Keeping Your Patients with Heart Failure Out of the Hospital: Preventing Drug-Induced Exacerbations of Heart Failure

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Disclosure

• The authors have no conflicts of interest to disclose
Learning Objectives

1. Distinguish medications that exacerbate heart failure (HF) from those that cause de novo myocardial dysfunction.
2. Given a medication associated with exacerbation of HF, describe a proposed mechanism for worsening myocardial function.
3. List general approaches to preventing drug-induced exacerbation of HF.
4. Given a patient with HF on a medication associated with HF exacerbation, devise a medication therapy plan for preventing further decompensation.
JW is transferred to your institution for further management of acute decompensated heart failure (ADHF) with cardiogenic shock. Please take a moment to review the pertinent information from his case.
What precipitated this patient’s ADHF?
The lifetime risk of developing heart failure is 1 in 5.

Polypharmacy commonly defined as taking ≥ 5 medications

Nearly half of patients with heart failure over the age of 65 have ≥ 5 co-existing conditions

Does not account for non-prescription medications, herbal supplements, and vitamins (1 in 9 report using)

Mechanisms of Drug-Induced Heart Failure

**Myocardial Toxicity**
Direct cellular injury (e.g., toxic free radicals), commonly seen with chemotherapeutic agents (not the focus of this presentation)

**Exacerbation of Underlying Myocardial Dysfunction**
- Decreased cardiac output
- Increased systemic vascular resistance
- Increased sodium and fluid retention
- Drug-drug interactions that impair benefit of heart failure therapies
Beta Blockers
“Start Low, Go Slow”

<table>
<thead>
<tr>
<th>Agent</th>
<th>Starting Dose</th>
<th>Target Dose</th>
<th>Titration Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg qday</td>
<td>10 mg qday</td>
<td>Every 1 week until 3.75 mg, then every 4 weeks</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125-6.25 mg bid</td>
<td>25-50 mg bid</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Metoprolol XL</td>
<td>12.5-25 mg qday</td>
<td>200 mg qday</td>
<td>Every 2 weeks</td>
</tr>
</tbody>
</table>

- Can be continued in ADHF (in absence of cardiogenic shock) unless thought to be the cause of ADHF
- Can be safely initiated at low doses at discharge from ADHF hospitalization

Other Indications for Beta Blockers

Risk of exacerbation often overlooked when treating other conditions (e.g., acute coronary syndrome, atrial fibrillation)

The COMMIT trial evaluated early beta blockade following acute myocardial infarction, where metoprolol was up-titrated to 200 mg in first 24-48 hours.

- 2.2% reduction in death due to arrhythmias
- 2.2% increase in death due to cardiogenic shock

Calcium Channel Blockers
Calcium Channel Blockers

Non-Dihydropyridines (Diltiazem, Verapamil)

• Can exacerbate heart failure via negative inotrope and chronotropic effects
• Unlike beta blockers, no long-term remodeling benefits

What about Dihydropyridines?

**PRAISE**

Any Chronic Heart Failure (EF < 30%)

- **50% increased risk** of both pulmonary edema and peripheral edema (p < 0.05)

**PRAISE-2**

Nonischemic Cardiomyopathy (EF < 30%)

- Nearly 3x **increased risk** of pulmonary edema,
- **60% increased risk** of peripheral edema (p=0.001)

EF = ejection fraction.

Antiarrhythmics
# Class I Antiarrhythmics

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Risk in Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Disopyramide</td>
<td>Negative inotropic effects</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>Proarrhythmic</td>
</tr>
<tr>
<td></td>
<td>Procainamide*</td>
<td>Negative inotropic effects</td>
</tr>
<tr>
<td></td>
<td>Lidocaine / Mexiletine</td>
<td>Concentration-dependent negative inotropic effects</td>
</tr>
<tr>
<td>1B</td>
<td>Flecainide</td>
<td>Proarrhythmic, negative inotropic effects</td>
</tr>
<tr>
<td></td>
<td>Propafenone</td>
<td>Negative inotropic effects</td>
</tr>
</tbody>
</table>

*Oral procainamide no longer available in the US.

