Chronic Heart Failure Management: Debunking Myths and Misconceptions

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Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
Learning Objectives

• Given a case of a patient with diabetes and heart failure with reduced ejection fraction (HFrEF), compare the risks and benefits of the oral antihyperglycemics.

• Given a case of a patient with HFrEF, identify which guideline-based medication(s) should be titrated or added.

• Given a case of a patient with HFrEF and hypertension, select a treatment regimen and blood pressure goal.
Heart Failure Reduced Ejection Fraction Management: Overview and Diabetes and Heart Failure

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Jefferson College of Pharmacy
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HFrEF Warm-Up Questions
HFrEF Review Question #1

Choose ALL that apply:

Which of the following statements best describes the role of loop diuretics in treating patients with HFrEF?

A. They help people live longer only
B. They keep people out of the hospital only
C. They help people live longer and keep them out of the hospital
D. They can be used to help control blood pressure

J Am Coll Cardiol 2013;62:1495–539
Polling Question

HFrEF Review Question #2
Choose ALL that apply:

Which of the following statements is true?

A. Angiotensin receptor blockers (ARBs) are less likely to cause angioedema as compared to angiotensin converting enzyme inhibitors (ACEi)
B. ACEi and ARBs are equally preferred in HFrEF patients
C. Use of an ARB or an ACEi has morbidity and mortality benefit even if a patient is not experiencing symptoms

J Am Coll Cardiol 2013;62:1495–539
Circulation. 2017;136:e137–e161
HFrEF Review Question #3

Name the three beta blockers that are proven to reduce mortality in HFrEF.
Polling Question

HFrEF Review Question #4
Choose the best answer:

Which of the following best depicts a patient who would clearly benefit from therapy with an aldosterone antagonist?

A. NYHA class II–IV HF and who have LVEF of 35% or less
B. Following an acute MI in patients who have LVEF of 40% or less who develop symptoms of HF or have a history of diabetes mellitus

LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association
Polling Question

HFrEF Review Question #5

It is ok to use the combination of hydralazine and isosorbide mononitrate to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACEi or ARB (unless contraindicated)

A. True
B. False
Pathophysiological Links Between Type 2 Diabetes and Heart Failure

4x increase in the incidence of hospitalization for HF compared to general population

<table>
<thead>
<tr>
<th>Accelerating atherosclerosis</th>
<th>Activation of the renin-angiotension-aldosterone system (RAAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired calcium handling in cardiomyocytes</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Myocardial fibrosis</td>
<td>Endothelial dysfunction</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol. 2018 In Press
Case

- AH is a 63 year-old Black man
- No known drug allergies (NKDA)
- Past Medical History
  - Obesity: BMI > 35
  - Type 2 diabetes mellitus (T2DM)
    - 15 years
    - A1c last week 8.3 %
  - ACC/AHA Stage C, NYHA Class II Heart failure with reduced ejection fraction (HFrEF)
    - Secondary to a non-ischemic cardiomyopathy
    - 2 years
  - Stage 3 chronic kidney disease (CKD)
    - Just diagnosed
- Social History:
  - (+) cocaine abuse for 15 years (abstinent for 2 years)
  - (-) alcohol and tobacco
- Current Medications:
  - Metformin 1000mg orally twice daily
  - Aspirin enteric-coated 81mg orally daily
  - Atorvastatin 80mg orally daily
  - Lisinopril 40mg orally daily
  - Metoprolol succinate 100mg orally daily
  - Furosemide 40mg orally daily

What can or should be done for his T2DM???
Case

- AH is a 63 year-old Black man
- No known drug allergies (NKDA)
- Past Medical History
  - Obesity: BMI > 35
  - Type 2 diabetes mellitus (T2DM)
    - 15 years
    - A1c last week 8.3%
  - ACC/AHA Stage C, NYHA Class II Heart failure with reduced ejection fraction (HFrEF)
    - Secondary to a non-ischemic cardiomyopathy
    - 2 years
  - Stage 3 chronic kidney disease (CKD)
    - Just diagnosed

**QUESTION**

Should metformin be discontinued?

A. Yes, it should be stopped immediately
B. No, it should be continued as is
C. No, BUT the dose should be reduced
D. Yes, BUT it should be tapered off
Is there concern with metformin?

