Solving the Revolving Door
Managing Heart Failure at Transitions of Care and Beyond

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Disclosures

I have no relevant personal or financial relationships to disclose.
Learning Objectives

1. Design a strategy for relieving ADHF symptoms and managing GDMT being taken prior to admission.

2. Given a patient failing to meet decongestion goals, determine etiologies of diuretic resistance and design a modified strategy.

3. Given a patient preparing for discharge, design a strategy for reducing risk of readmission, including initiation/titration of GDMT.

4. Given a patient with chronic heart failure and a history of hospitalization, list strategies for optimizing GDMT.

ADHF acute decompensated heart failure, GDMT guideline-directed medical therapy
Transitions: Scope of the Problem

- Medication-related problems contribute to a significant number of ADHF admissions
- Up to two-thirds are preventable

- 1 in 4 patients is readmitted within 30 days and nearly half are readmitted within 6 months
- Pharmacists can to reduce readmissions by 1/3 to nearly 1/2

CB is a 62 year-old white woman with nonischemic cardiomyopathy (EF 25%), diabetes mellitus, and osteoarthritis who presents to the emergency department with fatigue, shortness of breath, and abdominal discomfort of several weeks’ duration. She reports her heart failure always seems to get worse after her arthritis acts up. Her breathing effort is labored and she has bilateral crackles over two-thirds the height of the lung fields. Other findings include 2+ lower extremity edema and 10-kg weight gain. She is warm and well-perfused.

Medications Listed in EMR:
• Atorvastatin 40 mg daily
• Lisinopril 10 mg daily
• Metoprolol succinate 100 mg daily
• Spironolactone 25 mg once daily
• Furosemide 40 mg twice daily
• Metformin 1000 mg twice daily
• Insulin glargine 25 units subq at night

Vitals: BP 118/78 mmHg, HR 71 bpm

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<td>134</td>
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Hemoglobin A1c: 8.5%
NT-proBNP 12,800 pg/mL
Chest x-ray: cardiomegaly, bilateral interstitial/alveolar edema; no effusions

EF ejection fraction, EMR electronic medical record, NT-proBNP N-terminal pro-B-type natriuretic peptide
Questions

1. What factor(s) may have precipitated her ADHF?
2. How should her congestive symptoms be managed? (Provide recommendations regarding drug, dose, and frequency).
3. What should be done with her other GDMT?

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EF ejection fraction, EMR electronic medical record, NT-proBNP N-terminal pro-B-type natriuretic peptide
Medication reconciliation can identify drug-related causes of ADHF

- Most patients with heart failure have > 5 comorbidities and take > 6 chronic medications\(^1\)
- Use of nonprescription medications may be as high as 93\(^2\)
- Nonadherence remains a major contributor to decompensation

COPD chronic obstructive pulmonary disease.
Impaired Diuretic Response

Questions

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2. How should her congestive symptoms be managed? (Provide recommendations regarding drug, dose, and frequency).

ADHF acute decompensated heart failure, GDMT guideline-directed medical therapy
Acute Diuretic Response

Effects of Furosemide Over Time

- Preload
- Urine Output

Door-to-Furosemide Time

> 1 hour associated with 3-fold increase in mortality (6.0 vs. 2.3%, p=0.002)

References:

DOSE Trial

308 patients with ADHF randomized

High vs. Low-Dose
(1x home dose vs. 2.5x home dose)

Bolus vs. Infusion
(q12 hour bolus vs. continuous infusion)

Adjust at 48 hours per clinician discretion

Change to oral therapy

Continue regimen

Intensify regimen

Assess safety/efficacy outcomes at 72 hour

ADHF acute decompensated heart failure, IV intravenous, WRF worsening renal function

DOSE In Detail

High Dose
- Greater net fluid loss
- Greater weight loss
- More symptomatic relief

Low Dose
- Less transient worsening of renal function

- Low-dose less likely to be transitioned to oral diuretics and more likely to require a dose increase at 48 hours\(^1\)
- *Transient* worsening of renal function in ADHF no worse than no change\(^2\)

ADHF acute decompensated heart failure
DOSE In Detail

Intravenous Bolus

Continuous Infusion

• Continuous infusion arm did not receive an initial bolus
• Bolus arm twice as likely to receive a dose increase and/or thiazide-type diuretic\(^1\)
• Prior trials have shown greater fluid and weight loss with continuous infusions\(^2\)
• Did not include patients with diuretic resistance

BONUS Question

Would your recommendations for the management of congestion change if this patient had HFpEF rather than HFrEF? Why or why not?
What About HFpEF? (ROPA-DOP<sup>1</sup>)

