Disclosures

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Christopher Gans, M.D., FACC, FASE
• Pfizer: speakers bureau
Learning Objectives

- Review the principles of guideline-directed medical therapy (GDMT) for patients with heart failure
- Explain the role of the interprofessional team in managing patients with heart failure, including the pharmacist’s role
- Using case scenarios, illustrate effective components of collaborative practice agreements and titration clinics to optimally manage patient medication regimens

Abbreviations

- ACEi-angiotensin converting enzyme inhibitor
- ACC-American College of Cardiology
- AHA-American Heart Association
- ANP-atrial natriuretic peptide
- ARB-angiotensin receptor blocker
- BID-twice daily dosing
- BNP- brain natriuretic peptide
- BP- blood pressure
- bpm-beats per minute
- CAD-coronary artery disease
- CCB-calcium channel blocker
- CI-confidence interval
- CrCl-creatinine clearance
- CV-cardiovascular
- DM-diabetes mellitus
- ECG-electrocardiogram
- EF-ejection fraction
- eGFR-estimated glomerular filtration rate
- FC-functional class
- HF-heart failure
- HFrEF-heart failure with reduced ejection fraction
- HFpEF-heart failure with preserved ejection fraction
- HFSA-Heart Failure Society of America
- HR-heart rate
- HTN-hypertension
- MI-myocardial infarction
- MRA mineralocorticoid receptor antagonist
- NNT-number needed to treat
- NO-nitric oxide
- NYHA-New York Heart Association
- RAAS-renin angiotensin, aldosterone system
- RRR-relative risk reduction
- SOB-shortness of breath
- TID-three times a day dosing

All medications referred to within presentation are oral route of administration

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Pre-activity Survey Results
(Previous Heart Failure Activity Attendees)

• 41% can use a refresher on pathophysiology
• 71% do not care for patients with HF under a practice agreement
• Challenges
  – Managing dose changes with in patients with renal impairment
  – Patient adherence: meds and follow up
  – Patient education: time required and volume of patients
• Practice Satisfaction
  – Collaborative care
  – Improving outcomes/patient interactions

Overview of Guideline-Directed Medical Therapy in Heart Failure

Christopher Gans, M.D., FACC, FASE
<table>
<thead>
<tr>
<th>HF REDUCED EF</th>
<th>HF PRESERVED EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired ventricular contraction</td>
<td></td>
</tr>
<tr>
<td>➢ Consequence of loss of muscle mass, pressure or volume overload</td>
<td></td>
</tr>
<tr>
<td>➢ EF ≤40%</td>
<td></td>
</tr>
<tr>
<td>➢ May be referred to as:</td>
<td></td>
</tr>
<tr>
<td>• Systolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>• Dilated cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>➢ Abbreviation: HFrEF</td>
<td></td>
</tr>
<tr>
<td>Impaired ventricular relaxation</td>
<td></td>
</tr>
<tr>
<td>➢ Results from increased ventricular stiffness</td>
<td></td>
</tr>
<tr>
<td>➢ EF ≥50%</td>
<td></td>
</tr>
<tr>
<td>➢ Previously known as diastolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>➢ Abbreviation: HFpEF</td>
<td></td>
</tr>
</tbody>
</table>

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### Signs & Symptoms of HF

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>HFpEF %</th>
<th>HFrEF %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea on exertion</td>
<td>85</td>
<td>96</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>60</td>
<td>73</td>
</tr>
</tbody>
</table>

**Physical examination**

<table>
<thead>
<tr>
<th></th>
<th>HFpEF %</th>
<th>HFrEF %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jugular venous distention</td>
<td>35</td>
<td>46</td>
</tr>
<tr>
<td>Rales</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>Displaced apical impulse</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>S3</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>S4</td>
<td>45</td>
<td>66</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Edema</td>
<td>30</td>
<td>40</td>
</tr>
</tbody>
</table>

**Chest radiograph**

<table>
<thead>
<tr>
<th></th>
<th>HFpEF %</th>
<th>HFrEF %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomegaly</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>Pulmonary venous hypertension</td>
<td>75</td>
<td>80</td>
</tr>
</tbody>
</table>

*no statistical significance*

---

### Pathophysiology: HFrEF

**INITIAL CARDIAC INSULT:**
- Myocardial infarction
- Hypertension
- Idiopathic/Genetic
- Valve abnormalities
- Other (viral, alcohol, drugs, pregnancy, tachycardia, connective tissue disease)
- High Output States

**Secondary damage mediated by neurohormones**

**ACTIVATION OF COMPENSATORY MECHANISMS:**
- Increased preload
- Vasoconstriction
- Tachycardia
- Ventricular remodeling

---

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Renin Angiotensin & Sympathetic Activation

↓ Cardiac Output

- Angiotensin II
- Aldosterone
  - Na and H₂O retention
  - ↑ preload vascular congestion
- Angiotensin II
- NE
  - Vasoconstriction
  - ↑ afterload ↓ stroke volume ↑ MVO₂
- NE
- SNS excess
  - ↑ MVO₂ apoptosis
- Angiotensin II
- Aldosterone
  - NE
  - Cardiac remodeling
  - ↓ CO Arrhythmias

