A systematic review and meta-analysis of candesartan and losartan in the management of essential hypertension
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CRD summary
The authors concluded that candesartan was superior to losartan in reducing blood pressure. Candesartan seemed to cause fewer serious adverse events than losartan. The authors’ conclusion regarding blood pressure seemed appropriate for the short-term effects in the selected population. The limitations of the evidence suggest the reliability of the conclusions regarding serious adverse events remains uncertain.

Authors' objectives
To compare the effect of candesartan with losartan on blood pressure reduction, response and control rates and common and serious adverse events in patients with primary hypertension.

Searching
MEDLINE, Pre-MEDLINE and EMBASE were searched from inception to May 2009 for articles published in English. Cochrane Central Register of Controlled Trials (CENTRAL, issue 1 2009) was also searched. Search terms were reported. Review articles, prospective trial registers, relevant trials and abstracts from hypertension meetings were searched for additional studies.

Study selection
Eligible randomised controlled trials (RCTs) and quasi-RCTs compared candesartan to losartan in adults with primary hypertension and measured anti-hypertensive and tolerability effects at follow-up of at least four weeks. Studies were excluded if they contained participants with concomitant coronary disease, stroke, congestive heart failure, poorly controlled diabetes mellitus or chronic kidney disease. Studies were excluded if participants had taken any angiotensin converting enzyme inhibitors, angiotensin receptor blockers or other anti-hypertensive agents in the two weeks prior to trial.

Included studies compared candesartan (8mg or double or titration to double dose) to losartan (50mg or double or titration to double dose). Some studies also included placebo or hydrochlorothiazide arms. The results of these arms were not included in the meta-analysis. Follow-up ranged from six to 12 weeks.

Two reviewers independently selected the studies for review. Disagreements were resolved by consensus or consultation with a third reviewer.

Assessment of study quality
Study quality was assessed using the Jadad scale that assessed randomisation, allocation concealment, blinding and withdrawals/drop-outs. Studies were scored from 0 to 5; five represented high quality studies, 3-4 moderate quality and 0 to 2 low quality studies. Studies were also rated according to use of intention-to-treat analysis.

The authors did not state the number of reviewers performing the quality assessment.

Data extraction
The change from baseline in seated systolic blood pressure and diastolic blood pressure were extracted for each group and used to calculate mean differences with 95% confidence intervals (CI). The control rate, response rate and incidence of adverse events were extracted for each group and used to calculate relative risks (RR) with 95% confidence intervals.

The data appeared to have been extracted independently by two reviewers.

Methods of synthesis
For change in blood pressure, pooled weighted mean differences (WMD) with 95% confidence intervals were
calculated. For control rate, response rate and incidence of adverse effects, pooled relative risks (RRs) with 95% confidence intervals were calculated. The impact of dose on blood pressure reduction was investigated. Statistical heterogeneity was assessed using the Q test and $I^2$. Where there was evidence of significant statistical heterogeneity, a random-effects model was used, otherwise a fixed-effect model was used. Publication bias was assessed using Egger's test and visual inspection of funnel plots. The impact of baseline blood pressure, length of treatment and age of patients on treatment outcomes was investigated using a meta-regression analysis.

**Results of the review**

Twelve RCTs were included for review (3,644 patients analysed; sample sizes ranged from 40 to 1,161). No studies scored 5 on the Jadad; 11 scored 3 or 4 and one scored 2. Drop-outs ranged from three to 76 patients (total was 294). Follow-up ranged from six to 12 weeks.

Systolic blood pressure (WMD -2.97 95% CI -4.18 to -1.77; 12 studies, 3,644 patients) and diastolic blood pressure (WMD -1.76 95% CI -2.57 to -0.96; 12 studies, 3,644 patients) significantly reduced with candesartan compared to losartan at trough after 24 hour follow up. There was evidence of moderate statistical heterogeneity for both of these outcomes ($I^2= 40.4\%$ for systolic and $I^2= 55.6\%$ for diastolic blood pressure). Subgroup analyses demonstrated that candesartan was superior to losartan in reducing blood pressure at all dosages.

Candesartan demonstrated better control (RR 1.26 95% CI 1.06 to 1.50) and response rates (RR 1.12 95% CI 1.06 to 1.18) than losartan.

Candesartan was associated with significantly lower incidence of serious adverse events compared to losartan (RR 0.48 95% CI 0.25 to 0.92; six studies). There was no significant difference between candesartan and losartan in the occurrence of common adverse events (RR 0.98 95% CI 0.86 to 1.12; eight studies). There was no statistical heterogeneity for the outcomes of adverse events (common adverse events $I^2=0\%$ and serious adverse events $I^2=1\%$). There were no significant differences between candesartan and losartan in the occurrence of adverse events were headache, dizziness, respiratory infections, fatigue and gastroenteritis.

There was no evidence of publication bias. The results of the meta-regression were reported in the review.

**Authors' conclusions**

Candesartan was superior to losartan in reducing blood pressure. Candesartan seemed to cause fewer serious adverse events than losartan.

**CRD commentary**

The review addressed a clear question with well-defined inclusion criteria. Several relevant databases were searched, but the search was restricted to articles published in English which may have introduced language bias. Attempts were made to identify unpublished data. Information was not provided on the characteristics of patients included in the studies, which made it difficult to determine the generalisability of results. Suitable methods were taken in the selection of studies and data extraction to minimise the risk of reviewer error and bias. It was unclear whether similar steps were taken in the quality assessment stages.

The quality of included studies was moderate. Appropriate methods were used to combine the results. Statistical heterogeneity was assessed and reported for some outcomes. Follow-up duration was short. The number of serious adverse events reported for both groups was small, so there was insufficient evidence to reliably determine differences between groups for this outcome. The authors' conclusion regarding blood pressure seemed appropriate for the short-term effects in the selected population. The limitations of the evidence suggest the reliability of the conclusions regarding serious adverse events remains uncertain.

**Implications of the review for practice and research**

The authors did not state any implications for practice or research.

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