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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.

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Heart Failure Reduced Ejection Fraction Management: Overview and Diabetes and Heart Failure

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HFrEF Warm-Up Questions

Polling Question

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.

J Am Coll Cardiol 2013;62:1495–539.

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

J Am Coll Cardiol 2013;62:1495–539.

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

J Am Coll Cardiol 2013;62:1495–539.

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Diabetes and Heart Failure

Pathophysiological Links Between Type 2 Diabetes and Heart Failure

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

- Accelerating atherosclerosis
- Activation of the renin-angiotension-aldosterone system (RAAS)
- Impaired calcium handling in cardiomyocytes
- Oxidative stress
- Myocardial fibrosis
- Endothelial dysfunction

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 %
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    - 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

Metabolism. 2016;65(2):20-29

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

Diabetes Care. 2004; 27(7): 1791-1793.
Ann Intern Med. 87:591–595, 1977

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
Eur J Clin Pharmacol. 1993; 44:589–591
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

Ann Intern Med 1999;131:281–303
Metabolism. 2016;65(2):20-29
Cochrane Database Syst Rev. 2010;4:CD002967
Diabetes Care. 1998;21:1659–1663
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

CKD Stage	eGFR, mL/min per 1.73 m^2	Max Metformin Dose (mg)
1 and 2	> 60	2550
3A	45 -59	2000
3B	30 - 44	1000
4 and 5	< 30	Do not use

Ann Intern Med. 2017:166;191-200
JAMA. 2014;312(24):2668–2675.

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)

Abbreviated Summary of FDA Drug Safety Communication	
eGFR between 30 – 45 mL/minute/1.73m^2	Starting metformin not recommended; assess the risks and benefits in patients who are already taking
eGFR < 30 mL/minute/1.73 m^2	Contraindicated; discontinue medication

FDA Drug Safety Communication April 2016

Metformin, present day

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

Metformin vs. no metformin in patients with type 2 diabetes and comorbid conditions				
Outcomes	Comorbidity	Number of trials (n)	Hazard ration (95% CI)	GRADE of evidence
All-cause mortality	CKD	5 (33,442)	0.77 (0.61 to 0.97)	Low
	CHF	11 (35,410)	0.78 (0.71 to 0.87)	Low
CV mortality	CHF	3 (6468)	0.77 (0.53 to 1.12)	Insufficient
CHF readmission	CHF	4 (26,510)	0.87 (0.78 to 0.97)	Low

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 m^2 → 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

Ann Intern Med. 2017.166;191-200.
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

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  - 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

Case

- AH is a 63 year-old Black man
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- 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

Can a TZD be used?

A. Yes

B. No

C. It's complicated

Thiazolidinediones: Black Box Warning

- **[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."*

J Am Coll Cardiol 2013;62:e147–239

Bringing it back to the case

Case

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  - Obesity: BMI > 35
  - Type 2 diabetes mellitus (T2DM)
    - 15 years
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  - 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

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

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		
Study Group	Hospitalized for Heart Failure	Hazard Ratio (95% CI)
Alogliptin	3.9%	1.19 (0.90 to 1.58)
Placebo	3.3%	
Patients without a history of heart failure		1.76 (1.07 to 2.90)

N Engl J Med 2013;369:1327-35
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

History of, or were at risk for, cardiovascular events		
Study Group	Hospitalized for Heart Failure	Hazard Ratio (95% CI)
Saxagliptin	3.5%	1.27 (1.07 to 1.51)
Placebo	2.8%	

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

Stratified by Beta Blocker Tx

Saxaglipitn increased the risk of heart failure in		
Tx w/ beta blockers	18%	1.18 (0.97 to 1.43)
Without beta blockers	81%	1.81 (1.21 to 2.76

N Engl J Med 2013;369:1317-26
Circ Res. 2018;122:928-932

Trial Evaluating Cardiovascular Outcomes With Sitagliptin: TECOS 2015

Initial analysis

Patients with cardiovascular disease		
Study Group	Hospitalized for Heart Failure	Hazard Ratio (95% CI)
Sitagliptin	3.1%	1.00 (0.83 to 1.19)
Placebo	3.1%	
** Patients were more likely to be treated with metformin, and less likely to be treated with TZDs and insulin*		

N Engl J Med 2015; 373:232-242
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

FDA Drug Safety Communication: 2016

- *"…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."*

U.S. Food and Drug Administration 2016

Bringing it back to the case

Case

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  - Obesity: BMI > 35
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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