Impaired systolic function

CO = cardiac output, MVO₂ = myocardial oxygen consumption, NE = norepinephrine, SNS = sympathetic nervous system

Neurohormonal Imbalance in HF: Drug targets

**Symptoms:**
- Diuretics
- Digoxin

**Inhibit:**
- MRA
- ACEi/ARB
- Beta-Blocker
- I₁ current inhibition

**Enhance:**
- ANP
- BNP
- Bradykinin
- Prostacyclin
- Neprilysin inhibition
- Hydralazine/nitrate

**Vasoconstriction / Na Retention**

**Vasodilation / Natriuresis**

Patient Assessment

NYHA FC

<table>
<thead>
<tr>
<th>Class</th>
<th>Shortness of breath</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None with ordinary physical activity</td>
</tr>
<tr>
<td>II</td>
<td>Present with ordinary physical activity</td>
</tr>
<tr>
<td>III</td>
<td>Present with less than ordinary exertion</td>
</tr>
<tr>
<td>IV</td>
<td>Present at rest</td>
</tr>
</tbody>
</table>

AHA STAGES

A = At high risk for HF but without structural heart disease or symptoms
B = Structural heart disease (i.e., low EF) but without signs or symptoms
C = Structural heart disease with prior or current symptoms
D = Refractory HF requiring specialized interventions (end-stage)


Patient Assessment

Clinical status
- Symptoms
- Physical exam

Baseline Labs
- hemoglobin, electrolytes, renal and hepatic function, lipid profile, fasting blood glucose, thyroid panel

Diagnostic
- Chest X-ray
- Electrocardiogram
- Echocardiogram or Cardiac MRI (magnetic resonance imaging)

<table>
<thead>
<tr>
<th>Natriuretic peptides</th>
<th>BNP (pg/mL)</th>
<th>NT-proBNP (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion of HF diagnosis</td>
<td>&lt;100</td>
<td>&lt;300</td>
</tr>
<tr>
<td>Inclusion of HF diagnosis</td>
<td>&gt;400</td>
<td>450 (age &lt;50 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>900 (age 50-75 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1800 (age &gt;75 years)</td>
</tr>
</tbody>
</table>

**Symptoms**

- Pitting edema
- Jugular venous distention (JVD)
- Hepatojugular reflux (HJR)
- Hepatomegaly
- Ascites
- Weight gain
- Bibasilar rales
- Pulmonary edema
- S3 gallop
- Pleural effusion
- ↓ carotid upstrokes
- Tachycardia
- Cyanosis of digits/cool extremities
- Displaced point of maximal impulse (PMI)

**Physical Exam**

- Abdominal pain
- Anorexia/nausea
- Bloating/constipation
- Dyspnea on exertion (DOE)
- Exercise intolerance
- Paroxysmal nocturnal dyspnea (PND)
- Orthopnea
- Cough
- Fatigue/weakness
- Nocturia
- Confusion
- Altered mental status

---

**Patient Case**

AB is a 67 yo Hispanic female with long-standing HTN presents with cough, SOB when dressing/showering, PND, 8-lb weight gain, decreased appetite, and lower extremity edema

**Meds (taken orally):**

- Diltiazem ER 240 mg daily
- HCTZ 50 mg daily
- Ibuprofen 200 mg three times daily

**Vital signs:**

- BP: 150/94 mm Hg
- HR: 92 bpm

**Diagnostics:**

- EF = 20%
- Chest X-ray: vascular congestion
- ECG: left ventricular hypertrophy

**Labs:**

- Na/K within normal limits
- BUN/SCr 38/1.5 mg /dL
- BNP 1200 pg/mL

HCTZ = hydrochlorothiazide, Na = sodium, K = potassium, BUN = blood urea nitrogen, SCr = serum creatinine
In addition to discontinuing diltiazem, what is your plan for treating her HF?

a. Add furosemide, lisinopril, and carvedilol
b. Change HCTZ to furosemide and add lisinopril and carvedilol
c. Add furosemide and lisinopril
d. Change HCTZ to furosemide and add lisinopril

Drugs to Avoid in Chronic HF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most antiarythmics</td>
<td>Increase risk of death</td>
</tr>
<tr>
<td><em>Amiodarone and dofetilide are okay</em></td>
<td>Negative Inotrope</td>
</tr>
<tr>
<td>Non-dihydropyridine calcium channel blockers</td>
<td>Negative inotrope</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Increased inotrope</td>
</tr>
<tr>
<td>NSAIDS or COX-2 inhibitors</td>
<td>Increased risk of HF-related hospitalizations or HF symptoms</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Increased risk of HF-related hospitalizations or HF symptoms</td>
</tr>
</tbody>
</table>

NSAIDS = non-steroidal anti-inflammatory drugs
COX = cyclooxygenase
Drugs to use with Caution in Chronic HF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Dihydropyridine calcium channel blockers</td>
<td>Peripheral edema</td>
</tr>
<tr>
<td><em>Amlodipine is okay</em></td>
<td></td>
</tr>
<tr>
<td>Gabapentin or pregabalin</td>
<td>Peripheral edema</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>Sodium and fluid retention</td>
</tr>
</tbody>
</table>


