

Spironolactone reduced mortality in severe congestive heart failure

Pitt B, Zannad F, Remme WJ, et al for the Randomized Aldactone Evaluation Study Investigators. *The effect of spironolactone on morbidity and mortality in patients with severe heart failure*. *N Engl J Med* 1999 Sep 2;341:709–17

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

Randomised (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 centres 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 $\leq 35\%$. The major exclusion criterion was use of potassium-sparing diuretics. All patients were analysed.

Intervention

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

Main outcome measures

All-cause mortality. Secondary outcomes were cardiac mortality, admission to hospital for cardiac causes, change in New York Heart Association (NYHA) class, and adverse effects.

Main results

Patients in the spironolactone group had lower rates of all-cause, cardiac, and CHF mortality and admission to hospital for cardiac causes (table) ($p < 0.001$ for all outcomes) and greater improvement in NYHA class ($p < 0.001$) than patients in the placebo group. The groups did not differ for adverse effects: 82% of patients in the spironolactone group had ≥ 1 event compared with 79% of patients in the placebo group ($p = 0.17$), although men in the spironolactone group had a higher rate of gynaecomastia or breast pain (10% *v* 1%, $p < 0.001$).

Conclusion

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

*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 digitalis) decrease symptoms, prevent admissions to hospital, or both. Other agents (angiotensin-receptor blockers and amlodipine) have promising but unclearly shown clinical benefits.¹

This impressive trial by Pitt and colleagues emphasises 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 treatment 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 digitalis, which has no proven survival benefits? Because most patients receive $< 50\%$ of their recommended ACE inhibitor doses, would they be best served by maximising the ACE inhibitor dose, by adding spironolactone, or both? Because β -blockers are currently recommended for all patients with NYHA class II or III CHF¹ and were received by only 10% of participants in this trial, would patients be best served by carefully maximising 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.

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1 *Am J Cardiol* 1999;83:1A–38A.

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Spironolactone *v* placebo for severe congestive heart failure (CHF)†

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

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