

# A systematic review and economic evaluation of the clinical effectiveness and cost-effectiveness of aldosterone antagonists for postmyocardial infarction heart failure

C McKenna,<sup>1\*</sup> J Burch,<sup>2</sup> S Suekarran,<sup>2</sup>  
S Walker,<sup>1</sup> A Bakhai,<sup>3</sup> K Witte,<sup>4</sup> M Harden,<sup>2</sup>  
K Wright,<sup>2</sup> N Woolacott,<sup>2</sup> P Lorgelly,<sup>5</sup>  
L Fenwick<sup>5</sup> and S Palmer<sup>1</sup>

<sup>1</sup>Centre for Health Economics, University of York, York, UK

<sup>2</sup>Centre for Reviews and Dissemination, University of York, York, UK

<sup>3</sup>Barnet General Hospital, Barnet, UK

<sup>4</sup>University of Leeds and Leeds General Infirmary, Leeds, UK

<sup>5</sup>Section of Health Policy and Public Health, University of Glasgow, Glasgow, UK

\*Corresponding author



## Executive summary

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## Executive summary

### Background

A large myocardial infarction (MI) stimulates adaptations in cardiac structure and function which lead to impaired cardiac function and heart failure (HF). The incidence of postMI HF is increasing in the UK as a result of the shifting age distribution of the population and increased survival after acute MI. The number of people with postMI HF in the UK for the year 2000 was estimated to be between 130,000 and 202,000, with associated annual costs to the NHS in the region of £125M to £181M.

Two aldosterone inhibitors are currently licensed for the treatment of HF in the UK: spironolactone is licensed for use for HF in the UK, whereas eplerenone, a more recently developed drug, is specifically indicated for the reduction of risk of cardiovascular death in patients with HF and left ventricular (LV) dysfunction within 3–14 days of an acute MI. Although spironolactone is reported to be widely used postMI, in the absence of direct effectiveness evidence in this patient group, recent clinical guidelines have recommended treatment with eplerenone for patients who have had an acute MI and who have symptoms and/or signs of HF and LV dysfunction.

### Objectives

The primary objective was to evaluate the relative clinical effectiveness and cost-effectiveness of spironolactone and eplerenone in patients with HF following MI, and to explore the possibility of conducting an indirect comparison of spironolactone and eplerenone in postMI HF. A second objective was to undertake value-of-information (VOI) analyses to determine the need for further research, to identify the research questions critical to decision-making and to help inform the design of future studies.

### Methods

#### Methods for reviewing clinical effectiveness

A systematic review of clinical effectiveness was conducted. Relevant databases including

MEDLINE, EMBASE and CENTRAL were searched between September and December 2008.

For the assessment of clinical effectiveness, randomised controlled trials (RCTs) of any size of spironolactone, eplerenone, canrenone or potassium canrenoate were included if conducted in a postMI HF population. Trials of general HF patients that included a subgroup of patients whose HF was preceded at some point by an ischaemic event such as an MI, were considered further if they had at least 100 ischaemic participants per arm and the authors provided subgroup data when contacted. For the assessment of adverse events, summary data from recognised reference sources and RCTs or observational studies in any population that recruited more than 100 participants were sought. The narrative synthesis explored the exchangeability between the drugs on a pharmacological basis, and the trials in relation to the population recruited.

#### Methods for assessment of cost-effectiveness

A systematic review of existing cost-effectiveness evidence was conducted including full economic evaluations that compared two or more options and considered both costs and consequences. A probabilistic decision analytic model was also developed to estimate the cost-effectiveness of spironolactone and eplerenone, in addition to standard care, for the management of postMI HF. The objective was to provide estimates that were relevant to the UK NHS and to explore alternative approaches to informing an indirect comparison between the alternative aldosterone antagonists. The model incorporated a lifetime horizon to estimate outcomes in terms of quality-adjusted life-years (QALYs) and costs from the perspective of the NHS. In the base-case analysis, a 2-year treatment duration for spironolactone and eplerenone was assumed, which is consistent with the follow-up of the main RCTs considered. A range of additional scenarios were also explored to examine the robustness of alternative assumptions including the impact of different treatment durations.

The relative effectiveness of spironolactone and eplerenone were derived using a Bayesian

meta-regression approach. This drew on a wider 'network' of aldosterone trials to those considered in the main clinical effectiveness review, incorporating trials in postMI with LV systolic dysfunction, but not clinical HF, postMI HF and more general HF populations because of the difficulties in basing an indirect comparison on the results of the postMI HF trials alone. An alternative scenario was also considered assuming a 'class effect' for the aldosterone antagonists in terms of major clinical events but allowing for potential differences in their side effect profiles.

Cost-effectiveness was assessed using incremental cost-effectiveness ratios (ICERs) where appropriate. Uncertainty in the cost-effectiveness results was also presented and used to inform future research priorities using VOI analyses based on the expected value of perfect information (EVPI).

## Results

Searches yielded five RCTs. Two spironolactone trials were very small, and of poor methodological quality. Of the three trials that were considered further, only one (of eplerenone) specifically examined postMI heart failure (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, EPHESES). One trial of spironolactone (Randomised Aldactone Evaluation Study, RALES) and one of canrenone (Antiremodeling Effect of Aldosterone receptors blockade with canrenone mild Chronic Heart Failure, AREA IN-CHF) were of general HF patients; some data were available for the ischaemic subgroup.