• Biguanides can cause lactic acidosis
  – Metformin can increase arterial lactate levels up to 1-2 mmol/L (if at all)
    • Inhibiting mitochondrial respiration in tissues

• Lactic acidosis is associated 30 – 50% mortality rate

• Secondary to
  – Drug accumulation → renal insufficiency
  – Lactate over production (i.e. hypoxic tissues) → circulatory failure
  – Impaired lactate removal → liver damage
Before metformin, there was another...

• Phenformin was used from the 1950’s through 1976
  – Taken off the market in 1977
  – > 300 cases of phenformin associated lactic acidosis
  – Labeled an “imminent hazard”
  – Pulled off the market

• Metformin was FDA approved in 1995 after several years of use in Europe

So what do we know about metformin, specifically??

- Wiholm and colleagues from Sweden, 1993
  - 10x increase in risk of lactic acidosis for phenformin compared to metformin
  - Other studies have it as an even higher risk

- Discontinuing metformin in an aging population who has renal insufficiency or cardiovascular disease could further reduce the risk of lactic acidosis

- Wording of the labeling for brand metformin inferred causality and noted that risk could be mitigated with careful patient selection

Metabolism. 2016;65(2):20-29
Diabetes Care. 2004; 27(7): 1791-1793
So what do we know about metformin, specifically???

• Since FDA approval
  – Lots of prospective studies!!!
  – Lots of retrospective analysis!!!
  – Lots of patient experience!!!

• Incidence of metformin induced lactic acidosis is <10/100,000 patient years

• The incidence of lactic acidosis in patients with type 2 diabetes without metformin has been shown to be 9 – 16/100,000 patient years

Metabolism. 2016;65(2):20-29
Cochrane Database Syst Rev. 2010;4:CD002967
Diabetes Care. 2005;28:539-543
Metformin, closer to present day

2006

- FDA removed congestive heart failure (CHF) as a contraindication
  - But acute or unstable CHF is still a precaution

Inzucchi S, et al. 2014

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR, mL/min per 1.73 m²</th>
<th>Max Metformin Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 2</td>
<td>&gt; 60</td>
<td>2550</td>
</tr>
<tr>
<td>3A</td>
<td>45 -59</td>
<td>2000</td>
</tr>
<tr>
<td>3B</td>
<td>30 - 44</td>
<td>1000</td>
</tr>
<tr>
<td>4 and 5</td>
<td>&lt; 30</td>
<td>Do not use</td>
</tr>
</tbody>
</table>
Metformin, closer to present day

- **2016**
  - FDA revised its warning regarding metformin use in patients with CKD → from a serum creatinine-based (SCr) to estimated glomerular filtration-based (eGFR)

<table>
<thead>
<tr>
<th>Abbreviated Summary of FDA Drug Safety Communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR between 30 – 45 mL/minute/1.73m²</td>
</tr>
<tr>
<td>eGFR &lt; 30 mL/minute/1.73 m²</td>
</tr>
</tbody>
</table>
Crowley and colleagues, 2017

- Systematic review and meta analysis
- Trials from 1996 to Sept 2016
- Randomized controlled trials (RCTs), non-randomized clinical trials, prospective and retrospective cohort studies
- Funded by the U.S. Department of Veteran Affairs

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Comorbidity</th>
<th>Number of trials (n)</th>
<th>Hazard ratio (95% CI)</th>
<th>GRADE of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>CKD</td>
<td>5 (33,442)</td>
<td>0.77 (0.61 to 0.97)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>11 (35,410)</td>
<td>0.78 (0.71 to 0.87)</td>
<td>Low</td>
</tr>
<tr>
<td>CV mortality</td>
<td>CHF</td>
<td>3 (6468)</td>
<td>0.77 (0.53 to 1.12)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>CHF readmission</td>
<td>CHF</td>
<td>4 (26,510)</td>
<td>0.87 (0.78 to 0.97)</td>
<td>Low</td>
</tr>
</tbody>
</table>

Ann Intern Med. 2017:166;191-200
Ann Intern Med. 2017;166(8):JC46
Circ Heart Fail. 2013:6;395-402
Metformin: studies with subgroups of CKD and HF +/- metformin (as reported in Eurich, et al. 2013)

