THE MEDICAL LETTER®
on Drugs and Therapeutics

Objective Drug Reviews Since 1959

Volume 57
January 19, 2015

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Drugs for Chronic Heart Failure

Heart failure is usually associated with left ventricular dysfunction. According to recent guidelines, patients with a left ventricular ejection fraction (LVEF) ≤40% are considered to have heart failure with reduced ejection fraction (HFrEF) or systolic heart failure. Patients with a LVEF ≥50% and symptoms of heart failure are considered to have heart failure with preserved ejection fraction (HFpEF) or diastolic heart failure; there is little evidence that drug treatment improves clinical outcomes in these patients.\(^1,2\) The treatment of acute heart failure is not included here.

ACE INHIBITORS — All patients with heart failure with reduced ejection fraction should receive an angiotensin-converting enzyme (ACE) inhibitor. These drugs improve symptoms (generally over 4-12 weeks), decrease the incidence of hospitalization, and prolong survival in patients with heart failure.

Dosage — ACE inhibitors should be started at low doses and titrated to the highest tolerated dose, targeting the maximum daily dosages listed in Table 1 on page 11.

Cautions — ACE inhibitors should be used cautiously in patients with systolic blood pressure <80 mm Hg, serum creatinine >3 mg/dL, serum potassium >5.0 mEq/L, or bilateral renal artery stenosis. They should not be used in patients with a history of angioedema. Blood pressure, renal function, and serum potassium levels should be monitored in patients taking an ACE inhibitor. ACE inhibitors can increase fetal mortality and should not be used during pregnancy.

Adverse Effects — The most common adverse effects of ACE inhibitors are related to inhibiting breakdown of endogenous kinins (cough and, less commonly, angioedema), suppression of angiotensin II (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. Rash, taste disturbances, and neutropenia can occur with captopril, but appear to be uncommon at the currently recommended dosage.

Choice of an ACE Inhibitor — No data are available showing that any one ACE inhibitor is more effective than any other for treatment of heart failure. Some ACE inhibitors (perindopril and benazepril) have not been approved by the FDA for treatment of heart failure.

ARBs — Long-term therapy with an angiotensin receptor blocker (ARB) reduces the risk of death in patients with heart failure with reduced ejection fraction; results appear to be similar to those obtained with ACE inhibitors. ARBs can be used in patients who cannot tolerate (primarily due to cough) an ACE inhibitor. Routine use of an ACE inhibitor and an ARB together is generally not recommended.

Recommendations for Treatment of Chronic Heart Failure\(^1,2\)

- Unless there is a specific contraindication, all patients with heart failure with reduced ejection fraction (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 reduce mortality and hospitalization in patients with symptomatic heart failure or with left ventricular dysfunction after a myocardial infarction.
- Addition of a combination of hydralazine and isosorbide dinitrate to standard therapy has been shown to reduce mortality and symptoms in black patients with NYHA class III-IV heart failure with reduced ejection fraction.
- Digoxin can decrease symptoms and lower the rate of hospitalization for heart failure, but it does not reduce mortality.
- There is little evidence that drug treatment improves clinical outcomes in patients with heart failure with preserved ejection fraction (HFpEF).

Dosage – ARBs should be started at low doses and titrated to the highest tolerated dose, which is usually achieved by doubling the dose until the maximum daily dose (listed in Table 1) is reached.

Cautions – As with ACE inhibitors, blood pressure, renal function, and serum potassium concentrations should be monitored in patients taking an ARB. Angioedema could occur in patients taking an ARB who had previously developed it while taking an ACE inhibitor. Like ACE inhibitors, ARBs can increase fetal mortality and should not be used during pregnancy.

Adverse Effects – ARBs, like ACE inhibitors, block the effects of angiotensin II and may cause hypotension, renal insufficiency, and hyperkalemia, but they do not cause cough. Angioedema occurs less frequently with ARBs than with ACE inhibitors.

