Learning Objectives

- Identify key concepts for guideline-recommended therapy for heart failure with reduced ejection fraction (HFrEF).
- Recommend approaches to overcoming diuretic resistance.
- Discuss therapeutic approaches for patients with HF and comorbidities.
- Counsel HF patients about medication use and adherence.
- Discuss patient assessment tools for patients with HF.
Pharmacologic Treatment for Stage C HFrEF

**HFrEF Stage C**
**NYHA Class I – IV**
**Treatment:**

- Update: Consider angiotensin receptor-neprilysin inhibitor (ARNI)
- Update: HR ≥ 70 consider ivabradine

**Class I, LOE A**
ACEI or ARB AND Beta Blocker

For all volume overload, NYHA class II-IV patients:
- Add
  - **Class I, LOE C** Loop Diuretics

For persistently symptomatic African Americans, NYHA class III-IV:
- Add
  - **Class I, LOE A** Hydral-Nitrates

For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL:
- Add
  - **Class I, LOE A** Aldosterone Antagonist
Key Concepts – Optimizing Therapy

- To reduce morbidity and mortality all patients with symptomatic HFrEF should be considered for:
  - ACE inhibitor/ARB/ARNI
  - beta blocker
  - aldosterone antagonist
  - Symptom Relief Only – Loop diuretics

- For patients who tolerate ACE inhibitor/ARB, switch to ARNI should be considered

- Titrate patients to target doses if appropriate

- Lower doses of multiple therapies preferred vs. high dose of single therapy is preferred

- Patients should be evaluated for: ivabradine, hydralazine/isosorbide dinitrate, digoxin, fish oil


Key Concepts - Diuretics and Diuretic Resistance

- Assess effectiveness – Ask patients: “What happens after you take your diuretic/water pill?”

- Symptom relief (e.g., dyspnea, orthopnea)

- Weight, edema

- Urine output

- Electrolytes - Hypokalemia/hypomagnesemia

- Hypotension – Dehydration

- Renal function

- Hyperuricemia/gout

- Achieve diuretic threshold
Pharmacodynamics of Loop Diuretics

**Table: pharmacodynamics of loop diuretics**

<table>
<thead>
<tr>
<th></th>
<th>Furosemide</th>
<th>Bumetanide</th>
<th>Torsemide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual daily dose (pod)</strong></td>
<td>20–160 mg/d</td>
<td>0.5–4 mg/d</td>
<td>10–80 mg/d</td>
</tr>
<tr>
<td><strong>Ceiling dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal renal function</td>
<td>80-160 mg</td>
<td>1–2 mg</td>
<td>20–40 mg</td>
</tr>
<tr>
<td>( Cl_{\text{CR}} ) 20–50 mL/min</td>
<td>160 mg</td>
<td>2 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>( Cl_{\text{CR}} ) &lt;20 mL/min</td>
<td>400 mg</td>
<td>8–10</td>
<td>100 mg</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>10–100%</td>
<td>80–90%</td>
<td>80–100%</td>
</tr>
<tr>
<td>Average: 50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Affected by food</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>0.3–3.4 h</td>
<td>0.3–1.5 h</td>
<td>3–4 h</td>
</tr>
</tbody>
</table>

Furosemide–bumetanide conversion: ~ 40:1
Furosemide–torsemide conversion: ~ 2 to 4:1

Diuretic Resistance

What happens after you take your diuretic/water pill?

- Threshold dose
- Drug adherence
- Dietary adherence (sodium intake)
- Bioavailability, absorption
  ↓absorption with furosemide as patients decompensate
- Drug interactions (NSAID)
- Distal tubular hypertrophy

PD of Loop Diuretics
Diuretic Resistance

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Kidney Cortex Function

[Diagram of the kidney cortex function]
Distal Tubular Hypertrophy

- Enhanced sodium reabsorption at distal tubule
- Sequential blockade of loop of Henle and distal tubule
- Loop diuretic + thiazide diuretic
- Metolazone or hydrochlorothiazide (HCTZ)
  - Metolazone – 2.5mg to 10mg/day
  - HCTZ – 25mg to 100mg, QD to BID

Overcoming Diuretic Resistance

- Improve drug and dietary compliance
- Discontinue interacting drugs
- Ensure threshold dose
  - Increase dose to reach threshold
  - Increase frequency if at threshold (BID – TID dosing)
  - ↓absorption? – Change to torsemide or bumetanide
- Add thiazide diuretic if distal tubular hypertrophy is suspected
Patient Counseling - Diuretics

- Expected benefits: decrease dyspnea and edema (patient-specific symptoms associated with fluid overload)

- Expect increased urination. For most, take in morning vs at bedtime.

