Ask the Experts: Building a Toolkit for Managing Heart Failure

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Supported by an educational grant from Novartis Pharmaceuticals Corporation
Ask the Experts

Building a Toolkit for Managing Heart Failure

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Learning Objectives

- Identify clinical controversies & barriers leading to suboptimal use of guideline-directed medical therapy (GDMT) regimens for patients with heart failure with reduced ejection fraction (HFrEF).
- Develop plans to optimize GDMT regimens for patients with HFrEF.
- Adopt strategies to overcome barriers to implementing successful transitions of care programs for patients with HFrEF hospitalized for acute heart failure.

Abbreviations

- ACEI=angiotensin converting-enzyme inhibitor
- ADEs=adverse drug events
- ARB=angiotensin receptor blocker
- ARNI=angiotensin receptor-neprilysin inhibitor
- BID=twice daily
- BP=blood pressure
- BUN=blood urea nitrogen
- CI=confidence interval
- COR=class of recommendation
- CrCl=creatinine clearance
- CV=cardiovascular
- Non-DHP CCB=non-dihydropyridine calcium channel blocker
- ED=emergency department
- eGFR=estimated glomerular filtration rate
- EMR=electronic medical record
- GDMT=guideline-directed medical therapy
- HF=heart failure
- HFrEF=heart failure with reduced ejection fraction
- HYD=hydralazine
- HR=heart rate
- ISDN=isosorbide dinitrate
- LOE=level of evidence
- LVEF=left ventricular ejection fraction
- MTM=medication therapy management
- MRA=mineralocorticoid receptor antagonist
- NSAIDs=non-steroidal anti-inflammatory drugs
- NSR=normal sinus rhythm
- NYHA=New York Heart Association
- OACs=oral anticoagulants
- PCPs=primary care providers
- RR=respiratory rate
- TOC=transitions of care

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Clinical Barriers and Controversies in Heart Failure

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HF in 2019

• #big problem, #long way to go
• Prevalence: 5.7 million (U.S.)
• Annual mortality: 75,251
• Lifetime risk @ age 45 years: 1 in 2-5


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## Heart Failure Stages

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High risk for HF but without structural heart disease or symptoms of HF</td>
<td>Structural heart disease but without signs or symptoms of HF</td>
<td>Structural heart disease with prior or current symptoms of HF</td>
<td>Refractory HF requiring specialized interventions</td>
</tr>
<tr>
<td></td>
<td>ACEI or ARB in appropriate patients for vascular disease/diabetes mellitus Statins as appropriate</td>
<td>ACEI or ARB Beta-blocker</td>
<td>Diuretic ACEI or ARB (or ARNI) Beta-blocker MRA</td>
<td>Advanced measures Heart transplantation Chronic inotropes Mechanical Circulatory Support Palliative care</td>
</tr>
</tbody>
</table>

### Pharmacological Treatment for Stage B HFrEF

- **HFrEF Stage B NYHA I**
  - **Class I, LOE A**
    - ACEI or ARB
  - **Class I, LOE B/C**
    - Beta-blocker
  - **Class III: Harm, LOE B**
    - Non-DHP CCB

Pharmacological Treatment for Stage C HF With Reduced Ejection Fraction

- HFrEF Stage C
  - NYHA I-IV
    - ACEI or ARB* + Beta-blocker; diuretic as needed (COR I)

- NYHA II-IV, K<5.0, CrCl >30
  - MRA (COR I)

- NYHA II-III, BP okay
  - Switch to ARNI (COR I)

- NYHA III-IV, Black patients
  - HYD/ISDN (COR I)

- NYHA II-III, NSR, HR ≥70
  - Ivabradine (COR IIa)

*HYD/ISDN for ACEI/ARB intolerant


Titrating GDMT

- Generally, consider titrating doses of GDMT every 2 weeks

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25-50 mg twice daily</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5-25 mg daily</td>
<td>200 mg daily</td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>24/26-49/51 mg twice daily</td>
<td>97/103 mg twice daily</td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg three times daily</td>
<td>50 mg three times 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>Candesartan</td>
<td>4-8 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>
<tr>
<td>Spironolactone</td>
<td>12.5-25 mg daily</td>
<td>25-50 mg daily</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg daily</td>
<td>50 mg daily</td>
</tr>
<tr>
<td>Hydralazine/isosorbide dinitrate</td>
<td>25/20 mg three times daily</td>
<td>75/40 mg three times daily</td>
</tr>
</tbody>
</table>


