PHARMACOLOGICAL TREATMENT OF HEART FAILURE (HF)

HF is a clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with (diastolic dysfunction) or eject blood (systolic dysfunction).

The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and peripheral edema.

Coronary artery disease is the underlying cause of HF in approximately two thirds of patients with left ventricular systolic dysfunction. The remainders have non-ischemic causes of systolic dysfunction and may have an identifiable cause (e.g., hypertension, valvular disease, myocardial toxins, or myocarditis) or may have no discernible cause (e.g., idiopathic dilated cardiomyopathy).

The classification system that is most commonly used to quantify the degree of functional limitation imposed by HF is one first developed by the NYHA 1 (New York Heart Association). This system assigns patients to 1 of 4 functional classes depending on the degree of effort needed to elicit symptoms: patients may have symptoms of HF at rest (class IV), on less-than-ordinary exertion (class III), on ordinary exertion (class II), or only at levels that would limit normal individuals (class I).

This functional classification reflects the subjective assessment of physician and patient, may change frequently over short periods of time and the treatments used do not differ significantly across the classes. To overtake these limitations, the joined AHA/ACC committee developed a new staging system that would reliably and objectively identify patients in the course of their disease and would be linked to treatments that were uniquely appropriate at each stage of their illness.

According to this new approach, patients would be expected to advance from one stage to the next unless progression of the disease was slowed or stopped by treatment. Indeed, left ventricular dysfunction, which begins with some injury to the myocardium, is usually a progressive process, even in the absence of a new identifiable insult to the myocardium. The principal manifestation of such progression is a process known as remodeling, which occurs as a homeostatic attempt to decrease wall stress, through increases in wall thickness. This ultimately results in a change in the geometry of the left ventricle such that the chamber dilates, hypertrophies, and becomes more spherical. The process of cardiac remodeling generally precedes the development of symptoms, occasionally by months or even years. The process of remodeling continues after the appearance of symptoms and may contribute importantly to worsening of symptoms despite treatment.

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According to the joined AHA/ACC committee, the progressive nature of left ventricular dysfunction and HF can be appropriately accounted for by considering 4 stages in the evolution of the disease.

**Stage A**
This stage identifies patients who are at high risk for developing HF, since they have one or more risk factors, but they have no structural disorder of the heart;

**Stage B**
This stage refers to patients who, despite a structural disorder of the heart, have never developed symptoms of HF;

**Stage C**
This stage denotes patients with past or current symptoms of HF associated with underlying structural heart disease;

**Stage D**
This stage designates patients with end-stage disease who require specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care (see Table 1).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.</td>
<td>Systemic hypertension; coronary artery disease; diabetes mellitus; history of cardiotoxic drug therapy or alcohol abuse; personal history of rheumatic fever; family history of cardiomyopathy.</td>
</tr>
<tr>
<td>B</td>
<td>Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.</td>
<td>Left ventricular hypertrophy or fibrosis; left ventricular dilatation or hypocontractility; asymptomatic valvular heart disease; previous myocardial infarction.</td>
</tr>
<tr>
<td>C</td>
<td>Patients who have current or prior symptoms of HF associated with underlying structural heart disease.</td>
<td>Dyspnea or fatigue due to left ventricular systolic dysfunction; asymptomatic patients who are undergoing treatment for prior symptoms of HF.</td>
</tr>
<tr>
<td>D</td>
<td>Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.</td>
<td>Patients who are frequently hospitalized for HF or cannot be safely discharged from the hospital; patients in the hospital awaiting heart transplantation; patients at home receiving continuous intravenous support for symptom relief or being supported with a mechanical circulatory assist device; patients in a hospice setting for the management of HF.</td>
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HF indicates heart failure.
As previously stated, this classification recognizes that there are established risk factors and structural prerequisites for the development of HF and that therapeutic interventions performed even before the appearance of left ventricular dysfunction or symptoms can reduce the morbidity and mortality of HF.

This classification system is intended to complement but not to replace the New York Heart Association (NYHA) functional classification, which primarily gauges the severity of symptoms in patients who are in stage C or D.

**PHARMACOLOGICAL THERAPY**

**PATIENTS AT HIGH RISK OF DEVELOPING LEFT VENTRICULAR DYSFUNCTION (STAGE A)**

Many conditions or behaviors that are associated with an increased risk of HF can be identified before patients show any evidence of structural heart disease. Early modification and treatment of these factors can often reduce the risk of HF, providing the most precocious opportunity to reduce the impact of HF on public and individual health.

The recommendations for patients at high risk of developing HF (Stage A) can be summarized as follows:

**Class I recommendations**

Control of systolic and diastolic hypertension in accordance with recommended guidelines. *(Level of Evidence: A)*

Treatment of lipid disorders in accordance with recommended guidelines. *(Level of Evidence: B)*

Avoidance of patient behaviors that may increase the risk of HF (e.g., smoking, alcohol consumption, and illicit drug use). *(Level of Evidence: C)*

Control of ventricular rate in patients with supraventricular tachyarrhythmias. *(Level of Evidence: B)*

Treatment of thyroid disorders. *(Level of Evidence: C)*

Periodic evaluation for signs and symptoms of HF. *(Level of Evidence: C)*

Non-invasive evaluation of left ventricular function in patients with a strong family history of cardiomyopathy or in those receiving cardiotoxic interventions. *(Level of Evidence: C)*
**Class IIa recommendations**

Angiotensin converting enzyme inhibitors (ACEI) or Angiotensin II receptor blockers (ARB) can be useful to prevent HF in patients at high risk for developing HF who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors. (*Level of Evidence: A and C respectively*)

**PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION WHO HAVE NOT DEVELOPED SYMPTOMS (STAGE B)**

Patients who, despite being asymptomatic, had a myocardial infarction or have evidence of left ventricular dysfunction are at considerable risk of developing HF.

The likelihood of developing clinical HF can be diminished by the use of therapies that reduce the risk of additional injury, the process of remodeling, and the progression of left ventricular dysfunction.

In patients who are experiencing an acute MI, the infusion of a fibrinolytic agent or the use of percutaneous coronary intervention can decrease the risk of developing HF, and these interventions can reduce the risk of death, especially in patients with a prior myocardial injury (see specific section of syllabus). Patients with an acute infarction, as well as those with a history of MI and normal cardiac function, also benefit from the administration of both a beta-blocker\(^2\) and either an ACEI\(^3\) or ARB\(^4\), which can decrease the risk of reinfarction or death when initiated within days after the ischemic event, especially in patients whose course is complicated by HF. Combined neurohormonal blockade (beta-blocker and ACEI or ARB) produces additive benefits\(^5\).

In patients asymptomatic with left ventricular systolic dysfunction, due to a remote ischemic injury or to a non-ischemic cardiomyopathy\(^6\), long-term treatment with an ACE inhibitor has been shown to delay the onset of symptoms and decrease the combined risk of death and hospitalization for HF.

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Although a recent trial investigated patients with low EF and HF at the time of MI (reference number 4), there are no studies that specifically address use of ARBs in asymptomatic patients with reduced LVEF. However, given the results of studies in symptomatic patients with low EF, ARBs may be an appropriate alternative, particularly in patients who cannot tolerate an ACEI.

Furthermore, although controlled clinical trials are lacking, the use of beta-blockers in patients with a low ejection fraction and no symptoms (especially those with coronary artery disease) is also warranted⁷.

In contrast, there are no data to recommend the use of digoxin in patients with asymptomatic LV dysfunction, with the exception of those with atrial fibrillation. Because the only reason to treat such patients is to prevent the progression of HF, and because digoxin has minimal effect on disease progression in symptomatic patients, it is unlikely that the drug would be beneficial in those with no symptoms⁸.

Likewise, there are no data to recommend the routine use of calcium channel blockers in patients with asymptomatic reduction of LVEF. Nonetheless, since calcium channel blockers have not been shown to have adverse effects, they may be helpful for concomitant conditions such as hypertension. Caution should be used in the utilization of calcium channel blockers with negative inotropic effects, which are not recommended in asymptomatic patients with EF less than 40% after MI⁹.

Physicians should pay particular attention to patients whose cardiomyopathy is associated with a rapid arrhythmia of supraventricular origin (e.g., atrial flutter or atrial fibrillation). Although physicians frequently consider such tachycardias to be the result of an impairment of ventricular function, these rhythm disorders may lead to or exacerbate the development of a cardiomyopathy¹⁰. Therefore, in patients with a depressed left ventricular ejection fraction, every effort should be made to control the ventricular response to these tachyarrhythmias or to restore sinus rhythm.

Finally, in patients with severe valvular disease (severe aortic or mitral valve stenosis or regurgitation), but no symptoms valve replacement or repair surgery should be considered even when ventricular function is impaired. Long-term treatment with a systemic vasodilator drug may be considered for those with severe aortic regurgitation who are deemed to be poor candidates for surgery. Several studies have suggested that

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prolonged therapy with hydralazine\textsuperscript{11} and nifedipine\textsuperscript{12} in patients with severe aortic regurgitation and preserved LV function might act to minimize structural changes in the ventricle and thereby possibly delay the need for surgical intervention; however, these drugs are often poorly tolerated in this setting, and no trial has shown that these vasodilators can reduce the risk of HF or death. Conversely, there are no long-term studies of vasodilator therapy in patients with severe asymptomatic mitral regurgitation.

The recommendations for patients with asymptomatic left ventricular systolic dysfunction can be summarized as follows:

**Class I recommendations**

All Class I recommendations for Stage A should apply to patients with cardiac structural abnormalities who have not developed HF. (*Levels of Evidence: A, B, and C as appropriate*)

Beta-blockers and ACEI should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF. (*Level of Evidence: A*)

Beta-blockers are indicated in all patients without a history of MI who have a reduced LVEF with no HF symptoms. (*Level of Evidence: C*)

ACEI should be used in patients with a reduced EF and no symptoms of HF, even if they have not experienced MI. (*Level of Evidence: A*)

An ARB should be administered to post-MI patients without HF who are intolerant of ACE inhibitors and have a low LVEF. (*Level of Evidence: B*)

**CLASS IIA recommendations**

ACEI or ARBs can be beneficial in patients with hypertension and LVH and no symptoms of HF. (*Level of Evidence B*)

Angiotensin II receptor blockers can be beneficial in patients with low EF and no symptoms of HF who are intolerant of ACEIs. (*Level of Evidence: C*)

Placement of an ICD is reasonable in patients with ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30\% or less, are NYHA functional class I on chronic optimal medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 year. (*Level of Evidence: B*)


CLASS IIB recommendations

Placement of an implantable cardioverter-defibrillator might be considered in patients without HF who have non-ischemic cardiomyopathy and an LVEF less than or equal to 30% who are in NYHA functional Class I with chronic optimal medical therapy and have a reasonable expectation of survival with good functional status for more than 1 year. (Level of Evidence: C)

CLASS III recommendations

Digoxin should not be used in patients with low EF, sinus rhythm, and no history of HF symptoms, because in this population, the risk of harm is not balanced by any known benefit. (Level of Evidence: C)

Use of nutritional supplements to treat structural heart disease or to prevent the development of symptoms of HF is not recommended. (Level of Evidence: C)

Calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI (Level of Evidence: C)

PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION WITH CURRENT OR PRIOR SYMPTOMS (STAGE C)

General Measures

Measures listed as class I recommendations for patients in stages A and B are also appropriate for patients with current or prior symptoms of HF.

