Management of ACCF/AHA Stage C Heart Failure

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KEY POINTS

- American College of Cardiology Stage C heart failure (HF) includes those patients with prior or current symptoms of heart failure in the context of an underlying structural heart problem who are primarily managed with medical therapy.
- Although there is guideline-based medical therapy for those who have HF with reduced ejection fraction (HFrEF), therapies in heart failure with preserved ejection fraction (HFpEF) have thus far proven elusive.
- Emerging therapies, such as serelaxin, are currently under investigation and may prove beneficial.
- The role of advanced surgical therapies, such as mechanical circulatory support, in this population is not well defined; further investigation is warranted for these therapies in patients with Stage C HF.

STAGE C HEART FAILURE

Heart failure (HF) terminology is varied and at times imprecise. Stage C HF, as described by the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) classification system, includes patients with structural heart disease with prior or current symptoms of HF. The 2 most widely used HF classification schemes are the previously mentioned ACCF/AHA system and the New York Heart Association (NYHA) functional classification. The ACCF/AHA staging system, however, emphasizes the development and progression of disease, whereas the NYHA classes focus on exercise capacity and the symptomatic status of the disease. Both these classifications are complementary, but increasingly the ACCF/AHA staging system is being used more commonly. The ACCF/AHA staging system includes asymptomatic stages (risk factors, structural heart disease), thereby underscoring the importance of preventive medicine, and reflecting the progressive nature of the HF syndrome. The stages are progressive, as a patient may progress from stage A to stage D, but cannot return to stage A. This is in contrast to the NYHA classification in which response or lack thereof to treatment can alter the functional status of a patient and therefore the NYHA class.

EDUCATION AND EXERCISE

One of the most important and challenging parts of HF management is educating the patient regarding adherence and compliance with medications, salt restriction, appropriate physical activity, lifestyle modifications, and weight loss. It is critical to educate patients on understanding their disease process, symptoms, fluid changes, and weight fluctuations. Readmission rates were significantly

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lower in patients who were educated in all 6 categories of the HF core measures from the Joint Commission on Accreditation of Healthcare Organizations.[1] Discharge education led to fewer days of hospitalization, lower cost, and lower mortality rates within a 6-month follow-up.[2]

Physical activity must be encouraged in patients with HF, similar to other cardiovascular (CV) diseases (**Table 1**). In those able to participate, regular physical activity and exercise is safe and effective and helps in improving functional status.[3–7] Exercise and rehabilitation improves endothelial function, increases peripheral oxygen extraction, and reduces hospital readmissions. Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, health-related quality of life, and mortality.[8,9]

SODIUM RESTRICTION

Sodium intake is related to hypertension, left ventricular (LV) hypertrophy, and CV disease. Physicians have therefore traditionally recommended dietary sodium restriction in patients with HF for decades. Reduction in dietary sodium reduces fluid retention and risk for hospitalizations.[10,11] The 2013 ACCF/AHA guidelines recommend restricting sodium to 1500 mg/d for patients with stage A and B HF and less than 3000 mg/d for patients with stage C and D HF (see **Table 1**). Some studies have signaled a worsening neurohormonal profile with sodium restriction in HF[12,13]; however, these patients did not receive optimal medical therapy at that time. Further studies are required to evaluate the effects of sodium restriction on neurohormonal activation and outcomes in optimally treated patients with HF.

OBESITY AND OBSTRUCTIVE SLEEP APNEA

People with body mass index (BMI) of 30 kg/m^2 or higher are considered obese. The "obesity paradox" is well known in HF, as patients with BMI between 30 and 35 kg/m^2 have lower mortality and hospitalization rates than those with a BMI in the normal range.[14] However, this is not maintained in morbidly obese patients whose BMI is more than 35 kg/m^2. Advanced HF can lead to higher total energy expenditure that may lead to weight loss, contributing to cardiac cachexia, which has been demonstrated to predict a worse prognosis.[15]

Obesity is a major risk factor for obstructive sleep apnea (OSA). The prevalence of OSA progressively increases as BMI and associated markers (eg, neck circumference, waist-to-hip ratio) increase. Patients with HF and OSA do not routinely present with excessive daytime sleepiness. Hence, clinical judgment is imperative in identifying these patients. Continuous positive airway pressure (CPAP) can be beneficial to increase left ventricular ejection fraction (LVEF) and improve functional status in patients with HF and sleep apnea.[3,16–18] CPAP has been demonstrated to decrease the apnea-hypopnea index, improve nocturnal oxygenation, increase LVEF, lower norepinephrine levels, and increase the distance walked in the 6-minute walk test in those with OSA. These benefits were sustained for up to 2 years.[17]

Table 1
2013 ACCF/AHA recommendations for nonpharmacologic treatment in stage C HF

Non-Pharmacologic Intervention	Class of Recommendation	Level of Evidence
Patients with HF should receive specific education to facilitate HF self-care	I	B
Sodium restriction in patients with symptomatic HF to reduce congestive symptoms	IIa	C
CPAP can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea	IIa	B
Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status	I	A
Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, HRQOL, and mortality	IIa	B

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CPAP, continuous positive airway pressure; HF, heart failure; HRQOL, health-related quality of life; LVEF, left ventricular ejection fraction.

PHARMACOLOGIC THERAPY

Recommendations for stage A and B HF hold true for stage C as well. These include evaluation and treatment of hypertension, lipid disorders, advocating cessation of substance abuse, including smoking, alcohol, and illicit drug usage, obtaining detailed family history to assess for a familial component, assessing sudden cardiac death (SCD) risk and assessment for structural heart disease, left ventricular hypertrophy (LVH), ischemia, and valvular heart disease as clinically indicated.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme inhibitors (ACE-I) decrease the conversion of angiotensin I to angiotensin II, thereby reducing the maladaptive effects of angiotensin II. Furthermore, there is a decrease in the breakdown of bradykinin, which promotes vasodilatation in the vascular endothelium and promotes natriuresis. Unless contraindicated, ACE inhibitors are recommended in all patients with HF with reduced ejection fraction (HFrEF).[19–21] ACE-Is reduce the risk of death and hospitalization in HFrEF patients (Table 2). ACE-Is are frequently used in conjunction with beta blockers (BB). ACE-Is are beneficial in ischemic and nonischemic cardiomyopathies, as well as in patients with HF with mild, moderate, or severe symptoms.

Table 2
Recommendations for the use of ACE-I

Treatment – Use of ACE-I	Class of Recommendation	Level of Evidence
ACE-I in patients with a history of MI and reduced EF to prevent HF	I	A
ACE-Is should be used in all patients with a reduced EF to prevent HF	I	A
ACE-I in HFrEF with current or prior symptoms	I	A

Recommendations summarized from current literature and data referenced in this article; see reference list.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; EF, ejection fraction; HF, heart failure; HFrEF, HF with reduced ejection fraction; MI, myocardial infarction.

