The The Effect of Spironolactone on Ventricular Tachyarrhythmias in Patients With Implantable Cardioverter-Defibrillators

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Background—Previous studies have suggested that aldosterone blockade can reduce the incidence of ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients with heart failure. The SPIronolactone to Reduce ICD Therapy (SPIRIT) trial was designed to test the hypothesis that spironolactone reduces the incidence of VT/VF in patients with implantable cardioverter-defibrillators (ICDs) who are at moderately high risk for recurrent VT/VF.

Methods and Results—Ninety patients who had ICDs who were at moderately high risk for recurrent VT/VF and who were not candidates for spironolactone by current heart failure guidelines were randomized to receive spironolactone 25 mg daily or placebo in a double-blind fashion. All patients had previously received ICD therapy (shock or antitachycardia pacing) for VT/VF within 2 years of randomization or an ICD for secondary prevention of VT/VF within 6 months of randomization. The primary end point was time to first recurrence of VT/VF requiring ICD therapy. After a median follow-up of 35 months, the Kaplan–Meier probability estimates for VT/VF requiring ICD therapy were 68.7% in the placebo group and 84.7% in the spironolactone group. Compared with placebo, spironolactone was associated with a similar risk of VT/VF (hazard ratio, 1.01; 95% CI, 0.64–1.83; \( P = 0.71 \)). There was no significant difference between the median times to first VT/VF recurrence requiring ICD therapy in the 2 groups.

Conclusions—In patients with ICDs who were at moderately high risk for recurrent VT/VF on account of a recent VT/VF event that was either sustained or treated by the ICD and who were not candidates for spironolactone by current heart failure guidelines, spironolactone did not delay the first recurrence of VT/VF or reduce the risk of recurrent VT/VF. (Circ Arrhythm Electrophysiol. 2012;5:739-747.)

Key Words: antiarrhythmia agents ■ cardioversion ■ defibrillation ■ spironolactone ■ tachyarrhythmias

The implantable cardioverter-defibrillator (ICD) is highly effective in terminating ventricular tachycardia (VT) and ventricular fibrillation (VF) and reduces the risk of sudden cardiac death (SCD) in high-risk patients.\(^4\)\(^-\)\(^6\) ICD shocks can, however, produce detrimental psychosocial effects on the patient and the family\(^4\)\(^-\)\(^6\) and have recently been associated with an increased risk of mortality and heart failure (HF) hospitalizations among HF patients.\(^6\)\(^-\)\(^9\) Therapies that can reduce the incidence of ICD shocks and have minimal adverse side effects could, therefore, potentially benefit patients with ICDs. These therapies could include pharmacologic agents, the use of specific device programming parameters, and catheter ablation.

Clinical Perspective on p 747

In 2 clinical trials of aldosterone blockade in HF, spironolactone and eplerenone appeared to reduce the risk of SCD in patients with moderately to severely symptomatic HF or HF after myocardial infarction (MI).\(^10\)\(^-\)\(^11\) This observation has suggested that aldosterone blockade can reduce the incidence of VT/VF in HF patients. Basic experimental data support these findings. Aldosterone antagonists, for example, have been shown to produce favorable effects on ventricular electrical remodeling by modifying potassium, sodium, and calcium currents and ventricular refractoriness\(^12\)\(^-\)\(^14\) and improving the myocardial reuptake of norepinephrine.\(^15\) They also seem to have favorable effects on ventricular structural remodeling primarily by attenuating myocardial fibrosis.\(^16\)\(^-\)\(^17\) Finally, aldosterone blockers can prevent hypokalemia, and this could likewise help prevent VT/VF. The SPIronolactone to Reduce ICD Therapy (SPIRIT) trial was designed to test the hypothesis that spironolactone reduces the incidence of VT/VF and hospitalizations in patients with ICDs who are at moderately high risk for recurrent VT/VF and are otherwise not candidates for spironolactone by the 2009 American College of Cardiology Foundation/American Heart Association guidelines for chronic HF (ie, do not have a reduced left ventricular ejection fraction [EF] and moderately severe to severe symptoms of HF).\(^18\)