Sotalol (A Tale of Two Isomers)

D-Sotalol
Class III Antiarrhythmic
Increased mortality in patients with LV dysfunction after myocardial infarction

L-Sotalol
Beta Blocker
Reduced re-infarction rate and was associated with numerically fewer deaths after MI

LV = left ventricular, MI = myocardial infarction.
Dronedarone

**ANDROMEDA**
- Advanced heart failure (coexisting arrhythmia not a requirement for inclusion)
- Terminated early due to increased mortality

**PALLAS**
- Permanent atrial fibrillation (2/3 with heart failure history, most with preserved EF)
- Terminated early due to increased mortality

Atrial or Ventricular Arrhythmia?

Antiarrhythmic Indicated

Atrial

Amiodarone
Dofetilide

Sotalol in select patients

Ventricular

Amiodarone

Lidocaine (Mexiletine), Procainamide, or Sotalol

(Refractory patients or first-line therapy contraindicated)

Adapted from: Circulation. 2014 Dec 2;130(23):2071-104.
How could this patient’s atrial fibrillation have been managed differently?
Intravenous Sedatives
But does the effect of propofol on calcium exchange impair cardiac contractility?

GABA = gamma aminobutyric acid, NE = norepinephrine, NMDA = N-methyl-D-aspartate, R = receptor
\[ CO = HR \times SV \]

Propofol can decrease preload secondary to venodilation, especially in setting of hypovolemia

- Preload (volume)
- Afterload (impedance)
- Contractility (strength)

CO cardiac output, HR heart rate, SV stroke volume
PCWP = pulmonary capillary wedge pressure, LVEDP = left ventricular end-diastolic pressure
Dexmedetomidine

But what about the effects of dexmedetomidine on other $\alpha_2$ receptors?

GABA = gamma aminobutyric acid, NE = norepinephrine, 
NMDA = N-methyl-D-aspartate, $R$ = receptor
Effects of dexmedetomidine at cardiac α₂ receptors may result in decreased heart rate and thus cardiac output.

Effects on peripheral α₂ receptors results in variable effects on afterload.

\[ CO = HR \times SV \]

CO cardiac output, HR heart rate, SV stroke volume
Propofol vs. Dexmedetomidine

No significant differences in hemodynamic effects among patients admitted to neurocritical care unit (n = 324)

Adapted from: Crit Care Med. 2014 Jul;42(7):1696-702
Miscellaneous Agents

Negative inotropic and sympathetic activation effects often cancel out; caution in advanced heart failure

Ketamine

Minimal myocardial depression; preferred for inducing anesthesia in patients with structural heart disease

Etomidate

GABA = gamma aminobutyric acid, NE = norepinephrine, NMDA = N-methyl-D-aspartate, R = receptor
How should this patient’s sedation be managed?

(Assuming he is negative for alcohol withdrawal)
Illicit Substances
Alcohol

Relative Risk of Mortality vs Drinks per Day

Men vs Women

Alcohol

Chronic
• Common cause of dilated cardiomyopathy
• Risk increased at ≥ 7-8 drinks per day for 5-10 years
• Abstinence advocated but moderation may help

Acute
• ADHF may result from myocardial depression and/or volume overload
• Moderation should be recommended at a minimum

Stimulants

All stimulants increase sympathetic activity albeit by two different mechanisms:

- Reduced neurotransmitter reuptake (e.g., cocaine)
- Increased neurotransmitter release (e.g., amphetamines)
CO = HR \times SV

Increases in heart rate and contractility may offset afterload; effect on cardiac output will vary

Acute ingestion increases afterload, which can reduce stroke volume and provoke flash pulmonary edema

Chronic stimulant use contributes to the same neurohormonal mechanism responsible for other types of heart failure with reduced ejection fraction.

Stimulants

Illicit Substances
• Just stop!

Medically Indicated
• Avoid when possible
• Cognitive-behavioral therapy
• Consider non-stimulants (e.g., atomoxetine, $\alpha_2$ agonist)

What should be done about this patient’s reported alcohol use?
“My big left toe is killing me”

• At its worst, 9/10 pain
• Patient presents wearing flip-flops
• Pain similar to prior gout attack a few years ago
• Patient took three doses of ibuprofen 400 mg over the last 24 hours with some pain relief
• Additional data:
  – Creatinine clearance 50 ml/min
Non-steroidal anti-inflammatory drugs (NSAIDs)