In addition, moderate sodium restriction is indicated, along with daily measurement of weight, to permit effective use of lower and safer doses of diuretic drugs.

Immunization with influenza and pneumococcal vaccines may reduce the risk of a respiratory infection. Although most patients should not participate in heavy labor or exhaustive sports, physical activity should be encouraged, except during periods of acute decompensation or in patients with suspected myocarditis, because restriction of activity promotes physical deconditioning, which may adversely affect clinical status and contribute to the exercise intolerance of patients with HF.¹³

Three classes of drugs can exacerbate the syndrome of HF and should be avoided in most patients:

a) Antiarrhythmic agents\textsuperscript{14} can exert important cardiodepressant and proarrhythmic effects. Of available agents, only amiodarone has been shown not to adversely affect survival.

b) Calcium channel blockers\textsuperscript{15} can lead to worsening HF and have been associated with an increased risk of cardiovascular events. Of available agents, only amlodipine has been shown not to adversely affect survival.

c) Nonsteroidal anti-inflammatory drugs\textsuperscript{16} can cause sodium retention and peripheral vasoconstriction and can attenuate the efficacy, and enhance the toxicity, of diuretics and ACE inhibitors.

**Drugs Recommended for Routine Use**

Most patients with symptomatic left ventricular dysfunction should be routinely managed with a combination of 4 types of drugs: a diuretic, an ACE inhibitor, a beta-adrenergic blocker, and (usually) digitalis (21).

The value of these drugs has been established in numerous large-scale clinical trials, and the evidence supporting a central role for their use is compelling and persuasive.

Patients with evidence of fluid retention should be given a diuretic until a euvolemic state is achieved, and diuretic therapy should be continued to prevent the recurrence of fluid retention.

Even if the patient has responded favorably to the diuretic, treatment with an ACE inhibitor and a beta-blocker should be initiated and maintained in patients who can tolerate them, because they have been shown to favorably influence the long-term prognosis of HF.

Therapy with digoxin may be initiated at any time to reduce symptoms and enhance exercise tolerance.

**DIURETICS**

Diuretics interfere with the sodium retention typical of HF by inhibiting the reabsorption of sodium or chloride at specific sites in the renal tubules.

\textsuperscript{15} Packer M, Kessler PD, Lee WH. Calcium-channel blockade in the management of severe chronic congestive heart failure: a bridge too far. Circulation 1987;75:V56-64.
Bumetanide, furosemide, and torsemide act at the loop of Henle (thus, they are called loop diuretics), whereas thiazides, metolazone, and potassium-sparing agents (e.g., spironolactone) act in the distal portion of the tubule. These 2 classes of diuretics differ in their pharmacologic actions.

The loop diuretics increase sodium excretion up to 20% to 25% of the filtered load of sodium, enhance free water clearance, and maintain their efficacy unless renal function is severely impaired.

In contrast, the thiazide diuretics increase the fractional excretion of sodium to only 5% to 10% of the filtered load, tend to decrease free water clearance, and lose their effectiveness in patients with moderately impaired renal function (creatinine clearance less than 30 mL per min).

Consequently, the loop diuretics are the preferred diuretic agents for use in most patients with HF. However, thiazide diuretics may be preferred in hypertensive HF patients with mild fluid retention because they confer more persistent antihypertensive effects.

**Effect of diuretics in the management of HF**

Controlled trials have demonstrated the ability of diuretic drugs to increase urinary sodium excretion and decrease physical signs of fluid retention in patients with HF\(^\text{17}\). In these short-term studies, diuretic therapy has led to a reduction in jugular venous pressures, pulmonary congestion, peripheral edema, and body weight, all of which was observed within days of initiation of therapy.

In intermediate-term studies, diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in patients with HF\(^\text{18}\). There have been no long-term studies of diuretic therapy in HF, and thus, their effects on morbidity and mortality are not known. When using diuretics in patients with HF, physicians should keep in mind the following considerations:

1. Diuretics produce symptomatic benefits more rapidly than any other drug for HF. They can relieve pulmonary and peripheral edema within hours or days, whereas the clinical effects of digitalis, ACE inhibitors, or beta-blockers may require weeks or months to become apparent.

2. Diuretics are the only drugs used for the treatment of HF that can adequately control the fluid retention of HF. Although both digitalis and low doses of ACE inhibitors can

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enhance urinary sodium excretion, only few patients with HF can maintain sodium balance without the use of diuretic drugs. Attempts to substitute ACE inhibitors for diuretics can lead to pulmonary and peripheral congestion.

3. Diuretics should not be used alone in the treatment of HF. Even when diuretics are successful in controlling symptoms and fluid retention, diuretics alone are unable to maintain the clinical stability of patients with HF for long periods of time. The risk of clinical decompensation can be reduced, however, when diuretics are combined with digoxin, an ACE inhibitor, and a beta-blocker.

4. Appropriate use of diuretics is a key element in the success of other drugs used for the treatment of HF. The use of inappropriately low doses of diuretics will cause fluid retention, which can diminish the response to ACE inhibitors and increase the risk of treatment with beta-blockers. Conversely, the use of inappropriately high doses of diuretics will lead to volume contraction, which can increase the risk of hypotension with ACE inhibitors and vasodilators and the risk of renal insufficiency with ACE inhibitors and angiotensin II receptor antagonists. Optimal use of diuretics is the cornerstone of any successful approach to the treatment of HF.

Practical use of diuretic therapy

Selection of patients

Diuretics should be prescribed to all patients who have evidence of, and to most patients with a prior history of, fluid retention. Diuretics should generally be combined with an ACE inhibitor and a beta-blocker (and usually digoxin). Few patients with HF will be able to maintain dry weight without the use of diuretics.

Initiation and maintenance

The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond favorably to newer agents in this category (e.g., torsemide) because of their superior absorption. One study has suggested that torsemide may reduce the risk of

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worsening HF more effectively than furosemide\textsuperscript{23}, but this finding, which was published as an abstract and never translated into a full-length paper, remains controversial.

In outpatients with HF, therapy is commonly initiated with low doses of a diuretic, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0 kg daily. The ultimate goal of treatment is to eliminate physical signs of fluid retention, either by restoring jugular venous pressures toward normal or by eliminating the presence of edema, or both. When the ideal weight has been achieved, daily weighing should be suggested to the patient in order to prevent relapsing fluid retention. If a gain of weight is seen, despite the moderate dietary sodium restriction (less than 3 g daily) and a consistent alimentary intake, further increases in the dose or frequency of diuretic administration may be required to maintain an active diuresis and sustain the loss of weight.

If electrolyte imbalances are seen, these should be treated aggressively, but the diuretic should not be discontinued.

If hypotension or increased azotemia is observed before the goals of treatment are achieved, the physician may elect to slow the rapidity of diuresis, but diuresis should nevertheless be maintained until fluid retention is eliminated, even if this strategy results in mild or moderate decreases in blood pressure or renal function, as long as the patient remains asymptomatic.

Excessive concern about hypotension and azotemia can lead to the underutilization of diuretics and a state of refractory edema. Persistent volume overload not only contributes to the persistence of symptoms but may also limit the efficacy and compromise the safety of other drugs used for the treatment of HF\textsuperscript{24}. Once fluid retention has resolved, treatment with the diuretic should be maintained to prevent the recurrence of volume overload.

Patients are commonly prescribed a fixed dose of diuretic, but the dose of these drugs should be adjusted periodically. As previously stated, this adjustment can be accomplished by having the patient record his or her weight each day and allowing the patient to make changes in dose if the weight increases or decreases beyond a specified range.

The response to a diuretic is dependent on the concentration of the drug and the time course of its entry into the urine\textsuperscript{25}. Patients with mild HF respond favorably to low doses because diuretics are rapidly absorbed from the bowel and rapidly delivered to the renal tubules. However, as HF advances, the absorption of the drug may be delayed by bowel edema or intestinal hypoperfusion, and the delivery of the drug may be impaired by a

\textsuperscript{23} Murray MD, Forthofer MM, Bennett SK, et al. Effectiveness of Torsemide and Furosemide in the Treatment of Congestive Heart Failure: Results of a Prospective, Randomized Trial [abstr]. Circulation 1999;100 Suppl 1:300.
decline in renal perfusion and function\textsuperscript{26}. Consequently, the clinical progression of HF is characterized by the need for increasing doses of diuretics.

Patients may become unresponsive to high doses of diuretic drugs if they consume large amounts of dietary sodium, and/or take agents that can block the effects of diuretics (e.g., nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors)\textsuperscript{27,28} and/or have a significant impairment of renal function or perfusion\textsuperscript{29}. Diuretic resistance can generally be overcome by the intravenous administration of diuretics (including the use of continuous infusions), the use of 2 or more diuretics in combination (e.g., furosemide and metolazone)\textsuperscript{30}, or the use of diuretics together with drugs that increase renal blood flow (e.g., positive inotropic agents)\textsuperscript{31}.

\textbf{Risks of treatment}

The principal adverse effects of diuretics include electrolyte depletion as well as hypotension and azotemia. Diuretics may also cause rashes and hearing difficulties, but these are generally idiosyncratic or are seen with the use of very large doses, respectively.

Diuretics can cause the depletion of important cations (potassium and magnesium), which can predispose patients to serious cardiac arrhythmias, particularly in the presence of digitalis therapy\textsuperscript{32}. The risk of electrolyte depletion is markedly enhanced when 2 diuretics are used in combination.

The loss of electrolytes is related to enhanced delivery of sodium to distal sites in the renal tubules and the exchange of sodium for other cations, a process that is potentiated by activation of the renin-angiotensin-aldosterone system. Potassium deficits can be corrected by short-term treatment with potassium supplements, or if severe, by the addition of magnesium supplements\textsuperscript{33}.

\textsuperscript{32} Steiness E, Olesen KH. Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy. Br Heart J 1976;38:167-72.
Concomitant administration of ACE inhibitors alone or in combination with potassium-retaining agents (such as spironolactone) can prevent electrolyte depletion in most patients with HF who are taking a loop diuretic. When these drugs are prescribed, long-term oral potassium supplementation is frequently not needed and may be deleterious.

As previously mentioned, excessive use of diuretics can decrease blood pressure and impair renal function and exercise tolerance, but hypotension and azotemia may also occur as a result of worsening HF, which may be exacerbated by attempts to reduce the dose of diuretics. Hence, if there are no signs of fluid retention, hypotension and azotemia are likely to be related to volume depletion and may resolve after a reduction in diuretic dose. If there are signs of fluid retention, hypotension and azotemia are likely to reflect worsening HF and a decline in effective peripheral perfusion. Such patients should be managed by maintaining the dose of diuretic and improving end-organ perfusion, by adding an inotropic agent.34

A summary of the oral diuretics recommended for use in the treatment of fluid retention in HF is presented in the table below:

![Table of oral diuretics recommended for use in the treatment of fluid retention in HF](image)

**INHIBITORS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM.**

Inhibition of the renin-angiotensin-aldosterone system can take place at multiple sites: at the level of the enzyme that converts angiotensin I to angiotensin II (ACEIs), at the

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angiotensin receptor (ARBs), or at the receptor for aldosterone, which is under control of both the renin-angiotensin system and other systemic and local influences (aldosterone antagonists).

