Heart failure with preserved ejection fraction: spironolactone

Most of the evidence on treatment for heart failure is in patients with left ventricular systolic dysfunction (LVSD). In the NICE Clinical Guideline on Chronic heart failure the aldosterone antagonists (spironolactone and eplerenone) are recommended as a second-line option for people with heart failure due to LVSD.

Other people with heart failure have a preserved ejection fraction (HFPEF). A randomised controlled trial has shown that, in people with heart failure and a preserved ejection fraction, spironolactone (15 mg to 45 mg daily) did not reduce the incidence of the combined outcome of death from cardiovascular causes, aborted cardiac arrest or hospitalisation for heart failure compared with placebo over a mean follow-up of 3.3 years.

Overview and current advice

The NICE Clinical Guideline on Chronic heart failure states that heart failure is a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired. It is caused by structural or functional abnormalities of the heart. Some patients have heart failure due to left ventricular systolic dysfunction (LVSD) which is associated with a reduced left ventricular ejection fraction. Other people with heart failure have a preserved ejection fraction. Both heart failure with LVSD and HFPEF are considered in the guideline. Most of the evidence on treatment is for heart failure due to LVSD. The guideline recommends that the diagnosis and treatment of heart failure with preserved ejection fraction should be made by a specialist, and other conditions that present in a similar way may need to be considered. Patients in whom this diagnosis has been made should usually be treated with a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). Patients who do not respond to this treatment will require further specialist advice. Co-morbid conditions such as high-blood pressure, ischaemic heart disease and diabetes mellitus should be managed in-line with NICE guidance.

See the NICE Evidence topic page on heart failure for a general overview of the condition. The NICE Pathway: chronic heart failure brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.
New evidence

A randomised controlled trial (TOPCAT) has evaluated whether treatment with spironolactone would improve clinical outcomes in people with symptomatic heart failure and a preserved ejection fraction compared with placebo.

This multicentre, international (United States, Canada, Brazil, Argentina, Russia and Georgia) double-blind placebo-controlled RCT included 3445 people aged 50 and over with symptomatic heart failure and a left ventricular ejection fraction of 45% or more. Study participants also had to have a history of hospitalisation for heart failure in the previous 12 months or an elevated natriuretic peptide level within the previous 60 days, as well as controlled systolic blood pressure and a serum potassium level of less than 5.0 mmol per litre. Exclusion criteria included severe systemic illness with a life expectancy of less than 3 years, recent hyperkalaemia, severe renal dysfunction and certain other co-existing conditions and acute events, such as stroke or MI in the past 90 days. Participants were randomised to spironolactone (n=1722) or placebo (n=1723), at an initial dose of 15 mg once a day which could be increased to a maximum of 45 mg per day. The median age of participants was 69 years, 96% had mild to moderate heart failure (NYHA class II-III), 89% were white and 52% were female. Participants continued to receive other treatments for heart failure and co-existing illnesses throughout the study.

The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest or hospitalisation for the management of heart failure. Over a mean follow-up of 3.3 years, a total of 671 participants had at least one confirmed primary-outcome event: 320/1722 (18.6%) in the spironolactone group and 351/1723 (20.4%) in the placebo group. There was no statistically significant reduction in the primary outcome with spironolactone compared with placebo (unadjusted hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.77 to 1.04; p=0.14).

The study also looked at several secondary outcomes, including the individual components of the primary outcome. There was no statistically significant difference between the 2 groups for death from cardiovascular causes (9.3% in the spironolactone group compared with 10.2% in the placebo group; unadjusted HR 0.90, 95% CI 0.73 to 1.12; p=0.35) or aborted cardiac arrest (0.2% in the spironolactone group compared with 0.3% in the placebo group; unadjusted HR 0.60, 95% CI 0.14 to 2.50; p=0.48). There was a statistically significant lower incidence of hospitalisation for heart failure in the spironolactone group compared with the placebo group (12.0% compared with 14.2%; unadjusted HR 0.83, 95% CI 0.69 to 0.99; p=0.04). However, the study was not statistically powered to detect a risk reduction for this outcome on its own.

The incidence of hyperkalemia was higher in the spironolactone group (18.7% compared with 9.1% in the placebo group; p<0.001). In addition, the spironolactone group had a higher incidence of doubling of the serum creatinine level to a value above the upper limit of the normal range (10.2% compared with 7.0% in the placebo group; p<0.001). However there was no statistically significant difference between the 2 groups for the number of participants who had a serious adverse event (48.5% in the spironolactone group and 49.6% in the placebo group; p=0.517). During the course of the trial 590 participants (34.3%) in the spironolactone group and 541 (31.4%) in the placebo group discontinued the study medication.

Commentary

Commentary provided by Dr Richard Lehman, Senior Research Fellow at the Nuffield Department of Primary Care Health Sciences, Oxford University

Characterised by shortness of breath and often by oedema of the lungs and peripheries, heart failure is the common final pathway for a number of disease processes. In relatively young people, especially men, it is often the result of sudden loss of heart muscle due to myocardial infarction. In this kind of heart failure, which is accompanied by a reduction in systolic ejection fraction, the body reacts as all animals do to a sudden fall in cardiac output: it produces more of the hormones which retain salt and water - renin, angiotensin and aldosterone. As a result, the heart becomes more overloaded and tends to become dilated, which is known as adverse remodelling. The trials of the 1980s and 1990s
demonstrated modest improvements in symptoms and survival in some patients with heart failure with left ventricular systolic dysfunction using drugs which block the conversion of angiotensin into its active form, or which block its action on receptors. Later on, the RALES trial showed further benefits by directly blocking the action of aldosterone, using spironolactone

The TOPCAT investigators tried to repeat this success in heart failure with preserved systolic ejection fraction, but found no benefit from spironolactone compared with placebo using a primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalisation for the management of heart failure. This kind of heart failure does not respond to agents modifying the renin-angiotensin-aldosterone pathway, because its mechanisms are quite different. HFPEF is increasingly common in people of both sexes as they age, especially if they have a history of hypertension or diabetes. It has a number of causes, most of which relate to stiffening of the heart and the main capacitance vessels, i.e. the major arteries. These are mostly irreversible. For such patients, as for the majority of elderly people with heart failure, symptom relief may be a more realistic goal than extension of life. Here is an area where more research is definitely needed.

Study sponsorship

This randomised controlled trial was funded by the US National Heart, Lung and Blood Institute, National Institutes of Health.

References


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