THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

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ABSTRACT

Background and Methods   Aldosterone is important in the pathophysiology of heart failure. In a double-blind study, we enrolled 1663 patients who had severe heart failure and a left ventricular ejection fraction of no more than 35 percent and who were being treated with an angiotensin-converting–enzyme inhibitor, a loop diuretic, and in most cases digoxin. A total of 822 patients were randomly assigned to receive 25 mg of spironolactone daily, and 841 to receive placebo. The primary end point was death from all causes.

Results   The trial was discontinued early, after a mean follow-up period of 24 months, because an interim analysis determined that spironolactone was efficacious. There were 386 deaths in the placebo group (46 percent) and 284 in the spironolactone group (35 percent; relative risk of death, 0.70; 95 percent confidence interval, 0.60 to 0.82; P<0.001). This 30 percent reduction in the risk of death among patients in the spironolactone group was attributed to a lower risk of both death from progressive heart failure and sudden death from cardiac causes. The frequency of hospitalization for worsening heart failure was 35 percent lower in the spironolactone group than in the placebo group (relative risk of hospitalization, 0.65; 95 percent confidence interval, 0.54 to 0.77; P<0.001). In addition, patients who received spironolactone had a significant improvement in the symptoms of heart failure, as assessed on the basis of the New York Heart Association functional class (P<0.001). Gynecomastia or breast pain was reported in 10 percent of men who were treated with spironolactone, as compared with 1 percent of men in the placebo group (P<0.001). The incidence of serious hyperkalemia was minimal in both groups of patients.

Conclusions   Blockade of aldosterone receptors by spironolactone, in addition to standard therapy, substantially reduces the risk of both morbidity and death among patients with severe heart failure. (N Engl J Med 1999:341:709-17.)

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ALDOSTERONE has an important role in the pathophysiology of heart failure.[1-4] Aldosterone promotes the retention of sodium, the loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, and vascular damage and impairs arterial compliance.[4-8] Many physicians have assumed that inhibition of the renin–angiotensin–aldosterone system by an angiotensin-converting–enzyme (ACE) inhibitor will suppress the formation of aldosterone. In addition, treatment with an aldosterone-receptor blocker in conjunction with an ACE inhibitor has been considered relatively contraindicated because of the potential for serious hyperkalemia.[9,10]

Consequently, aldosterone-receptor blockers are used infrequently in patients with heart failure.[11,12] There is increasing evidence to suggest, however, that ACE inhibitors only transiently suppress the production of aldosterone.[7,13-16] Furthermore, treatment with the aldosterone-receptor blocker spironolactone at a daily dose of 12.5 to 25 mg in conjunction with standard doses of an ACE inhibitor, a loop diuretic, and in most cases digoxin is pharmacologically effective and well tolerated, decreases atrial natriuretic peptide concentrations, and does not lead to serious hyperkalemia (defined as a serum potas-

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sium concentration of at least 6.0 mmol per liter).[17] On the basis of this information, we designed the Randomized Aldactone Evaluation Study (RALES) to test the hypothesis that daily treatment with 25 mg of spironolactone would significantly reduce the risk of death from all causes among patients who had severe heart failure as a result of systolic left ventricular dysfunction and who were receiving standard therapy, including an ACE inhibitor, if tolerated.

METHODS

Patients

Patients were eligible for enrollment if they had had New York Heart Association (NYHA) class IV heart failure within the six months before enrollment and were in NYHA class III or IV at the time of enrollment, had been given a diagnosis of heart failure at least six weeks before enrollment, were being treated with an ACE inhibitor (if tolerated) and a loop diuretic, and had a left ventricular ejection fraction of no more than 35 percent within the six months before enrollment (with no clinically significant intercurrent event). Treatment with digitalis and vasodilators was allowed, but potassium-sparing diuretics were not permitted. Oral potassium supplements were not recommended unless hypokalemia (defined as a serum potassium concentration of less than 3.5 mmol per liter) developed.

Patients were excluded from the study if they had primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to left ventricular systolic heart failure), congenital heart disease, unstable angina, primary hepatic failure, active cancer, or any life-threatening disease (other than heart failure). Patients who had undergone heart transplantation or were awaiting the procedure were also ineligible. Other criteria for exclusion were a serum creatinine concentration of more than 2.5 mg per deciliter (221 μmol per liter) and a serum potassium concentration of more than 5.0 mmol per liter. The institutional review boards or ethics committees of all participating institutions approved the protocol, and all patients gave written informed consent.

