Comparative clinical- and cost-effectiveness of candesartan and losartan in the management of hypertension and heart failure: a systematic review, meta- and cost-utility analysis

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CRD summary
The review found that candesartan appeared to reduce blood pressure slightly more than losartan, but that the difference may not be clinically significant. There was no good evidence that candesartan was superior to losartan for treating heart failure. These conclusions require some caution in interpretation due to limitations in the review, which included incomplete adherence to the inclusion criteria.

Authors' objectives
To compare the efficacy of losartan and candesartan for treating essential hypertension and chronic heart failure.

Searching
Reviewers searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2009, Issue 2), MEDLINE and EMBASE (both to February 2010). Search terms were reported. The reference lists of retrieved articles were checked. The search was restricted to fully published articles in English.

Study selection
Parallel or crossover double-blinded randomised controlled trials (RCTs) that compared candesartan versus losartan in adults (aged over 18 years) with a treatment period of at least four weeks were eligible for hypertension outcomes (mean change in trough diastolic and systolic blood pressure). Double-blinded RCTs of adults with a left ventricular ejection fraction of 40% or less were eligible for heart failure outcomes (composite of cardiovascular death and hospital admission for heart failure). Studies that had an open-label phase, a response-conditional design or that used cointerventions were excluded.

In the included studies on hypertension, the mean participant age ranged from 51 to 60 years. Most participants were male and all had mild to moderate hypertension. Losartan at a low (50mg) and high (100mg) dose was compared with candesartan at a low (8mg), mid (16mg) and high dose (32mg). Most studies used non-forced titration. Treatment duration in the double-blinded phase was usually eight weeks (range four to 12).

No studies directly compared losartan to candesartan for heart failure. The reviewers found three RCTs of losartan (at differing doses or versus captopril) and three RCTs of candesartan (versus placebo) for heart failure. In these studies, mean participant age was 64 to 74 years and the proportion of black participants ranged from 3% to 91%.

Two reviewers selected the studies. Disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
Risk of bias was assessed using criteria recommended by the Cochrane Collaboration. Two reviewers conducted the assessment.

Data extraction
Mean differences and 95% confidence intervals (CIs) between the two groups in change from baseline to study endpoint were extracted or calculated for each outcome. Data were extracted on an intention-to-treat basis, even when primary studies used per protocol analysis.

Two reviewers independently extracted the data. Disagreements were resolved by discussion with a third reviewer.

Methods of synthesis
Studies reported that hypertension were combined using a random-effects model to calculate weighted mean differences (WMDs) and 95% CIs. Heterogeneity was assessed using Cochran's Q and I². Key studies of heart failure were reported in a qualitative analysis in the discussion section of the review.
Results of the review

Seven parallel and one cross-over RCT (nine comparisons, 3,619 participants, range 13 to 1,151) that compared losartan and candesartan head-to-head were included, all reported hypertension. Six RCTs of losartan or candesartan for heart failure were found, none of which were head-to-head comparisons (12,560 participants, range 270 to 3,840).

When nine comparisons were pooled, candesartan was significantly more effective than losartan in reducing trough diastolic blood pressure (WMD -1.89 mmHg, 95% CI -2.29 to -1.48) and systolic blood pressure (WMD -2.96 mmHg, 95% CI -3.60 to -2.32). There was mild heterogeneity for diastolic blood pressure ($I^2=33\%$) and moderate heterogeneity for systolic blood pressure ($I^2=52\%$).

Three RCTs of losartan or candesartan for heart failure were regarded as key studies and their results were reported in the discussion section of the review.

Cost information

The review included a 10-year economic analysis using a Markov model. For hypertension, the incremental cost per quality-adjusted life-year gained with candesartan over generic losartan ranged from £41,469 to £52,644 (men) and £41,591 to £85,244 (women). The cost-effectiveness of candesartan decreased with lower baseline risk, lower cost of losartan and in younger cohorts. The review concluded that use of generic losartan could save the UK National Health Service £200 million per annum.

Authors’ conclusions

Candesartan appeared to reduce blood pressure slightly more than losartan, but the difference may not have been clinically significant. There was no good evidence that candesartan was superior to losartan for treating heart failure.

CRD commentary

The objectives of the review were clear. The inclusion criteria were explicit with regard to studies of hypertension. There was some inconsistency in the inclusion criteria for studies of heart disease and the relevance of the six heart disease studies was unclear. Relevant sources were searched for studies but the restriction to fully published studies in English meant that some studies may have been missed. Publication bias was not formally assessed. Steps were taken to minimise risks of reviewer bias and error by having more than one reviewer select studies, undertake validity assessment and extract data. However, the criteria used to assess study validity were not described in detail and the results of the assessment were not reported; this made it difficult to determine the reliability of the review findings. Appropriate statistical methods were used to combine the hypertension studies and assess heterogeneity. Mild to moderate heterogeneity was detected and attributed to methodological and clinical differences between the studies. The authors acknowledged that the review was limited by the short duration of the studies, potential publication bias and may apply only to adults without comorbidity who received doses similar to those used in the trials. The authors’ lack of adherence to inclusion criteria and the suboptimal search mean that these conclusions require some caution in interpretation.

Implications of the review for practice and research

Practice: The authors stated that generic losartan should be prescribed for all patients for whom an angiotensin II receptor blocker (ARB) was indicated. Patients taking candesartan should be changed to losartan unless they are intolerant. The authors cautioned against routinely combining ARBs with angiotensin-converting enzyme inhibitors and commented on the dosage and dose escalation of ARBs; however, these recommendations did not arise directly from review findings.

Research: The authors did not state any implications for research.

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Bibliographic details
