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Heart Failure With Reduced Ejection Fraction
A Review

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IMPORTANCE Worldwide, the burden of heart failure has increased to an estimated 23 million people, and approximately 50% of cases are HF with reduced ejection fraction (HFrEF).

OBSERVATIONS Heart failure is a clinical syndrome characterized by dyspnea or exertional limitation due to impairment of ventricular filling or ejection of blood or both. HFrEF occurs when the left ventricular ejection fraction (LVEF) is 40% or less and is accompanied by progressive left ventricular dilatation and adverse cardiac remodeling. Assessment for heart failure begins with obtaining a medical history and physical examination. Also central to diagnosis are elevated natriuretic peptides above age- and context-specific thresholds and identification of left ventricular systolic dysfunction with LVEF of 40% or less as measured by echocardiography. Treatment strategies include the use of diuretics to relieve symptoms and application of an expanding armamentarium of disease-modifying drug and device therapies. Unless there are specific contraindications, patients with HFrEF should be treated with a β-blocker and one of an angiotensin receptor–neprilysin inhibitor, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker as foundational therapy, with addition of a mineralocorticoid receptor antagonist in patients with persistent symptoms. Ivabradine and hydralazine/isosorbide dinitrate also have a role in the care of certain patients with HFrEF. More recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors have further improved disease outcomes, significantly reducing cardiovascular and all-cause mortality irrespective of diabetes status, and vericiguat, a soluble guanylate cyclase stimulator, reduces heart failure hospitalization in high-risk patients with HFrEF. Device therapies may be beneficial in specific subpopulations, such as cardiac resynchronization therapy in patients with interventricular dyssynchrony, transcatheter mitral valve repair in patients with severe secondary mitral regurgitation, and implantable cardiac defibrillators in patients with more severe left ventricular dysfunction particularly of ischemic etiology.

CONCLUSIONS AND RELEVANCE HFrEF is a major public health concern with substantial morbidity and mortality. The management of HFrEF has seen significant scientific breakthrough in recent decades, and the ability to alter the natural history of the disease has never been better. Recent developments include SGLT2 inhibitors, vericiguat, and transcatheter mitral valve repair, all of which incrementally improve prognosis beyond foundational neurohormonal therapies. Disease morbidity and mortality remain high, with a 5-year survival rate of 25% after hospitalization for HFrEF.

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Heart failure is a complex clinical syndrome in which there is dyspnea or exertional limitation due to impairment of ventricular filling or ejection of blood, or a combination of both. Once developed, heart failure results in significant morbidity and mortality, with a 1-year mortality rate of 7.2% and a 1-year hospitalization rate of 31.9% in patients with chronic heart failure, and in patients hospitalized for acute heart failure, these rates increase to 17.4% and 43.9%.[1] Heart failure has traditionally been broadly subclassified according to the left ventricular ejection fraction (LVEF) into 3 categories: heart failure with preserved ejection fraction (LVEF≥50%), heart failure with midrange ejection fraction (LVEF 41%-49%), and heart failure with reduced ejection fraction (HFrEF, in which the LVEF is ≤40%).[2] The optimal care of patients with HFrEF continues to be refined with advancements in drug and device therapies. In this review, we present an evidence-based update on the contemporary management of HFrEF.

Methods

We conducted a search of MEDLINE, Embase, and the Cochrane Database of Systemic Reviews for publications with the search terms *heart failure*, *heart failure with reduced ejection fraction*, or *HFrEF*. We searched for relevant English-language articles published between January 1, 1985, and May 14, 2020, with a focus on randomized clinical trials, meta-analyses, systematic reviews,

and clinical practice guidelines. Additional publications were identified through bibliography review. Of the 112 articles referenced in this review, 59 were clinical trials, 4 were meta-analyses, 29 were observational studies, and 20 were guidelines and other reports.

Epidemiology

Heart failure affects an estimated 6.5 million US adults and accounts for an estimated 1 million hospitalizations annually, of which approximately 50% are caused by HFrEF, with the balance caused by heart failure with midrange or preserved ejection fraction.[3,4] The incidence and prevalence of heart failure are increasing: data from the National Health and Nutrition Examination Survey show that between 2009-2012 and 2013-2016, the prevalence of heart failure among US adults increased from 5.7 million to 6.2 million, while data from the Atherosclerosis Risk in Communities study has shown the annual incidence of heart failure among US adults older than 55 years increased from 870 000 cases in 2005-2011 to 1 million cases in 2014.[4,5] In a study from the UK, while the age-standardized incidence of heart failure decreased by 7% (from 358 per 100 000 person-years to 332 per 100 000 person-years) between 2002 and 2014, the absolute number of incident heart failure cases increased by 12% (from 170 727 to 190 798 cases), and prevalent heart failure increased by 23% (from 750 127 to 920 616 cases).[6] This increase in the absolute number reflects an aging population, improved survival from myocardial infarction and other cardiovascular diseases, and the increasing prevalence of predisposing risk factors such as diabetes and obesity.

Using Framingham Heart Study data, predictors of incident HFrEF after multivariable adjustment include older age, male sex, higher heart rate (per 12-beat-per-minute [bpm]–increase; hazard ratio [HR], 1.32 [95% CI, 1.19-1.48]), hypertension (HR, 1.76 [95% CI, 1.28-2.41]), coronary artery disease (HR, 1.73 [95% CI, 1.27-2.34]), previous myocardial infarction (HR, 3.49 [95% CI, 2.48-4.9]), diabetes (HR, 2.91 [95% CI, 2.21-3.85]), and valvular heart disease (HR, 2.44 [95% CI, 1.48-4.04]).[7]

Clinical Presentation and Diagnosis

Patients with HFrEF may present with a variety of signs and symptoms, although none are entirely sensitive or specific to the diagnosis (**Box 1**, **Box 2**, **Box 3**). Typical symptoms include dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and ankle swelling. Other symptoms of right-sided heart failure that may be present but are more nonspecific include abdominal bloating, right upper-quadrant discomfort, and early satiety. Bendopnea, defined as shortness of breath when leaning forward (such as when putting on shoes) is also suggestive of heart failure.[8] Symptom severity is most commonly graded according to the New York Heart Association (NYHA) functional class designations (class I, no limitation in normal physical activity; class II, mild symptoms only during normal activity; class III, marked symptoms during daily activity, comfortable only at rest; class IV, severe limitations and symptoms even at rest).

Box 1. Initial Evaluation for Diagnosing Symptoms and Signs in Heart Failure With Reduced Ejection Fraction

Typical Symptoms
- Dyspnea
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Fatigue
- Reduced exercise tolerance
- Ankle swelling

Less Typical Symptoms
- Cough
- Abdominal distension
- Wheeze
- Abdominal bloating
- Early satiety
- Bendopnea[8]

More Specific Signs
- Elevated jugular venous pressure
- Positive abdominojugular reflux
- S_3 (gallop rhythm)
- Laterally displaced apical impulse

Less Specific Signs
- Weight gain
- Lung rales
- Peripheral edema
- Ascites
- Cool and/or mottled extremities
- Narrow proportional pulse pressure (pulse pressure: systolic blood pressure ratio ≤0.25)[9]
- Murmur of valvular regurgitation or stenosis
- Weight loss and cachexia (advanced heart failure)

Patients should be examined for markers of congestion and reduced peripheral perfusion (Box 1, Box 2, Box 3). Patients with more signs of congestion (jugular venous distension, edema, lung rales, and S_3 gallop) are at higher risk of cardiovascular death or heart failure hospitalization independent of symptoms, natriuretic peptides, and validated risk scores.[15] As a result of compensatory upregulation in lymphatic drainage, patients with chronic HFrEF may lack lung rales or peripheral edema, even when pulmonary capillary wedge pressure is elevated.

