - Loss of Mg²⁺ and K⁺
  - Activation of SNS
  - Inhibition of parasympathetic NS
  - Myocardial and vascular fibrosis
  - Dysfunction of endothelium (formation of endothelin – potent vasoconstrictor)
**Aldosterone Receptor Antagonists**

- Aldosterone receptor antagonists are recommended in patients with NYHA class II-IV who have LVEF of \( \leq 35\% \) to reduce morbidity and mortality (unless contraindication).
  - Creatinine should be \( \leq 2.5 \text{ mg/dL} \) in men or \( \leq 2.0 \text{ mg/dL} \) in women.
  - Potassium should be \(< 5.0 \text{ mEq/L} \).
  - 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.

- Aldosterone receptor antagonists are recommended to reduce morbidity and mortality following an acute MI in patients who have LVEF of \( \leq 40\% \) who develop symptoms of HF or who have a history of diabetes mellitus.

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**Aldosterone Receptor Antagonists**

- **Spironolactone**
  - The RALES trial showed a 30% reduction in all cause mortality and a reduced risk of SCD and HF hospitalizations with the use of spironolactone in patients with chronic HFrEF and LVEF <35%.
  - Non-selective: blocks aldosterone and androgen, stimulates progesterone
    - Major side effects: gynecomastia, sexual dysfunction and menstrual problems
  - Causes K\(^+\) reabsorption – risk of hyperkalemia
- Eplerenone (Inspra)
  - Eplerenone has been shown to reduce all-cause deaths, cardiovascular deaths, or HF hospitalizations in patients with HFrEF
  - Indicated for treatment of hypertension and heart failure
  - Selective aldosterone receptor blocker
    - 1000 fold less binding to androgen receptor
    - 100 fold less binding to progesterone receptor
    - Results in blockade of aldosterone receptors without side effects associated with spironolactone

Reducing Risk of Hyperkalemia with Aldosterone Antagonists

- The risk of hyperkalemia is increased with concomitant use of higher doses of ACE inhibitors.
- Potassium supplements should be discontinued or reduced when initiating aldosterone antagonists.
- Patients should use salt substitutes that do not contain potassium.
- Close monitoring of serum potassium is required
  - K⁺ levels and renal function should be checked in 3 days and at 1 week after initiating therapy and at least monthly for the first 3 months.
Hydralazine and Isosorbide Dinitrate

- The combination of hydralazine (arterial dilator) and isosorbide dinitrate (venous dilator) 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.
- Can be useful to reduce morbidity or mortality in patients with HFrEF who cannot take ACE inhibitors or ARBs because of drug intolerance, hypotension, or renal insufficiency.
- Should not be used for the treatment of HFrEF in patients who have no prior use of ACEI or ARB therapy and should not be substituted for ACEI or ARBs in patients who are tolerating those drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aldosterone Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5 to 25 mg qd</td>
<td>25 mg qd or bid</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg qd</td>
<td>50 mg qd</td>
</tr>
<tr>
<td><strong>Hydralazine / isosorbide dinitrate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed-dose combination (Bidil)</td>
<td>37.5 mg hydralazine/20 mg isosorbide dinitrate tid</td>
<td>75 mg hydralazine/40 mg isosorbide dinitrate tid</td>
</tr>
</tbody>
</table>
| Hydralazine & isosorbide dinitrate | Hydralazine 25 to 50 mg tid or qid and Isosorbide dinitrate 20 to 30 mg tid or qid | Hydralazine 300 mg qd in divided doses

Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HFrEF.
**Digoxin** (the only safe & effective oral inotrope)

- Digitalis acts by inhibiting the Na-K-ATPase pump in myocardial cells.
  - Increased intracellular sodium promotes sodium-calcium exchange, leading to a rise in the intracellular calcium concentration which increases contractility and overall left ventricular systolic function.
- Inhibits sympathetic outflow and augments parasympathetic tone, decreases renin secretion.
  - Slows AV conduction in AF
  - Reduced levels of norepinephrine and renin activity
  - Weak positive inotrope
- Evidence from clinical trials supports the use of digoxin in patients with HFrEF for symptom management.
  - Improves symptoms and quality of life but no evidence that it improves survival.