Data supporting use of ACE inhibitors in HF dates back to more than 25 years ago when the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS-I) was reported in 1987 (Table 3).[22] In this trial, 253 patients in NYHA class IV HF were randomized to enalapril or placebo with

Table 3
ACE-I trials supporting current guideline recommendations

Study	Aim of Study	Baseline Therapy	Results
CONSENSUS,[22] 1987	Study the effect of enalapril on prognosis of NYHA class IV HF	Diuretics (spironolactone 53%), digitalis (93%), other; Vasodilators except ACE-I (nitrates 46%)	40% reduction in mortality at 6 mo ($P = .002$) 31% reduction in mortality at 1 y ($P = .001$)
SOLVD,[20] 1991	Study the effect of enalapril on mortality and hospitalization in patients with chronic HF and LVEF <35%	Diuretics and digoxin	16% reduction in mortality ($P = .0036$)
ATLAS,[23] 1999	To compare the efficacy and safety of low and high doses of ACE-I on the risk of death and hospitalization in chronic HF	Diuretics, digoxin, and vasodilators	High-dose ACE-I group: • 8% lower risk of all-cause mortality ($P = .128$) • 12% lower risk of death or hospitalization ($P = .002$) • 24% fewer hospitalizations for HF ($P = .002$)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

a 40% reduction in mortality demonstrated in the enalapril cohort. A 10-year follow-up to this study revealed a sustained 30% risk reduction in the enalapril group and a higher mortality among patients not receiving open ACE-I therapy.[24]

The SOLVD (Studies Of Left Ventricular Dysfunction) study randomized 2569 patients with symptomatic NYHA class II to III HF and ejection fraction of 35% or less to either placebo or enalapril. The predominant etiology was ischemic cardiomyopathy (72%). There was a 16% reduction in mortality demonstrated in the enalapril cohort.[20] In addition, the 12-year follow-up to the SOLVD study showed that enalapril extended median survival by 9.4 months in the combined SOLVD prevention and treatment trial.[25]

There are no significant differences among available ACE inhibitors in their effects on symptoms or survival.[21] Initial treatment usually begins with a low-dose ACE-I that is gradually uptitrated to goal doses used in clinical trials (**Table 4**).[20] If the target dose cannot be tolerated, then the maximum tolerable dose should be used for treatment. Serum potassium and creatinine should be assessed within 1 to 2 weeks of initiation of therapy and periodically thereafter.

Overall, ACE-Is are well tolerated. Adverse effects of ACE-Is are related to angiotensin suppression and kinin potentiation. ACE inhibitors are contraindicated in those who have experienced life-threatening adverse reactions (ie, angioedema) during previous medication exposure or if they are pregnant or plan to become pregnant. ACE inhibitors must also be avoided or used with extreme caution in patients with markedly increased serum creatinine (>3 mg/dL), bilateral renal artery stenosis, elevated levels of serum potassium (>5.0 mEq/L), and hypotension (systolic blood pressure <80 mm Hg). Other adverse effects include cough in up to 20% of the patients, rash and taste disturbances.

ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin II production continues in the presence of ACE inhibition, driven through alternative enzyme pathways. Angiotensin receptor blockers (ARBs) act by blocking the binding of angiotensin II to the AT1 receptor. ARBs are now considered an alternative to ACE-I as first-line drugs in patients with HFrEF. These agents are especially useful in patients who are ACE-I intolerant, as it does not lead to kinin production. Although the incidence of cough and angioedema are much lower compared with ACE-I, they have to be used cautiously, as these can be life-threatening as well.[26] As with ACE-I therapy, ARBs must be started at a low dose and uptitrated toward doses used in clinical trials (**Table 5**). The side effects of ARBs are from suppression of angiotensin stimulation. It is prudent to check renal function and potassium every week for the first 2 weeks and monthly thereafter.

ARBs have also been demonstrated to reduce mortality and morbidity in those who are already on an ACE inhibitor and a BB and do not have an indication for or are intolerant of an aldosterone antagonist in those who are persistently symptomatic (**Table 6**).[27] When used in such a combination it is especially important to closely monitor for renal function, potassium, and hypotension. It should be emphasized that this combination is not recommended routinely and only in those who remain symptomatic despite the approaches discussed. It is not recommended to combine ACE-I, ARB, and aldosterone antagonist therapy.

The ARBs studied in clinical trials (Candesartan [CHARM], Valsartan [Val-HeFT, VALIANT], and Losartan [HEAAL]) have all shown significant reduction in mortality and readmissions in patients with HF. The first major trial evaluating the use of ARBs in HF was the Val-HeFT study. Valsartan was added to ACE-I, BB, digoxin, and diuretic therapies to evaluate the long-term effects of adding ARBs to standard HF therapy. In this trial, valsartan significantly reduced the combined end point of mortality and morbidity as well as improved clinical signs and symptoms in patients with HF compared with placebo. This difference was predominantly driven by a 24% reduction in the rate of HF hospitalizations, without a clear benefit for mortality

Table 4
Recommendations for appropriate doses of ACEIs

Drug	Initial Dose	Maximum Dose	Clinical Trials	Mean Dose Achieved
Lisinopril	2.5–5.0 mg qD	20–40 mg qD	ATLAS	32.5–35 mg/d
Captopril	6.25 mg TID	50 mg TID	ELITE	122.7 mg/d
Enalapril	2.5 mg BID	10–20 mg BID	SOLVD	16.6 mg/d

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; BID, twice a day; qD, every day; TID, 3 times a day.

Table 5
Recommendations for appropriate doses of ARBs

Drug	Initial Dose	Maximum Dose	Clinical Trial	Mean Dose Achieved
Losartan	25–50 mg qD	50–150 mg qD	HEAAL	129 mg/d
Valsartan	20–40 mg BID	160 mg BID	Val-HeFT	254 mg/d
Candesartan	4–8 mg qD	32 mg qD	CHARM	24 mg/d

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviations: ARB, angiotensin receptor blocker; BID, twice a day; qD, every day.

alone (Table 7). However, the post hoc observation of adverse effects on mortality and morbidity in the subgroup receiving combined valsartan, an ACE inhibitor, and a β-blocker raised concern about the potential safety of this specific combination.[25] Hence, regular use of an ACE inhibitor, ARB, and aldosterone antagonist combination is not recommended and is potentially harmful for patients with HFrEF.[3]

The CHARM trial (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity) was a complementary parallel trial with CHARM-Alternative (2028 patients) investigating use of ARBs in patients who were ACE-I intolerant, and CHARM-Added (2548 patients) investigating use of ARBs in patients who were already on ACE-I.[28] NYHA II-IV patients with HF with LVEF of 40% or lower were randomized to candesartan or placebo. The primary end point was a composite of CV death or hospital admission for HF. The study revealed an absolute reduction of 7 major events per 100 patients treated in CHARM-Alternative and an absolute reduction of 4.4 major events per 100 patients treated in CHARM-Added.[29] However, the investigators concluded that because of adverse effects, especially with concomitant use of ACE-I therapy, routine monitoring of blood pressure, serum creatinine, and serum potassium is warranted.[32]

Other trials, including Evaluation of Losartan in the Elderly (ELITE II),[33] Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL),[34] and Valsartan in Acute Myocardial Infarction (VALIANT),[30] which have assessed ARBs in comparison with ACE-Is for treatment of HF have shown no clear benefit of one pharmacologic agent over the other for mortality in patients with HFrEF.

