State of the art paper

Update of treatment of heart failure with reduction of left ventricular ejection fraction

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Abstract

Underlying and precipitating causes of heart failure (HF) with reduced left ventricular ejection fraction (HFrEF) should be identified and treated when possible. Hypertension should be treated with diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers. Diuretics are the first-line drugs in the treatment of patients with HFrEF and volume overload. Angiotensin-converting enzyme inhibitors and β-blockers (carvedilol, sustained-release metoprolol succinate, or bisoprolol) should be used in treatment of HFrEF. Use an angiotensin II receptor blocker (ARB) (candesartan or valsartan) if intolerant to ACE inhibitors because of cough or angioneurotic edema. Sacubitril/valsartan may be used instead of an ACE inhibitor or ARB in patients with chronic symptomatic HFrEF class II or III to further reduce morbidity and mortality. Add an aldosterone antagonist (spironolactone or eplerenone) in selected patients with class II–IV HF who can be carefully monitored for renal function and potassium concentration. (Serum creatinine should be ≤ 2.5 mg/dl in men and ≤ 2.0 mg/dl in women. Serum potassium should be < 5.0 mEq/l). Add isosorbide dinitrate plus hydralazine in patients self-described as African Americans with class II–IV HF being treated with diuretics, ACE inhibitors, and β-blockers. Ivabradine can be used in selected patients with HFrEF.

Key words: heart failure, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, sacubitril/valsartan, nitrates, aldosterone antagonists, digoxin, hydralazine, ivabradine.

Introduction

Heart failure (HF) is the commonest cause of hospitalization and of early rehospitalization [1, 2]. Major risk factors for developing HF include hypertension [1, 3–6] and hypercholesterolemia [1, 7–9]. Hypercholesterolemia should be treated by statins to reduce the incidence of HF [1, 7–9]. Statin intolerance is extensively discussed elsewhere [10].

Numerous randomized double-blind trials have demonstrated that compared to placebo, antihypertensive drugs reduce the development of HF. At 4.5-year follow-up of 4736 older persons with isolated systolic hypertension, compared to placebo, antihypertensive drug therapy reduced the incidence of HF by 49% [11]. At 1.8-year follow-up of 3,845 persons aged 80 years and older with hypertension, compared to placebo, antihypertensive drug therapy reduced the incidence of HF by 64% [12]. At 1-year follow-up of 1,747 persons with HF and reduced left ventricu-

lar (LV) ejection fraction (HFrEF) and a history of hypertension, compared with placebo, metoprolol CR/XL reduced all-cause mortality by 39% [13].

At 3.26-year follow-up of 9,361 persons, mean age 67.9 years, with a systolic blood pressure of 130–180 mm Hg, compared to reducing the systolic blood pressure to < 140 mm Hg by antihypertensive drug therapy, reducing the systolic blood pressure to < 120 mm Hg reduced the incidence of HF by 38% [14]. However, this study excluded patients with recent HF or a LV ejection fraction < 35% [14].

We used propensity scores in the Digitalis Investigation Group trial to match 3,738 patients with HF and a systolic blood pressure of 120 mm Hg or lower with 3,738 patients with HF and a systolic blood pressure above 120 mm Hg who were well balanced in 32 baseline characteristics [15]. Follow-up was 5 years. Compared with a baseline systolic blood pressure higher than 120 mm Hg, a baseline systolic blood pressure of 120 mm Hg or lower was associated with a 15% increase in cardiovascular death, a 30% increase in HF mortality, a 13% increase in cardiovascular hospitalization, and a 21% increase in HF hospitalization [15]. Until randomized clinical trial data show what the optimal blood pressure goal is for patients with HF, I favor treating patients with HF and hypertension to a blood pressure goal of 130/80 mm Hg.

Underlying and precipitating causes of HF should be identified and treated when possible. This review article will discuss an update on the drug therapy of HFrEF [1, 16].

Diuretics

Diuretics are the first-line drugs in the treatment of patients with HFrEF and volume overload (Table I). Diuretics decrease venous return, reduce ventricular filling pressures, cause loss of fluid from the body, and decrease symptoms of pulmonary and systemic congestion and edema. Age-related decreases in renal function and in circulating plasma volume may reduce the efficacy of diuretics in patients with HFrEF.