Angiotensin converting enzyme inhibitors are the best studied class of agents in HF, with multiple mechanisms of benefit for both HF, coronary disease, and other atherosclerotic vascular disease, as well as diabetic nephropathy.

During chronic therapy with ACEIs, the renin-angiotensin system demonstrates partial “escape” from inhibition with “normalization” of angiotensin levels, in part owing to alternative local pathways for production of angiotensin. This leaves the potential for benefit from additional therapy with ARBs and with the aldosterone antagonists.

ACE INHIBITORS (ACEIs)

Angiotensin converting-enzyme inhibitors interfere with the renin-angiotensin system by inhibiting the enzyme responsible for the conversion of angiotensin I to angiotensin II, but it is not clear whether the effects of ACE inhibitors can be explained solely by the suppression of angiotensin II.

ACE inhibition not only interferes with the renin-angiotensin system but also enhances the action of kinins and augments kinin-mediated prostaglandin, and kinin potentiation may play an important role in mediating the effects of ACE inhibitors. This seems to be suggested by both experimental and clinical studies. In experimental models of HF, ACE inhibitors modify cardiac remodeling more favorably than angiotensin II receptor antagonists, and this advantage of ACE inhibitors is abolished by concurrent administration of kinin antagonists.

Furthermore, in the clinical setting, ACE inhibitors produce long-term benefits even though circulating levels of angiotensin II are not suppressed during prolonged treatment, and these benefits may be attenuated by the co-administration of aspirin, which can block kinin-mediated prostaglandin synthesis.

Effect of ace inhibitors in the management of HF

ACE inhibitors have been evaluated in more than 7000 patients with HF who participated in more than 30 placebo-controlled clinical trials\textsuperscript{39}. All of these trials enrolled patients with systolic dysfunction (ejection fraction less than 0.35 to 0.40) who were treated with diuretics, with or without digitalis. These trials recruited many types of patients, including women and the elderly, as well as patients with a wide range of causes and severity of left ventricular dysfunction. However, patients with preserved systolic function, low blood pressure (less than 90 mm Hg systolic), or impaired renal function (serum creatinine greater than 2.5 mg per mL) were not recruited or represented a small proportion of patients who participated in these studies.

Analysis of this collective experience indicates that ACE inhibitors can alleviate symptoms, improve clinical status, and enhance the overall sense of well-being of patients with HF. In addition, ACE inhibitors can reduce the risk of death as well as the combined risk of death or hospitalization. These benefits of ACE inhibition were seen in patients with mild, moderate, or severe symptoms and in patients with or without coronary artery disease.

**Practical use of ace inhibitors**

**Selection of patients**

ACE inhibitors should be prescribed without any delay in case of HF due to left ventricular systolic dysfunction with the exclusion of patients with contraindications or unable to tolerate treatment with these drugs.

In general, ACE inhibitors are used together with a beta-blocker (and usually with digitalis). In addition, ACE inhibitors should not be prescribed without diuretics in patients with a current or recent history of fluid retention, because diuretics are needed to maintain sodium balance and prevent the development of peripheral and pulmonary edema\textsuperscript{40}.

ACE inhibitors should be preferred over the use of angiotensin II receptor antagonists or direct-acting vasodilators (e.g., a combination of hydralazine and isosorbide dinitrate\textsuperscript{41}).

Absolute contraindications to the administration of ACEI are previously experienced life-threatening adverse reactions, such as angioedema or anuric renal failure, and pregnancy.


Caution is required in patients with very low systolic blood pressure (<80 mm Hg), markedly increased serum levels of creatinine (greater than 3 mg per dL), bilateral renal artery stenosis or elevated levels of serum potassium (greater than 5.5 mmol per L).

Finally, treatment with an ACE inhibitor should not be initiated in hypotensive patients who are at immediate risk of cardiogenic shock. Such patients should first receive appropriate treatment for their HF and then be re-evaluated for ACE inhibition once stability has been achieved.

**Initiation and maintenance**

Although most of the evidence supporting an effect of ACE inhibitors on the survival of patients with HF is derived from experience with enalapril, the available data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival\(^{42}\).

Although some have suggested that drugs in this class may differ in their ability to inhibit tissue ACE, no trial has shown that tissue ACE-inhibiting agents are superior to other ACE inhibitors in any clinical aspect of HF. Nevertheless, in selecting among ACE inhibitors, it is recommended to give preference to ACE inhibitors that have been shown to reduce morbidity and mortality in clinical trials (captopril, enalapril, lisinopril, and ramipril), because these studies have clearly defined a dose that is effective in modifying the natural history of the disease.

Treatment with an ACE inhibitor should be initiated at very low doses, followed by gradual increments in dose if lower doses have been well tolerated. Renal function and serum potassium should be assessed within 1 to 2 weeks of initiation of therapy and periodically thereafter, especially in patients with pre-existing hypotension, hyponatremia, diabetes, or azotemia or in those taking potassium supplements.

Because fluid retention can blunt the therapeutic effects and fluid depletion can potentiate the adverse effects of ACEI, physicians should ensure that patients are being given appropriate doses of diuretics before and during treatment with these drugs.

Short- and long-term therapy with ACE inhibitors is usually well-tolerated by the large majority (85% to 90%) of patients with HF. Physicians should attempt to prescribe doses of an ACE inhibitor that have been shown to reduce the risk of cardiovascular events in clinical trials. If these target doses, which are high rather than medium, cannot be used or are poorly tolerated, lower doses should be used. Once the drug has been titrated to the appropriate dose, patients can generally be maintained on long-term therapy with an ACE inhibitor with little difficulty.

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Although symptoms may improve in some patients within the first 48 hours of therapy with an ACE inhibitor, the clinical responses to these drugs are generally delayed and may require several weeks or months before becoming apparent. Even if symptoms do not improve, long-term treatment with an ACE inhibitor should be maintained to reduce the risk of death or hospitalization.

Abrupt withdrawal of treatment with an ACE inhibitor can lead to clinical deterioration and should be avoided in the absence of life-threatening complications (e.g., angioedema).

Every effort should be made to minimize the occurrence of sodium retention or depletion during long-term treatment with an ACE inhibitor, because changes in salt and water balance, as previously mentioned, can exaggerate or attenuate the cardiovascular and renal effects of treatment. Fluid retention can minimize the symptomatic benefits of ACE inhibition, whereas fluid loss increases the risk of hypotension and azotemia. The use of an ACE inhibitor can also minimize or eliminate the need for long-term potassium supplementation.

Nonsteroidal anti-inflammatory drugs can block the favorable effects and enhance the adverse effects of ACE inhibitors in patients with HF and should be avoided. Retrospective analyses of large-scale clinical trials have suggested that aspirin might interfere with the benefits of ACE inhibition in patients with HF by inhibiting kinin-mediated prostaglandin synthesis. In short-term hemodynamic studies, aspirin can attenuate the hemodynamic actions of ACE inhibitors in patients with HF, an effect not seen with non-aspirin anti-platelet agents (e.g., clopidogrel). In several multicenter trials, concomitant use of aspirin was associated with a diminution of the effect of ACE inhibitors on survival and on cardiovascular morbidity.

A recent comprehensive systematic overview of 22,060 patients from 6 long-term randomized trials of ACEIs re-evaluated the issue of the potential detrimental effect of combining aspirin with ACEI therapy. When all of these trials were considered together, the effects of ACEIs were significantly beneficial in patients with and without aspirin.

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therapy. The composite risk reduction was 20% for patients taking aspirin and 29% for those not taking aspirin, a difference that did not reach statistical significance.\(^{48}\)

A second retrospective review subsequently also reported no adverse effect of concomitant aspirin use with ACEIs on long-term survival.\(^{49}\)

Given these retrospective results, many physicians believe the data justify prescribing aspirin and ACEIs together when there is an indication for use of aspirin.

On the other hand, other physicians would consider not combining aspirin with an ACEI because there are no data to indicate that it can reduce the risk of ischemic events in patients with HF,\(^{50}\) or they might consider the use of an alternative antiplatelet agent such as clopidogrel, which does not interact with ACEIs and which may have superior effects in preventing ischemic events. However, clopidogrel does not have an indication for the primary prevention of ischemic events and is approximately 50 times more expensive than aspirin. In conclusion, there may be an important interaction between aspirin and ACEIs, but there is controversy regarding this point, and it requires further study.

Finally, clinical experience in patients who are hemodynamically or clinically unstable suggests that the hypotensive effects of ACE inhibition may attenuate the natriuretic response to diuretics.\(^{51}\) As a result, in patients who are responding poorly to diuretic drugs, it may be prudent to interrupt treatment with the ACE inhibitor temporarily until the clinical status of the patient stabilizes.

**Risks of treatment**

Most of the adverse reactions of ACE inhibitors can be attributed to the 2 principal pharmacological actions of these drugs, namely angiotensin suppression and kinin potentiation. However, other types of side effects, unrelated to either pharmacological effects, may also occur (e.g., rash and taste disturbances).

**Adverse Effects Related to Angiotensin Suppression**

The most common adverse effects of ACE inhibition in patients with HF are hypotension and dizziness. Blood pressure declines without symptoms in nearly every patient treated


with an ACE inhibitor, so hypotension is generally a concern only if it is accompanied by postural symptoms, worsening renal function, blurred vision, or syncope.

In patients treated with high-dose diuretics, in whom the activation of the renin-angiotensin system (induced by hypovolemia and hyponatremia) concurs to maintain blood pressure levels, the first doses of ACEI might cause symptomatic hypotension. In these patients, although hypotension should subside with repeated administration of the same doses of ACEI, it would be prudent to lessen their dependence on the renin-angiotensin system by reducing the dose of diuretics, liberalizing salt intake, or both, provided the patient does not have significant fluid retention.

In states characterized by reduced renal perfusion (such as HF), glomerular filtration is critically dependent on angiotensin-mediated vasoconstriction of the efferent arteriole, whose dilation, induced by ACE inhibition administration, may cause functional renal insufficiency. A significant increase in serum creatinine (e.g., greater than 0.3 mg per dl) with the use of ACE inhibitors is observed in 15% to 30% of patients with severe HF, but in only 5% to 15% of patients with mild to moderate symptoms.

The risks are substantially greater if patients have bilateral renal artery stenosis or are taking non-steroidal anti-inflammatory drugs. Renal function usually improves after a reduction in the dose of concomitantly administered diuretics, and thus, these patients can generally be managed without the need to withdraw treatment with the ACE inhibitor. However, if the dose of diuretic cannot be reduced because the patient has fluid retention, the physician and patient may need to tolerate mild to moderate degrees of azotemia to maintain therapy with the ACE inhibitor.

Hyperkalemia can occur during ACE inhibition in patients with HF and may be sufficiently severe to cause cardiac conduction disturbances. In general, hyperkalemia is seen in patients whose renal function deteriorates or who are taking oral potassium supplements or potassium-sparing diuretics, especially if they have diabetes mellitus.