Choice of an ARB – Candesartan and valsartan are the only ARBs approved by the FDA for treatment of heart failure; losartan, which is available generically, has also been widely used.3,4

BETA BLOCKERS – Unless there is a specific contraindication, all patients with stable heart failure with reduced ejection fraction should receive a beta blocker in addition to an ACE inhibitor. Use of bisoprolol, carvedilol, or extended-release metoprolol succinate in addition to an ACE inhibitor consistently leads to a 30-40% reduction in hospitalization and mortality in adults with New York Heart Association (NYHA) class II–IV heart failure. The efficacy of adding a beta blocker to standard therapy for heart failure is less certain in children and adolescents and in patients with a reduced ejection fraction who are asymptomatic.5

A recent observational cohort study in patients with heart failure with preserved ejection fraction found that use of a beta blocker was associated with a lower rate of all-cause mortality.6

Dosage – Beta blockers should be started at low doses and increased gradually, usually at 2-week intervals, to the highest tolerated dose. Full clinical benefits may not occur for 3-6 months or more.

Cautions – Beta blockers should be used cautiously, if at all, in patients with asthma or severe bradycardia.

Adverse Effects – Fatigue, hypotension, bradycardia, asymptomatic fluid retention, and worsening heart failure may occur during the first 2-4 weeks of treatment. Increasing the dose of a concurrent diuretic may be helpful for fluid retention.

Choice of a Beta Blocker – Carvedilol, extended-release metoprolol succinate, and bisoprolol have been shown to reduce mortality and hospitalization in patients with heart failure with reduced ejection fraction. Bisoprolol is not approved by the FDA for treatment of heart failure. There is no definitive clinical trial comparing extended-release metoprolol succinate with carvedilol. Carvedilol has been shown to reduce the incidence of diabetes mellitus,7 hospitalization for heart failure, and inappropriate defibrillator therapy.8 The advantages of extended-release metoprolol succinate are once-daily dosing, less hypotension, and more selective beta-1 blockade that may reduce the risk of bronchospasm.

ALDOSTERONE ANTAGONISTS – The addition of an aldosterone antagonist is recommended for patients with NYHA Class II-IV heart failure with a LVEF ≤35%. When added to standard therapy in patients with heart failure, aldosterone antagonists have been shown to reduce the risk of hospitalization and death.9-11 When used in addition to standard therapy in patients with heart failure after myocardial infarction, one study found that eplerenone significantly reduced the primary endpoints of all-cause mortality and mortality or hospitalization for cardiovascular reasons.12 Guidelines recommend adding an aldosterone antagonist after an acute myocardial infarction in patients with heart failure symptoms and an LVEF ≤40%.

In a study in patients with heart failure with preserved ejection fraction, spironolactone improved non-invasive measures of diastolic function, but it did not improve exercise capacity or quality of life.13 In another trial, use of spironolactone did not significantly reduce the incidence of the primary composite endpoint of cardiovascular death, cardiac arrest, or heart failure hospitalization compared to placebo.14

Cautions – Aldosterone antagonists should be avoided in patients with serum potassium >5.0 mEq/L and in those with reduced renal function (baseline serum creatinine >2.0 mg/dL for women or >2.5 mg/dL for men, or an estimated GFR <30 mL/min/1.73 m²). Renal function and serum creatinine concentrations should be monitored during treatment.