ALDOSTERONE ANTAGONISTS

Despite the inhibition of the ACE with ACE-I therapy, there is evidence of increased plasma levels of aldosterone. Aldosterone has pleiotropic effects, resulting in increased sodium retention, constriction of systemic arterioles, stimulation of cytokine production, inflammatory-cell adhesion, activation of macrophages, and stimulation of growth of fibroblasts and the synthesis of type I and III fibrillar collagens involved in scar formation.[35]

Table 6
Current recommendations for the use of ARBs

Treatment – Use of ARB	Class of Recommendation	Level of Evidence
ARB in patients with a history of MI and reduced EF to prevent HF	I	A
ARBs are recommended in patients with HFrEF with current or prior symptoms who are ACE-I intolerant	I	A
ARBs are reasonable to reduce morbidity and mortality as alternatives to ACE-Is as first-line therapy for patients with HFrEF, especially for patients already taking ARBs for other indications	IIa	A
Addition of an ARB may be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACE-I and a BB in whom an aldosterone antagonist is not indicated or tolerated	IIa	B

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; EF, ejection fraction; HF, heart failure; HFrEF, HF with reduced ejection fraction; MI, myocardial infarction.

Table 7
ARB trials supporting current guideline recommendations

Study	Aim of Study	Baseline Therapy	Results
CHARM Alternative,[28] 2003	To study the effect of ARBs in symptomatic HF with LVEF <40% and not taking an ACE-I (intolerant)	Diuretics BB 55% Spironolactone 24% Digoxin 46%	Absolute reduction of 7 major events per 100 patients treated NNT 14 patients to prevent 1 CV death or hospitalization HR: 0.77 (95% CI: 0.67–0.89); $P = .0004$
CHARM ADDED,[29] 2003	To investigate if ARB + ACE-I in patients with CHF and LVEF <40% improve clinical outcomes	BB 55% Digoxin 59% Spironolactone 17%	Absolute reduction of 4.4 major events per 100 patients treated NNT of 23 to prevent first event of CV death or CHF hospitalization RR: 0.85 (95% CI: 0.75–0.96); $P = .011$
VALIANT,[30] 2003	Compare the effect of an ARB, ACE-I, and the combination of the 2 on mortality in patients with LV systolic dysfunction (LVEF <35%)	BBs ASA	1-y mortality in the 3 groups: Valsartan 12.5% Captopril 13.2% Combination 12.3%
Val-HeFT,[25] 2001	Evaluate long-term effects of adding ARB to standard therapy for HF (NYHA II–IV with LVEF <40%)	Diuretics Digoxin 67% BB 35% ACE-I 93%	Mortality similar for the 2 treatment groups. For the combined end point of mortality and morbidity: RR: 0.87, 97.5% (CI, 0.77–0.97) $P = .009$
HEAAL,[31] 2009	To study the effects of high-dose vs low-dose losartan on clinical outcomes in patients with HF (NYHA class II–IV, LVEF <40%)	Diuretics (77%), BBs (72%), ARBs (38%)	635 patients in high-dose (150 mg) group vs 665 in 50-mg group died (HR: 0.94, 95% CI: 0.84–1.04, $P = .24$) 450 patients in high-dose vs 503 patients in low-dose group admitted for HF (0.87, 0.76–0.98, $P = .025$)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, aspirin; BB, beta blocker; CHF, chronic heart failure; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFrEF, HF with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NNT, number needed to treat; NYHA, New York Heart Association; RR, relative risk.

Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV and who have an LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality (**Table 8**).[3] In the landmark RALES (Randomized Aldactone Evaluation Study) trial, 1663 NYHA class III–IV patients with severe HF and LVEF of 35% or less who were being treated with an ACE-I, a loop diuretic, and in most cases digoxin, were randomly assigned to receive spironolactone daily (25 mg) or placebo. After a mean follow-up period of 24 months, there was a 46% mortality rate in the placebo group compared with a reduced mortality rate of 35% in the spironolactone group.[36] Reduced risk of SCD and HF hospitalizations were also demonstrated.

Eplerenone has been shown to reduce all-cause deaths, CV deaths, or HF hospitalizations in a wider range of patients with HFrEF.[37] The Eplerenone Post-Acute Myocardial Infarction Heart

Table 8
Current recommendations for the use of aldosterone antagonists

Treatment – Use of MRAs	Class of Recommendation	Level of Evidence
MRAs are recommended in patients with NYHA class II–IV and who have LVEF $\leq$35%	I	A
MRA in post-MI patients who have LVEF $\leq$40% who develop symptoms of HF or who have a history of diabetes mellitus	I	B

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association.

Failure Efficacy and Survival Study (EPHESUS) trial demonstrated that eplerenone significantly reduced mortality in patients with HF or diabetes mellitus with LVEF of 40% or less after myocardial infarction (MI).[38] More recently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial studied eplerenone in patients with HF with LVEF of 30% or less (or 30%–35% if QRS duration $\geq$130 ms) with milder NYHA class II symptoms. In this population, aldosterone antagonism was also associated with improved survival (**Table 9**).[37]

Mineralocorticoid receptor antagonists (MRAs) cannot be used in patients with serum creatinine more than 2.5 mg/dL in men or more than 2.0 mg/dL in women (or estimated glomerular filtration rate <30 mL/min/1.73 m^2), and/or potassium more than 5.0 mEq/L.[39,40] Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency.[36,37] In RALES, there was increased incidence (10%) of gynecomastia or breast pain with use of spironolactone (nonselective antagonist). The incidence of these adverse events was less than 1% in EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) and EMPHASIS-HF without any difference in adverse events between eplerenone and placebo.[39,40]

The initial dose for spironolactone is 12.5 to 25.0 mg daily, and for eplerenone is 25.0 mg/d, increasing to 50.0 mg daily. Every-other-day dosing can be used if there is any concern about hyperkalemia and renal insufficiency. Potassium levels and renal function should be checked within 2 to 3 days and again at 7 days after initiation of an aldosterone receptor antagonist.[3] Serial labs to monitor renal function and potassium must be performed at least monthly for the first 3 months and every 3 months thereafter.

