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■ ■FURTHER READING Aimo A et al: Cardiac remodeling - Part 2: Clinical, imaging and labo ratory findings. A review from the Study Group on Biomarkers of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 24:944, 2022. Alcaide P et al: Myocardial inflammation in heart failure with reduced and preserved ejection fraction. Circ Res 134:1752, 2024. Boorsma EM et al: Congestion in heart failure: A contemporary look at physiology, diagnosis and treatment. Nat Rev Cardiol 17:641, 2020. Bozkurt B et al: Heart failure epidemiology and outcomes statistics: A report of the Heart Failure Society of America. J Card Fail 29:1412, 2023. Bozkurt B et al: Universal definition and classification of heart failure: A report of the Heart Failure Society of America, Heart Failure Asso ciation of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail 27:387, 2021. Campbell P et al: Heart failure with preserved ejection fraction: Everything the clinician needs to know. Lancet 403:1083, 2024. Dunlay SM et al: Type 2 diabetes mellitus and heart failure: A scien tific statement from the American Heart Association and the Heart Failure Society of America. Circulation 140:e294, 2019. Heidenreich PA et al: 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 145:e895, 2022. Houston BA et al: Right ventricular failure. N Engl J Med 388:1111, 2023. Lam CSP et al: Classification of heart failure according to ejection frac tion. J Am Coll Cardiol 77:3217, 2021. Lembo M et al: Obesity: The perfect storm for heart failure. ESC Heart Fail 11:1841, 2024. McDonagh TA et al: 2021 ESC guidelines for the diagnosis and treat ment of acute and chronic heart failure. Eur Heart J 42:3599, 2021. Pandey A et al: Exercise intolerance in older adults with heart failure with preserved ejection fraction: JACC State-of-the-Art Review. J Am Coll Cardiol 78:1166, 2021. Talha KM et al: Frailty and heart failure: State-of-the-art review. J Cachexia Sarcopenia Muscle 14:1959, 2023. Xanthopoulos A et al: Heart failure and liver disease: Cardiohepatic interactions. JACC Heart Fail 7:87, 2019. Akshay Desai, Mandeep R. Mehra

Heart Failure:

Management Clinical management of patients with heart failure (HF) varies widely based on the clinical phenotype at presentation. Those in the earliest stage of disease with asymptomatic ventricular dysfunction (American College of Cardiology [ACC]/American Heart Association [AHA] stage B) may be amenable to treatment with neurohormonal antago nists, including angiotensin-converting inhibitors and β-adrenergic receptor antagonists, with the goal of facilitating ventricular

recovery and preventing the development of clinical HF (not further discussed). Those with symptomatic HF (ACC/AHA stage C) comprise a het erogeneous group in whom the approach to therapy is differentiated largely based on measurement of the left ventricular ejection frac tion (LVEF). Data from prospective, randomized clinical outcomes trials enrolling patients with symptomatic chronic HF and reduced

ejection fraction (HFrEF; LVEF ≤40%) have provided a rich evidence base that supports the efficacy of stepped pharmacologic therapy with renin-angiotensin-aldosterone system (RAAS) antagonists (including angiotensin-converting enzyme inhibitors, angiotensin receptor block ers, and mineralocorticoid receptor antagonists), neprilysin inhibitors, β-adrenergic receptor antagonists, and sodium-glucose cotransporter 2 (SGLT-2) inhibitors as a complement to device-based treatment with cardiac resynchronization therapy and implantable cardioverterdefibrillators. By contrast, treatment of patients with symptomatic chronic HF and mildly reduced (HFmrEF; LVEF 41–49%) or pre served ejection fraction (HFpEF; LVEF ≥50%) has, until recently, been symptom-focused owing to the lack of evidence-based therapies but is evolving in the wake of favorable results from recently reported trials of SGLT-2 inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and angiotensin-neprilysin inhibitors. Even with effective therapy, patients with HFrEF, HFmrEF, and HFpEF are at risk for clinical deterioration, typically because of progressive sodium and fluid retention that fuels the development of congestive symptoms and acute decompensated HF (ADHF). Management of these exacerbations (frequently hospitalbased) is heavily focused on hemodynamic stabilization, decongestion, and institution of appropriate disease-modifying therapy in the transi tion back to chronic ambulatory management. Recurrent episodes of ADHF despite careful follow-up and effective treatment may signal the onset of an advanced or refractory HF phenotype (ACC/AHA stage D) in which the risk of mortality from sudden death or end-stage HF is high, and consideration of salvage therapies including cardiac trans plant or mechanical circulatory support may be appropriate prior to escalation to palliative measures (Chap. 271).

CHAPTER 265 Heart Failure: Management HEART FAILURE WITH MILDY REDUCED OR PRESERVED EJECTION FRACTION ■ ■GENERAL PRINCIPLES Although clinical trials of RAAS antagonists, digoxin, β-adrenergic receptor blockers, and neprilysin inhibitors have been conducted in patients with HFpEF, none has conclusively demonstrated a mortal ity reduction. Variable benefits, measured in the form of reduced HF hospitalizations, have been seen with mineralocorticoid receptor antagonists, angiotensin receptor blockers, and angiotensin receptorneprilysin inhibitors, but benefits are principally confined to those with LVEF below the normal range (<0.60). This has led many to rec ommend that patients with HFmrEF should be treated with the same therapies as those with HFrEF. Patients with higher ejection fraction (EF) remain a therapeutic challenge. In the absence of specific phar macologic therapies proven to improve clinical outcomes, management of patients with HFpEF has historically been focused on improving symptoms and effort tolerance through lifestyle modification, control of congestion, stabilization of heart rhythm (particularly in those with atrial fibrillation), control of blood pressure to guideline-recommended targets, and management of comorbidities that may contribute to disease progression (including, for example, obesity, obstructive lung disease, obstructive sleep apnea, diabetes/insulin resistance, anemia, iron deficiency, and chronic kidney disease). More recently, however, targeted pharmacologic therapy is emerging, with clinical trials of SGLT-2 inhibitors supporting use of these agents to reduce cardiovascu lar mortality and HF hospitalizations in HFmrEF and HFpEF. Trials of angiotensin receptor-neprilysin inhibitors and GLP-1 agonists (in obese patients) also suggest possible benefits

in selected HFpEF patients. ■ ■CLINICAL TRIALS IN HFPEF Attempts to export the benefits of drugs that improve clinical outcomes in patients with HFrEF, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-adrenergic receptor blockers, digoxin, and mineralocorticoid receptor antago nists, to those with HFpEF have generally been unsuccessful. The Candesartan in Heart Failure—Assessment of Mortality and Morbidity (CHARM) Preserved study showed a statistically significant reduc tion in HF hospitalizations but no difference in all-cause mortality in patients with HFpEF who were treated with the ARB candesartan.

Similarly, the Irbesartan in Heart Failure with Preserved Systolic Func tion (I-PRESERVE) trial demonstrated no differences in the composite of cardiovascular death or HF hospitalization during treatment with the ARB irbesartan compared with placebo. Apparent early benefits of the ACE inhibitor perindopril on HF hospitalizations and functional capacity in the Perindopril in Elderly People with Chronic Heart Fail ure (PEP-CHF) study were attenuated over longer-duration follow-up. The Digitalis Investigation Group (DIG) Ancillary Trial found no impact of digoxin on all-cause mortality or on all-cause or cardiovas cular hospitalization among patients with chronic HF, EF >45%, and sinus rhythm, although a modest reduction in HF hospitalizations was noted. While no dedicated study of beta blockers has been conducted in HFpEF, the subgroup of elderly patients with prior hospitalization and HFpEF enrolled in the Study of the Effects of Nebivolol Interven tion on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial of nebivolol, a vasodilating beta blocker, did not appear to experience significant reductions in all-cause or cardiovas cular mortality.

PART 6 Disorders of the Cardiovascular System Regarding mineralocorticoid receptor antagonists, which have potent antifibrotic effects in HFrEF, the Treatment of Preserved Cardiac Func tion Heart Failure with an Aldosterone Antagonist (TOPCAT) trial explored the potential benefit of spironolactone compared to placebo in HFpEF. This trial demonstrated no improvement in the primary composite endpoint of cardiovascular death, HF hospitalizations, or aborted cardiac arrest but did show a reduction in HF hospitalizations among those allocated to spironolactone. Post hoc analyses of the study suggested significant regional differences in the baseline charac teristics, event rates, adverse effects, and adherence to spironolactone among patients randomized in Russia and the Republic of Georgia compared with those randomized in the Americas that raised concerns about study conduct in Russian and Georgian sites. Apparent reduc tions in cardiovascular death and HF hospitalization associated with spironolactone among the subgroup of patients randomized in the Americas suggest that these study design issues may have obscured a signal of spironolactone benefit. These data have supported a weak recommendation for spironolactone in patients with HFpEF who meet the inclusion criteria for the TOPCAT trial and are at low risk for adverse effects, including hyperkalemia and worsening renal func tion, in the most recent U.S. and European guidelines. However, the results of the Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) study in which spironolactone improved echocardio graphic indices of diastolic dysfunction but failed to improve exercise capacity, symptoms, or quality-of-life (QOL) measures highlight the need for further study. Ongoing trials, including the registry-based Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction (SPIRRIT-HFpEF) (SPIRRIT-HFpEF; clinicaltrials.gov identifier NCT02901184) and the randomized Study to Evaluate the Efficacy and Safety of Finerenone on Morbidity and Mortality in Participants with Heart Failure and Left Ventricular Ejection Fraction Greater than or Equal to 40% (FINEARTS-HF, clinicaltrials.gov identifier: NCT04435626) may provide additional insight in this

regard. Addition of the SGLT-2 inhibitors dapagliflozin and empagliflozin to guideline-directed medical therapy of HFrEF has been associated with reductions in cardiovascular mortality and HF hospitalization among patients with and without diabetes mellitus enrolled in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Fail ure (DAPA-HF) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPERORREDUCED) trials. These benefits have recently been extended to the population of patients with symptomatic HF and LVEF >40% based on observed reductions in the composite of cardiovascular death or HF hospitalization among those assigned to SGLT-2 inhibitors compared to placebo in the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) and Empagliflozin Outcome Trial in Patients with Chronic Heart Fail ure with Preserved Ejection Fraction (EMPEROR-PRESERVED) trials. Pooled analysis of the data from these trials is associated with a reduc tion in the composite or cardiovascular death or HF hospitalization.