<table>
<thead>
<tr>
<th>Outcome at 72 hours</th>
<th>Intermittent Bolus (n=43)</th>
<th>Continuous Infusion (n=47)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent increase in SCr (%)</td>
<td>4.6% (-1.2 to 10.4)</td>
<td>16.0% (8.6% to 23.5%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>5 (11.6%)</td>
<td>17 (36.2%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Urine output (L)</td>
<td>10.3 (9.2 to 11.4)</td>
<td>10.7 (9.3 to 12.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>-3.3 (-4.4 to -2.2)</td>
<td>-4.2 (-6.4 to -2.0)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

No information provided on initial doses, dose changes, or other volume management strategies (all left to clinician discretion)<sup>2</sup>

SCr serum creatinine
(1) *JACC Heart Fail* 2018;6(10):859-870. (2) *JACC Heart Fail* 2018;6(12):1049-1050.
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ADHF acute decompensated heart failure, GDMT guideline-directed medical therapy
**RAAS Inhibitors**

ACE inhibitor

RAAS Activation

- Increased vasoconstriction
- Increased volume retention
- Increased hypertrophy
- Increased fibrosis

Holding ACE inhibitor may increase length of stay (5.5 vs. 3.0 days, p=0.009)?

ACE angiotensin-converting enzyme, RAAS renin-angiotensin-aldosterone system

• In OPTIMIZE-HF, beta blocker continuation was associated with lower risk of death (HR 0.60, 95% CI 0.37-0.99, p=0.044)\(^1\)

• Confirmed in B-CONVINCED, which showed no worsening of ADHF with continuation during hospitalization\(^2\)

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## Considerations for Discontinuing GDMT

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Scenarios in Which Discontinuation May Be Considered</th>
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</thead>
<tbody>
<tr>
<td>ACE inhibitors, ARBs, or ARNI</td>
<td>Worsening SCr due to recent initiation or titration, symptomatic hypotension, severe hyperkalemia (&gt; 5.5 mEq/L)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>ADHF due to recent initiation or titration, worsening low output or cardiogenic shock, symptomatic hypotension or bradycardia</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>Worsening SCr, severe hyperkalemia (&gt; 5.5 mEq/L)</td>
</tr>
<tr>
<td>Nitrates/hydralazine</td>
<td>Symptomatic hypotension</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Contraindicated in ADHF per labeling</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Symptomatic bradycardia, life-threatening arrhythmias, elevated serum concentration (&gt;&gt; 1.0 ng/mL), signs/symptoms of toxicity</td>
</tr>
</tbody>
</table>

ADHF acute decompensated heart failure, ACE angiotensin-converting enzyme, ARB angiotensin II receptor blocker, ARNI angiotensin receptor neprilysin inhibitor, GDMT guideline-directed medical therapy, SCr serum creatinine,
CB experiences some minor improvements in congestive symptoms but she fails to meet goal diuresis for two consecutive days (goal 2-3 L net negative per day, but less than 2 L negative total for the past 48 hours). She reports ongoing dyspnea when laying flat as well as abdominal discomfort, which is only partially relieved by antiemetics.

Medication changes from admission:
• Beta blocker held (over weekend, before you could intervene)
• Furosemide 120 mg IV BID
• Insulin aspart sliding scale ACHS
• Metformin being held

Vitals: BP 112/72 mmHg, HR 74 bpm

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<td>94</td>
<td>24</td>
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<tr>
<td>3.8</td>
<td>28</td>
<td>1.4</td>
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<tr>
<td>118</td>
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Admission Values (For Reference)

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ACHS prior to meals and at bedtime, BID twice daily
Questions

5. What mechanisms might explain diuretic resistance?
6. What should be done to augment diuresis at this time? Provide recommendations regarding drug, dose, and frequency for at least two pharmacologic options.
Questions

5. What mechanisms might explain diuretic resistance?
Common Mechanisms of Diuretic Resistance

- Decreased gut absorption and/or renal perfusion
- Remodeling of the nephron
- Compensatory sodium reabsorption
- Neurohormonal activation

Deviations include:
- Renin-angiotensin-aldosterone system
- Arginine vasopressin

Structures highlighted:
- Glomerulus
- Loop of Henle
- Proximal convoluted tubule
- Distal convoluted tubule
- Collecting duct
Questions

5. What mechanisms might explain diuretic resistance?

6. What should be done to augment diuresis at this time? Provide recommendations regarding drug, dose, and frequency for at least two pharmacologic options.
What Works?
Augmenting Diuretics: Increasing Dose

- Optimize dose before increasing frequency
- Safe and efficacious per DOSE trial

**Diuretic threshold:** concentration that must be achieved to elicit a response

**Ceiling dose:** Higher doses do not elicit an additional response

Transition to Continuous Infusion

Trials other than DOSE:
- Increased total and net UOP
- No differences in ADRs
- Shorter length of stay?

