Overview of the therapy of heart failure due to systolic dysfunction

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INTRODUCTION — Heart failure (HF) is a common clinical syndrome representing the end-stage of a number of different cardiac diseases. It can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. There are two mechanisms by which reduced cardiac output and HF occur: systolic dysfunction and diastolic dysfunction.

An overview of the management of HF due to systolic dysfunction, including the treatment of associated conditions, will be presented here [1,2]. Drugs that should be avoided or used with caution in patients with HF, the management of refractory HF, and therapy of HF due to diastolic dysfunction are discussed separately. (See "Drugs that should be avoided or used with caution in patients with heart failure" and "Management of refractory heart failure" and "Treatment and prognosis of diastolic heart failure".)

Chronic versus acute decompensated HF — The following discussion will emphasize the therapeutic approach to the patient with chronic HF. The management of acute decompensated HF requiring hospitalization is presented separately. Such patients typically present with dyspnea and often have rales with or without peripheral edema [3]. (See "Treatment of acute decompensated heart failure: General considerations" and "Treatment of acute decompensated heart failure in acute coronary syndromes".)

Major society guidelines — Several major societies have published extensive guidelines for the treatment of HF [1,2,4,5]. These include the 2013 American College of Cardiology Foundation/American Heart Association guideline [2], the 2006 Canadian Cardiovascular Society consensus conference [4], the 2012 European Society of Cardiology guidelines [1], and the 2010 Heart Failure Society of America guidelines [5].

With few exceptions, these societies make similar recommendations regarding the treatment of HF due to systolic dysfunction. Our approach is in broad agreement with these guidelines.

GENERAL PRINCIPLES

Goals of therapy — The goals of heart failure (HF) therapy are clinical improvement of symptoms and ultimately a reduction in the risk of morbidity (including the rate of hospitalization) and mortality.

Components of therapy — Management of HF begins with an accurate assessment of the underlying etiology, contributing factors, and severity of the syndrome. (See "Evaluation of the patient with suspected heart failure".) This is followed by a therapeutic regimen aimed at the following factors as well as addressing underlying and concurrent cardiovascular conditions (see 'Treatment of underlying and concurrent cardiovascular disease' below):

Correction of systemic factors — Treatment should address systemic contributing factors (eg, thyroid dysfunction, infection, uncontrolled diabetes) (table 1), as well as comorbidities such as chronic obstructive pulmonary disease and sleep apnea. (See "Sleep disordered breathing in heart failure".)

Lifestyle modification — Recommendations for lifestyle modification are largely based upon observational studies and physiologic rationale, as there have been scant randomized trials on the effects of lifestyle modification.

- ●Cessation of smoking
- ●Restriction of alcohol consumption
- ●Salt restriction is commonly recommended, although there are insufficient data to support any specific level of sodium intake in patients with symptomatic HF as noted in the 2013 American College of Cardiology/American Heart Association (ACC/AHA) and 2012 European Society of Cardiology guidelines [1,2]. Observational studies have produced conflicting results [2] and two systematic reviews of clinical trials have been retracted [6,7].

  Given the available evidence, we suggest <2g/day sodium restriction in patients with symptomatic HF. The 2013 ACC/AHA guidelines suggest some degree (eg, <3 g/d) of sodium restriction in patients with symptomatic HF.
- ●Fluid restriction (1.5 to 2 L/d) is suggested in patients with refractory HF, particularly those with hyponatremia [2]
- ●Weight reduction in obese subjects with goal of being within 10 percent of ideal body weight
- ●Daily weight monitoring is recommended to detect fluid accumulation before it becomes symptomatic

Review of drugs — All drugs and supplements that the patient is taking should be reviewed and those that may contribute to HF (eg, nonsteroidal antiinflammatory drugs, antiarrhythmic drugs, calcium channel blockers, thiazolidinediones) should be avoided. (See "Drugs that should be avoided or used with caution in patients with heart failure".)

Preventative care — Appropriate preventative care includes pneumococcal vaccination and annual influenza vaccination [1,5]. (See "Pneumococcal vaccination in adults" and "Seasonal influenza vaccination in adults".)

Drug and device therapy — Pharmacologic therapy is aimed at relieving symptoms (including the risk of hospitalization), slowing the progression of the HF, and improving patient survival. (See 'Pharmacologic therapy of HF' below.)

Devices recommended in selected patients with HF include the following:

- ●An implantable cardioverter-defibrillator (ICD) for secondary prevention of sudden cardiac death and for primary prevention in selected patients. The criteria for ICD implantation are discussed separately. (See "Secondary prevention of sudden cardiac death in heart failure and cardiomyopathy" and "Primary prevention of sudden cardiac death in heart failure and cardiomyopathy".)
- ●Cardiac resynchronization therapy (CRT) with biventricular pacing can improve symptoms and survival in selected patients who are in sinus rhythm and have a reduced left ventricular ejection fraction, and a prolonged QRS duration. Most patients who satisfy criteria for CRT implantation are also candidates for an ICD and receive a combined device. Criteria for CRT use are discussed separately. (See "Cardiac resynchronization therapy in heart failure: Indications".)

Treatment of refractory heart failure — Specialized management is indicated for HF refractory to maximal oral pharmacologic therapy. (See "Management of refractory heart failure".) Cardiac transplantation and mechanical circulatory support are discussed separately. (See "Indications and contraindications for cardiac transplantation" and "Intermediate- and long-term mechanical circulatory support".)

Strategies to reduce hospitalization — Comprehensive outpatient and inpatient support programs may reduce hospitalization rates but less comprehensive approaches appear to be less effective. (See "Strategies to reduce hospitalizations in patients with heart failure".)

TREATMENT OF UNDERLYING AND CONCURRENT CARDIOVASCULAR DISEASE — Underlying or concomitant conditions that predispose to the development or exacerbation of heart failure (HF) should be identified and treated. Common concomitant disorders include hypertension, diabetes mellitus, coronary artery disease, and atrial fibrillation [2]. (See "Epidemiology and

causes of heart failure", section on 'Predisposing conditions for HF' and "Causes of dilated cardiomyopathy".)

Hypertension — Hypertension is the primary cause of HF in many patients. In addition, hypertension imposes an increased hemodynamic load on the failing ventricle in patients with established HF due to any etiology. The goals of therapy are to control blood pressure and to reduce left ventricular afterload, thereby improving cardiac function and decreasing the progression of pathologic remodeling.