- Self monitoring – urine output, weight gain (call if > 2lbs), dyspnea, edema

- Report dizziness (evaluate for dehydration and hypotension)

- Avoid NSAIDs – may cause diuretic resistance and renal impairment.

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Key Concepts - ACE Inhibitor, ARB, Angiotensin Receptor- Neprilysin Inhibitor (ARNI)

- Cough – often resolves, may take months. If persistent and bothersome can switch to ARB.

- ↑ in creatinine may be seen upon initiation or up-titration. Often minor and transient and may return to baseline over time. Chronic increase acceptable if limited. (If function is moderately or severely compromised, evaluate other drugs that could be discontinued.

- Renal impairment is not contraindication to therapy. Need to monitor closely

- Consider ARNI
Patient Counseling – ACE Inhibitor, ARB, ARNI

- Expected benefits – improve symptoms, decrease hospitalizations, increase survival.
- Report symptoms of dizziness, cough.
- Avoid NSAIDs – may interact with diuretic and damage kidneys (diuretic resistance and renal impairment).
- Serious allergic reactions may cause swelling of face, lips, tongue, and throat (angioedema) which may cause trouble breathing and death. Get emergency medical help right away.
- Do not take ARNI for at least 36 hours before or after taking an ACE inhibitor.

Key Concepts – Beta Blockers

- Start low:
  — Bisoprolol 1.25mg QD
  — Carvedilol 3.125mg BID
  — Metoprolol succinate 12.5 to 25mg QD
- Patients must be clinically stable and euvoletic before starting or increasing dose.
- Titrate upwards no sooner than every 2 weeks.
- BB initiation or dose increase may worsen HF symptoms (dyspnea, fatigue, edema) in some patients. This is often transient, can be managed by increasing diuretic dose. If persistent, may need to reduce BB dose.
- Symptom improvement may take months.
- For patients with asthma/COPD consider cardioselective BB (bisoprolol or metoprolol succinate). Metoprolol succinate preferred vs. metoprolol tartrate.
**Patient Counseling – Beta Blockers**

- Expected benefits: improve symptoms, decrease hospitalizations, increase survival.

- Improve symptoms may take months (3–6 months)

- May feel worse before feeling better (upon dose initiation or during up-titrination).

- Report worsening symptoms including weight gain. Emphasize that these symptoms can be managed. NEED to stay on therapy!

- Do not stop taking beta blocker unless directed by physician.

**Key Concepts – Aldosterone Antagonists**

*To initiate, creatinine should be:*

- ≤ 2.5 mg/dL in men
- ≤ 2.0 mg/dL in women

*OR*

- Estimated glomerular filtration rate (EGFR) > 30 mL/min/1.73m²

*AND*

- Potassium < 5.0 mEq/L

- Electrolytes (K+) should be checked upon initiation and rechecked within 2 to 3 days, again after 7 days.

- Additional monitoring is patient-dependent. At least monthly for first 3 months, every 3 months afterwards or sooner if warranted.

- Increase in serum creatinine may occur. Can be associated with increase diuresis seen with AA may need to reduce loop diuretic therapy. Often increase is transient – monitor over time.
Patient Counseling – Aldosterone Antagonists

- Expected benefits: Improve symptoms, decrease hospitalizations, increase survival
- Expect increased urination
- Report dizziness (evaluate for dehydration and hypotension)
- Avoid NSAIDs – may cause diuretic resistance and renal impairment
Diabetes

- Common in HF patients (~30%)
- Associated with increased morbidity and mortality
- Follow current ADA recommendations. HbA1c ~7% (<8%) reasonable for most HF patients.
- Consider initial therapy with metformin. Observational studies suggest improved outcomes.
- CI with renal insufficiency: metformin should not be used in men with serum creatinine levels ≥1.5 mg/dL and in women with levels ≥1.4 mg/dL.
- Avoid thiazolidinediones, saxagliptin, sitagliptin