Diuretic threshold

Bolus doses at initiation and with dose increases

Continuous infusion

Continuous Infusions

**Advantages**
- Can achieve higher total daily doses than boluses
- Avoids off-diuretic periods
- May be advantageous in specific populations (e.g., preload-dependent conditions, delayed transcapillary refill)

**Disadvantages**
- May encourage “set it and forget it” mentality
- Overnight urination (fall risk, decreased sleep quality)
- Drug mismanagement (omitting boluses, “titrate” orders)
Add a Thiazide-Type Diuretic

<table>
<thead>
<tr>
<th>Agent</th>
<th>Metolazone</th>
<th>Chlorothiazide</th>
<th>Hydrochlorothiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral bioavailability</td>
<td>40-65%</td>
<td>N/A</td>
<td>65-75%</td>
</tr>
<tr>
<td>Usual dose (max/day)</td>
<td>2.5–5 mg qday (20 mg)</td>
<td>500–1000 mg qday to bid (2000 mg)</td>
<td>25–50 mg qday to bid (100 mg)</td>
</tr>
<tr>
<td>Onset (peak)</td>
<td>2–3 h (6–8 h)</td>
<td>2 h (3–6 h)</td>
<td>2 h (3–6 h)</td>
</tr>
<tr>
<td>Duration of action</td>
<td>12–24 h</td>
<td>6–12 h</td>
<td>6–12 h</td>
</tr>
</tbody>
</table>
Add a Thiazide-Type Diuretic

Summary of Studies in ADHF$^{1-3}$

- HCTZ < chlorothiazide
- Chlorothiazide ≈ metolazone

ADHF acute decompensated heart failure, CTZ chlorothiazide, HCTZ hydrochlorothiazide, MTZ metolazone

What Maybe Works?

Strategies to consider in *select* patients.
Theoretical Benefits of Adding Vasodilators

Venous Vasodilation
- Increased venous capacitance
- Decongests kidneys

Nitroglycerin*
Nitroprusside

Arterial Vasodilation
- Improved renal blood flow due to reduced arterial impedance

Associated with improvements in some but not all congestive symptoms and cardiac filling pressures, but...

*At high-doses (> 100 mcg/min), nitroglycerin exerts venous and arterial dilating effects. *JAMA*. 2002 Mar 27;287(12):1531–40.
**Actual Benefits of Adding Vasodilators?**

ASCEND (Nesiritide)\(^1\)
Dyspnea at 6 hours
(p = NS)

- Placebo (n=3444)
- Nesiritide (n=3416)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Placebo</th>
<th>Nesiritide</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least moderately better</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Minimally better</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>No change</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>Worse</td>
<td>20%</td>
<td>5%</td>
</tr>
</tbody>
</table>

TRUE-AHF (Ularitide)\(^2\)
Persistent Heart Failure
(p = 0.63)

- Ularitide
- Placebo

<table>
<thead>
<tr>
<th>In-Hospital Events</th>
<th>6</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ularitide</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Placebo</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

*Assessed congestive symptoms, not urine output.

Heterogeneity in Recent Vasodilator Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Agent</th>
<th>Patients</th>
<th>Mean EF</th>
<th>Patients with HFpEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCEND-HF¹</td>
<td>2011</td>
<td>Nesiritide</td>
<td>7147</td>
<td>NR</td>
<td>19.9%</td>
</tr>
<tr>
<td>RELAX-AHF²</td>
<td>2012</td>
<td>Serelaxin</td>
<td>1161</td>
<td>38.7%</td>
<td>45.0%</td>
</tr>
<tr>
<td>ROSE-AHF³</td>
<td>2013</td>
<td>Dopamine / nesiritide</td>
<td>360</td>
<td>31.6%</td>
<td>24.4%</td>
</tr>
<tr>
<td>TRUE-AHF⁴</td>
<td>2017</td>
<td>Ularitide</td>
<td>2157</td>
<td>NR</td>
<td>34.8%</td>
</tr>
</tbody>
</table>

Reasonable to consider in HFrEF with refractory congestion (despite optimizing diuretics) and normal to elevated blood pressures.