Diagnostic Workup

If a diagnosis of HFrEF is suspected, initial testing involves the measurement of natriuretic peptides, electrocardiography, and chest x-ray. Signs of congestion on chest x-ray are sensitive (81%) for the diagnosis of acute heart failure, although individual signs tend to be more specific than sensitive: cardiomegaly is sensitive for heart failure (64%-79%); whereas a number of signs have 95% specificity or greater (peribronchial cuffing, Kerley B lines, alveolar edema, bilateral pleural effusions).[16,17] Approximately 1 in 5 patients presenting with acute heart failure have no signs of

Box 2. Studies to Perform During the Initial Evaluation for Diagnosing Heart Failure With Reduced Ejection Fraction

Laboratory Studies
- BNP/NT-proBNP
- Complete blood count
- Basic metabolic panel
- Liver function tests
- Iron studies
- Thyroid function tests
- Hemoglobin A_{1c}
- Lipid panel

Diagnostic Imaging
- Chest x-ray
- Transthoracic echocardiography
- Coronary angiography (or coronary computed tomography angiography if low pretest probability
- Consider cardiac magnetic resonance imaging, positron emission tomography scan, or ^{99m}technetium pyrophosphate scan

Other
- Electrocardiogram
- Consider right heart catheterization
- Consider endomyocardial biopsy

Abbreviations: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Box 3. Uses of Natriuretic Peptides as Part of the Initial Evaluation for Diagnosing HFrEF

Support or Exclude a Diagnosis of Heart Failure

To rule in acute heart failure[10]
- NT-proBNP >450 pg/mL (<50 y); >900 pg/mL (50-75 y); >1800 pg/mL (>75 y)
- BNP >100 pg/mL (values >400 pg/mL have higher specificity)

To rule out acute heart failure
- NT-proBNP <300 pg/mL[10]
- BNP <50 pg/mL[11]

To rule out chronic heart failure
- BNP <35 pg/mL or NT-proBNP <125 pg/mL[12]

Help Inform Prognostic Trajectory

For acute decompensated heart failure
- Natriuretic peptides measured prior to discharge can risk-stratify patients after hospitalization for acute heart failure, where a <30% reduction in NT-proBNP concentration relative to admission value is associated with increased risk of death or hospital readmission for heart failure[2,13]

For chronic HFrEF
- A decrease in NT-proBNP to ≤1000 pg/mL during treatment of chronic HFrEF is associated with a significantly lower risk of subsequent heart failure hospitalization or cardiovascular death (hazard ratio, 0.26 [95% CI, 0.15-0.46]; $P < .001$) or all-cause death (hazard ratio, 0.34 [95% CI, 0.15-0.77]; $P = .009$) compared with patients with NT-proBNP persistently ≥1000 pg/mL[14]

Factors That Increase Natriuretic Peptides
- Advancing age
- Atrial fibrillation or other arrhythmia
- Kidney failure

Factors That Decrease Natriuretic Peptides
- Obesity
- Pericardial constriction

Abbreviations: BNP, B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

congestion on chest x-ray.[16] Even among ambulatory patients with advanced heart failure with significantly elevated pulmonary capillary wedge pressure (mean [SD] 33 [6] mm Hg [normal reference level, <12 mm Hg]), 27% of patients had no radiographic evidence of pulmonary congestion, and interstitial or alveolar edema was present in only 32% of patients.[18] Transthoracic echocardiography is necessary to confirm the diagnosis by identifying the presence of left ventricular systolic dysfunction with LVEF of 40% or less (Box 1, Box 2, Box 3). The natriuretic peptides, B-type natriuretic peptide (BNP) and its precursor N-terminal pro-B-type natriuretic peptide (NT-proBNP), are the most commonly used biomarkers in HF. Guidelines recommend use of the natriuretic peptides to diagnose HF, assess its severity, and aid with prognosis and risk stratification.[2]

Given that approximately half of HFrEF cases are of ischemic etiology,[1] patients with a new diagnosis of HFrEF usually require an evaluation for coronary artery disease, although other patient-specific factors (eg, advanced age, multiple severe comorbidities, noncandidates for revascularization, or choosing not to undergo coronary revascularization procedures) should be considered prior to referral. Coronary angiography is the criterion standard test for identification of obstructive epicardial coronary artery disease, although noninvasive testing with coronary computed tomography angiography may be considered in patients with low pretest probability for coronary atherosclerosis. Stress testing is less useful because of lower sensitivity and specificity. Additional cardiac imaging (eg, cardiac magnetic resonance imaging, positron emission tomography, ^{99m}technetium pyrophosphate scan) may be indicated, depending on the clinical presentation, as identification of certain underlying but less common causes of HFrEF may require initiation of disease-specific therapies such as sarcoidosis, myocarditis, or amyloidosis (Box 1, Box 2, Box 3).

Once a diagnosis of HFrEF is made, counseling and education for patients and their caregivers is of critical importance (**Table 1**).

Drug Treatment

The cornerstone of guideline-directed medical therapy for HFrEF involves inhibition of the renin-angiotensin-aldosterone and sympathetic nervous systems and augmentation of favorable pathways with inhibition of neprilysin, a neutral endopeptidase that degrades several peptides involved in regulating cardiovascular and renal homeostasis and metabolism. Ivabradine, an inhibitor of pacemaker activity within the sinoatrial node that lowers the heart rate and the vasodilator hydralazine/isosorbide dinitrate may also have specific roles in the management of HFrEF.[2] More recently, further reductions in cardiovascular events and mortality in patients with

HFrEF were found in randomized clinical trials of dapagliflozin,[23] a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and vericiguat, an oral soluble guanylate cyclase stimulator,[24] and it is anticipated that these therapies will likely be recommended when heart failure guidelines are next updated in 2021.

Despite their proven efficacy in reducing morbidity and mortality in HFrEF, large gaps exist in the application of guideline-directed medical therapy in clinical practice. Registry data show that more than one-quarter of eligible patients are not prescribed an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), or an angiotensin receptor–neprilysin inhibitor (ARNI); more than one-third are not prescribed a β-blocker; and more than one-half are not prescribed a mineralocorticoid receptor antagonist (MRA).[25] Even when prescribed, doses are often below recommended targets. Despite evidence that doses below target levels are associated with poorer patient outcomes,[26-29] only 1% of eligible patients are simultaneously prescribed target doses of all 3 classes of drugs.[25]

ACE Inhibitors and ARBs

Deleterious upregulation of the renin-angiotensin-aldosterone system is involved in the pathophysiology and progression of HF, resulting in fluid retention, peripheral arterial vasoconstriction, cardiomyocyte hypertrophy, interstitial fibrosis, and adverse cardiac remodeling.[30] Numerous studies have shown that renin-angiotensin-aldosterone system antagonism with either ACE inhibitors or ARBs reduces morbidity and mortality in HFrEF, with reductions in all-cause mortality in the range of 20% to 30% (**Table 2**).[39,45-48] Caution is advised in patients with low blood pressure (systolic blood pressure <80 mm Hg), chronic kidney disease (creatinine >3.0 mg/dL), or hyperkalemia (potassium >5.5 mEq/L), and these therapies should be avoided in patients who are pregnant, plan to become pregnant, or have bilateral renal artery stenosis. As many as 20% of patients treated with ACE inhibitors develop a dry cough due to pulmonary accumulation of bradykinin, which is not dose dependent and is a class effect across all ACE inhibitors. Both ACE inhibitors and ARBs have a less than 1% risk of angioedema and are contraindicated in patients with this complication during previous exposure to the drug.

ARNIs

The PARADIGM-HF (Prospective Comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial found that the ARNI sacubitril/valsartan, when compared with enalapril, reduced cardiovascular mortality (13.3% vs 16.5%; HR, 0.80 [95% CI, 0.71-0.89]) and reduced hospitalization for heart failure (12.8% vs 15.6%; HR, 0.79 [95% CI, 0.71-0.89]) in patients with chronic HFrEF (Table 2).[40] These findings were then extended to patients with acute heart failure in the PIONEER-HF (Comparison of Sacubitril-Valsartan vs Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial, which included hemodynamically stable patients who were admitted to the hospital with a primary diagnosis of acute decompensated HFrEF. Over a follow-up period of 8 weeks, sacubitril/valsartan, when compared with enalapril, resulted in a greater reduction in NT-proBNP (−46.7% vs −25.3%; ratio of change, 0.71 [95% CI, 0.63-0.81]) and in heart failure hospitalization (8.0% vs 13.8%; HR, 0.56 [95% CI, 0.37-0.84]).[49] The TRANSITION (Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event) study evaluated the safety and efficacy of in-hospital initiation of sacubitril/valsartan in patients with acute heart failure compared with postdischarge initiation of the drug and found it to be feasible and well-tolerated, with similar proportions of patients at the goal dose of 97/103 mg twice daily after 10 weeks (45.4% vs 50.7%; relative risk, 0.90 [95% CI, 0.79-1.02]) and requiring permanent ARNI discontinuation due to adverse events (7.3% vs 4.9%; relative risk, 1.49 [95% CI, 0.90-2.46]); new-onset heart failure was a predictor of up-titration success after multivariable analysis.[50] Therefore, while current American College of Cardiology/American Heart Association guidelines do not yet endorse sacubitril/valsartan for acute HF, new-onset HF, or both, the evidence from PIONEER-HF and TRANSITION indicate earlier implementation of ARNI is feasible and may be preferable.