• Aguilar, et al. 2011
  – Veteran Affairs
  – Reduction in all-cause mortality in the renal impairment sub-group is nearly identical to the overall cohort
  – <60 mL/minute/1.73 m² → HR 0.81, 95% CI 0.64 – 1.02

• Masoudi, et al. 2005
  – Retrospective cohort study of Medicare beneficiaries
  – All cause mortality
    • ≥1.5 mg/dL → HR 0.86, 95% CI 0.75 – 0.98
    • <1.5 mg/dL → HR 0.89, 95% CI 0.74 – 1.06
  – Similar results in all cause hospitalization and heart failure specific hospitalization

Circ Heart Fail. 2013.6;395-402.
Circ Heart Fail. 2011;4:53–58
Circulation. 2005;111:583–590
Bringing it back to the case

Case

- AH is a 63 year-old Black man
- Past Medical History
  - Obesity: BMI > 35
  - Type 2 diabetes mellitus (T2DM)
    - 15 years
    - A1c last week 8.3 %
  - ACC/AHA Stage C, NYHA Class II Heart failure with reduced ejection fraction (HFref)
    - Secondary to a non-ischemic cardiomyopathy
    - 2 years
  - Stage 3 chronic kidney disease (CKD)
    - Just diagnosed
- Diabetes medication: metformin 1000mg orally twice daily

Pharmacotherapy Adjustments

- In general, the use of metformin in this patient is appropriate
- However, the dose should be reduced to no more than 1,000 mg per day to reduce the risk of lactic acidosis
- This change will likely cause the glucose to become elevated
- So what about adding another oral?
  - Thiazolidinedione (TZD)
  - Dipeptidyl peptidase – 4 (DPP-4) inhibitors
  - Sodium/glucose co-transport (SGLT-2) inhibitors
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**QUESTION**

*Can a TZD be used?*

A. Yes
B. No
C. It’s complicated
[US Boxed Warning]: Thiazolidinediones, including pioglitazone, may cause or exacerbate heart failure; closely monitor for signs and symptoms of heart failure (eg, rapid weight gain, dyspnea, edema), particularly after initiation or dose increases; if heart failure develops, treat accordingly and consider dose reduction or discontinuation of pioglitazone. Not recommended for use in any patient with symptomatic heart failure. Initiation of therapy is contraindicated in patients with NYHA class III or IV heart failure.
Thiazolidinediones and Heart Failure

**AHA/ADA Consensus Statement, 2003**

- Small increase in mean plasma volume seen in healthy volunteers compared with placebo
  - May result from a reduction in renal excretion of sodium and an increase in sodium and free water retention
- Pioglitazone
  - 1 – 2.5 kg weight gain as monotherapy
  - 2.3 – 3.6 kg weight gain when added to insulin
- Rosiglitazone → more weight gain
- Incidence of pedal edema
  - Monotherapy ranges from 3% to 5% for each of the TZDs
  - Higher when combined with a secretagogue
  - Higher still with insulin

**AHA/ACCF Science Advisory, 2010**

- About a 1.7-fold increase in risk of CHF
  - Rosiglitazone > pioglitazone
- No increase in risk of cardiovascular death
- No increase in ischemic cardiovascular outcomes
- Does not affect left ventricular systolic or diastolic function
  - NYHA functional class I or II

Circulation. 2003;108:2941–8
Circulation. 2010;121:1868–1877
Thiazolidinediones: 2013 ACCF/AHA guidelines

- 2013 ACCF/AHA guidelines
  - “Treatment with thiazolidinediones (e.g., rosiglitazone) is associated with fluid retention in patients with HF and should be avoided in patients with NYHA class II through IV HF.”
Bringing it back to the case

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**Pharmacotherapy Adjustments**

- So what about adding another oral?
  - Thiazolidinedione
  - Dipeptidyl Peptidase – 4 Inhibitors
  - Sodium/glucose co-transport inhibitor
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    • Secondary to a non-ischemic cardiomyopathy
    • 2 years
  – Stage 3 chronic kidney disease (CKD)
    • Just diagnosed

QUESTION

Can a DPP-4 inhibitor be used?
A. Yes
B. No
C. It’s complicated
Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes: EXAMINE 2013

Not in initial analysis

Either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Hospitalized for Heart Failure</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>3.9%</td>
<td>1.19 (0.90 to 1.58)</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.3%</td>
<td></td>
</tr>
<tr>
<td>Patients without a history of heart failure</td>
<td>1.76 (1.07 to 2.90)</td>
<td></td>
</tr>
</tbody>
</table>