Adding Tolvaptan

- Improved weight and fluid loss but not symptoms
- Increased risk of transient WRF
- 48 hours of therapy: $1200
- Alternative cost-effective options for hyponatremia exist (furosemide plus hypertonic saline)²⁻⁴

TACTICS-HF (Tolvaptan)¹
Dyspnea Improvement at 24 h (p=0.32)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Placebo</th>
<th>Tolvaptan</th>
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<tbody>
<tr>
<td>20%</td>
<td></td>
<td>16%</td>
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Adding or Substituting Ultrafiltration

**UNLOAD**

**Weight Loss and Dyspnea Scores**
- Weight Loss (kg): Ultrafiltration 5.0 vs. Standard care 3.1 kg (p=0.001)
- Dyspnea Score: Ultrafiltration 6.4 vs. Standard care 6.1 (p=0.35)

(Also reduced rehospitalizations at 90 days, p = 0.022)

**CARRESS-HF**

**Changes in Serum Creatinine**
- Primary: change at 96 hours, Ultrafiltration -0.04 vs. Pharmacologic +0.23 (p=0.003)
- More serious adverse events in ultrafiltration group, p = 0.03

Why the discrepancy?

### CARRESS-HF Design

Patients with ADHF and renal impairment randomized

Hypothesis 2) Stepped therapy group likely unmasked patients with low output by 48 hours

<table>
<thead>
<tr>
<th>Home Dose</th>
<th>Furosemide Starting Dose</th>
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<tbody>
<tr>
<td>≤ 80 mg</td>
<td>40 mg IVB, then 5 mg/h</td>
</tr>
<tr>
<td>81-160 mg</td>
<td>80 mg IVB, then 10 mg/h + MTZ 5 mg</td>
</tr>
<tr>
<td>161-240 mg</td>
<td>80 mg IVB, then 20 mg/h + MTZ 5 mg BID</td>
</tr>
<tr>
<td>&gt; 240 mg</td>
<td>80 mg IVB, then 30 mg/h + MTZ 5 mg BID</td>
</tr>
</tbody>
</table>

If patient fails to meet urine output goals:
1. At 24 hours, advance diuretics
2. At 48 hours, Step 1 and consider vasodilators/inotropes
3. At 72-96 hours, Step 1-2 and consider hemodynamic guided-therapy ± MCS

Hypothesis 1) Constant ultrafiltration rate likely disrupted renal counter-regulation

Ultrafiltration 200 mL/h for 96 hours

or

Patients with ADHF and renal impairment randomized

Hypothesis 2) Stepped therapy group likely unmasked patients with low output by 48 hours

ADHF acute decompensated heart failure, IVB intravenous bolus, MCS mechanical circulatory support, MTZ metolazone

*JAMA. 2013 Dec 18;310(23):2533-43.*
If you’re thinking about therapies in the “What Maybe Works” category, it’s probably time to investigate further for low output if you haven’t already.
What Doesn’t Work

Don’t do these things.
## Switching IV Furosemide to IV Bumetanide

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Dose Equivalence</th>
<th>Usual Bolus Doses (max)</th>
<th>Usual Infusion Doses (max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>5 min</td>
<td>2 h</td>
<td>4-6 h</td>
<td>20-40 mg</td>
<td>40-160 mg qday to tid (200 mg/dose)</td>
<td>5-20 mg/h (40 mg/h)</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>2-3 min</td>
<td>1-2 h</td>
<td>4-6 h</td>
<td>1 mg</td>
<td>0.5-4 mg qday to tid (5 mg/dose)</td>
<td>0.5-2 mg/h (4 mg/h)</td>
</tr>
</tbody>
</table>

- No differences in efficacy when used at equivalent doses
- Higher risk of ototoxicity with furosemide, higher risk of musculoskeletal toxicity with bumetanide
High-Dose Spironolactone (ATHENA-HF)

• Patients with ADHF receiving spironolactone 12.5-25 mg randomized to continuation vs. increasing dose to 100 mg
• No differences in congestive endpoints (NT-proBNP or dyspnea scores), urine output, or weight change

ADHF acute decompensated heart failure, NT-proBNP n-terminal pro-brain natriuretic peptide
JAMA Cardiol. 2017 Sep 1;2(9):950–8.
Low-Dose Dopamine (ROSE)\(^1\)

<table>
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<th>Outcome</th>
<th>Placebo</th>
<th>Dopamine</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative urine output</td>
<td>8296</td>
<td>8524</td>
<td>0.59</td>
</tr>
<tr>
<td>Change in cystatin C</td>
<td>0.11</td>
<td>0.12</td>
<td>0.72</td>
</tr>
<tr>
<td>Patient-reported symptoms (AUC)</td>
<td>4704</td>
<td>4553</td>
<td>0.43</td>
</tr>
<tr>
<td>Drug discontinued due to tachycardia</td>
<td>0.9%</td>
<td>7.2%</td>
<td>&lt; 0.001</td>
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</tbody>
</table>

Corroborating results from DAD-II and ROPA-DOP suggest that low-dose dopamine (2-3 mcg/kg/min) does not have renoprotective effects.\(^2-3\)

After a week of aggressive decongestion therapies, CB’s symptoms have significantly improved. She has been successfully weaned from non-diuretic therapies and is approaching her baseline weight. The team plans to send her home in the next several days and is preparing a discharge plan. Numerous changes have been made to her medication regimen during the hospitalization.