2017 ACC/AHA/HFSA Guidelines

NYHA FC I-IV
HFrEF → ACEi or ARB and GDMT
Beta-Blocker (BB); Diuretics as needed

**Class 1 Recommendations (Stage C):**
ACEi: All patients with prior or current symptoms to reduce morbidity and mortality
ARB: Use in patients with prior or current symptoms who are intolerant to ACEi because of cough or angioedema
Beta-blocker: All patients with current or prior symptoms to reduce morbidity and mortality


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Beta-blockers for Chronic HF

- Beta-blockers are typically thought of as negative inotropes and may seem counterintuitive in HF
- However, proven to reduce morbidity and mortality when used in conjunction with ACEi and ARBs
  - Blunting of sympathetic activation on the myocardium, thus reducing eventual fibrosis and apoptosis
  - Also ↓ decreases renin secretion, ↓ myocardial oxygen consumption and has antiarrhythmic effects
  - Only bisoprolol, carvedilol and metoprolol succinate proven beneficial


Initiating Beta-Blockade

- Decompensated heart failure relies on increased heart rates to maintain cardiac output
- It is recommended that initiation of beta blockers be deferred until patients are euvolemic or reasonably hemodynamically stable
- Start at a low doses and double every two weeks as tolerated

3 months later AB returns to clinic. In the interim, she has been titrated to goal doses of carvedilol and lisinopril by the HF pharmacist. She was hospitalized 2 weeks ago for acute HF but now is feeling much better. Currently has stable “2 pillow” orthopnea and dyspnea after walking 3 blocks. NYHA FC II

**Meds (taken orally):**
- Carvedilol 25 mg twice daily
- Furosemide 20 mg daily
- Lisinopril 20 mg daily
- Ibuprofen 200 mg three times daily

**Vitals:**
- BP: 135/84 mm Hg
- HR: 74 bpm

**Diagnostics:**
- EF = 30-35%
- Chest X-ray: cardiomegaly

**Labs:**
- Na/K normal
- BUN/SCr 22/1.5 mg/dL
- BNP 500 pg/mL (normal <100)

**What is your next step for treating her HF?**

a. Continue present management
b. Add hydralazine/isosorbide 37.5 mg/20 mg tid
c. Add ivabradine 5 mg bid
d. Add spironolactone 25 mg daily
e. Change lisinopril to sacubitril/valsartan 97 mg/103 mg bid
### 2017 ACC/AHA/HFSA Guidelines

- **NYHA FC I-IV HFrEF**
  - ACEi or ARB and GDMT BB titrated to target dose
  - Diuretic as needed

- **Persistent Symptoms**
  - NYHA FC II-IV
    - CrCl >30 mL/min & K <5 mEq/L
      - Add
        - MRA
    - NYHA FC III-IV
      - African American
      - Add
        - Hydralazine with ISDN
    - NYHA FC II-III
      - HR >70 bpm in sinus rhythm
      - Add
        - Ivabradine
  - Switch ACEi/ARB
    - Sacubitril/valsartan

- **NYHA FC II-III Adequate BP No contraindications**

---

**Ivabradine**

- Unlike beta-blockers, does not alter myocardial contractility or intracardiac conduction, even in patients with impaired systolic function
- Ivabradine is a specific inhibitor of the If current in the sinoatrial node
  - Slows diastolic depolarization phase → lowers HR
- No effect on other channels in the heart or vascular system

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**Why Lower the Heart Rate?**

HR \( \geq 75 \) bpm at hospital discharge

19\% increase in risk of all-cause mortality

\( >25\% \) increase in risk of composite of CV death or hospitalization for worsening HF

(sinus rhythm or atrial fibrillation at 0-30 days or 30-365 days)


**SHIFT TRIAL: Ivabradine vs. Placebo**

- 2.5-7.5 mg bid with goal HR of 50-60 bpm
- NYHA FC II/III HFrEF
- Aldosterone antagonist: 60\%
- Beta-blocker: 89\%
  - Only 25\% at target dose
  - 56\% on \( \geq 50\% \) target dose
- Composite of CV death or HF hospitalization: 17\% RRR
  - driven by ↓ hospitalizations
- Side Effects
  - 4-5\% ↑ bradycardia
  - 1\% ↑ new atrial fibrillation
  - 2\% ↑ phosphenes

**ARB/Nephrilysin Inhibitor (ARNI)**

- Nephrilysin is an enzyme that contributes to breakdown of biologically active natriuretic peptides and other vasoactive compounds
- Sacubitril/valsartan is a first-in-class nephrilysin inhibitor/angiotensin receptor blocker
- Inhibition of RAAS and augmented endogenous natriuretic peptides provides a distinctive mechanism of action