The benefits of sacubitril/valsartan in chronic HFrEF may also extend to patients beyond those studied in the PARADIGM-HF

Table 1. What to Discuss at the Time of Heart Failure With Reduced Ejection Fraction Diagnosis

Educational area	Suggestions for follow-up care
Heart failure and course of the disease	Inform patients that following a new diagnosis of heart failure, there is a substantial opportunity for improvement in symptoms, quality of life, and health outcomes with the appropriate initiation, titration, and adherence to guideline-directed medical therapy at target or maximally tolerated doses
	Guideline-directed medical therapy should be continued even if reverse remodeling occurs, and the left ventricular ejection fraction increases to >50% given that medication withdrawal is associated with relapse of depressed left ventricular ejection fraction and left ventricular dilatation[19]
Exercise	Regular aerobic exercise sufficient to provoke mild or moderate breathlessness to improve functional capacity, symptoms, and reduce heart failure rehospitalization risk[12]
Sodium and water intake	Moderate sodium restriction is reasonable for symptomatic patients to reduce congestive symptoms, as is fluid restriction (1.5-2 L per day) in patients with advanced heart failure, particularly those with hyponatremia[20]
	However, these recommendations are not well-supported by current evidence, particularly for sodium restriction
Medication use	Patient education regarding classes of medications
	Medication adherence should be stressed and asked directly (eg, "how many times a week do you miss taking your medicines"), given that estimates of patients not taking their medication are as high as 50% and are associated with worse outcomes[21,22]
	Access to medication and cost should be discussed, allowing clinicians to recognize which patients require financial assistance such as access to copay assistance and prescription of 90-day refills, which may reduce cost
	Avoid use of nonsteroidal anti-inflammatory drugs
Self-management strategies	Provide patients with individualized information, such as increasing their diuretic dose and/or alerting their clinician in the event of weight gain of >2 kg in 3 days or increasing dyspnea or edema
Vaccinations	Recommend uptake of influenza and pneumococcal vaccines as per local guidance and immunization practices
Smoking and alcohol use	Recommend smoking cessation and avoidance of excessive alcohol consumption

Table 2. Clinical Trials of Medical Therapies for Heart Failure With Reduced Ejection Fraction

	Clinical trial	No. of patients	Follow-up, mo	End point	Event rate, %		HR (95% CI)	*P* value
					Study drug	Control		
β-Blockers								
Bisoprolol	CIBIS II[31]	2647	15.6	All-cause mortality	11.8	17.3	0.66 (0.54-0.81)	<.001
				Sudden cardiac death	3.6	6.3	0.56 (0.39-0.80)	.001
Metoprolol succinate	MERIT-HF[32]	3991	12	All-cause mortality	7.2	11.0	0.66 (0.53-0.81)	<.001
				Deaths from HF	30	58	0.51 (0.33-0.79)	.002
Carvedilol	US Carvedilol[33]	1094	6.5	All-cause mortality	3.2	7.8	0.35 (0.20-0.61)	<.001
				CV hospitalization	14.1	19.6	0.73 (0.55-0.97)	.04
ACE inhibitors								
Captopril	SAVE[34]	2231	42	All-cause mortality	20.4	24.6	0.81 (0.68-0.97)	.02
				CV mortality	16.8	20.9	0.79 (0.65-0.95)	.01
Ramipril	AIRE[35]	2006	15	All-cause mortality	16.7	22.4	0.73 (0.60-0.89)	.002
Enalapril	SOLVD[36]	2569	41.4	All-cause mortality	35.2	39.7	0.84 (0.74-0.95)	.003
				Deaths from HF	16.3	19.5	0.78 (0.65-0.94)	
Angiotensin receptor blockers								
Candesartan	CHARM-Added[37]	2548	41	All-cause mortality	29.6	32.4	0.89 (0.77-1.02)	.09
				CV death, HF hospitalization	38	42	0.85 (0.75-0.96)	.01
Losartan	OPTIMAAL[38]	5477	32.4	All-cause mortality	18	16 (captopril)	1.13 (0.99-1.28)	.07
Valsartan	Val-HeFT[39]	5010	23	All-cause mortality	19.7	19.4	1.02 (0.88-1.18)	.80
				All-cause mortality, HF hospitalization, cardiac arrest	28.8	32.1	0.87 (0.77-0.97)	.009
Angiotensin receptor–neprilysin inhibitors								
Sacubitril/valsartan	PARADIGM-HF[40]	8442	27	All-cause mortality	17.0	19.8	0.84 (0.76-0.93)	<.001
				CV death, HF hospitalization	21.8	26.5	0.80 (0.73-0.87)	<.001
				HF hospitalization	12.8	15.6	0.81 (0.71-0.89)	<.001
	PIONEER-HF[41]	881	2	HF hospitalization	8.0	13.8	0.56 (0.37-0.84)	
Mineralocorticoid receptor antagonists								
Eplerenone	EPHESUS[42]	6642	16	All-cause mortality	14.4	16.7	0.85 (0.75-0.96)	.008
				CV death, CV hospitalization	26.6	30.0	0.87 (0.79-0.95)	.002
	EMPHASIS-HF[41]	2737	21	All-cause mortality	12.5	15.5	0.76 (0.61-0.94)	.01
				CV death, HF hospitalization	18.3	25.9	0.63 (0.54-0.74)	<.001
Spironolactone	RALES[42]	1663	24	All-cause mortality	35	46	0.70 (0.60-0.82)	<.001
				HF hospitalization	26.1	35.7	0.65 (0.54-0.77)	<.001
Vasodilators								
Hydralazine/ isosorbide dinitrate	A-HeFT[43]	1050	10	All-cause mortality	6.2	10.2		.02
				HF hospitalization	16.4	24.4		.001
Ivabradine	SHIFT[44]	6558	22.9	All-cause mortality	16	17		.092
				Death from HF	3	5	0.74 (0.58-0.94)	.01
				HF hospitalization	16	21	0.74 (0.66-0.83)	<.001
Sodium-glucose cotransporter 2 inhibitor								
Dapagliflozin	DAPA-HF[23]	4744	18.2	CV death, worsening HF event	16.3	21.2	0.74 (0.65-0.85)	<.001
				Worsening HF event	10.0	13.7	0.70 (0.59-0.83)	
				All-cause mortality	11.6	13.9	0.83 (0.71-0.97)	
Oral soluble guanylate cyclase stimulator								
Vericiguat	VICTORIA[24]	5050	10.8	CV death, HF hospitalization	35.5	38.5	0.90 (0.82-0.98)	.02
				CV death	16.4	17.5	0.93 (0.81-1.06)	
				HF hospitalization	27.4	29.6	0.90 (0.81-1.0)	

Abbreviations: ACE, angiotensin-converting enzyme; CV, cardiovascular; HF, heart failure.

trial. The PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure) study found that the magnitude of improvement in measures of cardiac structure and function was consistent across subgroups that were not represented in the PARADIGM-HF trial (namely those with NT-proBNP concentration lower than entry criteria for PARADIGM-HF, those not achieving target sacubitril/valsartan dose, and those with new-onset heart failure or ACE inhibitor and ARB naive), as with that of the group as a whole, suggesting that these subgroups may also derive similar morbidity and mortality benefit from sacubitril/valsartan.[51] Sacubitril/valsartan may also benefit some patients with heart failure and LVEF above 40%. In a subgroup analysis of the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction) trial, in which LVEF of 45% or above was an entry criterion, sacubitril/valsartan reduced the primary outcome of cardiovascular death and total hospitalizations for heart failure in patients with LVEF below the median (≤57%; HR, 0.78 [95% CI, 0.64-0.95]) but not with LVEF above 57%.[52] A pooled individual patient-level analysis of 13 195 patients enrolled in PARADIGM-HF and PARAGON-HF found that the benefit of sacubitril/valsartan varied across the spectrum of LVEF but likely also extended to patients with LVEF lower than normal, including those with heart failure with mid-range EF, and extended to a higher level of LVEF in women compared with men.[53]

From a safety standpoint, patients are at increased risk of symptomatic hypotension and angioedema. In PARADIGM-HF, 2.7% of patients had symptomatic hypotension with systolic blood pressure below 90 mm Hg, and 0.4% of patients developed angioedema. Therefore, patients with low blood pressure are less likely to tolerate ARNIs. Contraindications to ARBs (see ACE Inhibitors and ARBs section) also apply to sacubitril/valsartan.