Procedures

After the initial evaluation, patients were randomly assigned in a double-blind fashion to receive either 25 mg of spironolactone (Aldactone, Searle, Skokie, Ill.) once daily or a matching placebo. After eight weeks of treatment, the dose could be increased to 50 mg once daily if the patient showed signs or symptoms of progression of heart failure without evidence of hyperkalemia. If hyperkalemia developed at any time, the dose could be decreased to 25 mg every other day; however, the investigator was encouraged first to adjust the doses of concomitant medications. Follow-up evaluations and laboratory measurements, including measurements of serum potassium, were conducted every 4 weeks for the first 12 weeks, then every 3 months for up to 1 year and every 6 months thereafter until the end of the study. Additional clinical laboratory tests were also performed at weeks 1 and 5. Serum potassium was also measured at week 9 in patients for whom the dose was increased to 50 mg. Study medication could be withheld in the event of serious hyperkalemia, a serum creatinine concentration of more than 4.0 mg per deciliter (354 μmol per liter), 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.

An independent data and safety monitoring board periodically reviewed the results in a blinded fashion. Event committees whose members were unaware of the patients' treatment assignments assessed the causes of death and reasons for hospitalization.

End Points

The primary end point of the study was death from any cause. Secondary end points included death from cardiac causes, hospitalization for cardiac causes, the combined incidence of death from cardiac causes or hospitalization for cardiac causes, and a change in the NYHA class. The effect of spironolactone was also assessed with the use of six prerandomization variables: left ventricular ejection fraction, the cause of heart failure, the serum creatinine concentration, age, the use of ACE inhibitors, and the use of digitalis.

Statistical Analysis

The analysis of death from all causes (the primary end point) included all patients, according to the intention-to-treat principle. Kaplan–Meier[18] methods were used to construct cumulative survival curves for the two groups. The primary comparison between the two groups was based on a log-rank test.[19] Cox proportional-hazards regression models[20] were developed to explore the effects of base-line variables on the estimated effect of spironolactone. Formal assessment of efficacy used a group sequential monitoring plan with a Lan–DeMets[21] stopping boundary and an O'Brien–Fleming[22] spending function.

The sample size was calculated on the basis of the following assumptions: the mortality rate in the placebo group would be 38 percent, the risk of death would be 17 percent lower in the spironolactone group than in the placebo group, and approximately 5 percent of the patients in the spironolactone group would discontinue treatment during each year of the study.[23] The power of the study to detect a difference between treatment groups was set at 90 percent (with a two-tailed α level of 0.05).

At each of its meetings, the data and safety monitoring board evaluated the available data for evidence of efficacy and safety and calculated the cumulative type I error with respect to efficacy. In two large studies of patients with heart failure,[24,25] the distributions of the time to death were nonexponential; therefore, the computations for group sequential monitoring of mortality from all causes were based on life-table calculations of event rates. The critical z value required to establish that treatment with spironolactone was efficacious was 2.02, corresponding to a P value of 0.043.

RESULTS

Randomization was begun on March 24, 1995; recruitment was completed on December 31, 1996, with follow-up scheduled to continue through December 31, 1999. However, at the fifth planned interim analysis, the observed effect of spironolactone on the risk of death from all causes exceeded the prespecified critical z value. Hence, the trial was stopped on August 24, 1998, after a mean follow-up of 24 months, on the recommendation of the data and safety monitoring board. The analysis includes all events through midnight on August 24, 1998.

A total of 1663 patients from 195 centers in 15 countries underwent randomization: 841 were assigned to receive placebo and 822 were assigned to receive spironolactone. As shown in Table 1, the two groups had similar characteristics at base line. Seven patients (three in the placebo group and four in the spironolactone group) who had a history of NYHA class IV heart failure were in NYHA class II at the time of randomization. During the study, 414 patients (200 in the placebo group and 214 in the spironolactone group) discontinued treatment because of a lack of response, because of adverse events, or for