Drug therapy — A beta blocker, an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), and an aldosterone antagonist are the preferred antihypertensive agents because, as will be described below, they improve survival in patients with HF. Beta blockers can also provide anginal relief in patients with ischemic heart disease and rate control in those with atrial fibrillation. Beta blocker therapy should always be initiated at very low doses to minimize the risk of cardiac decompensation. (See 'Initiation of therapy' below.)

For patients who are still hypertensive after initiation of beta blockers and ACE inhibitors and/or ARBs, or who cannot tolerate these drugs, appropriate agents include loop diuretics, nitrates, some vasoselective calcium channel blockers (eg, amlodipine and felodipine), and hydralazine [8]. (See "Treatment of hypertension in patients with heart failure".)

Renovascular disease — Another consideration in patients with HF and hypertension is renovascular disease, particularly in those with HF due to ischemic heart disease.

Recurrent unexplained HF decompensation and/or flash (sudden-onset) pulmonary edema occurs in some patients with renovascular hypertension, often with preserved (normal or near normal) left ventricular systolic function. Flash pulmonary edema appears to be more common in patients with bilateral renal artery stenosis as compared to those with unilateral disease (eg, 41 versus 12 percent) [9,10]. The combination of bilateral renal artery stenosis and flash pulmonary edema has been named the Pickering syndrome [11,12]. Acute treatment of acute decompensated HF in patients with this syndrome includes blood pressure control and, in some cases, diuresis. However, in patients who are euvolemic or dehydrated, diuresis should be avoided as it may lead to renal insufficiency, and preload reduction with nitrates is preferable.

Only limited observational data are available on the efficacy of revascularization for this condition. A review of revascularization (percutaneous, largely with stenting, or surgery) in 87 reported cases of bilateral renal artery stenosis and flash pulmonary edema reported that renal function improved in 81 percent and 92 percent had no further episodes of flash pulmonary edema [11]. However, these data must be viewed with caution given the limited controls and risk of bias in these case series.

The 2005 American College of Cardiology/American Heart Association (ACC/AHA) peripheral arterial disease guidelines recommended percutaneous revascularization for patients with hemodynamically significant renal artery stenosis and recurrent, unexplained HF or sudden unexplained pulmonary edema [13]. However, an AHA writing group later noted that treatment of atherosclerotic renal artery disease is controversial since the benefits and risks are not well-defined [14]. (See "Treatment of bilateral atherosclerotic renal artery stenosis or stenosis to a solitary functioning kidney" and "Treatment of unilateral atherosclerotic renal artery stenosis".)

Ischemic heart disease — Coronary atherosclerosis is the most common cause of cardiomyopathy in the United States, comprising 50 to 75 percent of patients with HF. In addition, coronary disease (and other atherosclerotic disease) may be present in patients with HF of other causes, and may sometimes be overlooked as a contributing factor [15].

Patients with ischemic heart disease may have HF from one or both of two mechanisms: a prior myocardial infarction followed by left ventricular dysfunction and remodeling; or hibernating myocardium due to chronic but potentially reversible ischemic dysfunction [16,17]. A separate issue is that patients with idiopathic dilated cardiomyopathy with a normal coronary arteriogram at diagnosis may over time develop significant coronary atherosclerosis [18].

All patients with documented ischemic heart disease should be treated medically for relief of angina and with risk factor reduction, such as rigorous control of serum lipids. (See "Stable ischemic heart disease: Overview of care" and "Secondary prevention of cardiovascular disease".)

Myocardial revascularization with angioplasty or bypass surgery may improve symptom status, exercise capacity, and prognosis in selected patients with dysfunctional yet viable (hibernating or stunned) myocardium [17]. (See "Evaluation of hibernating myocardium" and "Diagnosis and management of ischemic cardiomyopathy".) Revascularization should also be considered in patients with a history of repeated episodes of acute left ventricular dysfunction and flash pulmonary edema. (See "Evaluation of acute decompensated heart failure".)

Valvular disease — Valvular heart disease is the primary cause of HF in perhaps 10 to 12 percent of patients [19] In addition, valvular dysfunction is a secondary or superimposed phenomenon in many cases of HF. As an example, some degree of mitral and tricuspid regurgitation is almost always present in patients with severe dilated cardiomyopathy, regardless of etiology [20]. (See "Functional mitral regurgitation".)

Valvular disease imposes a hemodynamic load on the ventricles, leading to further impairment in cardiac function, regardless of whether the valvular disease is primary or secondary. Surgical correction of valvular disease, such as aortic or mitral stenosis or regurgitation and/or tricuspid regurgitation, can lead to improvement in cardiac function and resolution of symptoms. (See appropriate topics for the indications for surgery with various valvular lesions).

Other factors — There are a variety of other potentially reversible conditions that can impair left ventricular function and cause, or worsen, HF. These include alcohol abuse, cocaine abuse, obstructive sleep apnea, nutritional deficiencies, myocarditis, hemochromatosis, sarcoidosis, thyroid disease, diabetes mellitus, and rheumatologic disorders such as systemic lupus erythematosus. The evaluation to detect these conditions should include a careful history, including a history of systemic or other noncardiac disease, and, in some cases, consideration of endomyocardial biopsy. (See "Causes of dilated cardiomyopathy" and "Evaluation of the patient with suspected heart failure" and "Endomyocardial biopsy".)

PHARMACOLOGIC THERAPY OF HF — The goals of pharmacologic therapy are to improve symptoms (including risk of hospitalization), slow or reverse deterioration in myocardial function, and reduce mortality (table 2). While the initial goal is to alleviate symptoms, drug therapy should be titrated as tolerated to target ranges for optimum clinical benefit. The benefits observed from aggressive monitoring strategies (eg, brain natriuretic peptide guided therapy) (see "Natriuretic peptide measurement in heart failure", section on 'Chronic HF') suggest that treatment beyond clinical congestion may improve outcomes. Additional pharmacologic therapy is directed at the prevention of arrhythmias and embolic events and the treatment of anemia and other possible exacerbating factors (table 1).

The treatment of heart failure (HF) in pregnancy involves specific concern about the effects of medications on the fetus and the mother, and therefore is discussed separately. (See "Management of heart failure during pregnancy".)

A number of drugs are recommended in HF for symptom relief and improvement in outcome (figure 1) [1,2]:

- Improvement in symptoms can be achieved by diuretics, beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), hydralazine plus nitrate, digoxin, and aldosterone antagonists.
- Prolongation of patient survival has been documented with diuretics, beta blockers, ACE inhibitors, ARBs, hydralazine plus nitrate, and aldosterone antagonists (table 2).

