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Speaker Introduction

Katie Fitton is the current PGY2 Cardiology Pharmacy Resident at University of Utah Health. She is from Atlanta, Georgia where she completed her Bachelor of Science in Biochemistry at Georgia Institute of Technology. She then attended University of Georgia where she received her Doctor of Pharmacy. After pharmacy school, she moved to Utah and completed her PGY1 Pharmacy Residency. She is passionate about transitions of care and hopes to finish her PGY2 year with a cardiology pharmacist job where she can facilitate the transition from inpatient to outpatient care. She discovered many new pearls about managing heart failure on her general cardiology rotation and from reading the new expert consensus pathway and is excited to share this information today.

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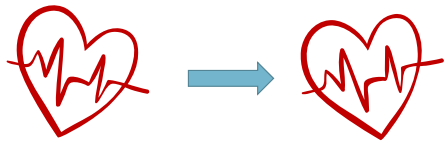
UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

Katie Fitton, PharmD
November 11th, 2021

Let's Have a Heart to Heart About Heart Failure



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Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Katie Fitton:**
    - None
  - **CE Mentor, Jessica Carey:**
    - None
- Off-Label Uses of Medications
  - Mavacamten
  - Omecamtiv mecarbil

Pharmacist Learning Objectives

Identify guideline-directed medical therapy (GDMT) for patients with heart failure with reduced ejection fraction

Assess appropriate dosing of heart failure medication therapies

Describe pearls and contraindications to consider when adding new medication therapies

Evaluate the decision-making process for adding, switching, and titrating heart failure therapies

Technician Learning Objectives

Identify guideline-directed medical therapy (GDMT) for patients with heart failure with reduced ejection fraction

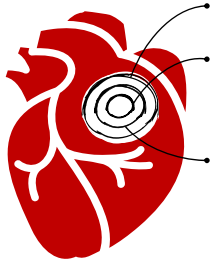
Recognize the cost of heart failure medication therapies and barriers to medication access

Analyze the importance of GDMT in heart failure

Compare and **contrast** common side effects of the different heart failure medications

Universal Definition of Heart Failure (HF)

A clinical syndrome



01 Symptoms and/or signs of HF

02 Caused by a structural and/or functional cardiac abnormality **And** corroborated by one of the following:

- Objective evidence of cardiogenic pulmonary or systemic congestion **or**
- Elevated brain natriuretic peptide (BNP) levels

03

Bozkurt B, et al. *J Card Fail.* 2021 Mar 1:S1071-9164(21)00050-6.

Stages and New York Heart Association (NYHA) Classification of HF

Stage A (At Risk for HF)	Without symptoms/signs of HF and without structural cardiac changes or elevated biomarkers
Stage B (Pre-HF)	No symptoms/signs of HF but evidence of structural heart disease, abnormal cardiac function, or elevated BNP
Stage C (HF)	Current and/or prior symptoms of HF caused by a structural and/or functional cardiac abnormality
Stage D (Advanced HF)	Severe symptoms and/or signs of HF at rest, recurrent hospitalizations, refractory to GDMT, advanced therapies

NYHA Classification:
- Class I: No limitation of activity
- Class II: Slight limitation of activity
- Class III: Marked limitation of activity
- Class IV: Symptoms occur at rest

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Heart Failure Classification

HFrEF	HFmrEF	HFimpEF	HFpEF
Heart failure with reduced left ventricular ejection fraction (LVEF)	Heart failure with mildly reduced LVEF	Heart failure with improved LVEF	Heart failure with preserved LVEF
LVEF ≤40%	LVEF 41-49%	LVEF baseline ≤40% and ≥10-point increase with 2nd measurement >40%	LVEF ≥50%

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Guideline-Directed Medical Therapy (GDMT)

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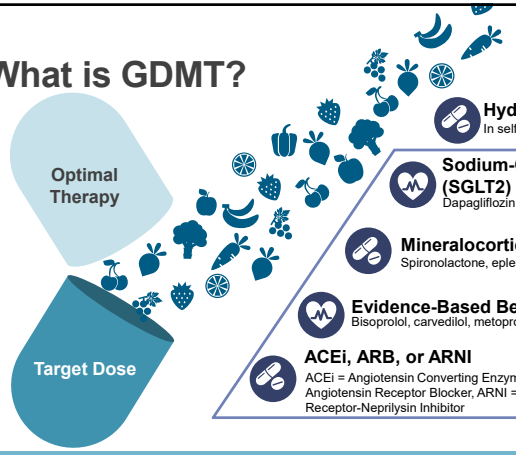
What is GDMT?