**Adverse Effects Related to Kinin Potentiation**

Cough related to the use of ACE inhibitors is the most common reason for the withdrawal of long-term treatment with these drugs\textsuperscript{58}; the frequency of cough is approximately 5\% to 10\% in white patients of European descent and rises to nearly 50\% in Chinese patients\textsuperscript{59}.

It is characteristically non-productive, is accompanied by a persistent and annoying “tickle” in the back of the throat, usually appears within the first months of therapy, disappears within 1 to 2 weeks of discontinuing treatment, and recurs within days of rechallenge. Other causes of cough, especially pulmonary congestion, should always be considered and the ACE inhibitor should be implicated only after these have been excluded. Demonstration that the cough disappears after drug withdrawal and recurs after rechallenge with another ACE inhibitor strongly suggests that ACE inhibition is the cause of the cough. Because of the long-term benefits of ACE inhibitors, physicians should encourage patients to continue taking these drugs if the cough is not severe. Only if the cough proves to be persistent and troublesome should the physician consider withdrawal of the ACE inhibitor and the use of alternative medications (e.g., an angiotensin II receptor antagonist).

Angioedema occurs in less than 1\% of patients taking an ACE inhibitor, but is more frequent in blacks. Because its occurrence may be life-threatening, the clinical suspicion of this reaction justifies subsequent avoidance of all ACE inhibitors for the lifetime of the patient. ACE inhibitors should not be initiated in any patient with a history of angioedema. Although ARBs may be considered as alternative therapy for patients who have developed angioedema while taking an ACEI, there are a small number of patients who have also developed angioedema with ARBs and extreme caution is advised when substituting an ARB in a patient who has had angioedema associated with ACEI use\textsuperscript{60}.

**ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)**

An alternative approach to inhibiting the actions of angiotensin II in patients with HF is the use of drugs that block the angiotensin II receptor. These agents were developed on the premise that interference with the renin-angiotensin system without inhibition of the angiotensin-converting enzyme (ACE) would produce all of the benefits of ACE inhibitors, while minimizing the risk of their adverse reactions. This approach was based on the assumption that the benefits of ACE inhibitors are related to the suppression of angiotensin II formation, whereas the side effects (mainly cough and angioedema) are due to the accumulation of kinins, namely the nonapeptide bradykinin and the decapeptide kallidin. This supposition, however, is only partially true. Bradykinin and kallidin are synthesized by kallicrein from two inactive precursors, high-molecular

weight kininogen (HMWK) and low-molecular weight kininogen (LMWK) respectively. The major physiological effects of kinins include endothelium-dependent vasodilation, contraction of non-vascular smooth muscle, and mediation of the inflammatory response. The angiotensin-converting enzyme (ACE), besides being responsible of the conversion of angiotensin I in angiotensin II, can also cleave and inactivate both kinins, so that the inhibition of ACE by means of ACEIs results in an amplification of the physiological effects of bradykinin and kallidin, including endothelium-dependent vasodilation, which may contribute to the beneficial effects of ACEIs in patients with HF. (Neutral endopeptidase also deactivates kinins and other mediators. Based on this, inhibitors of neutral endopeptidase, such as omapatrilat, are currently under investigation as experimental treatment for heart failure.

Several angiotensin II receptor antagonists (e.g., candesartan, eprosartan, irbesartan, losartan, telmisartan, and valsartan) are available for clinical use. Experience with ARBs in controlled clinical trials of patients with HF is considerably less than that with ACEIs. Nevertheless, in several placebo-controlled studies, long-term therapy with ARBs produced hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system.

In patients with evidence of LV dysfunction early after MI, a recent trial demonstrated that ARBs had a benefit that was not inferior to that of ACEIs without an advantage in terms of tolerability. However, the addition of an ARB to an ACEI did not improve outcomes and resulted in more side effects.

For patients unable to tolerate ACEIs because of cough or angioedema, the ARBs valsartan and candesartan have demonstrated benefit by reducing hospitalizations and mortality.

The combination of an ACEI and ARBs may produce more reduction of LV size than either agent alone. The addition of ARBs to chronic ACEI therapy caused a modest decrease in hospitalization in 2 studies, with a trend to decreased total mortality in one and no impact on mortality in another.

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**Recommendations Concerning ARBs**

Angiotensin receptor blockers should not be considered equivalent or superior to ACE inhibitors in the treatment of HF, and thus, they should not be used for the treatment of HF in patients who have no prior use of an ACE inhibitor and should not be substituted for ACE inhibitors in patients who are tolerating ACE inhibitors without difficulty. Hence, ACEIs the first choice for inhibition of the renin-angiotensin system in chronic HF, but ARBs can now be considered a reasonable alternative.

Candesartan improved outcomes in patients with preserved LVEF who were intolerant of ACEIs in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)\(^\text{67}\).

Angiotensin receptor blockers are as likely to produce hypotension, worsening renal function, and hyperkalemia as ACEIs. Although angioedema is much less frequent with ARBs, there are cases of patients who developed angioedema to both ACEIs and later to ARBs. There is little information available about the addition of ARBs to therapy with both ACEIs and aldosterone antagonists, but risks of renal dysfunction and hyperkalemia would be further increased. *Until further information is available, the routine combined use of all 3 inhibitors of the renin-angiotensin system cannot be recommended.*

**Practical use of ARBS**

Many of the considerations with ARB are similar to those with initiation of an ACEI, as discussed above.

Blood pressure (including postural blood pressure changes), renal function, and potassium should be reassessed within 1 to 2 weeks after initiation and followed closely after changes in doses.

Patients with systolic blood pressure below 80 mm Hg, low serum sodium, diabetes mellitus, and impaired renal function merit particular surveillance during therapy with inhibitors of the renin-angiotensin-aldosterone system.

Titration is generally achieved by doubling doses. For stable patients, it is reasonable to add therapy with beta-blocking agents before full target doses of either ACEIs or ARBs are reached. The risks of treatment with ARBs are those attributed to suppression of angiotensin stimulation, as discussed above for ACEIs. These risks of hypotension, renal dysfunction, and hyperkalemia are greater when combined with another inhibitor of this axis, such as ACEIs or aldosterone antagonists.

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ALDOSTERONE ANTAGONISTS (POTASSIUM-SPARING DIURETICS)

Although short-term therapy with both ACEIs and ARBs can lower circulating levels of aldosterone, such suppression may not be sustained during long-term treatment. The lack of long-term suppression may be important, because experimental data suggest that aldosterone exerts adverse effects on the structure and function of the heart, independently of and in addition to the deleterious effects produced by angiotensin II.

In a large-scale, long-term trial\(^\text{68}\), low doses of spironolactone (starting at 12.5 mg daily) were added to ACEI therapy for patients with class IV HF symptoms or class III symptoms and recent hospitalization. The risk of death was reduced from 46\% to 35\% (30\% relative risk reduction) over 2 years, with 35\% reduction in HF hospitalization and an improvement in functional class.

A recent trial investigated the newer aldosterone antagonist eplerenone in patients with LVEF less than or equal to 40\% and clinical evidence of HF or diabetes mellitus within 14 days of MI. Mortality was decreased from 13.6\% to 11.8\% at 1 year. Hyperkalemia occurred in 5.5\% of patients treated with eplerenone compared with 3.9\% of those given placebo overall and in up to 10.1\% versus 4.6\% of patients with estimated creatinine clearance less than 50 ml per min\(^\text{69}\).

Recommendations concerning aldosterone antagonists

The addition of low-dose aldosterone antagonists should be considered in carefully selected patients with moderately severe or severe HF symptoms and recent decompensation or with LV dysfunction early after MI. These recommendations are based on the strong data demonstrating reduced death and re-hospitalization in 2 clinical trial populations described above.

To minimize the risk of life-threatening hyperkalemia in patients with low LVEF and symptoms of HF, patients should have initial serum creatinine less than 2.0 mg per dl to 2.5 mg per dl, without recent worsening, and serum potassium less than 5.0 mEq per dl, without a history of severe hyperkalemia. The safety of the combination of ACEIs, ARBs, and aldosterone antagonists has not been explored adequately, and this combination cannot be recommended.

Practical use of Aldosterone Antagonists


Selection of patients

Decisions regarding the selection of patients for aldosterone antagonists reflect the balance between potential benefit to decrease death and hospitalization from HF and potential risks of life-threatening hyperkalemia, due to inhibition of potassium excretion.

Serum creatinine levels often underestimate renal dysfunction, particularly in the elderly, in whom estimated creatinine clearance less than 50 ml per min should trigger a reduction of the initial dose of spironolactone to 12.5 mg daily or of eplerenone to 25 mg daily, and aldosterone antagonists should not be given when clearance is less than 30 ml per min.

The recommendations for minimizing the risk of hyperkalemia in patients treated with aldosterone antagonist are summarized in the table below:

<table>
<thead>
<tr>
<th>1. Impaired renal function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when serum creatinine exceeds 1.6 mg per dl.* In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, determination that glomerular filtration rate or creatinine clearance exceeds 30 ml per min is recommended.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Aldosterone antagonists should not be administered to patients with baseline serum potassium in excess of 5.0 mEq per liter.</td>
</tr>
<tr>
<td>3. An initial dose of spironolactone 12.5 mg or eplerenone 25 mg is recommended, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate.</td>
</tr>
<tr>
<td>4. The risk of hyperkalemia is increased with concomitant use of higher doses of ACEIs (captopril greater than or equal to 75 mg daily; enalapril or lisinopril greater than or equal to 10 mg daily).</td>
</tr>
<tr>
<td>5. Nonsteroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors should be avoided.</td>
</tr>
<tr>
<td>6. Potassium supplements should be discontinued or reduced.</td>
</tr>
<tr>
<td>7. Close monitoring of serum potassium is required; potassium levels and renal function should be checked in 3 days and at 1 week after initiation of therapy and at least monthly for the first 3 months.</td>
</tr>
<tr>
<td>8. Diarrhea or other causes of dehydration should be addressed emergently.</td>
</tr>
</tbody>
</table>

ACEIs indicates angiotensin converting enzyme inhibitors.

*Although the entry criteria for the trials of aldosterone antagonists included creatinine greater than 2.5 mg per dl, the majority of patients had creatinine much lower; in 1 trial, 95% of patients had creatinine less than or equal to 1.7 mg per dl.

Initiation and monitoring
Spironolactone should be initiated at a dose of 12.5 to 25 mg daily, or occasionally on alternate days. Eplerenone was used after MI in one study at doses of 25 mg per day, increasing to 50 mg daily. Potassium supplementation is generally stopped after the initiation of aldosterone antagonists, and patients should be counseled to avoid high potassium–containing foods. However, patients who have required large amounts of potassium supplementation may need to continue receiving supplementation, albeit at a lower dose, particularly when previous episodes of hypokalemia have been associated with ventricular arrhythmias.

Patients should be cautioned to avoid the addition of nonsteroidal anti-inflammatory agents and cyclo-oxygenase-2 inhibitors, which can lead to worsening renal function and hyperkalemia.

