Spironolactone in Left-Sided Heart Failure: How Does It Fit In?

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The familiar diuretic spironolactone has taken on new life as a treatment for left-sided congestive heart failure. Spironolactone has been shown to decrease mortality in such patients who are New York Heart Association class IV. It can be used in addition to agents such as angiotensin-converting enzyme inhibitors and beta blockers, which also decrease mortality, and diuretics and digoxin, which are useful in treating symptoms. Spironolactone is safe, easy to use and reasonably priced. More research is necessary to determine the order and combinations of these medications in slowing the progression of this disease. (Am Fam Physician 2001;64:1393-8,1399.)

O *A patient information handout on heart failure, written by the authors of this article, is provided on page 1399.*

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Spironolactone (Aldactone) is a potassium-sparing diuretic that was approved many years ago. Until recently, it was used primarily to treat edema resulting from liver cirrhosis, primary hyperaldosteronism and nephrotic syndrome. It has been used in combination with potassium-wasting diuretics to prevent hypokalemia.

Recent research on this older diuretic has focused on its effect in patients with left-sided congestive heart failure (CHF). As an aldosterone-blocking agent, spironolactone is postulated to work synergistically with angiotensin-converting enzyme (ACE) inhibitors to provide more thorough blockade of the renin-angiotensin-aldosterone (RAA) system.

Pharmacology

The RAA system is the complex mechanism by which the kidneys control the cardiovascular system. The system goes awry in patients with heart failure; in these persons, the decreased renal blood flow is not due to low blood volume but to a heart pump that is not working efficiently. ACE inhibitors block the conversion of vasoconstrictor angiotensin I to the much more potent angiotensin II, also blocking the production of the sodium-retaining hormone aldosterone. This production is only transiently suppressed, thus allowing aldosterone production to "escape" the effects of the ACE inhibitors.[1]

Spironolactone is a specialized antagonist of aldosterone. It acts as a competitive binding agent at the aldosterone receptor site in the distal convoluted renal tubules, preventing the formation of a protein important in the sodium-potassium exchange in the kidneys. This action causes increased amounts of water and sodium to be excreted while potassium is conserved.

Evidence of Benefit in Heart Failure

Based on earlier work suggesting a benefit of therapy,[2] the Randomized Aldactone Evaluation Study (RALES) was undertaken to evaluate the role of spironolactone when used in addition to standard therapy for CHF. Standard therapy in this study did not include beta blockers.[3] The investigators prospectively enrolled 1,663 patients with severe (New York Heart Association [NYHA] class IV) CHF *(Table 1)*.[4] Most of the enrolled patients were white men averaging 65 years of age. These patients had a left ventricular ejection fraction of 35 percent or less and marked physical limitations related to CHF. Patients were excluded if they had unstable angina or moderate renal failure, and if they were hyperkalemic.

All patients who could tolerate the drug were given an ACE inhibitor and a loop diuretic, and 70 percent were taking digoxin.

The Randomized Aldactone Evaluation Study (RALES) results showed that spironolactone decreases mortality in class III and IV left-sided congestive heart failure when added to other standard therapies.

Only 10 percent were taking beta blockers. Patients were randomly assigned to receive placebo or 25 mg of spironolactone daily in addition to their current regimen. After eight weeks, if the patient showed worsening CHF and had a stable potassium level, the dosage was increased to 50 mg daily. The dosage was decreased to 25 mg every other day if at any time the patient became hyperkalemic.

Even with a 25 percent dropout rate (414 patients) among the two groups, related to adverse effects or lack of response, the results in the remaining patients in the study indicated a 30 percent reduction in death (35 versus 46 percent) over two years. During the study period, one death was avoided for every nine patients receiving spironolactone (number needed to treat [NNT] = 9).

The number of hospitalizations related to worsening CHF was lowered by 35 percent. NYHA classification improved in the spironolactone group more than in the placebo group. The primary adverse effect causing discontinuation of this agent in 10 percent of the men taking spironolactone was gynecomastia or breast pain. The incidence of serious hyperkalemia (5 versus 8 percent) was small.

TABLE 1
NYHA Functional Classification of Congestive Heart Failure

Class	*Description*
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue or dyspnea.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue or dyspnea.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

NYHA = New York Heart Association.

Adapted with permission from Criteria Committee, New York Heart Association. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston: Little, Brown, 1964:114.