- **Hydralazine + Isosorbide Dinitrate**
  In self-identified African Americans
- **Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitor**
  Dapagliflozin, empagliflozin
- **Mineralocorticoid Receptor Antagonist**
  Spironolactone, eplerenone
- **Evidence-Based Beta-Blocker**
  Bisoprolol, carvedilol, metoprolol succinate XL
- **ACEi, ARB, or ARNI**
  ACEi = Angiotensin Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ARNI = Angiotensin Receptor-Neprilysin Inhibitor

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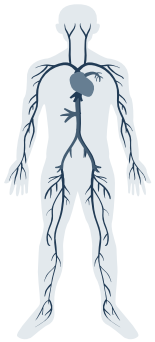
"Quadruple therapy with an angiotensin receptor-neprilysin inhibitor (ARNI), evidence-based β-blocker, mineralocorticoid receptor antagonist (MRA), and sodium glucose cotransporter 2 inhibitor (SGLT2i) may reduce risk of death by **73% over 2 years**."



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Greene SJ, et al. *JAMA Cardiol.* 2021 Jul 1;6(7):743-744.

GDMT for Who?

HFrEF	HFmrEF	HFimpEF	HFpEF
GDMT	Heart failure with mildly reduced LVEF	GDMT	Heart failure with preserved LVEF
ejection fraction (LVEF)		LVEF	
LVEF ≤40%	LVEF 41-49%	LVEF baseline ≤40% and ≥10-point increase with 2nd measurement >40%	LVEF ≥50%

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Bozkurt B, et al. *J Card Fail.* 2021 Mar 1:S1071-9164(21)00050-6.

Audience Response Question - Technician

Once patients are on two heart failure therapies, there is no need to add any other medications. True or false?

A. True
B. False

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The Problem

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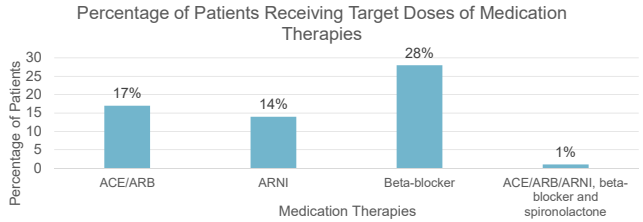
GDMT Problems

- In US outpatient practice, among patients with HFrEF who are eligible for therapy, **1 in 3** receive no beta-blocker and **2 in 3** receive no MRA
- Only **14%** prescribed ARNI therapy



Greene SJ, et al. *J Am Coll Cardiol.* 2019;73(19):2365-2383. Januzzi JL, et al. *JAMA* 2019;321(14):1385-1395.

17

Challenges

Frailty

Limited social, financial, and caregiver support

Elderly patients

Polypharmacy

End-stage HF

Renal dysfunction

Multiple comorbidities

Cognitive impairment

Less data in diverse patient populations

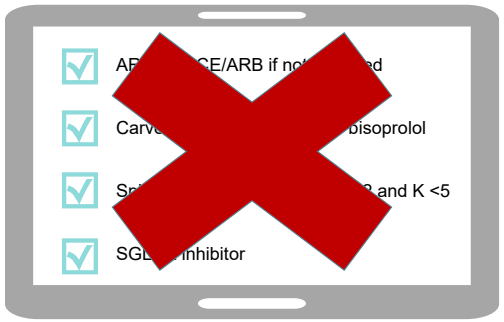
18

HFrEF Discharge Checklist

- ☑ ARNI or ACE/ARB if not tolerated
- ☑ Carvedilol, metoprolol XL, or bisoprolol
- ☑ Spironolactone if SCr ≤2.5 or ≤2 and K <5
- ☑ SGLT-2 inhibitor

19

HFrEF Discharge Checklist



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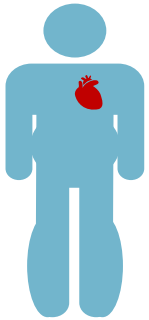
HF Patient: Val Copernicus



21

First Therapies to Consider

ACE Inhibitor
- 18 = estimated 5-year NNT for all-cause mortality

ARB
- 24 = estimated 5-year NNT for all-cause mortality

ARNI
- 11 = estimated 5-year NNT for all-cause mortality
- 21 = NNT vs enalapril

Beta-Blocker
- 8 = Estimated 5-year NNT for all-cause mortality

NNT = Number needed to treat

Srivastava PK, et al. *JAMA Cardiol.* 2018 Dec 1;3(12):1226-1231.