Potassium levels and renal function should be rechecked within 3 days and again at 1 week after initiation of an aldosterone antagonist. Subsequent monitoring should be dictated by the general clinical stability of renal function and fluid status but should occur at least monthly for the first 3 months and every 3 months thereafter. The addition or an increase in dosage of ACEIs or ARBs should trigger a new cycle of monitoring.

In view of the potential risk for hyperkalemia, the routine triple combination of ACEIs, ARBs, and an aldosterone antagonist should be avoided. The development of potassium levels in excess of 5.5 mEq per liter should generally trigger discontinuation or dose reduction of the aldosterone antagonist, unless patients have been receiving potassium supplementation, which should then be stopped. The drug should also be stopped if the patient develops painful gynecomastia.

Finally, patients should be instructed specifically to stop the aldosterone antagonist during an episode of diarrhea or while loop diuretic therapy is interrupted.

**BETA-ADRENERGIC RECEPTOR BLOCKERS**

Beta-blockers act principally to inhibit the adverse effects of the sympathetic nervous system in patients with HF. Indeed, although cardiac adrenergic drive initially supports the performance of the failing heart, long-term activation of the sympathetic nervous system exerts deleterious effects that can be antagonized by the use of beta-blockers.

Sympathetic activation can increase ventricular volumes and pressure by causing peripheral vasoconstriction and by impairing sodium excretion by the kidneys.

Norepinephrine can also induce cardiac hypertrophy, restricting, at the same time, the ability of the coronary arteries to supply blood to the thickened ventricular wall, leading to a latent status of myocardial ischemia.°

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Activation of the sympathetic nervous system can also provoke arrhythmias by increasing the automaticity of cardiac cells, increasing triggered activity in the heart, and promoting the development of hypokalemia. Norepinephrine can also increase heart rate and potentiate the activity and actions of other neurohormonal systems.

Finally, by stimulating growth and oxidative stress in terminally differentiated cells, norepinephrine can trigger programmed cell death or apoptosis.

These deleterious effects are mediated through actions on alpha-1-, beta-1-, and beta-2-adrenergic receptors.

Beta-blockers that have been shown to be effective in the treatment of HF, including those that selectively block beta-1-receptors (e.g., bisoprolol and metoprolol) and those that block alpha-1, beta-1-, and beta-2-adrenergic receptors (e.g., carvedilol).

**Effect of beta-blockers in the management of HF**

Beta-blockers have been evaluated in more than 10,000 patients with HF who participated in more than 20 published placebo-controlled clinical trials. All trials enrolled patients with systolic dysfunction (ejection fraction less than 0.35 to 0.45) who had already been treated with diuretics and an ACE inhibitor, with or without digitalis.

These trials recruited many types of patients, including women and the elderly, as well as patients with a wide range of causes and severity of left ventricular dysfunction, but patients with preserved systolic function, low heart rates (less than 65 beats per min), or low systolic blood pressure (less than 85 mm Hg) were not recruited or represented a small proportion of the patients who participated in these published studies. A recent prospective trial with carvedilol, carried out in clinically stable patients with severe symptoms (class IV HF), demonstrated a reduction in mortality also in patients with such advanced disease.

This collective experience indicates that long-term treatment with beta-blockers can lessen the symptoms of HF, improve the clinical status of patients, and enhance the overall sense of well-being. In addition, like ACE inhibitors, beta-blockers can reduce the risk of death and the combined risk of death or hospitalization.

These benefits of beta-blockers were seen in patients with or without coronary artery disease and in patients with or without diabetes.

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The favorable effects of beta-blockers were also observed in patients already taking ACE inhibitors, which suggests that combined blockade of 2 neurohormonal systems can produce additive effects.

**Practical use of beta-blockers**

**Selection of patients**

Beta-blockers should be prescribed without delay to all patients with stable HF due to left ventricular systolic dysfunction unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with these drugs.

Beta-blockers should be also administered to patients with mild symptoms or clinically stable, because, despite offering only a minimal benefit in terms of symptom control, they certainly reduce the risk of disease progression, future clinical deterioration, and sudden death.\(^{73}\)

In general, beta-blockers are used together with an ACE inhibitor, a diuretic and often digitalis.

Patients do not need to be taking high doses of ACE inhibitors before being considered for treatment with a beta-blocker, because most patients enrolled in the beta-blocker trials were not taking high doses of ACE inhibitors. Furthermore, in patients taking a low dose of an ACE inhibitor, the addition of a beta-blocker produces a greater improvement in symptoms and reduction in the risk of death than an increase in the dose of the ACE inhibitor.\(^{74}\)

Beta-blockers should not be prescribed without diuretics in patients with a current or recent history of fluid retention, because diuretics are needed to maintain sodium balance and prevent the development of fluid retention that can accompany the initiation of beta-blocker therapy.\(^{75}\)

As previously mentioned, beta-blockers should be only administered to patients with HF who are sufficiently stable. Candidates not eligible for immediate treatment with a beta-blocker are those hospitalized in an intensive care unit, those with evidence of fluid overload or volume depletion, and those who have required recent treatment with an intravenous positive inotropic agent. The patients excluded from treatment for these reasons should first receive intensified treatment with other drugs for HF (e.g., diuretics) and then be re-evaluated for beta-blockade after clinical stability has been achieved.

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Importantly, patients should not take a beta-blocker if they have reactive airways disease, symptomatic bradycardia or advanced heart block (unless treated with a pacemaker).

**Initiation and maintenance**

Treatment with a beta-blocker should be initiated at very low doses, followed by gradual increments in dose if lower doses have been well tolerated.

Patients should be monitored closely for changes in vital signs and symptoms during this up-titration period. In addition, because initiation of therapy with a beta-blocker can cause fluid retention\(^\text{76}\), physicians should ask patients to weigh themselves daily and to manage any increase in weight by immediately increasing the dose of concomitantly administered diuretics until weight is restored to pretreatment levels.

Planned increments in the dose of a beta-blocker should be delayed until any side effects observed with lower doses have disappeared. Using such a cautious approach, most patients (approximately 85%) enrolled in clinical trials with beta-blockers were able to tolerate short- and long-term treatment with these drugs and achieve the maximum planned trial dose.

As with ACE inhibitors, the dose of beta-blockers in controlled clinical trials was not determined by a patient’s therapeutic response but was increased until the patient received a pre-specified target dose. Low doses were prescribed only if the target doses were not tolerated, and thus, most trials did not evaluate whether low doses would be effective. Therefore, physicians should make every effort to achieve the target doses of the beta-blockers shown to be effective in major clinical trials. Once the target dose has been achieved, patients can generally be maintained on long-term therapy with a beta-blocker with little difficulty.

Patients should be advised that clinical responses to the drug are generally delayed and may require 2 to 3 months to become apparent. Even if symptoms do not improve, long-term treatment should be maintained to reduce the risk of major clinical events.

Abrupt withdrawal of treatment with a beta-blocker can lead to clinical deterioration and should be avoided\(^\text{77}\). Even if patients develop fluid retention, with or without mild symptoms, it is reasonable to continue the beta-blocker while the dose of diuretic is increased. However, if the deterioration in clinical status is characterized by hypoperfusion or requires the use of intravenous positive inotropic drugs, it may be prudent to stop treatment with the beta-blocker temporarily until the status of the patient

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stabilizes. In such patients, positive inotropic agents, whose effects are mediated independently of the beta-receptor (e.g., a phosphodiesterase inhibitor such as milrinone) may be preferred. Once stabilized, the beta-blocker should be reintroduced to reduce the subsequent risk of clinical deterioration.

**Risks of treatment**

Initiation of treatment with a beta-blocker may lead to adverse reactions requiring attention and management.

Initiation of therapy with a beta-blocker can cause **fluid retention**, which is usually asymptomatic, being primarily detected by an increase in body weight, but occasionally may become sufficiently marked to worsen the symptoms of HF. Patients with fluid retention before treatment are at greatest risk of fluid retention during treatment, and thus, physicians should ensure that patients are not volume overloaded before a beta-blocker is initiated. Furthermore, physicians should monitor patients closely for increases in weight and for worsening signs and symptoms of HF and should augment the dose of diuretic if weight increases whether or not other signs or symptoms of worsening HF are present. The occurrence of fluid retention or worsening HF is not generally a reason for the permanent withdrawal of treatment. Such patients generally respond favorably to intensification of conventional therapy, and once treated, such patients remain excellent candidates for long-term treatment with a beta-blocker.

Treatment with a beta-blocker can be accompanied by feelings of general **fatigue** or **weakness**. In many cases, the sense of lassitude resolves spontaneously within several weeks without treatment, but in some patients, it may be severe enough to limit increments in dose or require the withdrawal of treatment. Complaints of fatigue can generally be managed by a reduction in the dose of the beta-blocker (or the accompanying diuretic), but treatment should be discontinued if the syndrome of weakness is accompanied by evidence of peripheral hypoperfusion.

The slowing of heart rate and cardiac conduction produced by beta-blockers is generally asymptomatic and thus generally requires no treatment. However, if the **bradycardia** is accompanied by dizziness or lightheadedness or if **second- or third-degree heart block** occurs, physicians should decrease the dose of the beta-blocker. Physicians should also consider the possibility of the pharmacological interaction with other drug, which, being capable of inducing in their turn bradycardia or heart block, should be discontinued first. In selected patients developing symptomatic bradycardia or cardiac blocks despite the low doses of beta-blockers, the benefits of beta-blocker administration may be sufficiently important to consider cardiac pacing (implantation of a pacemaker).

Beta-blockers, especially those that also block alpha-1-receptors, such as carvedilol, can produce **hypotension**, which is usually asymptomatic, but may produce dizziness,

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lightheadedness, or blurred vision. These vasodilatory side effects are generally seen within 24 to 48 hours of the first dose or the first increments in dose and usually subside with repeated dosing without any change in dose. Physicians may minimize the risk of hypotension by administering the betablocker and ACE inhibitor at different times during the day. If this is ineffective, the occurrence of hypotension may require a temporary reduction in the dose of the ACE inhibitor. Hypotensive symptoms may also resolve after a decrease in the dose of diuretics in patients who are volume depleted, but in the absence of such depletion, relaxation of diuretic therapy may increase the risk or consequences of fluid retention.

A list of inhibitors of the renin-angiotensin-aldosterone system and beta-blockers that are commonly used for the treatment of patients with HF with low EF is presented below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Daily Dose(s)</th>
<th>Maximum Dose(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25 mg 3 times</td>
<td>50 mg 3 times</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg twice</td>
<td>10 to 20 mg twice</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5 to 10 mg once</td>
<td>40 mg once</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 to 5 mg once</td>
<td>20 to 40 mg once</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg once</td>
<td>8 to 16 mg once</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg twice</td>
<td>20 mg twice</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25 to 2.5 mg once</td>
<td>10 mg once</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg once</td>
<td>4 mg once</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 to 8 mg once</td>
<td>32 mg once</td>
</tr>
<tr>
<td>Losartan</td>
<td>25 to 50 mg once</td>
<td>50 to 100 mg once</td>
</tr>
<tr>
<td>Valsartan</td>
<td>20 to 40 mg twice</td>
<td>160 mg twice</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5 to 25 mg once</td>
<td>25 mg once or twice</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25 mg once</td>
<td>50 mg once</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg once</td>
<td>10 mg once</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg twice</td>
<td>25 mg twice (50 mg twice for patients &gt;95 kg)</td>
</tr>
<tr>
<td>Metoprolol succinate extended release (metoprolol CR/XL)</td>
<td>12.5 to 25 mg once</td>
<td>200 mg once</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; kg, kilograms; and mg, milligrams.