**Current medications:**
- Aspirin 81 mg daily
- Atorvastatin 40 mg daily
- Isosorbide dinitrate 20 mg TID
- Hydralazine 50 mg TID
- Spironolactone 25 mg once daily
- Furosemide 80 mg IV once daily
- Insulin glargine 40 units subq at night
- Insulin aspart sliding scale ACHS

**Vitals:** BP 114/80 mmHg, HR 78 bpm

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<td>96</td>
<td>24</td>
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Questions

7. What changes to this patient’s medication regimen should be considered as she approaches discharge?

8. What non-pharmacologic strategies might also reduce her risk of readmission?
Questions

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- Aspirin 81 mg daily
- Atorvastatin 40 mg daily
- Isosorbide dinitrate 20 mg TID
- Hydralazine 50 mg TID
- Spironolactone 25 mg once daily
- Furosemide 80 mg IV once daily
- Insulin glargine 40 units subq at night
- Insulin aspart sliding scale ACHS

Vitals: BP 114/80 mmHg, HR 78 bpm

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>96</td>
<td>24</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>4.3</td>
<td>24</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Transitioning Diuretic Therapy

Observing Patients on Oral Diuretics Prior to Discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>&lt; 24 hour (n=61)</th>
<th>≥ 24 hour (n=62)</th>
<th>p (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day heart failure readmission</td>
<td>11 (18%)</td>
<td>2 (3.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60-day heart failure readmission</td>
<td>18 (29.5%)</td>
<td>6 (9.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90-day heart failure readmission</td>
<td>23 (37.7%)</td>
<td>12 (19.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any heart failure readmission</td>
<td>34 (55.7%)</td>
<td>23 (37.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Patients were being discharged from cardiology services, questioning the “patients we know well” concept.

## Ambulatory IV Diuretic Clinic

### Example Protocol in Patients with Worsening Congestion (n=60)

<table>
<thead>
<tr>
<th>Category</th>
<th>Maintenance Diuretic (mg/day)</th>
<th>IV Bolus (mg)</th>
<th>IV Infusion (mg/hr x 3hr)</th>
<th>Optional (Inadequate UOP at 90 mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>≤ 40</td>
<td>20</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Medium dose</td>
<td>41-160</td>
<td>Equivalent of maintenance dose</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>High dose</td>
<td>161-300</td>
<td>200</td>
<td>20</td>
<td>Extra 200 mg dose</td>
</tr>
<tr>
<td>Mega dose</td>
<td>≥ 301</td>
<td>200</td>
<td>20</td>
<td>Extra 200 mg dose plus thiazide-type diuretic</td>
</tr>
</tbody>
</table>

- Median UOP 1.1 (0.6-1.4) L; only 8.9% transient WRF, 3.5% hypokalemia
- Hospitalization “imminent” for 52.8%, but only 31.7% had to be hospitalized

IV intravenous, WRF worsening renal function, UOP urine output
Isosorbide dinitrate/hydralazine

• Continue combination therapy?
• Switch back to lisinopril 10 mg once daily?
• Initiate sacubitril/valsartan?
# PARADIGM-HF: ARNI in Chronic HF

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NYHA Class II-IV symptoms</td>
<td>• Symptomatic hypotension</td>
</tr>
<tr>
<td>• Ejection fraction ≤ 35%</td>
<td>• Blood pressure &lt; 100/95 mmHg</td>
</tr>
<tr>
<td>• NT-proBNP &gt; 600 pg/mL or &gt; 400 if hospitalized in the last 12 months</td>
<td>• GFR &lt; 30 mL/min</td>
</tr>
<tr>
<td>• Enalapril equivalent ≥ 10 mg/day</td>
<td>• Serum potassium ≥ 5.4 mEq/L</td>
</tr>
<tr>
<td></td>
<td>• Unacceptable side effects</td>
</tr>
</tbody>
</table>

PARADIGM-HF Results

**Primary Composite Endpoint**
- NNT = 22

**Death from Cardiovascular Causes Alone**
- NNT = 32

**Safety of sacubitril/valsartan vs. enalapril**: higher rates of hypotension but lower rates of acute kidney injury and hyperkalemia