The structural similarity of spironolactone and eplerenone suggests that these drugs may be interchangeable in terms of efficacy, but there were a number of issues that severely limited a formal indirect comparison given the lack of exchangeability of the RALES, EPHESES and AREA IN-CHF trials, in particular, time since MI, beta-blocker use, differences in baseline LV ejection fraction, and other concomitant medication.

Data on the relative safety of eplerenone, spironolactone and canrenone were limited from both the RCTs and observational sources. The rates of hyperkalaemia varied widely for eplerenone, spironolactone and canrenone but were generally higher than those reported with placebo. Data were insufficient to assess discontinuation as a result of hyperkalaemia. The rates of gynaecomastia were

generally higher with spironolactone. Time to adverse event data were also sparse and few useful data were obtained.

The systematic review of existing economic evidence identified three main published studies. However, none of these studies used a UK perspective or had attempted to compare the cost-effectiveness of spironolactone versus eplerenone in postMI HF. These limitations were therefore addressed in the development of the new decision model.

The cost-effectiveness results from this model were presented for a base-case analysis assuming a 2-year treatment duration with aldosterone antagonists and a number of separate scenarios including lifetime treatment. In all except one of these analyses, eplerenone appeared to be the most cost-effective strategy for the management of postMI HF. In the base-case analysis, the ICER of eplerenone compared with standard care was £4457 per QALY. This increased to £7893 per QALY assuming that treatment with eplerenone was continued over a patient's lifetime. In both of these scenarios spironolactone did not appear cost-effective. The cost-effectiveness results remained robust to a range of alternative assumptions and the ICER of eplerenone was consistently under the £20,000–30,000 per QALY threshold of cost-effectiveness conventionally used to establish value for money in the NHS.

There appeared to be a relatively high-degree of uncertainty surrounding the cost-effectiveness results, which produced sizeable EVPI estimates between £820M (base-case) and £1265M (lifetime treatment duration scenario). These estimates demonstrate significant potential value to the NHS in undertaking additional research to reduce the existing decision uncertainty. This uncertainty was driven by the relative treatment effects of mortality between eplerenone and spironolactone, indicating that a future head-to-head RCT of these two treatments in a postMI HF population may be considered highly valuable. The fact that partial EVPI estimates indicated the treatment effect of aldosterone antagonists on mortality had the most value, meant that a change in the cost of eplerenone had only a small effect on EVPI relative to the effectiveness parameters.

Both the cost-effectiveness and EVPI results were demonstrated to be sensitive to the higher (mean) effectiveness for eplerenone compared with spironolactone based on the results of the evidence

synthesis. When a class effect for mortality and hospitalisations was assumed for the aldosterone antagonists, spironolactone emerged as the most cost-effective treatment and EVPI estimates were negligible. Consequently, if a class effect is considered more plausible than the results of the evidence synthesis model then there appears to be limited value in undertaking additional research in the future.

## Conclusions

The only good-quality trial evidence for aldosterone inhibitors in the postMI HF population comes from a trial of eplerenone (EPHESUS) and spironolactone was studied in HF in RALES. The lack of exchangeability of these trials with respect to study populations, beta-blocker use and other issues such as concurrent medication, means that a simple indirect comparison between these drugs using these trials could not produce clinically meaningful results. To evaluate the efficacy of spironolactone in postMI HF patients a contemporary trial comparing eplerenone and spironolactone directly appears warranted.

When the results of the Bayesian synthesis were applied within the economic model, eplerenone appeared to be the most cost-effective strategy for the management of postMI HF. The cost-effectiveness results were remarkably robust to a range of alternative assumptions and parameter inputs and the ICER of eplerenone was consistently under the threshold of cost-effectiveness conventionally used to establish value for money in the NHS. The only scenario considered, which resulted in a different conclusion regarding cost-effectiveness, was when the results from the evidence synthesis were ignored and instead a class effect was assumed for both of the aldosterone antagonists.

When the results from the Bayesian evidence synthesis were used, the EVPI results consistently demonstrated potential value to the NHS in undertaking additional research to reduce the existing decision uncertainty. Decision uncertainty and the population EVPI estimates were primarily caused by the level of uncertainty surrounding the relative treatment effects of mortality between eplerenone and spironolactone. However, in common with the cost-effectiveness

conclusions, when a class effect was assumed (i.e. equivalent efficacy in terms of all-cause mortality and hospitalisations for cardiovascular events for spironolactone and eplerenone) different conclusions were reached and further primary research would appear unlikely to represent value for money to the NHS.

Despite the challenges and difficulties that emerged in attempting to undertake a formal comparison of the effectiveness and cost-effectiveness of spironolactone and eplerenone, an important finding has consistently emerged. That is, compared with usual care, the use of an aldosterone antagonist more generally appears to be a highly cost-effective strategy for the management of postMI HF patients in the UK NHS.

## Recommendations for research

An adequately powered, well-conducted RCT that directly compares spironolactone and eplerenone is required to provide more robust evidence on the optimal management of postMI HF patients. Differences in mortality appear to be the major source of current uncertainty and hence the design and follow-up should reflect this. Given that there is also a lack of evidence for either drug in terms of hospitalisations, additional data on non-fatal events requiring hospitalisation and side effects would be important outcomes. The estimates of EVPI appear sufficiently high to conclude that a head-to-head RCT is likely to provide value for money. Should a future RCT be considered, then a more formal assessment of the costs and benefits should be conducted using the cost-effectiveness model presented here to ensure that this is done efficiently and to assess the feasibility of conducting such a trial.

## Publication

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