β-Blockers

An evidence-based β-blocker (metoprolol succinate, carvedilol, or bisoprolol) should be prescribed in all patients with HFrEF unless contraindicated or not tolerated (eg, patients with symptomatic bradycardia despite lowest dose, patients with advanced heart failure and low cardiac output confirmed by right heart catheterization or on home inotropes, or patients with high-grade atrioventricular block), as these agents reduce all-cause and cardiovascular mortality, sudden cardiac death, and heart failure hospitalizations in patients with HFrEF (Table 2).[31-33,54] In a large meta-analysis of 10 randomized clinical trials including 18 254 patients, β-blockers reduced all-cause mortality in patients with HFrEF who were in normal sinus rhythm (HR, 0.73 [95% CI, 0.67-0.80]) but not in patients with HFrEF and atrial fibrillation (HR, 0.97 [95% CI, 0.83-1.14]),[55] although guidelines recommend use of β-blockers irrespective of heart rhyhm.[12] Furthermore, other randomized clinical trials have found that β-blockers reduce all-cause mortality by 30% and cardiovascular mortality by 34% among patients with atrial fibrillation and HFrEF.[56] Following initiation, patients should be observed for fluid retention and worsening HF, bradycardia or heart block, and hypotension. A history of reactive airways disease is not a contraindication to attempting β-blocker therapy. Cardioselective β-blockers (eg, metoprolol succinate, bisoprolol) are preferred in this setting, and while population-based studies have shown no association between cardioselective β-blocker use and moderate to severe asthma exacerbations, some patients may not tolerate β-blockers due to worsening bronchospasm.[57] In contrast, the use of noncardioselective β-blockers has been associated with an increase in moderate to severe asthma exacerbations and should be avoided in patients with significant asthma at baseline.[57]

MRAs

The MRAs spironolactone and eplerenone contribute to renin-angiotensin-aldosterone system blockade and reduced mortality by 15% to 30% and reduced heart failure hospitalizations by 15% to 40% in 3 randomized clinical trials enrolling patients with chronic HFrEF, including patients who have had a myocardial infarction (Table 2).[42,58,59] An MRA should be added to therapy along with an ACE inhibitor/ARB/ARNI and β-blocker in patients with LVEF of 35% or less and NYHA class II to IV symptoms (which tends to be most patients), except in patients with a baseline serum creatinine level above 2.5 mg/dL (or estimated glomerular filtration rate <30mL/min/1.73m^2) or serum potassium level above 5.0 mEq/L.

Ivabradine

Ivabradine inhibits pacemaker activity in the sinoatrial node by selectively blocking the funny channel (I_f) current, resulting in a slower heart rate in sinus rhythm without affecting blood pressure, myocardial contractility, or intracardiac conduction.[60] In SHIFT (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial), ivabradine reduced heart failure hospitalization (HR, 0.74 [95% CI, 0.66-0.83]; $P < .001$) and heart failure mortality (HR, 0.74 [95% CI, 0.58-0.94]; $P = .01$) but not cardiovascular or all-cause mortality compared with placebo.[44] Patients treated with ivabradine had an average reduction in heart rate of 8 bpm, whereas in a meta-analysis of β-blockers in patients with HFrEF, heart rate was reduced by 12 bpm.[61] Given the mortality benefits of β-blocker use in patients with HFrEF that were not found with ivabradine, patients should be on maximally tolerated doses of β-blockers with a heart rate of at least 70 bpm prior to considering use of ivabradine, and they must be in sinus rhythm to respond to the drug, which solely affects the sinoatrial node. Ivabradine may cause transient blurring of vision and is contraindicated if there is bradycardia, advanced heart block, or severe liver dysfunction.[44]

Hydralazine/Isosorbide Dinitrate

The combination of hydralazine and isosorbide dinitrate results in vasodilation through enhancement of nitric oxide signaling and improves prognosis in Black patients with HFrEF. A-HeFT (the African-American Heart Failure Trial) found that hydralazine/isosorbide dinitrate reduced all-cause mortality by 6.2% vs 10.2% in control participants (HR, 0.57) and it reduced heart failure hospitalization by 16.4% vs 24.4% in control participants (HR, 0.67) among 1050 Black patients with HFrEF with NYHA class III-IV symptoms (Table 2).[43] Hydralazine/isosorbide dinitrate should be considered for use in Black patients with persistent symptomatic HFrEF with LVEF at or below 35%, despite therapy with ACE inhibitors/ARB/ARNI, β-blockers, and MRAs in whom systemic blood pressure may tolerate initiation of these drug therapies.

Table 3. Starting and Target Doses of Guideline-Directed Medical Therapy for Heart Failure With Reduced Ejection Fraction

	Starting dose[a]	Target dose[a]
β-Blockers		
Bisoprolol	1.25 mg	10 mg
Metoprolol succinate	12.5-25 mg	200 mg
Carvedilol	3.125 mg 2 times/d	25 mg 2 times/d (weight <85 kg) or 50 mg 2 times/d (weight >85 kg
Angiotensin-converting enzyme inhibitors		
Captopril	6.25 mg 3 times/d	50 mg 3 times/d
Ramipril	1.25 mg	10 mg
Enalapril	2.5 mg 2 times/d	10-20 mg
Lisinopril	2.5-5 mg	20-40 mg
Angiotensin receptor blocker		
Candesartan	4-8 mg	32 mg
Losartan	25-50 mg	150 mg
Valsartan	40 mg 2 times/d	160 mg 2 times/d
Angiotensin receptor–neprilysin inhibitor		
Sacubitril/valsartan	24/26 mg-49/51 mg 2 times/d	97/103 mg 2 times/d
Mineralocorticoid receptor antagonists		
Eplerenone	25 mg 2 times/d	50 mg 2 times/d
Spironolactone	12.5-25 mg	25-50 mg
Vasodilators		
Hydralazine	25 mg 3 times/d	75 mg 3 times/d
Isosorbide dinitrate	20 mg 3 times/d	40 mg 3 times/d
Fixed-dose hydralazine/isosorbide dinitrate	20/37.5 mg (1 tablet) 3 times/d	Two tablets 3 times/d
Ivabradine	2.5-5 mg 2 times/d	Titrate to heart rate 50-60/min
		Max dose 7.5 mg 2 times/d

[a] All doses indicate daily administration.

Diuretics

Most patients with chronic HFrEF require a diuretic to control fluid retention. Loop diuretics (furosemide, bumetanide, torsemide) are the preferred diuretic agents although thiazide-like agents (most commonly metolazone or intravenous chlorothiazide in hospitalized patients) might be added in patients with diuretic resistance. The main adverse effects of diuretics are volume or electrolyte depletion; excessive diuresis can predispose to hypotension and acute kidney injury. Some patients may benefit from a diuretic dosing regimen in which they record their body weight daily, and dosing is adjusted if weight increases or decreases beyond a specific range.