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Methods

Study Design and Study Population

This was a prospective, double-blind, randomized trial that assigned patients to receive either spironolactone 25 mg/day or a placebo. To ensure a relatively high rate of ICD shocks within the population, patients were considered eligible for enrollment only if they had received an ICD therapy, either a shock or antitachycardia pacing (ATP), for VT/VF in the previous 2 years or received an ICD for secondary prevention of sustained VT/VF in the previous 6 months. Because the occurrence of VT/VF in the recent past could be associated with a higher risk of VT/VF recurrence, randomization was stratified according to the event of VT/VF within at least 3 days during the 3-month period prior to randomization. In addition, because the best clinical evidence for the antiarrhythmic effect of spironolactone came from the Randomized Aldactone Evaluation Study (RALES), which enrolled patients with severe HF;19 randomization was also stratified according to the presence of severe HF, defined as either an EF of <35% or New York Heart Association (NYHA) functional class III or IV. Patients were, therefore, stratified according to the following 4 strata: (1) subjects without <3 days of VT/VF in the 3 months prior to randomization, EF of ≥35%, and NYHA class I or II; (2) subjects with <3 days of VT/VF in the 3 months prior to randomization and either EF of <35% or NYHA class III or IV; (3) subjects with 3 or more days of VT/VF in the 3 months prior to randomization, EF of ≥35%, and NYHA class I or II; and (4) subjects with 3 or more days of VT/VF in the 3 months prior to randomization and either EF of <35% or NYHA class III or IV.

Important exclusion criteria were an indication for spironolactone based on the RALES trial (EF of <35% and NYHA class III or IV), unstable angina, primary hepatic failure, known intolerance to spironolactone, a serum creatinine concentration of >2.5 mg/dL, a serum potassium concentration of <5.0 mmol/L, and a life expectancy of <2 years. Because the SPIRIT trial was conducted before the results of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial were published,20 patients with systolic HF and mild symptoms were not excluded from the SPIRIT trial, even though they would now be potential candidates for spironolactone based on EMPHASIS-HF.

The SPIRIT trial enrolled patients from the Portland Veterans Affairs Medical Center, Veterans Affairs Puget Sound Health Care System, Oregon Health and Science University, and the Little Rock Veterans Affairs Medical Center. The institutional review board or ethics committee at each site approved the protocol, and all patients provided written, informed consent before enrollment. Randomization of patients within each stratum at each of the participating sites was performed by the Research Pharmacy service of the Portland Veterans Affairs Medical Center using a computer-generated randomization scheme. The placebo and spironolactone capsules were identical in appearance. The investigators and clinicians who were involved with ICD interrogration, interpretation of tracings, ICD programming, outpatient and in-hospital management, assessment of reasons for hospitalization, and measurement of the ventricular effective refractory period (VERP) were blinded to the patients’ treatment assignments.

Patients were evaluated in an outpatient setting at the time of randomization and were subsequently followed up every 3 months until the termination of the study. ICD programming (detection intervals for VT/VF and therapies) and the use of membrane-active antiarrhythmic drugs were left to the discretion of the electrophysiologists who implanted the device or followed the patients in clinic. At each clinical visit, ICD interrogation was performed, and any ICD therapy (shock or ATP) was noted. The stored intracardiac electrograms and other details of each ICD therapy were downloaded, saved, and reviewed independently by 2 electrophysiologists. In addition, at each visit, information about potential drug side effects and any hospitalization after randomization, defined as an unplanned stay in a hospital or emergency department for over 24 hours, was obtained. Hospitalizations were classified as cardiac when they were primarily because of angina, MI, acutely decompensated HF, syncope of cardiac etiology, or ICD therapy. Otherwise, hospitalizations were considered noncardiac.

Serum potassium and creatinine concentrations were measured at the time of randomization, as well as 1, 2, 3, and 6 months after randomization and then every 6 months until the termination of the study. If hyperkalemia (defined as serum potassium concentration >5.0 mmol/L) occurred, then depending on the degree of potassium elevation, discontinuation of other drugs that could elevate serum potassium or dose reduction or discontinuation of the study drug was performed. Reinitiation of the study drug was allowed if the serum potassium concentration normalized. However, if hyperkalemia occurred more than once in the absence of another reversible etiology, the study drug was discontinued permanently.