- AH is a 63 year-old Black man
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- 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

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/1.73m^2)

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Empagliflozin Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME): 2015

All the patients had established cardiovascular disease

Study Group	Hospitalized for HF	Hazard Ratio (95% CI)
Empagliflozin	2.7%	0.65 (0.50 to 0.85)
Placebo	4.1%	

Study Group	CV death	Hazard Ratio (95% CI)
Empagliflozin	3.7%	0.62 (0.49 to 0.77)
Placebo	5.9%	

**Results of both endpoints were observed in patients with and without heart failure at baseline*

N Engl J Med 2015;373:2117-28

Canagliflozin Cardiovascular Assessment Study (CANVAS) Program: 2017

65.6% had a history of cardiovascular disease

Study Group	Hospitalized for HF per 1000 patient years	Hazard Ratio (95% CI)
Canagliflozin	5.5	0.67 (0.52 to 0.87)
Placebo	8.7	

Secondary Analysis

Canaglifozin arm only (n=5,795)	Hazard ratio for CV death or HF hospitalization (95% CI)
HF at baseline (13.9%)	0.61 (0.46 to 0.80)
No HF at baseline (86.1%)	0.87 (0.72 to 1.06)

N Engl J Med 2017;377:644-57
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???

J Am Coll Cardiol. 2018 In Press

Bringing it back to the case

Case

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    - 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

Assuming the eGFR stays > 30 ml/min/1.73m^2

Diabetes and Heart Failure: KEY TAKEAWAYS

1) **Metformin can be used safely in heart failure (and my 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***

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Misconceptions About Titration of Guideline-Directed Medical Therapy

Stormi E. Gale, Pharm.D., BCPS
Assistant Professor
University of Maryland School of Pharmacy

Polling Question

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%

ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist

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
J Am Coll Cardiol. 2018;72(4):351-366.

CHAMP-HF Results

ACEi/ARB/ARNI		Beta-Blocker		MRA	
% on therapy	% at target dose	% on therapy	% at target dose	% on therapy	% at target dose
73%	17% (ACEi/ARB) 14% ARNI	67%	14%	33%	28%

CHAMP-HF, Change the Management of Patients with Heart Failure
J Am Coll Cardiol. 2018;72(4):351-366.

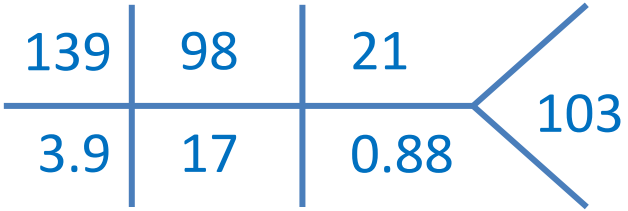
CHAMP-HF Results

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
J Am Coll Cardiol. 2018;72(4):351-366.

BW

- 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:



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

GDMT, guideline directed medical therapy

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)

ATLAS, Assessment of Treatment with Lisinopril and Survival;
HEAAL, Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan

Circulation. 1999;100:2312–2318.
Lancet 2009; 374: 1840–48

Titration Limitations

Hypotension

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

Clin Cardiol. 2008;31:153-8.
Am J Hypertens. 2002;15:709-16.
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
Circulation. 1999;100:2312–2318.
Lancet 2009; 374: 1840–48

Blood Pressure in Clinical Trials

	Enalapril	Valsartan	Sacubatril/ valsartan
Mean baseline SBP	~125 mmHg	~124 mmHg	~122 mmHg
SBP reduction with treatment group	4.7 mmHg	5.2 mmHg	3.2 mmHg