β-ADRENERGIC BLOCKADE

BBs are recommended in all patients with HFrEF (**Table 10**). Unlike ACE-Is, there is no class effect with BBs.[3] The 3 BBs that have been demonstrated to be effective in clinical trials are metoprolol succinate, carvedilol, and bisoprolol (**Table 11**). The current ACC guidelines recommend prompt initiation of BBs as well as initiation during ACE-I optimization in hemodynamically stable patients. BBs can be safely started in patients hospitalized for HF who are not on intravenous inotropes.[41] The addition of a BB produces greater symptom improvement and mortality risk reduction than ACE inhibition even when reaching target doses demonstrated in clinical trials.[23,42] The Carvedilol and ACE-inhibitor Remodeling Mild Heart Failure Evaluation (CARMEN) study revealed that combination of BB and ACE-I therapy is superior to ACE-I alone for left ventricular (LV) remodeling as assessed by LV end-systolic volume index on transthoracic echo.[43]

Table 9
Recommendations for appropriate doses of aldosterone antagonists

Drug	Initial Dose	Maximum Dose	Clinical Trial	Mean Dose Achieved
Spironolactone	12.5–25 mg qD	25 mg qD-BID	RALES	26 mg/d
Eplerenone	25 mg qD	50 mg qD	EPHESUS	42.6 mg/d

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviations: BID, twice a day; qD, every day.

Table 10
Current recommendations for the use of BBs

Treatment – Use of BBs	Class of Recommendation	Level of Evidence
BB in patients with a history of MI and reduced EF to prevent HF	I	B
BBs should be used in all patients with a reduced EF to prevent HF	I	C
Use of 1 of the 3 BBs (Bisoprolol, Carvedilol, and Sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF	I	A

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviations: BB, beta blocker; EF, ejection fraction; HF, heart failure; HFrEF, HF with reduced ejection fraction; HR, hazard ratio; MI, myocardial infarction.

The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) study group investigated whether metoprolol succinate, which selectively blocks beta-1 receptors, in addition to standard therapy (ACEI and diuretics) would lower mortality in patients with decreased LVEF and HF symptoms. The study randomized approximately 2000 NYHA class II–IV patients with chronic HF and with LVEF of 40% or less to either metoprolol succinate or placebo. All-cause mortality, sudden death, and death from worsening HF were lower in the metoprolol group.[44]

The CIBIS (Cardiac Insufficiency Bisoprolol Study) study group investigated the efficacy of bisoprolol, a beta-1 selective adrenergic receptor blocker, in decreasing all-cause mortality in chronic HF in a multicenter trial in Europe. In this trial, 2647 NYHA III–IV patients with LVEF of 35% or less receiving standard therapy (diuretics and ACE-Is) were randomized to bisoprolol or placebo. CIBIS-II was stopped early because bisoprolol showed a significant mortality benefit. Treatment effects were independent of the severity or cause of HF. The investigators concluded that BB therapy had survival benefit in stable patients with HF.[45]

The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial demonstrated the beneficial effects of carvedilol, which blocks alpha-1, beta-1, and beta-2 receptors, on mortality in NYHA class IV patients with chronic HF. All subgroups including those with the most advanced HF showed the same beneficial effect on mortality.[46]

The Carvedilol or Metoprolol European Trial (COMET) demonstrated a significant survival benefit for carvedilol over metoprolol tartrate in patients with mild-to-severe chronic HF.[47] However, target dosing of metoprolol tartrate (50 mg twice daily) and carvedilol (25 mg twice daily) is not equivalent, with the carvedilol dose reached being substantially higher.[48] Further, shorter-acting metoprolol tartrate was used in this trial rather than longer-acting metoprolol succinate (**Table 12**).

In the US Carvedilol Heart Failure Study, 1094 patients with chronic HF were randomly assigned to receive either placebo or the BB carvedilol; background therapy with digoxin, diuretics, and an ACE-I remained constant.[49] At the end of 6 months, the overall mortality rate was 7.8% in the placebo group and 3.2% in the carvedilol group; the reduction in risk attributable to carvedilol was 65% (95% confidence interval; $P<.001$). This finding led the Data and Safety Monitoring Board to recommend termination of the study before its scheduled completion. In addition, as compared with placebo, carvedilol therapy was accompanied by a 27% reduction in the risk of hospitalization for CV causes (19.6% vs 14.1%, $P<.036$).

Table 11
Recommendations for appropriate doses of BBs

Drug	Initial Dose	Maximum Dose	Clinical Trial	Mean Dose Achieved
Metoprolol succinate	12.25 mg qD	200 mg qD	MERIT-HF	159 mg/d
Carvedilol	3.125 mg BID	50 mg BID	CAPRICORN	37 mg/d
Bisoprolol	1.25 mg qD	10 mg qD	CIBIS-II	8.6 mg/d

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviations: BB, beta blocker; BID, twice a day; qD, every day.

Table 12
BB trials supporting current guideline recommendations

Study	Aim of Study	Baseline Therapy	Results
MERIT HF,[44] 1999	To investigate whether Metoprolol XL lowered mortality in patients with NYHA II–IV and LVEF <40%	Diuretics + ACE-I [Amiodarone NOT allowed]	All-cause mortality was 11.0% in the placebo group vs 7.2% in the Metoprolol Group (P = .00009)
CIBIS II,[45] 1999	To assess the efficacy of bisoprolol in decreasing all-cause mortality in chronic HF (NYHA class III or IV with EF <35%)	Diuretics + ACE-I (amiodarone allowed 16%)	Annualized mortality was 13.2% in the placebo group vs 8.8% in the Bisoprolol group HR: 0.66 (95% CI 0.54–0.81) P<.0001
COPERNICUS,[46] 2002	To study if Carvedilol is beneficial in patients with NYHA class IV and LVEF <25%	Diuretics + ACE-I (or ARB) (Amiodarone allowed 18%)	All-cause mortality was 18.5% in placebo group and 11.4% in Carvedilol group (P = .0014)
CAPRICORN,[49] 2001	To investigate the long-term efficacy of carvedilol on patients with LV dysfunction post-acute MI already treated with ACE-I	ACE-I 98% Aspirin 86%	All-cause mortality was 15.0% in the placebo group vs 12% in the Carvedilol Group (P = .03)
US CARVEDILOL,[50] 1996	To investigate the effect of BB on survival of patients with chronic heart failure	Digoxin + Loop Diuretic + ACE-I 90%	All-cause mortality was 7.8% in the placebo group vs 3.2% in the Carvedilol Group (P<.001)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CI, confidence interval; EF, ejection fraction; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study enrolled 1959 patients with a proven acute MI and a LVEF of 40% or less that were randomly assigned 6.25 mg carvedilol or placebo[50]; 98% of these patients were receiving an ACE-I and 86% were receiving aspirin. Carvedilol was progressively increased to a maximum of 25 mg twice daily during the next 6 weeks, and patients were followed until the requisite number of primary end points had occurred. The primary end point was all-cause mortality or hospital admission for CV problems. Analysis was by intention to treat. All-cause mortality was lower in the carvedilol group than in the placebo group (12% vs 15%, P = .03). CV mortality, nonfatal MIs, and all-cause mortality or nonfatal MI were also lower on carvedilol than on placebo. The reduction in all-cause mortality was additional to the effects of ACE inhibitors, which was prescribed in 98% of patients.