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	PLACEBO GROUP (N=841)	SPIRONOLACTONE GROUP (N=822)
Age — yr	65±12	65±12
White race — %	86	87
Sex — no. (%)		
Male	614 (73)	603 (73)
Female	227 (27)	219 (27)
Blood pressure — mm Hg		
Systolic	122±20	123±21
Diastolic	75±11	75±12
Heart rate — beats/min	81±15	81±14
New York Heart Association class — no. (%)		
II	3 (0.4)	4 (0.5)
III	581 (69)	592 (72)
IV	257 (31)	226 (27)
Left ventricular ejection fraction — %†	25.2±6.8	25.6±6.7
Cause of heart failure — no. (%)‡		
Ischemic	453 (54)	454 (55)
Nonischemic	386 (46)	368 (45)
Medications — %		
Loop diuretics	100	100
ACE inhibitors	94	95
Digitalis	72	75
Aspirin	37	36
Potassium supplements	27	29
Beta-blockers	10	11
Mean dose of ACE inhibitors — mg/day		
Captopril	62.1	63.4
Enalapril	16.5	13.5
Lisinopril	13.1	15.5

*Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme.

†The ejection fraction could be measured by contrast ventriculography, gated radionuclide ventriculography, or echocardiography.

‡The cause of heart failure was determined on the basis of a patient's history, angiographic evidence, or both. Data on the cause of heart failure were not available for two patients in the placebo group.

administrative reasons. Treatment was stopped in an additional 19 patients (11 in the placebo group and 8 in the spironolactone group) because of the need for heart transplantation; 2 patients, both of whom were in the placebo group, died after heart transplantation. Patients who discontinued treatment were followed by means of regularly scheduled telephone calls to determine their vital status. After 24 months of follow-up, the mean daily dose of study medication for the patients who continued to receive treatment was 31 mg in the placebo group and 26 mg in the spironolactone group.

Survival

There were 386 deaths in the placebo group (46 percent) and 284 deaths in the spironolactone group (35 percent), representing a 30 percent reduction in the risk of death (relative risk of death among the patients in the spironolactone group, 0.70 by a Cox proportional-hazards model; 95 percent confidence interval, 0.60 to 0.82; P<0.001) (Fig. 1 and Table 2). A total of 314 deaths in the placebo group (37 percent) and 226 deaths in the spironolactone group (27 percent) were attributed to cardiac causes, representing a 31 percent reduction in the risk of death from cardiac causes (relative risk, 0.69; 95 percent confidence interval, 0.58 to 0.82; P<0.001). The reduction in the risk of death among the patients in the spironolactone group was attributed to significantly lower risks of both death from progressive heart failure and sudden death from cardiac causes (Table 2).
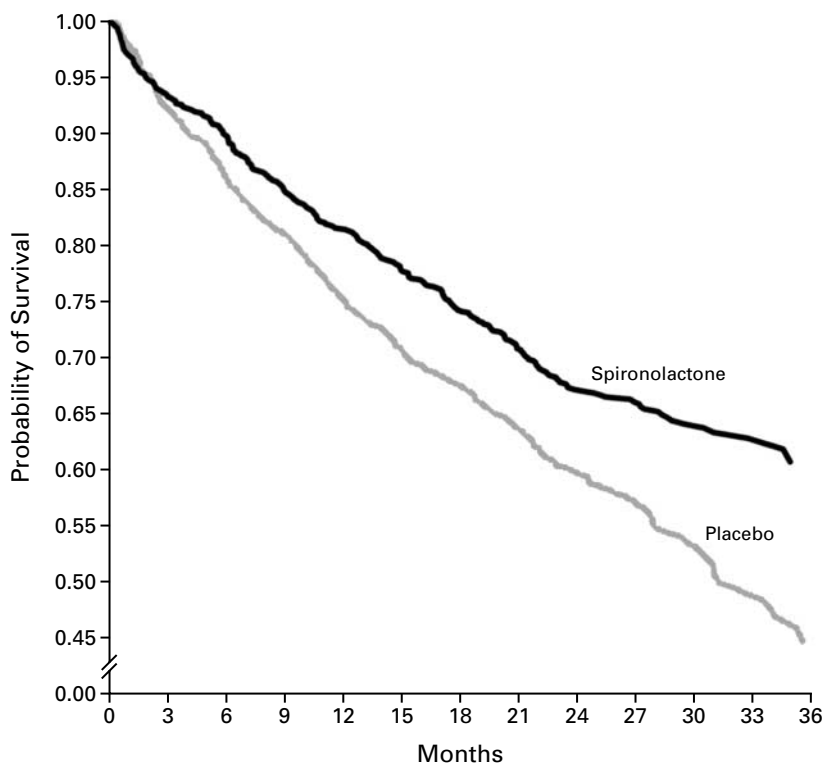
The reduction in the risk of death among patients in the spironolactone group was similar in analyses of all six prespecified subgroups as well as in retrospective analyses performed according to sex, NYHA class, base-line serum potassium concentration, use of potassium supplements, and use of beta-blockers (Fig. 2). The estimated beneficial effect was similar across geographic regions.