# PIONEER-HF: ARNI in ADHF

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Notable Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HFrEF (EF ≤ 40%) with ADHF</td>
<td>• Angioedema with ACEi/ARB</td>
</tr>
<tr>
<td>• BNP ≥ 400 or NT-proBNP ≥ 1600 pg/mL</td>
<td>• Estimated GFR &lt; 30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>• Signs/symptoms of volume overload</td>
<td>• Potassium &gt; 5.2 mEq/L</td>
</tr>
<tr>
<td>• SBP ≥ 100 mmHg for 6 hours</td>
<td></td>
</tr>
<tr>
<td>• No escalation of diuretics or use of vasodilators in prior 6 hours, or</td>
<td></td>
</tr>
<tr>
<td>inotropes in prior 24 hours</td>
<td></td>
</tr>
</tbody>
</table>

**SBP 100–119 mmHg**: sacubitril/valsartan 24/26 mg or enalapril 2.5 mg twice daily

**SBP > 120 mmHg**: sacubitril/valsartan 49/51 mg or enalapril 5 mg twice daily

PIONEER-HF Results

- **NT-proBNP (Primary Endpoint)**
  - Change in NT-proBNP from Baseline (%)
  - Weeks since Randomization
  - p < 0.001

- **Serum Creatinine**
  - Mean Serum Creatinine (mg/dL)
  - Weeks since Randomization

- **Potassium**
  - Mean Serum Potassium (mEq/L)
  - Weeks since Randomization

- **Systolic Blood Pressure**
  - Mean Systolic Blood Pressure (mmHg)
  - Weeks since Randomization
  - p = 0.0047

Aspirin for Primary Prevention

**ASCEND Trial**¹ (15,480 patients with diabetes)
- 1.1% reduction in cardiovascular events (p = 0.01)
- 0.9% increase in major bleeding events (p = 0.003)

**ARRIVE Trial**² (12,546 patients at low to moderate cardiovascular risk)
- 0.2% reduction in cardiovascular events (p = 0.60)
- 0.5% increase in gastrointestinal bleeding (p = 0.0007)

**ASPREE Trial**³ (19,114 patients who were aged 70 years or older)
- 0.6 Fewer vascular events per 1000 PY (p = NS)
- 2.4 more bleeding events per 1000 PY (p < 0.001)

Other Medication Adjustments

• How to resume beta blocker?
• What about diabetes medications?
## Beta Blocker Initiation

<table>
<thead>
<tr>
<th>Beta Blocker (Trial)</th>
<th>Initial Dose</th>
<th>Titration Scheme</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol (CIBIS II¹)</td>
<td>1.25 mg once daily</td>
<td>Increase by 1.25 mg every week until 5 mg, then 2.5 mg every 4 weeks</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>Carvedilol (COPERNICUS², US Carvedilol Trial³)</td>
<td>3.125-6.25 mg twice daily*</td>
<td>Double every 2 weeks</td>
<td>25 mg twice daily (50 mg if &gt; 85 kg)</td>
</tr>
<tr>
<td>Metoprolol succinate (MERIT-HF⁴)</td>
<td>12.5-25 mg once daily*</td>
<td>Double every 2 weeks</td>
<td>200 mg once daily</td>
</tr>
</tbody>
</table>

Pre-discharge initiation as late as 12 hours prior to departure shown to be safe.⁵

*Lower starting doses used in patients with New York Heart Association III to IV heart failure

Patients with Event (%)

**EMPA-REG OUTCOME**
Hospitalization for Heart Failure

- Hazard ratio 0.65 (95% CI 0.50-0.85)
p=0.002

- Empagliflozin also associated with reduction in cardiovascular death (3.7% vs. 5.9%, p<0.001)
- Patients may require reduction in diuretic dose

SGLT2 sodium-glucose cotransporter-2.
Questions

7. What changes to this patient’s medication regimen should be considered as she approaches discharge?

8. What non-pharmacologic strategies might also reduce her risk of readmission?
Pharmacist Education

- Pharmacist-provided patient education associated with > 40% reduction in readmissions across several trials\(^1,2\)
- Largest trial (PILL-CVD) did not impact readmissions but compared individualized to standardized education\(^3\)
- A single session at discharge unlikely to reduce readmissions significantly

Improving Medication Adherence

• Medication adherence remains a major contributor to readmissions
• Pharmacists improve adherence rates, which have been associated with reductions in readmission of 19-43%\textsuperscript{1-3}
• Benefits greatest with longitudinal programs vs. single intervention
Example Adherence-Improvement Strategies