BBs should be initiated at low doses and titrated up as tolerated by the patient to target doses used in clinical trials.[42] While uptitrating the dose, patients must be monitored for adverse effects that can include bradycardia, heart block, hypotension, fluid retention and worsening HF, fatigue and worsening of depression, and reactive airway disease. If there is evidence of fluid overload, BB must be used in conjunction with diuretics.[51,52] BBs have been demonstrated to reduce mortality and risk of hospitalization in HF,[23,42–45] as well as reduce the risks of disease progression, clinical deterioration, and sudden death.[53–55] Withdrawing BBs abruptly should be avoided, as it could lead to worsening of HF.[56] For these reasons, we recommend that adverse effects be closely monitored and dose reduction be pursued first before permanently and abruptly withdrawing BB therapy.

DIURETICS

Diuretics inhibit the reabsorption of sodium or chloride at specific sites in the renal tubules. Loop diuretics act in the thick ascending limb

of the loop of Henle, whereas thiazide-type diuretics act in the distal tubule and connecting segments. Potassium-sparing diuretics act in the aldosterone-sensitive principal cells in the cortical collecting tubule.

Fluid retention may be present in patients who have dyspnea, an increase in weight from baseline of more than 2 kg in fewer than 3 days, raised jugular venous pressure, crepitations on chest auscultation, hepatomegaly, or signs of peripheral edema. Diuretics are used to increase urinary sodium excretion and decrease physical signs of fluid retention in patients with HF (**Table 13**).[57,58] Although diuretics have not been shown to change mortality or morbidity, they have been shown to improve symptoms and exercise tolerance in patients with HF.[59,60]

Most patients with HF are initially treated with loop diuretics because of their potency. However, in hypertensive HF with mild congestion, thiazide diuretics are preferred, as they present a more persistent effect on blood pressure. Potassium-sparing diuretics may be helpful in people with hypokalemia and in conjunction with loop diuretics (**Table 14**).

Diuretic therapy is commonly initiated with low doses, and the dose is increased until urine output increases and weight decreases, generally by 1 to 2 lb daily. Lower doses may result in fluid retention, whereas higher doses can lead to volume contraction, which may lead to hypotension, renal insufficiency, and electrolyte abnormalities. Electrolyte abnormalities need to be monitored closely, as hypokalemia and hypomagnesemia can predispose patients to serious cardiac arrhythmias.[61] Other rare side effects are loop diuretic–induced ototoxicity and hypersensitivity reactions, as they are sulfonamides.

Furosemide has a bioavailability of only about 50% with substantial interpatient and intrapatient variability (10%–100%).[62,63] As a result, there may be a greater response to oral torsemide or bumetanide, which are more predictably absorbed.[53,54,64] In advanced stages, bowel edema and hypoperfusion may further delay absorption and delivery,[63] and, therefore, increasing doses may be required to achieve an appropriate effect. Diuretic resistance can usually be overcome by parenteral administration,[55] the use of 2 or more diuretics in combination (eg, furosemide and metolazone),[65] or the addition of drugs that increase renal blood flow (eg, positive inotropic agents).

Table 13
Current recommendations for the use of diuretics

Treatment – Use of Diuretics	Class of Recommendation	Level of Evidence
Diuretics for fluid retention in HFrEF	I	C

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviation: HFrEF, heart failure with reduced ejection fraction.

Table 14
Recommendations for appropriate doses of diuretics

Drug	Initial Dose	Maximum Dose
Loop diuretics		
Furosemide	20–40 mg qD/BID	600 mg
Bumetanide	0.5–1 mg qD/BID	10 mg
Torsemide	10–20 mg qD	200 mg
Thiazide diuretics		
Chlorthiazide	250–500 mg BID	1000 mg
Chlorthalidone	12.5–25 mg qD	100 mg
Hydrochlorothiazide	25 mg qD/BID	200 mg
Indapamide	2.5 mg qD	5 mg
Metolazone	2.5 mg qD	20 mg
Potassium-sparing diuretics		
Amiloride	5 mg qD	20 mg
Spironolactone	12.5–25 mg qD	50 mg
Triamterene	50–75 mg BID	200 mg
Eplerenone	25 qD	50 qD

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviations: BID, twice a day; qD, every day.

ORAL VASODILATORS

Hydralazine produces arterial vasodilation and systemic vascular resistance reduction by increasing intracellular cyclic guanosine monophosphate and promoting smooth muscle relaxation. Nitrates are transformed in smooth muscle cells into nitric oxide and subsequently vasodilation. The Vasodilator-Heart Failure Trial (V-HeFT) study randomized

HFrEF patients who were on digoxin and diuretic to receive additional therapy with placebo, prazosin, or combination of isosorbide dinitrate-hydralazine (ISDN-HYD). It showed reduced mortality in the ISDN-HYD cohort compared with placebo at 2 years.[66] In a subsequent study, the V-HeFT II trial randomized 804 patients to either ISDN-HYD or enalapril on background therapy of digoxin and diuretics. This study showed that enalapril resulted in significantly improved survival compared with ISDN-HYD in patients with HF.

In addition, the Hy-C trial demonstrated that captopril produced more favorable effects on survival in comparison with vasodilators.[67] A post hoc retrospective analysis of these vasodilator trials demonstrated particular efficacy of isosorbide dinitrate and hydralazine in the African American population.[68] This was subsequently validated in the A-Heft trial. This trial randomized African Americans with advanced HF, who were receiving standard therapy (including BBs and ACEIs), to ISDN-HYD or placebo. This study demonstrated that the addition of fixed-dose isosorbide dinitrate and hydralazine enhanced survival and decreased hospitalizations.[69]

Combination therapy with hydralazine and nitrates is recommended for patients with contraindications to ACE-Is or ARBs (angioedema, persistent hyperkalemia, acute kidney injury), as well as in African American patients with HF who remain symptomatic (NYHA functional class III–IV) despite optimal medical therapy (**Table 15**).[3]

Adverse effects of these vasodilators may include headache, dizziness, and gastrointestinal complaints.[66] Hypotension can be a major limitation to the use of vasodilator therapy in the elderly. However, nitrates are useful when a reduction of preload is necessary when diuretic use can be limited, such as in renal failure.[70]