---

**PARADIGM-HF TRIAL**

- Sacubitril/valsartan vs. enalapril
- **Inclusion**
  - **Currently on ACEi or ARB**
  - EF ≤35%
  - Current symptoms
  - Prior HF hospitalization or ↑BNP
- **Exclusion**
  - eGFR <30 mL/min
  - K >5.2 mmol/L
  - History of angioedema
  - Low BP
- **Primary outcome**: CV death or hospitalization for HF


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**PARADIGM-HF TRIAL**

- **NYHA FC II >> FC III (72%)**
- **EF 29%, BNP 250 pg/mL**
- **MRA: 54%**
- **Side effects**
  - 5% ↑symptomatic hypotension
  - 1.2% ↓Scr ≥2.5 mg/dL
  - 1.3% ↓K >6.0 mmol/L
  - 3% ↓cough

- **18% RRR in composite CV death or HF hospitalization**
  - All-cause mortality: 14% RRR
  - QOL score improved by 35%
  - New-onset heart failure or ACEi/ARB naïve not evaluated

QOL = quality of life


---

**Important Information on ARNI Dosing**

Select patients with acceptable BP, renal function, and potassium levels

<table>
<thead>
<tr>
<th>ACEi or ARB Dose</th>
<th>Sacubitril/valsartan Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or low dose</td>
<td>24/26 mg BID</td>
</tr>
<tr>
<td>Target or maximum dose</td>
<td>49/51 mg BID</td>
</tr>
<tr>
<td>Clinical characteristic</td>
<td></td>
</tr>
<tr>
<td>Severe renal impairment</td>
<td>24/26 mg BID</td>
</tr>
<tr>
<td>Moderate hepatic impairment</td>
<td>24/26 mg BID</td>
</tr>
<tr>
<td>History of angioedema</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Double every 2-4 weeks to target of 97 mg /103 mg BID</td>
<td></td>
</tr>
</tbody>
</table>

**ACEi to ARNI:**

- *WAIT 36 HOURS*
  - Take back old medication from patient
  - Cancel ACEi prescription at the pharmacy

**ARB to ARNI:**

- Start when next dose normally due

Entresto (sacubitril/valsartan) prescribing information. Novartis Pharmaceuticals Corp.

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**Guideline Recommendation: Digoxin**

- Added to standard of care in symptomatic HFrEF
  - Level of Evidence B, Class IIa 2013
  - Not addressed in 2017 guideline update

**Clinical benefits**

- Decreases hospitalization
- *No effect on mortality*
- Unknown whether these benefits exist in setting of current GDMT
  - Study population received only ACEi, diuretic; very few on beta-blocker
  - Target trough level of <1.0 ng/mL


---

**Key Takeaways**

**Magnitude of Benefit in Clinical Trials**

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RRR in mortality (%)</th>
<th>NNT for mortality reduction</th>
<th>RRR in HF hospitalizations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi 1991 or ARB 2001-2003</td>
<td>17</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Add: Beta-blocker 1996-2001</td>
<td>34</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>Add: MRA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FC III 1999</td>
<td>30</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>FC II 2012</td>
<td>19</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Add: Hydralazine/Isosorbide Dinitrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in African Americans 2004</td>
<td>43</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>Add: Ivabradine 2010</td>
<td>----</td>
<td>----</td>
<td>24</td>
</tr>
<tr>
<td>Switch to: ARNI 2015</td>
<td>14</td>
<td>35</td>
<td>18</td>
</tr>
</tbody>
</table>


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An Interprofessional Approach to Managing Patients with Heart Failure: Best Practices

Vicki Groo, Pharm.D.

and

Christopher Gans, M.D., FACC, FASE

Pharmacist’s Role in HF Clinic

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Domains of a HF Clinic

- Disease management
- Functional assessment
- Quality of life assessment
- Medical therapy and drug evaluation
- Device evaluation
- Nutritional assessment
- Follow up
- Advance planning
- Communication
- Provider education
- Quality assessment


HFrEF GDMT in the Real World

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>N</th>
<th>ACEi/ ARB/ARNI</th>
<th>Beta blocker</th>
<th>MRA</th>
<th>Dual</th>
<th>Triple</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAMP HF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2015-2017</td>
<td>3,518</td>
<td>73</td>
<td>67</td>
<td>33</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td><strong>Target Dose</strong></td>
<td></td>
<td></td>
<td>&lt;30</td>
<td>&lt;30</td>
<td>&gt;75</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Utah Health</td>
<td>2007-2013</td>
<td>989</td>
<td>69</td>
<td>79</td>
<td>28</td>
<td>58</td>
<td>19</td>
</tr>
<tr>
<td><strong>Target dose</strong></td>
<td></td>
<td></td>
<td>31</td>
<td>24</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESC Registry Ambulatory HF</td>
<td>2011-2013</td>
<td>4,792</td>
<td>92</td>
<td>93</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Target Dose</strong></td>
<td></td>
<td></td>
<td>29</td>
<td>17</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of GDMT prior to ICD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2007-2011</td>
<td>78,665</td>
<td></td>
<td></td>
<td></td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

Use of GDMT (%)