JACC Heart Fail. 2018 Jun;6(6):445-451
Circ Res. 2018;122:928-932
**Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus: SAVOR – TIMI 53**

### Initial Analysis

<table>
<thead>
<tr>
<th>History of, or were at risk for, cardiovascular events</th>
<th>Study Group</th>
<th>Hospitalized for Heart Failure</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin</td>
<td>3.5%</td>
<td>1.27 (1.07 to 1.51)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>2.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Heart failure directly associated with use of insulin and inversely associated with metformin*

### Stratified by Beta Blocker Tx

<table>
<thead>
<tr>
<th>Saxagliptin increased the risk of heart failure in</th>
<th>Tx w/ beta blockers</th>
<th>Without beta blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18%</td>
<td>1.18 (0.97 to 1.43)</td>
</tr>
<tr>
<td></td>
<td>81%</td>
<td>1.81 (1.21 to 2.76)</td>
</tr>
</tbody>
</table>

Circ Res. 2018;122:928-932
Trial Evaluating Cardiovascular Outcomes With Sitagliptin: TECOS 2015

**Initial analysis**

<table>
<thead>
<tr>
<th>Patients with cardiovascular disease</th>
<th>Study Group</th>
<th>Hospitalized for Heart Failure</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>3.1%</td>
<td>1.00 (0.83 to 1.19)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>3.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients were more likely to be treated with metformin, and less likely to be treated with TZDs and insulin

JACC Heart Fail. 2018 Jun;6(6):445-451
Dipeptidyl Peptidase – 4 (DPP-4) Inhibitors

• Inhibit the breakdown of more than just glucagon-like peptide 1

• Other non-insulin peptides like stromal cell-derived factor – 1 (SDF-1) also NOT broken down
  – Complex cascade of events
    • Distal tubular natriuresis vs. proximal
    • Increases cardiac fibrosis → limiting cardiac distensibility???
    • Promotes outflow of sympathetic activity from central nervous system
    • Protective nitric oxide pathways are less active in diabetes

• Glucagon-like peptide 1 receptor agonists (GLP-1 RA) do not affect SDF-1
  – Stimulate cyclic adenosine monophosphate (cAMP)
  – Proximal tubular natruresis
  – Increases heart rate

JACC Heart Fail. 2018 Jun;6(6):445-451

• “...type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease.”
Case

• AH is a 63 year-old Black man
• Past Medical History
  – Obesity: BMI > 35
  – Type 2 diabetes mellitus (T2DM)
    • 15 years
    • A1c last week 8.3 %
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    • Secondary to a non-ischemic cardiomyopathy
    • 2 years
  – Stage 3 chronic kidney disease (CKD)
    • Just diagnosed
• Diabetes medication: metformin 1000mg orally twice daily

Pharmacotherapy Adjustments

▌ So what about adding another oral?
▌ Thiazolidinedione
▌ Dipeptidyl Peptidase-4 Inhibitors
▌ Sodium/glucose co-transport inhibitor

Maybe sitagliptin is ok – numerous meta-analysis, observational studies, and post-marketing assessments are still working to clarify the picture
Case

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    • Secondary to a non-ischemic cardiomyopathy
    • 2 years
  – Stage 3 chronic kidney disease (CKD)
    • Just diagnosed

QUESTION
Can an SGLT-2 inhibitor be used?

A. Yes
B. No
C. It’s complicated
Sodium – Glucose Co – Transporter 2 (SGLT-2) Inhibitors

• 180 grams of glucose are filtered by the glomeruli

• Proximal convoluted tubule (PCT) reabsorbs almost all by way of SGLT-1 and SGLT-2
  – Coupled with sodium reabsorption
  – 90% of the glucose reabsorption occurs through SGLT2

• Drug-induced urinary glucose excretion requires moderately preserved renal function (eGFR > 30 ml/min/1.73m²)
Empagliflozin Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME): 2015

All the patients had established cardiovascular disease

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Hospitalized for HF</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>2.7%</td>
<td>0.65 (0.50 to 0.85)</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.1%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Group</th>
<th>CV death</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>3.7%</td>
<td>0.62 (0.49 to 0.77)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.9%</td>
<td></td>
</tr>
</tbody>
</table>

