Congestive Heart Failure: Update and Approach to Treatment

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ACPE Information

Target Audience: Pharmacists and Pharmacist Technicians

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Activity Type: Knowledge-based
I, Daniel Schwartz, declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.
Learning Objectives

- To better understand the principles of treating Acute and Chronic Heart Failure.

- To review new therapies in heart failure, specifically recently available medications.

- To better understand how to implement Guideline-Directed Medical Therapy (GDMT) in heart failure.
Assessment Question #1

An 82yo M with a history of hypertension, diabetes, and non-obstructive coronary artery disease who presents with 3 weeks of shortness of breath. He describes dyspnea after walking ½ block and climbing ½ flight of stairs. He has noticed some leg swelling as well. When you ask he admits he has been sleeping in his easy chair for the past week.

On exam this man has a laterally displaced PMI, a 4/6 holosystolic murmur at the apex, and he is short of breath while talking to you.

Which of the following physiologic derangements is most likely?

A. Decreased RAAS activation
B. Decreased natriuretic peptide signaling
C. Decreased vasopressin stimulation
D. Decreased sympathetic nervous tone
A 55yo man with a history of NICM, EF 25%, HTN, DM, and CKD admitted with AHF. On arrival: hypertensive and 10 kgs over usual weight. Home dose of diuretic is furosemide 40mg BID.

After 2 days of furosemide 40mg IV BID, he is less SOB but has lost only 1kg. Which of the following is the best next step?

A. Switch furosemide to bumetanide 1mg IV BID.
B. Increase furosemide to 80mg IV BID.
C. Start furosemide drip at 10mg/hour.
D. Add metolazone 5mg PO daily.
Same patient:
Now 5 days later, with escalating diuretics, his creatinine has gone from 1.6 to 2.6. His JVP is “difficult to assess” but he still has edema. Which of the following is the best next step?

A. Add nesiritide
B. Start ultrafiltration
C. Stop home ACE inhibitor
D. Add low dose dopamine
Epidemiology of HF

- >650,000 cases of HF/year
- ~6 million in US with HF
- HF is the leading cause of hospitalizations in US
- 5 year mortality 50-75%
- HF Prevalence is rising
  - Due to aging population
  - HFpEF higher vs. HFrEF
  - HFpEF is 50% of all HF cases

Heart Failure

Multiple ways to divide HF

- Systolic vs. Diastolic
- HFrEF vs. HFpEF
- Ischemic vs. Non-ischemic
- Dilated vs. Not dilated

Categories by Ejection Fraction

- **HF with preserved EF (HFpEF):** EF >50%
- **HF with reduced EF (HFrEF):** EF <40%
- HFmrEF/HFbEF: EF 40-50%
- Recovered EF

*These can overlap*
HF – Risk Factors

- Any condition that leads to an alteration in LV structure or function can predispose a patient to developing HF

- Risk factors differ for HFrEF and HFpEF, but there is overlap

- Hypertension is most common risk factor
  - Due to high prevalence
  - Contributes to the development of HF in 75% of patients

- In US, coronary artery disease (CAD) has greatest risk for HF
  - Highest hazard ratio

- In 20–30% of the cases of HFrEF, the exact etiology is not known
Assessment Question #1

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C. Decreased vasopressin stimulation
D. Decreased sympathetic nervous tone
Neurohormonal Activation

How does the body respond to decreased cardiac performance?

What drives those hemodynamic changes?

- ↑ SNS
- ↑ RAAS
- ↑ ADH/Vasopressin
- Natriuretic peptides

These mechanisms will ultimately worsen disease progression
Compensatory Mechanisms

Short-term compensatory changes can have beneficial effects (maintaining CO, BP and organ perfusion) but may have negative long-term consequences