A thiazide diuretic, such as hydrochlorothiazide, may be used to treat patients with mild HFrEF. However, a thiazide diuretic is ineffective if the glomerular filtration rate is less than 30 ml/min. Patients with moderate or severe HFrEF should be treated with a loop diuretic such as furosemide. These patients should not take nonsteroidal anti-inflammatory drugs because these drugs may inhibit the induction of diuresis by furosemide. Patients with severe HF or concomitant renal insufficiency may need the addition of metolazone to the loop diuretic. Severe volume overload should be treated with intravenous diuretics and hospitalization.

Patients with HFrEF treated with diuretics need close monitoring of their serum electrolytes. Hypokalemia and hypomagnesemia, both of which may precipitate ventricular arrhythmias and digitalis toxicity, may develop. Hyponatremia with activation of the renin-angiotensin-aldosterone system may occur.

Patients with HF are especially sensitive to volume depletion. Dehydration and prerenal azotemia may occur if excessive doses of diuretics are given. Therefore, the minimum effective dose of diuretics should be used. The dose of diuretics should be gradually reduced and stopped if possible when fluid retention is not present in patients with HFrEF. Patients on high doses of diuretics have an increased mortality [17].

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are balanced vasodilators that decrease both afterload and preload. ACE inhibitors reduce systemic vascular resistance, arterial pressure, LV and right ventricular end-diastolic pressures, cardiac work, and myocardial oxygen consumption, and increase cardiac output. ACE inhibitors decrease circulating levels of angiotensin II, reduce sympathetic nervous system activity, stimulate pros-

Table I. Class I recommendations for treating HFrEF

1. Use diuretics and salt restriction in patients with fluid retention.
2. Use ACE inhibitors.
3. Use angiotensin II receptor blockers (candesartan or valsartan) if intolerant to ACE inhibitors because of cough or angioneurotic edema.
4. Use β-blockers (carvedilol, sustained-release metoprolol succinate, or bisoprolol).
5. Sacubitril/valsartan may be used instead of an ACE inhibitor or angiotensin II receptor blocker for symptomatic HFrEF class II or III to further reduce morbidity and mortality.
6. Avoid or withdraw nonsteroidal anti-inflammatory drugs, most anti-arrhythmic drugs, and most calcium channel blockers.
7. Add an aldosterone antagonist (spironolactone or eplerenone) in selected patients with New York Heart Association class II–IV HFrEF who can be carefully monitored for renal function and potassium concentration. (Serum creatinine should be ≤ 2.5 mg/dl in men and ≤ 2.0 mg/dl in women. Serum potassium should be < 5.0 mEq/l).
8. Add isosorbide dinitrate plus hydralazine in patients self-described as African Americans with New York Heart Association class III-IV HFrEF who are being treated with diuretics, ACE inhibitors, and β-blockers.

HFrEF – heart failure with reduced left ventricular ejection fraction, ACE – angiotensin-converting enzyme. Adapted from references [1, 16].

taglandin synthesis, and decrease sodium and water retention by inhibiting angiotensin II stimulation of aldosterone release. ACE inhibitors are very effective in treating HFrEF (Table I). The ability of ACE inhibitors to block aldosterone production is only partial and limited to approximately the first 6 months of therapy, with loss of efficacy afterwards.

Angiotensin-converting enzyme inhibitors improve symptoms, quality of life, and exercise tolerance in patients with HFrEF. Angiotensin-converting enzyme inhibitors also increase survival in patients with HFrEF [18–22] and should be used to treat patients with HFrEF with a class I indication (Table I) [1, 16]. An overview of 32 randomized clinical trials in patients with HFrEF demonstrated that compared with placebo, ACE inhibitors reduced mortality by 23% and mortality or hospitalization for HFrEF by 35% [21]. Angiotensin-converting enzyme inhibitors also improve survival and reduce the incidence of HF and coronary events in patients with reduced LV ejection fraction but without HF [23–26]. ACE inhibitors should be used to treat these patients with a class-I indication [1, 16].

Angiotensin-converting enzyme inhibitors should be administered in patients with HFrEF in low doses after correction of hyponatremia or volume depletion. Avoid overdiuresis before initiating treatment with ACE inhibitors because volume depletion may cause hypotension or renal insufficiency when ACE inhibitors are started or when the dose of these drugs is increased to full therapeutic levels. After the maintenance dose of ACE inhibitors is reached, it may be necessary to increase the dose of diuretics.

