Treatment Guidelines
from The Medical Letter®

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Drugs for Treatment of Chronic Heart Failure

The range of drugs for treatment of chronic heart failure continues to expand. Some of those commonly used now are listed in the table on page 55. Mechanical therapies for the treatment of heart failure such as cardiac resynchronization, implanted cardiac defibrillators (ICDs), ventricular assist devices and ultrafiltration for the relief of congestion will not be reviewed here.

SYSTOLIC FUNCTION — Chronic systolic heart failure is usually associated with a left ventricular ejection fraction (LVEF) of ≤40%, but many patients with symptoms of heart failure have higher ejection fractions. There is no evidence that drug treatment of heart failure with preserved systolic function (LVEF >40%) improves clinical outcomes, but it can provide symptomatic relief. Patients with heart failure and preserved systolic function are often treated for comorbid conditions such as hypertension and coronary artery disease with the same drugs that are used to treat heart failure.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS — Guidelines from the American College of Cardiology (ACC), the American Heart Association (AHA) and the Heart Failure Society of America (HFSA) for management of chronic systolic heart failure recommend prescribing an ACE inhibitor for all patients with symptomatic heart failure and for asymptomatic patients with a decreased LVEF or a history of myocardial infarction (MI).[1,2] ACE inhibitors have also been used for patients at high risk for developing heart failure because of atherosclerotic disease, obesity, diabetes mellitus or hypertension. ACE inhibitors improve symptoms in patients with heart failure (sometimes within the first 48 hours, but more commonly over 4-12 weeks), decrease the incidence of hospitalization and MI, and prolong survival.[3]

Cautions – ACE inhibitors should be prescribed with a diuretic in patients with fluid retention and should be used cautiously in patients with systolic blood pressure <90 mmHg, creatinine levels >3 mg/dL, or potassium levels >5.5 meq/L (>5.0 meq/L in diabetics). They should not be used in patients with a history of angioedema or with bilateral renal artery stenosis. ACE inhibitors cause increased fetal mortality and are contraindicated for use in pregnancy.

Adverse Effects – The most common adverse effects of ACE inhibitors are thought to be related to inhibiting breakdown of endogenous kinins (cough and, less commonly, angioedema), suppression of angiotensin II (hyperkalemia, hypotension and renal insufficiency), and reduction of aldosterone production (hyperkalemia). Cough and angioedema can usually be relieved by replacing the ACE inhibitor with an angiotensin receptor blocker (ARB); ARBs do not increase concentrations of kinins to the same degree.

Formulary Considerations – No data are available showing that any ACE inhibitor is more effective than any other for treatment of heart failure or in its effects on symptoms or survival. Those in the table on page 55 have been shown in clinical trials to be effective in recommended doses in improving outcomes.

ANGIOTENSIN RECEPTOR BLOCKERS (ARBs) — Long-term therapy with ARBs reduces the risk of death, MI and other cardiovascular events in patients with systolic heart failure; results appear to be comparable to those obtained with ACE inhibitors. ARBs should be used in patients with heart failure and LVEF ≤ 40% who cannot tolerate an ACE inhibitor. Like ACE inhibitors, they have not improved clinical outcomes in patients with preserved systolic function.[4,5]

Cautions – As with ACE inhibitors, blood pressure, renal function and serum potassium concentrations

should be monitored in patients taking ARBs, and they are also contraindicated for use in pregnancy.

Adverse Effects – ARBs, like ACE inhibitors, may cause hypotension, renal insufficiency and hyperkalemia due to antagonism of angiotensin. They should be used cautiously in patients with a history of angioedema.

Formulary Considerations – Candesartan and valsartan are the only ARBs approved by the FDA for treatment of heart failure. Many Medical Letter consultants believe that all ARBs could be effective for this indication, but effective doses are best established for candesartan and valsartan.