These results have driven updates to treatment guidelines in the United States and Europe, which now embrace use of SGLT-2 inhibitors as foundational therapy in patients with symptomatic HF regardless of EF. However, cost-effectiveness analyses suggest that these agents may be of low to intermediate economic value, which may limit access until price reductions ensue. ■ ■OTHER THERAPEUTIC TARGETS Beyond pharmacologic therapy, small studies of exercise training and cardiac rehabilitation in patients with HFpEF have suggested benefits on functional capacity and QOL, indicating a possible role for lifestyle interventions to improve cardiorespiratory fitness in this population. For obese patients with HFpEF, aggressive efforts at weight loss (includ ing bariatric surgery) may also be associated with improvements in hemodynamics and exercise capacity. Recently, the randomized STEPHFpEF trial of the once-weekly GLP-1 agonist semaglutide in obese (body mass index ≥30 kg/m2) HFpEF patients without diabetes mellitus demonstrated improvements in functional capacity and QOL associated with incremental weight loss of nearly 12% relative to placebo. Several ongoing trials including STEP-HFpEF DM (Semaglutide Treatment Effect in People with Obesity and HFpEF and Type 2 Diabetes; clinical trials.gov identifier: NCT04916470) and the SUMMIT trial of the dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonist tirzepatide (clinicaltrials.gov identifier: NCT04847557) will provide further data for clinical utility in this population. A novel paradigm for understanding the pathophysiology of HFpEF has focused on the role of microvascular endothelial inflammation driven by comorbidities that results in impaired nitric oxide (NO) signaling and associated increases in myocardial stiffening. This para digm has emphasized the potential for improving outcomes in HFpEF by enhancing NO bioavailability and improving downstream protein kinase G–based signaling. In this regard, a small trial demonstrated that the phosphodiesterase-5 inhibitor sildenafil improved filling pres sures and right ventricular function in a cohort of HFpEF patients with pulmonary venous hypertension. This finding led to the phase 2 trial, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exer cise Capacity in Diastolic Heart Failure (RELAX), in HFpEF patients (LVEF >50%) with New York Heart Association (NYHA) functional class II or III symptoms, who received sildenafil at 20 mg three times daily for 3 months, followed by 60 mg three times daily for another 3 months, compared with a placebo. There was no improvement in functional capacity, QOL, or other clinical and surrogate parameters in those allocated to sildenafil compared to placebo. On the premise that nitrates, which are NO donors, might improve preload, coronary perfusion, endothelial function, and exercise tolerance, the Nitrate’s Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) study was conducted. Isosorbide mono nitrate did not improve QOL or submaximal exercise capacity and decreased overall activity levels

in treated patients. Inorganic nitrate compounds have also been shown to enhance NO signaling but did not improve functional capacity compared to placebo among patients with HFpEF randomized in the Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure with Preserved Ejection Fraction (INDIE-HFpEF) trial. Neprilysin inhibition is known to increase circulating levels of various vasoactive peptides, including the natriuretic peptides, which may facilitate cyclic guanosine 3′,5′-monophosphate–based signaling, enhance myocardial relaxation, and reduce ventricular hypertrophy. Composite angiotensin receptor-neprilysin inhibition (ARNI) with sacubitril-valsartan reduced cardiovascular mortality, overall mortality, and HF hospitalization compared with enalapril among patients with HFrEF randomized in the PARADIGM-HF trial. The PARAGONHF trial randomized 4822 patients with symptomatic HFpEF (LVEF ≥45%), elevated natriuretic peptides, and structural heart disease to treatment with either sacubitril-valsartan or valsartan with the novel composite primary endpoint of cardiovascular death and total hospi talizations for HF. Although there was a 13% reduction in the rate of the primary composite endpoint in those allocated to sacubitril-valsartan, this result narrowly missed the margin for statistical significance in the

Heart Failure with Preserved Ejection Fraction: Pathology and Management Pathology Hypertrophy Fibrosis/altered collagen Infarction/ischemia General Therapeutic Principles • Reduce the congestive state – Caution to not reduce preload excessively – Use of implantable hemodynamics monitors to guide management

is useful • Control blood pressure – Central aortic blood pressure control may be more relevant • Maintain atrial contraction and prevent tachycardia – Efforts to maintain sinus rhythm in atrial fibrilation may be beneficial

(atrial fibrillation ablation may reduce morbidity and mortality) • Treat and prevent myocardial ischemia – May mimic HF as an “angina equivalent” • Detect and treat sleep apnea – Common co-morbidity causing systemic hypertension, pulmonary

hypertension, and right heart dysfunction (adaptive servo-ventilation

ineffective) • Lifestyle modification – Diet and exercise to promote weight reduction and improve

functional capacity FIGURE 265-1 Pathophysiologic correlations, general therapeutic principles, and results of specific “directed” therapy in heart failure (HF) with preserved ejection fraction. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter 2; QOL, quality of life. primary statistical analysis (p = .06). Directional benefits in secondary endpoints including QOL, NYHA class, and renal function favoring sacubitril-valsartan support a possible modest benefit of neprilysin inhibition in this population, particularly among patients with lower (i.e., mildly reduced) EF and in women, subgroups who appeared to derive greater benefit. Based on these data, sacubitril-valsartan has recently been approved in the United States for treatment of symptom atic HF across the full spectrum of EF, with benefits acknowledged to be greatest in those with LVEF below normal. The PARAGLIDE-HF trial randomly assigned patients with HF and EF >40% within 30 days of a worsening HF event to treatment with sacubitril-valsartan or valsartan. Although those assigned to sacubitril-valsartan experienced greater reductions in N-

terminal prohormone of brain natriuretic peptide (NTproBNP) at 8 weeks, clinical benefits were modest and appeared to be confined to those with EF ≤60%, suggesting this therapy may be most effective in that subgroup. ■ ■CLINICAL GUIDING PRINCIPLES Beyond disease-modifying therapy, treatment of HFpEF should focus on decongestion, aggressive management of medical comorbidities, and relief of exacerbating factors. A careful diagnostic approach is critical, since patients with HF and a normal or near-normal LVEF compose a heterogenous group that includes patients with infiltrative heart disease (amyloidosis, hemochromatosis, sarcoidosis), storage disease (Fabry's disease, Gaucher's disease), hypertrophic cardiomy opathy, pericardial disease, pulmonary arterial hypertension, valvular heart disease, and primary right ventricular failure who may require a different management approach. For those with true HFpEF, aggres sive control of blood pressure to guideline-recommended targets and

CHAPTER 265 Risk markers Hypertension Aging Atherosclerosis Heart Failure: Management Diabetes Obesity Specific Therapy Targets (beyond general management) • Renin-angiotensin-aldosterone–directed therapy – ACEIs and ARBs ineffective (except in "prevention") – Aldosterone antagonists (may be beneficial) • Digoxin – Ineffective (may reduce hospitalizations) • Beta blockers and calcium channel blockers – Ineffective (useful in preventing tachycardia in patients

with AF) • Phosphodiesterase-5 inhibitors – Sildenafil ineffective • Novel Therapy – ARNIs (may be effective in selected patients) – SGLT-2 inhibitors (reduce HF hospitalization) • Chronotropic insufficiency – ? Targeted pacing (likely ineffective) • Obesity treatment – GLP-1 agonists (improve QOL irrespective of diabetes mellitus) relief of volume overload with diuretics are critical to symptom relief. Excessive decrease in preload with diuretics and vasodilators may lead to underfilling the ventricle and subsequent azotemia, hypotension, and syncope. For patients at risk for coronary heart disease, deliberate evaluation for ischemia and consideration of coronary revascularizа tion may be important. Since clinical outcomes in HFpEF are worse in the setting of atrial fibrillation, aggressive rate control, anticoagulation, and early consideration of sinus rhythm restoration are important. Comorbidities such as obesity, obstructive lung disease, sleep apnea, chronic kidney disease, and anemia/iron deficiency are increasingly recognized as important contributors to diminished functional capac ity and QOL in patients with HFpEF and may be additional targets for therapy. Some investigators have suggested that the exercise intolerance in HFpEF is a manifestation of chronotropic insufficiency. While this hypothesis appears to be supported by small trials randomized trials of beta blocker withdrawal, improving chronotropic response through rate-adaptive atrial pacing did not improve functional capacity in the randomized RAPID-HF trial (Fig. 265-1). ACUTE DECOMPENSATED HEART FAILURE ■ ■GENERAL PRINCIPLES ADHF is a heterogeneous clinical syndrome most often resulting in need for hospitalization due to confluence of interrelated abnormali ties of decreased cardiac performance, renal dysfunction, and altera tions in vascular compliance. Admission with a diagnosis of ADHF is associated with excessive morbidity and mortality, with nearly half of these patients readmitted for management within 6 months, and a high short-term (5% in-hospital) and long-term cardiovascular mortality

Heterogeneity of ADHF: Management Principles Hypertensive Acute Decompensation "Typical" (usually volume overloaded) (usually not volume overloaded) PART 6 Disorders of the Cardiovascular System Vasodilators Renal insufficiency Biomarkers of injury Acute coronary syndrome, arrhythmia, hypoxia, pulmonary embolism, infection Severe Pulmonary Congestion with Hypoxia Acute Decompensation "Pulmonary edema" Opiates Vasodilators Hypoperfusion with End-

Organ Dysfunction Acute Decompensation “Low output” Vasodilators Hypotension, Low Cardiac Output, and End-Organ Failure Acute Decompensation “Cardiogenic shock” Inotropic therapy (usually catecholamines) FIGURE 265-2 The distinctive phenotypes of acute decompensated heart failure (ADHF), their presentations, and suggested therapeutic routes. (Unique causes of ADHF, such as isolated right heart failure and pericardial disease, and rare causes, such as aortic and coronary dissection or ruptured valve structures or sinuses of Valsalva, are not delineated and are covered elsewhere.) CNS, central nervous system; IABP, intraaortic balloon pump; VAD, ventricular assist device. (20% at 1 year). Importantly, long-term outcomes remain poor, with a combined incidence of cardiovascular deaths, HF hospitalizations, myocardial infarction, strokes, or sudden death reaching 50% at 12 months after hospitalization. The management of these patients remains difficult and principally revolves around volume control and hemodynamic optimization to maximize end-organ perfusion. The first principle of management in ADHF is to identify and address the factors that precipitated decompensation. Important his torical factors to consider are nonadherence to medications, dietary salt indiscretion, and usage of medications (including over-the-counter preparations) that may exacerbate HF, including nonsteroidal antiinflammatory drugs, thiazolidinediones, tumor necrosis factor inhibi tors, selected antidepressants, selected cancer therapies, cold and flu preparations with cardiac stimulants, and some herbal preparations. Coronary ischemia frequently drives HF exacerbation in patients with atherosclerotic cardiovascular disease and should be systematically investigated (either invasively or noninvasively) in all patients at risk to identify candidates for revascularization. Atrial and ventricular arrhythmias are common contributors to HF exacerbation and may trigger the need for antiarrhythmic drug suppression, cardioversion, or catheter ablation. Valvular heart disease is increasingly recognized as a target for therapy in patients with recurrent HF exacerbations and can be readily identified through echocardiography. Systemic infec tion and pulmonary thromboembolism are additional triggers of HF decompensation and should be routinely considered. Concurrent with the identification of HF precipitants, effective management of ADHF requires pharmacologic therapy directed at hemodynamic optimization, including relief of congestion, reduction in afterload, and maximization of vital organ perfusion. The routine use of a pulmonary artery catheter is not recommended and should be restricted to those who present with features typical of low-output HF

Normotensive High-Risk Features Diuretics New onset arrhythmia Valvular heart disease Inflammatory heart disease Myocardial ischemia CNS injury Drug toxicity O2 and noninvasive ventilation Diuretics Low pulse pressure Cool extremities Cardio-renal syndrome Hepatic congestion Inotropic therapy (if low blood pressure or diuretic refractoriness) Hemodynamic monitoring (suboptimal initial therapeutic response) Extreme distress Pulmonary congestion Renal failure Mechanical circulatory support (IABP, percutaneous VAD, ultrafiltration) or cardiogenic shock who may require vasopressor or mechanical circu latory support, those who are resistant or refractory to diuretic therapy, those with combined cardiorenal dysfunction in whom therapeutic goals are difficult to define at the bedside, and those with known or sus pected pulmonary arterial hypertension in whom vasodilator therapy may be appropriate. Analysis of in-hospital registries has identified several parameters associated with worse outcomes: a blood urea nitro gen level >43 mg/dL (to convert to mmol/L, multiply by 0.357), systolic blood pressure <115 mmHg, a serum creatinine level >2.75 mg/dL (to convert to µmol/L, multiply by 88.4), and elevated cardiac biomarkers including natriuretic peptides and cardiac troponins. A useful clinical schema to identify treatment targets for the various phenotypic presen tations and management goals in ADHF is

depicted in Fig. 265-2. ■ ■VOLUME MANAGEMENT Intravenous Diuretic Agents Intravenous loop diuretic agents rapidly and effectively relieve symptoms of congestion and are essential when oral drug absorption is impaired. When high doses of diuretic agents are required or when the effect of bolus dosing is suboptimal, a continuous infusion may be needed to reduce toxicity and maintain stable serum drug levels. Randomized clinical trials of high- versus low-dose and bolus versus continuous infusion diuresis have not pro vided clear justification for the best diuretic strategy in ADHF, and as such, the use of diuretic regimens remains an art rather than science. For those refractory to loop diuretic treatment alone, addition of a thiazide diuretic agent such as chlorothiazide or metolazone to provide sequential nephron blockade may enhance natriuresis and facilitate decongestion, but also increases the risk of significant hypokalemia. Addition of acetazolamide to loop diuretic therapy in the randomized ADVOR trial was demonstrated to facilitate greater decongestion but was not associated with reduction in HF readmissions or mortality.