We recommend the following approach to the long-term management of patients with HF. This approach is generally in agreement with the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for the management of HF [2]. The data supporting these summary recommendations are discussed in detail in the appropriate topic reviews. Although the use of evidence-based HF therapies has improved due in part to national efforts such as the American Heart Association “Get With the Guidelines” program, the

underutilization of evidence-based HF therapies continues to contribute to substantial excessive mortality [21].

Order of therapy — We recommend the following sequence of drugs in the typical patient, with allowance for variations depending upon clinical response:

- Loop diuretics are introduced first for fluid control in patients in overt HF. The goal is relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema. (See 'Diuretics' below.)
- ACE inhibitors or, if not tolerated, ARBs are typically initiated during or after the optimization of diuretic therapy. These drugs are usually started at low doses and then titrated to goals based upon trial data. (See 'ACE inhibitors' below.)
- Beta blockers are initiated after the patient is stable on ACE inhibitors, again beginning at low doses with titration to trial goals as tolerated. (See 'Beta blockers' below.)

The following drugs should be given to selected patients in the absence of a contraindication:

- The addition of an aldosterone antagonist (spironolactone or, if not tolerated, eplerenone) to improve survival in patients who can be monitored for adequate renal function and a normal plasma potassium concentration, and have New York Heart Association (NYHA) functional class II HF and a left ventricular ejection fraction (LVEF) ≤30 percent; or NYHA functional class III to IV HF and an LVEF <35 percent (table 3); or are post-ST elevation myocardial infarction and already receiving therapeutic doses of ACE inhibitor, have an LVEF ≤40 percent, and have either symptomatic HF or diabetes mellitus. (See 'Aldosterone antagonists' below.)
- ARBs as an alternative to ACE inhibitors in patients who cannot tolerate these drugs. (See 'Angiotensin II receptor blockers' below.)
- The addition of the combination of hydralazine and a nitrate for patients (particularly blacks) with a reduced LVEF who have persistent symptoms despite therapy with an ACE inhibitor and beta blocker. (See 'Hydralazine plus nitrates' below.)
- Digoxin to improve symptoms and reduce hospitalization for HF or, for patients with concomitant atrial fibrillation, for rate control. (See 'Digoxin' below.)

ACE inhibitors or beta blockers first — We initiate ACE inhibitor therapy prior to beta blocker therapy based upon clinical trials that followed this approach. Randomized trials (eg, CIBIS III) suggest that eventual outcomes may be similar if beta blockers are given first [22-24]. The approach we recommend is based upon practical considerations related to differences in time to benefit and the importance of attaining target dose for these two drug classes:

- ACE inhibitors provide rapid hemodynamic benefit and will not exacerbate HF in the short run [2]. The rapid improvement in hemodynamics and renal function that can occur with ACE inhibitors may facilitate the subsequent initiation of beta blockers, which may transiently impair hemodynamics and symptoms. (See "ACE inhibitors in heart failure due to systolic dysfunction: Therapeutic use", section on 'Effect of dose'.)
- The hemodynamic benefits of beta blockers are delayed (and there may be a transient worsening in cardiac function when therapy is initiated), but the long-term improvements in LVEF and survival are dose-dependent in patients who can tolerate the target dose (figure 2) [25]. However, patients who cannot tolerate the target dose may derive similar benefit as those who can, if they attain the same degree of beta blockade, as assessed from the reduction in heart rate [26]. These observations suggest that some patients have higher sensitivity to beta blockers.

Given these considerations, we start with a low dose of an ACE inhibitor (eg, lisinopril 5 mg/day), increase to a moderate dose (eg, lisinopril 15 to 20 mg/day) at one- to two-week intervals, and then begin a beta blocker, gradually increasing toward the target dose or, if this cannot be achieved, the highest tolerated dose. When the beta blocker titration is completed, the ACE inhibitor titration is completed. In patients with low risk of adverse response to ACE inhibitors (good blood pressure, no hyponatremia, hyperkalemia, or risk of intravascular depletion), higher doses of the ACE inhibitor can be started and the titration can be quicker.

Complications that develop during dose titration of the beta blocker should be treated. For example, the diuretic dose should be increased for fluid overload [2]. Hypotension rarely limits metoprolol titration, but may occur with carvedilol due to its additional vasodilator activity. If hypotension limits carvedilol titration, one should consider a change to metoprolol.

Since many patients with HF have low blood pressures, we generally alter the regimen only for symptoms or signs of underperfusion. A cardiologist should be consulted for patients who have difficulty attaining target doses.

Diuretics — Sodium and water retention lead to the common congestive symptoms of pulmonary and peripheral edema. Fluid overload can typically be controlled and symptoms improved by diuretic therapy. Improvement in symptoms can occur within hours to days. In comparison, the clinical effects of digoxin, ACE inhibitors, and beta blockers may require weeks or months to become fully apparent.

Although data on diuretic efficacy are limited, a meta-analysis of a few small trials found that diuretics were associated with reduction in mortality as well as reduced admission for worsening HF [27]. (See "Use of diuretics in patients with heart failure", section on 'Efficacy and safety'.)

As stated in the ACCF/AHA HF guideline, the goal of diuretic therapy is to eliminate clinical evidence of fluid retention, such as elevated jugular venous pressure and peripheral edema [2]. This goal should be pursued while adverse effects are monitored (See "Use of diuretics in patients with heart failure", section on 'Goals of therapy'.)

Appropriate diuretic usage can also affect the success of other drugs given for the treatment of HF. Inappropriately low doses will result in fluid retention, which can diminish the response to ACE inhibitors and ARBs and increase the risk of decompensation with the use of beta blockers. Conversely, excessive diuresis will lead to volume contraction, which can increase the risk of hypotension and renal insufficiency with ACE inhibitors, ARBs, and beta blockers.

The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond better to bumetanide or torsemide because of superior and more predictable absorption. (See "Use of diuretics in patients with heart failure".)

The usual starting dose in outpatients with HF is 20 to 40 mg of furosemide or its equivalent. Subsequent dosing is determined by the diuretic response. In patients who are volume overloaded, a reasonable goal is weight reduction of 1.0 kg/day. If a patient does not respond, the diuretic dose should initially be increased to find the single effective dose, rather than giving the same dose twice a day.

Intravenous diuretics (either as a bolus or a continuous infusion) are more potent than their equivalent oral doses, and may be required for unstable or severe disease. Thiazide diuretics can be added for a synergistic effect. (See "Use of diuretics in patients with heart failure".)