*Results of both endpoints were observed in patients with and without heart failure at baseline*
Canagliflozin Cardiovascular Assessment Study (CANVAS) Program: 2017

65.6% had a history of cardiovascular disease

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Hospitalized for HF per 1000 patient years</th>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard ratio for CV death or HF hospitalization (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>5.5</td>
<td>0.67 (0.52 to 0.87)</td>
<td>0.61 (0.46 to 0.80)</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.7</td>
<td></td>
<td>0.87 (0.72 to 1.06)</td>
</tr>
</tbody>
</table>

Secondary Analysis

HF at baseline (13.9%)

J Am Coll Cardiol. 2018 In Press
Sodium – Glucose Co – Transporter 2 (SGLT-2) Inhibitors: Mechanisms in Heart Failure

- Reduce systolic blood pressure by 4 – 6 mmHg
- Reduce diastolic blood pressure by 1 – 2 mmHg
- Possible nephron remodeling
- Improvement in endothelial function
- Reduction in arterial stiffness
- Loss of body weight (from urinating out calories)
- Reduce epicardial fat → decreasing noxious stimuli
- Improvement of mitochondrial energy output
- Decline in RAAS activation
- Reno-protective effects???
Bringing it back to the case

Case
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Pharmacotherapy Adjustments
- So what about adding another oral?
  - Thiazolidinedione
  - Dipeptidyl Peptidase –4 Inhibitors
  - Sodium/glucose co-transport inhibitor

Assuming the eGFR stays > 30 ml/min/1.73m²
Diabetes and Heart Failure: KEY TAKEAWAYS

1) Metformin can be used safely in heart failure (and may be beneficial in T2DM patients) and CKD with appropriate monitoring.

2) Treatment with thiazolidinediones (e.g., rosiglitazone) is associated with fluid retention in patients with HF and should be avoided in patients with NYHA class II through IV HF.

3) Saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease.

4) SGLT-2 inhibitors may be beneficial in HF patients with preserved renal function.
Misconceptions About Titration of Guideline-Directed Medical Therapy

Stormi E. Gale, Pharm.D., BCPS
Assistant Professor
University of Maryland School of Pharmacy
Approximately what percentage of patients with HFrEF are on ACEi/ARB/ARNI, beta-blocker, and MRA, all at target doses?

A. 1%
B. 11%
C. 21%
D. 31%
GDMT, hasn’t this already been addressed?

CHAMP-HF Registry

- 3,518 patients with HFrEF in the United States who were on at least one oral medication for HF

CHAMP-HF, Change the Management of Patients with Heart Failure
CHAMP-HF Results

<table>
<thead>
<tr>
<th></th>
<th>ACEi/ARB/ARNI</th>
<th>Beta-Blocker</th>
<th>MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>% on therapy</td>
<td>73%</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>% at target dose</td>
<td>17% (ACEi/ARB)</td>
<td>14%</td>
<td>28%</td>
</tr>
</tbody>
</table>

CHAMP-HF, Change the Management of Patients with Heart Failure
CHAMP-HF Results

Only 1% of patients were at target doses of ACEi/ARB/ARNI, beta-blocker, and MRA

CHAMP-HF, Change the Management of Patients with Heart Failure
• 62-year-old Caucasian female who presents to heart failure clinic for routine follow up.
• PMH is significant for atrial fibrillation, hyperthyroidism, osteoarthritis, and non-ischemic cardiomyopathy (EF 25%).
• Heart failure medications include bumetanide 2 mg daily, eplerenone 25 mg daily, lisinopril 10 mg daily, and metoprolol succinate 200 mg daily.
• She reports stable symptoms and compliance to all medications.
• BP 106/68 mmHg and HR 72 bpm.
• She denies any othostatic symptoms.
• BMP (stable from prior) reveals the following:

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Creatinine (mg/dL)</th>
<th>Potassium (mEq/L)</th>
<th>Sodium (mEq/L)</th>
<th>Calcium (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>139</td>
<td>98</td>
<td>21</td>
<td>103</td>
<td>3.9</td>
</tr>
</tbody>
</table>

BMP, basic metabolic panel; BP, blood pressure; EF, ejection fraction; HR, heart rate
Polling Question

Which would be the most appropriate step in optimizing BW’s GDMT at this time?

a) Discontinue lisinopril
b) Reduce lisinopril to 5 mg daily
c) Increase lisinopril to 20 mg daily
d) No changes are warranted at this time
Should medications be uptitrated in patients with stable symptoms?
Why Should RAS inhibitors Continue to be Uptitrated?