• **Heerdink, ER et al. 1998**
  – Cohort study to evaluate risk of HF among those 50 yrs or older and receiving a diuretic and NSAID
  – Combination of diuretic and NSAID use associated with an increased risk of HF hospitalization
    adjusted relative risk (RR) 1.8 (95% confidence interval (CI), 1.4-2.4)

• **Rotterdam Study 2002**
  – Follow-up evaluation of a patients enrolled in prospective cohort study, which evaluated the
    prevalence, incidence and determinants of select diseases in the elderly
  – Relative risk of first occurrence of HF in those with current NSAID use was 1.1 (95% CI 0.7-1.7)
  – The adjusted RR of HF relapse was 9.9 (95% CI, 1.7-57.0) for patients with HF and at least 1 NSAID
    prescription

• **Huerta, C et al. 2006**
  – Cohort with nested case-control of patients in a general practice
  – Relative risk of HF admission in current users of NSAIDs with prior HF was 8.6 (95% CI 5.3 to 13.8)
  – No effect of NSAID dose or duration on HF admission risk

2006;92:1610–1615.
**NSAIDs/Cyclo-oxygenase 2 inhibitors**

- Cohort study to evaluate the risk of death and hospitalization due to acute MI or HF associated with use of NSAIDs in those with HF
- Dose-dependent increase risk of death, hospitalization for HF and MI

<table>
<thead>
<tr>
<th></th>
<th>Death HR* (95% CI), p value</th>
<th>HF hospitalization HR* (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>1.75 (1.63-1.88), p &lt;0.001</td>
<td>1.24 (1.12-1.39), p &lt;0.001</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2.08 (1.95-2.21), p &lt;0.001</td>
<td>1.35 (1.24-1.48), p &lt;0.001</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.31 (1.25-1.37), p &lt;0.001</td>
<td>1.16 (1.10-1.23), p &lt;0.001</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.22 (1.07-1.39), p=0.004</td>
<td>1.18 (1.00-1.40), p =0.05</td>
</tr>
<tr>
<td>Other NSAIDs</td>
<td>1.28 (1.21-1.35), p &lt;0.001</td>
<td>1.27 (1.18-1.36), p &lt;0.001</td>
</tr>
</tbody>
</table>

* Adjusted hazard ratio (HR) for age, sex, year of first hospitalization for HF, comorbidity, severity and concomitant medical treatment

Arch Intern Med. 2009;169(2):141-149.
NSAIDs/Cyclo-oxygenase 2 inhibitors

• Proposed mechanism of adverse effect in those with decreased effective circulating blood volume
  – Inhibition of prostaglandin synthesis leads to:
    • Decreased renal blood flow
    • Sodium and water reabsorption

• Recommendation:
  – Avoid use

# Corticosteroids

<table>
<thead>
<tr>
<th></th>
<th>Duration of actions (hours)</th>
<th>Relative glucocorticoid activity</th>
<th>Relative mineralocorticoid activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>8-12</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>12-36</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>12-36</td>
<td>5</td>
<td>minimal</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>36-72</td>
<td>30</td>
<td>minimal</td>
</tr>
<tr>
<td><strong>Mineralocorticoid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>12-36</td>
<td>10-15</td>
<td>125-150</td>
</tr>
</tbody>
</table>

Corticosteroids

• Current glucocorticoid use associated with elevated HF risk in retrospective, case-control study of patients ≥ 50 years old with at least one glucocorticoid prescription (adjusted odds ratio (OR) 2.66; 95% CI, 2.46-2.87)

<table>
<thead>
<tr>
<th>Prednisone daily equivalent dose</th>
<th>Adjusted OR for HF risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7.5 mg</td>
<td>1.95 (95% CI 1.72 to 2.21)</td>
</tr>
<tr>
<td>7.5 – 20 mg</td>
<td>2.27 (95% CI 2.00 to 2.59)</td>
</tr>
<tr>
<td>&gt; 20 mg</td>
<td>3.69 (95% CI 3.26 to 4.18)</td>
</tr>
</tbody>
</table>

Corticosteroids Effect on Sodium and Water Excretion

• Liu, C et al. 2015
  – Low-dose prednisone x 10 days (15 mg/d, n = 8) increased urine output in patients with symptomatic HF vs. standard of care (n=10, p < 0.05)
  – Medium (30 mg/d, n = 10) and high-dose prednisone (60 mg/d, n = 10) increased 24 hour sodium excretion vs. control (p<0.01 and p<0.05, respectively)
  – Weight reduction, at day 10
    Placebo 1.5 ± 1.1 kg
    Low-dose prednisone 3 ± 1.8 kg
    Medium-dose prednisone 3.9 ± 3.2 kg
    High-dose prednisone 4.1 ± 2.8 kg

