**Effects of beta-adrenergic antagonists in patients with chronic kidney disease: a systematic review and meta-analysis**


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**CRD summary**

This review concluded that treatment with beta-blockers reduced the risk of mortality in patients with chronic kidney disease and chronic systolic heart failure. Evidence for patients with no known heart failure was found insufficient. Concerns about study designs and the conduct of this review mean that its conclusions should be interpreted with caution.

**Authors' objectives**

To assess the benefits and risks of beta-blockers in patients with chronic kidney disease.

**Searching**

MEDLINE and EMBASE (up to October 2010) and Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 4, 2010) were searched. No language restrictions were applied. Reference lists of relevant review articles, systematic reviews, treatment guidelines, textbook chapters, conference proceedings and online trial registries were consulted. Unpublished, missing or incomplete data from trials were requested from study authors. Search terms were reported.

**Study selection**

Randomised controlled trials (RCTs) that compared an oral beta-blocking agent to a placebo, a cardiovascular agent of another class or no treatment were included. Trials had to include participants with chronic kidney disease stages 3 to 5 (estimated glomerular filtration rate \( \leq 60 \text{mL/min/1.73m}^2 \)). Patients on dialysis were included. Trials that included participants with kidney transplants were excluded. Studies had to follow-up patients for a minimum of three months following randomisation and report mortality outcomes.

Mean/median patient age ranged from 51 to 77.4 years and 53% to 71% of patients were male. Most participants had chronic systolic heart failure. Fewer than 2% of patients were on dialysis. In studies that included patients with no heart failure, none were on dialysis. Most patients with heart failure had decreased left ventricular ejection fraction and mild chronic kidney disease. Some patients had diabetes. Nearly all patients had concomitant angiotensin-converting enzyme (ACE) inhibition. Mean/median glomerular filtration rate varied between studies of patients with and without heart-failure. All studies of patients with heart failure compared a beta-blocker with a placebo. Studies that included patients with no heart failure had either enalapril (5mg to 10mg daily) or ramipril (2.5mg to 10mg daily) as comparators.

The authors did not state how many reviewers selected the studies.

**Assessment of study quality**

Cochrane risk of bias tool was used to assess the methodological quality of included studies with criteria of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other bias (insufficient rationale, study design).

The authors did not state how many reviewers assessed study quality.

**Data extraction**

The primary outcome was all-cause mortality. Other clinical outcomes included cardiovascular mortality, sudden death, all-cause hospitalisation, hospitalisation for worsening of heart failure and adverse events (bradycardia, hypotension, hyperkalaemia). Outcomes were extracted from each study to calculate risk ratios (RRs) and 95% confidence intervals (CIs).

The authors did not state how many reviewers extracted data.
Methods of synthesis
Studies were pooled using a random-effects model. Heterogeneity was assessed with $I^2$. Results of the meta-analysis were not reported where heterogeneity was high ($I^2 \geq 75\%$). Studies of patients with heart failure were analysed separately from those with other patients due to differences in cardiovascular morbidity, comparator and follow-up duration. Where possible, subgroup analyses stratified by chronic kidney disease severity were performed.

Results of the review
Eight RCTs were included in the review (6,949 patients). Two trials were performed in 977 patients with no known heart failure. Six trials were conducted in 5,972 patients with chronic systolic heart failure. Of those six studies, five were subgroup analyses of chronic kidney disease patients not on dialysis within a larger study of patients with chronic systolic heart failure. None of these subgroup analyses were prespecified. Follow-up ranged from one to two years for trials that involved patients with heart failure and between about three and four years for other studies. Allocation concealment was found to be adequate in only half of the trials. Randomisation and blinding of outcome assessors were deemed adequate in five trials. The risk of selective outcome reporting was unclear or high in all studies.

Studies of patients with heart failure (six trials): Compared with placebo, beta-blockers significantly reduced the risk of all-cause mortality (RR 0.72, 95% CI 0.64 to 0.80, $I^2=0\%$; six trials), risk of cardiovascular mortality (RR 0.66, 95% CI 0.49 to 0.89, $I^2=64.2\%$; four trials), risk of sudden death (RR 0.70, 95% CI 0.55 to 0.89, $I^2=0\%$; four trials). Beta-blockers did not significantly reduce the risk of all-cause hospitalisation ($I^2=67.1\%$; two trials).

Compared to placebo, beta-blockers significantly increased the risk of bradycardia (RR 4.92, 95% CI 3.20 to 7.55, $I^2=0\%$; four trials) and hypotension (RR 5.08, 95% CI 3.48 to 7.41, $I^2=0\%$; four trials). Risk of hyperkalaemia was not significantly different between intervention and placebo groups (RR 2.16, 95% CI 0.12 to 37.92, $I^2=68.2\%$; three trials). Risk of medication discontinuation was not significantly different between intervention and control.

Studies of patients with no heart failure (two trials): Significant differences between studies and a lack of available data meant that no pooled estimates were performed. No outcomes were reported.

Authors’ conclusions
Treatment with beta-blockers reduced risks of all-cause and cardiovascular mortality in chronic kidney disease patients who had heart failure and low left ventricular ejection fraction. Beta-blockers increased risks of bradycardia and hypotension in patient with heart failure. There was insufficient data on the effect of beta-blockers for patients without heart failure.

CRD commentary
The review question and inclusion criteria were clear. The bibliographic searches were thorough. It was unclear whether study selection, data extraction and quality assessment were carried out with sufficient attempts to minimise error and bias. Study details were adequate. Analysis methods and separate pooling of studies with symptomatic heart failure patients was appropriate. The decision not to pool the two studies that included patients with no heart failure was appropriate. It was not clear why individual study results from these long-term trials were not reported. Some outcomes included data from only a small number of studies and much of the data came from post-hoc subgroup analyses (which are subject to bias). Undue reliance on post-hoc subgroup analyses may undermine the reliability of the conclusions. Most patients with heart failure had decreased left ventricular ejection fraction and mild chronic kidney disease. This should be borne in mind when assessing the generalisability of the review findings.

Concerns about study designs and the conduct of this review mean that its conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that use of beta-blockers to reduce risks of cardiovascular events and improve clinical outcomes in patients with chronic kidney disease who did not have heart failure or those with symptomatic heart failure and a normal left ventricular ejection fraction could not be recommended based on evidence from existing RCTs.

Research: The authors stated that adequately powered RCTs were needed to assess the effect of beta-blockers for chronic kidney disease on patients with no heart failure, particularly those with advanced chronic kidney disease and
those receiving dialysis.

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