Patients with HFrEF were randomized to lisinopril 2.5 mg to 5.0 mg daily versus 32.5 mg to 35 mg daily [27]. At 39-month to 58-month follow-up, compared with low-dose lisinopril, high-dose lisinopril caused an 8% insignificant reduction in mortality, a significant 12% reduction in mortality or all-cause hospitalization, and a significant 24% reduction in hospitalization for HF [27]. The discontinuation of the study drug was similar for the 2 treatment groups. These data indicate that patients with HFrEF should be treated with high doses of ACE inhibitors unless low doses are the only doses that can be tolerated.

In the Veterans Administration Cooperative Vasodilator–Heart Failure Trial II, enalapril, compared with isosorbide dinitrate plus hydralazine, reduced 2-year mortality by 28% because of a greater response to enalapril in whites than in African Americans [19]. This finding led to the study of isosorbide dinitrate versus placebo in African Americans with HF [28]. A report from the Studies of Left Ventricular Dysfunction databases showed that whites but not African Americans randomized to enalapril had a significant reduction in the risk of hospitalization for HF [29]. However, a post hoc analysis of the 4054 African American and white participants in the Studies of Left Ventricular Dysfunction Prevention Trial was performed to investigate whether enalapril had similar efficacy in preventing symptomatic HFrEF in African Americans versus whites [30]. Despite the increased absolute risk in African Americans compared with whites for the progression of asymptomatic LV dysfunction, enalapril was equally efficacious in reducing the risk of HF in African Americans versus whites [30].

Patients at risk for excessive hypotension should have their blood pressure monitored closely for the first 2 weeks of ACE inhibitor therapy and whenever the physician increases the dose of ACE inhibitor or diuretic. Renal function should be monitored in patients treated with ACE inhibitors to detect increases in blood urea nitrogen and in serum creatinine, especially in older patients with renal artery stenosis. A doubling in serum creatinine should lead the physician to consider renal dysfunction caused by ACE inhibitors, a need to lower the dose of diuretics, or exacerbation of HFrEF. Potassium supplements and potassium-sparing diuretics should not be given to patients receiving ACE inhibitors because ACE inhibitor therapy may cause hyperkalemia by blocking aldosterone production.

Asymptomatic hypotension with a systolic blood pressure between 80 and 90 mm Hg and a serum creatinine of !2.5 mg/dl are side effects of ACE inhibitors that should not necessarily cause discontinuation of this drug but should cause the physician to reduce the dose of diuretics if the jugular venous pressure is normal and to consider decreasing the dose of ACE inhibitor. Contraindications to the use of ACE inhibitors are symptomatic hypotension, progressive azotemia, angioneurotic edema, hyperkalemia, intolerable cough, and rash.

Angiotensin-converting enzyme inhibitors inhibit the metabolic degradation of bradykinin, which promotes vascular synthesis of vasodilating prostaglandins [31]. Aspirin is a cyclooxygenase inhibitor that dose-dependently inhibits synthesis of prostaglandins in vascular tissues [32]. Aspirin in doses of $\leq$ 100 mg daily provides the desired antiplatelet effect without inhibiting synthesis of prostaglandins.

There are conflicting data about the importance of the negative interaction of aspirin with ACE inhibitors in the treatment of patients with HFrEF. Some hemodynamic studies support the importance of this negative interaction [33, 34], whereas other hemodynamic studies do not [35, 36]. Retrospective analyses of clinical studies have also found conflicting data, with some studies supporting [37, 38] and other studies not support-

ing [39–41] a negative interaction between aspirin and ACE inhibitors. Until data from controlled clinical trials are available, a prudent approach to this controversy might be to reduce the dose of aspirin to 80 mg to 100 mg daily or substitute clopidogrel as an antiplatelet drug in patients with HFrEF treated with ACE inhibitors. The dose of ACE inhibitors could also be increased to overcome aspirin-related attenuation.

Angiotensin receptor blockers

Angiotensin II is a potent vasoconstrictor that may impair LV function and cause the progression of HF through increased impedance of LV emptying, adverse long-term structural effects on the heart and vasculature [42], and activation of other neurohormonal agonists, including norepinephrine, aldosterone, and endothelin [43].