Death from Cardiac Causes and Hospitalization for Cardiac Causes

During the trial, 336 patients in the placebo group and 260 patients in the spironolactone group were hospitalized at least once for cardiac reasons (Table 2). In total, there were 753 hospitalizations for cardiac causes in the placebo group and 515 in the spironolactone group, representing a 30 percent reduction in the risk of hospitalization for cardiac causes among patients in the spironolactone group (relative risk, 0.70; 95 percent confidence interval, 0.59 to 0.82; P<0.001) (Table 2). Analysis of the combined end point of death from cardiac causes or hospitalization for cardiac causes revealed a 32 percent reduction in the risk of this end point among patients in the spironolactone group as compared with those in the placebo group (relative risk, 0.68; 95 percent confidence interval, 0.59 to 0.78; P<0.001) (Table 3).

Changes in NYHA Class

Three categories were used to assess changes in the symptoms of heart failure: improvement, no change, and worsening or death. The condition of patients who were in NYHA class III at base line was considered to have improved if they were in NYHA class I or II at the end of the study and considered to have worsened if they were in NYHA class IV (or had died). The condition of patients who were in NYHA class IV at base line was considered to have improved if they were in NYHA class I, II, or III at the end of the study; other patients in NYHA class IV at base line either had no change at the end of the study or died. In the placebo group, the condition of 33 percent of the patients improved; it did not change in 18 percent, and it worsened in 48 percent. In the spironolactone group, the condition of 41 percent of the patients improved; it did not change

Figure 1. Kaplan–Meier Analysis of the Probability of Survival among Patients in the Placebo Group and Patients in the Spironolactone Group.

The risk of death was 30 percent lower among patients in the spironolactone group than among patients in the placebo group (P<0.001).

No. at Risk													
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

in 21 percent, and it worsened in 38 percent. The difference between groups was significant (P<0.001 by the Wilcoxon test).

Safety

There were no significant differences between the two groups in serum sodium concentration, blood pressure, or heart rate during the study. The median creatinine and potassium concentrations did not change in the placebo group during the first year of follow-up, the period for which the data were most complete. During the same period, however, the median creatinine concentration in the spironolactone group increased by approximately 0.05 to 0.10 mg per deciliter (4 to 9 μmol per liter) and the median potassium concentration increased by 0.30 mmol per liter. The differences between the two groups were significant (P<0.001) but were not clinically important.

Table 4 lists the adverse reactions in the two groups. Serious hyperkalemia occurred in 10 patients in the placebo group (1 percent) and 14 patients in the spironolactone group (2 percent, P=0.42). Gynecomastia or breast pain was reported by 10 percent of the men in the spironolactone group and 1 percent of the men in the placebo group (P<0.001), causing more patients in the spironolactone group than in the placebo group to discontinue treatment (10 vs. 1, P=0.006).

DISCUSSION

We found that treatment with spironolactone reduced the risk of death from all causes, death from cardiac causes, hospitalization for cardiac causes, and the combined end point of death from cardiac causes or hospitalization for cardiac causes among patients who had severe heart failure as a result of left ventricular systolic dysfunction and who were receiving standard therapy including an ACE inhibitor. Spironolactone also improved the symptoms of heart failure, as measured by changes in the NYHA functional class. The reductions in the risk of death and

TABLE 2. RELATIVE RISKS OF DEATH AND HOSPITALIZATION.

VARIABLE	PLACEBO GROUP (N=841)	SPIRONOLACTONE GROUP (N=822)	RELATIVE RISK (95% CI)*	P VALUE
	no. of patients			
Cause of death				
Cardiac causes	314	226	0.69 (0.58–0.82)	<0.001
Progression of heart failure†	189	127	0.64 (0.51–0.80)	<0.001
Sudden death‡	110	82	0.71 (0.54–0.95)	0.02
Myocardial infarction	15	17		
Other cardiovascular causes	13	12		
Stroke	11	8		
Noncardiovascular causes	41	29		
Unknown	7	9		
Total	386	284	0.70 (0.60–0.82)	<0.001
	no. of patients/no. of events			
Reason for hospitalization				
Cardiac causes§	336/753	260/515	0.70 (0.59–0.82)	<0.001
Worsening heart failure	300/663	215/413	0.65 (0.54–0.77)	<0.001
Angina	35/44	43/66		
Ventricular arrhythmias	24/31	23/25		
Myocardial infarction	14/15	10/11		
Other cardiovascular causes	112/163	117/169		
Stroke	20/24	14/15		
Noncardiovascular causes	232/377	223/361		

*CI denotes confidence interval.