- ACEi: Angiotensin-Converting Enzyme Inhibitor
- ARB: Angiotensin Receptor Blocker
- ARNI: Angiotensin-Receptor Neprilysin Inhibitor
- MRA: Mineralocorticoid Receptor Antagonist
- ICD: Internal Cardiac Defibrillator

<sup>a</sup>Cardiologists better at prescribing GDMT than Gen Med but not at achieving target dose

<sup>b</sup>GDMT associated with ↓ mortality (11.1 vs. 16.2%)

ESC = European Society of Cardiology, ICD = Internal cardiac defibrillator

Pharmacists are proven to improve HF outcomes in which setting(s)?

a. Multidisciplinary clinic  
b. Pharmacist directed care  
c. Both A and B

HF Clinic Pharmacist Care: A Systematic Review

- 12 Randomized clinical trials with 2060 patients  
- Pharmacist directed care  
  - Pharmacist initiated and managed intervention  
- Pharmacist collaborative care  
  - Member of a multidisciplinary team  
- Outcomes  
  - All-cause and HF hospitalizations/mortality  
- Interventions  
  - Medication recommendations  
  - Medication & disease education  
  - Facilitation of adherence & medication management  
  - Self monitoring  
  - Telephone follow up


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HF Clinic Pharmacist Care: A Systematic Review

- Pharmacist care (all 11 studies)
  - Significant ↓ all-cause hospitalization
  - Significant ↓ HF hospitalization
  - No significant change in mortality
- Reduction in HF hospitalizations
  - Pharmacist collaborative care (p<0.05)
  - Pharmacist directed care (p=NS)

*Incorporation of pharmacists into HF care teams should be strongly considered*


HF Clinic: Adherence Study

Clinical Pharmacist vs. Usual Care

- 314 low-income patients, age ≥50 years, primary outcome = adherence
- Pharmacist Intervention x 9 months with 3-month follow up
  - Baseline medication history
  - Dispensed medications in 2-month intervals
  - Written instructions aimed at low health literacy
  - Protocol followed for solutions depending on problem category
- Results
  - 11% improvement in adherence
  - 3 months after study ended, no significant difference in adherence
  - 19.4% decrease in emergency department visits and hospitalizations

UI Health HF Medication Titration Clinic

Why
- Internal data on use of GDMT in HFrEF: general cardiology (GC) vs. HF team
  - Beta blocker 40% vs. 100% / aldosterone antagonist 8.6% vs. 31.4% (P<0.001)
- Start pharmacist-managed medication titration assistance clinic (MTAC)
- Compare outcomes at 12 months to patients managed by GC

How
- Start pharmacist-managed medication titration assistance clinic (MTAC)
- Compare outcomes at 12 months to patients managed by GC

Who
- 60-64 years old with HTN, CAD, DM
- Mostly NYHA FC I-II with ejection fraction of 20-40%

UI Health = University of Illinois at Chicago Hospital and Health Sciences System


U of Illinois HF Medication Titration Clinic

Of patients not on target or maximum tolerated doses at baseline:
- 68% MTAC vs. 23% GC achieved optimal doses
- P <0.001


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**U of Illinois HF Medication Titration Clinic**

Of patients not on target or maximum tolerated doses at baseline:
- 70% MTAC vs. 28% GC achieved optimal doses
- P < 0.001

*No significant difference in CV (0.45 vs. 0.35) or HF-related hospitalizations (0.18 vs. 0.11)*


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**Metro Health HF Medication Titration Clinic**

- Evaluate effectiveness of pharmacist in titrating GDMT for HFrEF patients
- 100 referrals
  - 25 lost to follow up
  - 39 in progress
  - 36 completed (21 included in LVEF analysis)
- 62-64 years old, primarily NYHA FC II

Metro Health HF Medication Titration Clinic

- Average of 4.9 visits over 12.7 weeks
- 78% achieved target dose beta-blocker
  - Fatigue, bradycardia, hypotension → dose limitations
- Of patients with baseline EF <35%
  - 66% with EF improvement to >35%
- Hospitalizations pre/post titration
  - 39 vs. 12 (p = 0.11)

Ingram A et al. J Pharm Pract, Aug 2019 (epub ahead of print)

I am inspired to start a Pharm.D. HF medication titration clinic but need a bit more information for administration

Are target doses that important?

How do I figure out which patients should be referred to me?
Why are target doses of GDMT important?

- **BIOSTAT CHF**: 2100 HFrEF patients followed for median 21 months
- Achieving <50% of target dose = ↑ risk of death and HF hospitalization

![Graphs showing survival time and cumulative percentage of patients](image)


Why are target doses of GDMT important?