CHAPTER 265 Change in weight is often used as a surrogate for adequate diuresis, but this objective measure of volume status may be surprisingly difficult to interpret, and weight loss during hospitalization does not necessarily correlate closely with outcomes. Effective decongestion may also be confirmed by improvement in clinical symptoms as well as the bedside examination documenting normalization of the jugular venous pres sure, clearance of pulmonary rales, suppression of cardiac gallops, and resolution of peripheral edema, hepatomegaly, and abdominal ascites. It is generally advisable to continue diuresis until euvolemia has been achieved, since residual congestion or volume overload is strongly associated with risk for recurrent decompensation. Predischarge mea surement of natriuretic peptide levels, which are highly correlated with risk for postdischarge mortality and readmission, may also be useful in assessing the adequacy of therapy and stratifying risk. Chronic oral loop diuretic therapy is appropriate at discharge for most patients to maintain decongestion. The TRANSFORM-HF trial did not demon strate any mortality or morbidity advantage of torsemide compared to furosemide for this purpose despite its greater oral bioavailability, longer half-life, and other potential beneficial effects on myocardial fibrosis, aldosterone production, sympathetic activation, ventricular remodeling, and natriuretic peptides noted in small studies. The Cardiorenal Syndrome The cardiorenal syndrome is increas ingly being recognized as a complication of ADHF. Multiple definitions have been proposed for the cardiorenal syndrome, but at its simplest, it can be thought to reflect the interplay between abnormalities of heart and kidney function, with deteriorating function of one organ while therapy is administered to preserve the other. Approximately 30% of patients hospitalized with ADHF exhibit abnormal renal func tion at baseline, and this is associated with longer hospitalizations and increased mortality. However, mechanistic studies have been largely unable to find correlation between deterioration in renal function, cardiac output, left-sided filling pressures, and reduced renal perfusion; most patients with cardiorenal syndrome demonstrate a preserved car diac output. It is hypothesized that in patients with established HF, this syndrome represents a complex interplay of neurohormonal factors, potentially exacerbated by “backward failure” resulting from increased intraabdominal pressure and impairment in return of renal venous blood flow. Continued use of diuretic therapy may be associated with a reduction in glomerular filtration rate and a worsening of the car diorenal syndrome when right-sided filling pressures remain elevated. In patients in the late stages of disease characterized by profound low cardiac output state, inotropic

therapy or mechanical circulatory sup port has been shown to preserve or improve renal function in selected individuals in the short term until more definitive therapy such as assisted circulation or cardiac transplantation is implemented. Ultrafiltration Ultrafiltration (UF) is an invasive fluid removal technique that may supplement the need for diuretic therapy. Proposed benefits of UF include controlled rates of fluid removal, neutral effects on serum electrolytes, and decreased neurohormonal activity. This technique has also been referred to as aquapheresis in recognition of its electrolyte depletion–sparing effects. In an initial study evaluating UF versus conventional therapy, fluid removal was improved, and subsequent HF hospitalizations and urgent clinic visits were reduced with UF; however, no improvement in renal function and no subjec tive differences in dyspnea scores or adverse outcomes were noted. In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, 188 patients with ADHF and worsening renal failure were randomized to stepped pharmacologic care or UF. The primary endpoint was a change in serum creatinine and change in weight (reflecting fluid removal) at 96 h. Although similar weight loss occurred in both groups (~5.5 kg), there was a rise in serum creatinine among patients allocated to the UF group. Deaths and hospitaliza tions for HF were no different between groups, but there were more adverse events in the UF group, mainly due to kidney failure, bleeding complications, and intravenous catheter-related complications. This investigation argues against using UF as a primary strategy in patients with ADHF who are diuretic-responsive. Whether UF is useful as a res cue strategy in diuretic refractory patients with advanced renal disease remains an open question, and this strategy continues to be employed judiciously in such situations. ■ ■VASOACTIVE THERAPY Vasodilators including intravenous nitroglycerin, sodium nitroprusside, and nesiritide (a recombinant brain-type natriuretic peptide) are fre quently used in ADHF to lower intracardiac filling pressures and reduce systemic vascular tone. Rapid reduction in ventricular preload and after load with these therapies may be effective in providing symptom relief in patients with pulmonary edema and in restoring end-organ perfusion for those with low cardiac output and high systemic vascular resistance. Nitroglycerine principally impacts venous tone and ventricular preload, whereas sodium nitroprusside is a potent arterial and venous vasodila tor with more comprehensive effects on both preload and afterload. While intravenous nitroglycerine is commonly utilized as an adjunct to diuretics for acute management of symptomatic HF and pulmonary edema, nitroprusside is typically reserved for use in those with adequate arterial pressure or invasive hemodynamic monitoring due to the risk for hypotension. The hemodynamic effects of nesiritide are intermediate between those of nitroglycerine and nitroprusside, with head-to-head comparisons with nitroglycerine suggesting more rapid reduction in pulmonary capillary wedge pressure and pulmonary vascular resistance. Clinical utilization of nesiritide has waned due to concerns raised regarding heightened risks of renal insufficiency and mortality identified in early trials. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) randomizing 7141 patients with ADHF to nesiritide or placebo did not confirm this risk but identified no clear clinical benefit regarding subsequent HF admissions, mortality, or symptom relief (reduction in dyspnea). Renal function did not worsen, but increased rates of hypotension were noted. A smaller study of low-dose nesiritide in acute HF (Renal Optimization Strategies Evaluation Acute Heart Failure Study [ROSE-AHF]) also showed no incremental benefit over intravenous diuretics for relief of congestion or preservation of renal function. Despite apparent safety in ADHF, the routine use of nesiritide is accordingly not recommended. Other novel vasodilators have been explored for the management of ADHF. Recombinant human relaxin-2, or serelaxin, is a vasodilatory hormone known to contribute to cardiovascular and renal adaptations during pregnancy. In the Relaxin in Acute Heart Failure (RELAXAHF) trial, 1161 patients

hospitalized with ADHF, evidence of conges tion, and systolic pressure >125 mmHg were randomized to treatment with serelaxin or placebo in addition to standard HF therapy. Serelaxin improved dyspnea, reduced signs and symptoms of congestion, and was associated with less early worsening of HF. A positive signal of reduced mortality identified in an exploratory analysis prompted a second study (RELAX-AHF2), which did not confirm an effect on cardiovascular death or worsening HF. Accordingly, this agent was not approved for use in clinical practice. One hypothesis for the failure of vasodilator therapies to improve clinical outcomes in ADHF despite favorable hemodynamic effects is related to the acute injury hypothesis; in this model, acute HF is analogous to presentation with an acute coronary syndrome, with the initial hours of presentation representing a period of vulnerability to myocardial damage (reflected in a rise in markers of myocyte injury such as cardiac troponins) as a consequence of abrupt increases in ven tricular wall stress related to acute plasma volume expansion. To test this hypothesis, the Trial of Ularitide Safety and Efficacy in Acute Heart Failure (TRUE-AHF) randomly allocated 2157 patients with acute HF to early treatment with the synthetic natriuretic peptide ularitide (at a dose sufficient to reduce ventricular wall stress) or placebo. Despite a very short duration between initial clinical presentation and phar macologic intervention (<6 h) and early hemodynamic benefits, no improvement in clinical outcomes was observed in patients allocated to ularitide at 6 months. Ularitide was associated with a higher rate of hypotension and worsening serum creatinine. These data under mine the notion that acute myocardial damage related to ventricular distension associated with HF exacerbation drives subsequent clinical outcomes and argue against the clinical importance of early vasodilator therapy in ADHF.

■ ■INOTROPIC THERAPY Impairment of myocardial contractility often accompanies ADHF, and pharmacologic agents that increase intracellular concentration of cyclic adenosine monophosphate via direct or indirect pathways, such as sympathomimetic amines (dopamine, dobutamine) and phosphodies terase-3 inhibitors (milrinone), respectively, serve as positive inotropic agents. Their activity leads to an increase in cytoplasmic calcium. Ino tropic therapy in those with a low-output state augments cardiac output, reduces systemic vascular resistance, improves perfusion, and relieves congestion acutely. Although systematic head-to-head comparisons are available to identify a “best” agent, slight variations in the hemodynamic effects of inotropic drugs may condition selection of the appropriate drug for a given clinical context. Dopamine exhibits dose-dependent effects on dopaminergic, α-, and β-adrenergic receptors, with vaso dilatory effects predominating at lower doses (<2 μg/kg per min), β-adrenergic (inotropic) effects at moderate doses, and α-adrenergic effects (vasoconstriction) at higher doses (typically >10 μg/kg per min). Low-dose (“renal dose”) dopamine has been explored as an adjunctive strategy for preservation of renal function and augmentation of diuresis in acute HF but does not appear to provide incremental advantage over routine therapy with intravenous diuretics (ROSE-AHF).