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DIGITALIS

The digitalis glycosides exert their effects in patients with HF by virtue of their ability to inhibit sodium-potassium (Na+-K+) adenosine triphosphatase (ATPase). Inhibition of this enzyme in cardiac cells results in increased intracellular sodium and calcium contents leading to an augmentation of cardiac contractility. For many decades, the benefits of digitalis in HF were ascribed exclusively to this positive inotropic action.

However, recent evidence suggests that the benefits of digitalis may be related in part to enzyme inhibition in non-cardiac tissues.

Inhibition of Na+-K+ ATPase in vagal afferent fibers acts to sensitize cardiac baroreceptors, which in turn reduces sympathetic outflow from the central nervous system. In addition, by inhibiting Na+-K+ ATPase in the kidney, digitalis reduces the renal tubular reabsorption of sodium; the resulting increase in the delivery of sodium to the distal tubules leads to the suppression of renin secretion from the kidneys. These observations have led to the hypothesis that digitalis acts in HF primarily by attenuating the activation of neurohormonal systems (sympathetic tone and renin-angiotensin system) and not as a positive inotropic drug. Although a variety of digitalis glycosides have been used in the treatment of HF for the last 200 years, the most commonly used preparation in the United States is digoxin.

Effect of digitalis in the treatment of HF

Several placebo-controlled trials have shown that treatment with digoxin for 1 to 3 months can improve symptoms, quality of life, and exercise tolerance in patients with mild to moderate HF. These benefits have been seen regardless of the underlying rhythm (normal sinus rhythm or atrial fibrillation), cause of HF (ischemic or non-ischemic cardiomyopathy), or concomitant therapy (with or without ACE inhibitors). In a long-term trial that enrolled patients who primarily had class II or III symptoms, treatment with digoxin for 2 to 5 years had little effect on mortality but modestly reduced the combined risk of death and hospitalization.

Practical use of digitalis in HF

Selection of patients

Physicians should consider using digoxin to improve the symptoms and clinical status of patients with HF, in conjunction with diuretics, an ACE inhibitor, and a beta-blocker.

Digoxin may be used early to reduce symptoms in patients who have been started on, but have not yet responded symptomatically to, treatment with an ACE inhibitor or a beta-blocker.

Alternatively, treatment with digoxin may be delayed until the patient’s response to ACE inhibitors and beta-blockers has been defined and used only in patients who remain symptomatic despite therapy with the neurohormonal antagonists.

If a patient is taking digoxin but not an ACE inhibitor or a beta-blocker, treatment with digoxin should not be withdrawn, but appropriate therapy with the neurohormonal antagonists should be instituted.

Digoxin is prescribed routinely in patients with HF who have chronic atrial fibrillation, but beta-blockers may be more effective in controlling the ventricular response, especially during exercise.\(^83\)

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); therapy with digoxin may be initiated at the same time as part of an effort to establish a long-term treatment strategy.

Patients should not be given digoxin if they have significant sinus or atrioventricular block, unless the block has been treated with a permanent pacemaker. The drug should be used cautiously in patients taking other drugs that can depress sinus or atrioventricular nodal function (e.g., amiodarone or a beta-blocker), even though such patients usually tolerate digoxin without difficulty.

**Initiation and maintenance**

Although a variety of glycosides have been used, digoxin is the most commonly used formulation in the United States and it is the only glycoside that has been evaluated in placebo-controlled trials. There is little reason to prescribe other cardiac glycosides for the management of HF.

Therapy with digoxin is commonly initiated and maintained at a dose of 0.125 to 0.25 mg daily. Low doses (0.125 mg daily or every other day) should be used if the patient is over 70 years old, has impaired renal function, or has a low lean body mass. Higher doses (e.g., digoxin 0.375 to 0.50 mg daily) are rarely used or needed in the management of patients with HF.

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There is no reason to use loading doses of digoxin to initiate therapy in patients with HF. Although some physicians have advocated using serum levels to guide the selection of the dose of digoxin\textsuperscript{84}, there is little evidence to support such an approach. The radioimmunoassay for digoxin was developed to assist in the evaluation of the toxicity and not the efficacy of the drug\textsuperscript{85}. When used for the treatment of HF, there may be little relationship between serum digoxin concentration and the drug’s therapeutic effects, and data suggest that large doses of digoxin may not be more effective than small doses in the treatment of HF\textsuperscript{86}.

**Risks of treatment**

Although physicians have traditionally been taught that digitalis produces frequent side effects, the drug (as currently prescribed) is well tolerated by most patients with HF\textsuperscript{87}. The principal adverse reactions occur primarily when digoxin is administered in large doses, but large doses may not be needed to produce clinical benefits. The major side effects include cardiac arrhythmias (e.g., ectopic and re-entrant cardiac rhythms and heart block), gastrointestinal symptoms (e.g., anorexia, nausea, and vomiting), and neurological complaints (e.g., visual disturbances, disorientation, and confusion).

Digitalis toxicity is commonly associated with serum digoxin levels more than 2 ng per mL, but may also occur with lower digoxin levels, especially if hypokalemia, hypomagnesemia, or hypothyroidism co-exist\textsuperscript{88}. The concomitant use of quinidine, verapamil, spironolactone, flecainide, propafenone, or amiodarone can increase serum digoxin levels and may increase the likelihood of digitalis toxicity. The dose of digoxin should be reduced if treatment with these drugs is initiated.

In addition, a low lean body mass and impaired renal function can also elevate serum digoxin levels, which may explain the increased risk of digitalis toxicity in elderly patients.

In addition to these established side effects, there is concern that levels of digoxin that are generally considered to be in the therapeutic range (0.7 to 2 ng per mL) may exert deleterious cardiovascular effects in the long term, even though such levels appear to be well tolerated in the short-term. In one major long-term trial, serum digoxin

\textsuperscript{84} Hoeschen RJ, Cuddy TE. Dose-response relation between therapeutic levels of serum digoxin and systolic time intervals. Am J Cardiol 1975;35:469-72.


concentrations in the therapeutic range were associated with an increased frequency of hospitalizations for cardiovascular events other than HF and an increased risk of death due to arrhythmias or myocardial infarction\textsuperscript{89}. These effects neutralized any benefit on survival that might otherwise have been seen as a result of the favorable effect of the drug on HF. These observations have raised the possibility that digoxin doses and serum digoxin concentrations that are generally considered by physicians to be safe may adversely affect the heart.

**Interventions to be Considered for Use in Selected Patients**

Controlled clinical trials have shown some interventions to be useful in a limited cohort of patients with HF. Several of these agents are undergoing active investigation in large-scale trials to determine whether their role in the management of HF might be justifiably expanded.

**ISOSORBIDE DINITRATE**

Isosorbide dinitrate was one of the first vasodilator agents reported to be useful for chronic therapy of HF. Nitrate therapy may decrease symptoms of dyspnea at night and during exercise and may improve exercise tolerance in patients who have persistent limitation despite optimization of other therapies\textsuperscript{90}.

The only common side effects of nitrate therapy are headaches and hypotension. In clinical use, nitrates are frequently prescribed to patients with persistent congestive symptoms. Nitrates are predominantly potent venodilators that also have effects on arterial tone, particularly when systemic vascular resistance is severely elevated.

**HYDRALAZINE AND ISOSORBIDE DINITRATE**

Hydralazine is an arterial vasodilator with relatively little effect on venous tone and cardiac filling pressures. In addition to its direct vascular actions, hydralazine in theory may interfere with the biochemical and molecular mechanisms responsible for the progression of HF and the development of nitrate tolerance.

Although very limited data are available regarding the use of hydralazine alone in HF, a combination of hydralazine and isosorbide dinitrate has been used in different studies.


The rationale for the combined use of hydralazine and nitrates was to achieve both venous and arterial vasodilation. A post hoc retrospective analysis of 2 vasodilator trials demonstrated particular efficacy of isosorbide dinitrate and hydralazine in the black cohort\(^91\).

A confirmatory trial has been done. In that trial, which was limited to the black population with HF, the addition of hydralazine and isosorbide dinitrate to therapy with an ACEI and/or a beta-blocker was shown to be of significant benefit\(^92\). The benefit was presumed to be related to enhanced nitric oxide bioavailability. Whether this benefit is evident in other patients with HF remains to be investigated.

The combination of hydralazine and isosorbide dinitrate should not be used for the treatment of HF in patients who have no prior use of an ACEI and should not be substituted for ACEIs in patients who are tolerating ACEIs without difficulty.

Despite the lack of data with the vasodilator combination in patients who are intolerant of ACEIs, *the combined use of hydralazine and isosorbide dinitrate may be considered as a therapeutic option in such patients*.

However, compliance with this combination has generally been poor because of the large number of tablets required and the high incidence of adverse reactions\(^93\). For patients with more severe symptoms and ACEI intolerance, the combination of hydralazine and nitrates is used frequently, particularly when ACEI therapy is limited by hypotension or renal insufficiency.

There are, however, no trials addressing the use of isosorbide dinitrate and hydralazine specifically in the population of patients who have persistent symptoms and intolerance to inhibitors of the renin-angiotensin system.

A summary of the cardiovascular drugs most useful for the treatment of the various stages of HF is provided in the table below:

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
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<tbody>
<tr>
<td><strong>Ace Inhibitors</strong></td>
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<tr>
<td>Benazepril</td>
<td>H</td>
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<tr>
<td>Captopril</td>
<td>H, DN</td>
<td>Post MI</td>
<td>HF</td>
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<tr>
<td>Enalapril</td>
<td>H, DN</td>
<td>Asymptomatic</td>
<td>HF</td>
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<td>Fosinopril</td>
<td>H</td>
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<td>HF</td>
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<td>Lisinopril</td>
<td>H, DN</td>
<td>Post MI</td>
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<td>Moexipril</td>
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<tr>
<td>Perindopril</td>
<td>H, CV Risk</td>
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<td>Quinapril</td>
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<td>HF</td>
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<tr>
<td>Ramipril</td>
<td>H, CV Risk</td>
<td>Post MI</td>
<td>Post MI</td>
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<tr>
<td>Trandolapril</td>
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<td>Post MI</td>
<td>Post MI</td>
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<td><strong>Angiotensin Receptor Blockers</strong></td>
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<tr>
<td>Candesartan</td>
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<td>HF</td>
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<tr>
<td>Losartan</td>
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<td>Post MI, HF</td>
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<tr>
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<td><strong>Beta Blockers</strong></td>
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<tr>
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<tr>
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<td>Post MI</td>
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<td>HF</td>
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<tr>
<td>Metoprolol tartrate</td>
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<td>Post MI</td>
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<tr>
<td>Pindolol</td>
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<td>Propranolol</td>
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<td>Post MI</td>
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<tr>
<td>Timolol</td>
<td>H</td>
<td>Post MI</td>
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<tr>
<td><strong>Digoxin</strong></td>
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<td></td>
<td>HF</td>
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</table>

*See Figure 1 for explanation of stages of heart failure.
Asymptomatic LVSD indicates asymptomatic left ventricular systolic dysfunction; CV Risk, reduction in future cardiovascular events; DN, diabetic nephropathy; H, hypertension; HF, heart failure; Post MI, reduction in heart failure or other cardiac events following myocardial infarction.
**Active Investigation**

Several drugs and interventions are under active evaluation in long-term large-scale trials because they showed promise in pilot studies that involved small numbers of patients. Until the results of definitive trials are available, none of these interventions can be recommended for use in patients with HF.