The angiotensin II type-1 receptor blocker (ARB) losartan reduced the rate of first hospitalization for HFrEF by 32%, compared with placebo, at 3.4-year follow-up of patients with type-2 diabetes mellitus and nephropathy [44]. Losartan also reduced hospitalization for HFrEF by 41% compared with atenolol at 4.7-year follow-up of diabetics with hypertension and electrocardiographic LV hypertrophy [45].

In the Losartan Heart Failure Survival Study (ELITE) II, 3152 patients aged ≥ 60 years with New York Heart Association (NYHA) class II to IV HFrEF and an LV ejection fraction of ≤ 40% were randomized in a double-blind trial to receive losartan 50 mg daily or captopril 50 mg three times daily [46]. Median follow-up was 555 days. More patients discontinued captopril because of adverse effects (14.7%) than discontinued losartan (9.7%) [46].

Mortality was insignificantly 13% less in patients treated with captopril than in patients treated with losartan, significantly 77% less in patients treated with captopril plus β-blockers than in patients treated with losartan plus β-blockers, and insignificantly 5% less in patients treated with captopril without β-blockers than in patients treated with losartan without β-blockers [46]. Hospital admissions for any cause were insignificantly 4% higher in patients treated with losartan than in patients treated with captopril [46].

The Valsartan Heart Failure Trial randomized 5010 patients with NYHA class II to IV HFrEF to valsartan 160 mg daily or to placebo [47]. Ninety-three percent of the patients were treated with ACE inhibitors, 85% with diuretics, 67% with digoxin, and 35% with β-blockers. At 23-month follow-up, mortality was similar in the two treatment groups [47]. Mortality plus morbidity was reduced by 13% in patients treated with valsartan. Valsartan decreased mortality in patients treated with neither an ACE inhibitor nor a β-blocker [47].

The Valsartan in Acute Myocardial Infarction trial randomized 14,703 patients after myocardial infarction complicated by HFrEF to valsartan 160 mg twice daily, valsartan 80 mg twice daily plus captopril 50 mg three times daily, or captopril 50 mg three times daily [48]. At 25-month median follow-up, all-cause mortality was similar in the 3 groups. Hypotension and renal dysfunction were more common in patients treated with valsartan, whereas cough, rash, and taste disturbance were more common in patients treated with captopril [48]. Combining valsartan with captopril increased the incidence of adverse effects without improving survival [48].

In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Alternative Study, 2028 patients with HFrEF and intolerance to ACE inhibitors were randomized to candesartan 32 mg once daily or to placebo [49]. At 34-month median follow-up, candesartan reduced the incidence of cardiovascular death or hospitalization for HFrEF by 30% [49].

In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Added Study, 2548 patients with HFrEF treated with ACE inhibitors were randomized to candesartan 32 mg daily or to placebo [50]. At 41-month median follow-up, addition of candesartan to the ACE inhibitor reduced cardiovascular death or hospitalization for HFrEF by 15% [50].

On the basis of these data [46–50], the author concurs with the ACC/AHA guidelines [1, 16] that (1) an ARB should be used for treating HFrEF if the patient cannot tolerate an ACE inhibitor because of cough or angioneurotic edema with a class-I indication (Table I), and (2) an ARB instead of an ACE inhibitor should be used if the patient is already on an ARB with a class-IIa indication (Table II) [1, 16].

Table II. Class IIa recommendations for treating HFrEF

1. Angiotensin II receptor blockers may be used instead of angiotensin-converting enzyme inhibitors if patients are already taking them for other indications.
2. Hydralazine plus a nitrate may be used in patients with persistent symptoms who cannot be given an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker because of drug intolerance, hypotension, or renal insufficiency.
3. Digoxin can be used in patients with persistent symptoms to reduce hospitalization for HFrEF.
4. Ivabradine can be beneficial to reduce hospitalization for class II–III stable chronic HFrEF in patients on guided directed medical therapy receiving a β-blocker at the maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 beats per minute or greater at rest.

HFrEF – heart failure with reduced left ventricular ejection fraction. Adapted from references [1, 16].