The fall in intracardiac filling pressure that results from diuretic-induced fluid removal may lower the cardiac output via the Frank-Starling relationship. This effect occurs when the rate of diuresis exceeds the rate of fluid mobilization from tissues, and may occur despite persistent peripheral edema and/or ascites. An otherwise unexplained fall in blood pressure or rise in blood urea nitrogen and serum creatinine should be viewed as a sign of a potentially important reduction in cardiac output. Further diuresis should be performed at a slower rate and only with careful monitoring for signs and symptoms attributable to hypoperfusion. (See "Use of diuretics in patients with heart failure".)

Over the long term, diuretic therapy should be maintained to prevent recurrent edema. In many cases, this adjustment can be facilitated by having the patient record his or her weight each day and allowing him or her to make changes in dose if the weight increases or decreases beyond a specified range.

ACE inhibitors — ACE inhibitors improve survival in patients with left ventricular systolic dysfunction (LVEF ≤40 percent), ranging from asymptomatic left ventricular dysfunction [28] to

moderate or severe HF (figure 3A-C) [29-32]. Although some concern has been raised concerning their effectiveness in blacks, the available evidence is **not** sufficient to support a difference in ACE inhibitor use based on race. (See "ACE inhibitors in heart failure due to systolic dysfunction: Therapeutic use" and 'Influence of race' below.)

All patients with asymptomatic or symptomatic left ventricular dysfunction should be started on an ACE inhibitor. Beginning therapy with low doses (eg, 6.25 mg of captopril three times daily, 2.5 mg of enalapril twice daily, or 5 mg of lisinopril once daily) will reduce the likelihood of hypotension and azotemia [33]. If initial therapy is tolerated, the dose is then gradually increased at one- to two-week intervals to, if tolerated, a target dose of 50 mg three times daily of captopril, 20 mg twice daily of enalapril, or up to 40 mg/day of lisinopril or quinapril. In hospitalized patients, the dose may be titrated at one- to two-day intervals. While therapy may be initiated with captopril in patients in whom there is concern about blood pressure reduction, we prefer once-per-day agents such as lisinopril for long-term therapy in these patients who typically receive several medications. Blood should be obtained in all patients one to two weeks after starting or changing a dose and periodically thereafter to assess the plasma potassium concentration and renal function.

These relatively high doses are recommended because they were used in the successful trials [2]. Although there is uncertainty if these doses are much more beneficial than lower doses, maximum dose therapy, if tolerated, is still recommended [2,34,35]. If the target doses cannot be administered or are poorly tolerated, lower doses should be used with the expectation that there are likely to be only small differences in efficacy between low and high doses [2,34]. (See "ACE inhibitors in heart failure due to systolic dysfunction: Therapeutic use", section on 'Effect of dose'.)

Impact of aspirin — Some evidence suggests that aspirin inhibits the acute hemodynamic effects of ACE inhibitors. However, most of the evidence does not support an inhibitory effect of aspirin on the long-term outcome benefits of ACE inhibitors in HF. For patients with known coronary artery disease, ASA is still recommended. However, there is no evidence for using aspirin in patients without coronary artery disease. (See "ACE inhibitors in heart failure due to systolic dysfunction: Therapeutic use", section on 'Use with aspirin' and "Drugs that should be avoided or used with caution in patients with heart failure", section on 'Aspirin'.)

Beta blockers — At least certain beta blockers, particularly carvedilol, metoprolol succinate, and bisoprolol, improve overall and event-free survival in patients with NYHA class II to III HF [36-38] and probably in class IV HF [39,40]. Beta blockers with intrinsic sympathomimetic activity (such as pindolol and acebutolol) should be **avoided** [36]. (See "Rationale for and clinical trials of beta blockers in heart failure due to systolic dysfunction".)

The beta blocker trials in HF were carried out in patients receiving therapy with an ACE inhibitor; thus, the improvement in survival is additive to that induced by ACE inhibitors (figure 4) [41,42].

The magnitude of benefit was illustrated in a meta-analysis that included 22 trials involving more than 10,000 patients [36]. Compared to placebo, beta blockers significantly reduced mortality at one year (odds ratio 0.65) and two years (odds ratio 0.72). During the first year, it was estimated that beta blocker therapy saved 3.8 lives per 100 patients treated and was associated with four fewer hospitalizations per 100 patients treated.

The controlled trials, which evaluated the role of beta blockers in HF, excluded patients with relative contraindications to beta blocker therapy. Relative contraindications in patients with HF include:

- Heart rate <60 bpm
- Symptomatic hypotension
- Greater than minimal evidence of fluid retention
- Signs of peripheral hypoperfusion
- PR interval >0.24 sec
- Second- or third-degree atrioventricular block
- History of asthma or reactive airways
- Peripheral artery disease with resting limb ischemia

Choice of agent — We recommend use of extended release metoprolol succinate, carvedilol, or bisoprolol since these beta blockers have been shown to reduce all-cause mortality and decrease hospitalization in patients with HF and left ventricular systolic dysfunction (LVEF ≤ 35 to 40 percent) in randomized controlled trials.

Limited data are available on the comparative efficacy of these three beta blockers. Indirect evidence suggests that carvedilol may produce greater improvement in LVEF than metoprolol. Patients with low blood pressure may be less likely to tolerate carvedilol because of its vasodilatory activity. Conversely, carvedilol may be preferred in patients with higher blood pressure. (See "Rationale for and clinical trials of beta blockers in heart failure due to systolic dysfunction", section on 'Comparison with other beta blockers'.)

Retrospective data suggest that some beta blockers other than those with proven benefit in randomized trials (eg, atenolol) may be beneficial in HF. However these observations are not sufficient to support a recommendation for use of beta blockers without benefit established by randomized studies.

Patients with low blood pressure may tolerate metoprolol better than carvedilol. Conversely, those with high blood pressure may have a greater lowering of blood pressure with carvedilol. In MERIT-HF, metoprolol succinate resulted in a higher blood pressure than placebo, presumably because of improved cardiac function.

Guidelines and recommendation — The 2013 ACCF/AHA guideline recommends use of one of the beta blockers proven to reduce mortality (carvedilol, extended release metoprolol succinate, and bisoprolol) in all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (table 3) [2]. (See "Use of beta blockers in heart failure due to systolic dysfunction".)

In the absence of a contraindication, our recommendation is to offer carvedilol, metoprolol succinate, or bisoprolol to patients with NYHA class II, III, or stable class IV HF with LVEF less than 40 percent.