**Vasopeptidase Inhibitors**

As previously stated, ACEIs can exert beneficial effects in heart failure not only blocking the conversion of angiotensin I in angiotensin II, with subsequent reduction of peripheral vasoconstriction, but also prevent the cleavage of bradykinin and kallidin, potentiating their vasodilatory effects. However, besides the angiotensin-converting enzyme, kinins are also cleaved and therefore inactivated by neutral endopeptidase. Hence, there has been interest in the development of vasopeptidase inhibitors that block not only the ACE, but also the neutral endopeptidase, which leads to enhanced activity of endogenous vasodilators. One vasopeptidase inhibitor, omapatrilat, is being developed for the treatment of hypertension and for the treatment of HF. In experimental and small-scale clinical studies, omapatrilat produced an improvement in cardiac performance and a reduction in the risk of death and worsening HF to a greater degree than a conventional ACE inhibitor. The possibility that omapatrilat may be superior to an ACE inhibitor is now being evaluated in a large-scale trial.

**Cytokine Antagonists**

Patients with HF have elevated levels of the cytokine, tumor necrosis factor, which can exert cardiodepressant and cardiotoxic effects in experimental models. The major source of tumor necrosis factor may be the heart itself, which appears to synthesize the cytokine in response to hemodynamic stresses. Two types of tumor necrosis factor antagonists are commercially available: a soluble receptor (etanercept) and a chimeric antibody (infliximab). Both are available for use in the management of non-cardiovascular disorders and are undergoing evaluation for use in the treatment of HF. In a short-term pilot study, etanercept produced dose-dependent increases in ejection fraction, decreases in left ventricular chamber size, and improvement in clinical status. However, a large-scale trial with etanercept in HF was stopped early because of the low likelihood that the drug would show favorable effects. Alternative approaches to cytokine inhibition are being evaluated at the present time, but until definitive studies with these newer agents are completed, cytokine antagonists cannot be recommended for the treatment of HF.

**Endothelin Antagonists**

Endothelin is a potent vasoconstrictor that can adversely affect the structure and function of the heart and peripheral blood vessels. Circulating levels of endothelin-1 are elevated in patients with HF, and endothelin antagonism can produce favorable hemodynamic and
prognostic effects in experimental models of HF. Two types of endothelin-1 antagonists are under evaluation: those that block the receptors for endothelin-1, and those that inhibit the endothelin converting-enzyme, which is responsible for the formation of endothelin-1. In two small pilot studies, high doses of the endothelin receptor antagonist bosentan produced favorable effects on cardiac performance and clinical status, but were associated with liver-function abnormalities. In another recently completed trial, treatment with the endothelin antagonist enrasentan was associated with no improvement in symptoms and an increased risk of worsening HF. The utility of low doses of bosentan is now being evaluated in a large-scale trial. No endothelin antagonist is presently available for clinical use for any indication.

In summary, the following are the AHA/ACC guidelines for patients with HF in stage C:

**Class I recommendations**

Measures listed as Class I recommendations for patients in stages A and B are also appropriate for patients in Stage C. (*Levels of Evidence: A, B, and C as appropriate*)

Diuretics and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention. (*Level of Evidence: C*)

Angiotensin converting enzyme inhibitors are recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated (*Level of Evidence: A*)

Beta-blockers (using 1 of the 3 proven to reduce mortality, ie. bisoprolol, carvedilol, and sustained release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated. (*Level of Evidence: A*)

Angiotensin II receptor blockers approved for the treatment of HF are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACEI intolerant (*Level of Evidence: A*)

Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HF and reduced LVEF should be avoided or withdrawn whenever possible (e.g., nonsteroidal anti-inflammatory drugs, most antiarrhythmic drugs, and most calcium channel blocking drugs; see text). (*Level of Evidence: B*)

Addition of an aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be less than or equal to 2.5 mg/dL in men or less
than or equal to 2.0 mg/dL in women and potassium should be less than 5.0 mEq/l. (Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists.) (Level of Evidence: B)

**CLASS IIA recommendations**

Angiotensin II receptor blockers are reasonable to use as alternatives to ACEIs as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications. (Level of Evidence: A)

Digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF. (Level of Evidence: B)

The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACEI and beta-blocker for symptomatic HF and who have persistent symptoms. (Level of Evidence: A)

**CLASS IIB recommendations**

A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency. (Level of Evidence: C)

The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy. (Level of Evidence: B)

**CLASS III recommendations**

Routine combined use of an ACEI, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF. (Level of Evidence: C)

Calcium channel blocking drugs are not indicated as routine treatment for HF in patients with current or prior symptoms of HF and reduced LVEF. (Level of Evidence: A)

**PATIENTS WITH REFRACTORY END-STAGE HF (STAGE D)**
Most patients with HF due to left ventricular systolic dysfunction respond favorably to pharmacological and non-pharmacological treatments and enjoy a good quality of life and enhanced survival. However, despite optimal medical therapy, some patients do not improve with treatment or experience rapid recurrence of symptoms. Such patients generally have symptoms (including profound fatigue) at rest or on minimal exertion, cannot perform most activities of daily living, frequently have evidence of cardiac cachexia, and typically require repeated or prolonged hospitalizations for intensive management.

These individuals represent the most advanced state of HF and should be considered for specialized treatment strategies such as mechanical circulatory support, continuous intravenous positive inotropic therapy, referral for cardiac transplantation, or hospice care.

Before a patient is considered to have refractory HF, it is critical that physicians confirm the accuracy of the diagnosis; identify and reverse, if possible, any contributing conditions; and ensure that all conventional medical strategies have been optimally employed. Many patients with advanced HF have symptoms that are related to the retention of salt and water and thus will respond favorably to interventions designed to restore sodium balance. Hence, a critical step in the successful management of end-stage HF is the recognition and meticulous control of fluid retention.

**Intravenous Peripheral Vasodilators and Positive Inotropic Agents**

Patients with refractory HF are hospitalized frequently for clinical deterioration, and during such admissions, they commonly receive infusions of both positive inotropic agents (dobutamine, dopamine, or milrinone) and vasodilator drugs (nitroglycerin, nitroprusside, or nesiritide) in an effort to improve cardiac performance, facilitate diuresis, and promote clinical stability. Once the clinical status of the patient has stabilized, every effort should be made to devise an oral regimen that can maintain symptomatic improvement and reduce the subsequent risk of deterioration.

Patients who cannot be weaned from intravenous to oral therapy despite repeated attempts may require placement of an indwelling intravenous catheter to allow for the continuous infusion of dobutamine or milrinone, or as has been used more recently, nesiritide. Such a strategy is commonly used in patients who are awaiting cardiac transplantation, but it may also be used in the outpatient setting in patients who otherwise cannot be discharged from the hospital.

The decision to continue intravenous infusions at home should not be made until all alternative attempts to achieve stability have failed repeatedly, because such an approach can present a major burden to the family and health services and may ultimately increase the risk of death. However, continuous intravenous support can provide palliation of symptoms as part of an overall plan to allow the patient to die with comfort at home.
An overview of the recommended therapeutic approach based on the different stages of HF is reported in the table below:

TREATMENT OF SPECIAL POPULATIONS AND CONCOMITANT DISORDERS

Many patients with HF are members of subpopulations or have comorbid conditions that either contribute to the development of their HF or make the management of their HF symptoms more difficult. These factors need to be considered in the management of such patients.

Special Subpopulations

Many subgroups are underrepresented in most trials, and some present unique problems in HF management. These include women and men, racial minorities, and elderly patients.

Concomitant Disorders

Patients with left ventricular dysfunction frequently have associated cardiovascular and non-cardiovascular disorders, the course or treatment of which may exacerbate the
syndrome of HF. In many patients, appropriate management of these concomitant illnesses may produce clinical and prognostic benefits that may be as important as the treatment of HF itself. These concomitant conditions include cardiovascular disorders such as hypertension, hyperlipidemia, and diabetes mellitus; coronary artery disease; supraventricular arrhythmias; ventricular arrhythmias and prevention of sudden death; and prevention of thrombotic events. Associated non-cardiovascular disorders include renal insufficiency, pulmonary disease, cancer, and thyroid disease.

The following are the AHA/ACC guidelines for the management of concomitant diseases in patients with HF

**Class I recommendations**

Control of systolic and diastolic hypertension in patients with HF in accordance with recommended guidelines. *(Level of Evidence: A)*

Nitrates and beta-blockers (in conjunction with diuretics) for the treatment of angina in patients with HF. *(Level of Evidence: B)*

Coronary revascularization in patients who have both HF and angina. *(Level of Evidence: A)*

Anticoagulants in patients with HF who have paroxysmal or chronic atrial fibrillation or a previous thromboembolic event. *(Level of Evidence: A)*

Control of the ventricular response in patients with HF and atrial fibrillation with a beta-blocker (or amiodarone, if the beta-blocker is contraindicated or not tolerated). *(Level of Evidence: A)*

Beta-adrenergic blockade (unless contraindicated) in patients with HF to reduce the risk of sudden death. Patients should have no or minimal fluid retention and should not have recently required treatment with an intravenous positive inotropic agent. *(Level of Evidence: A)*

Implantable cardioverter-defibrillator, alone or in combination with amiodarone, in patients with HF who have a history of sudden death, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia. *(Level of Evidence: A)*

**Class IIa recommendations**

Antiplatelet agents for prevention of myocardial infarction and death in patients with HF who have underlying coronary artery disease. *(Level of Evidence: B)*

Digitalis to control the ventricular response in patients with HF and atrial fibrillation. *(Level of Evidence: A)*
Class IIb recommendations

Coronary revascularization in patients who have HF and coronary artery disease but no angina. (Level of Evidence: B)

Restoration of sinus rhythm by electrical cardioversion in patients with HF and atrial fibrillation. (Level of Evidence: C)

Amiodarone to prevent sudden death in patients with HF and asymptomatic ventricular arrhythmias. (Level of Evidence: B)

Anticoagulation in patients with HF who do not have atrial fibrillation or a previous thromboembolic event. (Level of Evidence: B or C)

PATIENTS WITH HF AND NORMAL LEFT VENTRICULAR EJECTION FRACTION (DIASTOLIC DYSFUNCTION)

Approximately 20% to 40% of patients with HF have preserved left ventricular systolic function and (in the absence of valvular disease) are believed to have an impairment of ventricular relaxation as the primary mechanism leading to symptoms. Several recognized myocardial disorders are associated with diastolic dysfunction, including restrictive cardiomyopathy, obstructive and non-obstructive hypertrophic cardiomyopathy, and infiltrative cardiomyopathies. However, the vast majority of patients who present with HF and normal systolic function do not have a defined myocardial disease but nevertheless have a clinically significant impairment of diastolic function. Many of the changes that occur in the cardiovascular system as a result of aging have a greater impact on diastolic function than on systolic performance. HF associated with preserved systolic function is primarily a disease of elderly women, most of whom have hypertension. These patients suffer considerably from dyspnea and fatigue, which can limit their exercise tolerance and quality of life, and they are hospitalized frequently for clinical stabilization. Although the risk of death in these patients appears to be lower than in patients with HF and poor systolic function, the management of these patients still has major socioeconomic implications.