†This category includes death due to worsening heart failure (defined as increasing symptoms or signs requiring an increase in treatment).

‡This category includes witnessed death from cardiac causes heralded by abrupt loss of consciousness within one hour after the onset of symptoms in a patient in whom death was unexpected.

§Some patients were hospitalized for more than one cardiac cause.

hospitalization were observed after 2 to 3 months of treatment and persisted throughout the study (mean follow-up, 24 months). The results were consistent among subgroups. Serious hyperkalemia requiring the discontinuation of treatment was uncommon, occurring in one patient in the placebo group and three in the spironolactone group.

The patients in our study were at higher risk than those in studies of the effects of bisoprolol,[26] digoxin,[27] amlodipine,[28] or carvedilol[29] on heart failure resulting from systolic left ventricular dysfunction and treated with standard therapy, including an ACE inhibitor, but they were at lower risk than patients in a study of the effects of enalapril.[25] The reduction in the risk of death with spironolactone treatment was due to significant decreases in the risk of both death from progressive heart failure and sudden death from cardiac causes. These results are consistent with the current understanding of the effect of aldosterone in patients with heart failure.[30-32]

Aldosterone was originally thought to be important in the pathophysiology of heart failure only because of its ability to increase sodium retention and potassium loss. However, in the past several years, research has shown that aldosterone also causes myocardial and vascular fibrosis,[33,34] direct vascular damage,[8] and baroreceptor dysfunction[6] and prevents the uptake of norepinephrine by myocardium.[4,32] The reduction in the risk of death in our study does not appear to be due entirely to an effect of spironolactone on sodium retention or potassium loss; instead, it is likely that spironolactone is also cardioprotective. In our previous dose-finding study,[17] a dose of 25 mg of spironolactone daily had no apparent diuretic effect — that is, there was no change in total body weight, the sodium-retention score, or urinary sodium excretion. In the present study, spironolactone (mean dose, 26 mg daily) did not have a clinically significant hemodynamic effect. Although we cannot rule out the possibility that spironolactone had some effect on sodium excretion in the present study, this effect would most likely be minor, as compared with the effect of the high doses of loop diuretics used. Also, although there was a significant increase from base line in serum potassium concentrations in the patients in the spironolactone group, this change was not clinically important.

The 35 percent reduction in the risk of hospitalization for worsening heart failure may be attributable to the ability of spironolactone to reduce myocardial and vascular fibrosis. Although the exact cause of the reduction in the risk of death in our study re-
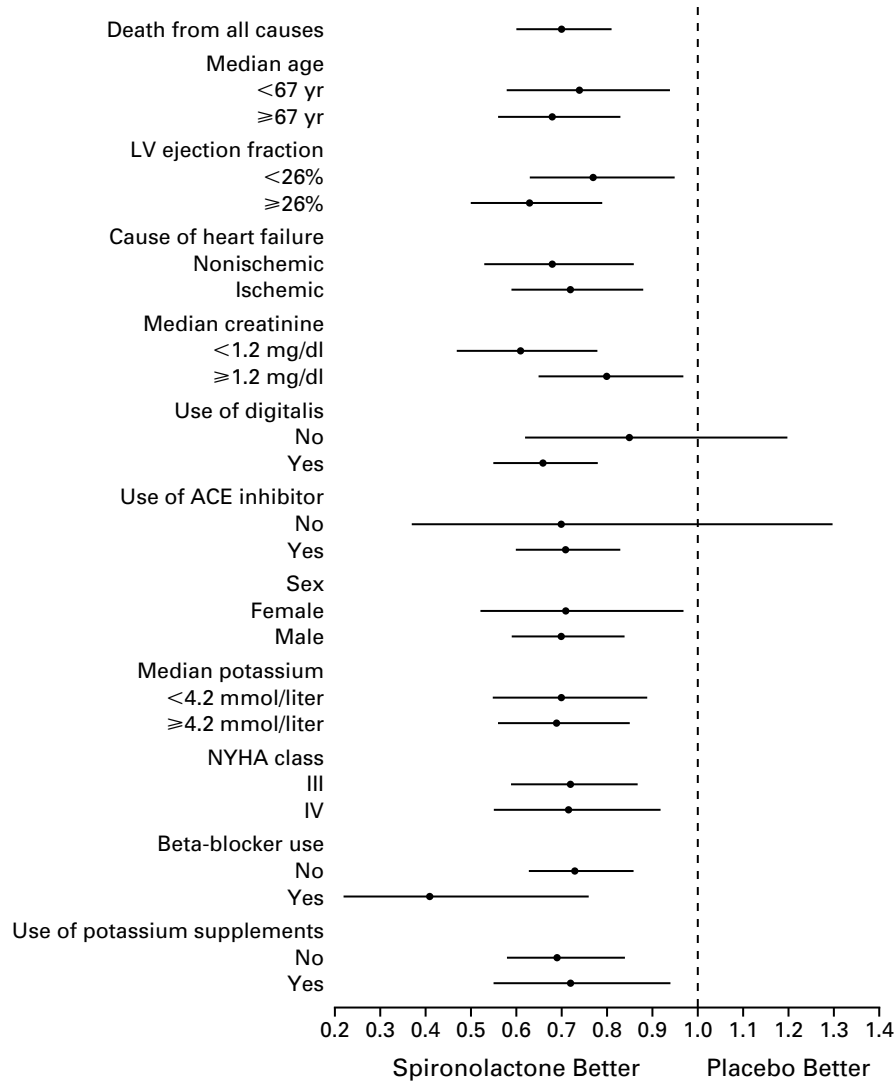
Figure 2. Relative Risks of Death from All Causes and According to Demographic and Clinical Characteristics.

