Spironolactone reduced mortality in severe congestive heart failure


**Question**

In patients with severe congestive heart failure (CHF) caused by systolic left ventricular dysfunction, does spironolactone combined with usual care reduce all-cause mortality?

**Design**

Randomized (allocation concealed*), blinded (patients, clinicians, and outcome assessors),* placebo-controlled trial with mean follow-up of 24 months. Interim analyses were done.

**Setting**

195 clinical centers in 15 countries.

**Patients**

1663 patients (mean age 65 y, 73% men, 87% white) with severe CHF who were using angiotensin-converting enzyme (ACE) inhibitors, if tolerated, and a loop diuretic and had had a recent left ventricular ejection fraction ≤ 35%. The major exclusion criterion was use of potassium-sparing diuretics. All patients were analyzed.

**Intervention**

All patients received usual care and were allocated to spironolactone, 25 mg/d, which could be doubled after 8 weeks on the basis of evidence of worsening CHF without hyperkalemia (n = 822) or placebo (n = 841). The dose could also be changed to 25 mg every other day if hyperkalemia occurred. Spironolactone vs placebo for severe congestive heart failure (CHF)†

<table>
<thead>
<tr>
<th>Outcomes at mean 24 mo</th>
<th>Spironolactone</th>
<th>Placebo</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>35%</td>
<td>46%</td>
<td>25% (15 to 33)</td>
<td>9 (7 to 16)</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>28%</td>
<td>37%</td>
<td>26% (15 to 36)</td>
<td>11 (7 to 19)</td>
</tr>
<tr>
<td>CHF mortality</td>
<td>16%</td>
<td>23%</td>
<td>31% (16 to 44)</td>
<td>15 (10 to 31)</td>
</tr>
<tr>
<td>Hospitalization for cardiac causes</td>
<td>32%</td>
<td>40%</td>
<td>21% (10 to 31)</td>
<td>13 (8 to 27)</td>
</tr>
</tbody>
</table>

†Abbreviations defined in Glossary. RRR, NNT, and CI calculated from data in article.

**Conclusion**

Spironolactone reduced all-cause mortality, death, and hospitalization from cardiac causes and death from CHF and improved NYHA functional class in patients with severe CHF.

For correspondence: Dr. B. Pitt, Division of Cardiology, University of Michigan Medical Center, 3910 Taubman, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0366, USA. FAX 734-936-5256.

*See Glossary.

**Commentary**

We welcome spironolactone to the ever-increasing arsenal of pharmacotherapeutic agents for left ventricular systolic dysfunction. 3 regimens increase survival and decrease symptoms in CHF: ACE inhibitors, β-blockers, and spironolactone. 2 additional agents (diuretics and digitals) decrease symptoms, prevent hospitalizations, or both. Other agents (angiotensin-receptor blockers and amlodipine) have promising but unclearly shown clinical benefits (1).

This impressive trial by Pitt and colleagues emphasizes the difficulty of treating severe CHF and its continuing high mortality rate despite the existence of several effective agents. Even though spironolactone was well tolerated, nearly 20% of patients discontinued therapy because of perceived lack of response or administrative problems, and 35% of treated patients died within 2 years.

Spironolactone provides large survival and symptomatic benefits for patients with severe symptoms despite conventional treatment, requires little dose titration, may decrease supplemental potassium requirements, has few important adverse effects, and is inexpensive. Clearly, clinicians should use this agent in patients with NYHA classes III and IV CHF, but several questions remain unanswered. Should spironolactone be chosen instead of or in addition to digitals, which has no proven survival benefits? Because most patients receive < 50% of their recommended ACE inhibitor doses, would they be best served by maximizing the ACE inhibitor dose, by adding spironolactone, or both? Because β-blockers are currently recommended for all patients with NYHA class II or III CHF (1) and were received by only 10% of participants in this trial, would patients be best served by carefully maximizing the β-blocker, adding spironolactone, or both? Clinicians face a formidable challenge: They must tailor individual treatment considering the severity of CHF; the balance between anticipated benefits and adverse effects, the optimal dose titration, and costs.

Mark Henderson, MD
Cynthia D. Mulrow, MD, MSc
Audie Murphy Veterans Affairs Hospital and the University of Texas Health Sciences Center
San Antonio, Texas, USA

Reference

1. Am J Cardiol. 1999;83:1A-38A.