PART 6 Disorders of the Cardiovascular System Milrinone is typically associated with a greater reduction in sys temic and pulmonary vascular resistance than dobutamine and, accord ingly, carries a higher risk of systemic hypotension. Moreover, because milrinone has a longer half-life and is renally excreted, it requires dose adjustments in the setting of kidney dysfunction. Because milrinone acts downstream from the β1-adrenergic receptor, it may provide an advantage in patients receiving beta blockers when admitted to the hospital. Long-term inotropic therapy is associated with a heightened risk of mortality in HF, perhaps due to the increased risk of arrhythmia and sudden death. Routine, short-term use of milrinone in patients hospitalized with

ADHF in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial was associated with increased risk of atrial arrhythmias and prolonged hypotension, but no benefit regarding subsequent mortality or HF hospitalization. Accordingly, routine use of inotropic support in ADHF is discouraged, and these agents are currently indicated principally for short-term use as bridge therapy (to either left ventricular assist device support or to transplant) in cardiogenic shock or as selectively applied palliation in end-stage HF. Novel inotropic agents that leverage the concept of myofilament calcium sensitization rather than increasing intracellular calcium levels have been introduced. Levosimendan is a calcium sensitizer that provides inotropic activity but also possesses phosphodiesterase-3 inhibition properties that are vasodilatory. Two trials, the second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) and Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE), have tested this agent in ADHF. SURVIVE compared levosimendan with dobuta mine, and despite an initial reduction in circulating B-type natriuretic peptide levels in the levosimendan group compared with patients in the dobutamine group, this drug did not reduce all-cause mortality at 180 days or affect any secondary clinical outcomes. The second trial compared levosimendan against traditional noninotropic therapy and found a modest improvement in symptoms with worsened short-term mortality and ventricular arrhythmias. Although levosimendan has been approved for use to support management of HF in several coun tries worldwide, it is not approved for use in the United States, largely owing to the lack of compelling data for incremental efficacy in com parison with conventional inotropic drugs or standard HF therapies. (Table 265-1 depicts typical inotropic, vasodilator, and diuretic drugs used in ADHF.) ■ ■OTHER THERAPIES FOR ADHF Other trials testing unique agents have yielded disappointing results in the situation of ADHF. Adenosine has been implicated as a mediator of worsening renal function and diuretic resistance, and accordingly, treatment with adenosine receptor antagonists was postulated to be

potentially beneficial in relieving symptoms and preserving renal func tion in patients with acute HF. Among patients with acute HF and renal dysfunction enrolled in the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Func tion (PROTECT) trial, no cardiovascular or renal benefit was observed. Similarly, despite compelling theoretical benefit of vasopressin receptor antagonism in acute HF (based on the central role of vasopressin in mediating the fluid retention that contributes to worsening HF), no benefit of the oral selective vasopressin-2 antagonist tolvaptan was seen regarding mortality or HF-associated morbidity in the Efficacy of Vaso pressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial. ■ ■CLINICAL GUIDING PRINCIPLES In the absence of data to support specific pharmacologic interven tions in ADHF, management is largely goal-directed and focused on decongestion to relieve symptoms, investigation and suppression of triggers for recurrent decompensation, and careful transition to lon gitudinal HF management. Patients who fail to respond adequately to medical therapy or who develop hemodynamic instability may benefit from pulmonary artery catheter placement to guide titration of vasoactive therapy or inotropic support; in those with hemody namics suggestive of cardiogenic shock, mechanical assist devices may be required (Chap. 271). Following stabilization, all patients should receive education regarding HF self-management prior to dis charge, including guidance regarding diet and lifestyle modification, identification of worsening HF symptoms, and whom to contact in the event of clinical deterioration. Early postdischarge follow-up of patients following

hospitalization for management of worsening HF is associated with lower rates of hospital readmission. For patients with HFrEF hospitalized with ADHF, data suggest that institution of appropriate guideline-directed medical therapy prior to hospital discharge is associated with higher rates of adherence to appropriate pharmacologic treatment in longitudinal follow-up and may be asso ciated with improved outcomes in the early postdischarge interval. In the Comparison of Sacubitril-Valsartan Versus Enalapril on Effect on NTproBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) study of patients with HFrEF stabilized after hospital admission for ADHF, predischarge initiation of sacubitril-valsartan compared with enalapril was associated with greater reductions in natriuretic peptides as well as lower rates of composite death and HF readmission at 8 weeks. Similarly, in the EMPULSE trial, predischarge initiation of the SGLT-2 inhibitor empagliflozin in hospitalized HF patients across the spectrum of EF was associated with reductions in a hierarchical clinical composite outcome at 90 days. More recently, in the STRONG-HF trial, an intensive postdischarge treatment strategy of frequent follow-up and rapid uptitration of guidelinerecommended medical therapy was associated with lower rates of death and HF readmission at 180 days compared with usual care. These results were consistent in those with EF ≤40% and those with EF >40%, underscoring the need for early postdischarge follow-up and medical optimization in high-risk patients following a worsening HF event, regardless of EF. HEART FAILURE WITH REDUCED EJECTION FRACTION The past 50 years have witnessed great strides in the manage ment of HFrEF. Treatment of symptomatic HF has evolved from a renocentric (diuretics) and hemodynamic therapy model (digoxin, inotropic therapy) to an era of disease-modifying therapy with neu rohormonal antagonism. In this regard, RAAS blockers (including ARNIs), β-adrenergic receptor blockers, and, most recently, SGLT-2 inhibitors form pillars of pharmacotherapy and facilitate stabiliza tion and even improvement in cardiac structure and function with consequent reduction in symptoms, improvement in QOL, decreased burden of hospitalizations, and a decline in mortality from both pump failure and arrhythmic deaths (Fig. 265-3).

TABLE 265-1 Vasoactive Therapy in Acute Decompensated Heart Failure DRUG CLASS GENERIC DRUG USUAL DOSING SPECIAL CAUTION COMMENTS Inotropic therapy Use in hypotension, end-organ hypoperfusion, or shock states Dobutamine 2–20 μg/kg per min Increased myocardial oxygen demand, arrhythmia Milrinone 0.375–0.75 μg/kg per min Hypotension, arrhythmia Decrease dose in renal insufficiency; avoid initial bolus; effectiveness retained in presence of beta blockers Levosimendan 0.1 μg/kg per min; range, 0.05–0.2 μg/kg per min Hypotension, arrhythmia Long acting; should not be used in presence of low blood pressure; similar effectiveness as dobutamine but effectiveness retained in presence of beta blockers Vasodilators Use in presence of pulmonary congestion for rapid relief of dyspnea, in presence of a preserved blood pressure Nitroglycerin 10–20 μg/min, increase up to 200 μg/min Headache, flushing, tolerance Nesiritide Bolus 2 μg/kg and infusion at 0.01 μg/kg per min Hypotension Decrease in blood pressure may reduce renal perfusion pressure; bolus may be avoided since it increases hypotension predilection Nitroprusside 0.3 μg/kg per min titrated to 5 μg/kg per min Thiocyanate toxicity in renal insufficiency (>72 h) Serelaxin N/A (tested at 30 μg/kg per d) Baseline blood pressure should be >125 mmHg Ularitide 15 ng/kg per min (48 h) Baseline blood pressure

116 mmHg Diuretics First line of therapy in volume overload with congestion; may use bolus or continuous dosing; initial low dose (1 × home dose) or high dose (2.5 × home dose) equally effective with higher risk of renal worsening with higher dose Furosemide 20–240 mg daily Monitor for electrolyte loss Torsemide 10–100 mg daily Monitor for electrolyte loss Bumetanide 0.5–5 mg daily Monitor for electrolyte loss Adjuvant diuretics for augmentation N/A Metolazone, chlorthalidone, spironolactone, acetazolamide Abbreviation: N/A, not applicable. Ineffective Adjuncts Higher • Erythropoietin for anemia • Warfarin/low-dose rivaroxaban to prevent thromboembolism (absent high-risk features) • SSRI for depression • Statins for HF • Adaptive servo-ventilation for central sleep apnea (increased mortality) Placebo ACE inhibitor/ARB Risk of mortality β-Blockers (carvedilol, metoprolol succinate, bisoprolol) Mineralocorticoid receptor antagonist ARNI (instead of ACEI/ARB) SGLT-2 i Vericiguat Lower FIGURE 265-3 Progressive decline in mortality with angiotensin-converting enzyme (ACE) inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), angiotensin receptorneprilysin inhibitors (ARNIs), beta blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and balanced vasodilators (*selected populations such as African Americans). Addition of selected therapies (ivabradine, vericiguat) may further reduce heart failure (HF) hospitalization but does not substantially impact mortality. Further stack-on neurohormonal therapy is ineffective or results in worse outcome. Management of comorbidity (e.g., iron deficiency, sleep apnea) is of unproven efficacy. HFrEF, heart failure with reduced ejection fraction; PUFA, polyunsaturated fatty acid; SSRI, selective serotonin reuptake inhibitor.

Short acting, an advantage; variable efficacy in presence of beta blockers (requires higher doses); clinical tolerance to prolonged infusions; concerns with hypersensitivity carditis (rare) CHAPTER 265 Heart Failure: Management Most common vasodilator but often underdosed; effective in higher doses Requires arterial line placement for titration for precise blood pressure management and prevention of hypotension Not widely commercially available; ineffective in confirmatory trials Excess hypotension and increased serum creatinine In severe congestion, use intravenously and consider continuous infusion (not trial supported) High bioavailability, can be given orally; anecdotally more effective in advanced heart failure states if furosemide less bioavailable (due to gut congestion) Can be used orally; intermediate bioavailability Acetazolamide is useful in presence of alkalosis (bicarbonate level

> 27mEq/L); metolazone given in 2.5- to 10-mg doses; concomitant use of loop diuretics and thiazides associated with risk for severe hypokalemia, careful laboratory monitoring advised; spironolactone is useful in presence of severe hypokalemia and normal renal function Potentially Effective • N-3 PUFA • Iron supplementation Special Populations • Hydralazine/isosorbide • Ivabradine Oral inotropes (vesnarinone, flosequinan) Moxonidine (imidazoline receptor agonist)

> Xamoterol (mixed β-agonist/antagonist) Endothelin antagonists Omecamtiv mecarbil

■ ■NEUROHORMONAL ANTAGONISM Meta-analyses suggest a 23% reduction in mortality and a 35% reduc tion in the combined endpoint of mortality and hospitalizations for HF in patients with symptomatic HFrEF treated with ACE inhibitors (ACEIs). Addition of β-adrenergic receptor blockers to background therapy with ACEIs provides a further 35% reduction in mortality. Although placebo-controlled studies are lacking, several noninferior ity trials have demonstrated comparable efficacy of ARBs and ACEIs in patients with HFrEF, making ARBs a suitable alternative for patients who are intolerant to ACEIs due to cough or angioedema. Abundant data support the efficacy across the full spectrum of HF severity (including those with NYHA class III–IV functional capacity), as well as the safety data of these agents. These observations demonstrate the basis for the tolerability of these agents even in subgroups at higher risk for adverse effects such as those with mild-moderate chronic kid ney disease. In diabetes mellitus and chronic obstructive lung disease, these agents have been established as foundational therapy for HFrEF as directed by consensus guidelines. Both agents are generally recom mended for all patients with HFrEF, independent of symptom burden, and should be titrated to the doses proven to provide clinical benefit or to the maximally tolerated dose. The inability to tolerate initiation or dose titration of neurohumoral antagonists due to hypotension, worsening HF, or progressive renal insufficiency is a poor prognos tic marker and may be a cardinal manifestation of transition to an advanced HF phenotype.