BETA-ADRENERGIC BLOCKERS — Clinical guidelines recommend use of a beta-blocker in addition to an ACE inhibitor for patients with symptomatic systolic heart failure and for asymptomatic patients with a decreased LVEF or a history of MI. Use of **bisoprolol**, **carvedilol** or sustained-release **metoprolol succinate** consistently leads to a 30-40% reduction in mortality and hospitalization in patients with New York Heart Association (NYHA) class II–IV heart failure. In one study, **nebivolol** lowered all-cause mortality and hospitalizations by 15% compared to placebo.[6]

Cautions – Beta-blockers should be started at a low dose; fatigue, hypotension, asymptomatic fluid retention, and worsening heart failure may occur during the first 2-4 weeks of treatment. Dosage should be increased gradually over several weeks. Full clinical benefits may not occur for 3-6 months or longer.

Formulary Considerations – There is no published evidence supporting the effectiveness of beta-blockers other than bisoprolol, carvedilol, sustained-release metoprolol succinate or nebivolol for treatment of heart failure. Bisoprolol and nebivolol are not approved for treatment of heart failure by the FDA, and nebivolol appears to be the least effective of the four.[7]

Adverse Effects – Beta-blockers should be used cautiously, if at all, in patients with asthma or severe bradycardia. Initial treatment with beta-blockers may result in fluid retention; increasing the dose of a concurrent diuretic may be helpful.

ALDOSTERONE ANTAGONISTS — The addition of **spironolactone** to previous therapy in 1663 patients with severe systolic heart failure reduced the risk of mortality by 30% and hospitalization by 35%, compared to placebo.[8] In a clinical trial in more than 6600 patients with acute MI complicated by left ventricular systolic dysfunction and heart failure, **eplerenone** added to previous therapy reduced all-cause and cardiovascular mortality by 15% and 17%, respectively, compared to placebo.[9]

Adverse Effects – Hyperkalemia may occur, especially in patients taking potassium supplements or an ACE inhibitor or ARB, and in those with renal impairment. To minimize the risk of life-threatening hyperkalemia, aldosterone antagonists should be avoided in patients with a baseline serum creatinine concentration higher than 2.0 (women) or 2.5 (men) mg/dL or a serum potassium concentration higher than 5.0 mEq/dL. In elderly patients, serum creatinine levels may underestimate renal dysfunction; aldosterone antagonists should not be used for these patients when creatinine clearance is less than 30 mL/min. Spironolactone has anti-androgenic activity and can cause painful gynecomastia and erectile dysfunction in men and menstrual irregularities in women; the incidence of these effects is lower with eplerenone.

Formulary Considerations – Eplerenone is probably similar in effectiveness to spironolactone and may be better tolerated, but it costs much more. Comparative studies of their use in heart failure are lacking.

VASODILATORS — Concurrent use of two oral vasodilators, **hydralazine** and **isosorbide dinitrate**, can produce sustained improvement in LVEF and has been recommended for use in patients who cannot tolerate an ACE inhibitor or an ARB. The addition of a fixed-dose combination of hydralazine and isosorbide dinitrate *(BiDil)* to standard therapy in African-American patients with class III-IV heart failure significantly lowered mortality and the rate of first hospitalization while improving quality-of-life scores.[10,11] Studies in other populations have shown little benefit.[12,13]

Adverse Effects – Hydralazine/isosorbide dinitrate can cause headache and dizziness. Hydralazine alone can cause tachycardia, peripheral neuritis and a lupus-like syndrome. A phosphodiesterase inhibitor such as sildenafil *(Viagra)*, vardenafil *(Levitra)* or tadalafil *(Cialis)* should not be taken concurrently with hydralazine/isosorbide dinitrate because of the risk of additive hypotension.

DIURETICS — Most patients with heart failure have fluid retention. In these patients, diuretics relieve symptoms, but their effect on survival is unknown. Diuretics provide symptomatic relief of pulmonary and peripheral edema more rapidly than other drugs used for the treatment of heart failure. Diuretics that act on the loop of Henle, such as **furosemide**, **bumetanide** or **torsemide**, are more effective than thiazide diuretics, such as hydrochlorothiazide, which act on the distal tubule.