Adaptation → Maladaptation
Therapies for chronic disease depend on

- Ejection Fraction (EF)
- ACC/AHA Stage
- NYHA Class
- Acute vs. Chronic

Remember EF Categories

- **HFpEF**: EF >50%
- **HFrEF**: EF <40%
- **HFmrEF/HFbEF**: EF 40-50%

Classification of HF

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF\textsuperscript{38}</th>
<th>NYHA Functional Classification\textsuperscript{46}</th>
</tr>
</thead>
<tbody>
<tr>
<td>A \hspace{1em} At high risk for HF but without structural heart disease or symptoms of HF</td>
<td>None</td>
</tr>
<tr>
<td>B \hspace{1em} Structural heart disease but without signs or symptoms of HF</td>
<td>I \hspace{1em} No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.</td>
</tr>
<tr>
<td>C \hspace{1em} Structural heart disease with prior or current symptoms of HF</td>
<td>I \hspace{1em} No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF. II \hspace{1em} Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF. III \hspace{1em} Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF. IV \hspace{1em} Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
<tr>
<td>D \hspace{1em} Refractory HF requiring specialized interventions</td>
<td>IV \hspace{1em} Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.</td>
</tr>
</tbody>
</table>

ACC/AHA Stage = Disease Progression

NYHA Class = Symptom Severity
ACC/AHA stages of systolic HF and treatment options

**Stage A**
- High risk with no symptoms

**Stage B**
- Structural heart disease, no symptoms

**Stage C**
- Structural disease, previous or current symptoms

**Stage D**
- Refractory symptoms requiring special intervention
  - Limited options for Stage D patients

- Hospice
- VAD, transplantation
- Inotropes
- Aldosterone antagonist, nesiritide
- Consider multidisciplinary team
- Revascularization, mitral-valve surgery
- Cardiac resynchronization if bundle-branch block present
- Dietary sodium restriction, diuretics, and digoxin
- ACE inhibitors and β-blockers in all patients
- ACE inhibitors or ARBs in all patients; β-blockers*
- Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs*
- Risk-factor reduction, patient and family education

*In appropriate patients

HF Treatment

Goals of therapy

• Improve symptoms
• Improve quality of life
• Prevent progression of LV dysfunction
  • Reverse remodeling
• Reduce hospitalization
• Reduce mortality
For HFpEF:

- Diuresis
- Blood Pressure control
- Reverse underlying cause (ischemia, arrhythmia)
- Treat comorbidities (DM, sleep apnea, obesity)

HF treatments (pharmacologic and device therapy) showing benefit for morbidity and mortality are for HFrEF, not HFpEF.
HF Treatment

For HFrEF:

**Chronic therapies** target neurohormonal pathways
- SNS
- RAAS
- NP

**Acute therapies** target hemodynamics
- Diuresis
- Vasodilators
- Inotropes (if needed)
For HFrEF:

The Classics:
• ACE inhibitor
• ARB
• Beta blocker
• Aldosterone Antagonist
• Hydralazine/Nitrate
• Digoxin

The New Kids:
• ARNI
• Ivabradine
• SGLT2 inhibitor
## ACE inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Structure</th>
<th>Patients</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>1987</td>
<td>Enalapril vs. placebo</td>
<td>n=253 NYHA IV</td>
<td>27% RRR in mortality</td>
</tr>
<tr>
<td>SOLVD</td>
<td>1991</td>
<td>Enalapril vs. placebo</td>
<td>n=2569 NYHAII-III EF≤35%</td>
<td>16% RRR in mortality 26% RRR in death or HF admission</td>
</tr>
<tr>
<td>SOLVD-Prevention</td>
<td>1992</td>
<td>Enalapril vs. placebo</td>
<td>n=4228 NYHAII EF≤35%</td>
<td>20% RRR death or hospitalization</td>
</tr>
</tbody>
</table>

Class I indication for HFrEF and current/prior symptoms

**Class effect** - all are OK
## ARB: Clinical outcomes

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Structure</th>
<th>Patients</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Val-HeFT</em></td>
<td>2001</td>
<td>Valsartan vs. placebo</td>
<td>n=5010</td>
<td>13% RRR morbidity and mortality (primarily HF admission) No difference in mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NYHA II-IV</td>
<td>EF&lt;40%</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td><em>CHARM-Added</em></td>
<td>2003</td>
<td>Candesartan vs. placebo</td>
<td>n=2548</td>
<td>15% RRR CV death and HF admission 17% RRR CV death 17% RRR HF admission No difference in all cause death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NYHA II-IV</td>
<td>EF≤ 40%</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>VALIANT</td>
<td>2003</td>
<td>Valsartan vs. captopril+valsartan vs. captopril</td>
<td>n=14703</td>
<td>No difference in all cause mortality No difference CV death, reinfarction or HF admission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post MI LVEF≤ 35</td>
<td></td>
</tr>
<tr>
<td>CHARM-Alternative</td>
<td>2004</td>
<td>Candesartan vs. placebo</td>
<td>n=2028</td>
<td>23% RRR in CV mortality or HF admission 15% RRR CV death 32% RRR HF admission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NYHA II-IV</td>
<td>EF≤ 40%</td>
</tr>
</tbody>
</table>