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Mortality Reduction in HFrEF

- ACEIs/ARBs: 18%
- Beta-blockers: 35%
- Hydralazine/isosorbide dinitrate: 43%
- Mineralocorticoid receptor antagonists: 30%
- Sacubitril/valsartan: 20%


Clinical Controversies and Barriers to Medication Optimization

- HP is a 67-year-old female with a history of HFrEF (LVEF 18%) being seen for the first time in clinic after a recent hospitalization. She remains in NYHA functional class III.
- **Current medications:** enalapril 10 mg once daily, metoprolol tartrate 25 mg twice daily, furosemide 20 mg once daily
- **Vitals:** BP 89/67 mm Hg, HR 84 bpm, RR 18 breaths/min
- **Pertinent labs:**
  - Sodium 136 mEq/L, potassium 4.8 mEq/L, creatinine 1.22 mg/dL, BUN 23 mg/dL, eGFR 46 mL/min/m²
  - NT-proBNP 4,300 pg/mL

➢ HOW DO WE FURTHER OPTIMIZE CARE FOR THIS PATIENT?
Which Beta-blocker?

### Beta-blocker Pharmacology Comparison

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol</th>
<th>Metoprolol succinate</th>
<th>Metoprolol tartrate</th>
<th>Bisoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology</td>
<td>β₁, β₂, α₁</td>
<td>β₁</td>
<td>β₁</td>
<td>β₁</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>7-10</td>
<td>3-7</td>
<td>3-4</td>
<td>9-12</td>
</tr>
<tr>
<td>Duration of action (hours)</td>
<td>12</td>
<td>24</td>
<td>8-12</td>
<td>24</td>
</tr>
<tr>
<td>Others</td>
<td>Antioxidant, ↓ Insulin resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hemodynamics, degree of neurohormonal blockade, cardioprotection?

Carvedilol Or Metoprolol European Trial (COMET)

- N=1511 HFrEF, NYHA II-IV
- Carvedilol 25 mg twice daily (41.8 mg/day) vs. metoprolol tartrate 50 mg twice daily (85 mg/day)

<table>
<thead>
<tr>
<th>%</th>
<th>Carvedilol</th>
<th>Metoprolol</th>
<th>Hazard Ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>34</td>
<td>40</td>
<td>0.83 (0.74–0.93)</td>
</tr>
<tr>
<td>CV death</td>
<td>29</td>
<td>35</td>
<td>0.80 (0.70–0.90)</td>
</tr>
<tr>
<td>Death or hospital admission</td>
<td>74</td>
<td>76</td>
<td>0.94 (0.86–1.02)</td>
</tr>
</tbody>
</table>


Carvedilol or Metoprolol Evaluation Study

- N=14,016 Norwegian HF and German HF registries
- Selecting 740 propensity-score matched pairs, comparing carvedilol vs. metoprolol succinate (at equivalent doses)

<table>
<thead>
<tr>
<th>% survival</th>
<th>Carvedilol</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio 1.00; 95% CI, 0.82–1.23; P=0.99

## Approach to Beta-blocker Selection

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol immediate release</th>
<th>Metoprolol succinate</th>
<th>Bisoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence</td>
<td>Controlled release</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Low BP</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>High BP</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence-based</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Target doses</td>
<td>25-50 mg twice daily</td>
<td>200 mg once daily</td>
<td>10 mg once daily</td>
</tr>
</tbody>
</table>

*If you must use metoprolol tartrate, use at least 75 mg twice daily*

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## ARNI or not to ARNI?
Angiotensin Receptor and Neprilysin Inhibitor (ARNI)

Valsartan + Sacubitril

Valsartan: Attenuate negative effects of angiotensin II
Sacubitril: Boost positive effects of the natriuretic peptides (& other vasodilatory peptides)

PARADIGM-HF – Study Design

Single-blind Active Run-in Period
- Enalapril 10 mg BID Run-in
- Sac/Val 100 mg BID Run-in
- Sac/Val 200 mg BID Run-in

Double-blind Treatment Period
- Sac/Val 200 mg BID
- Enalapril 10 mg BID

2 weeks 1-2 weeks 1-2 weeks

Sac/Val = sacubitril/valsartan

## PARADIGM-HF - Results

<table>
<thead>
<tr>
<th>%</th>
<th>Sac/Val (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>21.8</td>
<td>26.5</td>
<td>0.80 (0.73-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>13.3</td>
<td>16.5</td>
<td>0.80 (0.71-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>12.8</td>
<td>15.6</td>
<td>0.79 (0.71- 0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic Hypotension</td>
<td>14.0</td>
<td>9.2</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