22

Initiation of GDMT

ARNI/ACE/ARB
- Benefit in chronic kidney disease (CKD) and diabetes
- More afterload reduction augmenting diuretic effect
- Hold in acute kidney injury (AKI)
- ARNI > ACE/ARB to help reduce ventricular arrhythmias

BETA BLOCKER
- Caution with initiation in acute decompensated HF
- Indicated for rate control in atrial fibrillation
- Provides benefit in angina
- Shorter effect duration
- Reduction in ventricular arrhythmias

Maddox TM, et al. *J Am Coll Cardiol.* 2021 Feb 16;77(6):772-810.

23

Evidence-Based Beta-Blockers

Pearls for Beta-Blockers

- Use beta-1 selective in COPD/Asthma
- Caution in acute decompensation
- Avoid use in atrioventricular (AV) block
- Side effects: fatigue, dizziness, shortness of breath
- Twice daily vs once daily medications

McDonaghTA, et al. *Eur Heart J*. 2021 Sep 21;42(36):3599-3726. Packer M, et al. *Eur J Heart Fail*. 2021;23(6):882-894.

Titrating the Beta-Blocker Dose

- MERIT-HF
- COMET
- MOCHA
- BIOSTAT-CHF
- ACTION-HF

Continue to titrate dose if patient remains asymptomatic

McAlister FA, et al. *Ann Intern Med*. 2009 Jun 2;150(11):784-94, Vardeny O, et al. *Eur J Heart Fail*. 2016;18(10):1228-1234. Bristow MR, et al. *Circulation*. 1996 Dec 1;94(11):2807-16. Ouwerkerk W, et al. *Eur Heart J*. 2017 Jun 21;38(24):1883-1890.

Beta-Blocker Dosing

	Starting Dose	Target Dose
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight <85 kg and 50 mg twice daily for weight ≥85 kg
Metoprolol succinate	12.5 mg – 25 mg daily	200 mg daily

Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810.

ARNI

Pearls for ARNI

- Avoid starting during significant diuresis
  - Delay start if IV vasodilator or increase in IV diuretic in last 6 hours or inotrope in last 24 hours
- Caution in acute kidney injury
- Watch out for hypotension
- Side effects: hyperkalemia, angioedema, cough
- Wash out period with ACE inhibitors

ARNI Dosing

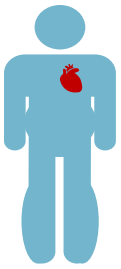
	Starting Dose	Target Dose
Sacubitril/Valsartan	• ACE/ARB naïve, previous low- or medium-dose ACE or ARB, eGFR <30 mL/min/1.73 m^2, Child-Pugh Class B, age ≥75: 24/26 mg twice daily	97/103 mg twice daily
	• Previous high-dose ACE or ARB (>10 mg enalapril TDD or >160 mg valsartan TDD) or SBP ≥120*: 49/51 mg twice daily	

*Based off the PIONEER-HF trial

Audience Response Question - Pharmacist/Technician

Val Copernicus is a 60-year-old Caucasian man NYHA Class II with heart failure with an ejection fraction of 35%. He presents to clinic today with a heart rate of 65 bpm and blood pressure of 122/80 mmHg. He is on metoprolol XL 100 mg daily, spironolactone 25 mg daily, and dapagliflozin 10 mg daily. He also takes furosemide 20 mg daily. What GDMT is he missing that you would ***most*** like to start on him today?

A. Hydralazine/isosorbide dinitrate
B. Lisinopril
C. Losartan
D. Sacubitril/valsartan



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Titrating the ARNI Dose

- Analysis of PARADIGM-HF study
  - Benefit of sacubitril/valsartan relative to enalapril maintained even at lower doses
    - HR 0.79 (95% CI 0.71-0.88) at target doses vs HR 0.80 (95% CI 0.69-0.92) at lower doses
  - Any dose reduction associated with a higher subsequent risk of primary event (HR 2.5, 95% CI 2.2-2.7)

Cost Considerations for ARNI

- Wholesale acquisition cost (WAC): $582.89/month
- GoodRx price: $574.67/month at Smith's
- Prior authorization based on the insurance
- Copay assistance: Copay card available for $10/month for private insurance + free trial offer
  - Annual limit: $3250
- Novartis patient assistance foundation for patients below income threshold with limited or no prescription coverage

Entresto prices, Coupons & Savings Tips. GoodRx. Retrieved September 30, 2021.
Active Ingredient: Sacubitril/valsartan. RED BOOK Online. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2021. Accessed September 30, 2021.