• Simplifying complex regimens (e.g., less frequently dosed medications, reducing unnecessary polypharmacy)
• Individualized education (e.g., adjusting diuretic based on weight)
• Improving medication-taking behavior (e.g., pillboxes, alerts, integrating medications into daily routines)
• Referral to pharmacist-managed bridge clinic\(^1\)
• Improving access by identifying lower cost alternatives

Improving Access

• Financial limitations remain a major barrier
• Even within the same geographic area, 75-fold variability in cost has been observed
• Made more challenging by the fragmented ways in which health care is paid for
• Using pharmacists to improve medication access requires a committed outpatient/retail pharmacy team

The price for 30 days of generic digoxin ranged from $4 to $306 across the St. Louis area

Transitions of Care Clinics

• Many of these interventions are best implemented longitudinally rather than one-and-done at hospital discharge

• A growing number of heart failure clinics are integrating pharmacists, where reductions in readmissions of 20-78% have been observed

CB presents to your clinic for 4-week follow-up after being initially seen in bridge clinic one week after discharge. She reports being able to complete her activities of daily living without becoming fatigued or short of breath, but she does have to stop and catch her breath when carrying laundry from the basement to her bedroom on the second floor. She has trace to 1+ lower extremity edema and her weight is down approximately 2 kg since discharge. She brought all of her medication bottles as instructed.

Current medications:
- Atorvastatin 40 mg daily
- Sacubitril/valsartan 49/51 mg twice daily
- Metoprolol succinate 50 mg daily
- Spironolactone 25 mg once daily
- Furosemide 20 mg once daily
- Metformin 1000 mg twice daily
- Empagliflozin 10 mg once daily
- Insulin glargine 10 units subq at night

Vitals: BP 126/82 mmHg, HR 74 bpm

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>102</td>
<td>18</td>
<td>98</td>
</tr>
<tr>
<td>4.2</td>
<td>24</td>
<td>1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Hemoglobin A1c: 8.0% (↓8.5%)
NT-proBNP: 780 pg/mL (↓12,800)

NT-proBNP N-terminal pro-B-type natriuretic peptide
Questions

9. What additional changes to her GDMT should be made to improve her outcomes related to heart failure?

More specifically:
• Should we increase ARNI, beta blocker, or both?
• Should we add ivabradine or digoxin?
Increase sacubitril/valsartan?

*Dose-related differences in hospitalizations but not mortality with ACEi and ARBs:*

**ATLAS Trial**

- **Low-dose lisinopril** vs. **High-dose lisinopril**
  - HR = 0.88 (95% CI 0.82-0.96)
  - p = 0.002

**HEAAL Trial**

- **Low-dose losartan** vs. **High-dose losartan**
  - HR = 0.90 (95% CI 0.82-0.99)
  - p = 0.027

---

ACEi angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker, CI confidence interval, HR hazard ratio

Increase beta blocker?

_Dose-related differences in ejection fraction and survival with beta blockers_

*Placebo

<table>
<thead>
<tr>
<th>Carvedilol Dose*</th>
<th>Change in EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
</tr>
<tr>
<td>6.25 mg</td>
<td>1</td>
</tr>
<tr>
<td>12.5 mg</td>
<td>2</td>
</tr>
<tr>
<td>25 mg</td>
<td>3</td>
</tr>
</tbody>
</table>

*Carvedilol Dose*

<table>
<thead>
<tr>
<th>Carvedilol Dose*</th>
<th>Ejection Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
</tr>
<tr>
<td>6.25 mg</td>
<td>1</td>
</tr>
<tr>
<td>12.5 mg</td>
<td>2</td>
</tr>
<tr>
<td>25 mg</td>
<td>3</td>
</tr>
</tbody>
</table>

*Hospitalizations*

<table>
<thead>
<tr>
<th>Carvedilol Dose*</th>
<th>Mean Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.4</td>
</tr>
<tr>
<td>6.25 mg</td>
<td>0.3</td>
</tr>
<tr>
<td>12.5 mg</td>
<td>0.2</td>
</tr>
<tr>
<td>25 mg</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Placebo

<table>
<thead>
<tr>
<th>Carvedilol Dose*</th>
<th>Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.25 mg</td>
</tr>
<tr>
<td>6.25 mg</td>
<td>12.5 mg</td>
</tr>
<tr>
<td>12.5 mg</td>
<td>25 mg</td>
</tr>
</tbody>
</table>

*Mean Number

<table>
<thead>
<tr>
<th>Carvedilol Dose*</th>
<th>Mean Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6</td>
</tr>
<tr>
<td>6.25 mg</td>
<td>1</td>
</tr>
<tr>
<td>12.5 mg</td>
<td>0</td>
</tr>
<tr>
<td>25 mg</td>
<td>0</td>
</tr>
</tbody>
</table>

*Mortality*

<table>
<thead>
<tr>
<th>Carvedilol Dose*</th>
<th>6-Month Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>16%</td>
</tr>
<tr>
<td>6.25 mg</td>
<td>14%</td>
</tr>
<tr>
<td>12.5 mg</td>
<td>12%</td>
</tr>
<tr>
<td>25 mg</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Doses listed were administered twice daily

_Circulation_. 1996 Dec 1;94(11):2807-16.
SHIFT: Initiate Ivabradine?