PART 6 Disorders of the Cardiovascular System Class Effect and Sequence of Administration ACEIs and ARBs exert their beneficial effects in HFrEF as a class; however, the beneficial effects of beta blockers are thought to be limited to spe cific drugs. Beta blockers with intrinsic sympathomimetic activity (xamoterol) and other agents, including bucindolol, have not dem onstrated a survival benefit. Based on the available data, beta blocker use in HFrEF should ideally be restricted to carvedilol, bisoprolol, and metoprolol succinate—agents tested and proven to improve survival in clinical trials. Whether beta blockers or ACEIs should be started first was answered by the Cardiac Insufficiency Bisoprolol Study (CIBIS) III, in which outcomes did not vary based on the sequence of drug initiation. Thus, it matters little which agent is initiated first; what does matter is that optimally titrated doses of both ACEIs and beta blockers be established in a timely manner. Dose and Outcome In general, the benefits of neurohumoral antagonists in HFrEF are closely related to the dose achieved, gird ing the rationale for aggressive titration to target doses as defined by clinical trials. Prospective trials of high- versus low-dose ACEIs (ATLAS), ARBs (HEAAL), and beta blockers (MOCHA) consistently favor the higher dose, with lower rates of death and HF hospitaliza tion seen in the higher-dose group. Clinical experience suggests that, in the absence of symptoms to suggest hypotension (fatigue and diz ziness), pharmacotherapy may be uptitrated every 2 weeks in stable ambulatory patients as tolerated. Notably, data from large registries in the United States and Europe suggest that guideline-directed medi cal therapy for patients with HFrEF is frequently underutilized and underdosed, leaving considerable room for quality improvement. ■ ■MINERALOCORTICOID RECEPTOR ANTAGONISTS Addition of mineralocorticoid receptor antagonists to treatment with ACEI/ARBs and beta blockers in patients with symptomatic HFrEF (NYHA class II–IV) is associated with further reductions in morbidity and mortality. Elevated aldosterone levels in HFrEF promote sodium retention, electrolyte imbalance, and endothelial

dysfunction and may directly contribute to myocardial fibrosis. Hyperkalemia and worsen ing renal function are concerns, especially in patients with underly ing chronic kidney disease, and renal function and serum potassium levels must be closely monitored. Spironolactone is the most utilized agent in this class based on efficacy demonstrated in the Randomized Aldactone Evaluation Study (RALES) in patients with HFrEF and NYHA class III–IV symptoms. Eplerenone (studied principally in patients with milder NYHA class II symptoms and those with HF or

left ventricular dysfunction complication myocardial infarction) lacks the antiandrogen effects of spironolactone and may be a suitable alter native for patients who experience sexual side effects (gynecomastia, erectile dysfunction, diminished libido). ■ ■RAAS THERAPY AND NEUROHORMONAL “ESCAPE” Since angiotensin II can be generated by non-ACE pathways, levels of angiotensin II may recover to pretreatment levels during long-term ACEI therapy. This phenomenon of neurohormonal “escape” has fueled interest in dual blockade of the RAAS using ACEI and ARBs in combination. In both the Valsartan Heart Failure Trial (Val-HeFT) and the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM-Added) trial, addition of an ARB to an ACEI and other HF therapy was associated with a lower risk of HF hospitalizations. Since neither trial mandated an evidence-based dose of an ACEI, it remains unclear whether combination therapy was clearly superior to a strategy of maximizing a single agent through dose titration. Subsequent data from the Valsartan in Acute Myocar dial Infarction (VALIANT) trial suggested that the addition of the ARB valsartan to an evidence-based dose of the ACEI captopril in patients with HF complicating myocardial infarction was associated with an increase in adverse events without any added benefit compared with monotherapy for either group. The findings of the VALIANT trial are also informed by the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE), which randomly allocated 7016 patients with HFrEF to treatment with enalapril (targeted dose 10 mg twice daily as recommended by guidelines), the plasma renin inhibitor aliskiren, or the combination on top of standard HF therapy. In that study, combination treatment with aliskiren and enalapril was associ ated with higher rates of hyperkalemia, hypotension, and worsening renal function, but no incremental benefit regarding HF hospital ization or cardiovascular mortality. Together, these data argue for a ceiling of benefit of angiotensin inhibition in HFrEF, beyond which further inhibition brings more adverse effects without additional effi cacy. Guidelines discourage the combination of an ACEI, ARB, and spironolactone in HFrEF due to the risks of hyperkalemia and renal dysfunction, and for patients, treatment with either an ACEI or ARB and spironolactone is deemed most appropriate. ■ ■ALTERNATIVE VASODILATORS The combination of hydralazine and nitrates has been demonstrated to improve survival in HFrEF. Hydralazine reduces systemic vascular resistance and induces arterial vasodilatation by affecting intracellular calcium kinetics; nitrates are transformed in smooth muscle cells into NO, which stimulates cyclic guanosine monophosphate produc tion and consequent arterial-venous vasodilation. This combination improves survival but to a lesser extent than ACEIs. However, in individuals with HFrEF unable to tolerate RAAS-based therapy for reasons such as renal insufficiency or hyperkalemia, this combina tion is preferred as a disease-modifying approach. A trial conducted in self-identified African Americans, the African-American Heart Failure Trial (A-HeFT), studied a fixed dose of isosorbide dinitrate with hydralazine in patients with advanced symptoms of HFrEF who were receiving standard background therapy including an ACEI and beta blocker. The study demonstrated improvements in survival and hospital admission for HF in the treatment group. Adherence to this regimen is limited by the thrice-daily dosing schedule. ■ ■NOVEL NEUROHORMONAL ANTAGONISTS Despite an abundance of animal and clinical data demonstrating

deleterious effects of activated neurohormonal pathways beyond the RAAS and sympathetic nervous system, targeting such pathways with incremental blockade has been largely unsuccessful. As an example, the endothelin antagonist bosentan is associated with worsening HF in HFrEF despite demonstrating benefits in right-sided HF due to pul monary arterial hypertension. Similarly, the centrally acting sympa tholytic agent moxonidine worsens outcomes in left HF. The combined drug omapatrilat hybridizes an ACEI with a neutral endopeptidase (neprilysin) inhibitor, and this agent was tested in the Omapatrilat

TABLE 265-2 Guideline-Directed Pharmacologic Therapy and Target Doses in Heart Failure with Reduced Ejection Fraction MEAN DAILY DOSE IN CLINICAL TRIALS (mg) INITIATION (mg) TARGET DOSE (mg) DRUG CLASS GENERIC DRUG Angiotensin-Converting Enzyme Inhibitors Lisinopril 4.5–33 2.5–5 qd 20–35 qd Enalapril

2.5 bid 10–20 bid Captopril

6.25 tid 50 tid Trandolapril N/A 0.5–1 qd 4 qd Angiotensin Receptor Blockers Losartan

50 qd 150 qd Valsartan

40 bid 160 bid Candesartan

4–8 qd 32 qd Aldosterone Antagonists Eplerenone 42.6 25 qd 50 qd Spironolactone

12.5–25 qd 25–50 qd Beta Blockers Metoprolol succinate CR/XL

12.5–25 qd 200 qd Carvedilol

3.125 bid 25–50 bid Bisoprolol 8.6 1.25 qd 10 qd Arteriovenous Vasodilators Hydralazine isosorbide dinitrate 270/136 37.5/20 tid 75/40 tid Fixed-dose hydralazine/isosorbide dinitrate 143/76 37.5/20 qid 75/40 qid Angiotensin Receptor-Neprilysin Inhibitor Sacubitril-valsartan

100 bid 200 bid SGLT-2 Inhibitor Dapagliflozin Empagliflozin Sotagliflozin

Novel Therapies Vericiguat (sGC stimulator) 9.2 2.5 qd 10 qd Omecamtiv mecarbil (myosin activator) Not reported 25 bid Up to 50 mg bid (based on plasma concentrations) Abbreviations: sGC, soluble guanylyl cyclase; SGLT-2, sodium-glucose cotransporter 2. Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial. This drug did not favorably influence the primary outcome measure of the combined risk of death or hospitalization for HF requiring intravenous treatment compared with enalapril alone, and notably, the risk of angioedema was increased in patients assigned to omapatrilat. The risk of angioedema with composite ACE/neprilysin inhibition appears to be related to excessive blockade of bradykinin breakdown by this combination. Blockade of angiotensin at the receptor level with an ARB leaves the ACE pathway for bradykinin breakdown intact and is associated with lower angioedema risk. Recently, a composite ARNI, sacubitril-valsartan (formerly LCZ696), was developed and applied to the treatment of patients with HFrEF. In the PARADIGM-HF trial, 8399 patients with HFrEF treated with guideline-directed medical therapy were randomly allocated to treatment with either enalapril or sacubitril-valsartan after a run-in period designed to ensure tolerabil ity of both drugs at target

doses. Compared to those assigned to enala pril, patients assigned to sacubitril-valsartan experienced a dramatic 20% reduction in the composite primary endpoint of cardiovascular death or HF hospitalization and a 16% reduction in all-cause mortal ity, as well as clinically important improvements in QOL measures. Sacubitril-valsartan was well tolerated and associated with lower rates of hyperkalemia and worsening renal function, but greater rates of symptomatic hypotension, than enalapril. Guidelines now advocate a switch to ARNI for patients with symptomatic HFrEF who tolerate ACEIs and ARBs, and emerging data suggest that up-front utilization of ARNI in patients with de novo HF naïve to ACEIs/ARBs may also

 be appropriate for those with adequate blood pressure to tolerate it. Given ongoing concern for angioedema, use of ARNI is contraindi cated in patients with prior history of angioedema, and those being transitioned from ACEIs should receive ARNI only after a 36-h gap to limit the risk of overlap. Table 265-2 lists the common neurohormonal and vasodilator regimens for HFrEF. ■ ■HEART RATE MODIFICATION Distinct from β-adrenergic receptor blockers, ivabradine, an inhibi tor of the If current in the sinoatrial node, selectively reduces heart rate without affecting cardiac contractility or vascular tone. The Systolic Heart Failure Treatment with Ivabradine Compared with Placebo Trial (SHIFT) was conducted in patients with NYHA class II or III HFrEF, prior HF hospitalization, sinus rhythm, and heart rate >70 beats/min. Ivabradine reduced the combined endpoint of cardiovascular-related death and HF hospitalization in proportion to the degree of heart rate reduction, which supports the notion that heart rate may be a therapeutic target in patients with HFrEF in sinus rhythm. Importantly, despite a protocol requirement for patients to be treated with a maximally tolerated dose of a beta blocker prior to study entry, 10% of patients randomized were not treated with a beta blocker, and 75% were treated at subtarget doses. Accordingly, it remains unclear whether this agent would have been effective in patients receiving robust, guideline-recommended therapy for HF; however, these data do support the potential value of ivabradine as an adjunct or alternative in those who are intolerant to initiation or dose titration of beta blockers. Clinical guidelines have been adapted

to encourage consideration of ivabradine in patients with HFrEF who remain symptomatic after treatment with guideline-based ACEI/ARB/ ARNIs, beta blockers, and mineralocorticoid receptor antagonists; are in sinus rhythm; and have a residual heart rate >70 beats/min.