*On background ACE inhibitor therapy*
ARB: Clinical outcomes

All cause mortality
- No difference vs. placebo or ACE inhibitor

Heart failure hospitalizations
- No difference compared to ACE inhibitor

Class I for ARB if ACE inhibitor-intolerant
Class IIa as an alternative to ACE inhibitor
## Beta Blockers

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Structure</th>
<th>Patients</th>
<th>Survival outcomes</th>
</tr>
</thead>
</table>
| USCP      | 1996 | Carvedilol vs. placebo     | n=1094 LVEF≤35%           | 65% RRR all cause death  
                                                        |                                         | 27% RRR CV hospitalization  
                                                        |                                         | 38% RRR hospitalization or death  |
| CIBIS II  | 1999 | Bisoprolol vs. placebo     | n=2647 NYHA III-IV LVEF≤35% | 34% RRR all cause death  
                                                        |                                         | 2.7% ARR SCD                  |
| MERIT HF  | 1999 | Metoprolol succinate vs. placebo | n=3991 NYHA II-IV LVEF≤40% | 34% RRR all cause mortality  
                                                        |                                         | 41% RRR SCD                  
                                                        |                                         | 38% RRR CV death               
                                                        |                                         | 49% RRR HF death               
                                                        |                                         | 31% RRR all cause mortality of HF hospitalization |
| COPERNICUS | 2001 | Carvedilol vs. placebo     | n=2289 NYHA IV LVEF<25%   | 35% RRR all cause death  
                                                        |                                         | 24% RRR death or hospitalization |

Class I for HFrEF pts with current or prior symptoms  
**NOT a class effect:** Use carvedilol, metoprolol succinate, bisoprolol
### Aldosterone Antagonists

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Structure</th>
<th>Patients</th>
<th>Survival outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES</td>
<td>1999</td>
<td>Spironolactone vs. placebo</td>
<td>N=1663 LVEF≤35% NYHA IV</td>
<td>30% RRR death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35% RRR HF hospitalization</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>2003</td>
<td>Eplerenone vs. placebo</td>
<td>N=6632 Post MI LVEF≤40%</td>
<td>15% RRR death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17% RRR CV death</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13% RRR CV death or CV hospitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21% RRR SCD</td>
</tr>
<tr>
<td>EMPHASIS</td>
<td>2011</td>
<td>Eplerenone vs. placebo</td>
<td>N=2737 NYHA II EF≤35%</td>
<td>37% RRR CV death or HF hospitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24% RRR death from any cause</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32% RRR HF hospitalization</td>
</tr>
</tbody>
</table>

Class I for LVEF ≤ 35%, NYHA II-IV
Also decrease SCD
## Vasodilators: Hydralazine and Nitrates

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Structure</th>
<th>Patients</th>
<th>Survival outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-HEFT-I</td>
<td>1986</td>
<td>Hydralazine/nitrates vs. prazosin vs. placebo</td>
<td>n=642 LVEF&lt;45%/LVIDD&gt;2.7cm/m²</td>
<td>34% RRR death at 2 years EF improvement at 8 weeks, 1 year</td>
</tr>
<tr>
<td>V-HEFT II</td>
<td>1991</td>
<td>Hydralazine/nitrates vs. enalapril</td>
<td>n=804 LVEF&lt;45%/LVIDD&gt;2.7cm/m²</td>
<td>No difference in all cause mortality Greater EF recovery with hydralazine/nitrates</td>
</tr>
<tr>
<td>A-HEFT</td>
<td>2004</td>
<td>Hydralazine/nitrates vs. placebo</td>
<td>n=1050 AA NYHA III-IV LVEF≤35%</td>
<td>43% RRR all cause death 33% RRR HF hospitalization Significant improvement QoL</td>
</tr>
</tbody>
</table>