Initiation of therapy — Because of the need for careful attention to initial dosing and the risk of transient worsening of symptoms, it is recommended that beta blocker therapy be initiated under the consultative guidance of an experienced HF center. Among inpatients, initiation of therapy prior to hospital discharge improves beta blocker use without an increase in side effects or drug discontinuation [43]. Prior to initiation of therapy, the patient should have no or minimal evidence of fluid retention and should not have required recent intravenous inotropic therapy. As discussed above, we recommend that patients not already on an ACE inhibitor be initiated and at least partially up-titrated prior to initiation of a beta blocker.

The patient should be informed that beta blockers may lead to an increase in symptoms for 4 to 10 weeks before any improvement is noted. Therapy should be begun at **very low doses** and the dose doubled at intervals of two weeks or more until the target dose is reached or symptoms become limiting [44]. Initial and target doses are:

- For carvedilol, 3.125 mg twice daily initially and 25 to 50 mg twice daily ultimately (the higher dose being used in subjects over 85 kg).
- For extended-release metoprolol (metoprolol succinate), 12.5 mg daily in patients with NYHA class III or IV or 25 mg daily in patients with NYHA II, and ultimately 200 mg/day. If patients receive short-acting metoprolol for cost reasons, we recommend 6.25 mg twice daily initially and 50 to 100 mg twice daily ultimately.
- For bisoprolol, 1.25 mg once daily initially and 5 to 10 mg once daily ultimately.

Even lower starting doses are suggested for patients with recent decompensation or a systolic pressure below 85 mmHg.

Every effort should be made to achieve the target dose since the improvement appears to be dose-dependent. The proportion of patients who reach the target dose is higher in clinical trials than in the general population in which the patients are older and have more comorbid disease.

However, although not optimal, even low doses appear to be of benefit and should be used when higher doses are not tolerated [26]. Not uncommonly, a dose that is not well tolerated during initial up-titration will be tolerated at a later time or with a slower rate of up-titration.

What may be most important is the degree of beta blockade [26]. However, aiming for a particular resting heart rate or a particular reduction in heart rate is not of proven value [45].

The patient should weigh himself or herself daily and call the physician if there has been a 1 to 1.5 kg weight gain. Weight gain alone may be treated with diuretics, but resistant edema or more severe decompensation may require dose reduction or cessation (possibly transient) of the beta blocker. (See "Use of beta blockers in heart failure due to systolic dysfunction".)

Although data about the duration of beta blocker therapy in HF are lacking, it has been suggested that patients who are doing well should not have the beta blocker withdrawn, since clinical deterioration and sudden death or death from progressive HF have been observed.

Aldosterone antagonists — Spironolactone and eplerenone, which compete with aldosterone for the mineralocorticoid receptor, prolong survival in selected patients with HF as demonstrated in randomized controlled trials [46-48] (See "Use of aldosterone antagonists in systolic heart failure".)

The 2013 ACCF/AHA HF guideline recommended addition of an aldosterone antagonist in patients with NYHA class II to IV HF and LVEF ≤35 percent who can be carefully monitored for preserved renal function and a normal plasma potassium concentration [2]. (See "Use of aldosterone antagonists in systolic heart failure", section on 'Eplerenone in EMPHASIS-HF trial'.)

We recommend aldosterone antagonist therapy to treat HF in patients who have NYHA functional class II HF and an LVEF ≤30 percent, or NYHA functional class III to IV HF and an LVEF <35 percent, who can be carefully monitored for serum potassium and renal function. We also recommend aldosterone antagonist therapy for patients post ST elevation myocardial infarction who are already receiving therapeutic doses of ACE inhibitor, have an LVEF ≤40 percent, and have either symptomatic HF or diabetes mellitus, who can be carefully monitored for serum potassium and renal function. The serum potassium should be <5.0 mEq/L and estimated glomerular filtration rate should be ≥30 mL/min per 1.73 m^2. (See "Use of aldosterone antagonists in systolic heart failure", section on 'Our approach'.)

The endocrine side effects of spironolactone result from nonselective binding to androgen and progesterone receptors; eplerenone has greater specificity for the mineralocorticoid receptor and therefore has a lower incidence of endocrine side effects (1 versus 10 percent in clinical trials). (See "Use of aldosterone antagonists in systolic heart failure".)

Although eplerenone is associated with fewer endocrine side effects than spironolactone (1 versus 10 percent in the respective trials), this advantage must be weighed against the marked difference in cost between the two drugs. It may be reasonable to begin with spironolactone (25 to 50 mg/day), and switch to eplerenone (25 and after four weeks 50 mg/day) if endocrine side effects occur. To the degree that blockade of a deleterious effect of aldosterone on the heart is important, a similar benefit would **not** be expected with other potassium-sparing diuretics (such as amiloride).

It is essential that serum potassium and creatinine be checked one to two weeks after starting spironolactone or eplerenone and periodically thereafter. Patients with poor renal function are particularly at risk for hyperkalemia. The following are risk factors for life-threatening hyperkalemia:

- Increasing age
- More severe HF
- Diabetes mellitus
- Underlying renal dysfunction
- Volume depletion
- Higher baseline plasma potassium concentration

- Spironolactone dose ≥50 mg/day
- Higher ACE inhibitor or angiotensin II receptor blocker dose
- Combined use of ACE inhibitors and angiotensin II receptor blockers
- Concomitant beta blocker use
- Use of potassium supplements or potassium-containing salt substitutes
- Use of nonsteroidal anti-inflammatory drugs

Renal dysfunction, which is an important risk factor for hyperkalemia in this setting, may be underestimated by the serum creatinine concentration, especially in elderly patients and other patients with reduced lean body mass in whom creatinine production is reduced. Formulas are available to estimate glomerular filtration rate from a stable serum creatinine that take into account age and body mass. (See "Assessment of kidney function", section on 'Estimation equations'.)

Angiotensin II receptor blockers — ARBs for the treatment of HF appear to be as or possibly slightly less effective than ACE inhibitors when compared directly [49,50]. The CHARM-Alternative trial demonstrated benefit from candesartan in patients with NYHA class II or III HF who could not tolerate ACE inhibitors, primarily because of cough [51].

The 2013 ACCF/AHA guideline recommended an ARB in patients who cannot tolerate ACE inhibitors for this use and a class IIa recommendation for the use of an ARB as an alternative to ACE inhibitors, particularly in patients already taking an ARB for another indication [2]. ARBs are more expensive than ACE inhibitors. A class IIb recommendation was made to consider the addition of an ARB in persistently symptomatic patients with HF with reduced ejection fraction who are already being treated with an ACE inhibitor and a beta blocker in whom an aldosterone antagonist is not indicated or tolerated. (See "Angiotensin II receptor blocker and neprilysin inhibitor therapy in heart failure due to systolic dysfunction".)