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**Digoxin**

- Dig level should be 0.5 – 0.9 ng/mL
  - Levels >1.2 ng/mL associated with toxicity and higher mortality rate.
  - Use small dose: 0.125 mg/day or every other day.
  - Draw dig levels at least 6 hours after dose (levels do not correlate with efficacy).
- Side effects
  - GI: anorexia, nausea, vomiting.
  - Neuro: confusion, agitation, yellow vision halos.
  - Cardiac: bradycardia, heart block (especially when combined with beta blockers), many arrhythmias.
  - Dig toxicity more common with ↓K⁺, ↓Mg++, and renal dysfunction (dig levels increase as renal function worsens in HF).
Tolvaptan (Samsca)

- Vasopressin receptor antagonist used to treat hypervolemic or euvolemic hyponatremia
  - Used for serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and resistant to fluid restriction.
  - Blockade of V2 receptor promotes the excretion of free water without loss of serum electrolytes, resulting in net fluid loss, increased urine output, and subsequent restoration of normal serum sodium levels.

Tolvaptan

- Dosing: oral
  - Initial: 15 mg once daily
  - After at least 24 hours, may increase to 30 mg once daily
  - Maximum of 60 mg once daily titrating at 24-hour intervals to desired serum sodium concentration.
  - Avoid fluid restriction during the first 24 hours of therapy.
  - Do not use for more than 30 days due to the risk of hepatotoxicity.
- Do not use in patients with liver disease (including cirrhosis)
  - Can cause fatal hepatic failure
Conivaptan (Vaprisol)

- Vasopressin receptor antagonist used to treat euvolemic or hypervolemic hyponatremia in hospitalized patients.
  - Nonselective – blocks both $V_{1A}$ and $V_2$ receptors.
  - $V_2$ receptor blockade promotes the excretion of free water without loss of serum electrolytes, resulting in net fluid loss, increased urine output, and subsequent restoration of normal serum sodium concentrations.

Conivaptan

- Dosing: IV
  - 20 mg infused over 30 minutes as a loading dose
  - Continuous infusion of 20 mg over 24 hours (0.83 mg/hour) for 2-4 days
  - May increase to a maximum dose of 40 mg over 24 hours (1.7 mg/hour) if serum sodium not rising sufficiently
  - Total duration of therapy not to exceed 4 days
- Does not cause liver failure like tolvaptan can, but should not be used in patients with severe hepatic impairment.
Recommendations for Management of HFpEF

- Control of systolic and diastolic HTN
  - The use of beta blockers, ACEI, and ARBs is reasonable to control blood pressure in HFpEF.
  - BP control reduces hospitalizations in HFpEF patients.
- Diuretics to control pulmonary congestion and peripheral edema
- Management of atrial fib according to published guidelines (rate control and anticoagulation).
  - Patients with HFpEF are dependent of adequate diastolic filling, so slower HR and atrial kick are important for ventricular filling.

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2013 ACCF/AHA Guideline for the Management of Heart Failure:
A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

_Circulation_. published online June 5, 2013
http://circ.ahajournals.org/content/early/2013/06/03/CIR.0b013e31829e8776.citation
Recommendations for Management of Stage A Heart Failure

Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF.

Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided.

Other Considerations (Stage A)

- Avoidance of behaviors that may increase risk of HF (smoking, excess alcohol, illicit drugs)
- Control of ventricular rate or restore NSR in patients with SVT, atrial fib or flutter
- Treatment of thyroid disorders
- Periodic evaluation for signs and symptoms of HF
- Noninvasive evaluation of LVEF in patients with family history of cardiomyopathy or in those receiving cardiotoxic interventions
### Recommendations for Treatment of Stage B HF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with a history of MI and reduced EF, <strong>ACE inhibitors or ARBs</strong> should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In patients with MI and reduced EF, evidence-based <strong>beta blockers</strong> should be used to prevent HF</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In patients with MI, <strong>statins</strong> should be used to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Blood pressure should be controlled to prevent symptomatic HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong> should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>Beta blockers</strong> should be used in all patients with a reduced EF to prevent HF</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>An ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF ≤30%, and on GDMT</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF</td>
<td>III: Harm</td>
<td>C</td>
</tr>
</tbody>
</table>