Initiation and Titration of Guideline-Directed Medical Therapy

The appropriate initial and target doses of guideline-directed medical therapies are presented in **Table 3**, and strategies for titration are shown in the **Figure** and **Table 4**. The goal is to achieve target or maximally tolerated doses, preferably after 3 to 6 months of treatment. However, this may not be logistically feasible for some patients, particularly those who are elderly and those with frailty, kidney dysfunction, or baseline low blood pressure. In such cases, the key is to ensure close follow-up and meticulous attention to gradual titration over more prolonged periods of time. The use of lower doses of guideline-directed medical therapies has been associated with poorer patient outcomes, and it is unclear what below-target doses are acceptable; even in patients whose treatment is challenging, titration to highest possible doses is crucial.[26-29]

All patients with HFrEF should be treated with ACE inhibitors/ARB/ARNI and an evidence-based β-blocker as foundational therapy, unless contraindications or intolerances exist (**Box 4**). For those already taking an ACE inhibitor or an ARB, transition to an ARNI is recommended given superior efficacy,[40,41] although a washout period of 36 hours is necessary when transitioning from ACE inhibitor to ARNI to avoid angioedema. Sufficient data now exist showing that patients naive to ACE inhibitors or ARBs may be initiated directly on sacubitril/valsartan given that this strategy appears safe, is associated with substantial reverse cardiac remodeling,[30] and reduces the risk for early rehospitalization in patients with recent acute HF.[41] Adjustment of ACE inhibitor/ARB/ARNIs may be performed every 1 to 2 weeks in stable patients or more gradually in those with lower blood pressure. When initiating sacubitril/valsartan, it may be advisable to reduce doses of loop diuretics in noncongested patients to reduce the risk for hypotension.

Adjustment of β-blocker should be performed once every 1-2 weeks, given that titration may transiently increase congestion and reduce cardiac output. Titration may be performed more rapidly in non-congested patients with normal blood pressure than in those with frailty or borderline hypotension.

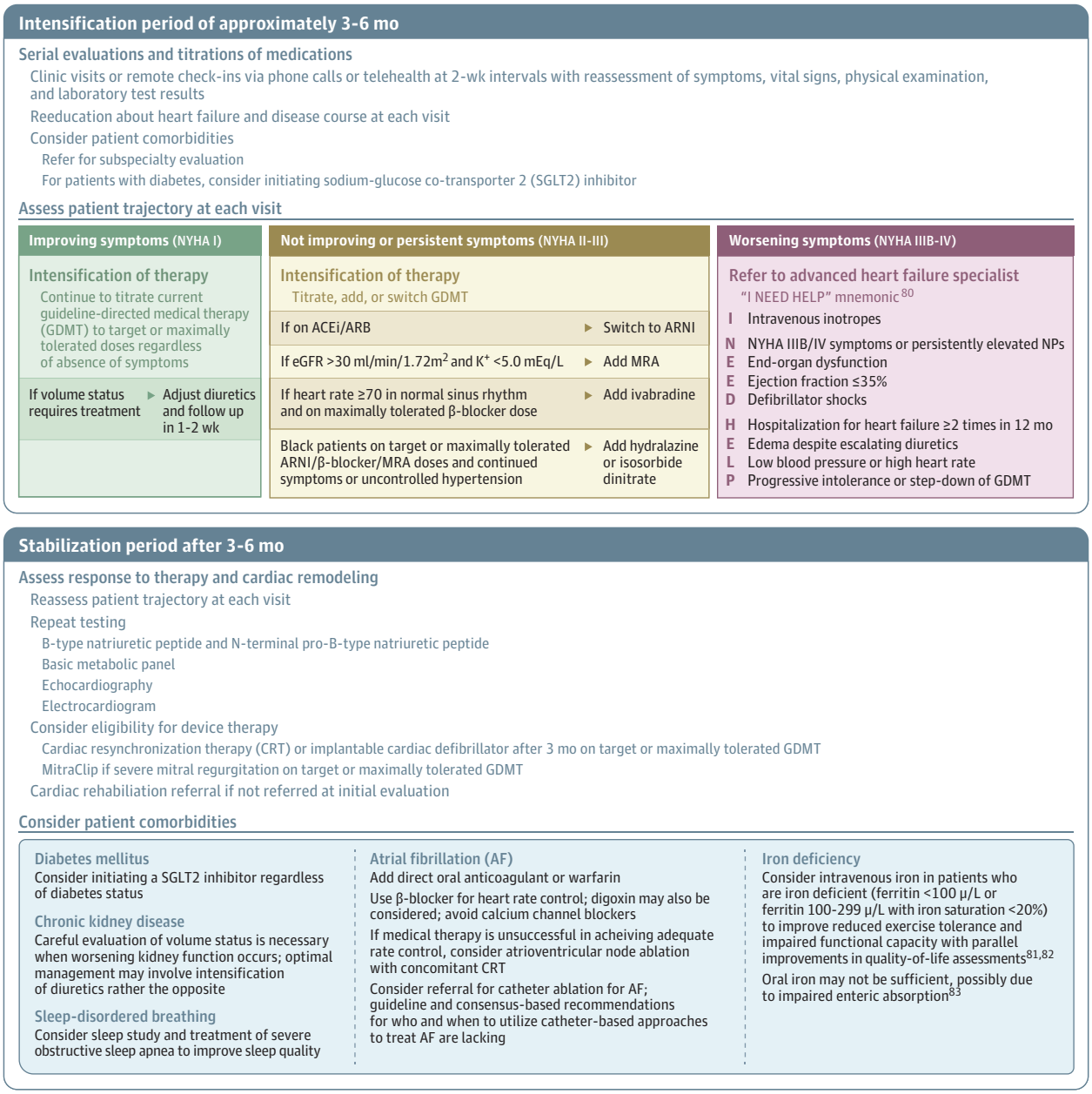
Following establishment of ACE inhibitors/ARB/ARNI and β-blocker therapy, an MRA should be added in patients with persistent NYHA class II to IV symptoms, in the absence of clear contraindications (baseline serum creatinine >2.5 mg/dL, estimated glomerular filtration rate <30 mL/min/1.73 m^2, or serum potassium >5.0 mEq/L). Hypotension is unusual following initiation and titration of MRA, even when baseline blood pressure is low, and the benefits of MRA are consistent irrespective of baseline blood pressure.[65] Kidney function and potassium monitoring are mandatory 1 week after initiation or increase in dose, monthly for the first 3 months, then quarterly for a year, and then every 6 months.

Other therapies can be considered in specific patient groups: ivabradine is indicated for patients in sinus rhythm with a heart rate of 70/min or greater, despite maximally tolerated β-blocker. Isosorbide dinitrate and hydralazine may either be initiated as individual medications or in fixed-dose combination for Black patients with persistent NYHA class III to IV symptoms, despite target or maximally tolerated doses of other guideline-directed medical therapy.

Barriers to Titration

Despite well-articulated goals for guideline-directed medical therapy, patients with HFrEF in usual care settings are often undertreated. Multiple contributing factors may undermine this ability to achieve optimal medical care, and occur at a physician-, patient- and system-level.[66]

Figure. Suggested Management of HFrEF: Intensification and Stabilization Periods



Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HR, heart rate; ICD, implantable cardiac defibrillator; IV, intravenous; K+, potassium; MRA, mineralocorticoid receptor antagonist; MR, mitral regurgitations; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.[21,62-64]

Patients' cases seen in clinical practice are often more challenging to initiate and titrate guideline-directed medical therapy than those in clinical trials, with different age and comorbidity profiles that may delay or prevent titration. Prohibitive cost and challenges with insurance coverage for newer medications are surmountable obstacles. Therapeutic inertia on behalf of the patient or clinician, where there may be a reluctance to titrate or add therapies in patients who appear to be doing well on current treatment is also an issue. Clinicians must recognize that even when perceived stable, patients with HFrEF have a high risk for complications from their diagnosis and benefit from achieving guideline-directed medical therapy. The fallacy of the "stable patient with HFrEF" should be avoided in order to achieve optimal titration.