Diabetes – SGLT2 inhibition

- Sodium-glucose cotransporter-2 (SGLT2)
  — Reabsorbs glucose (w/sodium) in proximal tubule
- SGLT2 inhibition
  — Increased urinary glucose secretion and mild reduction in hemoglobin A1c (0.7%)
  — Mild diuretic and BP lowering effect (4–6/1–2 mmHg)
- EMPA-REG OUTCOME (~7,000 pts)
  — Empagliflozin 10 and 25 mg vs placebo
  — Primary outcome: CV death + non-fatal MI + non-fatal stroke

Empagliflozin (SGLT2 Inhibitor)

- Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)

- **Indication: to reduce the risk of cardiovascular death in adult patients with T2DM and established cardiovascular disease.**

- Benefits (in patients with T2DM)
  - Reduced composite of CV mortality, non-fatal MI, non-fatal stroke
  - Reduced total mortality
  - **Reduced HF hospitalization (underpowered subgroup analysis)**
  - Reduced acute kidney injury and renal failure

- Risks
  - Increased risk of urinary tract infections (women) and genital infections (men/women)
  - Potential risk of volume depletion

- Place in therapy?
  - No guideline recommendations
  - Consideration for HF patients?
Depression

- Approximately 21% (9% to 60%) of HF patients may have depression
- Poor quality of life, limited functional status, increase morbidity and mortality.
- HF Guidelines – no guidance
- Screening tools – simple assessment that may be quickly done in clinic includes:
  - PHQ2 and PHQ9 (AHA recommends for CAD pts for routine screening)
  - Data available in HF patients (mostly inpatient)

Lichtman JH. Circulation. 2008;118:1768-1775

Clinical Assessment Tool – PHQ-2

<table>
<thead>
<tr>
<th>Over the past 2 weeks, how often have you been bothered by any of the following problems</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

http://www.phqscreeners.com/
Depression

- Avoid St. John’s Wort
- Counseling – Referral
- Sertraline (SADHART-CHF; Sertraline Against Depression and Heart Disease in Chronic Heart Failure)
- Avoid drugs that prolong QT interval – e.g., TCAs, citalopram
- Tai Chi, Yoga

Hyperkalemia Management

- Some patients cannot take ACE Inhibitors/ARBs/aldosterone antagonists due to development of hyperkalemia
- Patiromer – nonabsorbed potassium binder. Uses calcium as counter-ion in exchange for K+ in the colon
- Indicated for treatment of hyperkalemia
- Administer at least 3 hours before or 3 hours after other oral medications
- Administer with food
- Constipation and hypomagnesemia
Cough and Cold Management

- In most cases, avoid decongestants
- Antihistamines: avoid diphenhydramine – prolong QT interval
- Dextromethorphan
- Nasal saline wash
- Fluids
- Zinc
- Evaluate sodium content of liquid preparations

General Pain Management

- Avoid NSAIDs and corticosteroids if possible
- Acetaminophen
- Topical methyl-salicylate products (general pain); Topical capsaicin (OA, joint pain); Topical NSAIDs (OA, joint pain)
- Tramadol (renal function)
- Opiates
- Chondroitin sulfate, glucosamine (warfarin)
- Nonpharmacologic – Exercise, acupuncture, Tai chi
- Statin induced?
Laxatives and Antacids

- Laxatives
  - Risk of dehydration or electrolyte disturbances
  - Bulk-forming laxatives: drug-drug interactions
  - Hyperosmotic saline laxatives: hypermagnesemia

- Antacids
  - Drug-drug interactions
  - Sodium content
  - Hypermagnesemia


Adherence, Clinical Assessments, Patient Self-Management
Implications of Nonadherence in HF

- Rates vary widely, with most rates between 40–60%
- Contributes to hospital admission in approximately one-third of HF patients
- Associated with increased cardiac-related events and health care costs, reduced QOL

**Adherence to HF medications associated with a 35% reduction in mortality (HR 0.65, CI 0.57-0.75, P < 0.0001).**


Barriers to Adherence

- Complex medication schedule, multiple medications
- Cost of care/Transportation needs
- Lack of family support
- Health beliefs/cultural
- Low health literacy
- Cognitive impairment
Clinical Assessment – Cognitive Function

- Increase mortality, morbidity, hospitalizations
- Increase health care costs
- Affects self-care
  - Self Care of Heart Failure Index
    http://www.self-careofheartfailureindex.com/
- Cognitive impairment incidence in HF: 25%–75% (90% in hyponatremic patients)
- Young and old HF patients, HFrEF and HFpEF
- Every patient should be assessed (Clinic, Pharmacy)?
  - MMSE, Montreal Cognitive Assessment, Mini-Cog

Clinical Assessment Tool – Mini-Cog™

Figure 1. The Mini-Cog scoring algorithm. The Mini-Cog uses a three-item recall test for memory and the intuitive clock-drawing test. The latter serves as an “informative distractor,” helping to clarify scores when the memory recall score is intermediate.