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## Perceived Barriers to ARNI

- **Cost, access**
  - Patient assistance program:
    - Be a U.S. resident
    - Meet income requirements
    - Have limited or no private or public prescription coverage

- **Clinical**
  - Risk of hypotension
  - Twice daily regimen
  - Risk of angioedema
  - Risk of renal dysfunction
PARADIGM-HF Stratified

- **Systolic blood pressure** *(Eur Heart J. 2017; 38:1132–43.)*
  - Low systolic BP (<110 mm Hg) was associated with increased risk for primary endpoint and all-cause mortality
  - Similar tolerability and benefit compared to enalapril

- **LVEF** *(Circ Heart Fail. 2016; 9:e002744.)*
  - Lower LVEF was associated with increased risk of primary endpoint and all-cause mortality
  - Similar benefit compared to enalapril regardless of LVEF

---

**PARADIGM-HF and Hypotension**

<table>
<thead>
<tr>
<th>Single-blind Active Run-in Period</th>
<th>Double-blind Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril 10 mg BID Run-in</td>
<td>Sac/Val 200 mg BID</td>
</tr>
<tr>
<td>Sac/Val 100 mg BID Run-in</td>
<td>Enalapril 10 mg BID Run-in</td>
</tr>
<tr>
<td>Sac/Val 200 mg BID Run-in</td>
<td>Sac/Val 200 mg BID</td>
</tr>
</tbody>
</table>

2 weeks  1-2 weeks  1-2 weeks

10513 → 136 (1.3%) → 43 → 6 (14%) → 8442 → 976 (11.6%) → 588 (14.0%) Sac/Val
10377 → 9419 → 228 (2.4%) → 388 (9.2%) Enalapril

PARADIGM-HF and Hypotension

• Predictors:
  – Lower systolic BP
  – Older age
  – ICD implanted
  – Higher creatinine
  – Atrial fibrillation history
  – North America
  – Diabetes

• Outcomes:
  – Study drug did not affect predictors of hypotension (except diabetes – higher risk in enalapril arm)
  – Similar benefit compared to enalapril in those that experienced hypotension


Real World vs. Clinical Trial

• PARADIGM-HF exclusion criteria:
  – eGFR ≤30 mL/min/m²
  – Systolic BP ≤100 mm Hg
  – Potassium ≥5.2 mmol/L
  – Not on ACEI (enalapril 10 mg/day or equivalent)

• Cleveland Clinic analysis
  – Met FDA criteria: 71%
  – Met PARADIGM-HF criteria: 26%

Perez AL et al. JACC Heart Fail. 2017; 5:460-3.
PIONEER-HF

- Assess safety and efficacy of sacubitril/valsartan initiation among patients hospitalized for acute heart failure after hemodynamic stabilization
- Sacubitril–valsartan target dose 200 mg twice daily vs. enalapril target dose 10 mg twice daily

↓ NT-proBNP @ 4 and 8 weeks with sacubitril/valsartan

No significant differences: worsening renal function, hyperkalemia, symptomatic hypotension, angioedema, or clinical events


Low Blood Pressure?
BP and HF Outcomes

- Low BP has been associated with lower survival in ambulatory patients with HF, but changes in BP with therapy have not

Models of BP Association to Mortality in HF

- Systolic BP 110 mm Hg
  - Diastolic BP 70 mm Hg
  - Mortality

- Systolic BP 140-150 mm Hg
  - Mortality

Mortality

Systolic BP or Diastolic BP


GDMT, BP, and Outcomes*

- COPERNICUS trial

All-Cause Mortality

P>0.1 interaction

Favors carvedilol

Favors placebo


*slide contains corrected data

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Potential Benefits of Lower Blood Pressure in HF

- Reduced afterload
  - Reduced ventricular wall tension
  - Improved vascular vasoreactivity

  ➔

- Improved diastolic function
- Increased stroke volume
- Reduced myocardial oxygen consumption

Approach to Assessment of Low BP

- Symptomatic?
- Perfusing?
- Volume status?
- Separate dose administration times?
- Unnecessary polypharmacy?
Circling Back on Loops