We recommend addition of an aldosterone antagonist (rather than an ARB) to ACE inhibitor and beta blocker therapy to treat HF in patients who can be carefully monitored for serum potassium and renal function who have NYHA functional class II HF and an LVEF ≤30 percent; or NYHA functional class III to IV HF and an LVEF <35 percent; or are post-ST elevation myocardial infarction, have an LVEF ≤40 percent, and have either symptomatic HF or diabetes mellitus. (See 'Aldosterone antagonists' above.)

The combination of aldosterone antagonist therapy and ACE inhibitor plus ARB therapy is **not** generally recommended. (See "Angiotensin II receptor blocker and neprilysin inhibitor therapy in heart failure due to systolic dysfunction", section on 'Combination with aldosterone antagonist'.)

Based upon the above considerations and the VALIANT trial [52], an ARB should **NOT** be added to an ACE inhibitor in the immediate post-myocardial infarction setting. (See "Angiotensin converting enzyme inhibitors and receptor blockers in acute myocardial infarction: Clinical trials".)

Hydralazine plus nitrates — Hydralazine plus nitrate therapy may provide symptomatic and mortality benefit in selected patients with HF due to systolic dysfunction. Data supporting the efficacy of hydralazine plus nitrates in patients with HF due to systolic dysfunction are discussed separately. (See "Hydralazine plus nitrate therapy in patients with heart failure due to systolic dysfunction".)

In blacks, we recommend the addition of hydralazine plus oral nitrate therapy for patients with persistent NYHA class III to IV HF and LVEF <40 percent despite optimal therapy including a beta blocker, ACE inhibitor (or ARB), aldosterone antagonist (if indicated), and diuretics. Although the evidence of benefit is stronger in blacks, the addition of hydralazine plus oral nitrate may be considered in non-blacks who have persistent NYHA class II or IV HF despite optimal conventional therapy.

We suggest treatment with a combination of hydralazine plus nitrate in patients with HF and reduced LVEF who are unable to take either an ACE inhibitor or ARB due to drug intolerance (including hyperkalemia), hypotension, or worsening renal insufficiency. ARB intolerance can be presumed in patients who develop hyperkalemia or renal insufficiency on ACE inhibitor therapy.

Dosing — Starting doses of hydralazine 25 mg three times daily and isosorbide dinitrate 20 mg three times daily are recommended. Uptitration of dose should be considered every two to four weeks. The dose should not be increased if symptomatic hypotension develops. The target dose is hydralazine 75 mg three times daily and isosorbide dinitrate (40 mg three times daily). Although direct evidence of efficacy is lacking, isosorbide mononitrate (40 to 120 mg daily) may be used in place of isosorbide dinitrate to improve compliance.

Digoxin — Digoxin is given to patients with HF and systolic dysfunction to control symptoms (such as fatigue, dyspnea, and exercise intolerance) and, in patients with atrial fibrillation, to control the ventricular rate. As demonstrated in the DIG trial, digoxin therapy was associated with a significant reduction in hospitalization for HF but no benefit in terms of overall mortality [53].

However, subsequent subgroup analyses suggest that digoxin may have an effect on survival that varies with the serum digoxin concentration (SDC). Compared to placebo, survival was significantly improved when the SDC was between 0.5 and 0.8 ng/mL in men and significantly worsened when the SDC was ≥1.2 ng/mL (figure 5) [54]. A similar relationship was seen in women with a nonsignificant trend toward improved survival when the SDC was between 0.5 and 0.9 ng/mL and significantly worse survival when the SDC was ≥1.2 ng/mL [55]. (See "Use of digoxin in heart failure due to systolic dysfunction", section on 'Optimal digoxin level'.)

The use of digoxin for the treatment of symptoms in patients with left ventricular dysfunction was considered reasonable to decrease hospitalizations in the 2013 ACCF/AHA guideline [2]. We suggest starting digoxin in patients with left ventricular systolic dysfunction (LVEF <40 percent) who continue to have NYHA functional class II, III, and IV symptoms (table 3) despite appropriate therapy including an ACE inhibitor, beta blocker, an aldosterone antagonist if indicated, and an additional diuretic if necessary for fluid control. The usual daily dose of digoxin is 0.125 mg or less, based upon renal function. Based upon the data from the DIG trial correlating serum digoxin concentration and survival, we recommend maintaining the SDC between 0.5 and 0.8 ng/mL (figure 5) [54].

Digoxin is **NOT** indicated as primary therapy for the stabilization of patients with acutely decompensated HF. Such patients should first receive appropriate treatment for HF, usually with intravenous medications. Digoxin may be initiated after stabilization and prior to discharge as part of a long-term treatment strategy to reduce risk of rehospitalization.

TREATMENT OF SUBGROUPS

Influence of gender — Meta-analyses have defined the role of angiotensin converting enzyme (ACE) inhibitors and beta blockers in women with heart failure (HF). A meta-analysis of ACE inhibitor trials suggested that the benefit from these drugs may not apply to women [56]. Among trials of ACE inhibitor therapy in symptomatic HF, the relative mortality risk with an ACE inhibitor was significantly reduced in men at 0.80 (95% CI 0.68-0.93) but showed only a trend toward significance in women at 0.90 (95% CI 0.78-1.05). Until more definitive data are provided, ACE inhibitors should continue to be used in women with HF.

In contrast, women appear to benefit from beta blockers to the same degree as men [56,57]. A pooled analysis from MERIT-HF, COPERNICUS, CIBIS II, and the United States Carvedilol Heart Failure trials found that the mortality benefit from beta blocker therapy was the same in men and women (relative risk 0.66 and 0.63, respectively) [56].

Influence of race — Race may affect the response to ACE inhibitors, hydralazine plus isosorbide dinitrate, and beta blockers in patients with HF.

ACE inhibitors — The V-HeFT trial and a matched cohort study from the SOLVD trial suggested that there were important differences between blacks and whites in the response to ACE inhibitors [58-60]. Two major findings were noted:

- Blacks had higher rates of both progressive HF and overall mortality. In the SOLVD analysis, the respective values were 13 versus 8 per 100 patient-years in whites for hospitalization for HF and 12 versus 10 per 100 patient-years for overall mortality [58].