Adverse Effects – Hyperkalemia occurs frequently with aldosterone antagonists;15 the risk is higher in patients also taking an ACE inhibitor or an ARB, and in those with renal impairment. Spironolactone has anti-androgenic activity and can cause erectile dysfunction and painful gynecomastia in men and menstrual irregularities in women; the incidence of these effects has been reported to be lower with eplerenone.
## Table 1. Some Drugs for Chronic Heart Failure with Reduced Ejection Fraction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Oral Formulations</th>
<th>Usual Initial Adult Dosage</th>
<th>Usual Maximum Adult Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin-Converting Enzyme (ACE) Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril – generic</td>
<td>12.5, 25, 50, 100 mg tabs</td>
<td>6.25 mg tid</td>
<td>50 mg tid</td>
<td>$130.00*</td>
</tr>
<tr>
<td>Enalapril – generic</td>
<td>2.5, 5, 10, 20 mg tabs</td>
<td>2.5 mg bid</td>
<td>20 mg bid</td>
<td>$12.00*</td>
</tr>
<tr>
<td>Perindopril – generic</td>
<td>2, 4, 8 mg tabs</td>
<td>2 mg once/d</td>
<td>16 mg once/d</td>
<td>$20.20</td>
</tr>
<tr>
<td>Quinapril – generic</td>
<td>5, 10, 20, 40 mg tabs</td>
<td>5 mg bid</td>
<td>20 mg bid</td>
<td>$24.10</td>
</tr>
<tr>
<td>Ramipril – generic</td>
<td>1.25, 2.5, 5, 10 mg caps</td>
<td>1.25-2.5 mg once/d</td>
<td>10 mg once/d</td>
<td>$9.70</td>
</tr>
<tr>
<td><strong>Angiotensin Receptor Blockers (ARBs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azilsartan medoxomil* – Edarbi (Arbor)</td>
<td>40, 80 mg tabs</td>
<td>40-80 mg once/d</td>
<td>80 mg once/d</td>
<td>$135.60</td>
</tr>
<tr>
<td>Candesartan cilexetil – generic Atacand (AstraZeneca)</td>
<td>4, 8, 16, 32 mg tabs</td>
<td>4-8 mg once/d</td>
<td>32 mg once/d</td>
<td>$103.10</td>
</tr>
<tr>
<td>Losartan* – generic</td>
<td>25, 50, 100 mg tabs</td>
<td>25-50 mg once/d</td>
<td>150 mg once/d</td>
<td>$6.00</td>
</tr>
<tr>
<td>Valsartan* – generic</td>
<td>40, 80, 160, 320 mg tabs</td>
<td>20-40 mg bid</td>
<td>160 mg bid</td>
<td>$264.40</td>
</tr>
<tr>
<td><strong>Beta-Adrenergic Blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol* – generic</td>
<td>5, 10 mg tabs</td>
<td>1.25 mg once/d</td>
<td>10 mg once/d</td>
<td>$24.50</td>
</tr>
<tr>
<td>Carvedilol – generic</td>
<td>3.125, 6.25, 12.5, 25 mg tabs</td>
<td>3.125 mg bid</td>
<td>25 mg bid</td>
<td>$5.40*</td>
</tr>
<tr>
<td>Metoprolol succinate ER – generic Toprol-XL (AstraZeneca)</td>
<td>25, 50, 100, 200 mg ER tabs</td>
<td>12.5-25 mg once/d</td>
<td>200 mg once/d</td>
<td>$50.20</td>
</tr>
<tr>
<td><strong>Aldosterone Antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eplerenone – generic</td>
<td>25, 50, 100 mg tabs</td>
<td>25 mg once/d</td>
<td>50 mg once/d</td>
<td>$104.10</td>
</tr>
<tr>
<td>Spironolactone* – generic</td>
<td>25, 50, 100 mg tabs</td>
<td>12.5-25 mg once/d</td>
<td>25 mg once/d or bid*</td>
<td>$5.80*</td>
</tr>
<tr>
<td><strong>Vasodilators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate/hydralazine* – BiDil (Arbor)*</td>
<td>20/37.5 mg tabs</td>
<td>20 mg/37.5 mg tid</td>
<td>40 mg/75 mg tid</td>
<td>$228.60</td>
</tr>
<tr>
<td><strong>Loop Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide – generic</td>
<td>0.5, 1, 2 mg tabs</td>
<td>0.5-1 mg once/d or bid</td>
<td>10 mg once/d or in divided doses</td>
<td>$117.80*</td>
</tr>
<tr>
<td><strong>Digitalis Glycoside</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin – generic</td>
<td>0.125, 0.25 mg tabs</td>
<td>0.125 mg once/d</td>
<td>0.125-0.25 mg once/d or once every other day</td>
<td>$36.10*</td>
</tr>
<tr>
<td>Lanoxin (Covis)</td>
<td>0.0625, 0.125, 0.1875, 0.25 mg tabs</td>
<td>0.125 mg once/d</td>
<td>0.125-0.25 mg once/d or once every other day</td>
<td>$67.80</td>
</tr>
</tbody>
</table>