- **Class I indication:** self reported AA patients
  - NYHA III-IV, on beta blockers/ACE inhibitors
- **Class II indication:**
  - Patients who cannot tolerate ACE inhibitor or ARB
# Digoxin

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Structure</th>
<th>Patients</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RADIANCE</td>
<td>1993</td>
<td>Continue digoxin vs. withdrawal</td>
<td>N=178 EF≤35% NYHA II-III</td>
<td>5.9% increase in relative risk of worsening HF</td>
</tr>
<tr>
<td>Digitalis Investigation Group</td>
<td>1997</td>
<td>Digoxin vs. placebo</td>
<td>N=6800 EF≤45%</td>
<td>No difference in mortality 23% RRR hospitalization for worsening HF</td>
</tr>
</tbody>
</table>

**Class IIa indication in HFrEF to decrease hospitalizations**
## HF Treatment – Chronic

***Table. Demonstrated Benefits of Evidence-Based Therapies for Patients With Heart Failure and Reduced Ejection Fraction***

<table>
<thead>
<tr>
<th>Evidence-Based Therapy</th>
<th>Relative Risk Reduction in All-Cause Mortality in Pivotal Randomized Clinical Trial(s), %</th>
<th>NNT to Prevent All-Cause Mortality Over Time</th>
<th>NNT for All-Cause Mortalitya</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>17</td>
<td>22 over 42 mo</td>
<td>77</td>
</tr>
<tr>
<td>ARNIb</td>
<td>16 (33%)**</td>
<td>36 over 27 mo</td>
<td>80</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>34</td>
<td>28 over 12 mo</td>
<td>28</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>30</td>
<td>9 over 24 mo</td>
<td>18</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43</td>
<td>25 over 10 mo</td>
<td>21</td>
</tr>
<tr>
<td>CRT</td>
<td>36</td>
<td>12 over 24 mo</td>
<td>24</td>
</tr>
<tr>
<td>ICD</td>
<td>23</td>
<td>14 over 60 mo</td>
<td>70</td>
</tr>
</tbody>
</table>

**Compared to ACEI**

Fonarow et al. JAMA Card 2010
Target Doses for GDMT

Benefit was seen in trials at target doses

↑ benefit low dose vs. none

↑ benefit high dose vs. low dose
  ▶ Dose response may be stronger with Beta blockers (than ACEi/ARB)
## Target Doses for GDMT

**Table 1: Starting and Target Doses of Select Guideline-Directed Medical Therapy for HF (3,15)**

<table>
<thead>
<tr>
<th>Class</th>
<th>Starting dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta Blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once daily</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25 mg twice daily for weight &lt;85 kg and 50 mg twice daily for weight ≥85 kg</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5–25 mg/d</td>
<td>200 mg daily</td>
</tr>
<tr>
<td><strong>ARNI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>24/25 mg–49/51 mg twice daily</td>
<td>97/103 mg twice daily</td>
</tr>
<tr>
<td><strong>ACEI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg 3× daily</td>
<td>50 mg 3× daily</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice daily</td>
<td>10–20 mg twice daily</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–5 mg daily</td>
<td>20–40 mg daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
</tbody>
</table>

**ARB**

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>Starting dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>4–6 mg daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td>Losartan</td>
<td>25–50 mg daily</td>
<td>150 mg daily</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 mg twice daily</td>
<td>160 mg twice daily</td>
</tr>
</tbody>
</table>

**Aldosterone antagonists**

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>Starting dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eplerenone</td>
<td>25 mg daily</td>
<td>50 mg daily</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5–25 mg daily</td>
<td>25–50 mg daily</td>
</tr>
</tbody>
</table>

**Vasodilators**

<table>
<thead>
<tr>
<th>Vasoconstrictor</th>
<th>Starting dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochloride</td>
<td>25 mg 3× daily</td>
<td>75 mg 3× daily</td>
</tr>
<tr>
<td>Isosorbide dinitrate*</td>
<td>20 mg 3× daily</td>
<td>40 mg 3× daily</td>
</tr>
<tr>
<td><strong>Fixed-dose combination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate/hydralazine</td>
<td>20 mg/37.5 mg (one tab)</td>
<td>1 tab 3× daily</td>
</tr>
</tbody>
</table>