ACE Inhibitor/ARB

Pearls for ACE Inhibitors/ARBs

- Caution in acute kidney injury
- Watch out for symptomatic hypotension
- Side effects: hyperkalemia, angioedema, cough
- Wash out period with ARNI

Maddox TM, et al. *J Am Coll Cardiol.* 2021 Feb 16;77(6):772-810. Velazquez EJ, et al. *N Engl J Med.* 2019 Feb 7;380(6):539-548. McDonagh TA, et al. *European Heart Journal*, Volume 42, Issue 36, 21 September 2021, Pages 3599–372

ACE Inhibitor Dosing

	Starting Dose	Target Dose
Captopril	6.25 mg three times daily	50 mg three times daily
Enalapril	2.5 mg twice daily	10 – 20 mg twice daily
Lisinopril	2.5 mg – 5 mg daily	20 - 40 mg daily
Ramipril	1.25 mg daily	10 mg daily

Maddox TM, et al. *J Am Coll Cardiol.* 2021 Feb 16;77(6):772-810.

ARB Dosing

	Starting Dose	Target Dose
Candesartan	4 – 8 mg daily	32 mg daily
Losartan	25 – 50 mg daily	150 mg daily
Valsartan	40 mg twice daily	160 mg twice daily

Titrating the ACE Inhibitor/ARB Dose

- HEAAL
- ATLAS
- NETWORK
- BIOSTAT-CHF

Next Therapies to Consider

MRA
5-year NNT for all-cause mortality ~ **15**

SGLT2i
3-year NNT for all-cause mortality ~ **22**

Hydralazine + Isosorbide dinitrate
3-year NNT for all-cause mortality in African Americans ~ **7**

Diuretic Agent
Volume Overload

OPTIMIZE-HF Registry
- Fewer HF readmissions and deaths at 30 days in patients discharged on loop diuretics vs those who were not

Mineralocorticoid Receptor Antagonists

Pearls for MRAs

- Caution in renal dysfunction
  - SCr >2.5 mg/dL in males or >2 mg/dL in females or eGFR <30
- Side effects: hyperkalemia, gynecomastia
- Usually do not see BP lowering with doses in HF

EMPHASIS-HF: Placebo-corrected reduction in SBP at 6 months after eplerenone initiation was < 3 mmHg

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McDonaghTA, et al. *Eur Heart J*. 2021 Sep 21;42(36):3599-3726.

Mineralocorticoid Receptor Antagonist (MRA) Dosing

	Starting Dose	Target Dose
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5 – 25 mg daily	25 – 50 mg daily

If K^+ rises above 5.5 mEq/L or SCr >2.5 mg/dL, halve the dose
If K^+ rises above 6 mEq/L or SCr >3.5 mg/dL, stop immediately

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McDonaghTA, et al. *Eur Heart J*. 2021 Sep 21;42(36):3599-3726.

SGLT-2 Inhibitors

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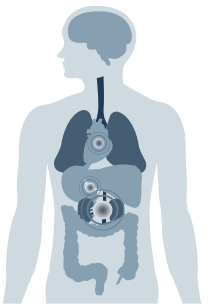
SGLT-2 Inhibitor Benefits

Reduction in cardiovascular events

Kidney protection



Diabetes treatment

Weight loss

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Pearls for SGLT-2 Inhibitors

- Avoid use with history of genital yeast infections
- Caution in severe renal dysfunction
  - eGFR <30 with dapagliflozin or eGFR <20 with empagliflozin
- Watch out for diabetic ketoacidosis
  - Discontinue ≥72-96 hours before surgery and hold if decreased oral intake
- Side effects: yeast infection, dehydration

Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810. Velazquez EJ, et al. *N Engl J Med*. 2019 Feb 7;380(6):539-548. McDonagh TA, et al. *European Heart Journal*, Volume 42, Issue 36, 21 September 2021, Pages 3599–372

Cost Considerations for SGLT-2 Inhibitors

- Wholesale acquisition cost (WAC): $532.84/month for dapagliflozin or $548.54/month for empagliflozin
- GoodRx price: $515-530/month
- Prior authorization based on the insurance
- Copay assistance: Copay card for up to $0/month for dapagliflozin and $10/month for empagliflozin with up to $175/month savings for patients with commercial insurance, copay card to save $150/month for cash paying patients for dapagliflozin
- AZ&Me dapagliflozin prescription savings program for patients without insurance
- BI Cares patient assistance program for low income and uninsured or underinsured patients

Coupons & Savings Tips. GoodRx. Retrieved September 30, 2021.
RED BOOK Online. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2021. Accessed September 30, 2021.