DIGOXIN

Digoxin is a positive inotropic agent. Digoxin also attenuates carotid sinus baroreceptors and has sympatho-inhibitory effects that lead to a decrease in norepinephrine, renin, and possibly aldosterone levels.[71,72] In the only randomized controlled trial of digoxin therapy (DIG trial), patients with HF (LVEF<45%) were randomized to receive digoxin or placebo and were followed for 37 months; approximately 30% of these patients were older than 70 years. There was no difference in the primary end point of mortality from any cause with digoxin compared with placebo, but fewer patients were hospitalized for worsening HF when treated with digoxin as compared with placebo (relative risk [RR] 0.72; 95% confidence interval [CI] 0.66–0.79, $P<.001$).[73]

A Cochrane systematic review of 13 studies showed that digoxin reduced the combined end point of death and hospital admission in those with both HF with reduced ejection fraction and HF with preserved ejection fraction. However, most of these studies were conducted in patients who were not taking a BB.[74,75] Other placebo-controlled trials have shown that treatment with digoxin for 1 to 3 months can improve symptoms, health-related quality of life, and exercise tolerance in patients with mild to moderate HF (**Table 16**).[76–79] In HFrEF patients who are symptomatic despite optimal therapy with neurohormonal antagonists, digoxin may be added for symptomatic relief. In patients with atrial fibrillation, BBs are usually more effective when added to digoxin in controlling the ventricular response, particularly during exercise.[80,81]

The dosage of digoxin should be adjusted to obtain serum levels between 0.6 and 1.2 ng/mL. A post hoc analysis found that patients with HF with LVEF less than 45% with serum digoxin

Table 15
Current recommendations for the use of oral vasodilators

Treatment: Use of Oral Vasodilators	Class of Recommendation	Level of Evidence
The combination of hydralazine and isosorbide dinitrate in African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE-I and BB	I	A
The combination of hydralazine and isosorbide dinitrate in patients with current or prior symptomatic HFrEF who cannot be given an ACE-I or ARB because of drug intolerance, hypotension, or renal insufficiency	IIa	B

Recommendations summarized from current literature and data referenced in this article; see reference list.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; HFrEF, HF with reduced ejection fraction; NYHA, New York Heart Association.

Table 16
Current recommendations for the use of digoxin

Treatment: Use of Digoxin	Class of Recommendation	Level of Evidence
Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF	IIa	B

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviations: HF, heart failure; HFrEF, HF with reduced ejection fraction.

concentrations of 0.5 to 0.8 ng/mL had a 6% reduced mortality compared with those who had concentrations of 0.8 to 1.1 ng/mL. Thus, serum digoxin concentrations and targeting lower concentrations seem to be the critical point of digoxin therapy, especially in elderly and lean patients in whom adverse effects, such as increased volume of distribution, renal insufficiency, and hypokalemia, are frequent. Other common side effects include cardiac arrhythmias (heart block, ectopic and re-entrant cardiac rhythms), gastrointestinal symptoms (eg, anorexia, nausea, and vomiting), and neurologic complaints (eg, visual disturbances, disorientation, and confusion). Although toxicity is commonly associated with high serum digoxin levels (>2 ng/mL), it may occur with lower levels, especially if there is concomitant hypokalemia, hypomagnesemia, or hypothyroidism.[82,83]

HF WITH PRESERVED EJECTION FRACTION

HF with preserved ejection fraction (HFpEF) is a clinical syndrome encompassing symptoms and signs of HF together with a normal LVEF. The prevalence of HFpEF increases with age (15%, 33%, and 50% at ages 50, 50–70, and 70 years, respectively).[84] Despite improved understanding of the pathophysiology of HFpEF, specific pharmacologic treatment has thus far proven disappointing. Management for HFpEF is currently directed at symptoms, especially comorbidities, and risk factors that may worsen CV disease (such as treatment of hypertension, ventricular rate in atrial fibrillation) as trials for HFpEF have generally been disappointing with various therapies.[85] For example, atrial fibrillation with rapid ventricular rate may worsen HF symptoms in this population by leading to shortened diastolic filling time and the loss of atrial contribution to LV diastolic filling.

In those patients with HFpEF and hypertension, the major therapeutic goal is the improvement of diastolic function by controlling blood pressure and regression of left ventricular hypertrophy. Improved blood pressure control reduces hospitalization for HF.[86] It also leads to decreased CV events and mortality.[87] In the hypertensive population, ACE inhibitors and/or ARBs may be used. Coronary artery disease (CAD) is also common in patients with HFpEF[88]; however, there are no studies examining the impact of revascularization on symptoms or outcomes in this population. It is reasonable to consider revascularization in symptomatic HFpEF patients for whom ischemia appears to contributing to HF symptoms (**Table 17**).

The CHARM-Preserved trial,[89] which enrolled 3023 patients with NYHA class II to IV HF and

Table 17
Current recommendations for treatment of stage C HF with preserved EF

Heart Failure with Preserved Ejection Fraction	Class of Recommendation	Level of Evidence
Systolic and diastolic blood pressure to be controlled	I	B
Diuretics for symptomatic relief from volume overload	I	C
Use BB, ACE-I, ARBs in patients with HTN	IIa	C
Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HFpEF despite optimized medical therapy	IIa	C
Consider use of ARBs to decrease hospitalizations	IIb	B

Recommendations summarized from current literature and data referenced in this article; see reference list.
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CAD, coronary artery disease; HFpEF, HF with preserved ejection fraction; HTN, hypertension.

LVEF greater than 40%, demonstrated that candesartan was not significantly associated with mortality or morbidity reduction in patients with HFpEF (CV-related death or hospitalization for HF: hazard ratio [HR] = 0.86; 95% CI, 0.74–1.00). In this trial, diastolic function was not strictly defined and patients with ejection fraction greater than 40% were included. This could have allowed inclusion of patients who had systolic HF but had improved their ejection fraction by use of ACE inhibitors and BBs.

The I-PRESERVE study examined the effects of irbesartan in patients with HFpEF. This study had a more specific definition of HFpEF than CHARM-Preserved. Patients were included if LVEF was greater than 45% and a there was corroborative objective evidence of HF or a cardiac substrate for diastolic dysfunction. After a mean follow-up duration of 49.5 months, the primary event rates of death from any cause or hospitalization for a CV cause in the irbesartan and placebo groups were similar (HR = 0.95; 95% CI 0.86–1.05).[90] The PEP-CHF (Perindopril in Elderly People with Chronic Heart failure) trial evaluated the effects of perindopril in 850 elderly patients with HFpEF. Unfortunately, perindopril was not associated with improved primary outcomes in a subgroup of patients with HFpEF.[91] See **Box 1** for the ABC strategy to achieve success with drug therapy in patients with stage C HF.

Box 1
The ABC strategy to achieve success with drug therapy in patients with Stage C HF

A: ACE-I/ARB: in all patients with HF unless contraindicated.