- **ATLAS**:
  - Lisinopril high dose = 12% ↓ in mortality/hospitalizations vs. low dose
- **Carvedilol dose ranging study**:
  - Higher dose = ↓ mortality/hospitalizations, ↑ EF
- **HEAAL**:
  - 150 mg/day of losartan ↓ death or HF hospitalization compared with 50 mg/day
- **PARADIGM**:
  - Any dose reduction regardless of treatment assignment: ↑ risk of primary outcome: HR 2.5, 95% CI 2.2-2.7

Which of these patients is appropriate for referral to the Pharm.D. HF clinic?

a. Euvolemic, asymptomatic 62 year-old male with EF of 45%, but hypertensive
b. Euvolemic, NYHA FC II-III 58 year-old female with EF of 25%, hypertensive with CKD stage 3
c. Hypervolemic, NYHA FC III 73 year-old male with EF of 20%, who is relatively hypotensive
d. Hypervolemic, NYHA FC II 45 year-old female with EF of 35%, who is hypertensive

HF patients, here I come!!

Establishing a role for the pharmacist at your institution
Components of Comprehensive Medication Management

- Organizational
  - Leadership support, clinic space, billing/budget
- Care delivery process
  - Identifying patients, scheduling, care documentation
- Care team engagement
  - Scope of practice, interprofessional collaboration, staff support
- Evaluating services
  - Measuring/reporting data: IT support vs. manual collection
- Ensuring consistent and quality care
  - Practitioner training, quality assurance


Getting Started

- Do you have data for your HF patients?
  - Readmission rates
  - Use of ACE inhibitors
  - Use of beta blockers
  - Use of aldosterone antagonists
  - Doses of ACE inhibitors and beta blockers

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Getting Started

• Who sees the HF patients?
  – HF specialist/general cardiologist/primary care provider
• Can you identify a physician collaborator/champion?
• How many HF patients in your system?
  – Admission databases or ambulatory visit databases (ICD 10 codes)
  – What is the average follow-up time before next MD appointment?
    • UI Health busier M.D.s: next available appointment about 90 days
    • UI Health Pharm.D.: next available appointment 1-2 weeks, never >4 weeks

Getting Started

• What do you want the pharmacist’s role to be?
  – Medication reconciliation only
  – Counseling and education only
    • Medications, adherence aids, written instructions
  – Comprehensive Medication Management
    • Recommend appropriate evidence-based therapies
    • Avoid drug interactions
    • Assure appropriate laboratory follow up
  – Follow up
    • Telephone monitoring for high-risk patients
Getting Started

Which patients do you want to target?

**UI Health**
- Referred from outpatient cardiologist if HFrEF, not optimized on GDMT
- **Clinically stable**
- Recently hospitalized or volume overloaded should be seen by MD or APN prior to referral
- Vital signs, lab tests, symptom assessment, edema

**MetroHealth**
- Referred from inpatient or outpatient cardiologist or Primary care MD if HFrEF, not optimized on GDMT
- **Clinically stable**
- Internal standardized HF symptom questionnaire, vital signs, lab test, focused physical exam

Ingram A. *J of Pharmacy Practice*. October 2019 (epub ahead of print)

Getting Started

- Write a proposal
  - How many staff members do you need?
  - Background info/justification for position
  - Significance/benefit to your healthcare system
  - Pharmacists role: collaborative practice agreement / protocol
- Sell it to administration

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Pharmacist Privileging

**Collaborative Practice Agreement (CPA)**
- Prescriber delegates patient care functions
  - Initiating, modifying, or discontinuing drug therapy
  - Ordering/interpreting lab tests
- Extent of authority and requirements highly variable based on individual state pharmacy practice acts
- Legal document between prescriber and pharmacist

**Protocol**
- Reviewed/approved by hospital medical staff and leadership
- Outlines delegation of patient care functions
  - Initiating, modifying, or discontinuing drug therapy
  - Ordering/interpreting lab tests
- Content experts include the prescriber(s) who will be referring patients to the pharmacist

**Pharmacist Privileging Variables in State CPA Laws**
- CPA participants
  - Number of pharmacists, prescribers, and patients
  - Pharmacist-to-prescriber ratio
- Authorized functions
  - Initiate, modify, discontinue drugs
  - Physical assessment
  - Order/interpret labs
- Requirements/restrictions
  - Qualifications, continuing education
  - Practice setting
  - Medications to be managed
  - Involvement of patient
  - Disease state of patient
  - Entity approving CPA
  - Liability insurance
  - Physician review/ duration of agreement

CDC. Advancing Team-Based Care Through Collaborative Practice Agreements. Available at www.cdc.gov/dhdsp/pubs/docs/cpa-team-based-care.pdf
Pharmacist Privileging
Variables in Institutional Protocol Requirements

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Drug therapy adjustment or titration will be based on current clinical status (i.e., physical assessment and laboratory data) and evidence-based medicine</td>
</tr>
<tr>
<td>2019</td>
<td>Drug therapy adjustment or titration will be based on current clinical status (i.e., physical assessment and laboratory data), current medication regimen, and physician preference if documented in the progress note</td>
</tr>
<tr>
<td>2019</td>
<td>Interventions may include adding, removing, or adjusting doses. Doses ↑ no &gt;100% at each visit. Doses ↑ in smaller increments (25-50%) if: Dizziness, fatigue, worsening edema, HR &lt;70 bpm, BP &lt;100 mm Hg, Scr rise &gt;0.3 mg/dL, potassium &gt;5.0 mEq/L</td>
</tr>
</tbody>
</table>

UIC HF Medication Titration Clinic

- Referral to Pharm.D.
- HFrEF
- Exclude transitions of care
- Progress notes and prescription to M.D. for co-signature
- M.D. available as needed
- Target or maximum tolerated dose
- BP at goal
- Assessment HF ± HTN medication titration
- Education

Follow up every 2 weeks


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HF Clinic has a Pharmacist: Now What?