ATLAS
Lisinopril
High (32.5-35 mg) vs. low dose (2.5-5 mg)

- 13% lower risk of all-cause hospitalization ($p = 0.021$)
- 24% lower risk of HF hospitalization ($p = 0.002$)

HEAAL
Losartan
High (150 mg) vs. low dose (50 mg)

- 10% lower risk of mortality/HF admission ($p = 0.027$)
- 13% lower risk HF hospitalization ($p = 0.025$)

Titration Limitations

Hypotension

• Symptoms
• Diuretic
• Other potential causes (i.e. polypharmacy)

Circulation. 2017;136:e137–e161
Why Should RAS inhibitors Continue to be Uptitrated?

**ATLAS**
Lisinopril
High (32.5-35 mg) vs. low dose (2.5-5 mg)
- 13% lower risk of all-cause hospitalization ($p = 0.021$)
- 24% lower risk of HF hospitalization ($p = 0.002$)
- 4.4 mmHg lower SBP at three months ($p < 0.001$)

**HEAAL**
Losartan
High (150 mg) vs. low dose (50 mg)
- 10% lower risk of mortality/HF admission ($p = 0.027$)
- 13% lower risk HF hospitalization ($p = 0.025$)
- 1.4 mmHg lower mean SBP at six months ($p = 0.008$)

ATLAS, Assessment of Treatment with Lisinopril and Survival;
HEAAL, Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan
SBP, systolic blood pressure
Lancet 2009; 374: 1840–48
Blood Pressure in Clinical Trials

- **Mean baseline SBP**
  - Enalapril: ~125 mmHg
  - Valsartan: ~124 mmHg
  - Sacubitril/valsartan: ~122 mmHg

- **SBP reduction with treatment group**
  - Enalapril: 4.7 mmHg
  - Valsartan: 5.2 mmHg
  - Sacubitril/valsartan: 3.2 mmHg

SBP, systolic blood pressure

*N Engl J Med* 2001;345:1667-75
Blood Pressures in Clinical Trials

- **Bisoprolol**
  - Trial SBP Exclusion Criteria: < 100 mmHg
  - Blood Pressures Outcomes: Fewer hospitalizations for hypotension with bisoprolol

- **Carvedilol**
  - Trial SBP Exclusion Criteria: < 85 mmHg
  - Blood Pressures Outcomes: No difference in change in BP

- **Metoprolol Succinate**
  - Trial SBP Exclusion Criteria: < 100 mmHg
  - Blood Pressures Outcomes: Smaller decrease in BP with metoprolol

BP, blood pressure; SBP, systolic blood pressure

Image reformatted with permission from presenter.
Heart Failure Hemodynamics

BP = CO x SVR

BP, blood pressure
SVR, systemic vascular resistance
Image used with permission from presenter
When it comes to BP in patients with HFrEF, how low is too low?
GM

- 58-year-old African American Male who was admitted to the cardiac intensive care unit ~one week ago for acute decompensated heart failure.
- PMH is significant for diabetes mellitus, hypertension, hyperlipidemia, ischemic cardiomyopathy (EF 35%), STEMI s/p DES x 1 to LAD (2011).
- Home heart failure medications include furosemide 40 mg daily, lisinopril 10 mg daily, carvedilol 3.125 mg twice daily, spironolactone 25 mg daily.
- One week later, GM’s ADHF is now resolved and he has since been transferred to the medical floor.
- GM’s carvedilol was held on admission secondary to hypotension but was restarted yesterday in preparation for discharge.