The horizontal lines indicate 95 percent confidence intervals. LV denotes left ventricular, ACE angiotensin-converting enzyme, and NYHA New York Heart Association. To convert values for creatinine to micromoles per liter, multiply by 88.4.

TABLE 3. RELATIVE RISKS OF THE COMBINED END POINTS OF DEATH OR HOSPITALIZATION IN THE SPIRONOLACTONE GROUP.*

END POINT	RELATIVE RISK (95% CI)	P VALUE
Death from cardiac causes or hospitalization for cardiac causes	0.68 (0.59–0.78)	<0.001
Death from any cause or hospitalization for any reason	0.77 (0.68–0.86)	<0.001
Death from any cause or hospitalization for cardiac causes	0.68 (0.60–0.77)	<0.001

*Each analysis represents the time to the first occurrence of an event. For patients with both events, the analysis includes only the first event. CI denotes confidence interval.

mains speculative, we postulate that an aldosterone-receptor blocker can prevent progressive heart failure by averting sodium retention and myocardial fibrosis and prevent sudden death from cardiac causes by averting potassium loss and by increasing the myocardial uptake of norepinephrine. Spironolactone may prevent myocardial fibrosis by blocking the effects of aldosterone on the formation of collagen,[5,35,36] which in turn could play a part in reducing the risk of sudden death from cardiac causes, since myocardial fibrosis could predispose patients to variations in ventricular-conduction times and, hence, to reentry ventricular arrhythmias.[32,35-37]

Few patients (11 percent) in the spironolactone

TABLE 4. ADVERSE EVENTS.

ADVERSE EVENT	PLACEBO GROUP (N=841)	SPIRONOLACTONE GROUP (N=822)
	no. of patients (%)	
One or more events	667 (79)	674 (82)*
Discontinuation because of adverse event	40 (5)	62 (8)
Cardiovascular disorders	251 (30)	248 (30)
Angina	83 (10)	103 (13)
Heart failure	80 (10)	52 (6)
Respiratory tract disorders	285 (34)	262 (32)
Cough	117 (14)	103 (13)
Dyspnea	39 (5)	34 (4)
Pneumonia	25 (3)	17 (2)
Pulmonary edema	7 (0.8)	5 (0.6)
Pleural effusion	11 (1)	3 (0.4)
Metabolic and nutritional disorders	215 (26)	269 (33)
Hyperuricemia	25 (3)	16 (2)
Neoplasm	10 (1)	13 (2)
Urinary system disorders	89 (11)	99 (12)
Disorders of skin and appendages	72 (9)	73 (9)
Musculoskeletal disorders	118 (14)	101 (12)
Nervous system disorders	173 (21)	185 (23)
Psychiatric disorders	126 (15)	122 (15)
Gastrointestinal disorders	241 (29)	236 (29)
Endocrine disorders	26 (3)	84 (10)
Gynecomastia in men†	8 (1)	55 (9)‡
Breast pain in men†	1 (0.1)	10 (2)§
Gynecomastia or breast pain in men†	9 (1)	61 (10)‡
Edema	21 (2)	18 (2)
Serious hyperkalemia	10 (1)	14 (2)

*P=0.17 for the comparison with the placebo group.