Inclusions

- Stable heart failure (EF ≤ 35%)
- Sinus rhythm
- Resting heart rate ≥ 70 bpm
- Hospitalization for heart failure within prior 12 months

Relevant Exclusions

- Recent myocardial infarction
- Atrial fibrillation or flutter
- Symptomatic hypotension

Therapy was titrated every two weeks to a maximum of 7.5 mg twice daily to achieve a resting heart rate of 60-70 bpm.

EF ejection fraction

Ivabradine: SHIFT Revisited

Primary endpoint driven by differences in heart failure hospitalizations (not survival)

CI confidence interval, HR hazard ratio, NNT number needed-to-treat
Adapted from Lancet. 2010 Sep 11;376(9744):875-85.
### SHIFT in Detail

<table>
<thead>
<tr>
<th>Baseline Characteristic (Select)</th>
<th>Placebo (n=3264)</th>
<th>Ivabradine (n=3241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>80.1 ± 9.8</td>
<td>79.7 ± 9.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121.4 ± 15.9</td>
<td>122.0 ± 16.1</td>
</tr>
<tr>
<td>Patients receiving a beta blocker (%)</td>
<td>2923 (90%)</td>
<td>2897 (89%)</td>
</tr>
<tr>
<td>Patients at target dose of beta blocker</td>
<td>745 (26%)</td>
<td>743 (26%)</td>
</tr>
<tr>
<td>Patients at ≥ 50% target dose beta blocker</td>
<td>1600 (56%)</td>
<td>1581 (56%)</td>
</tr>
</tbody>
</table>

### SHIFT in Detail

<table>
<thead>
<tr>
<th>Baseline Characteristic (Select)</th>
<th>Placebo (n=3264)</th>
<th>Ivabradine (n=3241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to reach target - hypotension</td>
<td>952 (45%)</td>
<td>933 (44%)</td>
</tr>
<tr>
<td>Failure to reach target - fatigue</td>
<td>670 (32%)</td>
<td>676 (32%)</td>
</tr>
<tr>
<td>Failure to reach target - dizziness/bradycardia</td>
<td>370 (26%)</td>
<td>284 (14%)</td>
</tr>
<tr>
<td>Reason for no beta blocker - COPD</td>
<td>109 (32%)</td>
<td>126 (37%)</td>
</tr>
<tr>
<td>Reason for no beta blocker - hypotension</td>
<td>68 (20%)</td>
<td>59 (17%)</td>
</tr>
<tr>
<td>Reason for no beta blocker - dizziness/bradycardia</td>
<td>17 (5%)</td>
<td>24 (7%)</td>
</tr>
</tbody>
</table>

Ivabradine vs. Digoxin

Ivabradine
• Decreases heart failure hospitalizations
• *Maybe* reduces heart failure mortality in certain subgroups
• $400/month
• “Cleaner” for clinicians who would rather not be bothered with monitoring patients

Digoxin
• Decreases heart failure hospitalizations
• *Maybe* reduces heart failure mortality if SDC < 1 ng/mL
• $15/month
• Requires fulfilling minimum expectations (i.e., monitoring for adverse effects)

SDC serum digoxin concentration
BONUS Question #2

What GDMT would be helpful if this patient had HFpEF?
HFpEF Guideline-Directed Medical Therapy

• ACE inhibitor, ARB, or beta blocker for blood pressure (IIa, LOE C)
• ARB to reduce risk of hospitalization (IIb, LOE B)
• Spironolactone in select patients to reduce risk of hospitalization (IIb, LOE B)
• PARAGON trial (sacubitril/valsartan in HFpEF) ongoing

ACE angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker, GDMT guideline-directed medical therapy, HFpEF heart failure with preserved ejection fraction, LOE level of evidence

Solving the Revolving Door
Managing Heart Failure at Transitions of Care and Beyond

Brent N. Reed, PharmD, BCCP
Associate Professor
University of Maryland School of Pharmacy
ATRIUM Cardiology Collaborative

@brentnreed or @ATRIUMRx