Measurement of the VERP was performed in veteran patients who were able to travel to the Portland Veterans Affairs Medical Center for their 3-month follow-up visit. To determine the VERP, pacing through the ICD was performed at twice the diastolic pacing threshold. Drive trains consisting of 8 beats, with cycle lengths of 400, 500, and 600 milliseconds, were used. Using a step-up method with 10-millisecond increments, a single extrastimulus was delivered after each drive train. The step-up method was used to minimize delivery of captured extrastimuli and, therefore, reduce the risk of inducing VT/VF.

Study End Points

The primary end point of the study was time to first recurrence of VT or VF requiring ICD therapy. Secondary end points included times to first hospitalization, first hospitalization from cardiac causes, and first hospitalization from noncardiac causes, as well as first recurrence of VT and first recurrence of VF. Although not a prespecified end point, the burden of VT/VF was also calculated by dividing the number of days that a patient had VT/VF by the total number of days of follow-up. All end points were adjudicated by 2 independent electrophysiologists who were blinded to randomization.

Statistical Analysis

The sample size of the study was calculated on the basis of 2 assumptions. First, the primary end point would occur in 65% of patients assigned to placebo within 2 years of enrollment, as suggested by a post hoc analysis of the Antiarrhythmic Versus Implantable Defibrillators (AVID) trial.21 Second, the 2-year risk of VT/VF requiring ICD therapy would be reduced by 30% by spironolactone. This was, in part, based on the RALES trial, which showed a 29% relative risk reduction in SCD with spironolactone during a 2-year follow-up period.10 For the SPIRIT trial to be powered at 80% in detecting a 30% relative reduction in the 2-year risk of VT/VF events in the spironolactone group, at an α level of 0.05, a total of 200 patients would be needed for randomization.

Times to events (VT, VF, and hospitalizations) and burden of VT/VF were compared between the treatment groups. Analyses of these end points were conducted according to the intention-to-treat principle. A post hoc on-treatment analysis of the primary end point was also performed to evaluate the impact of study drug discontinuation on the results. Univariate analyses were performed using a log-rank test. Probability estimates and plots for the various events were generated by the Kaplan–Meier method. Hazard ratios (HRs) were obtained by multivariate analyses using the Cox proportional hazards model. For multivariate analyses, the following covariates were evaluated as potential confounders in the relationship between treatment and event-free survival: reason for study enrollment (ICD treatment for VT/VF in the previous 2 years versus ICD implantation for secondary prevention of sustained VT/VF in the previous 6 months); randomization stratum; comorbidity at enrollment (including HF, coronary artery disease, hypertension, diabetes mellitus, and atrial fibrillation or atrial flutter); and concurrent drug use at enrollment (including angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker, β-blockers, digoxin, statin, and membrane-active antiarrhythmic drugs). Models were built by stepwise covariate selection as well as individual covariate evaluation. Covariates whose effects did not contribute significantly to the models (defined as having Wald probability values >0.10) were
excluded from the models for simplicity. In the analysis of VERP, the VERPs of the 2 treatment groups at each drive cycle length were compared using the \( t \) test.

**Results**

**Study Patients**

Between July 28, 2004, and May 28, 2008, a total of 90 patients underwent randomization, of whom 46 were assigned to placebo and 44 to spironolactone (Figure 1). The trial was terminated before the intended number of patients (200) could be enrolled because of slow recruitment of patients. To help maximize the event rate, the follow-up period was extended from 2 years to 3 years. Follow-up was completed on August 12, 2009. Demographic and clinical data for the 2 treatment groups are shown in Table 1. There were no significant differences between the 2 groups at baseline. The majority of the patients were receiving standard therapies for HF, including ACE inhibitors or angiotensin receptor blockers (in 87% of patients) and \( \beta \)-blockers (in 89%). Only one third of the patients were taking membrane-active antiarrhythmic drugs at baseline, and of these patients, the vast majority was taking amiodarone. The median duration of follow-up was 35 (range, 3–40) months. No patient was lost to follow-up, and no patient crossed over to the other treatment arm. During the study, 34 patients (15 in the placebo group and 19 in the spironolactone group; \( P=0.39 \)) permanently discontinued the study medication, most frequently because of adverse events (Figure 1). The median time from randomization to the last dose was 16 months for patients in the placebo group and 7 months for those in the spironolactone group.