†There were 614 men in the placebo group and 603 in the spironolactone group.

‡P<0.001 for the comparison with the placebo group.

§P=0.006 for the comparison with the placebo group.

group were receiving a beta-blocker at base line, and the reduction in the risk of death did not differ significantly between those who were treated with a beta-blocker and those who were not so treated. Since our patients were at higher risk than patients who were evaluated in recent studies of beta-blockers in heart failure,[26,29] studies are needed to examine both the tolerability and the effectiveness of beta-blockers in such a high-risk population as well as the effects of the concomitant use of an aldosterone-receptor blocker and a beta-blocker.

Our finding that an aldosterone-receptor blocker reduced the risk of both morbidity and death among patients who were receiving an ACE inhibitor emphasizes the point that standard doses of an ACE inhibitor do not effectively suppress the production of aldosterone.[7,14] Although higher doses of ACE inhibitors may be more effective than lower doses in reducing the risk of morbidity and death among pa-

tients with heart failure,[38] there is no evidence that higher doses suppress aldosterone production more effectively in the long term. ACE inhibitors cannot totally suppress the production of aldosterone, because other factors in addition to angiotensin II (e.g., serum potassium) are important in the production of aldosterone and may override the effects of angiotensin II.[39-41] Since aldosterone remains in the circulation, only the presence of an aldosterone-receptor blocker will completely suppress the effects of this hormone.

The fact that spironolactone significantly reduced the risk of both morbidity and death among the high-risk patients in our study with only a very low incidence of serious hyperkalemia can be attributed to our previous efforts in determining an effective and safe dose of spironolactone when used in conjunction with an ACE inhibitor.[17] We found that spironolactone at a dose of 12.5 to 25 mg daily was pharmacologically effective in blocking the aldosterone receptors and decreasing atrial natriuretic peptide concentrations and that serious hyperkalemia occurred most frequently with daily doses of 50 mg or greater.[17] In the present study, therefore, spironolactone therapy was initiated at a daily dose of 25 mg, and physicians were given the option of reducing the dose to 25 mg every other day if serum potassium concentrations started to rise to a hyperkalemic level or of increasing the dose to 50 mg daily after eight weeks in patients who had symptoms or signs of worsening heart failure but no evidence of hyperkalemia. It should be emphasized, however, that a serum creatinine concentration of more than 2.5 mg per deciliter and a serum potassium concentration of more than 5.0 mmol per liter were exclusion criteria. In addition, the long-term use of agents known to interact with spironolactone, increase the risk of hyperkalemia, or do both was not allowed. Although potassium supplements were used by 29 percent of the patients in the spironolactone group, the benefit of spironolactone in these patients was similar to that in patients who did not use potassium supplements.

Overall, spironolactone therapy was tolerated well: 8 percent of the patients in the spironolactone group discontinued treatment because of adverse events, as compared with 5 percent of the patients in the placebo group. This difference was due in part to a significant incidence of gynecomastia or breast pain among men in the spironolactone group (P<0.001). The rate of discontinuation of treatment because of this event was higher in the spironolactone group than in the placebo group (2 percent vs. 0.2 percent, P=0.006). Gynecomastia has previously been observed in patients who were treated with spironolactone.[42,43] Specifically, gynecomastia has been reported to occur in 6.9 percent of men who received daily doses of spironolactone of 50 mg or less for hyper-

tension.[43] The use of a selective aldosterone-receptor antagonist such as eplerenone, which has a lower affinity for androgen and progesterone receptors than does spironolactone,[44] may minimize the risk of gynecomastia. The risk of gynecomastia should not, however, be an argument against the use of spironolactone in men with severe heart failure, since spironolactone reduces the risk of both morbidity and death. The effectiveness and risks of treatment with spironolactone in patients at lower risk than those in our study, such as those with less severe heart failure, will require further prospective study.

Our finding that an aldosterone-receptor antagonist, when used in conjunction with an ACE inhibitor, reduces the risk of both death from progressive heart failure and sudden death from cardiac causes contributes to our understanding of the pathophysiology of heart failure and has implications for the treatment of patients with other conditions in which ACE inhibitors are beneficial, such as patients with hypertension and those who have had a myocardial infarction.