Loop Diuretic Comparison

<table>
<thead>
<tr>
<th></th>
<th>Furosemide</th>
<th>Bumetanide</th>
<th>Torsemide</th>
<th>Ethacrynic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative Potency</strong></td>
<td>40</td>
<td>0.5-1</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td><strong>Bioavailability (%)</strong></td>
<td>≈50 (10-90)</td>
<td>&gt;90</td>
<td>&gt;90</td>
<td>100</td>
</tr>
<tr>
<td><strong>Half-life (hours)</strong></td>
<td>2-3</td>
<td>1-1.5</td>
<td>3-6</td>
<td>0.25-2</td>
</tr>
<tr>
<td><strong>Duration of Action (hours)</strong></td>
<td>6-8</td>
<td>4-6</td>
<td>18-24</td>
<td>2-4</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Absorption reduced by meals</td>
<td>Absorption not reduced in HF; antifibrotic</td>
<td>No sulfur group</td>
<td></td>
</tr>
</tbody>
</table>
**Torsemide vs. Furosemide in HF: Meta-Analysis of RCTs**

<table>
<thead>
<tr>
<th>HF READMISSIONS</th>
<th>Sample Size</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mueller et al. (2003)</td>
<td>237</td>
<td>0.62 (0.10, 3.79)</td>
</tr>
<tr>
<td>Murray et al. (2001)</td>
<td>234</td>
<td>0.25 (0.14, 0.45)</td>
</tr>
<tr>
<td>Stroupe et al. (2000)</td>
<td>193</td>
<td>0.43 (0.22, 0.85)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>664</strong></td>
<td><strong>0.33 (0.22, 0.50)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MORTALITY</th>
<th>Sample Size</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mueller et al. (2003)</td>
<td>237</td>
<td>1.27 (0.43, 3.79)</td>
</tr>
<tr>
<td>Murray et al. (2001)</td>
<td>234</td>
<td>0.73 (0.37, 1.42)</td>
</tr>
<tr>
<td>Stroupe et al. (2000)</td>
<td>193</td>
<td>0.77 (0.37, 1.61)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>664</strong></td>
<td><strong>0.82 (0.52, 1.28)</strong></td>
</tr>
</tbody>
</table>

**Torsemide vs. Furosemide in HF: Duke Experience**

- N=4,580 admitted with HF to Duke Hospital (2000–2010), then discharged on either torsemide (14%) or furosemide (86%)

<table>
<thead>
<tr>
<th>Adjusted Model</th>
<th>Odds Ratio or Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality or hospitalization</td>
<td>1.22</td>
<td>0.1789</td>
</tr>
<tr>
<td>30-day hospitalization</td>
<td>1.29</td>
<td>0.1607</td>
</tr>
<tr>
<td>5-year mortality</td>
<td>1.09</td>
<td>0.2279</td>
</tr>
</tbody>
</table>
**Approach to Selection of Loop in HFrEF**

<table>
<thead>
<tr>
<th></th>
<th>Furosemide</th>
<th>Bumetanide</th>
<th>Torsemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing for persistent volume overload</td>
<td>Twice daily</td>
<td>Two to three times daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Absorption issues</td>
<td></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Adherence issues</td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Higher doses needed</td>
<td></td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

*Ethacrynic Acid for true sulfonamide intolerance*

---

**Tools to Address Barriers for Optimizing Heart Failure Transitions of Care**

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How Do We Further Optimize Care for This Patient Prior to Discharge?

- HP is a 67-year-old African-American female with HFrEF (LVEF 18%) hospitalized for the first time for acute heart failure. Poor historian, lives with her daughter who assists with her care.
- **Current medications**: enalapril 10 mg once daily, metoprolol tartrate 25 mg twice daily, furosemide 20 mg once daily, metformin 500 mg twice daily, atorvastatin 40 mg daily, levothyroxine 0.1 mg daily, enteric-coated aspirin 81 mg daily.
- **Vitals**: BP 109/67 mm Hg, HR 84 bpm, RR 18 breaths/min.
- **Pertinent labs**:
  - Sodium 136 mEq/L, potassium 4.8 mEq/L, creatinine 1.22 mg/dl, BUN 23 mg/dl, eGFR 46 mL/min/m².

Clinical Predictors of HF Readmission

**Opportunities for Improvement?**

- Acute coronary syndrome, ischemia
- Increasing age
- Anemia
- Arrhythmia
- Depression
- Hyponatremia
- Low LVEF

- NYHA class IV symptoms
- Pneumonia/respiratory pathology
- **Suboptimal HF medication regimen**
  - Uncontrolled hypertension
  - Worsening renal function

GDMT for Patients with HFrEF at Discharge
Are we optimizing regimens?