**Primary End Point**

A total of 30 patients (65%) in the placebo group and 34 patients (77%) in the spironolactone group experienced VT/VF that required ICD therapy. Among these patients, VT was the first event in 25 patients (83%) in the placebo group and 28 patients (82%) in the spironolactone group. The Kaplan–Meier curves for ICD-treated VT/VF in the 2 groups, using an intention-to-treat analysis, are shown in Figure 2A. The Kaplan–Meier probability estimates for ICD-treated VT/VF in the placebo and spironolactone groups, respectively, were 47.8% and 48.7% at 1 year, 68.7% and 66.5% at 2 years, and 68.7% and 84.7% at 3 years. The corresponding estimate for the primary end point in the entire cohort was 76.6% at 3 years. Compared with placebo, spironolactone was associated with a similar risk of ICD-treated VT/VF (multivariate HR, 1.01; 95% CI, 0.64–1.83; \( P=0.71 \)). There was no significant difference between the median times to first recurrence of ICD-treated VT/VF in the 2 groups: 12.3 (range, 0.2–38.5) months in the placebo group and 8.8 (range, 0–37.2) months in the spironolactone group.

When the analysis was confined to primary end point events that occurred prior to study drug discontinuation (on-treatment analysis), there was still no significant difference observed between the event rates and times to first event recurrence in the placebo and spironolactone groups. The Kaplan–Meier curves for ICD-treated VT/VF in the 2 groups, using an on-treatment analysis, are shown in Figure 2B.

**Secondary End Points**

Patients in both groups showed a similar risk of ICD-treated VT, with 29 patients (63%) in the placebo group and 29
patients (66%) in the spironolactone group experiencing at least 1 episode of ICD-treated VT (multivariate HR 0.95; 95% CI, 0.56–1.61; \( P = 0.84 \)). Figure 3A shows the Kaplan–Meier curves for ICD-treated VT in the 2 groups. The median time from randomization to first occurrence of ICD-treated VT was similar in the 2 groups: 12.4 (range, 0.2–38.5) months for the placebo group and 13.5 (range, 0–37.2) months for the spironolactone group.

As with VT, the risk of ICD-treated VF was similar in both groups. Seven patients (15%) in the placebo group and 11 patients (25%) in the spironolactone group experienced at least 1 episode of ICD-treated VF (multivariate HR, 1.23; 95% CI, 0.66–4.41; \( P = 0.27 \)). Figure 3B shows the Kaplan–Meier curves for ICD-treated VF in the 2 groups. The median time from randomization to first occurrence of ICD-treated VF was similar in the 2 groups: 35.3 (range, 0.4–38.6) months for the placebo group and 30.0 (range, 4.5–37.2) months for the spironolactone group.

The burden of VT/VF was 0.0074 day with VT/VF per day of follow-up in the placebo group and 0.0081 day with VT/VF per day of follow-up in the spironolactone group. The burden was similar in both groups (\( P = 0.81 \); Table 2).

There were 32 hospitalizations (70%) in the placebo group and 37 (84%) in the spironolactone group. Figure 4A shows the Kaplan–Meier curves for hospitalization for any cause in the 2 groups. Patients randomized to spironolactone had a higher risk of hospitalization, which was of borderline statistical significance (multivariate HR, 1.58; 95% CI, 0.97–2.60; \( P = 0.07 \)). They also tended to be hospitalized sooner than those randomized to placebo, with a median time to first hospitalization of 14.2 (range, 0.1–39.7) months versus 17.3 (range, 0.4–37.1) months, respectively.