B: BB: use as early as possible in patients withHFrEF.

C: Compliance with medications, sodium restriction, and follow-up visits must be reinforced.

D: Dosage: Start low; go slow, try to achieve target doses used in clinical trials.

E: Education: Educate patient, family, and caretakers.

F: Fluid status to be carefully assessed at every visit.

G: Guidelines-based therapy to be followed.

H: Hydralazine and…

I: Isosorbide dinitrate as combination in African Americans with HF.

J: Judicious use while combining any of the following: ACE-I, ARB, MRA, diuretics.

K: K1 Mg1 BUN, Cr to be closely monitored.

L: Loop diuretics (first line) and other diuretics in appropriate doses to maintain euvolemia.

M: MRAs can also be used in NYHA Class II.

N: Nonsteroidal anti-inflammatory drugs to be avoided in HF.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; BUN, blood urea nitrogen; Cr, creatinine; HF, heart failure; HFrEF, HF with reduced ejection fraction; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association.

DEVICE THERAPY

Implantable Cardioverter-Defibrillator

Despite optimal medical therapy, patients with HF with reduced ejection fraction (HFrEF) carry a residual increased risk for SCD due to tachyarrhythmias. Evidence supporting the current guideline recommendations for implantable cardioverter-defibrillator (ICD) therapy is summarized in **Table 18**. Additionally, separate topics on arrhythmias and heart failure, and sudden cardiac death and heart failure are discussed in this series.

Primary prevention

According to the 2013 ACCF/AHA guidelines for the management of HF, there are 2 Class I indications for ICD therapy in the context of primary prevention[3]:

1. In patients with nonischemic or ischemic heart cardiomyopathy 40 or more days post-MI with LVEF of 35% or less and NYHA class II or III symptoms on optimal medical therapy, who have expected survival for more than 1 year (Level of Evidence: A)
2. In patients 40 or more days post-MI with LVEF of 30% or less and NYHA class I symptoms on optimal medical therapy, who have expected survival for more than 1 year (Level of Evidence: B)

Secondary prevention

There are several Class I indications for ICD therapy in the setting of secondary prevention for survivors of SCD and individuals with previously documented ventricular arrhythmias, based on the 2008 ACC/AHA/Heart Rhythm Society device-based therapy guidelines[100]:

1. In patients who are survivors of cardiac arrest due to ventricular fibrillation (VF) or hemodynamically unstable sustained ventricular tachycardia (VT) after exclusion of any completely reversible cause (Level of Evidence: A)
2. In patients with structural heart disease and spontaneous sustained VT (Level of Evidence: B)

Table 18
ICD trials supporting current guideline recommendations

Study (Year, Reference)	Patient Population	Primary End Point/Findings
Primary prevention		
MADIT,[92] 1996	196 pxs, prior MI, NSVT, or inducible VT/VF EF ≤35% ICD vs medical therapy	All-cause mortality: ICD associated with a 54% risk reduction during mean follow up of 27 mo (P = .009)
MUSTT,[93] 1999	704 pxs, CAD/MI, NSVT, or inducible VT EF ≤40% EP-guided therapy (ICD or anti-arrhythmic drugs) vs none	Cardiac arrest or arrhythmic death: EP-guided therapy (largely due to ICDs) associated with 27% risk reduction during median follow-up of 39 mo (P = .04)
MADIT-II,[94] 2002	1232 pxs, prior MI EF ≤30% ICD vs medical therapy	All-cause mortality: ICD associated with a 31% risk reduction during mean follow-up of 2 y (P = .016)
DINAMIT,[95] 2004	674 pxs, 6–40 d post-MI EF ≤35%, impaired cardiac autonomic function ICD vs medical therapy	All-cause mortality: HR for ICD: 1.08 (P = .66)
SCD-HeFT,[96] 2005	2521 pxs, CAD and DCM EF ≤35%, NYHA II–III ICD vs amiodarone vs medical therapy	All-cause mortality: ICD associated with a 23% risk reduction during median follow-up of 46 mo (P = .007)
Secondary prevention		
AVID,[97] 1997	1016 pxs, survivors of VF or sustained VT, EF ≤40% CAD 81%; mean EF 32% ± 13% ICD vs anti-arrhythmic drugs	Overall survival: 89.3% vs 82.3% (1 y) 81.6% vs 74.7% (2 y) 75.4% vs 64.1% (3 y) (P<.02)
CIDS,[98] 2000	659 pxs, resuscitated VF or VT or with unmonitored syncope 77% prior MI, mean EF = 34% ± 14% ICD vs amiodarone	All-cause mortality: ICD reduced risk from 10.2%/y to 8.3%/y (19.7% RRR) (P = .142)
CASH,[99] 2000	288 pxs, survivors of SCD 73% CAD, mean EF = 46% ± 18% ICD vs amiodarone vs metoprolol	All-cause mortality: ICD associated with a 23% risk reduction during 9 y of follow-up (P = .081)

Abbreviations: CAD, coronary artery disease; DCM, dilated cardiomyopathy; EF, ejection fraction; EP, electrophysiology; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; pxs, provexis; RRR, relative risk reduction; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

3. In patients with syncope of undetermined origin with hemodynamically significant sustained VT or VF during electrophysiological study (EPS) (Level of Evidence: B)
4. In patients with nonsustained VT due to prior MI, LVEF of 40% or less, and inducible VF or sustained VT at EPS (Level of Evidence: B).

Cardiac Resynchronization Therapy

Progressive LV dysfunction may result in ventricular electromechanical discoordination or LV dyssynchrony, which constitutes the rationale for cardiac resynchronization therapy (CRT). In addition to improving systolic function, functional mitral regurgitation, exercise capacity, and hospitalization rates, CRT has been shown to prolong survival. Current guidelines support Class I recommendations for CRT in patients with LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB), QRS duration of 150 ms or more, and NYHA class II, III, or ambulatory IV symptoms on optimal medical therapy (Level of Evidence: A for NYHA class III/IV; Level of Evidence: B for NYHA class II). Class IIa recommendations are applicable in similar patients with non-LBBB pattern with QRS duration of 150 ms or more, LBBB and QRS 120–149 ms, or atrial fibrillation requiring

near 100% ventricular pacing. Trial data supporting these guidelines for CRT are summarized in Table 19.

