Effects of Spironolactone on Long-term Mortality and Morbidity in Patients With Heart Failure and Mild or No Symptoms

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Abstract: *Background:* The purpose of this study is to evaluate long-term effects of spironolactone, an affordable and widely used aldosterone receptor blocker, in patients with heart failure (HF) and mild or no symptoms. *Methods:* The study is a single-blind, placebo-controlled, blinded endpoint, randomized study. Patients with New York Heart Association (NYHA) classes I to II HF and left ventricular ejection fraction < 40% were randomized to spironolactone or placebo in addition to optimal therapy. The primary endpoint was the composite of death from any cause or cardiovascular hospitalization. *Results:* A total of 130 patients were randomized to spironolactone (n = 65) or placebo (n = 65). Patients on spironolactone had a better event-free survival for cardiovascular death or cardiovascular hospitalizations and for cardiovascular hospitalizations alone. At multivariable analysis, only spironolactone therapy, left ventricular ejection fraction and serum creatinine levels had an independent prognostic value for the combined endpoint, whereas only spironolactone therapy and serum creatinine levels had an independent prognostic value for cardiovascular hospitalizations alone. *Conclusions:* Administration of spironolactone reduced the composite of death and cardiovascular hospitalization in patients with NYHA classes I to II HF. These results suggest that spironolactone could be beneficial when administered on top of optimal therapy among patients with HF and mild or no symptoms.

Key Indexing Terms: Spironolactone; Heart failure; Prognosis. **[Am J Med Sci 2014;347(4):271–276.]**

Chronic heart failure (CHF) is a major public health problem representing 1 of the leading causes of death in developed countries. Approximately 1% to 2% of the population in developed countries has heart failure (HF), with the prevalence rising to 10% or more among persons aged 70 years or older.[1,2] Aldosterone plays an important role in the pathophysiology of HF causing endothelial dysfunction, inflammation, coagulation activation,[3–5] myocardial fibrosis and hypertrophy.[4–6] Besides, mineralocorticoid receptors are overexpressed in the myocardium of the failing heart.[7]

Aldosterone receptor antagonists (ARA) have been shown to improve outcomes in patients with CHF. Aldosterone blockade in conjunction with other neurohormonal modulators has been tested in some randomized-controlled trials.[8] Spironolactone showed to reduce mortality and morbidity when added to standard therapy in patients with left ventricular systolic dysfunction (LVSD) and advanced symptomatic HF (New York Heart Association [NYHA] functional classes III–IV) in the Randomized Aldactone Evaluation Study (RALES).[7] In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[8] another aldosterone receptor blocker, eplerenone, reduced morbidity and mortality in patients with recent acute myocardial infarction (MI) complicated by LVSD and HF. On the basis of these 2 large randomized trials, the current guidelines recommend aldosterone receptor blockers in patients with low ejection fraction (<35%) and severe symptomatic, NYHA class III or heart failure (IVHF) and in selected patients after acute MI.[9,10] Until recently, it was not clear whether these agents were effective in mild-to-moderate CHF or asymptomatic LVSD. Few and small studies addressed this issue,[11–14] and only 1 evaluated clinical outcomes in a midterm follow-up.[12] The large-scale randomized trial Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF)[15] has recently been stopped prematurely for benefit. The trial showed that eplerenone reduces the rate of death from cardiovascular causes or hospitalization for HF by approximately 37%, compared with placebo, in patients with functional class II HF.[16]

In this study, we evaluated effects of spironolactone, a less-expensive ARA, on long-term mortality and morbidity in patients with HF and mild or no symptoms (NYHA classes I–II).

METHODS

Patients Population and Study Design

From February 2001 to September 2004, 132 patients (aged 18–80 years) were enrolled in a single-center study at our institute. The local ethics committee approved the protocol, and all patients gave their written informed consent for their participation to the study.

Patients were eligible for enrollment if they had a diagnosis of CHF, a left ventricular ejection fraction (LVEF) < 40% of either ischemic or nonischemic causative factor, with NYHA class I or II symptoms and no history of acute decompensation (NYHA class III or IV) in the previous year and were treated with an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin receptor blocker [ARB] if not tolerated) and a beta-blocker, unless contraindicated, in addition to loop diuretic if clinically indicated.

Exclusion criteria included the following: Cockroft-Gault formula estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2; serum K > 5.0 mEq/L; valvular heart disease amenable to surgical treatment; unstable angina or acute MI or coronary revascularization procedure within 3 months before enrollment; intravenous therapy with inotropic drugs within 3 months before enrollment; congenital heart disease, primary hepatic failure, active cancer or any life-threatening disease (other than HF); K+-sparing diuretics; history of resuscitated ventricular arrhythmias (unless this occurred within 24 hours of a previous acute MI or in subjects with

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an implantable cardioverter defibrillator); and other clinical or general conditions contraindicating participation in a clinical trial.

