Valsartan vs. other angiotensin II receptor blockers in the treatment of hypertension: a meta-analytical approach

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CRD summary
The review compared the effectiveness of valsartan with other angiotensin II receptor blockers in reducing systolic and diastolic blood pressure in essential hypertension. Valsartan at doses of 160 or 350mg/day was more effective than 100mg/day losartan and had comparable antihypertensive efficacy to other angiotensin II receptor blockers. The authors' conclusions are unlikely to be reliable given limitations in the analysis.

Authors' objectives
To compare the effectiveness of valsartan with other angiotensin II receptor blockers in reducing systolic and diastolic blood pressure in essential hypertension.

Searching
MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL) and SciSearch were searched, from October 1997 to May 2008, for publications in English and German. Search terms were not reported.

Study selection
Parallel group double-blind randomised controlled trials (RCTs) with at least one angiotensin II receptor blocker monotherapy arm with no or forced titration, of patients representative of the general hypertension population were eligible for inclusion. RCTs had to be of short duration (six to 12 weeks). The general hypertension population was defined as patients aged 18 or more years, diagnosed with mild/moderate essential hypertension, with diastolic blood pressure of 90 to 115mmHg. Trials were only eligible if office blood pressure was measured by automatic or cuff mercury sphygmomanometer, with either baseline plus follow-up diastolic/systolic blood pressure or baseline plus change in baseline diastolic/systolic blood pressure.

Trials were excluded if: withdrawals were not reported; patients had secondary hypertension; patients had cardiovascular disease (except diabetes, left ventricular hypertrophy or cardiomegaly).

The primary outcomes were changes in diastolic and systolic blood pressure from baseline to follow-up.

The doses of angiotensin II receptor blockers in the included trials were classified as low, medium or high in the included trials; candesartan (8, 16 and 32mg/day); irbesartan (150 or 300mg/day); losartan (50 or 100mg/day); olmesartan (10, 20 and 40mg/day); telmisartan (40 and 80mg/day); and valsartan (80, 160 and 320mg/day). The mean baseline diastolic blood pressure of included patients ranged from 94.2 to 104mmHg and the mean baseline systolic blood pressure ranged from 149.5 to 169mmHg; the mean age ranged from 51 to 60 years; the proportion of males ranged from 42 to 70%.

Two independent reviewers were involved in the literature search and study selection, with disagreements resolved by consensus with a third reviewer.

Assessment of study quality
Methodological quality was assessed by two reviewers independently according to the following criteria: method of randomisation, allocation concealment, performance bias, blinding, attrition bias, withdrawals, intention-to-treat, and validity of outcome tools.

Data extraction
Two reviewers independently extracted data on diastolic blood pressure and systolic blood pressure at baseline and follow-up in each intervention group, and calculated the mean change and standard deviation (SD). Where more than one result was available for a study, the latest result was used. Data were cross-checked for consistency and
disagreements resolved by consensus with a third reviewer.

**Methods of synthesis**
Only studies that provided data on follow-up of between six and 12 weeks were included in the meta-analysis. The pooled mean change and 95% confidence intervals (CI) in diastolic blood pressure and systolic blood pressure from baseline to follow-up were estimated using a random-effects meta-regression model adjusted for baseline blood pressure. Data were pooled for individual doses of specific drugs. Treatment effects were determined by drug and dose. In forced titration studies, the dose used in calculations was the maximum dose the patient received rather than the start dose. Efforts were made to input missing values.

**Results of the review**
Thirty one relevant RCTs were identified (n=13,110 patients). Six RCTs had trial arms that assessed candesartan, six assessed irbesartan, 13 assessed losartan (13), two assessed olmesartan, five assessed telmisartan, and 12 assessed valsartan.

**Drug/dose-response relationships**: There was a positive dose-response relationship for all the angiotensin II receptor blockers; all of them had a significant benefit for reducing diastolic and systolic blood pressure at low, moderate or high doses. There was a particularly large reduction in systolic blood pressure for valsartan when the dose was increased from 80 mg/day to 160 mg/day or above.

The mean reduction in systolic blood pressure for treatment with valsartan were -11.52mmHg (95% CI -14.39 to -8.70) for 80mg/day, -15.32mmHg (95% CI -17.09 to -13.63) for 160mg/day, and -15.85 (95% CI -17.60 to -14.20) for 320mg/day.

The relative reduction in diastolic blood pressure for treatment with valsartan were -8.71mmHg (95% CI -9.94 to -7.50) for 80mg/day, -11.33mmHg (95% CI -12.15 to -10.52) for 160mg/day and -11.97mmHg (95% CI -12.81 to -11.16) for 320mg/day.

**Indirect drug/dose comparisons for mean change in blood pressure from baseline**: A positive result indicated that valsartan was superior to the other angiotensin II receptor blocker in reducing blood pressure.

For 80mg/day valsartan, there was no significant difference in mean change for diastolic or systolic blood pressure when compared to other angiotensin II receptor blockers.

For 160mg/day valsartan there was a significant benefit for lowering diastolic blood pressure compared with 16mg/day candesartan (mean change 1.85mmHg, 95% CI 0.34 to 3.40). There was also a significant benefit with 160mg/day valsartan for lowering both diastolic blood pressure (mean change 2.06mmHg, 95% CI 0.71 to 3.45) and systolic blood pressure (mean change 3.56mmHg, 95% CI 0.77 to 6.38) compared with 150mg/day irbesartan. Similarly, a significant benefit was found when 160mg/day valsartan was compared with 100mg/day losartan for both diastolic blood pressure (mean change 1.95mmHg, 95% CI 0.81 to 3.11) and systolic blood pressure (mean change 3.31mmHg, 95% CI 0.86 to 5.79).

For 320 mg/day valsartan compared with other angiotensin II receptor blockers, the only significant differences were reductions in diastolic blood pressure (mean change from baseline 2.60mmHg, 95% CI 1.45 to 3.76) and systolic blood pressure (mean change 3.84mmHg, 95% CI 1.34 to 6.31) when compared with 100mg/day losartan.

**Authors' conclusions**
Valsartan at doses of 160 or 350mg/day was more effective in reducing blood pressure than losartan at 100mg/day; it had comparable efficacy to other angiotensin II receptor blockers in patients with essential hypertension. Valsartan had a strong dose-response relationship when increased from 80 to 160 and 320mg/day.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched in English and German. It appeared that unpublished studies were not considered, so some studies may have been missed. Publication bias was not assessed. Generally, efforts were made to reduce error and bias in the review process.
Trial quality was assessed using suitable criteria, but no comparison of the quality of the included trials was provided and no relevant data. Relevant trial details were reported, but no details of length of follow-up or loss to follow-up were given. There were no data relevant to the placebos used. Statistical heterogeneity was not assessed. The statistical method used for the meta-analysis of the RCTs may not have been appropriate. The authors commented that the analysis was limited by the scarcity of trials of valsartan at high doses and the relative lack of head-to-head trials.

The authors’ conclusions are unlikely to be reliable given limitations in the analysis.

Three authors disclosed links with Novartis Pharma AG.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors identified a need for further head-to-head trials of angiotensin II receptor blockers.

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