**Nitrates**

<table>
<thead>
<tr>
<th>Nitrates</th>
<th>Starting dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>2.5–5 mg twice daily</td>
<td>Titrated to heart rate 50–60 bpm. Maximum dose 7.5 mg twice daily</td>
</tr>
</tbody>
</table>

*Depens remains indicated for HF/EF, but there are no contemporary data to warrant additional comments in this document. The reader is referred to already available guideline statements (3). *Isosorbide dinitrate is not recommended by the ACC/AHA/HFSA guideline. The ACC/AHA/HFSA guideline considers either the fixed-dose combination or the separate combination of isosorbide dinitrate and hydralazine as appropriate guideline-directed therapy for HF.

Target Doses for GDMT

We do a really bad job of getting to target dose
Target Doses for GDMT

Even if SBP>110mmHg

This must be a priority

“...every contact between clinician and patient must be seen as a critical opportunity to escalate GDMT, as tolerated.”

HF Treatment – Chronic

New(er) pharmacologic agents

- Sacubitril-Valsartan
- Ivabradine
- SGLT2 inhibitors
HF Treatment – ARNI

**ARNI** = Angiotensin receptor – neprilysin inhibitor

**Sacubitril**: blocks *neprilysin*, the endopeptidase that breaks down Natriuretic Peptides → increases NP levels

Clinically given as combo with Valsartan to prevent angioedema (bradykinin/AngII effect)

---

[Diagram showing Heart Failure pathways and ARNI effects.]

PARADIGM trial

Patients with LVEF≤ 35% (<40% initially)
  ▶ NYHA II-IV (most II and III)
  ▶ Elevated BNP or NT proBNP

Compared vs Enalapril 10 mg BID

Exclusion criteria
  ▶ Hypotension
  ▶ eGFR≤30
  ▶ Hyperkalemia
  ▶ Side effects with ACE inhibitor or ARB

20% Reduction in Death & HF hospitalization

PARADIGM trial

Adverse Reactions:
ARNI led to more symptomatic hypotension

No significant difference in hyperkalemia, renal failure, angioedema
HF Treatment – ARNI

Controversies:

Superior?
- Appropriate ACE comparison dose?
- Compared to ARB instead?
- Few NYHA Class IV

When to switch?

Side effects
- Hypotension, angioedema (rare)

Cost
Ensure 36 hours off ACEI, adequate blood pressure, and eGFR ≥30 mL/min/1.73 m² before initiating sacubitril/valsartan.

Select starting dose:
See Tables 1 and 3 for dosing information

If patient is taking equivalent of ≤10 mg daily of enalapril or equivalent of ≤160 mg daily of valsartan:
24/26 mg twice daily

If patient is taking equivalent of >10 mg daily of enalapril or equivalent of >160 mg daily of valsartan:
49/51 mg twice daily

In 2–4 weeks, assess tolerability
If possible, increase dose stepwise to target of 97/103 mg twice daily
Monitor blood pressure, electrolytes, and renal function after initiation and during titration

# ACEI or ARB vs. ARNI

**What are the possible burdens or risks of each?**

<table>
<thead>
<tr>
<th>All 3 medication types can cause:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- lower blood pressure</td>
<td>- high blood potassium levels</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACEI or ARB</th>
<th>ARNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A pill taken by mouth, usually once, twice, or three times a day</td>
<td>How it is taken</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cough can occur with an ACEI</th>
<th>Risks and Side Effects</th>
<th>Dizziness is more common with an ARNI than with an ACEI</th>
</tr>
</thead>
</table>

**What are the possible benefits of each?**

A study comparing an ACEI to an ARNI in more than 8,000 adults with heart failure found:

- After two years on an **ACEI**, 80 of 100 patients were still living and 20 died.
- After two years on an **ARNI**, 83 of 100 patients were still living and 17 died.