SBP, systolic blood pressure

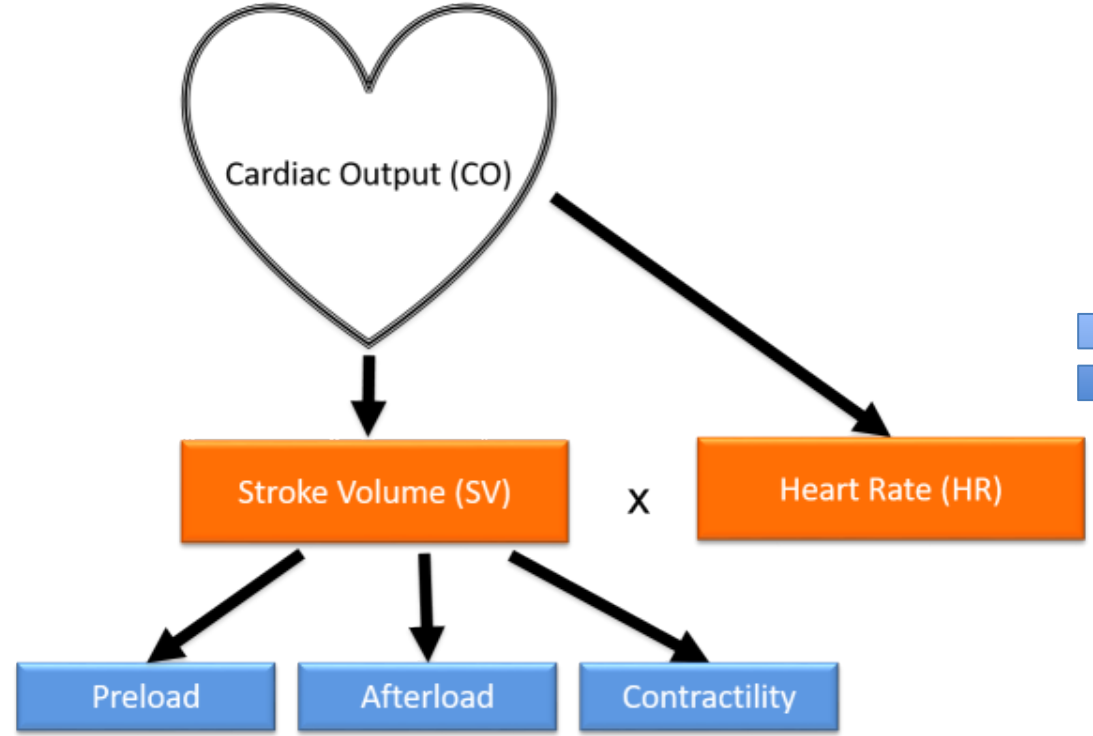
N Eng J Med 1991;325:293-302
N Engl J Med 2001;345:1667-75
N Engl J Med 2014; 371:993-1004

Blood Pressures in Clinical Trials

	Bisoprolol	Carvedilol	Metoprolol Succinate
Trial SBP Exclusion Criteria	< 100 mmHg	<85 mmHg	< 100 mmHg
Blood Pressures Outcomes	Fewer hospitalizations for hypotension with bisoprolol	No difference in change in BP	Smaller decrease in BP with metoprolol

BP, blood pressure; SBP, systolic blood pressure
Image reformatted with permission from presenter.
CIBIS-II. Lancet 1999;353:9-13.
Packer M, et al. N Engl J Med 2001;344:1651-8.
MERIT-HF. Lancet 1999;353:2001-7.
Packer M, et al. N Engl J Med 1996;334:1349-55.

Heart Failure Hemodynamics



$$BP = CO \times SVR$$

$$= \uparrow \downarrow$$

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

J Am Coll Cardiol 2013;62:1495–539.
Circulation. 2017;000:e000–e000.

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
Circulation. 1996;94:2807-2816.

Titration Limitations

Renal dysfunction and Hyperkalemia

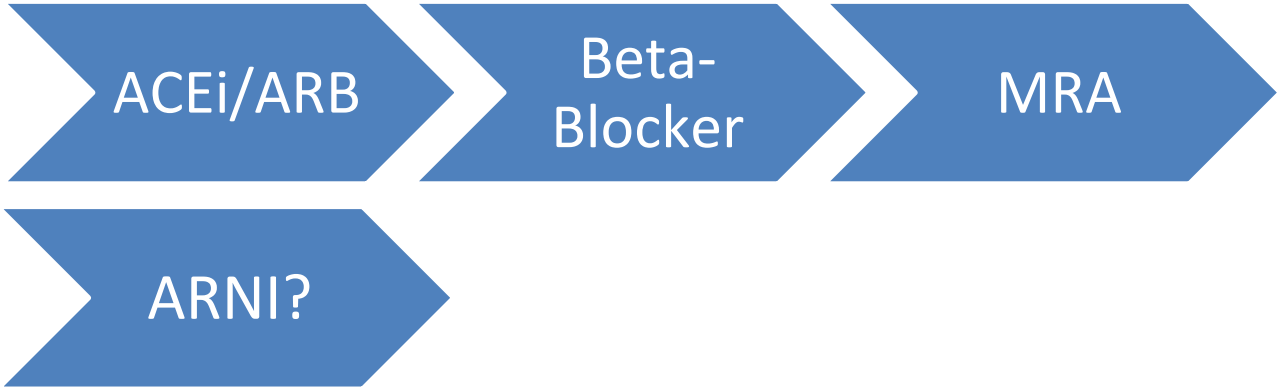
- Ensure appropriate patient selection
- Attentive monitoring
- Dose adjustments

Hyperkalemia

- Discontinue potassium supplements
- Potassium lowering therapies?