Clinical Assessment Tool – Medication Adherence

- Many approaches
  - Pill count
  - Drug levels
  - Refill rates
  - Self-report

- Medication Adherence Tools
  - Morisky-4 (MMAS-4)
  - Adherence Estimator (3 questions - http://www.adherenceestimator.com/)
  - Others

Improve Medication Adherence

- Identity reasons for medication nonadherence
- Ask patient how they take their medication
- Involve family and caregivers
- Motivational interviewing
- Pill reminders, pill boxes, etc.
- MTM review
- Keep it simple
Keep it…SIMPLE

Simplify the regimen
Impart knowledge
Modify patient beliefs and behavior
Provide communication and trust
Leave the bias
Evaluate adherence


Patient Access to Technology

- Single-center study of HF patients (n=100)

  Internet access 85%
  Computer 79%
  Smart device 44%

- Younger patients more likely to have access ($P < 0.005$), no difference between genders.
- Majority of patients accessed smart devices > 10 x/day (71%), only 11% accessed < 5 x/day.

Technology: E-Health Apps

- Smart Device
  - 69% above average in navigating
  - 70% looks up health problems (< 50% for computer only)
  - 39% e-mailed providers vs. 14% computer only users
  - Opportunities!! (Only 15% of HF pts did not have internet access)

- Medication adherence (248!)

- Smart scales (44)

- Diet, cholesterol, weight loss (5,530)

- Personal activity/fitness trackers (1,807)

- Multi-Measure wellness tracking tools (121)

- Social media? (Friends, family, patients)

- OPPORTUNITY for you and your patient!

**Featured:**
- On-line data entry
- Database of medications
- Cloud data storage
- Sync/export/print data
- Multiplatform app
- Free-only apps
- Provider data input\(^{\text{MMS}}\)
- Reminders w/o connectivity\(^{\text{MM, MS}}\)
- HPPA\(^{\text{MMS, MM}}\)
- Complex med instructions\(^{\text{MMS, MM}}\)
- Multiple profiles\(^{\text{MM}}\)

**Not Featured:**
- Track missed/taken doses
- Multilingual

MMS = MyMedSchedule
MM = MyMeds
MS = MedSimple

Assess Patients For Worsening HF:
The One Minute Clinic for Heart Failure (TOM-C HF)

- Simple assessment tool for worsening HF
- Easily and quickly administered by anyone (techs, students)
- **Community setting, clinic, long-term care, or phone assessment**
- Assessed in community pharmacy setting
- Can be driven by pharmacy curriculum (i.e. students) in any setting

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TOM-C HF: 121 self-identified HF patients assessed in 10 community pharmacy settings

**Figure 2.** Percentage of patients reporting specific signs and symptoms of heart failure (n = 75)

Abbreviations used: SOB, shortness of breath; PND, paroxysmal nocturnal dyspnea; WT gain, weight gain >5 pounds (2.3 kg).

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**Patient Self Management – REINFORCE**

- Take medication as directed
- Follow dietary recommendations (Therapeutic Lifestyle Choices)
- Check weight daily (log) and take action **right away** when weight goes up
- Monitoring for symptoms and take action **right away** when they occur
- Report dizziness or lack of diuretic effect
- Stay active
- See doctor and pharmacist regularly
Patient Tools – Many Examples (e.g., HFSA Pt APP)

Conclusions

- Optimize guideline-recommended therapy
- Counsel patients on expected benefits and what to monitor
- Evaluate medication adherence – keep it SIMPLE
- Technology may be useful for some patients
- Assessments beyond medication adherence: Depression, cognitive function, therapeutic lifestyle
- Simple HF assessment can be performed in any setting and by any trained personnel
- Reinforce patient self-management – engage family and caregivers