Patients also had a 3% reduction in hospitalization, or 3 out of 100 fewer patients went to the hospital while on an ARNI.
Targeting heart rate beyond beta blockade

Inhibits If current in the sinoatrial node

No effect on contractility or conduction

Prior trials in patients with CAD

- BEAUTIFUL: patients with EF<40%
- SIGNIFY: patients without heart failure

Patients with LVEF≤35%

- HF admission within prior 12 months
- Sinus rhythm with HR≥70

Ivabradine vs placebo

Results:

- Greater decrease in HR (~10bpm)
- Reduced HF admissions, HF deaths

HF Treatment – Ivabradine

To reduce risk of HF hospitalization

Class IIa indication

- EF≤35%
- Sinus rhythm with resting HR≥70
- On maximally tolerated beta blockade

**HF Treatment – Ivabradine**

**Figure 2** Dosing Approach for Ivabradine

- **Normal Starting Dose:**
  5 mg twice daily.
  In patients with conduction defects or other patients in whom bradycardia could lead to hemodynamic compromise, initiate therapy at 2.5 mg twice daily.

- **Assess in 2-4 weeks:**

  - **If heart rate >60 bpm and well tolerated:**
    Increase each dose by 2.5 mg.

  - **If heart rate 50-60 bpm:**
    Maintain the dose.

  - **If heart rate <50 bpm or not tolerated:**
    Decrease each dose by 2.5 mg.

HF Treatment – Ivabradine

**TABLE 1** Incidence of Selected Adverse Drug Reactions Occurring on Ivabradine Versus Placebo in the SHIFT Trial

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine (n = 3,232)</th>
<th>Placebo (n = 3,260)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>2,439 (75)</td>
<td>2,423 (74)</td>
<td>0.303</td>
</tr>
<tr>
<td>Heart failure</td>
<td>804 (25)</td>
<td>937 (29)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>150 (5)</td>
<td>32 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>184 (6)</td>
<td>48 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AF</td>
<td>306 (9)</td>
<td>251 (8)</td>
<td>0.012</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>89 (3)</td>
<td>17 (1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>17 (1)</td>
<td>7 (&lt;1)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Values are n (%). Adapted with permission from Swedberg et al (9).

AF = atrial fibrillation; SHIFT = Systolic Heart failure treatment with the I1 Inhibitor ivabradine Trial.

**TABLE 2** Drugs to Avoid With Ivabradine

- Ivabradine use is avoided/contraindicated with moderate to strong CYP3A4 inhibitors, as they can result in toxicity.
- Nondihydropyridine calcium antagonists: Diltiazem, verapamil
- Macrolide antibiotics: e.g., clarithromycin, telithromycin
- Antiretroviral drugs: Nelfinavir
- Antifungal agents: e.g., ketoconazole, itraconazole
- Others: Grapefruit juice, nefazodone
- Ivabradine use should be avoided with inducers of CYP3A4, as they can lower efficacy
- St. John’s wort, rifampicin, barbiturates, and phenytoin

HF Treatment – SGLT2i

- **Empagliflozin**
- **Canagliflozin**
- **Dapagliflozin**

- Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor
- Mechanism of action: reduces reabsorption of filtered glucose from renal tubule

- Increased urinary exertion of glucose

- Weight loss ~2%
- Renal Protection

- Practical considerations:
  - UTI, candidiasis
  - Small risk of DKA
Empagliflozin vs placebo in patients with T2DM and CVD (not HF)

38% reduction in CV mortality

► No significant decrease in nonfatal MI or stroke
► 35% reduction in HF hospitalization

HF Treatment – SGLT2i

Is the patient ≥ 18 y/o and have all of the following?
• T2D*
• Established clinical ASCVD†

If yes:
Do any of the following apply to the patient?
• ESRD
• Ongoing pregnancy
• Currently breastfeeding

If yes:
Do not start SGLT2 inhibitor or GLP-1RA at this time

If no:
Insufficient evidence to recommend SGLT2 inhibitor or GLP-1RA for ASCVD risk reduction.

Consider the timing of starting a SGLT2 inhibitor or GLP-1RA (see Table 10††).

Initiate discussion incorporating patient and clinician preferences and priorities (see Table 11).

