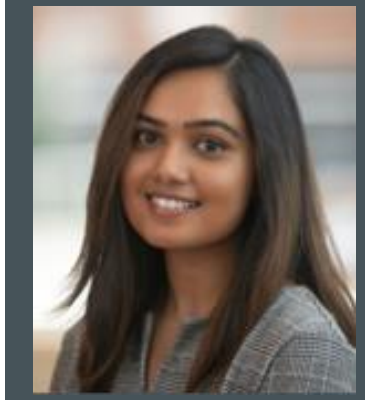
Updates on Heart Failure with Reduced Ejection Fraction (HFrEF): A Focus On Emerging Therapies

A PRESENTATION FOR HEALTHTRUST MEMBERS
MARCH 8, 2022



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OBJECTIVES FOR PHARMACISTS AND NURSES

- Recall rationale behind therapeutic updates addressed in the 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment
- Recognize the proposed mechanisms of action and adverse effects of vericiguat and omecamtiv mecarbil and their potential role in heart failure
- Identify clinical evidence supporting the use of vericiguat and omecamtiv mecarbil in heart failure

OBJECTIVES FOR PHARMACY TECHNICIANS

- Recall barriers and cost considerations associated with novel treatments in heart failure
- Recognize how emerging heart failure therapies are supplied and dosed
- Identify safety considerations with vericiguat and omecamtiv mecarbil

PRESENTATION OUTLINE

Heart Failure with Reduced Ejection Fraction (HFrEF)

- Background
- Pathophysiology

Treatment Overview

- Guideline-Directed Medical Therapy (GDMT)

Review of Emerging Therapies

- Vericiguat
- Omecamtiv Mecarbil

BACKGROUND

HEART FAILURE OVERVIEW

- Clinical syndrome resulting from a structural or functional impairment of ventricular filling or ejection of blood leading to dyspnea or fatigue
- Epidemiology
  - ~ 6 million adults in the United States have heart failure
    - Approximately 50% of cases are HFrEF
  - ~ 1 million hospitalizations annually
  - 5 year-survival rate remains approximately 50% for those with a diagnosis of HF
- Etiology
  - Most cases due to myocardial infarction or long-standing hypertension
  - Other causes include medications and cardiomyopathies
  - Risk factors: hypertension, type 2 diabetes mellitus, alcoholism, atherosclerotic diseases

Heart Failure with Reduced Ejection Fraction (HFrEF)

- Systolic Dysfunction
- Ejection Fraction (EF) ≤ 40%

Heart Failure with Preserved Ejection Fraction (HFpEF)

- Diastolic Dysfunction
- Ejection Fraction (EF) ≥ 50%

Sources: Murphy SP, et al. *JAMA*. 2020;324(5):488–504.
Virani SS, et al. *Circulation*. 2021 Feb 23;143(8):e254-e743.

HEART FAILURE CLASSIFICATION SYSTEMS

ACC/AHA Staging System	NYHA Functional Classification
STAGE A: High risk of HF, but NO structural heart disease of symptoms of HF	CLASS I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
STAGE B: Structural heart disease, but no symptoms of HF	CLASS II: Slight limitation of physical activity. Comfortable at rest, but ordinary activity results in symptoms of HF.
STAGE C: Structural heart disease, AND symptoms of HF	CLASS III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
STAGE D: Refractory HF requiring specialized interventions	CLASS IV: Unable to carry on any physical activity without symptoms of HF. Showing symptoms of HF at rest.

ACC: American College of Cardiology; AHA: American Heart Association; NYHA: New York Heart Association

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

CLINICAL PRESENTATION

Symptoms

- Dyspnea
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Fatigue
- Reduced exercise tolerance
- Less common: cough, abdominal distension and bloating

Signs

- Jugular venous distension
- S_3 (gallop rhythm)
- Lung rales
- Peripheral edema
- Ascites

Source: Murphy SP, et al. *JAMA*. 2020;324(5):488–504.

DIAGNOSIS

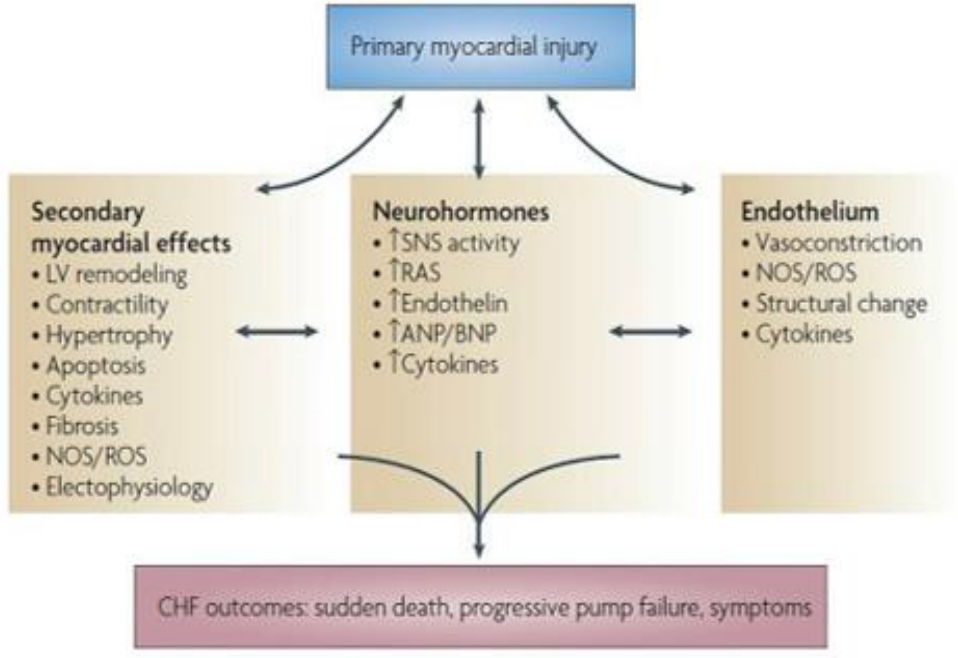
- **Labs**
  - B-type natriuretic peptide (BNP) or *N*-terminal proBNP (NT-proBNP)
    - Released by myocardial tissue in the presence of stress
    - BNP > 100 pg/mL
    - NT-proBNP > 300 pg/mL

- **Cardiac Imaging**
  - Echocardiogram (ECHO): assess Left Ventricular Ejection Fraction (LVEF)
    - LVEF: measurement of how much blood is pumped out of the left ventricle with each contraction
      - Normal EF: ~50-70%
      - HFrEF: ≤ 40%
    - Chest X-ray: assess cardiomegaly, pulmonary congestion, and edema

Source: Yancy CW, et al. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-239.