*Only 23% of patients had GDMT modified before discharge*

<table>
<thead>
<tr>
<th>Prescribed at Discharge (%)</th>
<th>GWTG 2011</th>
<th>GWTG 2012</th>
<th>ARIC *</th>
<th>REALITY-AHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td>90%</td>
<td>80%</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>90%</td>
<td>80%</td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td>MRA</td>
<td>10%</td>
<td>20%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>ACEI/ARB + Beta-blocker</td>
<td>10%</td>
<td>20%</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Prescribed at Discharge (%)


GDMT Modification During Hospitalization Impacts Survival

Adjusted Hazard Ratio 0.41
(95% CI, 0.23-0.71) vs. no therapy
Hazard Ratio 1.30
(95% CI, 1.02-1.66) vs. maintaining therapy

Tran RH. Pharmacotherapy. 2018; 38:406-16.

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Consider Additional GDMT for HFrEF

- ACEI or ARB
- Beta-blocker
- Diuretic
- Aldosterone antagonist
- Hydralazine/nitrate
- Sacubitril/valsartan
- Ivabradine
- Digoxin

Hospitalization = Opportunity to Titrate Dose!

- Generally, consider titrating doses of GDMT every 2 weeks

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice daily</td>
<td>25-50 mg twice daily</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>12.5-25 mg daily</td>
<td>200 mg daily</td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>24/26-49/51 mg twice daily</td>
<td>97/103 mg twice daily</td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg three times daily</td>
<td>50 mg three times 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>Candesartan</td>
<td>4-8 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>
<tr>
<td>Spironolactone</td>
<td>12.5-25 mg daily</td>
<td>25-50 mg daily</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg daily</td>
<td>50 mg daily</td>
</tr>
<tr>
<td>Hydralazine/isosorbide dinitrate</td>
<td>25/20 mg three times daily</td>
<td>75/40 mg three times daily</td>
</tr>
</tbody>
</table>

GDRT Dose Matters!
Dose-dependent Effect on Left Ventricle

• MOCHA
  – Dose-related increase in LVEF with carvedilol

• REVERT
  – Dose-dependent improvement in left ventricular remodeling


---

GDRT Dose-dependent Effect on Outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Hazard Ratio for death or HF hospitalization</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACEI or ARBs</td>
<td></td>
</tr>
<tr>
<td>ATLAS (lisinopril)</td>
<td>0.85</td>
<td>0.78-0.93</td>
</tr>
<tr>
<td>HEAAL (losartan)</td>
<td>0.90</td>
<td>0.82-0.99</td>
</tr>
<tr>
<td>Egiziano et al.</td>
<td>ACEI: 0.91</td>
<td>0.87-0.95</td>
</tr>
<tr>
<td></td>
<td>ARB: 0.85</td>
<td>0.77-0.95</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Beta-blockers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HF-ACTION</td>
<td>0.96 per 10-mg dose increase</td>
<td>0.93-0.99</td>
</tr>
<tr>
<td>McAlister et al.</td>
<td>No dose-response relationship</td>
<td></td>
</tr>
</tbody>
</table>

GDMT Dose Matters!
Dose-dependent Effect on Mortality

ACEI or ARB

Hazard Ratio (95% CI) vs. ≥100%
1.76 (1.54-1.98)
1.50 (1.33-1.67)
0.82 (0.61-1.02)

Beta-Blockers

Hazard Ratio (95% CI) vs. ≥100%
2.41 (2.13-2.68)
1.91 (1.74-2.08)
1.29 (1.07-1.51)

Cumulative deaths (%)
Time (days)

% of target dose 0% 1-49% 50-99% ≥100%

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Beta-Blocker Dosage Adjustments During & After Hospitalization

In-Hospital Dosage Adjustment

- Carvedilol
  - Decreased: 40%
  - Unchanged: 50%
  - Increased: 10%

- Metoprolol succinate
  - Decreased: 30%
  - Unchanged: 50%
  - Increased: 20%

Dosage Adjustment At 60-90 days

- Carvedilol
  - Decreased: 9%
  - Unchanged: 80%
  - Increased: 11%

- Carvedilol-new
  - Decreased: 10%
  - Unchanged: 80%
  - Increased: 10%

- Metoprolol succinate
  - Decreased: 9%
  - Unchanged: 80%
  - Increased: 11%

- Metoprolol succinate-new
  - Decreased: 10%
  - Unchanged: 80%
  - Increased: 10%

~23% patients have dose increased

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Effective Care Transitions to Optimize Post-Discharge Outcomes