Table 1. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=46)</th>
<th>Spironolactone (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.5±9.3</td>
<td>66.6±10.9</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>43 (93)</td>
<td>44 (100)</td>
</tr>
<tr>
<td>VT/VF in prior 2 y, n (%)</td>
<td>40 (87)</td>
<td>35 (80)</td>
</tr>
<tr>
<td>VT/VF in prior 3 mo, n (%)</td>
<td>26 (57)</td>
<td>29 (66)</td>
</tr>
<tr>
<td>Left ventricular EF, %</td>
<td>34.6±12.2</td>
<td>33.3±13.2</td>
</tr>
<tr>
<td>Left ventricular EF ≥55%, n (%)</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (22)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>II</td>
<td>34 (74)</td>
<td>34 (77)</td>
</tr>
<tr>
<td>III</td>
<td>2 (4)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>IV</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Serum potassium concentration, mmol/L</td>
<td>4.2±0.3</td>
<td>4.3±0.4</td>
</tr>
<tr>
<td>Serum creatinine concentration, mg/dL</td>
<td>1.2±0.3</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction (EF&lt;40%)</td>
<td>30 (65)</td>
<td>32 (72)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>39 (85)</td>
<td>41 (93)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (61)</td>
<td>29 (66)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (35)</td>
<td>13 (29)</td>
</tr>
<tr>
<td>Atrial fibrillation/atrial flutter</td>
<td>18 (39)</td>
<td>14 (32)</td>
</tr>
<tr>
<td>Medications, n (%)</td>
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</tr>
<tr>
<td>ACE inhibitor or angiotensin receptor blocker</td>
<td>39 (85)</td>
<td>39 (89)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>43 (93)</td>
<td>37 (84)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>16 (35)</td>
<td>15 (34)</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>29 (66)</td>
<td>22 (50)</td>
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<tr>
<td>Aspirin</td>
<td>26 (57)</td>
<td>28 (64)</td>
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<tr>
<td>Warfarin</td>
<td>14 (30)</td>
<td>18 (40)</td>
</tr>
<tr>
<td>Statin</td>
<td>39 (85)</td>
<td>36 (82)</td>
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<tr>
<td>Membrane-active antiarrhythmic drugs</td>
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<tr>
<td>Amiodarone</td>
<td>9 (20)</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Mexiletine</td>
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<td>0 (0)</td>
</tr>
<tr>
<td>Procainamide</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Propafenone</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>2 (4)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Device characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-chamber ICD, n (%)</td>
<td>34 (74)</td>
<td>28 (64)</td>
</tr>
<tr>
<td>Dual-chamber ICD, n (%)</td>
<td>12 (26)</td>
<td>16 (36)</td>
</tr>
<tr>
<td>Mean interval cut-off for detection of ventricular tachycardia, ms</td>
<td>372±29</td>
<td>389±57</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia; EF, ejection fraction; NYHA, New York Heart Association; VF, ventricular fibrillation; ACE, angiotensin-converting enzyme; ICD, implantable cardioverter-defibrillator.
A total of 24 patients (52%) in the placebo group and 28 patients (64%) in the spironolactone group had a hospitalization that was attributed to a cardiac cause. Figure 4B shows the Kaplan–Meier curves for cardiac hospitalization in the 2 groups. Compared with placebo, spironolactone was associated with a higher risk of cardiac hospitalization, but this did not meet statistical significance (multivariate HR, 1.54; 95% CI, 0.87–2.72; P=0.14). Patients randomized to spironolactone tended to be hospitalized sooner for a cardiac cause than those randomized to placebo, with a median time to first cardiac hospitalization of 16.1 (range, 0.1–39.7) months versus 24.4 (range, 0.4–38.5) months, respectively.

Twenty-two patients (48%) in the placebo group and 26 patients (59%) in the spironolactone group had a hospitalization for a noncardiac etiology. Figure 4C shows the Kaplan–Meier curves for noncardiac hospitalization in the 2 groups. Compared with placebo, spironolactone was associated with a similar risk of noncardiac hospitalization (multivariate HR, 1.13; 95% CI, 0.64–2.00; P=0.67). The median time to first noncardiac hospitalization was likewise similar in the 2 groups: 22.9 (range, 0.4–39.7) months for the spironolactone group and 25.3 (range, 0.9–37.1) months for the placebo group.

VERP was obtained in 12 patients in the spironolactone group and 13 patients in the placebo group at their 3-month follow-up. At each of the drive cycle lengths, there was no significant difference in VERPs between the 2 groups (Table 3).