APPENDIX

In addition to the authors, the following persons participated in the study: *Data and Safety Monitoring Board* — D. Julian (chair), J.-P. Boissel, C. Furberg, H. Kulbertus, S. Pocock; *Primary End-Point Committee* — J. Blumenfeld, J.A. Ramires; *Nonfatal Hospitalization End-Point Committee* — S. Sasayama (chair), C. Brilla, D. Duprez, R. Muñoz; *Medical Monitors* — D. Asner, B. Roniker; *Investigators: Belgium* — P. Block, G. Boxho, J.-M. Chaudron, V. Conraads, J. Creplet, P. De Salle, F. Deman, D. Duprez, O. Gurnee, G. Heyndrickx, S. Janssens, G. Jouret, C. Mortier, L. Pierard, P. Timmermans, J.L. Vandenbossche, W. Van Mieghem, J. Vanwelden, J. Vincke; *Brazil* — F.M. Albanesi Filho, F.A. de Almeida, J.C.A. Ayoub, E.T. Barbosa, M. Batlouni, L.C. Bodanese, R.M. Carrasco, A.C. de C. Carvalho, I. Castro, O.R. Coelho, D. Dauar, C. Drumond Neto, G.S. Feitosa, R.A. Franken, P.C.B.V. Jardim, C. Mady, M.F. de C. Maranhão, J.A. Marin Neto, L.F. de Miranda, J.C. Nicolau, W. Oigman, W.A. de Oliveira Júnior, W.C. Pereira Filho, J.A.F. Ramires, J.J.F. Rapozo Filho, S. Rassi, J.M. Ribeiro, J.P. Ribeiro, P.R.F. Rossi, J.F.K. Saraiva, A.S. Sbissa, M.A.D. da Silva, J.E. de Sigueira, J. Souza Filho; *Canada* — I.M. Arnold, D. Beanlands, C. Koilpillai, S. Lepage, A. Morris, M. White; *France* — F. Albert, G. Amat, F. Apffel, M.C. Aumont, S. Baleynaud, P. Battistella, J. Beaune, L. Bonnefoy, A. Bonneau, J. Bonnet, M. Bory, J.P. Bousser, J.A. Boutarin, B. Charbonnier, A. Cohen, A. Cohen-Solal, M.T. Courbet-Andrejak, A. Cribier, F. Delahaye, C. D'Ivernois, J.P. Doazan, V. Dormagen, H. Douard, F. Dravet, A. Dutoit, J.M. Fayard, M. Ferriere, C. Fournier, Y. Frances, F. Funck, M. Galinier, L.F. Garnier, P. Gibelin, P. Gosse, B. Grivet, L. Guize, B. d'Hautefeuille, A. Heraudeau, J.F. Huret, L. Janin-Manificat, G. Jarry, Y. Jobic, E. Jullien, J.C. Kahn, K. Khalife, A. Koenig, F. Latour, C. Leclercq, F. Leclercq, L. Ledain, H. Le Marec, S. Levy, J.M. Mallion, P. Maribas, G. Mialet, P.L. Michel, J.P. Millet, B. Moquet, J.P. Normand, T. Olive, P. Poncelet, J. Ponsonnaille, J. Puel, A. Riffer, P. Sans, J.P. Simon, M. Toussaint, A. Verdun, B. Veyre, S. Werquin; *Germany* — C. Brilla, G. Riegger, M. Zehender; *Japan* — Y. Aizawa, M. Hori, H. Inoue, H. Kasanuki, A. Kitabatake, M. Matsuzaki, S. Ogawa, M. Omata, S. Sasayama, A. Takeshita, Y. Yazaki, M. Yokoyama; *Mexico* — L. Avila, J.E. Guerrero, H. Gutiérrez-Leonard, J.L. Leyva-Garza; *the Netherlands* — P.J.L.M. Bernink, H. Fintelman, J.A. Kragten, J.B.L. ten Kate, D.J.A. Lok, A.R. Ramdat Misier, G.P. Molhoek, G.M.G. Paulussen, L.H.J. van Kempen, D.J. van Veldhuisen, L.G.P.M. van Zeijl, A.J.A.M. Withagen; *New Zealand* — H. Ikram; *South Africa* — J.D. Marx, D.P. Naidoo; *Spain* — J.M. Aguirre, S.

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