ADHF, acute decompensated heart failure; DES, drug-eluting stent; EF, ejection fraction; LAD, left anterior descending; STEMI, ST-segment elevation myocardial infarction;
Polling Question

GM is feeling well after reinitiating carvedilol 3.125 mg twice daily yesterday. GM’s BP today is 132/84 and HR is 78. The attending physician would like to increase GM’s carvedilol dose in order to optimize GM’s GDMT prior to discharge. What do you recommend?

a) Discontinue carvedilol
b) Increase carvedilol to 6.25 mg BID
c) Increase carvedilol to 12.5 mg BID
d) No changes are warranted at this time
GDMT Titration

Start at the lowest possible dose

Titrate no sooner than every 2 weeks to “target” dose

Patient education is KEY
If my patient has symptomatic hypotension, which GDMT agent should be adjusted first?
Why Should Beta-Blockers Continue to be Uptitrated?

MOCHA

Carvedilol Doses:
High (25 mg BID) vs.
Medium (12.5 mg BID) vs.
Low (6.25 mg)

• Dose-related improvements in left ventricular function (p<0.01)
• Dose-related increase in survival (p<0.001)
• Mortality 1.1% with high dose vs. 6% with low dose

MOCHA, Multicenter Oral Carvedilol Heart Failure Assessment
Titration Limitations

Renal dysfunction and Hyperkalemia

- Ensure appropriate patient selection
- Attentive monitoring
- Dose adjustments

Hyperkalemia

- Discontinue potassium supplements
- Potassium lowering therapies?

Circulation. 2017;136:e137–e161
Timing of Initiation and Uptitration

- It is not imperative to wait for one therapy to be at target dose before initiating a different class.

- CIBIS-III: bisoprolol first strategy noninferior to enalapril-first

- ACEi and BB usually initiated/uptitrated relatively simultaneously

CIBIS, Cardiac Insufficiency Bisoprolol Study
Circulation. 2005;112:2426-2435; Circulation. 2017;136:e137–e161
Keys to Successful ARNI Initiation/Titration

Appropriate patient selection
- Insurance considerations, adequate blood pressure, renal function
- Stable ACEi/ARB therapy (BB preferred, MRA not required)

Appropriate transition
- 36 hour washout of ACEi therapy
- Initial dose based on previous ACEi/ARB strength

Appropriate titration
- TITRATION Trial: In patients on low-dose ACEi/ARB, conservative titration is beneficial

BB, beta-blocker; TITRATION, Initiating sacubitril/valsartan in heart failure
KEY TAKEAWAYS

1) GDMT TITRATION IS COMPLICATED, BUT IMPORTANT
   Start low and go slow

2) GDMT SHOULD BE TITRATED TO A TARGET DOSE NOT TO A BP GOAL
   Let patient symptoms determine limitations rather than BP cutoffs

3) PATIENT EDUCATION IS IMPERATIVE FOR OPTIMAL DOSE TITRATION
   Particularly important for beta-blockers
Treating Hypertension in Patients with Heart Failure: What’s Fact vs. Fiction?

Kristin Watson, Pharm.D., BCPS-AQ Cardiology
Associate Professor and Vice Chair for Clinical Services
University of Maryland School of Pharmacy
Mr. M

- 45 y/o Caucasian male with non-ischemic cardiomyopathy (LVEF < 35%) with stable NYHA class II symptoms
- PMH
  - Cocaine abuse – stopped 4 years ago
  - Hypertension
  - Seasonal allergies
  - HFrEF x 4 years
- Medications
  - Lisinopril 40 mg daily
  - Metoprolol succinate 200 mg daily
  - Spironolactone 25 mg daily
- Labs are stable and within normal limits

<table>
<thead>
<tr>
<th>BP readings (mmHg)</th>
<th>Today</th>
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<td>138/96</td>
<td>142/92</td>
<td>136/88</td>
<td>138/90</td>
</tr>
</tbody>
</table>
Fact or Fiction?

Patients with HFrEF who are receiving optimal GDMT do not need to antihypertensive therapy if their BP is above “goal”
Polling Question

Should patients with HFrEF receive additional antihypertensive therapy if their BP is above goal despite optimal doses of GDMT?

A. Yes
B. No
<table>
<thead>
<tr>
<th>2013 ACCF/AHA Heart Failure</th>
<th>2017 ACC/AHA/HFSA Heart Failure Focused Update</th>
<th>2017 High Blood Pressure Clinical Practice Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attempt to use doses that have been shown to decrease the risk of cardiovascular events</td>
<td>Prescribe GDMT and titrate to a SBP &lt; 130 mmHg in those with HFrEF and hypertension</td>
<td>Prescribe GDMT therapy and titrate to attain BP &lt; 130/80 mmHg</td>
</tr>
</tbody>
</table>

ACC – American College of Cardiology; ACCF – American College of Cardiology Foundation; AHA – American Heart Association; HFSA – Heart Failure Society of America
Circulation 2013;128:e240-e327; Circulation 2017;136:e137-61
Fact or Fiction?