PATHOPHYSIOLOGY

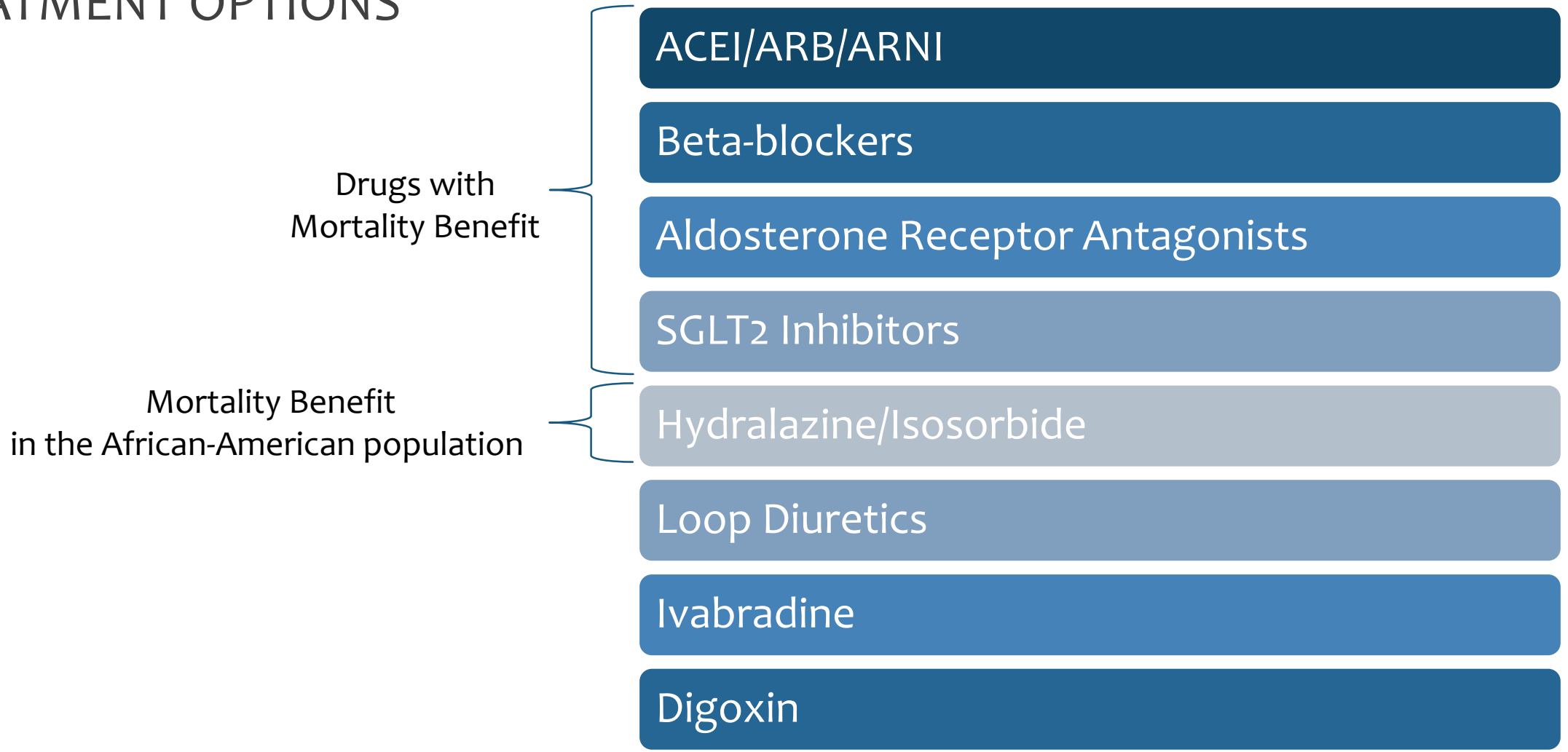
- **"Pump Failure": State of Low Cardiac Output (CO)**
- Compensatory mechanisms to increase CO
  - Neurohormonal activation
    - Activation of Renin Angiotensin-Aldosterone System (RAAS) and Sympathetic Nervous System (SNS)
  - Increased preload and myocardial stretch to increase stroke volume
- Impaired nitric oxide-soluble guanylyl cyclase-cyclic guanosine monophosphate (NO-sGC-cGMP) pathway
  - Vascular dysfunction and myocardial dysfunction
- Cardiac remodeling



Source: Mazurek JA, et al. *Heart Fail Clin*. 2017 Jan;13(1):1-19.

TREATMENT OVERVIEW

TREATMENT OPTIONS



ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor neprilysin inhibitor; SGLT2: Sodium-glucose co-transporter 2

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

TREATMENT OPTIONS

Class	Agents	Mechanism of Action	Safety Considerations
ACEI	• Captopril • Enalapril • Lisinopril • Ramipril	• Blocks conversion of angiotensin I to angiotensin II: decreased vasoconstriction and aldosterone secretion	• BBW: Teratogenic • C/I: History of angioedema, use within 36 hours of neprilysin inhibitor • ADRs: cough, hyperkalemia, angioedema, renal impairment

ARB	• Candesartan
	• Losartan
	• Valsartan
		• Binds to angiotensin receptor-1 blocking the effect of angiotensin on the RAAS system	• Same as ACEI except:
			  • Less cough and angioedema
			  • NO washout period with neprilysin inhibitor

ARNI	• Sacubitril/ Valsartan	• Valsartan = ARB
		• Sacubitril = Neprilysin inhibitor
		  • Neprilysin: degradation of vasodilatory peptides
			• C/I: Within 36 hours of ACEI use, history of angioedema, pregnancy, lactation, severe hepatic impairment (Child-Pugh C)
			• Cautions:
			  • Renal dose adjustment in eGFR <30 mL/min/ 1.73 m^2
			  • SBP <100 mm Hg, volume depletion

Beta-blockers	• Bisoprolol • Metoprolol Succinate • Carvedilol	• Inhibition of β1 and/or β2 receptors resulting in decreased sympathetic stimulation	• BBW: Abrupt discontinuation • C/I: Severe bradycardia, 2nd/3rd degree AV block, sick sinus syndrome, cardiogenic shock • ADRs: bradycardia, depression, impotence, cold extremities

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor neprilysin inhibitor; BBW: Black box warning; C/I: Contraindication; ADRs: Adverse drug reactions; eGFR: estimated glomerular filtration rate

Sources: Yancy CW, et al. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-239.
Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810.

TREATMENT OPTIONS (CONT.)

Class	Agents	Mechanism of Action	Safety Considerations
Aldosterone receptor antagonists (ARA)	• Spironolactone • Eplerenone	• Competes with aldosterone for receptor sites in distal tubules, increase sodium and water excretion	• C/I: hyperkalemia, anuria, significant renal impairment • Spironolactone: gynecomastia, breast tenderness, impotence, amenorrhea
Hydralazine/Isosorbide		• Hydralazine: direct arterial vasodilator → decreases afterload • Nitrates: increases nitric oxide → venous dilation and decreases preload	• C/I: In combination with PDE-5 inhibitors (sildenafil, tadalafil) due to risk of severe hypotension • ADRs: Hypotension, headache, flushing, dizziness, tachyphylaxis, syncope, reflex tachycardia
SGLT2 Inhibitors	• Dapagliflozin • Empagliflozin	• Inhibition of sodium-glucose co-transporter 2 in the renal proximal tubule leading to multiple direct and indirect mechanisms of action	• Genital mycotic infections • Euglycemic ketoacidosis • Hypotension/volume depletion

SGLT2: Sodium-glucose co-transporter 2; C/I: Contraindication; ADRs: Adverse drug reactions

Sources: Yancy CW, et al. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-239.
Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810.

TREATMENT OPTIONS (CONT.)