Spironolactone in Left Ventricular CHF

Left ventricular CHF is a problem commonly seen in family practice, with a prevalence close to 2 percent. In a typical panel of 2,500 patients, about 50 will have heart failure. In mild failure, the annual mortality is 5 to 10 percent annually; in severe cases, it increases to 30 to 40 percent annually.[5]

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[6] trial in 1987 was the first to show that ACE inhibitors could decrease mortality related to heart failure. ACE inhibitors are generally well tolerated except in patients with an elevated creatinine level (usually greater than 3 mg per dL [265 µmol per L]). The angiotensin-II receptor antagonist losartan has also been shown to decrease mortality in patients with heart failure.[7]

Loop diuretics have been universally used to reduce the symptoms of heart failure, but they have not been shown to reduce mortality.[8] Digoxin has recently had a resurgence of use in patients with severe CHF; it does not reduce mortality but has been shown to reduce symptoms and hospitalizations.[9]

In stark contrast to previous conventional wisdom, beta blockers have been shown to reduce mortality in patients with heart failure who can tolerate them. In the Cardiac Insufficiency Bisoprolol Study (CIBIS-II),[10] patients taking bisoprolol, a $beta_1$ selective blocker, had

fewer hospital admissions (NNT = 17.5) and cardiovascular deaths (NNT = 31) than the control group. All patients had NYHA class III or IV failure, were taking ACE inhibitors and diuretics, and had been clinically stable for at least six weeks.

Numerous other studies have demonstrated the benefit of beta blockers in patients with heart failure, with a 31 percent reduction in mortality overall. The benefit occurs primarily in reductions in non-sudden rather than sudden cardiac death and is similar in patients with ischemic and nonischemic cardiomyopathy.[11]

Carvedilol (Coreg) is the only beta blocker specifically labeled for treatment of patients with heart failure. However, studies of metoprolol, bisoprolol and propranolol have shown them to be effective in decreasing mortality, hospitalizations and hospitalizations related to heart failure. Carvedilol was found to be more effective than the other agents in patients without ischemic heart disease.[12]

The combination of hydralazine and isosorbide dinitrate has been shown to decrease mortality by 25 to 30 percent (Veterans Administration Cooperative Study [V-HEFT I]).[13] This combination of agents has been supplanted by ACE inhibitors, which are easier to use and more effective. However, the combination would be appropriate to consider in a patient who cannot tolerate ACE inhibitors.

Given the wide variety of choices, how do physicians decide which agents to use and when? *Table 2*[2,13-16] shows the NNT for each of these agents, and *Table 3* gives an indication for each agent's use, as some guidance for this complicated decision.

Cardiac Medications for Prevention

The prescribing of ACE inhibitors, beta blockers and spironolactone in patients with heart failure presents the physician with challenges because while these agents do slow long-term decline related to heart failure, they have little or no effect on symptoms. In addi-

TABLE 2
Number Needed to Treat* for Different Drugs in CHF

Drug or drug class	*NNT*	*Outcome prevented*
ACE inhibitors[14]	6	One death over one year in patients with NYHA class III and IV failure
	100	One death over one year in patients with NYHA class I or II failure
Beta blockers[15]	23	One death over one year
	13	One hospitalization over one year
Spironolactone[2]	9	One death over two years in patients with NYHA class IV failure
Hydralazine and isosorbide dinitrate[13]	14	One death over one year
Digoxin[16]	9	Emergency department visits or hospitalizations

ACE = angiotensin-converting enzyme; CHF = congestive heart failure; NYHA = New York Heart Association.

**—Number needed to treat (NNT) is the number of patients who need to be treated to prevent one outcome from occurring. NNT = 100/absolute risk reduction.*

Information from references 2 and 13 through 16.

TABLE 3
Recommendations for Treating Patients with Left Ventricular CHF

Medications	*Patients who should take them*
Decrease mortality	
ACE inhibitors	All patients with CHF
Spironolactone (Aldactone)	Patients with class III or IV CHF
Beta blockers	All patients with CHF (if tolerated)
Hydralazine (Apresoline)/ isosorbide dinitrate (Isorem)	Patients who do not tolerate ACE inhibitors
Angiotensin-II receptor blockers	Unknown
Decrease symptoms	
Loop diuretics	Patients with congestive symptoms
Digoxin (Lanoxin)	Patients who are still symptomatic despite maximal dosages of other medications

CHF = congestive heart failure; ACE = angiotensin-converting enzyme.

Angiotensin-converting enzyme inhibitors and beta blockers reduce mortality in heart failure.

tion, it is not clear how quickly therapy should be started, whether all three approaches should be combined at once or which drugs should be added first. Research to date suggests benefit from all of the options in patients with an ejection fraction of less than 30 percent. A prudent approach would be to begin with an ACE inhibitor (or an angiotensin-II receptor blocker) and spironolactone in most patients *(Table 4)*, slowly adding a beta blocker after the patient is stabilized on the first two drugs.