The goal BP for all patients with HFrEF should be < 130/80 mmHg
< 130/80 mmHg

Achieve lowest tolerated BP
What is Mr. M’s goal BP?
SBP $\geq 130$ mmHg and/or
DBP $\geq 80$ mmHg

Optimize GDMT

Evaluate and maximize lifestyle changes
Fact or Fiction?

Cardioselective and non-cardioselective beta-blockers have similar BP lowering effects.
Metoprolol succinate

Carvedilol
Should Mr. M’s metoprolol succinate be switched to carvedilol?
Sacubitril/valsartan

PARADIGM-HF

• SBP ~ 4-6 mmHg lower at 4 mo. with sacubitril/valsartan vs. enalapril

PARAMETER

• 24-hr ambulatory SBP 4.1 mmHg lower at 12 wk with sacubitril/valsartan vs. olmesartan

PARADIGM-HF: Prospective comparison of ARNI w/ an ACEi to determine impact on global mortality & morbidity in HF
PARAMETER: Prospective comparison of ARNI with ARB measuring arterial stiffness in the elderly
SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg

Optimize GDMT

Change ACEi/ARB to ARNI

Evaluate and maximize lifestyle changes
SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg

Optimize GDMT

Change ACEi/ARB to ARNI

Aldosterone antagonist*
Hydralazine/nitrate*^
Fact or Fiction?

All other antihypertensive classes are appropriate additions for BP control in those with HFrEF once GDMT is optimized.
**Calcium Channel Blockers**

- Non-dihydropyridines and 1\textsuperscript{st} generation dihydropyridines
  - Increased risk of HF hospitalization and worsening HF

- Amlodipine
  - No difference in the rate of death or HF hospitalization
  - Increased risk of pulmonary and peripheral edema

Other Options

Thiazide-like diuretics
• Safe and effective for lowering BP
• “Consider in those with mild edema”

SGLT-2 inhibitors
• Use decreases risk of CV outcomes and HF hospitalizations in those with type 2 diabetes
• SBP decrease ranges from ~ 2-10 mmHg

## Other Options

<table>
<thead>
<tr>
<th>Minoxidil</th>
<th>Non-selective alpha-blockers</th>
<th>Clonidine</th>
<th>Aliskiren</th>
</tr>
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<tbody>
<tr>
<td>• Reflex tachycardia can occur</td>
<td>• Conflicting results on safety</td>
<td>• Side effect profile limits use in the elderly</td>
<td>• Combination with enalapril did not improve outcomes; side effects increased</td>
</tr>
<tr>
<td>• May promote sodium retention</td>
<td>• <em>Use uroselective alpha-blocker for BPH if GDMT is NOT optimized</em></td>
<td>• Thrice daily dosing</td>
<td>• Risk of hyperkalemia, renal impairment</td>
</tr>
</tbody>
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BPH - benign prostatic hyperplasia

Mr. M

- 45 y/o Caucasian male with non-ischemic cardiomyopathy (LVEF < 35%) with stable NYHA class II symptoms
- PMH
  - Cocaine abuse – stopped 4 years ago
  - Hypertension
  - Seasonal allergies
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Would your recommendation be the same if he was African American?
**SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg**

- Optimize GDMT
  - Change ACEi/ARB to ARNI
    - Aldosterone antagonist*
      - Hydralazine/nitrate*^*
    - Thiazide-like diuretic
      - Amlodipine (or felodipine)
      - SGLT-2 inhibitor, if diabetes

*If not previously prescribed
^ For select patients
Key Points

• The BP goal for patients with HFrEF should be at least < 130/80 mmHg

• In addition to the other known benefits of therapy, sacubitril/valsartan should be considered as an alternative to ACEi or ARB for those who BP is not at goal with other GDMT

• A thiazide-like diuretic, amlodipine and a SGLT-2 inhibitor (in patients with type 2 diabetes) can be considered as add-on therapy in patients whose BP remains evaluated despite the use of GDMT
Questions