Patient Education & Discharge Counseling Heart Failure and Post-Myocardial Infarction

- Address barriers
- **Perform thorough review of medications**
- Use inpatient and outpatient settings
- Assess readiness to learn
- Vary teaching methods
- Engage caregivers
- Engage other team members

- Optimize written materials
- Emphasize self-care
- Employ teach-back method
- **Assess patient resources**
- Refer to disease management programs
- Focus on smooth care transitions

Inpatient Medication Histories & Reconciliation

Clinical & Economic Outcomes

Medication Histories
• ↓ Adverse drug events (ADEs)
• ↓ Drug costs
• ↓ Total costs
• ↓ Inpatient mortality

Medication Reconciliation
• ↓ Medication discrepancies
• ↓ Potential ADEs
• ↓ Preventable ADEs
• ↓ Health care resource use


Pharmacist Involvement in TOC Improves Outcomes!

OPTIMIST Study


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OPTIMIST Study Design
Transition of Care Interventions

Inclusion Criteria
- Age ≥18 years
- Polypharmacy (≥5 chronic meds)

Usual Care
Not described

Basic Intervention
- Med review by pharmacist
  - Meds of interest/focus: aspirin, diuretics, OACs, NSAIDS
- Propose med changes, if appropriate
- Communicate with physicians via EMR ± verbally

Extended Intervention
- Basic Intervention
- Med reconciliation at discharge
- Motivational interview/education
- Fax/mail PCPs: drug-related problems
- Day 3: Call to PCP, caregiver, & pharmacy
- Week 1, 6 months: f/u phone call

### Heart Failure Transitions of Care Programs
#### Barriers & Potential Solutions

**Barriers**
- Lack of time/resources
- Patient out-of-pocket costs/insurance issues
- Lack of administration/leadership support

**Potential Solutions**
- Utilize technicians ± students
- Focus intervention(s) on ”high-risk” patients
- Partner with outpatient pharmacy
- Bill for MTM services?

---

### Pharmacy Student Medication Reconciliation

**Student-managed services**
- Pharmacist ”reach” ↑ more than 2-fold
- Clinical interventions
- Post-discharge calls

**RXCARES**
- Reconciliation
- X-Drug Interaction
- Coordination & Communication
- Access & Adherence
- Risk reduction
- Evidence-Based Medicine review / Elimination of meds
- Savings

**MoPhE**
- Mobile Pharmacy Education

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Lancaster JW. *Am J Pharm Educ.* 2014; 78:34.

Bursua A, Thambi M. University of Illinois Hospital.

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Focus Efforts on “High-Risk” Patients

- Targeted patients (e.g., elderly, polypharmacy)
  - OPTIMIST: ≥5 meds
  - RXCARES
    - ≥10 meds
    - Age ≥65 AND ≥5 meds OR ≥2 admissions in last 1 year

- Targeted medications/disease states
  - MoPhE: anticoagulants, diabetes, inhaler technique

- Utilize EMR/Clinical Decision Support?

Reimbursement for Transitions of Care?

- Several inpatient clinical pharmacy services eligible under evaluation & management inpatient procedural codes
  - History-taking, physical exam, medical decision-making
  - Categorized by complexity

- Medicare/Medicaid ineligible

Steps to Consider

1. Review payer mix
2. Review state laws governing MTM criteria
3. Establish billing values with finance department
4. Pharmacist must conduct face-to-face visit & document
5. Establish reporting system

Optimizing GDMT for Patients with HFrEF
What Should Be in Your Toolkit?

- Knowledge to identify & resolve clinical barriers for optimization of GDMT
- Skills for medication histories, reconciliation, & patient education for appropriate patients
- Post-discharge follow-up
- Human resource management
  - More efficient use of technicians ± students
- Reimbursement capabilities (MTM billing?)

Guidelines & Consensus Statements


Other Selected Resources


Selected Resources
Consider these practice changes. Which will you make?

- Read the 2017 ACC Expert Consensus Pathway.
- Compare my organization’s protocols with the most up to date heart failure treatment guidelines.
- Evaluate my organization’s utilization & escalation of GDMT for HFrEF prior to discharge.
- Assess my pharmacy department’s participation in care transitions (e.g., frequency of medication histories upon admission & medication reconciliation upon discharge, participation in patient education).
- Engage both patients & caregivers in educational encounters.
- Determine the feasibility of post-discharge pharmacist involvement (e.g., post-discharge telephone contact, multidisciplinary clinic).