### Pharmacological Therapy for Management of Stage C HFrEF

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics are recommended in patients with HFrEF with fluid retention</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors are recommended for all patients with HFrEF</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARBs are recommended in patients with HFrEF who are ACE inhibitor intolerant</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>ARBs are reasonable as alternatives to ACE inhibitor as first line therapy in HFrEF</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>The addition of an ARB may be considered in persistently symptomatic patients with HFrEF on GDMT</td>
<td>IIb</td>
<td>A</td>
</tr>
<tr>
<td>Routine <em>combined</em> use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful</td>
<td>III: Harm</td>
<td>C</td>
</tr>
</tbody>
</table>
Pharmacological Therapy for Management of **Stage C HFrEF** (cont.)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta Blockers</strong></td>
<td></td>
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</tr>
<tr>
<td>Use of 1 of the 3 beta blockers proven to reduce mortality is recommended for all stable patients</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>Aldosterone Antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone receptor antagonists are recommended in patients with NYHA class II-IV HF who have LVEF ≤35%</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Aldosterone receptor antagonists are recommended in patients following an acute MI who have LVEF ≤40% with symptoms of HF or diabetes</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Inappropriate use of aldosterone receptor antagonists may be harmful</td>
<td>III: Harm</td>
<td>B</td>
</tr>
<tr>
<td><strong>Hydralazine and Isosorbide Dinitrate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The combination of hydralazine and isosorbide dinitrate is recommended for African-Americans, with NYHA class III-IV HFrEF on GDMT</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A combination of hydralazine and isosorbide dinitrate can be useful in patients with HFrEF who cannot be given ACE inhibitors or ARBs</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

Pharmacologic Therapy for Management of **Stage C HFrEF** (cont.)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digoxin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin can be beneficial in patients with HFrEF</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td><strong>Anticoagulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>The selection of an anticoagulant agent should be individualized</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but without an additional risk factor for cardioembolic stroke</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Anticoagulation is not recommended in patients with chronic HFrEF without AF, prior thromboembolic event, or a cardioembolic source</td>
<td>III: No Benefit</td>
<td>B</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
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<tr>
<td>Statins are not beneficial as adjunctive therapy when prescribed solely for HF</td>
<td>III: No Benefit</td>
<td>A</td>
</tr>
<tr>
<td><strong>Omega-3 Fatty Acids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in HFrEF or HfPEF patients</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>
Pharmacological Therapy for Management of Stage C HFrEF (cont.)

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<tr>
<td><strong>Other Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional supplements as treatment for HF are not recommended in HFrEF</td>
<td>III: No Benefit</td>
<td>B</td>
</tr>
<tr>
<td>Hormonal therapies other than to replete deficiencies are not recommended in HFrEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
<tr>
<td>Drugs known to adversely affect the clinical status of patients with HFrEF are potentially harmful and should be avoided or withdrawn</td>
<td>III: Harm</td>
<td>B</td>
</tr>
<tr>
<td>Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation</td>
<td>III: Harm</td>
<td>C</td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td></td>
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</tr>
<tr>
<td>Calcium channel blocking drugs are not recommended as routine in HFrEF</td>
<td>III: No Benefit</td>
<td>A</td>
</tr>
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</table>

Treatment of HFpEF

<table>
<thead>
<tr>
<th>Recommendations</th>
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<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Diuretics should be used for relief of symptoms due to volume overload</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Management of AF according to published clinical practice guidelines for HFpEF to improve symptomatic HF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HFpEF</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ARBs might be considered to decrease hospitalizations in HFpEF</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Nutritional supplementation is not recommended in HFpEF</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>
Implantable Cardioverter Defibrillators

- ICD therapy is recommended for **primary prevention** of SCD to reduce total mortality in the following patients who are on chronic GDMT and who have reasonable expectation of meaningful survival for more than 1 year:
  - Nonischemic DCM or ischemic heart disease at least 40 days post-MI with LVEF $\leq 35\%$ and **NYHA class II or III** symptoms.
  - Patients at least 40 days post-MI with LVEF of $\leq 30\%$ and **NYHA class I** symptoms.
- ICD should be considered only after a minimum of 3 to 6 months of GDMT.
- Repeat assessment of EF after GDMT to make sure EF still meets threshold for ICD implantation.
- Frequent ICD shocks may require amiodarone therapy to decrease number of shocks.
- Discuss deactivating shock therapies in patients with end stage HF (not the same as “withdrawing life support”)

Device Therapy in HF
Cardiac Resynchronization Therapy

- Biventricular Pacing
  - Atrial lead
  - RV apex lead
  - LV lead via coronary sinus into lateral or posterior vein in LV
- Goal is to force ventricles to contract together (resynchronization) and to program AV interval to optimize ventricular filling