- Advertise
  - Send letter and flyer to providers
- Collect data on your interventions
- Evaluate patient outcomes
- If time and staffing allow
  - Look for ways to expand your role
  - Look for ways to intervene for more patients

Case Study on Collaborative Practice Agreements

Vicki Groo, Pharm.D.

and

Christopher Gans, M.D., FACC, FASE
Patient Case

CD is a 52 yo African American male seen by M.D. 3 weeks s/p discharge for ST elevation MI, drug eluting stent, and new onset HF. Euvolemic on exam. Lisinopril was increased to 20 mg daily, he was referred to Pharm.D. for medication titration, and he is at your clinic 2 weeks later. EF 25%. Labs normal at discharge.

Today, he has DOE at 1 block or ½ flight of stairs, baseline was no limitations. 2 pillow orthopnea, no PND or edema.

Patient Case

• Medications (all new and taken orally):
  – Aspirin 81 mg daily
  – Carvedilol 6.25 mg bid
  – Lisinopril 20 mg daily
  – Atorvastatin 80 mg daily
  – Furosemide 40 mg bid
  – Prasugrel 10 mg daily

• Vitals: BP 110/70 mm Hg, HR 90 bpm
• Weight: 85 kg, stable
• Assessment:
  – Stage C HFrEF secondary to CAD, NYHA FC II
What is your plan to treat his HF today?

a. Increase lisinopril to 40 mg daily
b. Increase carvedilol to 12.5 mg bid
c. Add spironolactone 12.5 mg daily
d. Add hydralazine/isosorbide 37.5 mg/20 mg tid

HF Plan Documentation

- Increase carvedilol to 12.5 mg bid
- CPM lisinopril 10 mg daily
- CPM furosemide 40 mg bid
- Basic metabolic panel

- Increase carvedilol to 12.5 mg bid for HF with plan to titrate to target dose as tolerated
- CPM lisinopril 10 mg daily. Plan to titrate to target dose at future appointment
- CPM furosemide 40 mg bid, patient without volume overload today
- Basic metabolic panel because ACEi recently increased

CPM = continue present management
Patient Education

• Patient had a comprehensive education session at discharge but states he is overwhelmed by his condition and all the new information
• He is concerned about how many medications he is taking
• He has stopped using a salt shaker at the table since discharge

What is your priority for education at this visit?

a. Purpose and plan for his medications
b. Low salt diet
c. Daily weights
d. HF signs/symptoms
e. All of the above
Health Education Retention

- 100 stroke patients received Joint Commission mandated stroke education
- Average age of 60 years, 57% male, 56% African American, 43% urban dwelling, 75% low income, 59% low health literacy
- Stroke knowledge retention
  - Name all 5 warning signs (12%) / call 911 (85%)
  - Personal risk factors (43%)
  - Medications prescribed for stroke (76%)


Patient Case (Continued)

2 weeks later he returns for follow up and is taking his medications as prescribed. He is complaining of new frequent dizziness and dry mouth.

DOE improved to 1 block, no edema or PND.

Vitals: BP 98/60 mm Hg, HR 95 bpm, weight ↓2 kg

Labs from prior visit: rise in SCr from 0.8 mg/dL to 1.0 mg/dL

Assessment: NYHA FC II, symptomatic hypotension
What is your plan to manage his HF at this time?

a. Decrease lisinopril to 10 mg daily
b. Decrease carvedilol to 6.25 mg bid
c. Discontinue furosemide
d. Check basic metabolic panel

Case Summary

• Data provided to support target dosing in HF and role of pharmacist in achieving this.

• Highlights of case
  – Drug / dosing / monitoring decisions
  – Good documentation
  – Prioritizing patient education based on current needs

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Case Study on Titration Clinics

Vicki Groo, Pharm.D.

and

Christopher Gans, M.D., FACC, FASE

Guides for Troubleshooting Medication Titration
Common problems with GDMT Titration

**Low blood pressure**
- If asymptomatic, usually requires no change in therapy
- If symptomatic: dizziness is common during titration and often improves with time
  - Reassure patient, slow down titration
  - Change carvedilol to beta-1 selective agent
- Consider stopping/reducing CCB, nitrates, or other vasodilator
- Consider decreasing diuretic dose if euvoletic and stable

**Renal dysfunction**
- Some rise (10-30%) in BUN and SCr is expected, and no action is necessary if increase is small and patient is asymptomatic
- Consider stopping other nephrotoxic agents (NSAIDs)
- Consider decreasing diuretic dose if euvoletic
- If SCr rises more than 50% above baseline, ↓ACE/ARB dose by half and recheck labs in 1-2 weeks

Patient Case (Continued)