Table 1. Some Drugs for Treatment of Heart Failure

Drug	Initial Daily Dosage	Maximum Daily Dosage	Cost[1]
Angiotensin-Converting Enzyme (ACE) Inhibitors			
Captopril – generic	6.25 mg tid	50 mg tid	$4.00[2]
Capoten (Par)			282.60
Enalapril – generic	2.5 mg bid	10-20 mg bid	4.00[2]
Vasotec (Biovail)			150.00
Lisinopril – generic	2.5-5 mg once	20-40 mg once	4.00[2]
Prinivil (Merck)			36.30
Zestril (AstraZeneca)			50.10
Perindopril* – *Aceon* (Solvay)	2 mg once	8-16 mg once	87.60
Ramipril – generic	1.25-2.5 mg once	10 mg once	54.00
Altace (King)			83.40
Trandolapril – generic	1 mg once	4 mg once	36.90[3]
Mavik (Abbott)			41.10
Angiotensin Receptor Blockers (ARBs)			
Candesartan cilexetil –	4-8 mg once	32 mg once	
Atacand (AstraZeneca)			88.20
Valsartan – *Diovan* (Novartis)	20-40 mg bid	160 mg bid	158.40
Beta-Adrenergic Blockers			
Bisoprolol* – generic	1.25 mg once	10 mg once	4.00[2]
Zebeta (Duramed)			90.00
Carvedilol – generic	3.125 mg bid	25 mg bid	4.00[2]
Coreg (GlaxoSmithKline)		(50 mg bid for pts >85kg)	145.80
Coreg CR	10 mg once	80 mg once	124.80[3]
Metoprolol succinate ext release – generic	12.5-25 mg once	200 mg once	65.10
Toprol-XL (AstraZeneca)			78.90
Nebivolol* – *Bystolic* (Forest)	1.25 mg once	10 mg once	55.80
Aldosterone Antagonists			
Eplerenone – generic	25 mg once	50 mg once	106.20
Inspra (Pfizer)			135.30
Spironolactone – generic	12.5-25 mg once	25 mg once or bid	4.00[2]
Aldactone (Pfizer)			28.20
Vasodilators			
Isosorbide dinitrate/hydralazine – generic*	20 mg/37.5 mg tid	40 mg/75 mg tid	108.90[4]
BiDil (Nitromed)[5]			387.00
Loop Diuretics			
Bumetanide – generic	0.5-1 mg once or bid	1-10 mg once or	4.00[2]
Bumex (Roche)		in divided doses	26.70
Furosemide – generic	20-40 mg once or bid	40-600 mg once or	4.00[2]
Lasix (Aventis)		in divided doses	12.30
Torsemide – generic	10-20 mg once	10-200 mg once or	17.70
Demadex (Meda)		in divided doses	36.60
Digitalis Glycosides			
Digoxin – generic	0.125-0.25 mg once	0.125 mg once, or every other	4.00[2]
Lanoxin (GlaxoSmithKline)		day for CrCl <40 mL/min	4.05

* Not approved by the FDA for treatment of heart failure.
1. Cost for 30 days' treatment at the lowest maximum dosage, based on April 2009 data from retail pharmacies nationwide, available from Wolters Kluwer Health.
2. A 30-day supply costs $4.00 and a 90-day supply costs $10.00 at Walmart, Target, and some other stores.
3. AWP according to *Drug Topics RedBook 2009*.
4. Cost based on the use of two 20-mg isosorbide dinitrate tablets, one 50-mg and one 25-mg hydralazine tablet tid.
5. *BiDil* is a fixed-dose combination that contains 20 mg isosorbide dinitrate and 37.5 mg hydralazine in each tablet.

Dosage – Diuretics should be started at a low dose, which can be titrated up until urine output increases and weight decreases. Patients may experience diuretic resistance if they consume large amounts of sodium or take medications that block diuretic effects such as nonsteroidal anti-inflammatory drugs (NSAIDs), or if heart failure progresses. IV administration, concurrent use of 2 diuretics (1 loop, 1 thiazide-like) or addition of an aldosterone antagonist can sometimes overcome diuretic resistance.

