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# Spironolactone for heart failure

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## Keywords

ACE inhibitor, aldosterone receptor, severe heart failure, spironolactone

# Comments

This is a large clinical trial, providing Level I evidence of the importance of complete blockade of aldosterone effects in the management of severe heart failure. In the era of evidence-based medicine, a resurgence in the use of an old drug (the aldosterone-receptor antagonist, spironolactone) in severe heart failure is inevitable.

# Introduction

Aldosterone plays an important role in heart failure through a variety of mechanisms which have only recently been recognised. Consequently inhibition of aldosterone is considered efficacious in treating heart failure. Spironolactone (which has long been known to block the aldosterone receptor) is rarely used in this condition since it was felt that angiotensin-converting-enzyme (ACE) inhibitors alone would block aldosterone synthesis, and that combining them with spironolactone might precipitate dangerous hyperkalemia. Emerging evidence has cast doubt on these assumptions, and addition of spironolactone to an ACE inhibitor and diuretic may have benefits.

# Aims

To investigate whether the addition of spironolactone to conventional therapy (with an ACE inhibitor if tolerated) in patients with severe heart failure may reduce mortality.

# Methods

Inclusion criteria included New York Health Association (NYHA) class IV heart failure during the six months prior to study commencement, treatment with an ACE inhibitor (if tolerated) and loop diuretic, and an ejection fraction = 35%. Exclusions included creatinine 221 ?mol/l and potassium 5 ?mol/l (http://www.nejm.org/content/pitt/1.asp). Randomisation to spironolactone 25 mg or placebo occurred and after eight weeks the dose could be doubled to 50 mg providing there were no complications. Follow-up included measurements of potassium and creatinine concentrations. An independent review board regularly reviewed the data for safety monitoring. Death was the primary end point, but various secondary end points were explored, along with measurements of ejection fraction to examine the influence of spironolactone.

# Results

A total of 1663 patients (841 placebo, 822 spironolactone) from 15 countries were recruited for the study during 1995-1996, and the study was discontinued early during follow-up on the advice of the safety monitoring board. In total 200 patients in the placebo group and 214 in the spironolactone group stopped treatment, were demographically similar. A 30% reduction in mortality was shown in the spironolactone group with 284 deaths (35%) compared to 386 (46%) in the placebo group. In the spironolactone treated group, deaths from cardiac-related causes and hospital admissions for cardiac reasons showed similar reductions, 31% and 30% respectively. Spironolactone treated patients also showed an improvement in the NYHA classification.

Creatinine and potassium concentrations rose significantly in the spironolactone group although these changes were not considered medically important. Gynaecomastia or breast pain occurred in 10% of males treated with spironolactone causing some to stop treatment.

# Discussion

Spironolactone used with an ACE inhibitor has an impressive effect on outcome in the management of heart failure. Concerns over dangerous hyperkalemia appear to be unfounded and the tolerability of the drug was good. Effects on sodium and potassium handling, mediated by the total blockade of aldosterone, probably play a minor role in the large reduction in mortality. Recently described pathophysiological effects, such as prevention of myocardial fibrosis, may well be important.

# Additional information

An editorial accompanies this paper.

# References

1. The Randomised Aldactone Evaluation Study Investigation: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999, 341: 709-717.