It is difficult to be precise about the diagnosis of diastolic dysfunction. Non-invasive methods, especially those that rely on Doppler echocardiography, have been developed to assist in such diagnosis. In practice, however, the diagnosis of diastolic HF is generally based on the finding of typical symptoms and signs of HF in a patient who is shown to have a normal left ventricular ejection fraction and no valvular abnormalities on echocardiography.

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In contrast to the treatment of HF due to systolic dysfunction, few clinical trials are available to guide the management of patients with HF due to diastolic dysfunction.

In the absence of controlled clinical trials, the management of these patients with HF and preserved LVEF is based on the control of physiological factors (blood pressure, heart rate, blood volume, and myocardial ischemia) that are known to exert important effects on ventricular relaxation\textsuperscript{95}. Likewise, diseases that are known to cause HF with normal LVEF should be treated, such as coronary artery disease, hypertensive heart disease, or aortic stenosis. Clinically, it seems reasonable to target symptom reduction, principally by reducing cardiac filling pressures at rest and during exertion.

Hypertension exerts a deleterious effect on ventricular function by causing both structural and functional changes in the heart. Increases in systolic blood pressure have been shown to slow myocardial relaxation\textsuperscript{96}, and the resulting hypertrophy may adversely affect passive chamber stiffness. Physicians should make every effort to control both systolic and diastolic hypertension with effective antihypertensive therapy in accordance with published guidelines. Consideration should at least be given to achieving target levels of blood pressure lower than those recommended for patients with uncomplicated hypertension (e.g., less than 130 mm Hg systolic and less than 80 mm Hg diastolic).

Because myocardial ischemia can impair ventricular relaxation, coronary revascularization should be considered in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is believed to be exerting a deleterious effect on cardiac function.

In addition, since tachycardia can shorten the time available for ventricular filling and coronary perfusion, drugs that slow the heart rate or the ventricular response to atrial arrhythmias (e.g., beta-blockers, digoxin, and some calcium channel blockers) can provide symptomatic relief in patients with HF and normal LVEF.

Similarly, patients with HF and preserved LVEF may be particularly sensitive to loss of atrial kick, which supports a potential benefit for restoration of sinus rhythm in patients with atrial fibrillation. The benefits of restoring sinus rhythm in these individuals are less clear, and the large trials of rhythm versus rate control in atrial fibrillation published recently have excluded patients with HF.

Circulating blood volume is a major determinant of ventricular filling pressure, and the use of diuretics may improve breathlessness in patients with HF and normal LVEF as well as those with reduced LVEF. Other possible agents used to reduce diastolic filling pressures are nitrates or agents that block neurohumoral activation. Hypotension may be

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a significant problem in this population, especially in the very elderly, because they can be quite sensitive to preload reduction.

The following are the joined AHA/ACC recommendations for the management of patients with HF and preserved systolic function:

**Class I recommendations**

Control of systolic and diastolic hypertension in accordance with published guidelines. *(Level of Evidence: A)*

Control of ventricular rate in patients with atrial fibrillation. *(Level of Evidence: C)*

Diuretics to control pulmonary congestion and peripheral edema. *(Level of Evidence: C)*

**Class IIa recommendations**

Coronary revascularization in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is judged to have an adverse effect on diastolic function. *(Level of Evidence: C)*

**Class IIb recommendations**

Restoration of sinus rhythm in patients with atrial fibrillation. *(Level of Evidence: C)*

Use of beta-adrenergic blocking agents, ACE inhibitors, angiotensin receptor blockers, or calcium antagonists in patients with controlled hypertension to minimize symptoms of HF. *(Level of Evidence: C)*

Digitalis to minimize symptoms of HF. *(Level of Evidence: C)*

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**ACUTE DECOMPENSATION IN HF**

**PULMONARY EDEMA**

Acute systolic or diastolic dysfunction, frequently due to acute coronary occlusion, results in a rapid rise in left ventricular filling pressures, and hence pulmonary capillary wedge pressure (PCWP), may rise rapidly after acute coronary occlusion. The rise in PCWP leads to rapid redistribution of fluid from the intravascular space into the extravascular space (lung interstitium and alveoli), with subsequent pulmonary edema, which represents a medical emergency.
Immediate management goals include adequate oxygenation and preload reduction to relieve pulmonary congestion. Because of sympathetic stimulation, the blood pressure should be elevated in the presence of pulmonary edema. Patients with this appropriate response can typically tolerate the required medications, all of which lower blood pressure.

If acute pulmonary edema is not associated with elevation of the systemic blood pressure, impending cardiogenic shock must be suspected. If pulmonary edema is associated with hypotension, cardiogenic shock is diagnosed. Those patients often need circulatory support with inotropic and vasopressor agents and/or intra-aortic balloon counterpulsation to relieve pulmonary congestion and maintain adequate perfusion.

Pulmonary edema may occur as an acute event with the onset of STEMI or reinfarction or as the culmination of slowly progressive CHF, and in the latter case is often associated with hypervolemia.

Management includes the use of agents that acutely reduce preload (i.e., nitrates, morphine sulfate, and diuretics), and avoidance of acute administration of negative inotropic agents (i.e., beta-blockers and calcium channel antagonists).

**Nitrates** are initially administered by sublingual tablets or spray nitroglycerin followed by intravenous nitroglycerin. Intravenous nitroglycerin is a venodilator that acutely reduces ventricular filling pressures. At high doses, it dilates arterioles. It is effective at relieving pulmonary congestion and ischemia and may be used in patients who have normal or elevated systemic arterial pressure. A 10- to 20-mcg bolus should be administered, followed by 10 mcg per minute, increased by 5 to 10 mcg per minute every 5 to 10 minutes until dyspnea is relieved, the mean arterial pressure is lowered by 10% in normotensive patients or 30% in hypertensive patients, or until the heart rate increases by more than 10 bpm.

**Loop diuretics** (furosemide, torsemide, or bumetanide) should be initiated in low to intermediate doses only in patients with associated hypervolemia. Low doses should be used unless there is renal insufficiency, chronic diuretic use, or the presence of chronic CHF and hypervolemia as described above. Typical furosemide doses range from 20 to 80 mg IV (0.5 to 1.0 mg/kg).

**Angiotensin converting enzyme inhibitors** are indicated for patients with pulmonary congestion. Oral ACE inhibitors, preferably a short-acting agent such as captopril, beginning with 1 to 6.25 mg, should be instituted early in normotensive or hypertensive patients. The dosage may be doubled with each subsequent dose as tolerated up to 25 to 50 mg every 8 hours, then changed to a long-acting agent. ACE inhibitors are the only adjunctive medication (beyond aspirin and reperfusion therapy) demonstrated to reduce 30-day mortality when CHF complicates STEMI. Therefore, if blood pressure limits use of vasodilators, ACE inhibitors are preferred.
Intravenous **sodium nitroprusside** substantially reduces afterload and preload; however, its use has been associated with coronary steal.

**Digitalis** has no role in the management of pulmonary edema complicating STEMI unless rapid AF is present.

Nesiritide (synthetic natriuretic brain peptide) is a new vasodilator agent that promotes diuresis in patients with volume overload and decompensated chronic CHF (class 3 to 4). It has not been investigated in STEMI and is not indicated for treatment of pulmonary edema in these patients. Nesiritide is a potent vasodilator and may result in hypotension, particularly in patients with STEMI, in whom CHF usually is not due to volume overload.

An **aldosterone antagonist**, eplerenone, was found to be effective for secondary prevention of death and recurrent hospitalization in patients 3 to 14 days after MI with CHF and LVEF less than 0.40. Spironolactone has been demonstrated to improve survival in a population of patients with chronic CHF, which includes those with remote MI.

In contrast to the recommendation to avoid initiation of beta-blockade during pulmonary edema, beta-blockers are strongly recommended before hospital discharge for secondary prevention of cardiac events. The initial dose and titration should be based on clinical heart failure status and LVEF. For patients who remain in heart failure during the hospitalization, a low dose should be initiated and gradually titrated as an outpatient. This is supported by the beneficial effects of beta-blockade in patients with LV dysfunction after STEMI.

A summary of the joined AHA/ACC guidelines for the treatment of patients with pulmonary congestion are provided below:

**Class I recommendations**

**Oxygen supplementation to arterial saturation greater than 90%** is recommended for patients with pulmonary congestion. *(Level of Evidence: C)*

**Morphine sulfate** should be given to patients with pulmonary congestion. *(Level of Evidence: C)*

**ACE inhibitors**, beginning with titration of a short-acting ACE inhibitor with a low initial dose (e.g., 1 to 6.25 mg of captopril) should be given to patients with pulmonary edema unless the systolic blood pressure is less than 100 mm Hg or more than 30 mm Hg below baseline. Patients with pulmonary congestion and marginal or low blood pressure often need circulatory support with inotropic and vasopressor agents and/or intra-aortic balloon counterpulsation to relieve pulmonary congestion and maintain adequate perfusion. *(Level of Evidence: A)*
Nitrates should be administered for patients with pulmonary congestion unless the systolic blood pressure is less than 100 mm Hg or more than 30 mm Hg below baseline. Patients with pulmonary congestion and marginal or low blood pressure often need circulatory support with inotropic and vasopressor agents and/or intra-aortic balloon counterpulsation to relieve pulmonary congestion and maintain adequate perfusion. *(Level of Evidence: C)*

A diuretic (low- to intermediate-dose furosemide, or torsemide or bumetanide) should be administered to patients with pulmonary congestion if there is associated volume overload. Caution is advised for patients who have not received volume expansion. *(Level of Evidence: C)*

Beta-blockade should be initiated before discharge for secondary prevention. For those who remain in heart failure throughout the hospitalization, low doses should be initiated, with gradual titration on an outpatient basis. *(Level of Evidence: B)*

Long-term aldosterone blockade should be prescribed for post-STEMI patients without significant renal dysfunction (creatinine should be less than or equal to 2.5 mg/dL in men and less than or equal to 2.0 mg/dL in women) or hyperkalemia (potassium should be less than or equal to 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF of less than or equal to 0.40, and have either symptomatic heart failure or diabetes. *(Level of Evidence: A)*

Echocardiography should be performed urgently to estimate LV and RV function and to exclude a mechanical complication. *(Level of Evidence: C)*

**Class III**

Beta-blockers or calcium channel blockers should not be administered acutely to STEMI patients with frank cardiac failure evidenced by pulmonary congestion or signs of a low-output state. *(Level of Evidence: B)*