β-Blockers

Chronic administration of β-blockers after myocardial infarction decreases mortality, sudden cardiac death, and recurrent myocardial infarction, especially in older patients [51–53]. These benefits are more marked in patients with a history of HFrEF [53].

β-Blockers have been shown to reduce mortality in older patients with complex ventricular arrhythmias associated with prior myocardial infarction and abnormal [54] or normal [55] LV ejection fraction. In patients with prior myocardial infarction, abnormal LV ejection fraction, and complex ventricular arrhythmias, β-blockers caused a 32% decrease in occurrence of new or worsened HF [54]. The benefit of β-blockers in decreasing coronary events in older patients with prior myocardial infarction is also especially increased in patients with diabetes mellitus [56], peripheral arterial disease [57], and abnormal LV ejection fraction [25, 58]. β-Blockers reduce mortality in patients with HFrEF [59–63].

At 1.3-year follow-up of 2,647 patients with NYHA class III or IV HFrEF, compared with placebo, bisoprolol reduced all-cause mortality by 34% [60]. At 1-year follow-up of 3,991 patients with NYHA class II to IV HFrEF, compared with placebo, metoprolol CR/XL reduced all-cause mortality by 34% [61]. At 10.4-month follow-up of 2,289 patients with severe HFrEF, compared with placebo, carvedilol reduced all-cause mortality by 35% [62]. At 32-month follow-up of 1,369 patients with NYHA class II or III HFrEF, compared with placebo, nebivolol reduced all-cause mortality or cardiovascular hospital admission by 14% [63].

β-blockers are effective in antagonizing neurohormonal systems that cause myocyte apoptosis, myocyte necrosis, myocyte hypertrophy, fetal gene program activation, extracellular matrix alterations, and β-receptor uncoupling [64]. β-Blockers may prevent or reverse increased systemic vascular resistance and increased afterload caused by excessive sympathetic nervous system activation. β-Blockers also reduce levels of atrial natriuretic peptide, brain natriuretic peptide, and tumor necrosis α levels [65]. β-Blockers are also effective in preventing cardiovascular events because of their antihypertensive, anti-ischemic, anti-arrhythmic, and anti-atherogenic effects [66]. The increase in ventricular rate that occurs after exercise can also be prevented with modest doses of β-blockers, especially in older patients.

β-Blockers reduce all-cause mortality, cardiovascular mortality, sudden death, and death from worsening HFrEF in patients with HFrEF [59–63]. β-Blockers decrease mortality in African Americans [59, 61, 62] and in whites [59–63] with HFrEF, in women and in men with HFrEF [59–63], in older and in younger patients with HFrEF [59–63], in diabetics and in nondiabetics with HFrEF [59–63], and in patients with severe HFrEF or with mild or moderate HFrEF [59–63]. β-Blockers should be used to treat patients with HFrEF with a class I indication [1, 16] unless there are contraindications to their use. Carvedilol and extended-release or controlled-release metoprolol (metoprolol CR/XL) are the only β-blockers that have been approved by the US Food and Drug Administration for the treatment of HFrEF in the United States. Bisoprolol is also approved for the treatment of HFrEF in Europe.

Patients with prior myocardial infarction and asymptomatic abnormal LV ejection fraction should be treated with ACE inhibitors plus β-blockers [1, 26, 67, 68]. An observational prospective study was performed in 477 patients (196 men and 281 women; mean age: 79 years) with prior myocardial infarction and abnormal LV ejection fraction (mean LV ejection fraction: 31%) [26]. At 34-month follow-up, ACE inhibitors alone reduced new coronary events by 17% and new HFrEF by 32%, and β-blockers alone reduced new coronary events by 25% and new HFrEF by 41%, compared with no β-blocker or ACE inhibitor [26]. At 41-month follow-up, ACE inhibitors plus β-blockers reduced new coronary events by 37% and new HFrEF by 61%, compared with no β-blocker or ACE inhibitor [26]. The longer follow-up time in patients treated with ACE inhibitors plus β-blockers indicates that β-blockers plus ACE inhibitors delayed as well as decreased the occurrence of new coronary events and HFrEF [26].