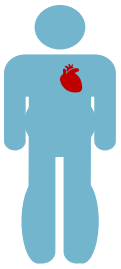
Audience Response Question - Technician

Val Copernicus tells you that he is having trouble affording one of his heart failure medications. When doing his medication reconciliation, he tells you he is taking the following medications for heart failure:

Dapagliflozin
Sacubitril/valsartan
Metoprolol XL
Spironolactone

Which of the following medications may be cost-prohibitive or not covered by insurance?

A. Dapagliflozin
B. Carvedilol
C. Sacubitril/valsartan
D. A and C



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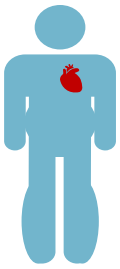
Audience Response Question - Pharmacist

Val Copernicus presents a year later with some medication changes. He is now on sacubitril/valsartan 97/103 mg twice daily, metoprolol XL 100 mg daily, spironolactone 50 mg daily, and dapagliflozin 10 mg daily. Which medication therapy is NOT at the target dose?

A. Sacubitril/valsartan
B. Metoprolol XL
C. Spironolactone
D. Dapagliflozin



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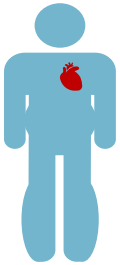
Audience Response Question - Pharmacist

Val Copernicus developed diabetes and now has a diabetic foot infection. He went to the OR for debridement on admission and on post-op day three his heart failure medications were restarted. He is on his home metoprolol XL, dapagliflozin, spironolactone, and sacubitril/valsartan. His blood pressure today is 122/84, HR 62, K 4.5, and SCr 1.2 mg/dL. On rounds, the team mentions the patient has not been eating post-operatively due to a difficulty swallowing. Which therapy should be held today?

A. Sacubitril/valsartan
B. Metoprolol XL
C. Spironolactone
D. Dapagliflozin



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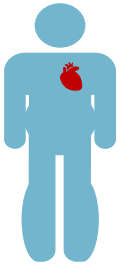
49

Audience Response Question - Technician

Two days later, Val Copernicus notices in Electronic Health Record his potassium is 6 mEq/L. You are asking him about his medication insurance for his dapagliflozin copay and he asks you if any medications are contributing to his high potassium. Which of the following therapies can increase potassium?

A. Metoprolol XL
B. Sacubitril/valsartan
C. Spironolactone
D. B and C
E. All of the above



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50

Managing Side Effects with GDMT

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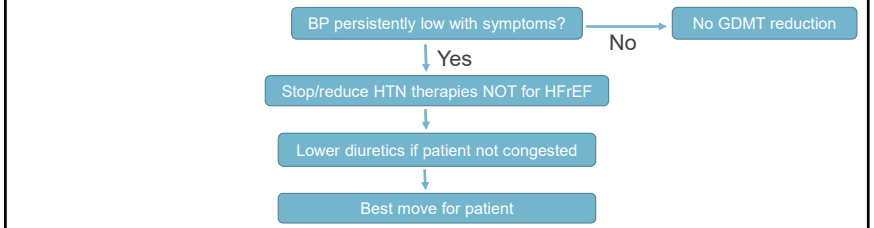
How to Manage Side Effects with GDMT



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Girerd N. *J Am Coll Cardiol.* 2021 Sep 28;78(13):1349-1351.