Recommendations for CRT in Stage C HFrEF Patients

- CRT is indicated for patients who have the following criteria (class I recommendation):
  - EF ≤ 35%
  - Sinus rhythm
  - LBBB with QRS ≥ 150 msec
  - NYHA class II, III or ambulatory class IV despite optimal medical therapy
- Class II recommendations include these patients:
  - Non-LBBB pattern with a QRS ≥ 150 ms and NYHA class III/ambulatory class IV
  - QRS duration of 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms
  - Patients with AF if the patient requires ventricular pacing or otherwise meets CRT criteria and atioventricular nodal ablation or pharmacological rate control will allow near 100% ventricular pacing with CRT.
### Device Therapy for Stage C HFrEF

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<tbody>
<tr>
<td><strong>ICD</strong> therapy is recommended for <strong>primary prevention</strong> of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF ≤35%, and NYHA class II or III symptoms on chronic GDMT, who are expected to live ≥1 year*</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td><strong>CRT</strong> is indicated for patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS ≥150 ms</td>
<td>I</td>
<td>A (NYHA class II/III/IV)</td>
</tr>
<tr>
<td><strong>ICD</strong> therapy is recommended for <strong>primary prevention</strong> of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF ≤30%, and NYHA class I symptoms while receiving GDMT, who are expected to live ≥1 year*</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td><strong>CRT</strong> can be useful for patients who have LVEF ≤35%, sinus rhythm, a <strong>non-LBBB pattern with a QRS ≥150 ms</strong>, and NYHA class III/ambulatory class IV symptoms on GDMT.</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td><strong>CRT</strong> can be useful for patients who have LVEF ≤35%, sinus rhythm, <strong>LBBB with a QRS 120 to 149 ms</strong>, and NYHA class II, III, or ambulatory IV symptoms on GDMT</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td><strong>CRT</strong> can be useful in patients with AF and LVEF ≤35% on GDMT if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or rate control allows near 100% ventricular pacing with CRT</td>
<td>IIa</td>
<td>B</td>
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### Device Therapy for Stage C HFrEF (cont.)

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<tbody>
<tr>
<td><strong>CRT</strong> can be useful for patients on GDMT who have LVEF ≤35%, and are undergoing new or replacement device with anticipated (&gt;40%) ventricular pacing</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>An ICD is of uncertain benefit to prolong meaningful survival in patients with high risk of nonsudden death such as frequent hospitalizations, frailty, or severe comorbidities</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td><strong>CRT</strong> may be considered for patients who have LVEF ≤35%, sinus rhythm, a <strong>non-LBBB pattern with QRS 120 to 149 ms</strong>, and NYHA class III/ambulatory class IV on GDMT</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td><strong>CRT</strong> may be considered for patients who have LVEF ≤35%, sinus rhythm, a <strong>non-LBBB pattern with a QRS ≥150 ms</strong>, and NYHA class II symptoms on GDMT</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td><strong>CRT</strong> may be considered for patients who have LVEF ≤30%, ischemic etiology of HF, sinus rhythm, LBBB with a QRS ≥150 ms, and NYHA class I symptoms on GDMT</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td><strong>CRT</strong> is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS &lt;150 ms</td>
<td>III: No Benefit</td>
<td>B</td>
</tr>
<tr>
<td><strong>CRT</strong> is not indicated for patients whose comorbidities and/or frailty limit survival to &lt;1 year</td>
<td>III: No Benefit</td>
<td>C</td>
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</table>
Therapies for Stage D HF

- Fluid restriction (1.5 to 2 L/d) is reasonable in stage D, especially in patients with hyponatremia, to reduce congestive symptoms.
  - Strict fluid restriction in patients who are refractory to diuretics or have hyponatremia.

- Inotropic drugs
- Mechanical circulatory support
- Cardiac transplant

Inotropes

- Positive inotropic agents have not demonstrated improved outcomes in patients with HF in either the hospital or outpatient setting.
  - Used short-term to maintain systemic perfusion and preserve end-organ function in cardiogenic shock and in patients with low cardiac index, hypoperfusion, and pulmonary congestion.
  - Used short-term as “bridge therapy” until MCS or transplant.
  - Used long-term as palliative therapy and symptom control in end-stage patients not eligible for MCS or transplant.
Positive Inotropes

- **Dobutamine**
  - Primarily a β1 stimulant – increases contractility & HR
  - May ↓SVR in some patients (usually because it ↑CO)
  - Effects may be decreased by beta blocker therapy
  - Usual dose = 2-15 mcg/Kg/min infusion
  - SE: tachycardia, may ↑ ischemia, may ↑ AV conduction