Adverse Effects – The most common adverse effect of diuretic therapy is hypokalemia, which can be ameliorated or prevented by taking oral potassium supplements or by concurrent use of an ACE inhibitor or ARB and/or a potassium-sparing agent such as spironolactone or eplerenone.

Formulary Considerations – Torsemide is better absorbed than furosemide and has a longer duration of action, but there is no clinical evidence that torsemide

or bumetanide is more effective than furosemide, which has been used longer.

DIGITALIS — Digoxin can decrease the symptoms of heart failure, increase exercise tolerance and decrease the rate of hospitalization, but does not increase survival.[14]

Dosage – The optimal dosage of digoxin is not clear. Use of a dosing nomogram may assist in choosing a safe and effective dose.[15]

Adverse Effects – The most common adverse effects of digitalis glycosides are conduction disturbances, cardiac arrhythmias, nausea, vomiting, confusion and visual disturbances.

CONCLUSION — Unless there is a specific contraindication, all patients with heart failure and systolic dysfunction (LVEF ≤40%) should take both an ACE inhibitor and a beta-blocker, and if volume overloaded, a diuretic as well. An angiotensin receptor blocker (ARB) is recommended for patients who cannot tolerate an ACE inhibitor. Addition of an aldosterone antagonist can be beneficial for patients with moderately-severe to severe heart failure or for patients with left ventricular dysfunction after an MI. A combination of hydralazine and isosorbide dinitrate added to an ACE inhibitor and a beta-blocker has been effective in African-American patients with class III-IV heart failure. Digoxin can decrease symptoms and lower the rate of hospitalization for heart failure, but does not decrease mortality. There is no evidence that any drug improves clinical outcomes in patients with heart failure with preserved systolic function.

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Issue 83 Questions

1. In patients with chronic systolic heart failure, ACE inhibitors:
   a. improve symptoms
   b. decrease hospitalizations
   c. improve survival
   d. all of the above

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2. ACE inhibitors should not be used in patients with:
   a. diabetes
   b. a history of myocardial infarction
   c. bilateral renal artery stenosis
   d. hypertension

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3. Like ACE inhibitors, ARBs have not improved clinical outcomes in patients with:
   a. LVEF >40%
   b. LVEF <40%
   c. diabetes
   d. renal impairment

   Pg. 53

4. A beta-blocker is recommended for treatment of systolic heart failure:
   a. in addition to an ACE inhibitor
   b. as an alternative to an ACE inhibitor
   c. only for patients with symptoms
   d. in maximum doses from the outset

   Pg. 54

5. Beta-blockers should be used cautiously, if at all, in a patient with:
   a. diabetes
   b. asthma
   c. hypertension
   d. all of the above

   Pg. 54

6. Addition of spironolactone to standard therapy in patients with severe systolic heart failure reduced the risk of:
   a. hospitalization and death
   b. myocardial rupture
   c. atrial fibrillation
   d. none of the above

   Pg. 54

7. The main concern with aldosterone inhibitors is:
   a. hyperglycemia
   b. hypernatremia
   c. renal failure
   d. hyperkalemia

   Pg. 54

8. Vasodilators are used in heart failure as:
   a. first-choice therapy
   b. alternative initial therapy
   c. add-on therapy for Caucasian patients
   d. all of the above

   Pg. 54

9. Loop diuretics used to treat systolic heart failure have been shown to:
   a. improve survival
   b. decrease symptoms
   c. cause hyperkalemia
   d. all of the above

   Pg. 54

10. Digoxin used to treat heart failure can:
    a. decrease symptoms
    b. increase exercise tolerance
    c. decrease hospitalizations
    d. all of the above

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11. Initial treatment of most patients with systolic heart failure should include:
    a. an ACE inhibitor and an ARB
    b. an ARB and a vasodilator
    c. an ACE inhibitor and a beta-blocker
    d. a beta-blocker and an aldosterone antagonist

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12. Addition of hydralazine and isosorbide dinitrate has been effective particularly in:
    a. diastolic heart failure
    b. patients with left ventricular dysfunction after an MI
    c. African-Americans
    d. patients who cannot tolerate an ACE inhibitor

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