### Table 2. Burden of VT/VF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of days with VT/VF</th>
<th>No. of days of follow-up</th>
<th>Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.2±9.3</td>
<td>922.4±278.3</td>
<td>0.0074±0.0110</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>7.3±13.0</td>
<td>926.4±248.0</td>
<td>0.0081±0.0146</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia; VF, ventricular fibrillation.

### Safety

After initiation of the study drug, the mean serum potassium concentration tended to be higher among patients in the spironolactone group (by up to 0.3 mmol/L) than among patients in the placebo group. A similar observation was made with the mean serum creatinine concentration in the
2 groups (Figure 5). In each group, there was no consistent trend in the mean serum potassium or creatinine concentrations over time.

Serious hyperkalemia (serum potassium concentration ≥6.0 mmol/L) occurred in 2.2% and 4.5% of the placebo and spironolactone patients, respectively (P = 0.61). One patient in the spironolactone group was hospitalized for a serum potassium of 6.5 mmol/L in the setting of acute renal failure. No patient had a serum potassium ≥7.0 mmol/L. There were no deaths that resulted from serious hyperkalemia.

Table 4 shows the adverse reactions in the 2 groups. Gynecomastia was reported by 9% of the men in the spironolactone group and none of the men in the placebo group. Among the 19 patients who permanently discontinued spironolactone, the most frequent reasons were gynecomastia, hyperkalemia, renal dysfunction, dizziness, and diarrhea.

Discussion

The results of this randomized trial indicate that the time to first recurrence of ICD-treated VT/VF among patients with ICDs and a recent history of VT/VF, and who did not have an indication for spironolactone by current HF guidelines, was not significantly altered by treatment with spironolactone. In addition, spironolactone did not significantly affect the risk of subsequent VT/VF after a median follow-up period of 35 months. When VT and VF were analyzed as separate outcomes, spironolactone did not significantly affect the risk of or time to first recurrence of VT or VF. Spironolactone likewise did not reduce the overall burden of VT/VF; although this was not a prespecified end point of this trial and could have been confounded by initiation of or changes in the use of membrane-active antiarrhythmic drugs over time. It should be noted that most of the patients in this trial had mildly symptomatic HF (mean left ventricular EF of <35% and mean NYHA class II) and were on a standard HF medical regimen of an ACE inhibitor/angiotensin receptor blocker and a β-blocker.

Recurrences of VT/VF are known to exhibit a time-dependent behavior. Because the patients selected for this study had a history of VT/VF within 2 years of enrollment, they were individuals whose risk of another VT/VF event was presumably high. Consequently they represented a cohort in which a protective effect of spironolactone on VT/VF recurrence could be optimally tested and demonstrated. The VT/VF recurrence rate observed in this cohort was comparable to what had been observed in ICD trials for secondary prevention.
of SCD. In the AVID trial, which enrolled patients with a history of sustained VT/VF, 65% of the patients assigned to receive an ICD experienced an ICD-terminated VT/VF event within 2 years of device implant. In the present study, the Kaplan–Meier probability estimate for ICD-treated VT/VF in the entire cohort of patients was 76.6% at the end of 3 years. The rationale for testing the antiarrhythmic effect of spironolactone on VT/VF in a clinical trial was based on the results of large randomized trials of aldosterone antagonists, which established a mortality benefit from their use by HF patients with mild symptoms (EMPHASIS-HF), severe symptoms (RALES), or HF after MI (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, or EPHEBUS). Importantly, detailed analyses of the RALES and EPHEBUS trials indicated that part of this benefit might come from a reduction in the risk of SCD, which has often been attributed to VT/VF. The present trial, however, failed to demonstrate any benefit from spironolactone with respect to the occurrence of ICD-treated VT/VF.