- Labs from prior visit
  - BUN of 40 mg/dL (baseline 16 mg/dL)
  - SCr of 1.4 mg/dL (1.0 mg/dL at last visit)
- Furosemide was held x 1 dose then decreased to 40 mg daily, and dizziness resolved
- He was seen by M.D. in the interim, carvedilol was increased to 25 mg bid, and went back to Pharm.D. for evaluation after dose change
- He had been steadily improving: no SOB walking 4 blocks or in cardiac rehab
- However went to Bears game last week and has gained 5 lb, had PND 3 times in past week and has 2+ lower extremity edema
Patient Case (Continued)

• Vitals: BP 120/70 mm Hg, HR 80 bpm
• Medications (taken orally):
  – Aspirin 81 mg daily
  – Carvedilol 25 mg bid
  – Lisinopril 20 mg daily
  – Atorvastatin 80 mg daily
  – Furosemide 40 mg daily
  – Prasugrel 10 mg daily
• You notice that his prasugrel and atorvastatin bottles are empty (3 months post MI) and have no refills

Your CPA or protocol does not cover diuretic management. You want to increase his furosemide to 40 mg bid. How do you proceed?

a. Call referring M.D. who is out of town and enter as verbal order
b. Discuss with M.D. in clinic and enter as verbal order
c. Enter as protocol order and notify referring M.D. in your progress note
Order Authentication

• Review state and Centers for Medicare & Medicaid Services (CMS) requirements

• Illinois:
  – Verbal order: signed before provider “leaves the area”
  – Telephone order: authenticated by provider within 72 hours

• CMS:
  – Protocol order: authenticated “promptly”
  – UIC considers this 72 hours


How are you going to refill his atorvastatin and prasugrel?

a. Advise him to call the prescribing M.D.
b. Refill as a protocol order
c. Get verbal order from M.D. in the clinic
UIC Titration Clinic Experience

Medications other than HF titration
- discontinue duplicate therapy (n = 7)
- Added /↑antihypertensive (n = 5) or discontinue /↓antihypertensive (n = 6)
- Added / changed antiplatelet therapy (n = 3)
- Added / changed statins/nonstatins to more appropriate therapy (n = 6)
- Discontinue potassium chloride supplements (n = 1)

Pharmacist management other than HF
- 1 additional comorbidity in 16 (31%) patients
- 2 or more additional comorbidities in 21 (41%) patients

UIC Titration Clinic Expansion

- 4 slots every other week
  - 4 slots weekly
  - 6 slots weekly
  - 7 slots weekly
  - 2nd day added

HFrEF from general cardiology
- New attending:
  - referrals for HFP EF with HTN

HFrEF from HF clinic
- HF clinic attending shortage
- Also receiving referrals for resistant HTN and lipid management

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Case Summary

- Managing medication related problems that are outside the scope of your CPA or protocol
- Identifying and overcoming barriers to medication titration

Consider these practice changes. Which will you make?

- Read the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment.
- Read the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure Web Addenda (focusing on guides for managing problems with ACEi, ARB, beta-blockers, and MRA)
- Compare my organization’s protocols with the most up to date heart failure treatment guidelines.
- Develop a plan to evaluate my organization’s utilization of GDMT for HFrEF in the ambulatory setting.
- Determine what CPA or protocols for pharmacist management of chronic disease exist at my organization.
- Determine the feasibility of pharmacist involvement in the ambulatory management of heart failure.
Vickie Groo, Pharm.D., is Clinical Associate Professor in the College of Pharmacy, Department of Pharmacy Practice and College of Medicine, Section of Cardiology at the University of Illinois at Chicago. She practices clinical pharmacy in the Heart Center at the UI Health Outpatient Care Center.

Dr. Groo received her Bachelor of Science degree in pharmacy from the University of Toledo in Toledo, Ohio and her Doctor of Pharmacy degree from The Ohio State University in Columbus. She completed a residency in Cardiology and Critical Care at the University of Illinois at Chicago (UIC).

Dr. Groo is currently the pharmacist on a multi-disciplinary team that primarily cares for heart failure patients. She worked for more than 10 years in the Medical and Cardiac Intensive Care units before transitioning to ambulatory care. In 2011 she started a pharmacy managed medication titration clinic focusing on use of guideline directed medical therapy for heart failure with reduced ejection fraction. The clinic has expanded to include heart failure with preserved ejection fraction and resistant hypertension. Dr. Groo’s other areas of interest include anticoagulation, arrhythmias, coronary artery disease, and hyperlipidemia.

Dr. Groo has certifications in Pharmacy Based Lipid Management and Immunization Delivery from the American Pharmacists Association and is a Certified Hypertension Clinician. In addition to patient care, she is actively involved in teaching and research at UIC, serving on committees with the American College of Clinical Pharmacy and American College of Cardiology Cardiovascular Team Section.

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**ADDITIONAL ACTIVITIES ON HEART FAILURE**

- Ask the Experts: Teaming Up for Interprofessional Heart Failure Care

[www.ashpadvantage.com/hfcare](http://www.ashpadvantage.com/hfcare)

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