- ●Blacks had a lesser response than whites to ACE inhibition with enalapril despite receiving similar doses. In the SOLVD matched cohort study, enalapril therapy in whites was associated with a significant 44 percent reduction in hospitalization for HF compared to placebo; in contrast, there was no significant reduction among blacks (figure 6) [58].

The apparent lack of response in blacks has some biologic plausibility since similar findings have been noted in patients with hypertension. Blacks respond less well to ACE inhibitors than to most other antihypertensive drugs (figure 7) [61]. In the matched cohort study from SOLVD, there were significant reductions in systolic and diastolic pressure with enalapril in whites (5/3.6) but not blacks [58]. (See "Treatment of hypertension in blacks".) In addition to genetic disparities, environmental differences (such as diet) could contribute to the varying response.

In contrast to these findings, another analysis of the SOLVD trials using mortality as the end point found that the relative risk (RR) of death was reduced to the same degree in both blacks and whites (RR for blacks 0.89, 95% CI 0.74-1.06; RR for whites 0.89, 95% CI 0.82-0.97) [56]. The risk reduction was significant in whites but not blacks, an observation that is likely to be explained by the smaller number of blacks in the trials (800 versus 5718). Thus, ACE inhibitors should continue to be used in black patients with HF.

Beta blockers — There are conflicting data on the efficacy of beta blockers in black patients. In the carvedilol trials, the benefit of beta blockade was of similar magnitude in blacks and nonblack patients [62]. In comparison, it appeared that blacks derived no benefit with bucindolol in the BEST trial [63].

A meta-analysis of beta blocker trials in HF confirmed this distinction, finding different results depending upon whether or not the BEST data were included [56]. In the COPERNICUS, MERIT-HF, and United States Carvedilol Heart Failure trials, the reduction in all-cause mortality with beta blockers was the same for blacks and whites (relative risk 0.67 and 0.63, respectively). With inclusion of the data from BEST, the benefit of beta blockers remained significant for whites but was no longer significant in blacks (relative risk 0.69 and 0.97, respectively).

These observations demonstrate that bucindolol, a beta blocker with partial beta agonist activity [64], is not effective in reducing mortality in blacks. The reasons for this difference are not clear, but (as speculated by the authors of BEST) may include race-specific differences in the beta adrenergic pathway [63].

Hydralazine with nitrates — In the V-HeFT trials, blacks had a lesser benefit from ACE inhibition than whites, while the benefit of the hydralazine-nitrate combination was more pronounced [60]. This observation led to the design of the A-HeFT trial (African-American Heart Failure Trial), in which black patients with class III to IV HF on standard HF therapy (including an ACE inhibitor if tolerated) were randomly assigned to a fixed combination of hydralazine and isosorbide dinitrate or placebo. (See 'Hydralazine plus nitrates' above.)

Influence of diabetes — Diabetic patients with HF are treated in the same fashion as nondiabetics. Data supporting this approach are available for both beta blockers and ACE inhibitors. (See "Heart failure in diabetes mellitus", section on 'Therapy'.)

The thiazolidinediones and metformin, which are often used in type 2 diabetics, are relatively contraindicated in patients with HF. (See "Drugs that should be avoided or used with caution in patients with heart failure".)

OTHER DRUGS

N-3 polyunsaturated fatty acids — Evidence from a randomized trial indicates that supplementation with N-3 polyunsaturated fatty acids (PUFA) in patients with heart failure (HF) can reduce mortality. The GISSI-HF investigators randomly assigned 6975 class II to IV chronic HF patients to 1 g/day N-3 PUFA or placebo with a median follow-up of 3.9 years [65]. Death from any cause was reduced with N-3 PUFA compared to placebo from 29 to 27 percent (adjusted hazard ratio 0.91, 95.5% CI 0.833-0.998) and the end point of death or admission to the hospital for cardiovascular reasons was also reduced (59 to 57 percent, adjusted hazard ratio 0.92, 99% CI 0.849-0.999).

The potential role of supplementation with N-3 polyunsaturated fatty acids for prevention of HF is discussed separately. (See "Fish oil and marine omega-3 fatty acids".)

Statins — Clinical trials have evaluated the efficacy of statins on mortality in patients with both ischemic and nonischemic systolic HF. (See "Statin therapy in patients with heart failure".)

Summarized briefly, no benefit from statin therapy has generally been demonstrated in patients with moderate to severe HF due to systolic dysfunction with or without coronary artery disease. Limited data suggest that statins may benefit patients with diastolic dysfunction.

Calcium channel blockers — Some initial studies suggested a possible deleterious effect of calcium channel blockers in patients with HF, while later trials with vasoselective calcium channel blockers amlodipine and felodipine showed a neutral effect on mortality (figure 8 and figure 9) [8]. Thus, there is **NO** direct role for these drugs in the management of systolic HF. However, amlodipine and felodipine appear to be safe in patients with systolic HF and can be used if treatment with a calcium channel blocker is necessary for another indication, such as angina or hypertension. (See "Calcium channel blockers in heart failure due to systolic dysfunction".)

Drugs to avoid — A variety of drugs should be avoided or used with caution in patients with HF. This issue is presented separately. (See "Drugs that should be avoided or used with caution in patients with heart failure".)

EXERCISE TRAINING — Both chronic hypoperfusion and a reduction in physical activity lead to skeletal muscle dysfunction and exercise intolerance in patients with chronic heart failure (HF). (See "Skeletal muscle dysfunction and exercise intolerance in heart failure".)

Randomized controlled trials have shown that exercise training can lessen symptoms, increase exercise capacity, improve the quality of life, reduce hospitalization, and increase survival in patients with chronic HF. These improvements are additive to the benefits of angiotensin converting enzyme inhibitors and beta blockers. These issues are discussed in detail separately. (See "Cardiac rehabilitation in patients with heart failure" and "Components of cardiac rehabilitation and exercise prescription".)

Based upon the available data, we recommend that cardiac rehabilitation be offered to patients with stable New York Heart Association class II to III HF (table 3) who do not have advanced arrhythmias and who do not have other limitations to exercise. Exercise training should be used in conjunction with drug therapy. The beneficial effects of exercise are seen with high or low levels of training, and are apparent as early as three weeks after training. There are not enough data at present to recommend cardiac rehabilitation for patients with advanced HF.

SERIAL ASSESSMENT — Patients with heart failure should be evaluated serially to assess status, the response to therapy, and potential need for changes in management. Each visit should include assessment of ability to perform activities of daily living, volume status and weight, current use of alcohol, tobacco, illicit drugs, alternative therapies, and chemotherapy drugs, as well as diet and sodium intake.