■ ■SGLT-2 INHIBITION Inhibitors of SGLT-2 have been shown to reduce cardiovascular events and mortality among patients with type 2 diabetes mellitus at high cardiovascular risk or with established atherosclerotic cardiovascular disease. A particular signal of benefit has been seen regarding the inci dence of HF hospitalization, which was reduced by 35% in comparison to placebo in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOMES) study. Because the cardiovascular benefits of SGLT-2 inhibition appear to be unrelated to the degree of reduction in hemoglobin A1c, it has been postulated that the HF benefits of this therapy might be extended to patients without diabetes mellitus. Recently, the Dapagliflozin in Heart Failure (DAPA-HF) study randomized 4744 patients with symptom atic HFrEF treated with guideline-directed medical therapy (includ ing a beta blocker, ACEI/ARB/ARNI, and spironolactone in >70% of patients) to treatment with either the SGLT-2 inhibitor dapagliflozin (dosage 10 mg daily) or placebo over a median duration of followup of 18.2 months. Patients allocated to dapagliflozin experienced a highly significant 26% reduction in the primary composite

endpoint of worsening HF or death from cardiovascular causes, an effect that was consistent in both patients with (42%) and without diabetes mellitus at baseline. These results have been reinforced by the results of the EMPEROR-Reduced trial, in which 3730 patients with symptomatic HF and EF of ≤40% were randomized to treatment with empagliflozin (dosage 10 mg once daily) or placebo in addition to recommended therapy. Over a median 16-month follow-up, patients allocated to empagliflozin experienced a 25% reduction in the primary composite endpoint of cardiovascular death or hospitalization for HF, an effect that was again consistent regardless of the presence or absence of diabetes mellitus. Together, these studies have driven consensus guide lines to consider use of SGLT-2 inhibitors as foundational therapy for HF alongside ARNIs, beta blockers, and mineralocorticoid receptor antagonists. PART 6 Disorders of the Cardiovascular System ■ ■SOLUBLE GUANYLYL CYCLASE STIMULATION Soluble guanylyl cyclase (sGC) is a key enzyme of the NO signaling pathway that catalyzes synthesis of cyclic guanosine monophosphate (GMP), producing vasodilation. Vericiguat is a novel oral sGC stimu lator that enhances cyclic GMP and NO signaling by directly stimu lating sGC and sensitizing sGC to endogenous NO. The Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) randomly assigned 5050 patients with chronic HF, NYHA class II–IV symptoms, LVEF <45%, elevated natriuretic peptide levels, and evidence of worsening HF (requiring recent hospi talization or intravenous diuretic therapy) despite guideline-directed medical therapy to treatment with vericiguat (target dose 10 mg) or matching placebo over a median follow-up of 11 months. The primary study results were notable for a modest 10% relative risk reduction in the primary composite outcome of cardiovascular death or HF hospitalization among those assigned to vericiguat, an effect driven principally by effects on HF hospitalization, rather than cardiovas cular death. As vericiguat was generally well tolerated with a low rate of serious adverse events, these data suggest a potential role for sGC stimulation as an adjunct to guideline-directed medical therapy in the high-risk group of HFrEF patients with recent congestive exacerba tions requiring treatment, although these data await further review by regulatory agencies and guidelines committees. ■ ■MYOSIN ACTIVATION A novel approach to augmentation of cardiac output is to prolong ventricular systole without increasing myocardial contractility. As a selective myosin activator, omecamtiv mecarbil prolongs the ejection period and increases fractional shortening without altering the force of contraction. This agent, distinct from inotropic agents, is not asso ciated with an increase in myocardial oxygen demand. Importantly,

the drug is available for oral, rather than intravenous, administration, enabling chronic use in the ambulatory setting. In the COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) trial of 448 patients with chronic HF and left ventricular systolic dysfunction, treatment with omecamtiv mecarbil for 20 weeks was associated with significant improvements in cardiac function and indices of left ventricular remodeling, as well as reductions in natriuretic peptide levels. Notably, the safety profile was comparable to placebo, with no increase in cardiac adverse events despite a mod est increase in cardiac troponins in patients allocated to omecamtiv mecarbil. These promising preliminary data fueled a larger clinical outcomes trial (GALACTIC-HF), in which 8256 patients with symp tomatic chronic HF and EF of ≤35% were randomized to treatment with omecamtiv mecarbil (25–50 mg twice daily based on plasma levels) or placebo in addition to standard HF therapy. Over a median follow-up of 21.8 months, patients allocated to omecamtiv mecarbil experienced a 14% reduction in the primary composite endpoint of death from cardiovascular causes or first HF event (hospitalization or urgent visit for HF), an outcome driven principally by reduction in HF events (no measurable effect on cardiovascular

death alone). A pos sible signal of greater benefit in patients with features of advanced HF (lower EF, higher natriuretic peptide levels, more severe symptoms) combined with a favorable safety and tolerability profile suggests a possible role for this agent in patients with late-stage disease, although additional study is needed. ■ ■DIGOXIN Digitalis glycosides exert a mild inotropic effect, attenuate carotid sinus baroreceptor activity, and are sympatho-inhibitory. These effects decrease serum norepinephrine levels, plasma renin levels, and pos sibly aldosterone levels. The Digitalis Investigation Group (DIG) trial demonstrated a reduction in HF hospitalizations in the treatment group (patients with HF and sinus rhythm) but no reduction in mor tality or improvement in QOL. Importantly, treatment with digoxin resulted in a higher mortality rate and hospitalizations in women than men. It should be noted that low doses of digoxin are sufficient to achieve any potentially beneficial outcomes, and higher doses breach the therapeutic safety index. Although digoxin levels should be checked to minimize toxicity and although dose reductions are indi cated for higher levels, no adjustment is made for low levels. Generally, digoxin is now relegated as late-line therapy for patients who remain profoundly symptomatic despite optimal neurohormonal blockade and adequate volume control. ■ ■ORAL DIURETICS Neurohormonal activation results in avid salt and water retention. Diuretic therapy is typically required in patients with symptomatic HF to remedy congestive symptoms as a prelude to initiation and titration of neurohormonal therapy. Because of their potent effect on renal sodium excretion, loop diuretic agents are the preferred agents, with thiazide diuretics reserved for use in combination with loop diuretics for those with refractory volume overload. Frequent dose adjustments of loop diuretics may be necessary during longitudinal follow-up of patients with HF because of variable oral absorption and fluctuations in renal function. Patients who fail to respond to furosemide at high doses may benefit from transition to torsemide or bumetanide, which have greater oral bioavailability, but recent studies have not confirmed a greater benefit for alternatives to furosemide as a loop diuretic. Importantly, clinical trial data confirming efficacy are limited, and no data suggest that these agents improve survival. Since loop diuretics do enhance neurohumoral activation, dosing should be minimized as possible to maximize the balance of risk and benefit. ■ ■CALCIUM CHANNEL ANTAGONISTS Amlodipine and felodipine, second-generation calcium channel– blocking agents, safely and effectively reduce blood pressure in HFrEF but do not affect morbidity, mortality, or QOL. The first-generation agents, including verapamil and diltiazem, may exert negative inotro pic effects and destabilize previously asymptomatic patients. Accord ingly, their use should be discouraged in patients with HFrEF.

■ ■ANTI-INFLAMMATORY THERAPY Targeting inflammatory cytokines such as tumor necrosis factor α (TNF-α) for the management of HF by using anticytokine agents such as infliximab and etanercept has been unsuccessful and associated with worsening HF. Use of intravenous immunoglobulin therapy in nonischemic etiology of HF has not been shown to result in beneficial outcomes. Nonspecific immunomodulation has been tested in the Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy (ACCLAIM-HF) trial where ex vivo exposure of a blood sample from systolic HF patients to controlled oxidative stress was hypothesized to initiate apoptosis of leukocytes soon after intramuscular gluteal injection of the treated sample. The physiologic response to apoptotic cells results in a reduction in inflammatory cytokine production and upregulation of anti-inflammatory cyto kines. This promising hypothesis was not proven, although certain subgroups (those with no history of previous myocardial infarction and those with mild HF) showed signals in favor of immunomodula tion. Most recently, in the Canakinumab Anti-inflammatory Throm bosis Outcomes Study (CANTOS), treatment of post–myocardial infarction patients with elevated high-sensitivity C-reactive protein using a monoclonal antibody targeted at

interleukin 1β was associ ated with a dose-dependent reduction in hospitalization for HF and HF-associated mortality in post hoc analyses. Whether this approach might have relevance for patients with established HF remains unclear. ■ ■HMG-CoA REDUCTASE INHIBITORS (STATINS) Potent lipid-altering and pleiotropic effects of statins reduce major cardiovascular events and improve survival in non-HF populations. Once HF is well established, this therapy may not be as beneficial and theoretically could even be detrimental by depleting ubiquinone in the electron transport chain. Two trials, Controlled Rosuvastatin Mul tinational Trial in Heart Failure (CORONA) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiac (GISSI-HF), have tested low-dose rosuvastatin in patients with HFrEF and demon strated no improvement in aggregate clinical outcomes. If statins are required to treat progressive atherosclerotic vascular disease or signifi cant dyslipidemia in the background setting of HF, then they should be employed. However, no clear rationale appears to exist for routine use of statin therapy in nonischemic HF. ■ ■ANTICOAGULATION AND ANTIPLATELET THERAPY HFrEF is accompanied by a hypercoagulable state and therefore a high risk of thromboembolic events, including stroke, pulmonary embolism, and peripheral arterial embolism. Although the value of long-term oral anticoagulation is established in certain groups, including patients with atrial fibrillation, the data are insufficient to support the use of warfarin in patients in normal sinus rhythm without a history of thromboembolic events or echocardiographic evidence of left ventricular thrombus. In the large Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, full-dose aspi rin or international normalized ratio–controlled warfarin was tested with follow-up for 6 years. Among patients with reduced LVEF in sinus rhythm, there was no significant overall difference in the pri mary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. A recent trial of the direct oral anticoagulant rivaroxaban at low dose (2.5 mg daily) for patients with ischemic heart disease, HFrEF, and sinus rhythm also indicated no reduction in stroke or ischemic events compared with placebo. Aspirin blunts ACEI-mediated prostaglandin synthesis, but the clini cal importance of this finding remains unclear. Current guidelines support the use of aspirin in patients with ischemic cardiomyopathy who do not have a contraindication, although the risk-benefit balance in older patients at higher risk for bleeding complications may be less favorable. ■ ■FISH OIL Treatment with long-chain omega-3 polyunsaturated fatty acids (ω-3 PUFAs) has been shown to be associated with modestly improved

clinical outcomes in patients with HFrEF. This observation from the GISSI-HF trial was extended to measurements of ω-3 PUFAs in plasma phospholipids at baseline and after 3 months. Three-month treatment with ω-3 PUFAs enriched circulating eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Low EPA levels are inversely related to total mortality in patients with HFrEF.