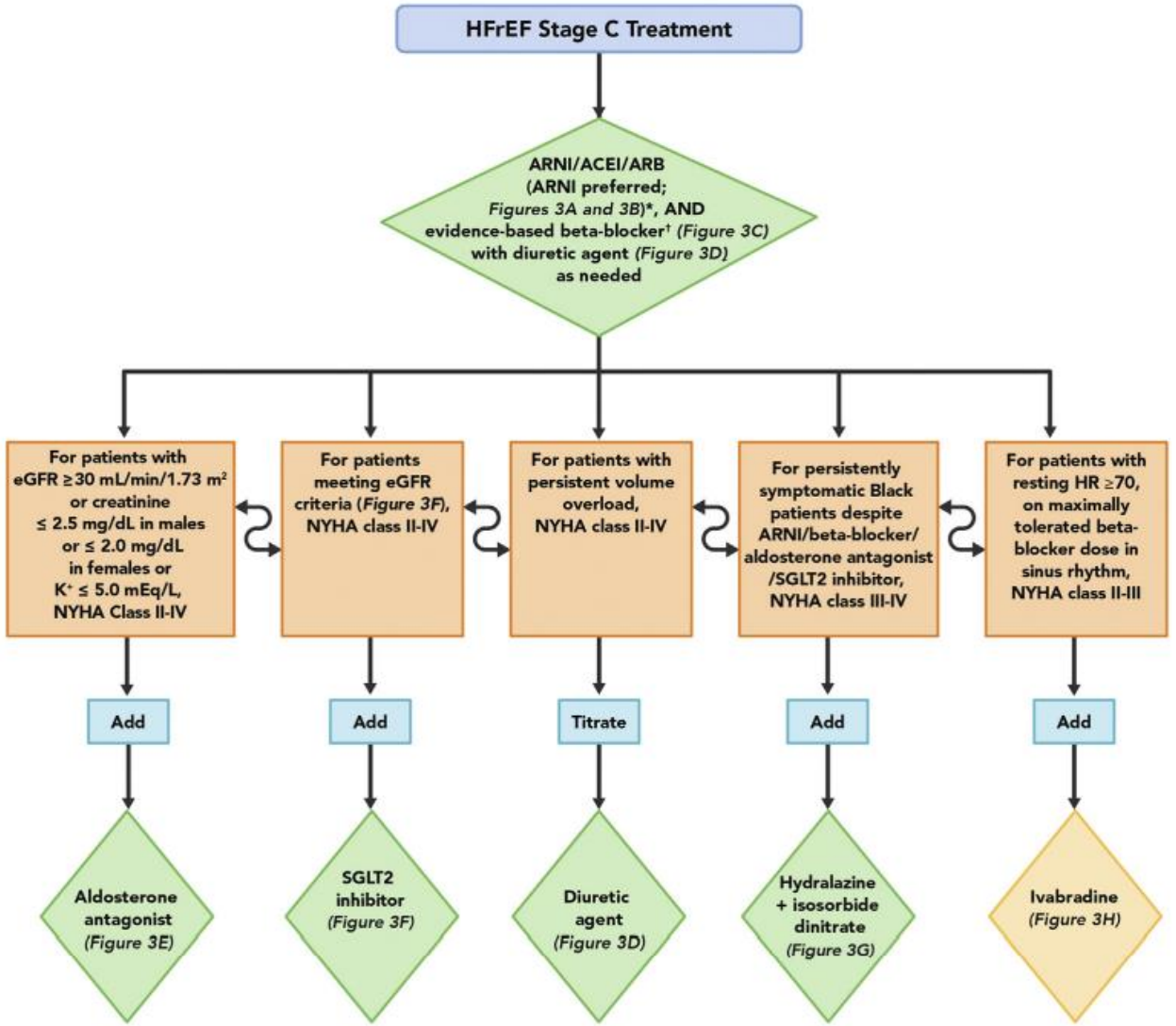
Class	Agents	Mechanism of Action	Safety Considerations
Loop Diuretics	• Furosemide • Bumetanide • Torsemide • Ethacrynic acid	• Blocks Na^+-K^+-$2Cl^-$ transporter in the thick ascending of limb of loop of Henle	• BBW: fluid and electrolytes loss • C/I: Anuria • Warnings: Sulfa allergy with all except Ethacrynic acid • ADRs: ↓Na^+ ,↓Cl^- ,↓K^+, Ca^{2+}, ↓Mg^{2+},↑HCO3 /metabolic alkalosis, ↑ uric acid, ↑blood glucose, ↑triglycerides, ↑ total cholesterol, orthostatic hypotension, photosensitivity, ototoxicity
Ivabradine		• Inhibits I_f current resulting in hyperpolarization, reducing SA node firing and therefore, reduces HR of patients without lowering BP	• C/I: acute decompensated heart failure, BP < 90/50 mmHg, sick sinus syndrome or 3rd degree AV block, HR <60 bpm • Warnings: ↓HR and bradycardia, ↑ risk of QT prolongation and ventricular arrhythmia, fetal toxicity • ADRs: hypertension
Digoxin		• Inhibits the Na+/K+ ATPase pump which results in positive inotropic effects (↑ CO) and also has a negative chronotropic effect (↓HR)	• Warnings: 2nd or 3rd degree heart block, Wolff Parkinson White syndrome • C/I: Ventricular fibrillation • ADRs : dizziness, mental disturbance, headache, nausea, vomiting, diarrhea • Therapeutic range for HF: 0.5 - 0.9 ng/mL

BBW: Black box warning; C/I: Contraindication; ADRs: Adverse drug reaction

Sources: Yancy CW, et al. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-239.
Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810.

PLACE IN THERAPY

2021 ACC GUIDELINE-DIRECTED MEDICAL THERAPY



ACC: American College of Cardiology

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

2021 GUIDELINE UPDATE

Initiating, adding, or switching therapies to new guideline-directed treatments

2017 Update

- Provides algorithm regarding initiating GDMT with a dosing chart
- No updates from 2013 guidelines on titration or monitoring of GDMT

2021 Update

- Updated treatment algorithm for GDMT with novel therapies, including indication and monitoring
- Consider increasing dose of most therapies every 2 weeks until maximum tolerated or target dose is achieved
  - Includes ACEI/ARB/ARNI, evidence-based beta-blockers, ARA, hydralazine/isosorbide dinitrate
- Aim to achieve optimal GDMT within 3 to 6 months of initial diagnosis of HF

Sources: Yancy CW, et al. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-239.
Yancy CW, et al. *J Am Coll Cardiol*. 2017;70:776–803.
Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810.

TITRATIONS PARAMETERS FOR GDMT

- Diuretics
  - Titrate dose to relief of congestion over days to weeks
  - If reaching high doses of loop diuretic, consider changing to a different loop diuretic or adding thiazide diuretic
  - May need to lower loop diuretics when optimizing titration for ACEI/ARB/ARNI or adding SGLT2 inhibitors

- Hydralazine/Isosorbide dinitrate
  - Indicated for African-American patients once target or maximally tolerated doses of beta-blocker, ARNI/ACEI/ARB, and aldosterone receptor antagonists are achieved

- Ivabradine
  - Initiated only after maximally tolerated doses of beta-blockers achieved if HR remains $\geq$ 70 beats/min

- **NOT** necessary to achieve target or maximally tolerated doses of other drugs before adding:
  - Aldosterone receptor antagonists
  - SGLT2 inhibitors

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

2021 GUIDELINE UPDATE

Initiating, adding, or switching therapies to new guideline-directed treatments
Initiating beta-blocker vs ACEI/ARB/ARNI first in patients with new-onset Stage C HFrEF

2017 Update

- No consensus provided on the order of initiation between ARNI/ACEI/ARB or beta-blocker

2021 Update

- Either an ARNI/ACEI/ARB or beta-blocker can be started first, or can be started at the same time
- Initiation of an ARNI/ACEI/ARB is often better tolerated when patient is still congested ("wet")
- Beta-blockers are better tolerated when the patient is less congested ("dry") with an adequate resting heart rate

Sources: Yancy CW, et al. *J Am Coll Cardiol*. 2017;70:776–803.
Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810.

2021 GUIDELINE UPDATE

Initiating, adding, or switching therapies to new guideline-directed treatments
Use of ARNIs as a de novo therapy

2017 Update

- In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, **replacement by an ARNI** is recommended to further reduce morbidity and mortality

2021 Update

- Can use as **de novo** therapy in some patients naïve to ACEI or ARB therapies
- Based on:
  - Recent data from clinical studies
  - Aggregate clinical experience
- **Preferred** agent over ACEI/ARB
- Indicated in NYHA Class II-IV HFrEF and EF ≤ 40%

Sources: Yancy CW, et al. *J Am Coll Cardiol*. 2017;70:776–803.
Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810.

SACUBITRIL/VALSARTAN TRIALS

Data in ACEI/ARB naïve population leading to de novo use approval

	PIONEER-HF (2019)	PROVE-HF (2019)	TITRATION (2016)
Description	Assessing safety and efficacy of ARNI in patients hospitalized for ADHF	Determining if NT-proBNP changes with ARNI correlate with changes in measures of cardiac volume and function	Comparing the tolerability of different initiation strategies of ARNI
Intervention	ARNI (n=440) vs. Enalapril (n=441)	ARNI (n=654)	ARNI (n=498)

Primary outcome in ACEI/ARB naive subgroup	• Ratio of change in NT-proBNP from baseline through weeks 4 and 8:
	  • 0.48 vs 0.66
	  • Ratio of change 0.72; 95% CI, 0.60 to 0.86; P<0.001
		• Significant correlation between reductions in NT-proBNP and cardiac remodeling parameters
		  • Specifically, 12% increase in LVEF at 12 months
			• Patients in subgroup demonstrated no unexpected adverse effects compared with those already taking an ACEI/ARB

ADHF: Acute Decompensated Heart Failure; CI: Confidence interval

Consistent reductions in NT-proBNP and comparable safety profile in ACEI/ARB naïve subgroup

Sources: Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810.
Velazquez EJ, et al. *N Engl J Med.* 2019;380:539– 48.
Januzzi JL, et al. *JAMA.* 2019;322(11):1085–1095.