• Recommendations:
  – Use when clinically indicated and no alternative exists
  – Use lowest dose and shortest course of therapy possible
  – Monitor for worsening/progression of HF symptoms

What medication(s) should be recommended to manage this patient’s gout?
Acute Gout Treatment Recommendations

Colchicine

- Use if early presentation

Corticosteroids

- Unable to use colchicine
- Intra-articular: monoarticular gout
- Oral: Polyarticular gout

NSAIDs

- Use should be avoided

Pharmacy Curb-side Consult

- You practice in a HF clinic and provide care for JW
- His primary care provider would like to know if it would be OK for him to receive one of the newer medications for type 2 DM
- HF status (at visit two weeks ago): New York Heart Association (NYHA) Class II symptoms and euvolemic
- Hemoglobin A1c is 8.6% (two years ago it was 8%)
- Current medications for DM: metformin 1000 mg BID
- Laboratory data: within normal limits except serum creatinine 2 mg/dl (stable)

DM = diabetes mellitus
Antihyperglycemic Therapy for Type 2 Diabetes*

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Dual therapy</th>
<th>Triple therapy</th>
</tr>
</thead>
</table>
| - Initiation of therapy: A1c < 9%  
- Metformin, unless contraindicated | - Initiation of therapy: A1c ≥ 9%  
- A1c not achieved with 3 mo. of monotherapy | A1c not achieved with 3 mo. of dual therapy |

- Sulfonylurea
- Thiazolidinedione (TZD)
- Basal Insulin
- Glucagon-like peptide (GLP)-1 receptor agonist
- Dipeptidyl Peptidase (DPP)-4 inhibitor
- Sodium-glucose co-transporter-2 (SGLT2) inhibitor

* If A1c ≥ 10%, blood glucose ≥ 300 mg/dl or overt symptoms– consider injectable therapy

• Metformin
  - Recommended as first-line therapy
  - Contraindications similar to general population

• Sulfonylurea
  - Safe for use
  - Contraindications similar to general population

• Insulin
  - Safe for use
  - Use may predict risk for developing HF

• GLP-1 receptor agonist
  - No increased risk of HF observed in clinical trials with lixisenatide, liraglutide or semaglutide

Thiazolidinediones

- **Mechanism of adverse effect**
  - Not established
  - Dose-related fluid retention; risk increased when combined with insulin

- **Boxed warning**
  - Initiation of therapy in those with NYHA Class III/IV symptoms is contraindicated
  - Use not recommended for those with symptomatic HF
  - Reduce the dose or discontinue therapy if HF symptoms develop during therapy
  - Use can cause or exacerbate HF

- **Recommendations for use**
  - Consider alternative treatment options for those with a depressed left ventricular ejection fraction (LVEF)
  - Do not initiate in those with HF symptoms
  - Discontinue therapy if HF symptoms develop

DPP-4 Inhibitors

Alogliptan

EXAMINE Trial

- Overall, no difference in the risk of HF hospitalization with alogliptin vs. placebo: HR, 1.19 (95% CI, 0.90–1.58), p=0.220

- Without HF history, alogliptin associated with increased HF hospitalization risk: HR, 1.76 (95% CI, 1.07–2.90), p=0.026

- Product labeling
  - Consider risk vs. benefit prior to initiation if patient at risk for developing HF
  - Consider discontinuation if HF develops

Linagliptan

- Not associated with an increased risk of HF hospitalization

- Product labeling: no comment

DPP-4 Inhibitors

**Saxagliptan**

- **SAVOR-TIMI 53 Trial**: risk of HF hospitalization increased with saxagliptan (3.5%) vs. placebo (2.8%) HR, 1.27 (95% CI, 1.07-1.51), p = 0.007
  - Risk increased: prior HF symptoms, an elevated baseline N-terminal pro-natriuretic peptide, or an estimated glomerular filtration rate (eGFR) < 60 ml/min/m²
- **Product labeling**
  - Consider risk vs. benefit in those at risk for developing HF
  - Monitor for signs and symptoms during therapy; patients to report symptoms immediately
  - Consider discontinuation if HF develops

