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[Intervention Review]

# Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction

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## ABSTRACT

### Background

Beta-blockers and inhibitors of the renin-angiotensin aldosterone system improve survival and reduce morbidity in people with heart failure with reduced left ventricular ejection fraction. There is uncertainty whether these treatments are beneficial for people with heart failure with preserved ejection fraction and a comprehensive review of the evidence is required.

### Objectives

To assess the effects of beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, and mineralocorticoid receptor antagonists in people with heart failure with preserved ejection fraction.

### Search methods

We searched CENTRAL, MEDLINE, Embase and two clinical trial registries on 25 July 2017 to identify eligible studies. Reference lists from primary studies and review articles were checked for additional studies. There were no language or date restrictions.

### Selection criteria

We included randomised controlled trials with a parallel group design enrolling adult participants with heart failure with preserved ejection fraction, defined by a left ventricular ejection fraction of greater than 40 percent.

### Data collection and analysis

Two review authors independently selected studies for inclusion and extracted data. The outcomes assessed included cardiovascular mortality, heart failure hospitalisation, hyperkalaemia, all-cause mortality and quality of life. Risk ratios (RR) and, where possible, hazard ratios (HR) were calculated for dichotomous outcomes. For continuous data, mean difference (MD) or standardised mean difference (SMD) were calculated. We contacted trialists where neccessary to obtain missing data.

### Main results

37 randomised controlled trials (207 reports) were included across all comparisons with a total of 18,311 participants.

Ten studies (3087 participants) investigating beta-blockers (BB) were included. A pooled analysis indicated a reduction in cardiovascular mortality (15% of participants in the intervention arm versus 19% in the control arm; RR 0.78; 95% confidence interval (CI) 0.62 to 0.99;

number needed to treat to benefit (NNTB) 25; 1046 participants; 3 studies). However, the quality of evidence was low and no effect on cardiovascular mortality was observed when the analysis was limited to studies with a low risk of bias (RR 0.81; 95% CI 0.50 to 1.29; 643 participants; 1 study). There was no effect on all-cause mortality, heart failure hospitalisation or quality of life measures, however there is uncertainty about these effects given the limited evidence available.

12 studies (4408 participants) investigating mineralocorticoid receptor antagonists (MRA) were included with the quality of evidence assessed as moderate. MRA treatment reduced heart failure hospitalisation (11% of participants in the intervention arm versus 14% in the control arm; RR 0.82; 95% CI 0.69 to 0.98; NNTB 41; 3714 participants; 3 studies; moderate-quality evidence) however, little or no effect on all-cause and cardiovascular mortality and quality of life measures was observed. MRA treatment was associated with a greater risk of hyperkalaemia (16% of participants in the intervention group versus 8% in the control group; RR 2.11; 95% CI 1.77 to 2.51; 4291 participants; 6 studies; high-quality evidence).

Eight studies (2061 participants) investigating angiotensin converting enzyme inhibitors (ACEI) were included with the overall quality of evidence assessed as moderate. The evidence suggested that ACEI treatment likely has little or no effect on cardiovascular mortality, all-cause mortality, heart failure hospitalisation, or quality of life. Data for the effect of ACEI on hyperkalaemia were only available from one of the included studies.

Eight studies (8755 participants) investigating angiotensin receptor blockers (ARB) were included with the overall quality of evidence assessed as high. The evidence suggested that treatment with ARB has little or no effect on cardiovascular mortality, all-cause mortality, heart failure hospitalisation, or quality of life. ARB was associated with an increased risk of hyperkalaemia (0.9% of participants in the intervention group versus 0.5% in the control group; RR 1.88; 95% CI 1.07 to 3.33; 7148 participants; 2 studies; high-quality evidence).

We identified a single ongoing placebo-controlled study investigating the effect of angiotensin receptor neprilysin inhibitors (ARNI) in people with heart failure with preserved ejection fraction.

**Authors' conclusions**

There is evidence that MRA treatment reduces heart failure hospitalisation in heart failure with preserverd ejection fraction, however the effects on mortality related outcomes and quality of life remain unclear. The available evidence for beta-blockers, ACEI, ARB and ARNI is limited and it remains uncertain whether these treatments have a role in the treatment of HFpEF in the absence of an alternative indication for their use. This comprehensive review highlights a persistent gap in the evidence that is currently being addressed through several large ongoing clinical trials.

## PLAIN LANGUAGE SUMMARY

**Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction**

**Review question**

We investigated the effects of beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and angiotensin receptor neprilysin inhibitors (ARNI) on survival, hospital admissions for heart failure, quality of life and potassium levels in people with heart failure with preserved ejection fraction.

**Background**

Heart failure is a common condition that occurs when the function of the heart muscle is impaired that is associated symptoms of breathlessness and fatigue, and a reduction in survival. In around half of cases where there is reduced contraction (heart failure with reduced ejection fraction, HFrEF), several treatments are known to be effective at improving survival and reducing hospitalisation. In the remaining cases where relaxation is impaired (heart failure with preserved ejection fraction, HFpEF), it is not clear whether the same drug treatments are also effective at improving outcomes.

**Selection criteria**

We sought to investigate whether HFrEF treatments are also effective in HFpEF. We conducted a comprehensive search for all trials investigating BB, MRA, ACEI, ARB or ARNI (evidence current to 25 July 2017).

**Results and conclusions**

We included 10 studies with 3087 randomised participants for BB, 12 studies with 4408 randomised participants for MRA, eight studies with 2061 randomised participants for ACEI and eight studies with 8755 randomised participants for ARB. We combined the evidence in a pooled analysis for each drug class and for each of the outcomes assessed. Not all included studies are part of each analysis.

We found that beta-blockers may improve cardiovascular mortality, however the evidence quality was low due to small trials and uncertainty about the methods used. For MRA, the results suggest a reduction in heart failure hospitalisation and have little or no effect on cardiovascular and all-cause mortality, however the evidence quality was only moderate. For ACEI, treatment probably has little or

no effect on the outcomes of cardiovascular mortality, all-cause mortality and heart failure hospitalisation, however the evidence quality was only moderate. We found high quality evidence for ARB treatment and the results suggest little or no effect from this treatment. No completed studies were available for ARNI. Treatment with MRA and ARB was found to increase the risk of high potassium in the blood.

In conclusion, BB may improve outcomes in patients with HFpEF however this remains uncertain. MRA was found to result in a slight reduction in the risk of hospitalisation due to heart failure. Treatment with ACEI probably has no effect, however this remains uncertain. The evidence suggested that treatment with ARB is of little or no benefit in people with HFpEF.

**Quality of the evidence**

The quality of evidence ranged from high to low across the outcomes and drug classes studied. With the exception of ARB, there was a lack of large scale trials in HFpEF for the interventions and outcomes tested.