Clin Cardiol. 2008;31:153-8.
Am J Hypertens. 2002;15:709-16.
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

N Engl J Med 2014; 371:993-1004
Eur J Heart Fail. 2016 Sep;18(9):1193-202.

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

BP, blood pressure

ashp MIDYEAR 2018
Clinical Meeting & Exhibition

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

BP readings (mmHg)	Today	1 mo ago	3 mo ago	6 mo ago
	138/96	142/92	136/88	138/90

- Labs are stable and within normal limits

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

2013 ACCF/AHA Heart Failure	2017 ACC/AHA/HFSA Heart Failure Focused Update	2017 High Blood Pressure Clinical Practice Guideline
Attempt to use doses that have been shown to decrease the risk of cardiovascular events	Prescribe GDMT and titrate to a SBP < 130 mmHg in those with HFrEF and hypertension	Prescribe GDMT therapy and titrate to attain BP < 130/80 mmHg

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
J Am Coll Card 2017; doi: 10.1016/j.jacc.2017.11.006.

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 ≥ 130 mmHg and/or
DBP ≥ 80 mmHg

↓

Optimize GDMT

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

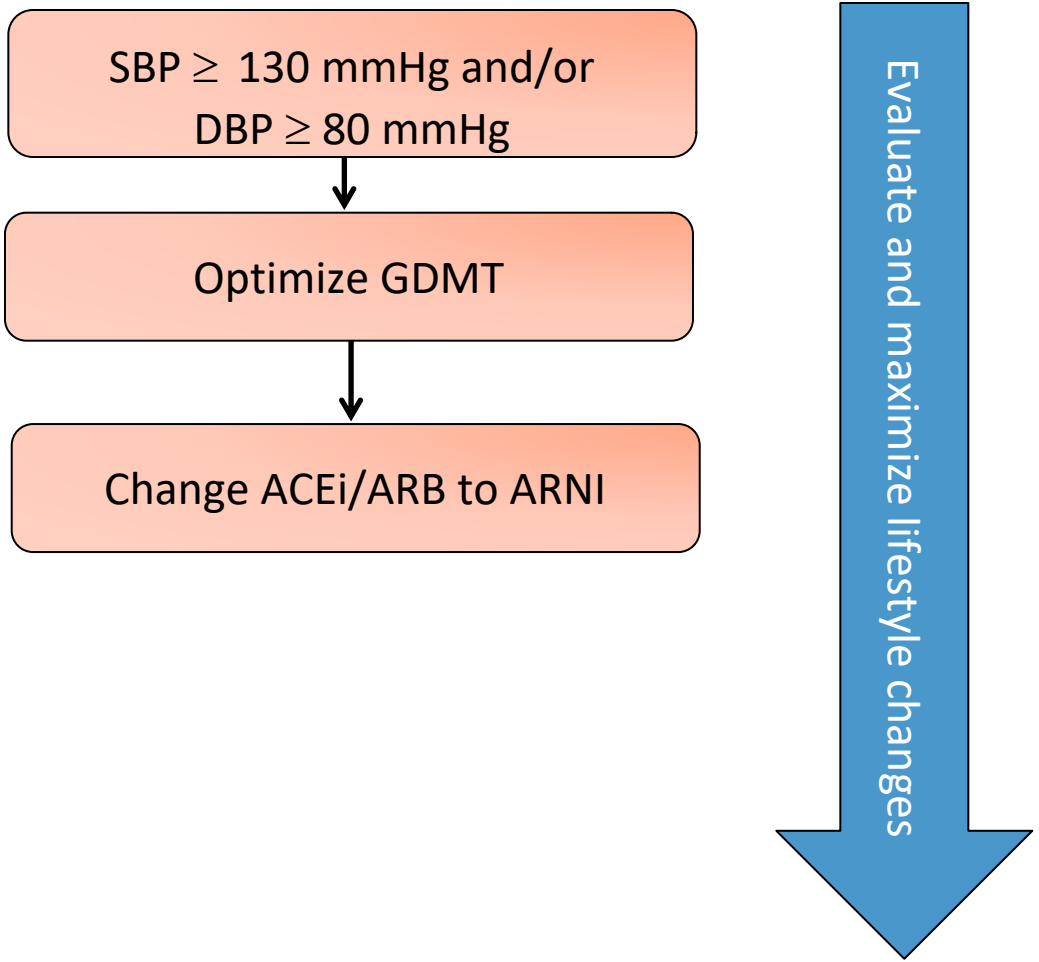
PARADIGM-HF

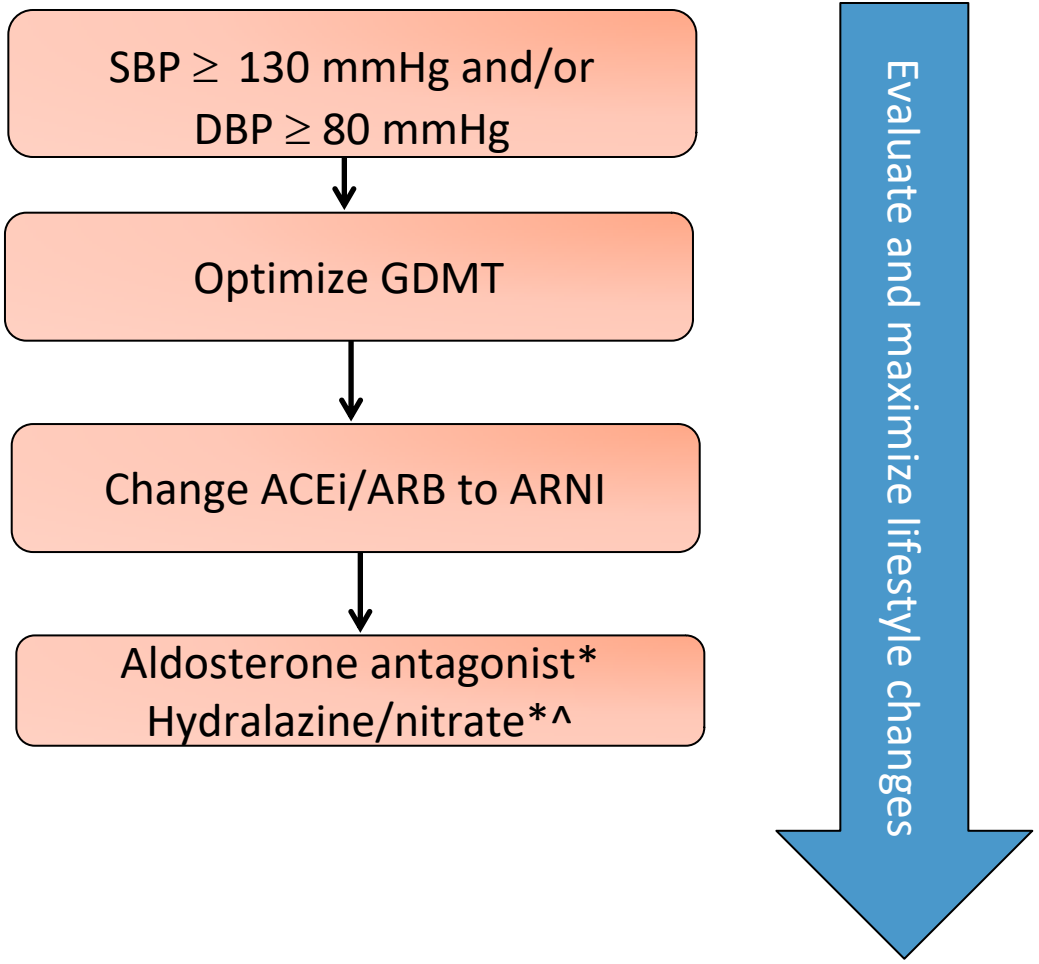
- SBP ~ 4-6 mmHg lower at 4 mo. with sacubitril/valsartan vs. enalapril

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
Eur Heart J 2017;38:1132–43; Hypertension 2017;69: 411–20.