SURGICAL INTERVENTIONS

Coronary Artery Bypass Graft Surgery

The goals of coronary artery bypass graft (CABG) surgery in ischemic cardiomyopathy are to increase survival and improve symptoms. In addition to the severity of LV systolic dysfunction and CAD, the presence of angina and myocardial viability need to be considered before revascularization. Contemporary guidelines designate a Class I recommendation for CABG for patients with HF with angina and left main stenosis (>50%) or left main equivalent (LMEQ) disease (ie, ≥70% stenosis in the proximal left anterior descending [LAD] and proximal left circumflex coronary arteries) and who are on optimal medical therapy (Level of Evidence: C).[3,108] Data from the Coronary Artery Surgery Study (CASS) Registry

Table 19
CRT trials supporting current guideline recommendations

Study (Year, Reference)	Patient Population	Primary End Point/Findings
NYHA Class III-IV		
MUSTIC,[101] 2001	58 pxs, EF ≤35%, QRS >150 ms, SR, NYHA III CRT-P vs no pacing	6-min walk distance: 22% improved during 6 mo of follow-up (*P*<.001)
MIRACLE,[102] 2002	453 pxs, EF <35%, QRS >130 ms, SR, NYHA III–IV CRT vs medical therapy	6-min walk distance improved: +39 vs +10 m (*P* = .005); functional class improved (*P*<.001); quality of life improved: −18.0 vs −9.0 points (*P* = .001)
COMPANION,[103] 2004	1520 pxs, EF <35%, QRS >120 ms, SR, NYHA III–IV CRT-P vs CRT-D vs medical therapy	Time to death from or hospitalization for any cause: decreased in the CRT-P group (HR 0.81, *P* = .014) and in the CRT-D (HR 0.80, *P* = .01) compared with medical therapy alone over 15 mo
CARE-HF,[104] 2005	814 pxs, EF <35%, QRS >120 ms, SR, NYHA III-IV CRT-P vs medical therapy	Time to death from any cause or an unplanned hospitalization for a major CV event: reached by 39% in the CRT group vs 55% in the control group (HR, 0.63; *P*<.001) for a mean follow-up of 29 mo
NYHA Class I-II		
REVERSE,[105] 2008	610 pxs, EF ≤40%, QRS ≥120 ms, NYHA I–II CRT-D vs no CRT	HF clinical composite response: 16% worsened in the CRT vs 21% in the no CRT group over 12 mo; *P* = .10
MADIT-CRT II,[106] 2009	1820 pxs, EF ≤30%, QRS ≥130 ms, NYHA I–II CRT-D vs ICD	HF event or death: 17.2% in CRT-D vs 25.3% in ICD only; 34% risk reduction (HR in the CRT-D group: 0.66) in 28 mo; *P* = .001
RAFT,[107] 2010	1798 pxs, EF ≤30%, QRS ≥120 ms/≥200 ms paced, NYHA II–III CRT-D vs ICD	HF hospitalization or death: 33.2% in CRT-D vs 40.3% in ICD only; 25% risk reduction (HR in CRT-D: 0.75) over 40 mo; *P*<.001; when confined to NYHA II patients only, there was 27% reduction in the primary end point; *P* = .001

Abbreviations: CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CRT-P, CRT-pacing; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; SR, sinus rhythm.

revealed that among patients with LMEQ disease, the median survival was 13.1 years and 6.2 years in the CABG surgery and medical therapy groups, respectively ($P<.0001$).[109] However, CABG surgery did not prolong median survival in the subset of patients with normal LVEF.

Class IIa indications are endorsed for CABG in 2 groups: (1) to improve survival in patients with LVEF of 35% to 50% and significant ($\geq$70% diameter stenosis) multivessel CAD or proximal LAD stenosis when viability is present (Level of Evidence: B), and (2) to improve morbidity and CV mortality for patients with LVEF less than 35%, HF, and significant CAD (Level of Evidence: B). (3) Although older studies have shown lower mortality in patients with mild to moderate LV systolic dysfunction who are treated surgically than medically,[110,111] survival benefit from CABG is less compelling in those with much lower LVEF. The Surgical Treatment for Ischemic Heart Failure (STICH) trial randomized patients with LVEF of 35% or less and surgically amenable CAD to medical therapy plus CABG or medical therapy alone.[112] Over a follow-up of 56 months, there was no significant difference in the primary outcome of all-cause death in the comparison groups (HR with CABG, 0.86; 95% CI 0.72–1.04; $P = .12$). CABG was superior to medical therapy for the secondary outcomes of CV death, and of death from any cause or CV hospitalization. A substudy of the STICH trial evaluated whether myocardial viability, assessed by single-photon-emission computed tomography, dobutamine echocardiography, or both, could identify patients with greater survival benefit from CABG.[113] The presence of viable myocardium was associated with a greater likelihood of survival in this population (HR for death in patients with viability, 0.64; 95% CI 0.48–0.86; $P = .003$), but this association was not significant after adjustment for other baseline variables ($P = .21$).

Mitral Valve Repair

In patients with HF with severe LV systolic dysfunction and significant functional mitral regurgitation (MR), mitral valve repair (MVR), either surgically or percutaneously, has been associated with improved ventricular mechanics and patient morbidity but has not shown any survival benefit superior to medical therapy. Among 73 patients with LVEF higher than 30% and moderate MR who were randomized to receive CABG plus MVR or CABG alone, 1-year mortality was similar in both groups (9% vs 5%, respectively; $P = .66$).[114] Combined MVR and CABG resulted in better LV reverse remodeling, B-type natriuretic peptide levels, and functional capacity compared with CABG alone. In reference to the impact of a percutaneously implanted MV clip on patient outcomes, the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II trial investigated 279 patients with at least moderately severe MR (mean LVEF 61%) who were randomized to undergo either percutaneous or conventional MVR.[115,116] The primary efficacy end point (freedom from death and from surgery for MV dysfunction at 12 months) was reached in 55% in the percutaneous group and 73% in the surgery group ($P = .007$). Major adverse events at 30 days occurred in 15% and 48% in the percutaneous and surgery groups, respectively ($P<.001$). An observational study on patients with end-stage HF and severe LV systolic dysfunction reported that at 6 months, percutaneous MVR significantly improved B-type natriuretic peptide levels, LVEF and volumes, NYHA functional class, and 6-minute walk test.[117]

Ventricular Reconstruction

Surgical reverse remodeling or LV reconstruction is a Class IIb indication for carefully selected patients with LV systolic dysfunction and specific conditions, including intractable HF and ventricular arrhythmias (Level of Evidence: B).[3] In post-anterior MI patients with HF with LVEF of 35% or lower, data have shown that surgical ventricular restoration is associated with improved LV systolic function and geometry, and NYHA functional class but is not associated with a significant reduction in death and CV hospitalizations.[117,118]

SUMMARY

ACC Stage C HF includes those patients with prior or current symptoms of HF in the context of an underlying structural heart problem who are primarily managed with medical therapy. Although there is guideline-based medical therapy for those with HFrEF, therapies in HFpEF have thus far proven elusive. Emerging therapies, such as serelaxin, are currently under investigation and may prove beneficial. The role of advanced surgical therapies, such as mechanical circulatory support, in this population is not well defined. Further investigation is warranted for these therapies in patients with stage C HF.

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