- **Milrinone** (Primacor) – “inodilator”
  - Phosphodiesterase inhibitor – increased contractility, peripheral and pulmonary vasodilation
  - Initial doses of 0.1 mcg/kg/min and final doses of 0.2 to 0.3 mcg/kg/min (without bolus)
  - SE: hypotension, arrhythmias, may ↑ AV conduction

Inotropic Support in Stage D HF

- Patients with **cardiogenic shock** should receive temporary IV inotropic support until definitive therapy (coronary revascularization, MCS, heart transplantation) or resolution of the acute precipitating problem. (Class 1c)
- Continuous IV inotropic support is reasonable as “bridge therapy” in patients who are eligible for and awaiting MCS or cardiac transplantation. (Class IIa)
- Short-term, continuous IV inotropic support may be reasonable in hospitalized patients presenting with severe systolic dysfunction, low blood pressure, and significantly depressed cardiac output. (Class IIb)
- Long-term, continuous IV inotropic support may be considered as **palliative therapy** for symptom control in patients who are not eligible for either MCS or cardiac transplantation. (Class IIb)
Mechanical Circulatory Support (MCS)

- Bridge to decision or bridge to recovery
  - Temporary support in cardiogenic shock until patient recovers or a decision can be made about further therapy.
- Bridge to transplant (BTT)
  - Support circulation until patient receives heart transplant.
- Destination Therapy (DT)
  - Permanent support for patients who are not eligible for heart transplantation.

Ventricular Assist Devices (VAD)

- Many types of VADs available
  - Implantable versus extracorporeal
  - Percutaneous versus surgical insertion
  - Pulsatile versus continuous flow
  - Ventricle(s) supported: left, right, biventricular
- VADs can be used for:
  - Short-term (hours to days) management of acute decompensated, hemodynamically unstable HFrEF that is refractory to inotropic support
  - Long-term (months to years) management of stage D chronic HFrEF
Types of MCS for Bridge to Recovery

• Intraaortic balloon pump (IABP)
  • Used in cardiogenic shock to augment aortic diastolic pressure, improve coronary blood flow, and reduce LV afterload.
  • Temporary support for a few days.

• Impella
  • Inserted percutaneously via the femoral artery, advanced up the aorta and placed across the aortic valve.
  • A rotary pump on the catheter pulls blood from the left ventricle through the inlet area and expels it into the aorta through the outlet area.
  • Temporary support for days.

• Tandem Heart
  • Uses transseptal left atrial inflow via a percutaneous femoral venous cannula and outflow via a femoral arterial cannula.
  • Up to 5 L/min flow.
  • Temporary support for days.

• Heartmate II (2nd generation VAD)
  • Implantable continuous, axial-flow pump with a small external controller.
  • Blood flows through an inflow cannula from the apex of the LV to the pump and returns back through an outflow cannula to the ascending aorta.
  • Can generate up to 10 L/min of flow at a pressure of 100 mmHg.
  • Powered by batteries worn in belt or holster.
  • Patient “plugs in” at night to charge the batteries.
MCS for BTT or DT

- **Heartware** (3rd generation, approved in US for BTT, being evaluated for DT)
  - Implantable continuous flow centrifugal pump.
  - Implanted directly adjacent to the heart in the pericardial space.
  - Generates up to 10 L/min of blood flow.

- Completely implantable VAD expected by 2014

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Recommendations for MCS

- **Indications for referral for MCS therapy:**
  - LVEF <25% and NYHA class III-IV functional status despite GDMT (including CRT when indicated)
  - Either high predicted 1- to 2 year mortality or dependence on continuous IV inotropic support.

- Patient selection requires a multidisciplinary team of experienced advanced HF and transplantation cardiologists, cardiothoracic surgeons, nurses, social workers and palliative care clinicians.
Mechanical Circulatory Support

MCS use is beneficial in carefully selected patients with stage D HFrEF in whom definitive management (e.g., cardiac transplantation) or cardiac recovery is anticipated or planned. (Bridge to therapy or recovery)

Nondurable MCS, including the use of percutaneous and extracorporeal ventricular assist devices (VADs), is reasonable as a “bridge to recovery” or a “bridge to decision” for carefully selected patients with HFrEF with acute, profound hemodynamic compromise.

Durable MCS is reasonable to prolong survival for carefully selected patients with stage D HFrEF. (Destination therapy)

Heart Transplant

- Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite GDMT, device, and surgical management. (Class Ic)
- The gold standard for the treatment of refractory end-stage HF.
- Improved survival, functional status and quality of life.
Sunset at my house