SBP ≥ 130 mmHg and/or
DBP ≥ 80 mmHg
Optimize GDMT
Change ACEi/ARB to ARNI
Evaluate and maximize lifestyle changes



*If not previously prescribed
^ For select patients

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 1st 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

Circulation. 1991;83:52; Circulation. 1990;82:1954–61; N Eng J Med 1996;335:1107-14. JACC Heart Failure 2013;1:308-14; Circulation. 1997;96(3):856

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

J Am Soc Hypertens 2014;8:330–39; J Am Coll Cardiol 2018;71:2628-39; Eur Heart J 2016;37:1526-34.

Other Options

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

BPH - benign prostatic hyperplasia

J Am College Cardiol 2017;69: 1216M-05; Circulation. 2018;130:A19599; N Engl J Med 2016;374:1521-32

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  - Cocaine abuse – stopped 4 years ago
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  - Seasonal allergies
  - HFrEF x 4 years
- Medications
  - Lisinopril 40 mg daily
  - Metoprolol succinate 200 mg daily
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Would your recommendation be the same if he was African American?

BP readings (mmHg)	Today	1 mo ago	3 mo ago	6 mo ago
	138/96	142/92	136/88	138/90

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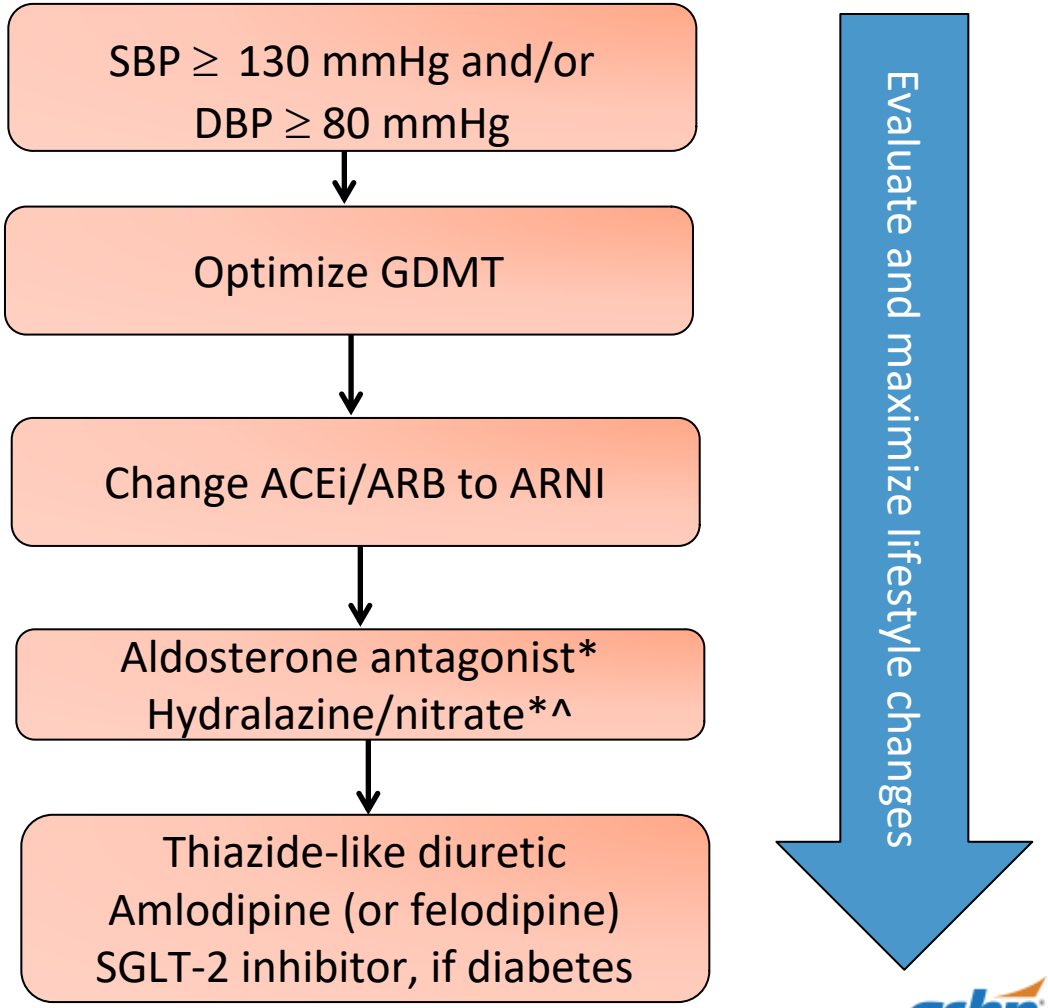

*If not previously prescribed
^ For select patients

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