Patients should be treated with an ACE inhibitor or ARB and be in a relatively stable condition without the need of intravenous inotropic therapy and without signs of marked fluid retention before initiating β-blocker therapy in patients with HFrEF [69]. β-Blockers should be initiated in a low dose, such as carvedilol 3.125 mg twice daily or metoprolol CR/XL 12.5 mg daily if there is NYHA class III or IV HFrEF, or 25 mg daily if there is NYHA class II HFrEF. The dose of β-blockers should be doubled at 2- to 3-week intervals with the maintenance dose of β-blockers reached over 3 months (carvedilol 25 mg twice daily or 50 mg twice daily if over 187 pounds or metoprolol CR/XL 200 mg once daily). The patient may experience fatigue during the initiation or up-titration of the dose of β-blockers, with this effect dissipating over time. The need to continue β-blockers in this patient must be stressed because of the importance of β-blockers in decreasing mortality.

During titration, the patient should be monitored for HF symptoms, fluid retention, hypotension, and bradycardia [69]. If there is worsening of symptoms, increase the dose of diuretics or ACE inhibitors. Temporarily reduce the dose of β-block-

ers if necessary. If there is hypotension, decrease the dose of vasodilators and temporarily decrease the dose of β-blockers if necessary. Reduce or discontinue drugs that may decrease heart rate in the presence of bradycardia. Contraindications to the use of β-blockers in patients with HFrEF are bronchial asthma, severe bronchial disease, symptomatic bradycardia, and symptomatic hypotension [69].

Aldosterone antagonists

At 2-year follow-up of 1663 patients (mean age: 65 years) with severe HFrEF treated with diuretics, ACE inhibitors, 73% with digoxin, and 10% with β-lockers, spironolactone 25 mg daily reduced mortality by 30% and hospitalization for worsening HFrEF by 35% [70]. At 16-month follow-up of 6632 patients (mean age: 64 years) with acute myocardial infarction complicated by HFrEF treated with diuretics, ACE inhibitors, and 75% with β-blockers, eplerenone 50 mg daily reduced mortality by 15% and death from cardiovascular causes or hospitalization for cardiovascular events by 13% [71]. At 21-month follow-up of 2737 patients with class II HFrEF, compared with placebo, eplerenone 50 mg daily reduced cardiovascular death or hospitalization for HFrEF by 37% [72].

The ACC/AHA guidelines recommend with a class I indication the addition of an aldosterone antagonist in selected patients with class II to IV HFrEF who can be carefully monitored for preserved renal function and normal serum potassium concentration [1, 16]. Patients should have a serum creatinine 2.5 mg/dl or less in men and 2.0 mg/dl or less in women, and the serum potassium should be less than 5.0 mEq/l (Table I) [1, 16].

Sacubitril/valsartan

The PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) was a double-blind trial that randomized 8,442 patients with class II–IV HFrEF and an LV ejection fraction of ≤ 40% (later amended to ≤ 35%) to receive twice daily dosing of either 200 mg of sacubitril (a neprilysin inhibitor)/valsartan or 10 mg of enalapril in addition to standard medical therapy for HF [73]. If participants tolerated both study drugs during two run-in periods, they were then randomized to double-blind treatment. The primary endpoint was a composite of death from cardiovascular causes or hospitalization for HFrEF. At 27-month follow-up, sacubitril/valsartan caused a 20% reduction in the primary endpoint [73]. Use of this drug combination is discussed extensively elsewhere [74]. The 2016 ACC/AHA/Heart Failure Society of America updated guidelines state with a class I recommendation that sacubitril/valsartan may be used instead of an ACE inhibitor or ARB in patients with chronic symptomatic HFrEF class II or III to further reduce morbidity and mortality [16] (Table I). Clinical experience will provide additional information on the optimal titration and tolerability of sacubitril/valsartan with regard to blood pressure, adjustment of concomitant HF drugs, and the rare complication of angioneurotic edema [16].

Isosorbide dinitrate plus hydralazine

Oral nitrates reduce preload and pulmonary congestion in patients with HFrEF. Hydralazine reduces afterload, improving perfusion at the same level of LV filling pressure. In the Veterans Administration Cooperative Vasodilator–Heart Failure Trial I, oral isosorbide dinitrate plus hydralazine, compared with placebo, decreased mortality by 38% at 1 year, 25% at 2 years, and 23% at 3 years in men [75].