If SGLT2 inhibitor is selected (see Table 1 for dosing, Table 4 for cautions and contraindications):
Start SGLT2 inhibitor.
• Empagliflozin is currently preferred.
• For dosing, see Table 1.
• No up titration required.
• Adjust other antihyperglycemic agents as indicated**

If GLP-1RA is selected (see Table 6 for dosing, Table 8 for cautions and contraindications):
Start GLP-1RA.
• Liraglutide is currently preferred.
• For dosing, see Table 6.
• Uptitrate slowly to avoid nausea.
• Adjust other antihyperglycemic agents as indicated**

2018 ACC Expert Consensus Decision Pathway on Novel Therapies.
HF Treatment – SGLT2i

**DAPA-HF**

- Presented at ESC, Sept 2019
  - Dapagliflozin vs placebo in HF patients
  - Reduction in CV death, HF hospitalization, mortality, and QoL
  - Regardless of Diabetes

**DEFINE-HF**

- Small study, 12 weeks → Improved symptoms
- Regardless of DM

**EMPEROR-Reduced, SOLOIST-WHF** – ongoing
**HF Treatment – No No’s**

### Anticoagulation
Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke should receive chronic anticoagulant therapy.

The selection of an anticoagulant agent should be individualized.

Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without an additional risk factor for cardioembolic stroke.

**Anticoagulation is not recommended in patients with chronic HF/EF without AF, a prior thromboembolic event, or a cardioembolic source.**

### Statins
Statins are not beneficial as adjunctive therapy when prescribed solely for HF.

### Omega-3 fatty acids
Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in HF/EF or HF/EF patients.

### Other drugs
- Nutritional supplements as treatment for HF are not recommended in HF/EF.
- Hormonal therapies other than to correct deficiencies are not recommended in HF/EF.
- Drugs known to adversely affect the clinical status of patients with HF/EF are potentially harmful and should be avoided or withdrawn.
- Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation.

### Calcium channel blockers
Calcium channel-blocking drugs are not recommended as routine treatment in HF/EF.
Acute HF

Treatment
- Diuretics
- What to do with home medications
- Diuretic Resistance
- GDMT

Transitions of Care
Loop diuretics are mainstay of AHF treatment

ACEi/ARB/ARNI may be used to decrease afterload if Hypertensive or felt to need lower SVR

Chronic therapy: **ACEi/ARB/ARNI** and **BB** usually started once euvolemic (or close)

- **MRA** (spironolactone/eplerenone) usually secondary
- **Hydralazine/nitrate** if Black or contraindication to above
Assessment Question #2

A 55yo man with a history of NICM, EF 25%, HTN, DM, and CKD admitted with AHF.
On arrival: hypertensive and 10 kgs over usual weight. Home dose of diuretic is furosemide 40mg BID.
After 2 days of furosemide 40mg IV BID, he is less SOB but has lost only 1kg. Which of the following is the best next step?

A. Switch furosemide to bumetanide 1mg IV BID.
B. **Increase furosemide to 80mg IV BID.**
C. Start furosemide drip at 10mg/hour.
D. Add metolazone 5mg PO daily.
AHF – Diuretic Strategy

- **Diuretic naïve:**
  - Start ≥ 20-40mg furosemide IV or equivalent

- **Diuretic before:**
  - Start 1-2.5 times total 24-hour oral home dose (as IV)

- Double loop dose to maximum before adding thiazide

2019 ACC Expert Consensus Decision Pathway for Patients Hospitalized with Heart Failure.
Assessment Question #3

Same patient as above:
Now 5 days later, with escalating diuretics, his creatinine has gone from 1.6 to 2.6. His JVP is “difficult to assess” but he still has edema. Which of the following is the best next step?

A. Add nesiritide
B. Start ultrafiltration
C. Stop home ACE inhibitor
D. Add low dose dopamine
E. None of the above
AHF – Treatment

Same patient as above:
Now 5 days later, with escalating diuretics, his creatinine has gone from 1.6 to 2.6. His JVP is “difficult to assess” but he still has edema. Which of the following is the best next step?