Specific Use of Spironolactone

Spironolactone is contraindicated in patients with anuria, acute renal insufficiency, significant renal insufficiency or hyperkalemia. Potassium supplementation should not be combined with spironolactone. Other drug interactions include errors in measurement of and an increase in the half-life of digoxin, decreased effectiveness when used with salicylates and variable effects or side effects (i.e., increased potassium) with use of nonsteroidal anti-inflammatory drugs. Gynecomastia and hyponatremia can occur, along with metabolic acidosis, which is usually associated with hyperkalemia. Other side effects are rare and include drug fever, drowsiness, lack of coordination, lethargy and gastrointestinal signs and symptoms.

Dosages range from 25 to 50 mg per day in patients with heart failure, although much higher dosages are used to treat other disorders. Patients pay less than $10 per month for typical dosages. This cost compares with that of other medications used for CHF, such as $31 to $33 per month for generic metoprolol, $97 for carvedilol and $22 to $87 for low to moderate doses of ACE-inhibitor therapy.

Spironolactone absorption is increased significantly when taken with food, but the clinical significance of this effect is not known. The metabolites are excreted primarily in the urine and secondarily in the bile, with half-lives of approximately 14 to 16 hours.

Final Comment

One study[3] has shown that spironolactone improves morbidity and mortality in patients with severe heart failure. The particular advantages of spironolactone for prevention are that it is inexpensive, is taken once daily and has relatively few side effects. This study suggests that all patients with class IV heart failure should be given a trial of spironolactone. Further research is needed to understand its usefulness in patients with less severe heart failure and whether its benefit is present in patients who are also taking beta blockers. Research is also necessary to determine which order and combinations of medications are the most beneficial in slowing the progression of this disease.

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TABLE 4

Agents Used to Decrease Mortality in Patients with Heart Failure

Agent	*Dosage*	*Comments on drug class*	*Comments on specific drug*	*Cost (generic)**
ACE inhibitors				
Benazepril (Lotensin)	20 to 40 mg daily, single dose or two divided doses	Start with low dose and titrate up		$27
Captopril (Capoten)	75 to 150 mg daily in three doses		Risk of neutropenia	87 (58.50 to 68)
Enalapril (Vasotec)	5 to 20 mg daily in divided doses	Caution with creatinine level > 3 mg per dL (265 mmol per L); do not use in pregnancy		53 (46 to 53)
Fosinopril (Monopril)	20 to 40 daily, single dose			29
Lisinopril (Zestril, Prinivil)	5 to 20 mg daily, single dose		Risk of neutropenia	28
Moexipril (Univasc)	7.5 to 30 daily, one hour before meals, single or two divided doses			22
Quinapril (Accupril)	20 to 40 mg daily in two divided doses	Can cause angioedema		66
Ramipril (Altace)	5 mg twice daily			67
Trandolapril (Mavik)	1 to 4 mg daily			24
Angiotensin receptor antagonists				
Losartan (Cozaar)	25 to 100 mg daily, single or divided doses	Pregnancy class C		41
Valsartan (Diovan)	80 to 320 daily, single dose	Hypotension with volume depletion		41
Irbesartan (Avapro)	150 to 300 daily, single dose	May precipitate acute renal failure in patients with renal impairment		39
Candesartan (Atacand)	8 to 32 mg daily, single or two divided doses	Black patients have less response	Increases concentration of digoxin	39
Telmisartan (Micardis)	20 to 80 mg daily, single dose	Possible increase in liver enzymes		40
Beta blockers				
Carvedilol (Coreg)	3.125 mg twice daily for two weeks, slowly increase to maximum 25 mg twice daily (< 85 kg [187 lb]) or 50 mg twice daily (> 85 kg)	Contraindicated in patients with dizziness, bradycardia or asthma, and in patients with second- or third-degree AV block		97
Metoprolol (Lopressor, Toprol XL)	100 to 400 mg daily in a single dose (Toprol XL) or two divided doses (Lopressor)	Potentiates effects of calcium channel blockers	Metoprolol increases effect of phenothiazines	27 (Toprol XL) 46 (31 to 33; Lopressor)
Cardiac glycoside				
Digoxin (Lanoxin)	0.125 to 0.25 mg once daily	Small therapeutic window		6 (2 to 7)
Diuretics				
Furosemide (Lasix)	20 to 80 mg daily, single or two divided doses			6 (3 to 4)
Spironolactone (Aldactone)	25 to 50 mg daily, single dose or two divided doses			16 (2 to 6)

ACE = angiotensin-converting enzyme; AV = atrioventricular.

**—Estimated cost to the pharmacist of long-term therapy for one month based on average wholesale prices (rounded to the nearest dollar) for the lowest dosage in Red Book. Montvale, N.J.: Medical Economics Data, 2001. Cost to the patient may be greater, depending on prescription filling fee.*

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