2021 GUIDELINE UPDATE

Initiating, adding, or switching therapies to new guideline-directed treatments
Approval of SGLT2 Inhibitors

2017 Update

- Not mentioned

2021 Update

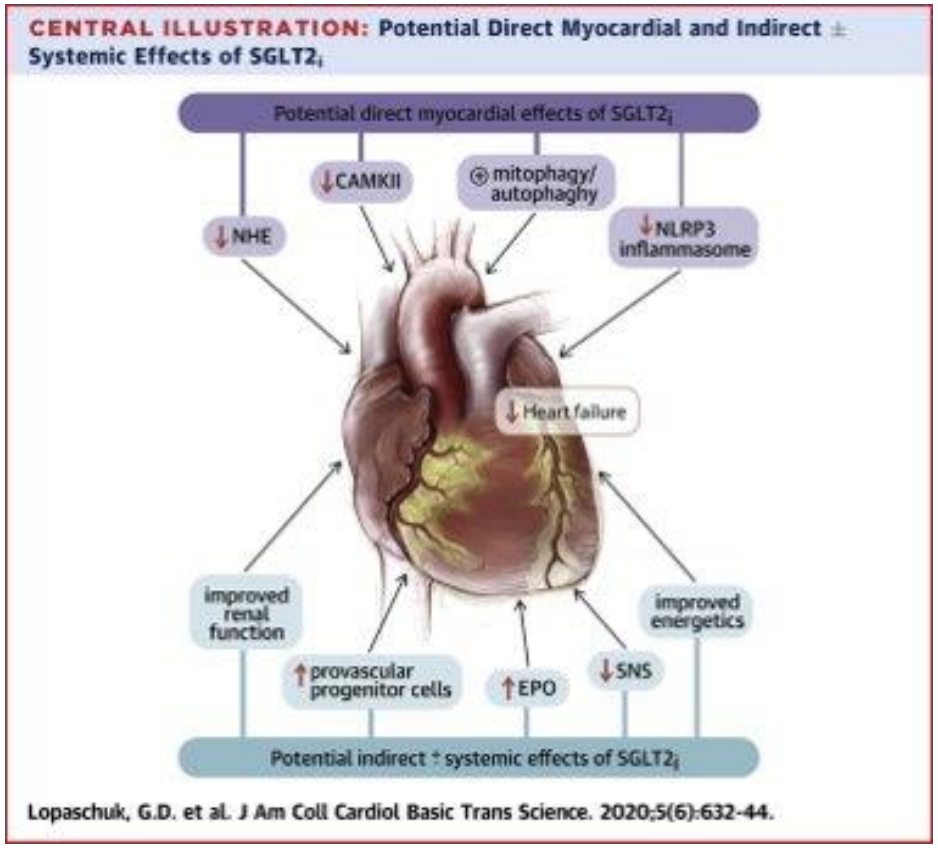
- Indications:
  - HFrEF (EF ≤40%) with or without diabetes
  - NYHA class II–IV HF
  - Administered in conjunction with a background of GDMT for HF
- Dapagliflozin and Empagliflozin shown to reduce combined risk of cardiovascular (CV) death and hospitalization for HF in those with HFrEF with or without diabetes
- Check to ensure patients meet eGFR criteria

Sources: Yancy CW, et al. *J Am Coll Cardiol*. 2017;70:776–803.
Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810.

SGLT2 INHIBITORS

Mechanism of Action

- Osmotic Diuresis and Natriuresis: Excretion of sodium and glucose
  - Reduction in blood pressure
- Improved cardiac energy metabolism
- Preventing adverse cardiac remodeling
- Maintenance of kidney function



Sources: Farxiga (dapagliflozin) [prescribing information].Wilmington, DE: Astrazeneca Pharmaceuticals LP; April 2021
Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; August 2021
Lopaschuk GD, et al. *JACC Basic transl sci*. 2020;5(6):632-644

SGLT2 INHIBITORS

Medications	Dosing in HFrEF	Renal Dosing	Safety
Dapagliflozin	10 mg orally daily	• eGFR <25: Initiation not recommended • Dialysis: Contraindicated	• Genital mycotic infections • Urinary tract infections • Euglycemic ketoacidosis • Hypotension/volume depletion • Acute kidney injury and impairment in renal function • Necrotizing fasciitis of the perineum (Fournier's gangrene)
Empagliflozin	10 mg orally daily	• eGFR <20: Caution (Data insufficient) • Dialysis: Contraindicated	

eGFR expressed in mL/minute/1.73 m^2

Sources: Farxiga (dapagliflozin) [prescribing information].Wilmington, DE: Astrazeneca Pharmaceuticals LP; April 2021
Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; August 2021

SGLT2 INHIBITORS IN HEART FAILURE

	DAPA-HF (2019) Dapagliflozin	EMPEROR-Reduced (2020) Empagliflozin
Population	NYHA Class II-IV HFrEF (EF < 40%) • 45% with T2DM, 55% without T2DM	NYHA Class II-IV HFrEF (EF < 40%) • 49.8% with T2DM, 50.2% without T2DM
Intervention	Dapagliflozin (n=2,373) vs placebo (n=2,371)	Empagliflozin (n=1,863) vs placebo (n=1,867)

Primary Outcome	• CV death or hospitalization for heart failure
	  • 16.3% vs. 21.2%
	  • HR 0.74; 95% CI 0.65-0.85; P<0.001
	  • 26% RRR (4.9% ARR)
	• Results consistent across patients with T2DM and without T2DM
		• CV death or hospitalization for heart failure
		  • 19.4% vs. 24.7%
		  • HR 0.75; 95% CI 0.65-0.86; P<0.001
		  • 25% RRR (5.3% ARR)
		• Results consistent across patients with T2DM and without T2DM

T2DM: Type 2 diabetes mellitus; HR: hazard ratio; RRR: relative risk reduction; ARR: absolute risk reduction; CI: Confidence interval

Sources: Mcmurray JJV, et al. *N Engl J Med*. 2019;381(21):1995-2008.
Packer M, et al. *N Engl J Med*. 2020;383(15):1413-1424.

2021 GUIDELINE UPDATE

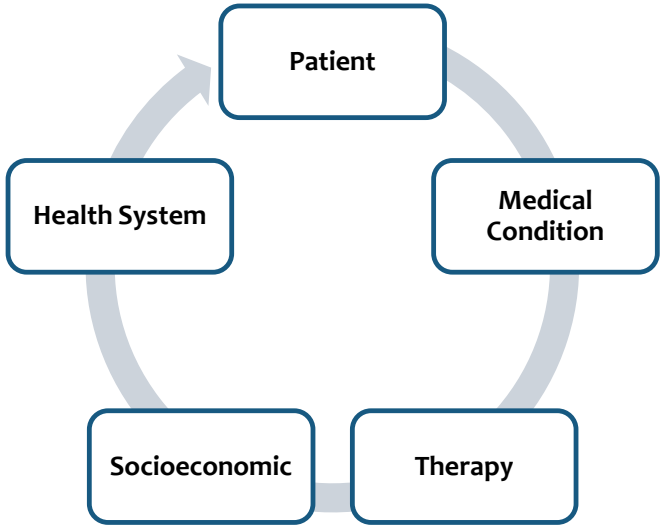
Achieving optimal therapy with multiple drugs for HF
Barriers to Medication Titration, Adherence, and Access

2017 Update

- Not mentioned

2021 Update

- Barriers to titration to recommended target doses:
  - Patient profile differing from those enrolled in trials
  - Abnormal renal function and/or hyperkalemia
  - Socioeconomic barriers: cost (ARNI, SGLT2 Inhibitors), transportation
  - Practitioners' hesitancy and unfamiliarity in implementing a new drug into clinical practice
- Considerations when evaluating adherence
  - Health literacy, comorbidities, high HF regimen complexity, cost, and access



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

2021 GUIDELINE UPDATE

Considerations for Specific Patient Cohorts

2017 Update

- Not mentioned

2021 Update

Patient Cohorts	Recommendations	Risks and Uncertainties
African-American patients	GDMT	• Possibly higher risk of angioedema vs. ACEI/ARB/ARNIs • Uncertain outcomes and risk of hypotension when combining new drugs with hydralazine/isosorbide
Older adults (≥ 75 years of age)	May consider starting with lower doses of GDMT	• Potential falls, worsening renal function, polypharmacy, comorbidities • Uncertainty with efficacy of lower-dose GDMT on outcomes
Frail patients	GDMT as tolerated	• Possibly increased risk for adverse drug reactions

Sources: Yancy CW, et al. *J Am Coll Cardiol*. 2013 Oct 15;62(16):e147-239.
Yancy CW, et al. *J Am Coll Cardiol*. 2017;70:776–803.
Maddox TM, et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810.