A. Add nesiritide
B. Start ultrafiltration
C. Stop home ACE inhibitor
D. Add low dose dopamine

All are IIb recommendations, or worse

Consider RHC if:
- Persistent symptoms
- Filling pressures unclear
- Concern for low output
AHF – Treatment

**Not Improved/Worsening**
Inadequate decongestion with low cardiac output, worsening end-organ damage

- Consider escalation of diuretics or other decongestion strategies
- Consider hemodynamic monitoring with right heart catheterization
- Consider IV inotropes or pressors, along with IV diuretics
- Consider percutaneous or durable mechanical support devices
- Consult long term advanced treatment strategies such as cardiac transplant
- Re-evaluate comorbidities and alternative diagnoses
- Seek additional expertise, e.g. cardiology or advanced HF input; consider palliative care

2019 ACC Expert Consensus Decision Pathway for Patients Hospitalized with Heart Failure.
AHF – Treatment

• No vasoactive medications in AHF have been shown to improve outcomes
  – **Dopamine** low dose
  – **Nesiritide**
  – **Milrinone/dobutamine**
  – **Nitroprusside/nitroglycerin**

• **Ultrafiltration**
  - Safe, aids diuresis, but no significant clinical benefit, high cost

---

- Decreases SOB, no outcome benefit
- Class I for temporary support
- Limited data, useful in HTN, severe MR
When should I hold home meds?

You shouldn’t

Unless you really have to
GDMT
What to do with Home meds

• Withdrawal (BB and ACEi) leads to worse clinical outcomes

• Starting GDMT
  – well tolerated
  – more likely to be on at follow up

• Low BP and WRF are main reasons to consider holding

### AKI/WRF:
Creatinine
$\geq 0.3\text{mg/dL}$
or
$\geq 1.5\times$ increase
Is WRF actually bad?

- Decongestion likely more important than WRF
  - WRF with no congestion better than no WRF with congestion
  - Temporary WRF likely OK
- WRF is not associated with tubular injury
- WRF may do better clinically

AHF – Treatment

**IV diuretics**: equal or > home dose

**Do not stop home meds** unless unstable

---

**Table 28. Recommendations for Therapies in the Hospitalized HF Patient**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF patients hospitalized with fluid overload should be treated with intravenous diuretics</td>
<td>I</td>
<td>B</td>
<td>737,738</td>
</tr>
<tr>
<td>HF patients receiving loop diuretic therapy should receive an initial parenteral dose greater than or equal to their chronic oral daily dose; then dose should be serially adjusted</td>
<td>I</td>
<td>B</td>
<td>739</td>
</tr>
<tr>
<td>HF/EF patients requiring HF hospitalization on GDMT should continue GDMT except in cases of hemodynamic instability or where contraindicated</td>
<td>I</td>
<td>B</td>
<td>195,735,736</td>
</tr>
<tr>
<td>Initiation of beta-blocker therapy at a low dose is recommended after optimization of volume status and discontinuation of intravenous agents</td>
<td>I</td>
<td>B</td>
<td>195,735,736</td>
</tr>
<tr>
<td>Thrombosis/thromboembolism prophylaxis is recommended for patients hospitalized with HF</td>
<td>I</td>
<td>B</td>
<td>21,770–774</td>
</tr>
<tr>
<td>Serum electrolytes, urea nitrogen, and creatinine should be measured during titration of HF medications, including diuretics</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ARNI for Acute HF

- **PIONEER-HF**
- Sacubitril-valsartan vs. enalapril in Acute HFrEF
  - SBP>100
  - Stable diuretics
  - No IV vasodilators w/in 6 hrs
  - No inotropes w/in 24 hrs

  - BNP lower
  - Safe
  - Signal of improved clinical outcomes
  - 20% in both arms discontinued by 8 weeks

ACC Expert Consensus Decision Pathway for Hosp HF, 2019
AHF – Treatment

Once out of AHF:
Guideline directed medical therapy
Almost all patients will be Stage C
Close follow up
Good Transitions of Care
Take Aways

HF therapies guided by EF, NYHA Class, ACC/AHA Stage and Acuity
Chronic HF therapy targets Neurohormonal axes, Acute HF targets hemodynamics

Chronic HF
- Get to target doses of GDMT
- Expanding role for ARNIs, SGLT2i

Acute HF
- Loop diuretics are mainstay of treatment
- Maintain home GDMT if possible
- Try to start GDMT before discharge

Always feel free to call your friendly neighborhood Heart Failure Specialist
Thank you