The African-American Heart Failure Trial randomized 1040 African Americans with class III–IV HFrEF (only 23% with ischemic heart disease) treated with diuretics, ACE inhibitors, and β-blockers to isosorbide dinitrate plus hydralazine or to placebo [28]. At 10-month follow-up, isosorbide dinitrate plus hydralazine reduced mortality by 43% and rate of first hospitalization for HFrEF by 33% [28].

The ACC/AHA guidelines recommend using isosorbide dinitrate plus hydralazine in patients self-described as African Americans with NYHA class III or IV HFrEF who are being treated with diuretics, ACE inhibitors, and β-blockers with a class I recommendation (Table I) [1]. These guidelines recommend use of isosorbide dinitrate plus hydralazine in patients with symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency with a class IIa indication (Table II) [1].

The initial dose of oral isosorbide dinitrate in patients with HFrEF is 10 mg 3 times daily, with subsequent titration up to a maximum dose of 40 mg 3 times daily. Nitrates should be given no more than 3 times daily, with daily nitrate washout intervals of 12 h to prevent nitrate tolerance from developing. The initial dose of oral hydralazine in patients with HFrEF is 10 mg to 25 mg 3 times daily, with subsequent titration up to a maximum dose of 100 mg 3 times daily.

Digoxin

At 37-month follow-up of 6,800 patients with HFrEF in the Digitalis Investigator Group (DIG) study, mortality was similar in patients treated with digoxin or placebo [76, 77]. HFrEF hospitalization was reduced by 28% in these patients [76, 77]. Hospitalization for any cause was reduced by

8% in these patients [77]. Hospitalization for suspected digoxin toxicity in patients treated with digoxin was 0.67% in patients aged 50 to 59 years, 1.91% in patients aged 60 to 69 years, 2.47% in patients aged 70 to 79 years, and 4.42% in patients aged ≥ 80 years [77].

A post hoc subgroup analysis of data from women with HFrEF in the DIG study showed by multivariate analysis that digoxin increased the risk of death among women by 23% (absolute increase of 4.2%) [78]. A *post hoc* subgroup analysis of data from men with HFrEF in the DIG study showed that digoxin reduced mortality by 6% if the serum digoxin level was 0.5 to 0.8 ng/ml, insignificantly increased mortality by 3% if the serum digoxin level was 0.8 to 1.1 ng/ml, and increased mortality by 12% if the serum digoxin level was ≥ 1.2 ng/ml [79].

Another post hoc subgroup analysis of data from all 1366 women with HFrEF in the DIG study showed that digoxin increased mortality for women by 80% if the serum digoxin level was ≥ 1.2 ng/ml and insignificantly increased mortality by 5% if the serum digoxin level was 0.5 to 1.1 ng/ml [80]. If the serum digoxin level was 0.5 to 1.1 ng/ml and the LV ejection fraction was < 35%, digoxin reduced HFrEF hospitalization by 37% in women [80].

Digoxin reduces the rapid ventricular rate associated with supraventricular tachyarrhythmias and may be used along with β-blockers to treat patients with HFrEF and supraventricular tachyarrhythmias, such as atrial fibrillation. Digoxin may also be used to treat patients with persistent symptoms of HFrEF despite treatment with diuretics, ACE inhibitors, and β-blockers to reduce HFrEF hospitalization with a class IIa indication (Table II) [1]. The maintenance dose of digoxin should be 0.125 mg daily in older patients with HFrEF, and the serum digoxin level should be between 0.5 and 0.8 ng/ml.

Digoxin has a narrow therapeutic index, especially in older patients. Age-related reduction in renal function increases serum digoxin levels in older persons. The decrease in skeletal muscle mass in older patients reduces the volume of distribution of digoxin, increasing serum digoxin levels. Older patients are also more likely to be taking drugs that interact with digoxin by interfering with its bioavailability or excretion. For example, spironolactone, triamterene, amiodarone, quinidine, verapamil, propafenone, erythromycin, tetracycline, propantheline, and other drugs increase serum digoxin levels. Therefore, older patients receiving these drugs are at increased risk for developing digitalis toxicity. In addition, hypokalemia, hypomagnesemia, myocardial ischemia, hypoxia, acute and chronic lung disease, acidosis, hypercalcemia, and hypothyroidism may cause digitalis toxicity despite normal serum digoxin levels [81].