Several factors help explain the difference between the results of this trial and those of RALES and EPHEBUS. First, the SPIRIT trial analyzed VT/VF events that resulted in ICD therapy, which are, at best, only surrogate markers of SCD. Second, in RALES and EPHEBUS, the suggested antiarrhythmic effect of aldosterone antagonists was only a hypothesis borne out of a post hoc analysis. Third, although the patients enrolled in the 2 previous and the present trials were all at risk for VT/VF, there were important differences in their characteristics. In the RALES trial, the use of β-blockers was significantly lower than in the SPIRIT trial (<15% versus >80%). Because β-blockers can suppress VT/VF recurrence and because some of the beneficial effects of spironolactone may be because of antiadrenergic effects, it is conceivable that any incremental antiarrhythmic benefit provided by spironolactone would be more difficult to detect in the SPIRIT trial. Furthermore, RALES enrolled patients with NYHA class III or IV HF; in the SPIRIT trial, only a small minority of patients had NYHA class III HF, and none had class IV HF at the time of enrollment. The patients in the EPHEBUS trial, on the other hand, were enrolled shortly after an acute MI. This period immediately following myocardial injury could constitute an opportune time for aldosterone antagonists to positively influence structural and cardiac remodeling. In contrast, the patients enrolled in the SPIRIT trial, like most other ICD patients, had chronic, stable scars and substrates that were probably more difficult to modify structurally and electrically by a pharmacologic approach. In fact, in the subgroup of patients who underwent VERP measurements, no difference in VERPs was observed between the placebo and spironolactone patients.

Of the patients enrolled in the 3 large trials of aldosterone antagonists in HF, it was the EMPHASIS-HF patients whose characteristics most closely resembled those of the SPIRIT patients. Although the mean left ventricular EF in SPIRIT (34%) was higher than in EMPHASIS-HF (26%), the majority of patients in SPIRIT, like those in EMPHASIS-HF, had NYHA class II HF and were taking a β-blocker. That EMPHASIS-HF did not detect a reduction in the rate of SCD in its eplerenone arm supports the lack of antiarrhythmic benefit of aldosterone antagonists when used as an add-on therapy to β-blockers outside the setting of moderately to severely symptomatic HF or a recent MI. If spironolactone could afford any clinically important suppressive effect on VT/VF outside the above scenarios, then its dose–response curve remains elusive. The dose used in this trial (25 mg daily) is the standard recommended dose for HF therapy. A larger daily dose, such as 50 mg, might have demonstrated antiarrhythmic potency but could carry serious risks of hyperkalemia and renal failure.

Spironolactone did not reduce the incidence of cardiac and noncardiac hospitalizations in this study. The majority of the patients had well-compensated HF and good medical regimens at baseline, making it less likely for spironolactone to contribute significantly to the prevention of hospitalizations from acutely decompensated HF. There was a tendency for hospitalizations to occur sooner among patients assigned to spironolactone, but this finding did not reach statistical significance and was more likely a chance finding than a true pathophysiologic phenomenon.

Despite attempts to minimize the risk of hyperkalemia by excluding patients with a baseline serum potassium concentration of >5.0 mmol/L or a baseline serum creatinine concentration of >2.5 mg/dL, 4.5% of patients in the spironolactone arm developed serious hyperkalemia. This was twice the incidence of serious hyperkalemia in the placebo arm (2.2%) and was comparable to the incidences observed in the aldosterone-antagonist arms of the RALES and EPHEBUS trials (1.7% and 5.5%, respectively). This observation once again highlights the importance of close laboratory monitoring in patients using spironolactone, especially those with HF and taking an ACE inhibitor/angiotensin receptor blocker.