**Sitagliptan**

- **TECOS trial**: No difference in the risk of HF between those receiving sitagliptan or placebo
- **Retrospective cohort studies**:
  - Baseline HF: adjusted OR, 1.84 (95% CI, 1.16 to 2.92)
  - Those on dialysis: adjusted HR, 1.52 (95% CI, 1.21–1.90)
- **Product labeling**: no comment

# DPP-4 Inhibitors: Recommendations for Use

<table>
<thead>
<tr>
<th>Patient Presentation</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>New or worsening HF symptoms after initiation of therapy</td>
<td>Evaluate potential causes. Consider replacing DPP-4 inhibitor therapy with an alternative.</td>
</tr>
<tr>
<td>Current or prior HF symptoms and/or renal impairment</td>
<td>Use an alternative agent.</td>
</tr>
<tr>
<td>Left ventricular dysfunction (i.e., left ventricular ejection fraction &lt; 40%) without current/prior HF symptoms</td>
<td>Consider alternative agent.</td>
</tr>
<tr>
<td></td>
<td>If used, monitor for HF signs/symptoms.</td>
</tr>
<tr>
<td>Known cardiovascular disease or risk of heart failure</td>
<td>Consider risk vs. benefit.</td>
</tr>
<tr>
<td></td>
<td>If used, monitor for HF signs/symptoms.</td>
</tr>
</tbody>
</table>

[22x222] Known cardiovascular disease or risk of heart failure

SGLT2 Inhibitors

• EMPA-REG Outcome Trial
  – Type 2 DM, ≥ 18 y/o, established CVD and eGFR ≥ 30 ml/min/m²
  – Risk of CV death causes, nonfatal myocardial infarction, or nonfatal stroke: lower with empagliflozin (10.5%) vs. placebo (12.1%)
    HR 0.86 (95.02% CI, 0.74 to 0.99; P=0.04
  – Hospitalization for HF: empagliflozin (9.4%) vs. placebo (14.5), p=0.003
  – Why a benefit?
    • Diuretic and natriuretic properties
    • Reduction in SBP

• Late-breaking/on going clinical trials
  – CVD-REAL Study
  – Canagliflozin Cardiovascular Assessment Study (CANVAS)
  – Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58)

Which antihyperglycemic medication(s) could be considered for this patient?
Pregabalin

- Mechanism: not well established
- Peripheral edema
  - Alone: ~ 6-8%
  - Combination with TZD: 19%
- Several case reports/series
- Onset: 3 days – 2 months
- Resolution: with discontinuation and management of HF symptoms
- Product labeling
  - May cause edema; no association with complications including HF
  - Use caution in NYHA III/IV HF
  - Use caution with TZD

Additional Medications that Can Exacerbate HF

<table>
<thead>
<tr>
<th>Medication</th>
<th>Onset of Symptoms</th>
<th>Possible Mechanism</th>
<th>Recommendations for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>Immediate to intermediate</td>
<td>Negative inotrope</td>
<td>Serious, life-threatening infections</td>
</tr>
<tr>
<td>Carbamezepine</td>
<td>Immediate (if overdose) to</td>
<td>Negative chronotrope and inotrope suppresses sinus node</td>
<td>Evaluate risk vs. benefit</td>
</tr>
<tr>
<td></td>
<td>intermediate</td>
<td>node automaticity and AV conduction</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Intermediate to delayed</td>
<td>Negative inotrope, proarrhythmic</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

# Additional Medications that Can Exacerbate HF

<table>
<thead>
<tr>
<th>Onset of Symptoms</th>
<th>Possible Mechanism</th>
<th>Recommendations for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Intermediate</td>
<td>Dose-dependent QTc prolongation</td>
</tr>
<tr>
<td>TNF-alpha inhibitors</td>
<td>Intermediate</td>
<td>Cytokine mediated</td>
</tr>
</tbody>
</table>

Summary

LVEF < 40% +/- HF symptoms

New medication required

Contraindicated
• Use alternative treatment option

Precaution/risk
• Risk vs. benefit
• If used, lowest dose & shortest duration possible; monitor

Safe/no known risk
• Use therapy
• General monitoring for HF signs and symptoms
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