After the initial evaluation, patients underwent a 4-week run-in phase and were subsequently randomized in a single-blind fashion to receive either 25 mg of spironolactone (once daily or a matching placebo). At 4 weeks, provided that serum potassium was ≤5.0 mmol/L, the dose of study drug could be increased to 50 mg once daily if eGFR was ≥50 mL/min/1.73 m^2 and remained 25 mg once daily if eGFR was in the range of 30 to 49 mL/min/1.73 m^2. At 8 weeks, if study drug was well tolerated, the dose could be increased to 100 mg 4 times a day. Potassium and renal function were tested every week during the up-titration and then every 2 to 4 weeks as clinically indicated. If hyperkalemia developed at any time or eGFR ranged below 30/mL/min/1.73 m^2, the dose could be decreased to 25 mg every other day. Study medication could be withheld in the event of serious hyperkalemia (>6.0 mEq/L), an eGFR of less than 30 mL/min/1.72 m^2 after minimal dosage achieved, intercurrent illness or any condition in which such a course was deemed medically necessary to protect the patient's best interests. However, all patients remained in the study so that we could track hospitalizations and deaths. The review of medical records and the endpoints adjudication were performed by a committee of 3 cardiologists who were blinded to the treatment assignment.

Endpoints

The primary endpoint was cardiovascular death or cardiovascular hospitalizations. Secondary endpoints were all-cause death, cardiovascular death, cardiovascular hospitalizations and HF hospitalizations.

The criterion of HF hospitalization was according to European Society of Cardiology CHF guidelines.

Statistical Analysis

Intergroup comparison between continuous variables was performed by paired samples *T* test, whereas comparison between categorical variables was performed by χ^2 test. Kaplan-Meier methods and log-rank test were used to analyze cumulative event-free survival for primary and secondary endpoints. Multivariable survival analysis was performed by Cox proportional stepwise hazards regression analysis. A P value < 0.01 was considered as statistically significant.

RESULTS

A total of 130 patients were randomized to spironolactone or placebo (65 in the spironolactone arm and 65 in the placebo arm). The mean duration of follow-up was 44 ± 16 months. There were 30 cardiovascular hospitalizations, 18 HF hospitalizations, 7 cardiovascular deaths and 9 noncardiovascular deaths. The study design and patient population is included in a flow chart (Figure 1). The mean dose-equivalent of study medication was 49.8 ± 16.5 mg/d (minimum, 12.5 mg/d and maximum, 100 mg/d). In the spironolactone group, 4 patients (6.2%) reached the dose of 100 mg per day die of drug, 3 patients (4.6%) were on 75 mg per die, 47 (72.3%) were on 50 mg per die, 10 patients (15.4%) were on 25 mg per die and 1 (1.5%) patient received 12.5 mg per die. Baseline characteristics of the 130 patients are listed in Table 1. Patients in spironolactone group were slightly younger, with a higher prevalence of NYHA class I HF and a lower prevalence of idiopathic-dilated cardiomyopathy and a lower LVEF. No differences were found between the 2 study groups with respect to any other baseline characteristics.

Primary Outcome

Patients on spironolactone had a better event-free survival for cardiovascular death + cardiovascular hospitalizations and for

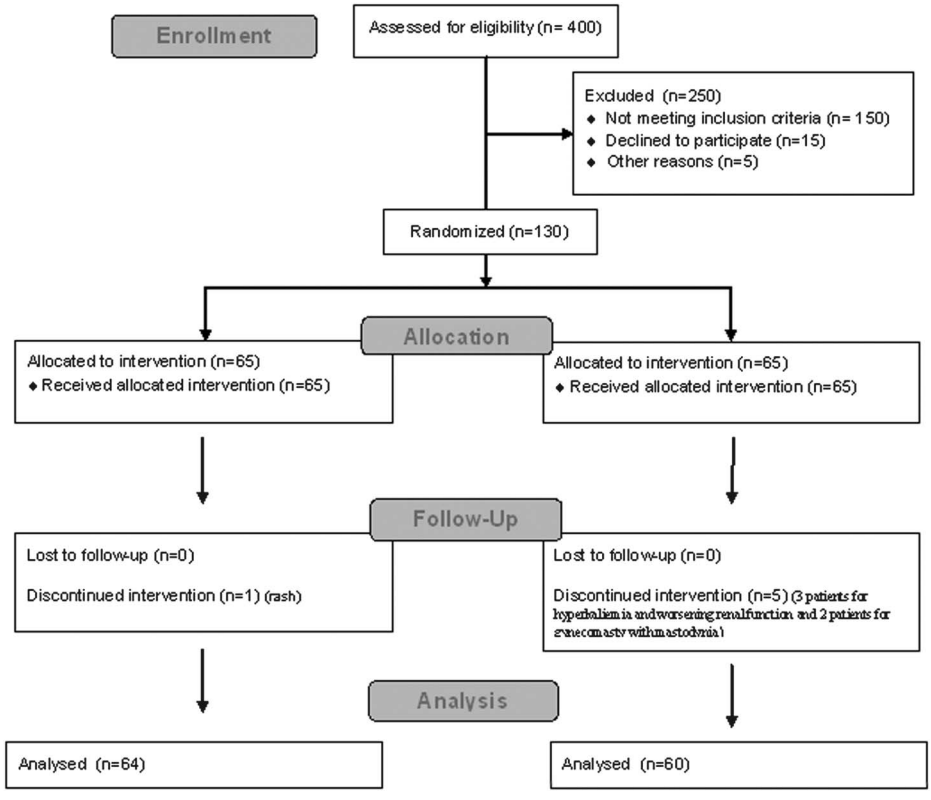

FIGURE 1. Study flow chart.