Other neurohormonal antagonists

Other neurohormonal antagonists have not been shown to be effective in the treatment of HFrEF [82–86]. The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial was a phase III randomized double-blind trial that compared omapatrilat with enalapril in 5770 patients with class II–IV HFrEF for a mean duration of 14.5 months [82]. Results from this trial showed that omapatrilat was neither superior nor inferior to enalapril in reducing the primary endpoint of combined all-cause mortality and HFrEF hospitalizations requiring intravenous treatment [82].

Calcium channel blockers

Calcium channel blockers, such as nifedipine, diltiazem, and verapamil, exacerbate HFrEF in patients with HFrEF [87]. Diltiazem increased mortality in patients with pulmonary congestion and abnormal LV ejection fraction after myocardial infarction [88]. The Multicenter Diltiazem Postinfarction Trial also showed in patients with an LV ejection fraction ≤ 40% that late HFrEF at follow-up increased in patients randomized to diltiazem (21%) compared with patients randomized to placebo (12%) [89].

The vasoselective calcium channel blockers amlodipine [90] and felodipine [91] did not affect survival in patients with HFrEF. In these studies, the incidence of pulmonary edema was higher in patients treated with amlodipine (15%) than in patients treated with placebo (10%) [90], and the incidence of peripheral edema was higher in patients treated with amlodipine [90] or felodipine [91] than in those treated with placebo. On the basis of the available data, calcium channel blockers should not be administered to patients with HFrEF (Table I) [1].

Nesiritide

Intravenous nesiritide (human B-type natriuretic peptide) causes hemodynamic and symptomatic improvement in hospitalized patients with decompensated HFrEF through balanced vasodilatory effects, neurohormonal suppression, and enhanced natriuresis and diuresis [92]. Nesiritide improved hemodynamic function and some self-reported symptoms more effectively than intravenous nitroglycerin or placebo in a randomized, double-blind trial of 489 patients with dyspnea at rest from decompensated HFrEF in the Vasodilation in the Management of Acute HF (VMAC) study [92].

However, in the VMAC study, intravenous nesiritide, compared with intravenous nitroglycerin, insignificantly increased hospital stay and 30-day

and 6-month mortality [92, 93]. This trial was also not powered for mortality. A review of US Food and Drug Administration files available via the website also showed that nesiritide (1) significantly increases the risk of worsening renal function in patients with acute decompensated HF [94] and (2) that nesiritide insignificantly increased mortality 1.8 times in patients with acute decompensated HFrEF [95]. In a study of 7,141 patients, of median age 67 years, with acute decompensated HFrEF randomized to intravenous nesiritide or to placebo, compared to placebo, nesiritide caused no effect on dyspnea at 6 h or at 24 h, caused no effect on rehospitalization for HFrEF or death within 30 days, and caused an increase in hypotension (26.6% for nesiritide vs. 15.3% for placebo) [96]. These data do not support the use of nesiritide in patients with acute decompensated HFrEF.

Inotropic therapy

Inotropic therapy increases mortality in patients with HFrEF [97–105]. Positive inotropic drugs other than digoxin should not be used to treat chronic HFrEF unless they are being used for palliative therapy or as a bridge to cardiac transplantation. These drugs may be used for a short duration in patients who have acute decompensated HFrEF and in life-threatening situations.

Ivabradine

Ivabradine is a new therapeutic drug that selectively inhibits the I_f current in the sinoatrial node, causing a reduction in ventricular rate [106]. Data were available for analysis of 6505 patients with HFrEF and an LV ejection fraction ≤ 35% in sinus rhythm with a heart rate ≥ 70 beats per minute on background medical therapy including a β-blocker if tolerated who were randomized to ivabradine 7.5 mg twice daily or to placebo [107]. At 22.9-month follow-up, the primary outcome of cardiovascular death or hospitalization for worsening HF was reduced by 18% by ivabradine, driven mainly by hospitalization for worsening HF [107]. The 2016 ACC/AHA/Heart Failure Society of America guidelines state with a class IIa recommendation that ivabradine can be beneficial to reduce hospitalization for class II–III stable chronic HFrEF in patients on guided directed medical therapy receiving a β-blocker at the maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 beats per minute or greater at rest [16].

Conflict of interest

The author declares no conflict of interest.

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