ER = extended-release

* Not approved by the FDA for treatment of heart failure.
1. For treatment of heart failure with reduced ejection fraction (HFrEF).
2. Dosage adjustment may be needed for hepatic or renal impairment.
3. Approximate WAC for 30 days' treatment at the lowest maximum dosage. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. January 5, 2015. Reprinted with permission by First Databank, Inc. All rights reserved. ©2015. www.fdbhealth.com/policies/drug-pricing-policy.
4. A 30-day supply costs $4.00 at some large discount pharmacies.
5. Available as scored tablets.
6. For patients with an eGFR <50 mL/min/1.73 m². For patients with an eGFR 50-89 mL/min/1.73 m², the initial dose is 25 mg every other day for eplerenone and 12.5 mg once daily or every other day for spironolactone and the maintenance dose is 25 mg once daily for eplerenone and 12.5-25 mg once daily for spironolactone.
7. Both of these drugs are available generically as single agents. Isosorbide dinitrate is available in 5, 10, 20, and 30-mg tablets and hydralazine in 10, 25, 50, and 100-mg tablets.
8. FDA-approved as adjunctive therapy for treatment of heart failure in black patients.
Choice of an Aldosterone Antagonist – Eplerenone may be similar in effectiveness to spironolactone and may have less anti-androgenic activity, but it costs much more. Comparative studies of their use in heart failure are lacking.

VASODILATORS – Use of hydralazine plus isosorbide dinitrate may be beneficial for some patients. The addition of a fixed-dose combination of hydralazine and isosorbide dinitrate (BiDil) to standard therapy in African-American patients who remained symptomatic despite standard therapy significantly reduced mortality and symptoms. Its benefit in non-African-American patients is less well established, but the combination can be considered in those intolerant to an ACE inhibitor or an ARB or in those who need additional blood pressure control despite maximal doses of standard therapy.

Adverse Effects – Hydralazine/isosorbide dinitrate frequently causes headache and dizziness. Hydralazine alone can cause tachycardia, peripheral neuritis, and a lupus-like syndrome. Phosphodiesterase inhibitors, such as sildenafil (Viagra, Revatio, and generics), 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 such 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 for treatment of heart failure than thiazide-type diuretics, such as hydrochlorothiazide or chlorothalidone, which act on the distal tubule.

Dosage – Diuretics should be started at a low dose, which can be titrated upward until urine output increases and weight decreases. Patients with renal dysfunction or prior refractoriness to loop diuretics can be started at higher doses. Intravenous 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. Diuretics can also cause worsening of renal function.

Choice of a Diuretic – 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 in use much longer.

DIGOXIN – Digoxin can decrease the symptoms of heart failure, increase exercise tolerance, and decrease the rate of hospitalization, but it does not prolong survival.

Dosage – A low dose of digoxin (0.125 mg/d) is generally recommended for patients with heart failure with reduced ejection fraction. Dose adjustments based on renal function, age, and concomitant medications may be required. Digoxin levels of 0.5-0.9 ng/mL are recommended.

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

OTHER DRUGS – A large trial in patients with NYHA class II-IV systolic heart failure (GISSI-HF) found that the addition of n-3 polyunsaturated fatty acids 1 gram daily to standard therapy for a median of 3.9 years modestly reduced all-cause mortality and cardiovascular hospitalizations compared to placebo. Aliskiren (Tekturna) is a direct renin inhibitor approved for treatment of hypertension. Although it offers the theoretical benefit of upstream renin-angiotensin system inhibition, one study in patients hospitalized for heart failure found that addition of aliskiren to standard therapy did not reduce cardiovascular death or rehospitalization for heart failure at 6 months or 12 months after discharge.

Sacubitril plus Valsartan – A recent trial (PARADIGM-HF) found that the combination of the investigational neprilysin inhibitor sacubitril and the ARB valsartan was superior to the ACE inhibitor enalapril alone in reducing the rate of death from cardiovascular causes or hospitalization for heart failure, the primary composite endpoint, in patients with heart failure with reduced ejection fraction.