ASSESSMENT QUESTION #1

Pharmacy Technicians

Which of the following are potential barriers associated with prescribing ARNIs? Select all that apply:

A. Practitioners' unfamiliarity with ARNIs
B. Drug-drug interactions
C. Cost and affordability
D. Undesirable formulation
E. Unpredictable pharmacokinetic profile

ASSESSMENT QUESTION #1: CORRECT RESPONSE

Pharmacy Technicians

Which of the following are potential barriers associated with prescribing ARNIs? Select all that apply:

A. Practitioners' unfamiliarity with ARNIs
B. Drug-drug interactions
C. Cost and affordability
D. Undesirable formulation
E. Unpredictable pharmacokinetic profile

SUMMARY: 2021 GUIDELINE UPDATES

Initiating, adding, or switching therapies to new evidence-based guideline-directed treatments for HFrEF

- Initiation of ACEI/ARB/ARNI vs Beta-blocker
- Initiation of de novo ARNI therapy
- Utilization of SGLT2 inhibitors for HFrEF

Achieving optimal therapy with multiple drugs for HF

- Barriers to medication titration, adherence, and access

Considerations for specific patient cohorts

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

ASSESSMENT QUESTION #2

Pharmacists and Nurses

Which of the following statements describes the correct rationale behind the therapeutic updates presented in the 2021 guidelines? Select all that apply:

A. SGLT2 inhibitors are approved for patients with NYHA class II-IV HFrEF due to evidence showing a reduced risk for HF hospitalizations and CV death regardless of the presence of diabetes
B. ARNIs are approved as a de novo therapy following evidence showing decreased risk of acute kidney injury in the subgroup of ACEI/ARB naïve patients
C. ARNIs are approved as a de novo therapy following consistent reductions in NT-proBNP and comparable safety profile seen in the subgroup of ACEI/ARB naïve patients
D. Beta-blockers should always be initiated prior to ACEI/ARB/ARNI due to benefits on mortality in hospitalized patients shown in recent trials

ASSESSMENT QUESTION #2: CORRECT RESPONSE

Pharmacists and Nurses

Which of the following statements describes the correct rationale behind the therapeutic updates presented in the 2021 guidelines? Select all that apply:

A. SGLT2 inhibitors are approved for patients with NYHA class II-IV HFrEF due to evidence showing a reduced risk for HF hospitalizations and CV death regardless of the presence of diabetes

B. ARNIs are approved as a de novo therapy following evidence showing decreased risk of acute kidney injury in the subgroup of ACEI/ARB naïve patients

C. ARNIs are approved as a de novo therapy following consistent reductions in NT-proBNP and comparable safety profile seen in the subgroup of ACEI/ARB naïve patients

D. Beta-blockers should always be initiated prior to ACEI/ARB/ARNI due to benefits on mortality in hospitalized patients shown in recent trials

EMERGING THERAPIES

TARGETS FOR HFrEF THERAPIES

- Vericiguat
  - Guanylyl cyclase

- Omecamtiv Mecarbil
  - Cardiac myosin

TABLE 14 Important Pathophysiological Targets in Chronic, Hemodynamically Stable HFrEF and Treatments

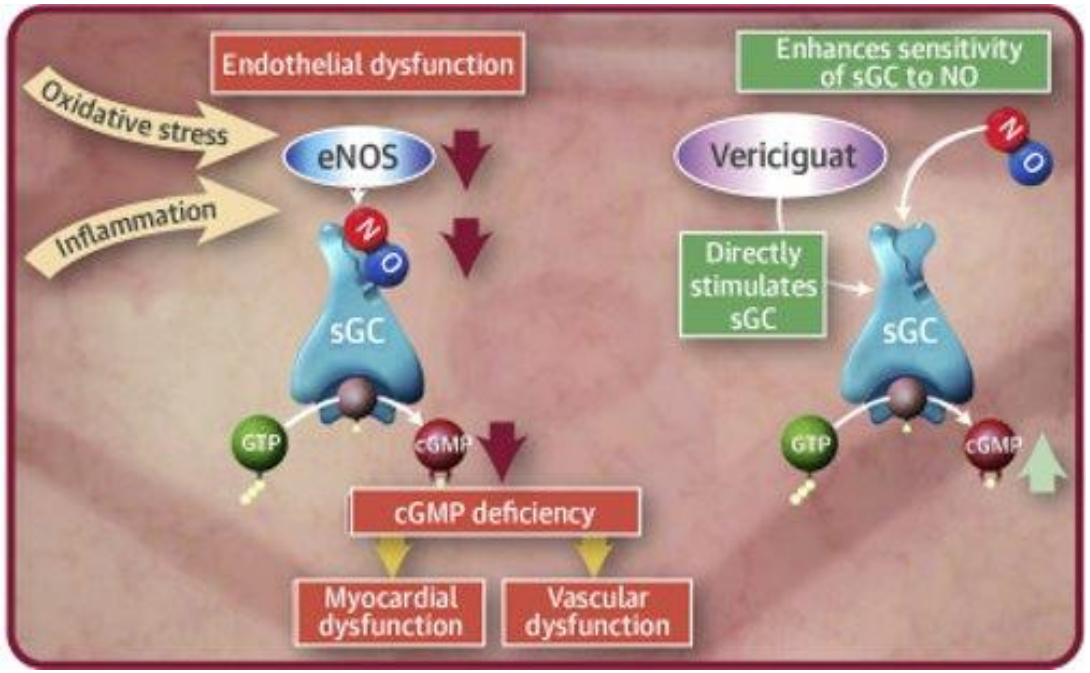
Target	Therapy
Renin-angiotensin-aldosterone system	ARNIs/ACEIs/ARBs, aldosterone antagonists
Sympathetic nervous system	Beta-blockers
Natriuretic and other vasodilator peptides	Neprilysin inhibitor (ARNI)
Sodium-glucose cotransporter-2	SGLT2 inhibitors
Balanced vasodilation and oxidative stress modulation	HYD/ISDN
Elevated heart rate	Beta-blocker, ivabradine
Guanylyl cyclase	Soluble guanylyl cyclase stimulators
Relief of congestion	Diuretic agents

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

VERICIGUAT

Mechanism of Action

- Stimulator of soluble guanylate cyclase (sGC), an important enzyme in the nitric oxide (NO) pathway
  - NO binds to sGC, catalyzing synthesis of cGMP
  - Leads to smooth muscle relaxation and vasodilation
- Targeting endothelial dysfunction and regulation of reactive oxygen species



Sources: Vericiguat (Verquvo) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc; June 2021
Armstrong PW, et al. *JACC Heart Fail*. 2018 Feb;6(2):96-104.

VERICIGUAT

FDA Approval: January 20, 2021

Indicated to reduce the risk of cardiovascular death and HF hospitalization following a hospitalization for HF or need for outpatient IV diuretics in adults with symptomatic chronic HF and EF <45%

2.5 mg orally once daily → Double the dose every 2 weeks (5 mg) → **10 mg** target dose, as tolerated

Dosing considerations

- Not studied in *severe* hepatic impairment
- Not studied in eGFR < 15, or on dialysis

How Supplied

- 2.5 mg (x14 tablets)
- 5 mg (x14 tablets)
- 10 mg (x30 tablets)

Administration

- Take with food
- Can be crushed and mixed with water immediately before administration

Pharmacokinetics

- 93% bioavailability with food
- 98% protein bound
- Metabolized via glucuronidation to inactive metabolite
- Half-life: 30 hours

eGFR expressed in mL/minute/1.73 m^2

Source: Vericiguat (Verquvo) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc; June 2021

VERICIGUAT

Black Box Warning

- Embryo-Fetal Toxicity
  - Exclude pregnancy before start of treatment
  - Use effective forms of contraception during and for at least 1 month after last dose
  - Breastfeeding not recommended due to limited data

Contraindications

- Pregnancy
- Use with other PDE-5 inhibitors or sGC stimulators

Adverse Reactions

- Hypotension
- Anemia

Source: Vericiguat (Verquvo) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc; June 2021

VICTORIA TRIAL (2021)

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction	
Population	• Patients with symptomatic chronic HF (NYHA Class II-IV) and EF <45% following a worsening HF event • BNP ≥ 300 (or ≥ 500)* • NT-proBNP ≥ 1000 (or ≥ 1600)* • Majority of the patients were on GDMT
Intervention	• Vericiguat titrated to 10 mg daily (n-2,526) vs placebo (n= 2,524) • Both added on to standard of care HF therapies

Primary Outcome	• Composite of CV death or first hospitalization for HF
	  • Vericiguat (35.5%) vs Placebo (38.5%)
	  • HR 0.90; 95% CI, 0.82 to 0.98; P=0.019
	  • 10% RRR (4.2% annualized ARR)

BNP/NT-proBNP expressed in pg/mL; HR: hazard ratio; RRR: relative risk reduction; ARR: absolute risk reduction; CI: Confidence interval
*with history of atrial fibrillation

Source: Armstrong PW, et al. *N Engl J Med.* 2020;382(20):1883-1893.