It is reasonable to repeat measurement of left ventricular ejection fraction and structural remodeling in patients who have a change in clinical status, have experienced or recovered from a clinical event, or have received treatment that might significantly change these parameters. The efficacy of serial measurement of serum brain natriuretic peptide is less well established.

MANAGEMENT OF REFRACTORY HF — Although the majority of patients with heart failure due to systolic dysfunction respond to optimal medical therapy, some patients do not improve or experience rapid recurrence of symptoms. These patients have symptoms at rest or on minimal exertion and often require repeated prolonged hospitalizations for intensive management. Specialized strategies are generally considered for these patients, including continuous intravenous positive inotropic therapy, cardiac resynchronization therapy, extracorporeal ultrafiltration via hemofiltration, mechanical circulatory support, surgery, or cardiac transplantation. (See "Management of refractory heart failure".)

OTHER ISSUES

Heart failure disease management programs — Because heart failure (HF) is a chronic disease that often leads to repeated hospitalization, and because many interventions (as described above) can influence morbidity and mortality, the expertise of those providing clinical care for a patient with HF may have a significant influence on outcomes. HF disease management is a multidisciplinary framework for the care of HF patients including discharge planning, patient education, and frequent outpatient assessment. The impact of disease management and other strategies is discussed separately. (See "Strategies to reduce hospitalizations in patients with heart failure".)

Associated conditions — Patients with HF may have a variety of associated conditions that require therapy, each of which is discussed in detail elsewhere. These include:

- Supraventricular tachycardias, particularly atrial fibrillation (see "Tachycardia-mediated cardiomyopathy" and "The management of atrial fibrillation in patients with heart failure")
- Ventricular arrhythmias and risk for sudden cardiac death (see "Ventricular arrhythmias in heart failure and cardiomyopathy" and "Secondary prevention of sudden cardiac death in heart failure and cardiomyopathy")
- Use of cardiac pacemakers and cardiac resynchronization therapy (see "Overview of cardiac pacing in heart failure" and "Cardiac resynchronization therapy in heart failure: Indications")
- Thromboembolism (see "Antithrombotic therapy in patients with heart failure")
- Anemia (see "Approach to anemia in adults with heart failure")

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Heart failure (The Basics)" and "Patient information: Medicines for heart failure (The Basics)" and "Patient information: Reducing the costs of medicines (The Basics)" and "Patient information: Heart failure and atrial fibrillation (The Basics)" and "Patient information: Systolic heart failure (The Basics)")
- Beyond the Basics topics (see "Patient information: Heart failure (Beyond the Basics)" and "Patient information: Reducing the costs of medicines (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Management of heart failure (HF) due to systolic dysfunction includes correction of systemic factors, lifestyle modification, treatment of underlying cardiac disease, device (implantable cardioverter-defibrillator and cardiac resynchronization) therapy as indicated, as well as pharmacologic therapy to relieve symptoms and prolong survival. (See 'General principles' above and 'Treatment of underlying and concurrent cardiovascular disease' above.)
- Treatment of systolic HF is accomplished via appropriate combinations of the following agents: (see 'Pharmacologic therapy of HF' above)
  - For patients with systolic HF and volume overload, we recommend diuretics (**Grade 1A**). (See 'Diuretics' above.)
  - For patients with HF with left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] ≤40 percent), we recommend angiotensin converting enzyme (ACE) inhibitor therapy (**Grade 1A**). (See 'ACE inhibitors' above.)

- For patients with systolic HF who do not tolerate ACE inhibitors, we recommend an angiotensin II receptor blocker (ARB) as an alternative that provides a similar survival benefit (**Grade 1A**). (See 'Angiotensin II receptor blockers' above.)
- For patients with current or prior HF and an LVEF ≤40 percent, we recommend therapy with a beta blocker (**Grade 1A**). We believe that clinicians should choose one of the beta blockers of proven benefit (including reduction in all-cause mortality) in randomized trials (ie, carvedilol, extended-release metoprolol succinate, or bisoprolol). (See 'Beta blockers' above.)
- For patients who can be monitored for preserved renal function and a normal plasma potassium concentration and meet one of the following criteria, we recommend the addition of an aldosterone antagonist (spironolactone or, if not tolerated, eplerenone): New York Heart Association (NYHA) functional class II HF and a LVEF ≤30 percent; or NYHA functional class III to IV HF and an LVEF <35 percent (table 3); or post-ST elevation myocardial infarction and already receiving therapeutic doses of ACE inhibitor, and an LVEF ≤40 percent, and either symptomatic HF or diabetes mellitus; (**Grade 1A**). Given the relative cost differences, we suggest spironolactone rather than eplerenone for initial therapy, with switch to eplerenone if endocrine side effects occur (**Grade 2B**). (See 'Aldosterone antagonists' above.)
- The combination of aldosterone antagonist therapy and ACE inhibitor plus ARB therapy is **not** generally recommended.
- For black patients with persistent moderate to severe HF symptoms and LVEF <40 despite optimal therapy including a beta blocker, ACE inhibitor (or ARB), and aldosterone antagonist (if indicated) and other diuretics, we recommend the addition of the combination of hydralazine and an oral nitrate (**Grade 1A**). (See 'Hydralazine plus nitrates' above.)
- For select non-black patients with LVEF <40, particularly those with low output syndromes, hypertension, or mitral regurgitation with persistent symptoms despite optimal therapy including a beta blocker, ACE inhibitor (or ARB), and aldosterone antagonist (if indicated) and other diuretics, we suggest the addition of the combination of hydralazine and an oral nitrate (**Grade 2B**). (See 'Hydralazine plus nitrates' above.)
- For patients with systolic HF who are unable to take an ACE inhibitor or ARB due to drug intolerance, hypotension, or renal insufficiency, we suggest hydralazine plus a nitrate (**Grade 2B**). (See 'Hydralazine plus nitrates' above.)
- For patients with left ventricular systolic dysfunction (LVEF <40 percent) who continue to have NYHA functional class II, III, and IV symptoms (table 3) despite optimal therapy (eg, ACE inhibitor or ARB, beta blocker, aldosterone antagonist and, if necessary for fluid control, a diuretic) we suggest administration of digoxin (**Grade 2B**). (See 'Digoxin' above.)

- For patients with stable NYHA functional class II to III, we recommend an exercise training program (**Grade 1B**). (See 'Exercise training' above.)
- Patients with HF should be evaluated serially to assess status, the response to therapy, and potential need for changes in management.

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