Lack of health care access may be an impediment to titration. In regions of limited resources or for patients who have trouble traveling to outpatient appointments, titration and follow-up

Table 4. Suggested Approach for Adding or Switching Guideline-Directed Medical Therapies

	ACE inhibitor/ARB	ARNI	β-blocker	MRA	Hydralazine/isosorbide dinitrate	Ivabradine	SGLT2 inhibitors
Patient selection	All patients If tolerated, plan to switch to ARNI	All patients Can be started in ACE inhibitor and ARB-naive patients	All patients	Patients with persistent symptoms on target or maximally tolerated doses of ACE inhibitors/ARBs/ARNI plus β-blocker	Black patients with persistent symptoms on target or maximally tolerated doses of ACE inhibitors/ARBs/ARNI plus β-blocker	Patients with heart rate 2:70 and in sinus rhythm Re-assess that β-blocker is prescribed at target or maximally tolerated dose	Patients with type 2 diabetes and HbA_{1c} ≥7%
Starting dose	See Table 3	If taking ACE inhibitors, ensure 36-h washout period prior to starting ARNI If taking equivalent of ≤10 mg twice daily enalapril or ≤160 mg daily valsartan, start 49/51 mg 2 times/d	See Table 3	See Table 3	See Table 3	Age ≥75 years, start 2.5 mg twice daily Age <75 years, 5 mg 2 times/d	Dapagliflozin 10 mg daily Empagliflazin 10 mg daily Canagliflozin 100 mg daily Ertugliflozin 5 mg daily eGFR must be ≥45-60 mL/min/1.73m^2 Consider diuretic dose reduction
Titration schedule	Increase dose every 2 weeks until target or maximally-tolerated dose is achieved For stable patients, titration interval can be 3-5 days	Increase dose every 2-4 weeks until target or maximally- tolerated dose is achieved For stable patients, titration interval can be weekly	Increase dose every 2 weeks until target or maximally tolerated dose is achieved	Increase dose every 3-5 days until target or maximally tolerated dose is achieved	Increase dose every 1-2 weeks until target or maximally tolerated dose is achieved	Reassess heart rate in at least 2-4 weeks: Heart rate <50 bpm, reduce dose by 2.5 mg twice daily or discontinue Heart rate 50-60 bpm, maintain current dose Heart rate >60 bpm, increase dose by 2.5 mg 2 times/d to a maximum of 7.5 mg 2 times/d	Titration not generally performed
What to monitor	Blood pressure, kidney function, potassium	Blood pressure, kidney function, electrolytes	Heart rate, blood pressure, and monitor for signs of congestion	Kidney function, potassium: 2-3 Days after initiation 7 Days after initiation/ titration Monthly for 3 months Every 3 months thereafter	Blood pressure	Heart rate	Kidney function, blood pressure, ensure diabetes specialist follow-up

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; bpm, beats per minute; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose cotransporter 2.

communication can be remote via telehealth, by home-based nurse visits, or through telephone conversation. Blood tests can be checked at home or at a location convenient for the patient.

New Drug Therapies for HFrEF Awaiting Guideline Recommendations

SGLT2 Inhibitors

The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial evaluated the effect of dapagliflozin in patients with HFrEF with and without type 2 diabetes and found that dapagliflozin reduced the primary end point of worsening heart failure or cardiovascular death (HR, 0.74 [95% CI, 0.65-0.85]; $P < .001$), cardiovascular mortality (HR, 0.82 [95% CI, 0.69-0.98]), and all-cause mortality (HR, 0.83 [95% CI, 0.71-0.97]) compared with placebo.[23] Subsequent analyses have shown the benefits of dapagliflozin were not significantly different between patients with and without diabetes.[67] The US Food and Drug Administration recently approved the use of dapagliflozin for treatment of HFrEF, irrespective of diabetes status, and it is anticipated that dapagliflozin will be added to guideline-directed medical therapy for all patients with HFrEF in the 2021 American College of Cardiology/American Heart Association heart failure guideline. Several other ongoing trials are investigating the role of SGLT2 inhibitors in patients with HFrEF, with and without type 2 diabetes, as well as patients with heart failure with preserved EF.

How SGLT2 inhibitors improve prognosis in HFrEF remains unknown, although some proposed mechanisms include beneficial effects on myocardial metabolism, fibrosis, inflammation, vascular function, and ion transport.[68-70] While SGLT2 inhibition results in natriuresis, osmotic diuresis, weight loss, and blood pressure reduction, these effects in isolation should not account for the improvement in prognosis, as other trials of weight loss and blood pressure reduction have not shown similar benefit and patients who received dapagliflozin in DAPA-HF had a weight loss of only 1 kg compared with controls.[23]

Vericiguat

Vericiguat is an oral soluble guanylate cyclase stimulator that increases activity of the second messenger cyclic guanosine monophosphate (cGMP), which is involved in regulation of protective cardiovascular, kidney, and metabolic actions. The recent VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial enrolled patients with higher-risk HFrEF than those included in other contemporary clinical trials, and found that vericiguat reduced the composite primary outcome of cardiovascular death or first heart failure hospitalization (35.5% vs 38.5%; HR, 0.90 [95% CI, 0.82-0.98]) over median follow-up of 10.8 months, although this was driven by the reduction in heart failure hospitalization with a statistically nonsignificant reduction in cardiovascular death (16.4% vs 17.5%; HR, 0.93 [95% CI, 0.81-1.06]).[24] However, the high annualized event rate that reflected the risk profile of the study population meant that median follow-up was only 10.8 months, compared with 27 months in PARADIGM-HF and 18 months in DAPA-HF, and whether longer-duration exposure to vericiguat would have resulted in a significant reduction in cardiovascular death is unknown.[71] Given its vasodilating properties, vericiguat resulted in symptomatic hypotension in 9.1% of patients and syncope in 4.0%, although these were not significantly higher than placebo.[24]

Box 4. Common Questions Asked by Physicians

"Should all guideline-directed medical therapies be started together or staggered?"
In a patient with new-onset HFrEF, initiation of either a β-blocker or ACEi/ARB first is safe. β-blocker should not be newly initiated in those with congestion until congestion is relieved. Stable patients who do not have significant congestion, borderline low blood pressure, or frailty can be started on both β-blocker and ACEi/ARB simultaneously. It is not necessary to achieve target or maximally tolerated doses of β-blockers and ACEi/ARB before adding MRA

"What should I up-titrate first?"
This depends on the degree of congestion, the heart rate, and kidney function. Titration of β-blockers is less preferred than titration of ACEi/ARB when the patient is still congested; significant caution should be taken when titrating β-blockers in patients who are more tachycardic, as this may be compensatory to maintain cardiac output

"How quickly can I up-titrate β-blockers and ARNI?"
β-Blockers should be titrated no more frequently than once every 1-2 weeks in stable patients. ARNI can be titrated weekly in those with higher blood pressures, and every 2-4 weeks in those with lower blood pressures

"At what level of kidney dysfunction should I stop ACEi/ARB/ARNI?"
A decrease in eGFR of >30% or the development of hyperkalemia should prompt consideration of a dose reduction in ACEi/ARB/ARNI

"When to refer for LVAD or transplantation?"
Early identification and timely referral of select patients to a heart failure specialist is critical so that those with advanced disease can be considered for heart transplantation or LVAD placement. This window of opportunity is missed if referral is delayed until multiorgan failure develops, as such patients may no longer candidates for these therapies. A useful acronym 'I-NEED-HELP' was developed to assist clinicians recognize such appropriate patients (Table 4)[21]

"When should I repeat a TTE?"
A TTE should be repeated after 3-6 months of guideline-directed medical therapy optimization so that patients with progressive left ventricular dysfunction and worsening LVEF can be identified early and considered for referral to an advanced heart failure specialist, those with persistent severe MR can be referred for consideration of MitraClip, and to allow re-assessment of the LVEF in patients who otherwise meet criteria for consideration of CRT or ICD implantation. A TTE should also be repeated if there are significant changes in clinical status

Abbreviations: ARB, angiotensin receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

Device Treatment

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) involves implantation of pacing leads to the right and left ventricles via the coronary sinus, which are timed to pace at an interval maximizing synchrony. The

Table 5. Clinical Trials of Device Therapies for Heart Failure With Reduced Ejection Fraction