52

Hydralazine + Isosorbide Dinitrate

Hydralazine/Isosorbide Dinitrate

- NYHA Class III or IV
- Self-identified African-American patients
- Add on after maximally tolerated doses of beta-blocker, ARNI/ACE/ARB, and spironolactone achieved
- A-HeFT trial
  - Mortality in combination-therapy group was 6.2% versus 10.2% with placebo
  - 43% improvement in survival (HR 0.57, P=0.01)
  - 33% relative reduction in rate of hospitalization for HF (P = 0.001)

Hydralazine + Isosorbide Dinitrate Dosing

	Starting Dose	Target Dose
Hydralazine	25 mg three times daily	75 mg three times daily
Isosorbide Dinitrate	20 mg three times daily	40 mg three times daily
Combination Product	20 mg/37.5 mg (1 tablet) three times daily	2 tablets three times daily

GDMT Benefit

GDMT for HFrEF

Guideline Recommended Therapy	Relative Risk Reduction in Mortality	NNT for Mortality (Standardized to 36 Months)
ACEi/ARB	17%	26
ARNI (replacing ACEi/ARB)	16%	27
Beta-blocker	34%	9
Aldosterone Antagonist	30%	6
SGLT2 inhibitor	17%	22
Hydralazine/nitrate[a]	43%	7

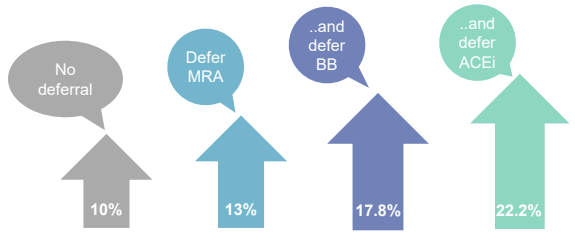
[a]Self-identified African Americans

GDMT for HFrEF

Guideline Recommended Therapy	HF Patient Population Eligible for Treatment, n	Current HF Population Eligible and Untreated, %	Potential Lives Saved per Year	Potential Lives Saved per Year (Sensitivity Range)
ACEi/ARB	2,459,644	20.4%	6,516	(3,336 – 11,260)
ARNI (replacing ACEi/ARB)	2,287,296	100%	28,484	(18,230 – 41,017)
Beta-blocker	2,512,560	14.4%	12,922	(6,616 – 22,329)
Aldosterone Antagonist	603,014	63.9%	21,407	(10,960 – 36,991)
SGLT2 inhibitor	2,132,800	0%	34,125	(21,840 – 49,140)
Hydralazine/nitrate[a]	150,754	92.7%	6,655	(3,407 – 11,500)

[a]Self-identified African Americans

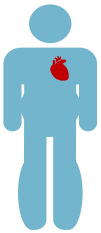
1-Year Mortality from Deferring Therapy for 1 Year



Audience Response Question - Pharmacist

Val Copernicus presents to the ED due to symptomatic hypotension. He is currently taking metoprolol XL 100 mg daily, dapagliflozin 10 mg daily, spironolactone 25 mg daily, and sacubitril/valsartan 97/103 mg twice daily. His blood pressure today is 85/60, HR 70 and K 4.5 with SCr 0.82 mg/dL. ED workup is negative for any concern for shock. What do you recommend the patient do to his home HF regimen to help his symptoms?

A. Discontinue dapagliflozin until follow up with his HF provider
B. Discontinue spironolactone until follow up with his HF provider
C. Decrease metoprolol XL to 75 mg daily
D. Decrease sacubitril/valsartan to 49/51 mg twice daily



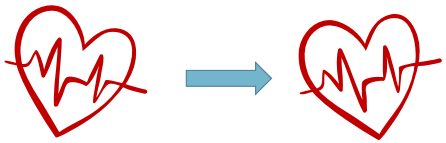
Other Therapies

Benefits of Additional HFrEF Therapies

Ivabradine	• Reduction in composite of CV death and admission for HF • Driven by HF admissions
Digoxin	• 28% decrease in HF hospitalization
Vericiguat	• Reduction in combined endpoint of CV death or hospitalization for HF • Increased incidence of anemia
Omecamtiv mecarbil	• Less HF events or death from CV causes
Mavacamten	• Reduction of symptoms and improved exercise capacity

Maddox TM, et al. *J Am Coll Cardiol.* 2021 Feb 16;77(6):772-810. Swedberg K, et al. *Lancet.* 2010 Sep 11;376(9744):875-85. Campbell TJ, MacDonald PS. *Med J Aust.* 2003 Jul 21;179(2):98-102. Armstrong PW, at al. *N Engl J Med.* 2020 May 14;382(20):1883-1893. Lim GB, et al. *Nat Rev Cardiol.* 18, 71 (2021). Teerlink JR, et al. *N Engl J Med.* 2021 Jan 14;384(2):105-116. Spertus JA,et al. *Lancet.* 2021 Jun 26;397(10293):2467-2475.

Let's Have a Heart to Heart About Heart Failure



CE Code: (USHP will fill in)

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