VICTORIA TRIAL (2021)

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction	
Primary Outcome (Subgroups)	• Subgroups with potential further benefit

Patients < 75 years	HR 0.84; 95% CI, 0.75 to 0.94
Chronic renal insufficiency (eGFR >30 to ≤60)	HR 0.84; 95% CI, 0.73 to 0.96
LVEF < 40%	HR 0.88; 95% CI 0.80 to 0.97
NYHA Class III or IV	HR 0.87; 95% CI, 0.77 to 0.99

Safety Outcomes	• No statistically significant difference between groups with incidences of prespecified adverse events of clinical interest (symptomatic hypotension and syncope) • Anemia (7.6% vs 5.7%)

eGFR expressed in mL/minute/1.73 m^2

Source: Armstrong PW, et al. *N Engl J Med.* 2020;382(20):1883-1893.

VERICIGUAT

PLACE IN THERAPY

- Patients with advanced HFrEF with a recent history of acute decompensation despite optimal medical therapy are optimal candidates for starting treatment with vericiguat
- Canadian Cardiovascular Society HF 2021 guidelines suggest considering vericiguat for HFrEF patients just recovered from HF hospitalization on top of a therapy including a beta-blocker, an ACEI/ARB/ARNI, an ARA and an SGLT2 inhibitor
- European Society of Cardiology 2021 guidelines state that vericiguat may be considered to reduce the risk of CV mortality and hospitalizations for HF in addition to standard therapy

Sources: Armstrong PW, et al. *N Engl J Med.* 2020;382(20):1883-1893.
McDonald M, et al. *Can J Cardiol*. 2021 Apr;37(4):531-546.
McDonagh TA, et al. *Eur Heart J*. 2021 Sep 21;42(36):3599-3726.
Lee A, et al. ACC: The role of vericiguat in the expanding realm of heart failure pharmacotherapy. 2020 July 8.

ASSESSMENT QUESTION #3

Pharmacy Technicians

Which of the following statements is TRUE about vericiguat?

A. Vericiguat is not safe for patients who are pregnant
B. A common side effect of vericiguat is hypertension
C. Vericiguat should be taken on an empty stomach
D. Vericiguat is dosed twice daily

ASSESSMENT QUESTION #3: CORRECT RESPONSE

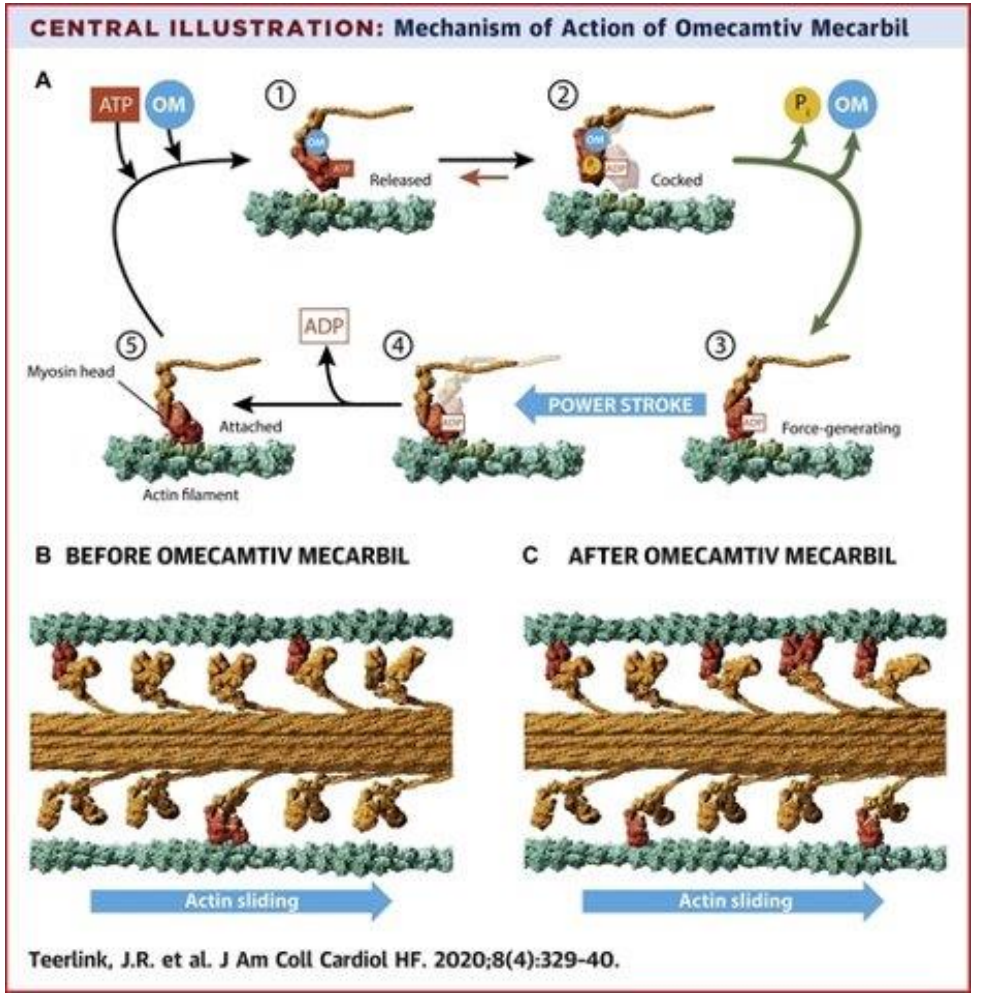
Pharmacy Technicians

Which of the following statements is TRUE about vericiguat?

A. **Vericiguat is not safe for patients who are pregnant**
B. A common side effect of vericiguat is hypertension
C. Vericiguat should be taken on an empty stomach
D. Vericiguat is dosed twice daily

OMECAMTIV MECARBIL (OM)

- Mechanism of Action
  - Myosin specific activator that increases myocardial contractility independent of calcium fluxes.
  - Increases the number of myosin heads that are able to connect and pull-on actin filaments during systole
  - Directly enhances systolic function
- New class of myotropes
- NOT currently FDA approved



Source: Teerlink JR, et al. *JACC Heart Fail*. 2020 Apr;8(4):329-340.