Clinicial trial	No. of patients	Follow-up	End point	Event rates, %		RR (95% CI)	*P* value
				Device	Control		
Cardiac resynchronization therapy							
CARE-HF[72]	813	29 mo	All-cause mortality	20	30	0.64 (0.48-0.85)	<.002
			HF hospitalization	18	33	0.48 (0.36-0.64)	<.001
MADIT-CRT[73]	1820	29 mo	All-cause mortality or HF hospitalization	17.2	25.3	0.66 (0.52-0.84)	.001
Implantable cardiac-defibrillator							
MADIT-I[74]	1232	20 mo	All-cause mortality	14.2	19.8	0.69 (0.51-0.93)	.02
SCD-HeFT[75]	2521	45 mo	All-cause mortality	21.9	28.8	0.77 (0.62-0.96)	.007
DEFINITE[76]	458	29 mo	Sudden cardiac death	1.3	6.1	0.20 (0.15-0.90)	.02
			All-cause mortality	7.9	14.1	0.65 (0.40-1.06)	.08
MitraClip							
COAPT[77]	614	24 mo	HF hospitalization	35.8[a]	67.9[a]	0.53 (0.40-0.70)	<.001
			All-cause mortality	29.1	46.1	0.62 (0.46-0.82)	<.001
MITRA-FR[78]	304	12 mo	HF hospitalization	48.7	47.4	1.13 (0.81-1.56)	
			All-cause mortality	24.3	22.4	1.11 (0.69-1.77)	
CardioMEMS device							
CHAMPION[79]	456	18 mo	HF hospitalization	0.49 events[a]	0.69 events[a]	0.72 (0.59-0.88)	.001
			All-cause mortality	17.6	24.4	0.68 (0.45-1.02)	.06

[a] Indicates per patient year.

largest benefit from CRT is in patients with a wide QRS complex (>150 milliseconds) with left bundle-branch block (LBBB) morphology and normal sinus rhythm, although CRT may also be considered in certain patients with QRS duration of 120 to 149 milliseconds or non-LBBB morphology, depending on additional criteria such as NYHA functional class, LVEF, and etiology of HF.[20] Clinical trials have established the morbidity and mortality benefit of CRT in certain patients with HFrEF, including CARE-HF (Cardiac Resynchronization in Heart Failure Trial), which found that CRT reduced all-cause mortality (20% vs 30%; HR, 0.63 [95% CI, 0.51-0.77]) compared with optimal medical therapy over a mean follow-up of 29.4 months (**Table 5**).[72] Subgroup analysis from the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial, found that CRT reduced all-cause mortality or heart failure hospitalization only in patients with QRS duration of 150 milliseconds or greater (HR, 0.48 [95% CI, 0.37-0.64]; HR for QRS duration <150 milliseconds, 1.06 [95% CI, 0.74-1.52]; *P* = .001 for interaction) and LBBB morphology (HR, 0.47 [95% CI, 0.37-0.61]; *P* < .001; HR for non-LBBB morphology, 1.24 [95% CI, 0.85-1.81]; *P* .26).[73,80] CRT is of no benefit when QRS complex is narrow, even when there is left ventricular dyssynchrony.[81]

Implantable Cardiac Defibrillator

Sudden cardiac death is a leading cause of death in patients with HFrEF, who may be eligible for an implantable cardiac defibrillator (ICD) to reduce this risk. One of the important trials establishing the survival benefit of ICD implantation in patients with ischemic cardiomyopathy was MADIT II (Multicenter Automatic Defibrillator Implantation Trial II), which found that ICD reduced all-cause mortality compared with optimal medical therapy (HR, 0.69 [95% CI, 0.51-0.93]; *P* = .02) (Table 5).[74] The utility of ICD implantation in patients with nonischemic cardiomyopathy was then evaluated in the DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) trial, which found that ICD therapy reduced sudden cardiac death (HR, 0.20 [95% CI, 0.15-0.90]; *P* = .02) but not the primary end point of all-cause mortality (HR, 0.65 [95% CI, 0.40-1.06]; *P* = .08) compared with optimal medical therapy.[76] In contrast, in SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), ICD therapy reduced all-cause mortality (HR, 0.77 [95% CI, 0.62-0.96]; *P* = .007) with similar reductions among patients with ischemic heart failure (21% reduction) and nonischemic heart failure (27% reduction).[75] Although recent data suggest patients with nonischemic HFrEF might accrue less obvious benefit from ICD placement, guideline recommendations still support ICD use in this population.[82]

Transcatheter Mitral Valve Repair

Transcatheter mitral valve repair (tMVR) may be considered for patients with HFrEF and severe secondary mitral regurgitation (MR). In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, among 614 patients with HFrEF and severe mitral regurgitation, there was a significant reduction in the primary end point of heart failure hospitalization (35.8% vs 67.9%; HR, 0.53 [95% CI, 0.40-0.70]) and the secondary end point of all-cause mortality (29.1% vs 46.1%; HR, 0.62 [95% CI, 0.46-0.82]) in patients treated with tMVR compared with placebo (Table 5).[77] Conversely, the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial found that tMVR did not reduce mortality or heart failure hospitalization at 1 year.[78] The discrepant results between these 2 trials may potentially be explained by patients in the COAPT trial having mitral regurgitation severity out of proportion to the degree of left ventricular remodeling compared with the MITRA-FR trial, in which patients had larger left ventricular volumes

and less severe mitral regurgitation. Additionally, the use of maximally tolerated guideline-directed medical therapy prior to enrollment was required only by the COAPT trial, although the impact of this is unclear. Reconciling the contrasting results from these 2 studies is a subject of significant interest with a number of proposed theories,[83,84] and further investigation is necessary to improve understanding of which patients benefit from tMVR for severe secondary mitral regurgitation.

Wireless Pulmonary Artery Pressure Monitors

Following hospitalization for acute HF, patients with persistent NYHA class III symptoms may be considered for implantation of a wireless pulmonary artery pressure monitor. In the CHAMPION (CardioMEMS Heart Sensor Allowing Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial, the device reduced heart failure hospitalizations (0.49 vs 0.69 events per patient-year; HR, 0.72 [95% CI, 0.59-0.88]), and there was a statistically nonsignificant reduction in mortality (HR, 0.68 [95% CI, 0.45-1.02]; $P = .06$) over a mean follow-up period of 18 months (Table 5).[79]

Management of Comorbidities

In one study, 40% of heart failure patients had at least 5 noncardiovascular comorbidities. The presence and number of comorbidities often complicates management and may lead to worse prognosis (Figure).[85]

Diabetes

Useful recent consensus documents[86,87] and clinical practice guidelines[88] exist regarding optimizing the care of patients with heart failure and type 2 diabetes. First-line treatment of type 2 diabetes in heart failure should include metformin and SGLT2 inhibitors; whereas the use of saxagliptin[89] or thiazolidinediones should be avoided as they increase the risk of heart failure hospitalization.[88] Glucagon-like peptide-1 receptor agonists may also be considered in patients with type 2 diabetes and HF,[88] although caution is recommended in patients with recently decompensated HFrEF given a statistically nonsignificant increase in heart failure hospitalization (41% vs 34%; HR, 1.30 [95% CI, 0.89-1.88]) in the FIGHT (Functional Impact of GLP-1 for Heart Failure Treatment) trial.[90]

Atrial Fibrillation

Atrial fibrillation is an adverse prognostic marker in HF.[91] Patients with HFrEF who develop atrial fibrillation should be initiated on oral anticoagulation due to high risk for cardioembolic stroke. Recommendations for heart rate control are outlined in the Figure; importantly, calcium channel blockers should be avoided as they are contraindicated in HFrEF.

Rhythm control using antiarrhythmic- or catheter-based approaches may be considered, although no antiarrhythmic drug has shown a mortality benefit in patients with atrial fibrillation and HFrEF. An antiarrhythmic strategy with catheter ablation of paroxysmal or persistent atrial fibrillation in HFrEF was evaluated in the CASTLE-AF (Catheter Ablation vs Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial, which randomized patients to catheter ablation or medical therapy (either rate or rhythm control) and found that catheter ablation significantly reduced all-cause mortality (HR, 0.53 [95% CI, 0.32-0.86]), heart failure hospitalization (HR, 0.56 [95% CI, 0.37-0.83]), and cardiovascular death (HR, 0.49 [95% CI, 0.29-0.84]).[92] Subgroup analysis revealed a significant interaction between atrial fibrillation duration and LVEF and the primary end point of death or heart failure hospitalization, which found that patients with LVEF≥25% were more likely to benefit from ablation than those with LVEF of 25% or less (HR, 0.48 [95% CI, 0.31-0.74] vs HR, 1.36 [95% CI, 0.69-2.65]), and patients with persistent atrial fibrillation were more likely to benefit than those with paroxysmal atrial fibrillation (HR, 0.64; [95% CI, 0.41-0.99] vs HR, 0.60 [95% CI, 0.34-1.08]). The optimal use of atrial fibrillation ablation in HFrEF remains unclear; guideline and consensus-based recommendations for who and when to utilize catheter-based approaches to treat atrial fibrillation remain lacking.