CHAPTER 265 ■ ■MICRONUTRIENTS A growing body of evidence suggests an association between HF and micronutrient status. Reversible HF has been described because of severe thiamine and selenium deficiency. Thiamine deficiency has received attention in HF because malnutrition and diuretics are prime risk factors for thiamine loss. Small exploratory randomized studies have suggested a benefit of supplementation with thiamine in HFrEF with evidence of improved cardiac function. This finding is restricted to chronic HF states and does not appear to be beneficial in the ADHF phenotype. Due to the exploratory nature of the evidence, no recom mendations for routine supplementation or testing for thiamine defi ciency can be made. Heart Failure: Management ■ ■ENHANCED EXTERNAL COUNTERPULSATION Peripheral lower extremity therapy using graded

external pneumatic compression at high pressure is administered in 1-h sessions for 35 treatments (7 weeks) and has been proposed to reduce angina symp toms and extend time to exercise-induced ischemia in patients with coronary artery disease. The Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH) study assessed the benefits of enhanced external counterpulsation in the treatment of patients with mild-to-moderate HF. This random ized trial improved exercise tolerance, QOL, and NYHA functional classification but without an accompanying increase in peak oxygen consumption. A placebo effect due to the nature of the intervention simply cannot be excluded. ■ ■EXERCISE The Heart Failure: A Controlled Trial Investigating Outcomes of Exer cise Training (HF-ACTION) study investigated short-term (3-month) and long-term (12-month) effects of a supervised exercise train ing program in patients with moderate HFrEF. Exercise was safe, improved patients' sense of well-being, and correlated with a trend toward mortality reduction. Maximal changes in 6-min walk distance were evident at 3 months with significant improvements in cardiopul monary exercise time and peak oxygen consumption persisting at 12 months. Therefore, exercise training is recommended as an adjunctive treatment in patients with HF. ■ ■MANAGEMENT OF SELECTED COMORBIDITY Sleep-disordered breathing is common in HF and particularly in HFrEF. A range of presentations exemplified by obstructive sleep apnea, central sleep apnea, and its extreme form of Cheyne-Stokes breathing are noted. Frequent periods of hypoxia and repeated micro- and macro-arousals trigger adrenergic surges, which can worsen hypertension and impair systolic and diastolic function. A high index of suspicion is required, especially in patients with difficult-to-control hypertension or with predominant symptoms of fatigue despite reverse remodeling in response to optimal medical therapy. Worsening of right heart function with improvement of left ventricular function noted on medical therapy should immediately trigger a search for underlying sleep-disordered breathing or pulmonary complications such as occult embolism or pulmonary hypertension. Treatment with nocturnal positive airway pressure improves oxygenation, LVEF, and 6-min walk distance. However, no conclusive data exist to support this therapy as a disease-modifying approach with reduction in mortality. A recent trial using adaptive servo-ventilation triggered by a minute ventilation sensor in patients who had HFrEF and predominantly central sleep apnea increased all-cause and cardiovascular mortality, so this approach should be avoided; however, modification of this approach using lower background pressures and an alternative trigger based on peak airflow appeared to be safe in patients with sleep apnea and HFrEF enrolled in the ADVENT-HF trial, although there was

no discernible benefit with regard to clinical outcomes. Whether this modified approach to adaptive servo-ventilation will be appropriate for management of selected patients with HFrEF and central sleep apnea requires further study.

Anemia is common in HF patients, reduces functional status and QOL, and is associated with increased proclivity for hospital admis sions and mortality. Anemia in HF is more common in the elderly, in those with advanced stages of HFrEF, in the presence of renal insuf ficiency, and in women and African Americans. The mechanisms include iron deficiency, dysregulation of iron metabolism, and occult gastrointestinal bleeding. Intravenous iron using either iron sucrose or carboxymaltose (Ferric Carboxymaltose Assessment in Patients with Iron Deficiency and Chronic Heart Failure [FAIR-HF] trial) has been shown to correct anemia and improve functional capacity. Another trial, CONFIRM-HF, enrolled similar patients with iron deficiency (ferritin <100 ng/mL or 100–300 ng/mL if transferrin saturation <20%) and demonstrated that use of ferric carboxymaltose

in a simplified high-dose schedule resulted in improvement in functional capacity, symptoms, and QOL. These symptomatic benefits of iron repletion, however, do not appear to translate clearly to benefits on longer term clinical outcomes. In the AFFIRM-AHF trial of patients with HF, LVEF <50%, and iron deficiency, randomization to ferric carboxymaltose compared with placebo was associated with a lower rate of cardio vascular death and total HF hospitalizations that narrowly missed the margin for statistical significance. Similar results were seen in the IRONMAN trial of another iron polysaccharide, ferric derisomaltose. The results of both of these trials may have been confounded by the coronavirus disease 2019 (COVID-19) pandemic, and pooled data suggested a possible favorable effect on HF hospitalizations. However, the HEART-FID trial, which randomized 3065 ambulatory HF patients with LVEF ≤40% and iron deficiency to treatment with ferric carboxy maltose or placebo, showed no benefit with regard to the primary hierarchical composite of death, hospitalizations for HF, or 6-minute walk distance. Accordingly, it seems that benefits of iron repletion in this population are likely confined to reduction in symptoms, and perhaps HF hospitalizations, particularly among those with iron defi ciency. Oral iron supplementation does not appear to be effective in treating iron deficiency in HF. Erythropoiesis-regulating agents such as erythropoietin analogues have been studied with disappointing results. The Reduction of Events by Darbepoetin Alfa in Heart Failure (REDHF) trial demonstrated that treatment with darbepoetin alfa did not improve outcomes in patients with systolic HF but increased the risk of thromboembolism-related adverse events. PART 6 Disorders of the Cardiovascular System Depression is common in HFrEF, with a reported prevalence of one in five patients, and is associated with a poor QOL, limited functional status, and increased risk of morbidity and mortality in this popula tion. However, the largest randomized study of depression in HFrEF, the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) trial, showed that although sertraline was safe, it did not provide greater reduction in depression or improve car diovascular status among patients with HF and depression compared with nurse-driven multidisciplinary management. Atrial arrhythmias, especially atrial fibrillation, are common and serve as a harbinger of worse prognosis in patients with HF. When rate control is inadequate or symptoms persist, pursuing a rhythm control strategy is reasonable. Rhythm control may be achieved via pharmacotherapy or by percutaneous or surgical techniques, and referral to practitioners or centers experienced in these modalities is recommended. Antiarrhythmic drug therapy should be restricted to amiodarone and dofetilide, both of which have been shown to be safe and effective but do not alter the natural history of the underlying disease. The Antiarrhythmic Trial with Dronedarone in Moderateto-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) studied the effects of the novel antiarrhythmic agent dronedarone and found an increased mortality due to worsening HF. Given the potential adverse effects and limited efficacy of pharma cologic strategies for maintenance of sinus rhythm, catheter ablation has been explored as an alternative. In the CASTLE-AF trial, among

363 patients with HF, LVEF ≤35%, and paroxysmal or persistent atrial fibrillation randomized to treatment with catheter ablation or medical therapy, those assigned to catheter ablation experienced a significantly lower rate of death or hospitalization. These results are supported by similar outcomes in the CASTLE-HTX trial, which sought to include patients with advanced HF; however, this aspect is disputed. These data argue for consideration of restoration of sinus rhythm with catheter ablation as a preferred strategy to antiarrhythmic drugs in patients with HF and reduced EF. Diabetes mellitus is a frequent comorbidity in HF. Prior stud ies using thiazolidinediones (activators of peroxisome proliferatoractivated receptors) have been associated

with worsening HF. GLP-1 agonists such as liraglutide have also been tested and do not lead to worsening in HF but require more study. The role of SGLT-2 inhibitors in HF has been previously discussed, and they represent an important disease-modifying therapy in diabetic patients with HF. ■ ■NEUROMODULATION USING DEVICE THERAPY Autonomic dysfunction is common in HF, and attempts at using devices to modulate the sympathetic and parasympathetic systems have been undertaken. Broadly, devices that achieve vagal nerve stimulation, baroreflex activation, renal sympathetic denervation, spinal cord stimulation, or left cardiac sympathetic denervation have been employed. While small preclinical and clinical studies have dem onstrated benefits, large, randomized trials, when conducted, have failed. The INOVATE-HF study tested vagal nerve stimulation versus optimal medical therapy among individuals with stable HF. Vagus nerve stimulation did not reduce the rate of death or hospitalization for HF. However, functional capacity and QOL were favorably affected by vagus nerve stimulation. The ANTHEM-HFrEF trial, which enrolled only half its intended population, did not show a signal for benefit of vagal nerve stimulation. ■ ■CARDIAC CONTRACTILITY MODULATION Cardiac contractility modulation (CCM) is a device-based therapy for HF that involves nonexcitatory electrical stimulation to the right ven tricular septal wall during the absolute myocardial refractory period to augment the strength of subsequent myocardial contraction. A series of small, randomized, prospective clinical trials, as well as several realworld observational registries, have suggested that application of CCM to selected patients with HF may improve symptoms, functional capac ity, and QOL, although no effect on hard clinical outcomes such as HF hospitalization or mortality has been established. The predominant benefits of CCM appear to accrue to those with symptomatic HFrEF (EF 25–45%) and narrow QRS duration (for whom cardiac resynchro nization therapy is not an option), and the approach can be combined with an implantable defibrillator. The device is not currently endorsed for routine use by clinical treatment guidelines in the United States or Europe and is deemed to require more evidence prior to widespread adoption. CARDIAC RESYNCHRONIZATION THERAPY Nonsynchronous contraction between the walls of the left ventricle (intraventricular) or between the ventricular chambers (interven tricular) impairs systolic function, decreases mechanical efficiency of contraction, and adversely affects ventricular filling. Mechanical dys synchrony results in an increase in wall stress and worsens functional mitral regurgitation. The single most important association of extent of dyssynchrony is a widened QRS interval on the surface electrocardio gram, particularly in the presence of a left bundle branch block pattern. With placement of a pacing lead via the coronary sinus to the lateral wall of the ventricle, cardiac resynchronization therapy (CRT) enables a more synchronous ventricular contraction by aligning the timing of activation of the opposing walls. Early studies showed improved exercise capacity, reduction in symptoms, and evidence of reverse remodeling. The Cardiac Resynchronization in Heart Failure Study (CARE-HF) trial was the first study to demonstrate a reduction in allcause mortality with CRT placement in patients with HFrEF on opti mal therapy with continued moderate-to-severe residual symptoms of

NYHA class III or IV HF. More recent clinical trials have demonstrated disease-modifying properties of CRT in even minimally symptomatic patients with HFrEF, including the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Ther apy (MADIT-CRT), both of which sought to use CRT in combination with an implantable defibrillator. Most benefit in mildly symptomatic HFrEF patients accrues from applying this therapy in those with a QRS width of >149 ms and a left bundle branch block pattern. Attempts to further optimize risk stratification and expand indications for CRT using modalities other than electrocardiography have proven disap

pointing. Echocardiographically derived measures of dyssynchrony vary tremendously, and narrow QRS dyssynchrony has not proven to be a good target for treatment. Uncertainty surrounds the benefits of CRT in those with ADHF, a predominant right bundle branch block pattern, atrial fibrillation, and evidence of scar in the lateral wall, which is the precise location where the CRT lead is positioned. His-Purkinje conduction system or left bundle branch area pacing are evolving alter natives to biventricular pacing; however, the evidence supporting their benefits over conventional CRT remains less certain. SUDDEN CARDIAC DEATH PREVENTION IN HEART FAILURE Sudden cardiac death (SCD) due to ventricular arrhythmias is the mode of death in approximately half of patients with HF and is par ticularly proportionally prevalent in HFrEF patients with early stages of the disease. Patients who survive an episode of SCD are at very high risk and qualify for placement of an implantable cardioverterdefibrillator (ICD). Although primary prevention is challenging, the degree of residual left ventricular dysfunction despite optimal medical therapy (≤35%) to allow for adequate remodeling and the underlying etiology (post–myocardial infarction or ischemic cardiomyopathy) are the two single most important risk markers for stratification of need and benefit. Currently, patients with NYHA class II or III symptoms of HF and an LVEF <35%, irrespective of etiology of HF, are appropriate candidates for ICD prophylactic therapy. In patients with a myocardial infarction and optimal medical therapy with residual LVEF ≤30% (even when asymptomatic), placement of an ICD is appropriate. A recent Danish trial suggested that prophylactic ICD implantation in patients with symptomatic systolic HF not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care. In this trial, benefits were noted in those aged <60 years. In patients with a terminal illness and a predicted life span of <6 months or in those with NYHA class IV symptoms who are refractory to medications and who are not candi dates for transplant, the risks of multiple ICD shocks must be carefully weighed against the survival benefits. If a patient meets the QRS crite ria for CRT, combined CRT with ICD is often employed (Table 265-3). SURGICAL THERAPY IN HEART FAILURE Coronary artery bypass grafting (CABG) is considered in patients with ischemic cardiomyopathy with multivessel coronary artery disease. The recognition that hibernating myocardium, defined as myocardial tissue with abnormal function but maintained cellular function, could recover after revascularization led to the notion that revascularizа tion with CABG would be useful in those with living myocardium. Revascularization is most robustly supported in individuals with ongoing angina and left ventricular failure. Revascularizing those with left ventricular failure in the absence of angina remains controversial. The Surgical Treatment for Ischemic Heart Failure (STICH) trial in patients with an EF of ≤35% and coronary artery disease amenable to CABG demonstrated no significant initial benefit compared to medi cal therapy. However, patients assigned to CABG had lower rates of death from cardiovascular causes and of death from any cause or hos pitalization for cardiovascular causes over 10 years than among those who received medical therapy alone. An ancillary study of this trial also determined that the detection of hibernation (viability) before revascularization did not materially influence the efficacy of this