ASSESSMENT QUESTION #4

Pharmacists and Nurses

The mechanism of omecamtiv mecarbil in heart failure is:

A. Inhibits the Na^{2+}/K^{+} ATPase pump which results in positive inotropic effects
B. Selectively targets the β_1 receptors to increase cardiac contractility
C. Decreases afterload and preload due to arterial and venous dilation
D. Augments cardiac contractility by selectively binding to cardiac myosin

ASSESSMENT QUESTION #4: CORRECT RESPONSE

Pharmacists and Nurses

The mechanism of omecamtiv mecarbil in heart failure is:

A. Inhibits the Na^{2+}/K^{+} ATPase pump which results in positive inotropic effects
B. Selectively targets the β_1 receptors to increase cardiac contractility
C. Decreases afterload and preload due to arterial and venous dilation
D. Augments cardiac contractility by selectively binding to cardiac myosin

COSMIC-HF TRIAL (2016)

Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure	
Population	• NYHA Class II-III with EF ≤ 40% • NT-proBNP ≥200 (or ≥ 1200)* • Treated with stable, optimum therapy for ≥ 4 weeks (Beta-blocker and ACEI/ARB)
Intervention	• Pharmacokinetic (PK)-guided titration of OM to 50 mg BID (n=149) vs OM 25 mg BID (n=150) vs Placebo (n=149) • 20 weeks

Primary Outcome	• Mean maximum concentration of OM at week 2 and 12 visits and predose concentrations at week 2, 8, 12, 16, and 20 visits
	  • Mean maximum concentration of OM at week 12:
	  • Fixed-dose group: 200 ng/mL
	  • PK-titration group: 318 ng/mL
	  • Target plasma concentration of more than 200 ng/mL at week 12:
	  • PK-titration group: 87% of patients
	  • Fixed-dose group: 46% of patients

BNP/NT-proBNP expressed in pg/mL
*with history of atrial fibrillation

Source: Teerlink JR, et al. *Lancet*. 2016 Dec 10;388(10062):2895-2903.

COSMIC-HF TRIAL (2016)

Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure	

Other Outcomes	**PK-guided titration group vs placebo**
	• Systolic ejection time increased by 25.0 msec ($p<0.0001$)
	• Stroke volume increased by 3.6 mL ($p=0.0217$)
	• Left ventricular end-systolic and end-diastolic dimensions decreased by 1.8 mm ($p=0.0027$) and 1.3 mm ($p=0.0128$), respectively
	  • Associated with statistically significant reductions in left ventricular end-systolic and end-diastolic volumes
	• NT-proBNP decreased by 970 pg/mL ($p=0.0069$)
	Adverse events
	• Frequency of adverse events, serious adverse events, and deaths were similar across groups
	• Median changes from baseline in concentration of cardiac troponin I
	  • Fixed dose group: 0.001 ng/mL
	  • PK-titration group: 0.006 ng/mL
	  • Concentrations returned to baseline within 4 weeks of discontinuing OM

Improved cardiac function and decreased ventricular diameter

Source: Teerlink JR, et al. *Lancet*. 2016 Dec 10;388(10062):2895-2903.

GALACTIC-HF TRIAL (2021)

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure	
Population	• NYHA Class II-IV with EF ≤35% • BNP ≥ 125 (or ≥ 375)* • NT-proBNP ≥ 400 (or ≥ 1200)* • Patients currently hospitalized for HF (inpatients) or had either made an urgent visit to the emergency department or been hospitalized for HF within 1 year before screening (outpatients) • Patients required to receive pharmacologic and device therapy for HF

Intervention	• Placebo (n=4,112) vs OM (n=4,120)
	  • OM 25 mg BID (n=1,192)
	  • OM 37.5 mg BID (n=559)
	  • OM 50 mg BID (n=1,961)

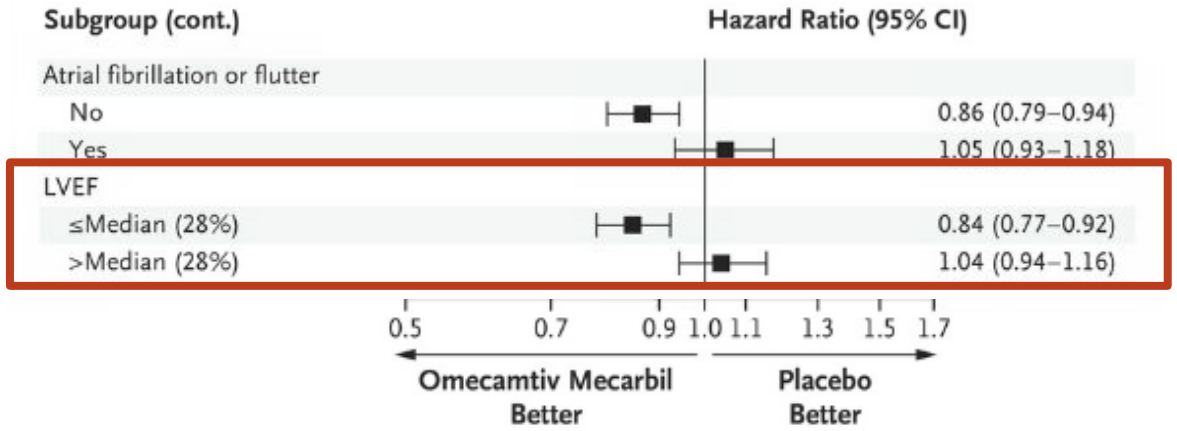
Primary Outcome	• Composite of CV death or first heart-failure event (hospitalization or urgent visit for HF)
	  • OM (37%) vs. Placebo (39.1%)
	  • HR, 0.92; 95% CI, 0.86 to 0.99; P=0.03
	  • 8% RRR (2.1% ARR)

BNP/NT-proBNP expressed in pg/mL; HR: hazard ratio; CI: confidence interval; RRR: relative risk reduction; ARR: absolute risk reduction
*with history of atrial fibrillation

Source: Teerlink JR, et al. *N Engl J Med*. 2021 Jan 14;384(2):105-116.

GALACTIC-HF TRIAL (2021)

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure	
Primary Outcome (Subgroups)	• Effect of OM consistent across most prespecified subgroups except for possible interaction between trial group and EF at baseline



Source: Teerlink JR, et al. *N Engl J Med*. 2021 Jan 14;384(2):105-116.

GALACTIC-HF TRIAL (2021)

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure	

Other Outcomes	• Laboratory Measures
	  • Change from baseline in median NT-proBNP: 10% lower in OM group
	  • Median change from baseline in cardiac troponin I at week 24: 4 ng/L higher in OM group
	
	• Safety Outcomes
	  • No statistically significant differences in incidences of serious adverse events, discontinuation due to adverse events, major cardiac ischemic events, or ventricular tachyarrhythmias

OM improved the composite primary outcome of CV death or hospitalization, but did not improve any secondary outcomes

Source: Teerlink JR, et al. *N Engl J Med*. 2021 Jan 14;384(2):105-116.

METEORIC-HF TRIAL (IN PROGRESS)

Study to Assess the Effect of Omecamtiv Mecarbil on Exercise Capacity in Subjects With Heart Failure	
Population	• NYHA Class II or III with EF ≤35% • Reduced exercise capacity compared to age matched controls • NT-proBNP level > 200
Intervention	• OM vs. placebo • N=276
Outcomes	• Change in peak oxygen uptake (VO_2) on cardiopulmonary exercise testing from baseline to Week 20 • Trial completed November 2021, awaiting results • Preliminary results from the company state no effect of OM on exercise capacity

OM granted Fast Track designation by FDA on May 8, 2020

NDA filed with PDUFA date of November 30, 2022

BNP/NT-proBNP expressed in pg/mL; PDUFA: Prescription Drug User Fee Act

Source: Clinicaltrials.gov. METEORIC-HF. NCT03759392.

ASSESSMENT QUESTION #5

Pharmacists and Nurses

What was the primary outcome of the GALACTIC-HF Trial?

A. Patients with HFrEF and HFpEF receiving omecamtiv mecarbil had fewer heart failure exacerbations than those who received placebo
B. Patients with HFrEF receiving omecamtiv mecarbil showed significant dyspnea relief compared to placebo
C. Patients with HFrEF receiving omecamtiv mecarbil had a lower incidence of a composite of a heart failure event or death from cardiovascular causes than those who received placebo
D. Patients with HFrEF receiving omecamtiv mecarbil demonstrated improvements in New York Heart Association functional class

ASSESSMENT QUESTION #5: CORRECT RESPONSE

Pharmacists and Nurses

What was the primary outcome of the GALACTIC-HF Trial?