Kidney Dysfunction

The term *cardio-renal syndrome* refers to the nuanced and highly interdependent relationship between the heart and kidneys, whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other. Chronic kidney disease is highly prevalent in HFrEF and is associated with significant morbidity and mortality; among 22 981 patients in the Swedish Heart Failure Registry, chronic kidney disease was present in 45% and was associated with increased 1-year mortality (HR, 1.49 [95% CI, 1.42-1.56]).[93]

The pathophysiology of cardio-renal syndrome is complex, and may be caused by a number of factors, including direct effects of renin-angiotensin-aldosterone system inhibitors or diuretics and progressive medical-renal disease, or more ominously, it may signify progression of cardiac dysfunction. Notably, though inadequate cardiac output from worsening left ventricular function can unmistakably cause worsening kidney function through underperfusion and further activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, a more common cause of cardio-renal syndrome is fluid retention and renal venous hypertension.[94] Thus, careful evaluation of volume status is necessary when worsening kidney function occurs, as optimal management of the situation might involve intensification of diuretics rather than the opposite, a common error in the care of such patients. The approach to diuretic therapy and management of diuretic resistance in heart failure has recently been reviewed in detail.[95] Diuretics recommended for use in patients with HFrEF and chronic kidney disease are the same as for the heart failure population in general, although the dose-response curve is blunted in those with chronic kidney disease due to impaired secretion of diuretics into the tubular lumen. This may be overcome by the use of higher-loop diuretic doses, although peak absolute sodium excretion remains diminished.[95,96] The half-life of furosemide is prolonged in patients with chronic kidney disease, which increases its potential to cause deafness or tinnitus, particularly when very large bolus doses are administered that result in high serum concentrations.[97,98] The half-lives of torsemide and bumetanide are preserved in chronic kidney disease due to differences in drug metabolism.[97]

Coronary Artery Disease

While there is randomized clinical trial evidence that coronary artery bypass grafting, in addition to medical therapy, improves

all-cause mortality and cardiovascular hospitalization in patients with HFrEF in the absence of acute coronary syndrome, there is insufficient data to recommend for or against percutaneous coronary intervention in this setting, although a randomized clinical trial is ongoing.[99] The STICH (Surgical Treatment for Ischemic Heart Failure) trial randomized 1212 patients with ischemic cardiomyopathy and LVEF of less than or equal to 35% to coronary artery bypass grafting or optimal medical therapy and found that surgical revascularization did not reduce the primary end point of all-cause death (36% vs 41%; HR, 0.86 [95% CI, 0.72-1.04]; P = .12) at a median 56 months follow-up,[100] although 10-year data subsequently demonstrated a reduction in all-cause mortality (58.9% vs 66.1%; HR, 0.84 [95% CI, 0.73-0.97]; P = .02) and cardiovascular mortality (40.5% vs 49.3%; HR, 0.79 [95% CI, 0.66-0.93]; P = .006) with coronary artery bypass grafting, which had an incremental median survival benefit of 18 months and a number needed to treat of 14.[101] Importantly, the long-term survival benefit of coronary artery bypass grafting was most apparent in younger patients and diminished with increasing age and was greatest in patients with more advanced ischemic cardiomyopathy, such as 3-vessel disease or more severe left ventricular systolic dysfunction.

Specific Populations

Black Patients

Black patients are disproportionately affected by heart failure and have greater risk of HF-related hospitalization and mortality; these differences arise as a result of a complex interplay of physiologic, genetic, environmental, and social factors.[102] Black patients have also been consistently underrepresented in heart failure clinical trials. While the risk of angioedema with ACE inhibitors or ARNIs is slightly higher in Black patients, the absolute risk is low (1.8% in PARADIGM-HF and 0.56% in PROVE-HF), and therefore, Black patients should be prescribed these therapies unless there is a history of angioedema with prior use.[51,103] As described previously, the combination of hydralazine and isosorbide dinitrate has been shown to have survival and heart failure hospitalization benefits in Black patients.[43]

Patients 75 Years of Age and Older

The evidence base for guideline-directed medical therapy has been derived from randomized clinical trials that typically enrolled only a modest number of patients older than 65 years, and very few older than 80 years. Observational data support similar treatment benefits as in younger patients, but also suggest higher risk of adverse events.[104] Caution is often needed with initiation and titration of therapy in older patients, with lower initial doses and slower dose titration. Nonetheless, whenever possible, during the care of older patients with HFrEF, titration to target doses is always recommended.

Cardiac Rehabilitation

Cardiac rehabilitation can be useful to improve exercise duration, health-related quality of life, and mortality.[105-107] The HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial found that a prescribed exercise training program modestly reduced clinical events when added to optimal medical therapy. After adjustment for prognostic variables, the risk of all-cause mortality and hospitalization was 11% lower in cardiac rehabilitation participants (P = .03), and cardiovascular mortality and heart failure hospitalization was reduced by 15% (P = .03).[107] Cardiac rehabilitation was safe, with no excess risk of cardiovascular adverse events or hospitalization after exercise. Besides the benefits of exercise therapy, participation in a cardiac rehabilitation program affords valuable opportunity for ongoing symptom and vital sign surveillance, medication titration, patient education, and monitoring for mood disorders.

Prognosis

While significant progress has been made in the management of HFrEF, improvement in survival appears to be leveling off over time despite an expanding list of therapies that have been shown to improve survival in clinical trials. For example, the 5-year mortality rate of heart failure decreased by 24% to 33% between the time periods of 1970-1974 to 1990-1994,[108] yet the mortality rate in HFrEF remained unchanged between 1990-1999 and 2000-2009 (HR of mortality, 0.97 [95% CI, 0.81-1.15]),[109] and prognosis remains particularly poor after hospitalization; the 5-year survival after hospitalization for HFrEF is 24.7%.[3]

Estimation of prognosis helps patients and clinicians engage in shared decision making on the appropriate type and timing of therapy, such as rapid transition to advanced therapies. Prognosis should be re-assessed at every office visit, and especially following major events, such as heart failure hospitalization.

A number of methods are available to establish prognosis. Biomarkers such as NT-proBNP are helpful to establish longitudinal prognosis; patients with low concentrations (eg, <1000 pg/mL) tend to have a more benign course with less left ventricular remodeling and fewer events; those with low concentrations might therefore merit less aggressive follow up evaluation or imaging. In addition to biomarkers, multivariable prognostic risk scores may be of value, however in general, most of these variables are only moderately accurate for predicting mortality and heart failure hospitalizations; they are nonetheless additive to clinical judgment for prognostication.[110,111] Recently, the PREDICT-HF (PARADIGM Risk of Events and Death in the Contemporary Treatment of Heart Failure) risk score was derived and validated for the prediction of cardiovascular and all-cause death and heart failure hospitalization; the model performed well, with a C-statistic of 0.71 (95% CI, 0.69-0.74) for the prediction of all-cause mortality at 1 year and 0.70 (95% CI, 0.68-0.72) at 2 years.[112]

Limitations

This review has several limitations. First, unlike the time period in which cornerstone neurohormonal blockade therapies (ACE inhibitors, ARBs, ARNIs, β-blockers, and MRA) were studied in clinical trials, there has been a more rapidly changing landscape of available therapies for HFrEF in recent years, making direct comparisons between medical and device therapies challenging. For example, only a minority of patients were on ARNIs in the COAPT trial (3.5%), DAPA-HF (10.5%), and the VICTORIA trial (14.5%). Second, contemporary real-world outcomes data for patients with HFrEF treated with current guideline-directed medical therapies are also lacking.

Conclusions

HFrEF is a major public health concern with substantial morbidity and mortality. The management of HFrEF has seen significant scientific breakthrough in recent decades, and the ability to alter the natural history of the disease has never been better. Recent developments include SGLT2 inhibitors, vericiguat, and transcatheter mitral valve repair, which incrementally improve prognosis beyond foundational neurohormonal therapies. Disease morbidity and mortality remain high with a 5-year survival rate of 25% after hospitalization for HFrEF.

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