TABLE 265-3 Principles of ICD Implantation for Primary Prevention of Sudden Death PRINCIPLE COMMENT Arrhythmia–sudden death mismatch Sudden death in heart failure patients is generally due to progressive LVD, not a focal arrhythmia substrate (except in patients with post-MI HF with scar) CHAPTER 265 Diminishing returns with advanced disease Intervention at early stages of HF most successful since sudden death incidence diminishes as cause of death with increasing severity of HF Timing of benefits LVEF should be evaluated on optimal medical therapy or after

revascularization before ICD therapy is employed; no benefit to ICD implant within 40 days of an MI (unless for secondary prevention) Heart Failure: Management Estimation of benefits and prognosis Patients and clinicians often overestimate benefits of ICDs; an ICD discharge is not equivalent to an episode of sudden death (some ventricular arrhythmias terminate spontaneously); appropriate ICD discharges are associated with a worse near-term prognosis; recent trials with uncertain benefit in nonischemic cardiomyopathy (especially in those >68 years old) Abbreviations: HF, heart failure; ICD, implantable cardioverter-defibrillator; LVD, left ventricular disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction. approach, nor did it help to define a population unlikely to benefit if hibernation was not detected. Notably, a strategy of percutaneous cor onary revascularization in patients with ischemic left ventricular dys function in the REVIVED-BCIS2 study did not show clinical benefit. Surgical ventricular restoration (SVR), a technique character ized by infarct exclusion to remodel the left ventricle by reshaping it surgically in patients with ischemic cardiomyopathy and dominant anterior left ventricular dysfunction, has been proposed. However, in a 1000-patient trial in patients with HFrEF who underwent CABG alone or CABG plus SVR, the addition of SVR to CABG had no disease-modifying effect. However, left ventricular aneurysm surgery is still advocated in those with refractory HF, ventricular arrhythmias, or thromboembolism arising from an akinetic aneurysmal segment of the ventricle. Other remodeling procedures, such as use of an external mesh-like net attached around the heart to limit further enlargement, have not been shown to provide hard clinical benefits, although favor able cardiac remodeling was noted. Functional (or secondary) mitral regurgitation (MR) occurs with varying degrees in patients with HFrEF and dilated ventricles, and its severity is correlated inversely with prognosis. Annular dilatation and leaflet noncoaptation related to distorted papillary muscle geom etry in the context of ventricular remodeling is typically responsible, although in patients with ischemic heart disease and prior myocardial infarction, leaflet tethering and displacement may contribute. The primary approach to management of functional MR is optimization of guideline-directed medical therapy, followed by CRT in eligible patients, but relief may be incomplete for many patients with advanced HF. In these patients with HF and severe left ventricular dysfunc tion who are not candidates for surgical coronary revascularization, surgical mitral valve repair (MVR) to remedy functional MR car ries significant risk and remains controversial. The development of percutaneous approaches to edge-to-edge MVR has provided a less invasive approach that enables reduction in functional MR at lower risk than conventional surgery. Recently, two large, randomized tri als of transcatheter MVR using this approach have been conducted in patients with symptomatic HFrEF and moderate-severe functional MR. In the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) study, patients allocated to MVR versus standard HF therapy experienced a marked reduction in both HF hospitalizations and mortality at 2 years, supporting the efficacy of this approach. In the second trial, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgi tation (MITRA-FR), which employed a similar design, the rates of

death or HF hospitalization did not differ between the percutaneous MVR and medical therapy groups. The precise reason for discrepant results between these studies remains unclear but may be related to differences in background utilization of guideline-directed medical therapy, procedural success rates, and patient selection (particularly whether the severity of MR is proportionate or disproportionate to the degree of left ventricular cavity dilation). Because mortality rates at 2 years remain high even with percutaneous MVR, patients with advanced symptoms of HF in whom MR severity is driven principally by end-stage left ventricular remodeling

should also be considered for advanced therapies such as mechanical circulatory support if symp toms remain refractory to medical therapy.

PART 6 Disorders of the Cardiovascular System CELLULAR AND GENE-BASED THERAPY The cardiomyocyte possesses regenerative capacity, and such renewal is accelerated under conditions of stress and injury, such as an isch emic event or HF. Investigations that use either bone marrow–derived precursor cells or autologous cardiac-derived cells have gained trac tion but have not generally improved clinical outcomes in a convinc ing manner. More promising, however, are cardiac-derived stem cells. Two preliminary pilot trials delivering cells via an intracoronary approach have been reported. In one, autologous c-kit–positive cells isolated from the atria obtained from patients undergoing CABG were cultured and reinfused. In another, cardiosphere-derived cells grown from endomyocardial biopsy specimens were used. These small trials demonstrated improvements in left ventricular function but require far more work to usher in a clinical therapeutic success. Efforts to utilize mesenchymal stem cells to facilitate left ventricular recovery and weaning from mechanical circulatory support in patients with left ventricular assist devices have also been disappointing. The appropri ate route of administration, the quantity of cells to achieve a minimal therapeutic threshold, the constitution of these cells (single source or mixed), the mechanism by which benefit accrues, and short- and longterm safety remain to be elucidated. Targeting molecular aberrations using gene transfer therapy, mostly with an adenoviral vector, has been tested in HFrEF. A cel lular target includes calcium cycling proteins such as inhibitors of phospholamban such as SERCA2a, which is deficient in patients with HFrEF. Primarily responsible for reincorporating calcium into the sarcoplasmic reticulum during diastole, this target was tested in the CUPID (Efficacy and Safety Study of Genetically Targeted Enzyme Replacement Therapy for Advanced Heart Failure) trial. This study used coronary arterial infusion of adeno-associated virus type 1 carrying the gene for SERCA2a and initially demonstrated that natriuretic peptides were decreased, reverse remodeling was noted, and symptomatic improvements were forthcoming. However, a confirmatory trial failed to meet its primary efficacy endpoint. The DREAM-HF trial was a randomized, double-blind, multicenter study of a single transendocardial administration of mesenchymal precur sor cells in patients in HFrEF. The primary and secondary endpoints of the trial were negative. More advanced therapies for late-stage HF such as left ventricu lar assist devices and cardiac transplantation are covered in detail in Chap. 271. DISEASE MANAGEMENT AND SUPPORTIVE CARE Despite stellar outcomes with medical therapy, admission rates fol lowing HF hospitalization remain high, with nearly half of all patients readmitted to hospital within 6 months of discharge. Recurrent HF and related cardiovascular conditions account for only half of read missions in patients with HF, whereas other comorbidity-related conditions account for the rest. The key to achieving enhanced out comes must begin with the attention to transitional care at the index hospitalization with facilitated discharge through comprehensive discharge planning, patient and caregiver education, appropriate use of visiting nurses, and planned follow-up. Early postdischarge followup, whether by telephone or clinic-based, may be critical to ensuring

stability because most HF-related readmissions tend to occur within the first 2 weeks after discharge. The results of the recent STRONG-HF trial suggest that a strategy of intensive titration of medical therapy to guideline-recommended targets within 2 weeks of hospital discharge and frequent ambulatory follow-up through 2 months is associated with a substantial reduction in all-cause mortality and HF readmis sion at 180 days, underscoring the importance of timely application of targeted pharmacologic therapy and intensive clinical surveillance in the early

postdischarge interval. Although routinely advocated, intensive surveillance of weight and vital signs with use of telemonitoring has not decreased hospi talizations. Serial measurement of intrathoracic impedance has been utilized to identify early signals of worsening congestion to guide preemptive management to obviate the need for hospitalization. How ever, when systematically studied in randomized trials, this approach has not been proven to improve outcomes in comparison with routine HF care and may even enhance the rate of hospitalization due to the high frequency of impedance threshold crossings and device alerts. Implantable hemodynamic monitoring systems that directly measure pulmonary artery pressure tend to provide signals for early decom pensation, and in patients with HF and moderately advanced symp toms across the full spectrum of EF, such systems have been shown to provide information that can allow implementation of therapy to avoid hospitalizations by as much as 39% (in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients [CHAMPION] trial). More recently, in the larger Hemodynamic Guided Management of Heart Failure (GUIDE-HF) Trial, hemodynamic-guided management with the same sensor did not result in a lower rate of composite mortality and total HF events in the primary analysis, the results of which were confounded by the impact of the COVID-19 pandemic on overall hos pitalization rates. In a prespecified analysis of patients enrolled prior to the pandemic onset, there was a statistically significant reduction in the composite endpoint driven by lower rates of HF hospitalization in those assigned to the hemodynamic-guided therapy arm. Benefits were consistent across patients with prior HF hospitalization within 12 months and in those with elevated natriuretic peptide levels but no recent hospitalization. These data in aggregate suggest that hemody namic-guided management is a useful adjunct to routine clinical care in selected high-risk patients with chronic HF across the spectrum of EF. Alternate approaches to longitudinal HF monitoring that lever age multiparameter signals derived from implantable cardiac rhythm devices such as pacemakers and defibrillators to provide a global index of congestion are also being explored as adjuncts to longitudinal HF management. Once HF becomes advanced, regularly scheduled review of the disease course and options with the patient and family is recom mended, including discussions surrounding end-of-life preferences when patients are comfortable in an outpatient setting. As the disease state advances further, integrating care with social workers, pharma cists, and community-based nursing may be critical in improving patient satisfaction with the therapy, enhancing QOL, and avoid ing HF hospitalizations. Equally important is attention to seasonal influenza vaccinations and periodic pneumococcal vaccines that may obviate non-HF hospitalizations in these ill patients. When nearing end of life, facilitating a shift in priorities to outpatient and hospice palliation is key, as are discussions around advanced therapeutics and continued use of ICD prophylaxis, which may worsen QOL and prolong death. Small, randomized trials have suggested that systematic integration of palliative care considerations in high-risk HF patients by a specialized team has been demonstrated to improve QOL, anxiety, depression, and spiritual well-being and to facilitate goal-concordant care. GLOBAL CONSIDERATIONS Substantial differences exist in the practice of HF therapeutics and outcomes by geographic location. The penetrance of CRT and ICD is higher in the United States than in Europe. Conversely, therapy unavailable in the United States, such as levosimendan, is designated

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