A. Patients with HFrEF and HFpEF receiving omecamtiv mecarbil had fewer heart failure exacerbations than those who received placebo
B. Patients with HFrEF receiving omecamtiv mecarbil showed significant dyspnea relief compared to placebo
C. Patients with HFrEF receiving omecamtiv mecarbil had a lower incidence of a composite of a heart failure event or death from cardiovascular causes than those who received placebo
D. Patients with HFrEF receiving omecamtiv mecarbil demonstrated improvements in New York Heart Association functional class

ASSESSMENT QUESTION #6

Pharmacy Technicians

Which of the following regimens is appropriate? (Select all that apply)

A. Vericiguat 10 mg by mouth once daily
B. Vericiguat 10 mg intravenous twice daily
C. Omecamtiv mecarbil 50 mg via inhalation once daily
D. Omecamtiv mecarbil 50 mg by mouth twice daily

ASSESSMENT QUESTION #6: CORRECT RESPONSE

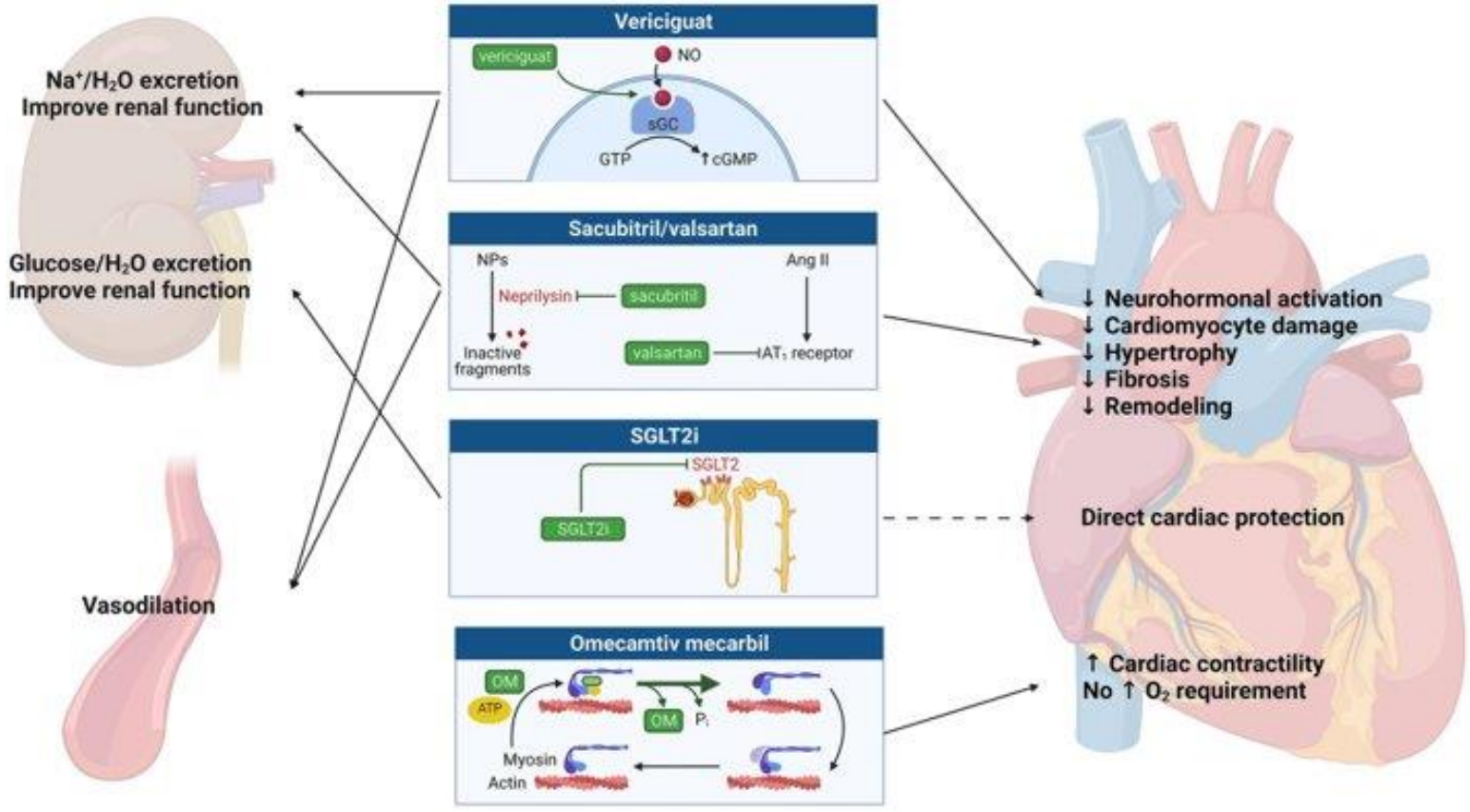
Pharmacy Technicians

Which of the following regimens is appropriate? (Select all that apply)

A. Vericiguat 10 mg by mouth once daily
B. Vericiguat 10 mg intravenous twice daily
C. Omecamtiv mecarbil 50 mg via inhalation once daily
D. Omecamtiv mecarbil 50 mg by mouth twice daily

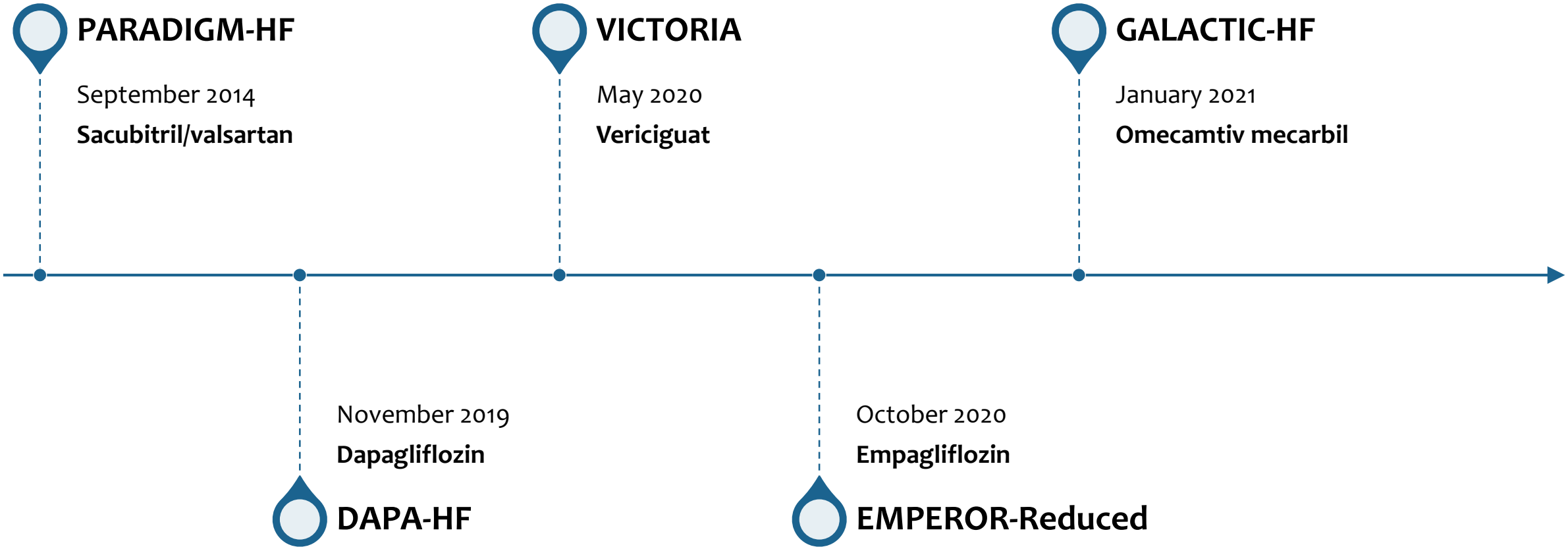
SUMMARIZING THE NOVEL THERAPIES

MECHANISM OF ACTION



Source: Aimo A, et al. *Heart Fail Rev.* 2021 Jul 21.

TRIAL TIMELINE



SUMMARY

2021 Therapeutic Updates

- Initiation of ACEI/ARB/ARNI vs Beta-blocker
  - Recommended titration frequency of 2 weeks
- Initiation of de novo ARNI therapy
- Utilization of SGLT2 inhibitors for HFrEF
- Addressing barriers to titration and improving medication adherence
- Considerations for specific patient cohorts

Vericiguat

- Small but statistically significant reduction in a composite clinical endpoint of cardiovascular death or first hospitalization for heart failure
- Further investigation needed to elucidate the role of vericiguat amongst available evidence-based therapies and target populations

Omecamtiv Mecarbil

- Decreases composite outcome of CV death and hospitalization for HF
- Role in HF is unestablished

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THANK YOU!

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