**Study Limitations**

A major limitation of this study was its small sample size. Fewer patients were enrolled than had been intended using the original statistical assumptions. However, the event rate was high, and after an extended follow-up period of 3 years, the Kaplan–Meier probability estimate for ICD-treated VT/VF in the entire cohort was 77%. This was more likely to be an accurate measure of the expected event rate in the control arm because spironolactone had no apparent effect on the primary end point. Because of the extended follow-up, the original assumption of 30% relative risk reduction in the primary end point was likely a conservative estimate. In the RALES trial, the 29% reduction in SCD was a 2- rather than a 3-year estimate. Furthermore, ICD therapies for VT/VF have been previously shown to outnumber actual sudden deaths by 2-fold. If a 35% relative risk reduction in the primary end point were assumed, the sample size of this trial would have given it 76% power to detect a difference between the 2 treatment arms using a 2-sided test and with a type I error rate of 0.05. Importantly, this trial showed no trend toward benefit with spironolactone to suggest that enrolling more patients would have produced a positive result. Furthermore, at the present time, conducting a larger trial of this kind would be hampered by the expanding indication for aldosterone antagonists in HF patients, including the group of mildly symptomatic patients enrolled in the EMPHASIS-HF trial.
A fair number of patients (15 in the placebo group and 19 in the spironolactone group, constituting 38% of the entire cohort) discontinued the study drug in this trial because of adverse effects. In the RALES, EPHESUS, and EMPHASIS-HF trials, the discontinuation rates were also evenly split between placebo and either spironolactone or eplerenone, but were lower (25%, 15%, and 16%, respectively). The higher discontinuation rate in the SPIRIT trial could simply be a reflection of the smaller number of patients who were followed. Nonetheless, it reflects what is likely to be seen in clinical practice and thus remains relevant to the utility of the therapy. In addition, the differences observed in serum potassium and creatinine concentrations between the placebo and spironolactone groups demonstrated a significant biological effect of spironolactone in the spironolactone group throughout the duration of follow-up, despite the above discontinuation rates. Most importantly, it should be noted that among the 34 patients who discontinued the study drug, 21 (8 in the placebo group and 13 in the spironolactone group) experienced VT/VF requiring ICD therapy, and in 16 of these 21 patients (6 in the placebo group and 10 in the spironolactone group), the primary end point was met before the study drug was discontinued. Therefore, incorporating the discontinuation rate of the study drug into the analysis is unlikely to change the main conclusion of the trial. This is corroborated by the results of the on-treatment analysis of the primary end point (Figure 2B).

Finally, post hoc analyses of the RALES and EPHESUS trials have suggested that the mortality and hospitalization benefits from aldosterone blockade were confined to trial patients who had excessive cardiac extracellular matrix turnover and hypertension, respectively. One could speculate that if patients who had the SPIRIT trial profile and also had the above high-risk features were studied, the antiarrhythmic benefits of spironolactone could have become more evident. However, measurement of markers of cardiac collagen synthesis and degradation was not a part of the SPIRIT trial design. Also, although the trial enrolled some patients with hypertension, it did not have adequate power to evaluate these patients, and a post hoc analysis of this subgroup would not be appropriate.

Conclusion
In patients with ICDs who were at high risk for VT/VF, on account of a recent VT/VF event that was either sustained or treated by the ICD, and who were not candidates for spironolactone by current HF guidelines, this trial showed no benefit from spironolactone use with respect to delaying the first recurrence of VT/VF or reducing the risk of recurrent VT/VF. Importantly, the majority of patients enrolled in this trial had mildly symptomatic HF and were on a regimen of ACE inhibitor/angiotensin receptor blocker and β-blocker.

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**CLINICAL PERSPECTIVE**

Clinical trials of aldosterone blockade in heart failure (HF) have suggested that spironolactone and eplerenone may reduce the risk of sudden cardiac death in patients with moderately to severely symptomatic HF or postmyocardial infarction HF. Basic experimental data have likewise suggested that aldosterone antagonists allow favorable structural and electrical remodeling in the ventricles. These observations led to the hypothesis that aldosterone blockade can reduce the incidence of ventricular tachycardia or ventricular fibrillation in HF patients and reduce the risk of shocks in those with implantable cardioverter-defibrillators (ICDs). The SPironolactone to Reduce ICD Therapy (SPIRIT) trial was a randomized, placebo-controlled, double-blind trial that tested this hypothesis in patients with ICDs who were at moderately high risk for recurrent ventricular tachycardia/ventricular fibrillation on the basis of recent sustained or ICD-treated ventricular tachycardia/ventricular fibrillation and were otherwise not candidates for spironolactone by the 2009 guidelines for chronic HF. Ninety patients were randomized to receive spironolactone, 25 mg daily or placebo. After a follow-up period of nearly 3 years, spironolactone was not found to reduce the risk of recurrence of ICD-treated ventricular tachycardia/ventricular fibrillation or delay its first recurrence. Although the trial enrolled less than the intended number of patients, it showed no trend toward benefit with spironolactone. Furthermore, conducting a larger trial of this kind will be hampered by the expanding indication for aldosterone antagonists in HF patients, including the group of mildly symptomatic patients.
The Effect of Spironolactone on Ventricular Tachyarrhythmias in Patients With Implantable Cardioverter-Defibrillators
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